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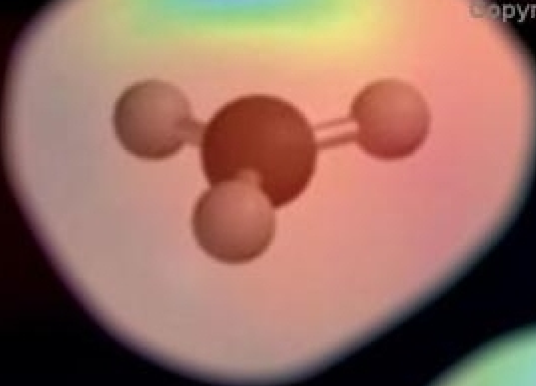
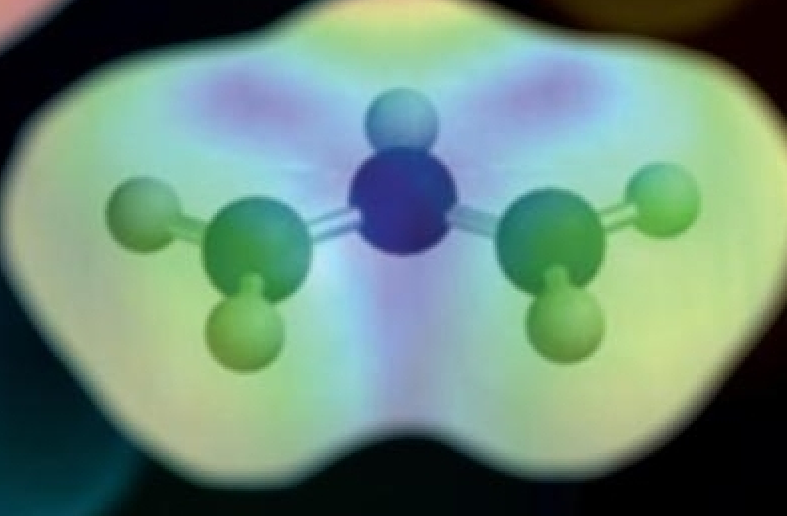
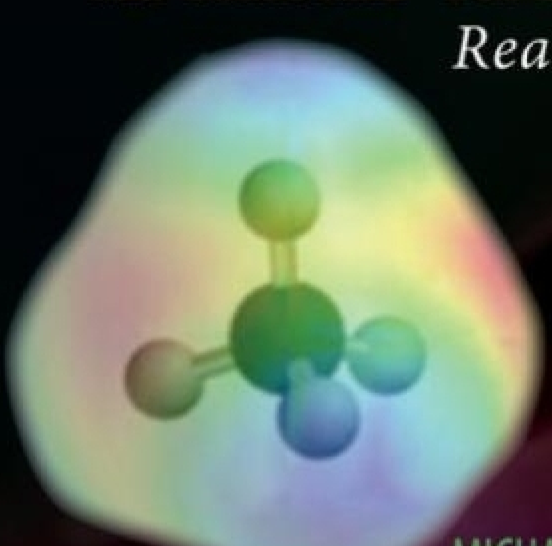




MARCH'S
ADVANCED ORGANIC CHEMISTRY
Reactions, Mechanisms, and Structure



6TH EDITION

MICHAEL B. SMITH and JERRY MARCH

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MARCH'S ADVANCED ORGANIC CHEMISTRY

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MARCH'S ADVANCED ORGANIC CHEMISTRY

REACTIONS, MECHANISMS, AND STRUCTURE

SIXTH EDITION

Michael B. Smith
Professor of Chemistry

Jerry March
Professor of Chemistry

WILEY-INTERSCIENCE
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Published by John Wiley & Sons, Inc., Hoboken, New Jersey
Published simultaneously in Canada

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Library of Congress Cataloging-in-Publication Data is available.

Smith, Michael B., March, Jerry
March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Sixth Edition

ISBN 13: 978-0-471-72091-1
ISBN 10: 0-471-72091-7

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

CONTENTS

PREFACE v

BIOGRAPHICAL NOTE xv

ABBREVIATIONS xvii

PART 1 1

1. Localized Chemical Bonding 3
2. Delocalized Chemical Bonding 32
3. Bonding Weaker than Covalent 106
4. Stereochemistry 136
5. Carbocations, Carbanions, Free Radicals, Carbenes, and Nitrenes 234
6. Mechanisms and Methods of Determining Them 296
7. Irradiation Processes in Organic Chemistry 328
8. Acids and Bases 356
9. Effects of Structure and Medium on Reactivity 395

PART 2 417

10. Aliphatic Substitution: Nucleophilic and Organometallic 425
11. Aromatic Substitution, Electrophilic 657
12. Aliphatic, Alkenyl, and Alkynyl Substitution, Electrophilic and Organometallic 752
13. Aromatic Substitution, Nucleophilic and Organometallic 853
14. Substitution Reactions: Free Radicals 934
15. Addition to Carbon–Carbon Multiple Bonds 999

16. Addition to Carbon–Hetero Multiple Bonds **1251**

17. Eliminations **1477**

18. Rearrangements **1559**

19. Oxidations and Reductions **1703**

Appendix A The Literature of Organic Chemistry **1870**

Appendix B Classification of Reactions by Type of Compounds Synthesized **1911**

Indexes

Author Index **1937**

Subject Index **2190**

PREFACE

Organic chemistry is a vibrant and growing scientific discipline that touches a vast number of scientific areas. This sixth edition of "March's Advanced Organic Chemistry" has been thoroughly updated to reflect new areas of Organic chemistry, as well as new advances in well-known areas of Organic chemistry. Every topic retained from the fifth edition has been brought up to date. Changes include the addition of a few new sections, significant revision to sections that have seen explosive growth in that area of research, moving sections around within the book to better reflect logical and reasonable chemical classifications, and a significant rewrite of much of the book. More than 7000 new references have been added. As with the fifth edition, when older references were deleted and in cases where a series of papers by the same principal author were cited, all but the most recent were deleted. The older citations should be found within the more recent one or ones. The fundamental structure of the sixth edition is essentially the same as that of all previous ones, although acyl substitution reactions have been moved from chapter 10 to chapter 16, and many oxidation or reduction reactions have been consolidated into chapter 19.

Like the first five editions, the sixth is intended to be a textbook for a course in advanced organic chemistry taken by students who have had the standard undergraduate organic and physical chemistry courses.

The goal, as in previous editions is to give equal weight to the three fundamental aspects of the study of organic chemistry: reactions, mechanisms, and structure. A student who has completed a course based on this book should be able to approach the literature directly, with a sound knowledge of modern basic organic chemistry. Major special areas of organic chemistry: terpenes, carbohydrates, proteins, many organometallic reagents, combinatorial chemistry, polymerization and electrochemical reactions, steroids, etc. have been treated lightly or ignored completely. I share the late Professor March's opinion that these topics are best approached after the first year of graduate study, when the fundamentals have been mastered, either in advanced courses, or directly, by consulting the many excellent books and review articles available on these subjects. In addition, many of these topics are so vast, they are beyond the scope of this book.

The organization is based on reaction types, so the student can be shown that despite the large number of organic reactions, a relatively few principles suffice to explain nearly all of them. Accordingly, the reactions-mechanisms section of this book (Part 2) is divided into 10 chapters (10–19), each concerned with a different type of reaction. In the first part of each chapter the appropriate basic

mechanisms are discussed along with considerations of reactivity and orientation, while the second part consists of numbered sections devoted to individual reactions, where the scope and the mechanism of each reaction are discussed. Numbered sections are used for the reactions. Since the methods for the preparation of individual classes of compounds (e.g., ketones, nitriles, etc.) are not treated all in one place, an index has been provided (Appendix B) by use of which all methods for the preparation of a given type of compound will be found. For each reaction, a list of *Organic Syntheses* references is given where they have been reported. Thus for many reactions the student can consult actual examples in *Organic Syntheses*. It is important to note that the numbers for each reaction *differ* from one edition to the other, and many of the sections in the fifth edition do not correlate with the fourth. A correlation table is included at the end of this Preface that directly correlates the sections found in the 5th edition with the new ones in the 6th edition.

The structure of organic compounds is discussed in the first five chapters of Part 1. This section provides a necessary background for understanding mechanisms and is also important in its own right. The discussion begins with chemical bonding and ends with a chapter on stereochemistry. There follow two chapters on reaction mechanisms in general, one for ordinary reactions and the other for photochemical reactions. Part 1 concludes with two more chapters that give further background to the study of mechanisms.

In addition to reactions, mechanisms, and structure, the student should have some familiarity with the literature of organic chemistry. A chapter devoted to this topic has been placed in Appendix A, though many teachers may wish to cover this material at the beginning of the course.

The IUPAC names for organic transformations are included, first introduced in the third edition. Since then the rules have been broadened to cover additional cases; hence more such names are given in this edition. Furthermore, IUPAC has now published a new system for designating reaction mechanisms (see p. 420), and some of the simpler designations are included.

In treating a subject as broad as the basic structures, reactions, and mechanisms of organic chemistry, it is obviously not possible to cover each topic in great depth. Nor would this be desirable even if possible. Nevertheless, students will often wish to pursue individual topics further. An effort has therefore been made to guide the reader to pertinent review articles and books published since about 1965. In this respect, this book is intended to be a guide to the secondary literature (since about 1965) of the areas it covers. Furthermore, in a graduate course, students should be encouraged to consult primary sources. To this end, more than 20,000 references to original papers have been included.

Although basically designed for a one-year course on the graduate level, this book can also be used in advanced undergraduate courses, but a one-year course in organic chemistry prior to this is essential, and a one year course in physical chemistry is strongly recommended. It can also be adapted, by the omission of a large part of its contents, to a one-semester course. Indeed, even for a one-year course, more is included than can be conveniently covered. Many individual sections can be easily omitted without disturbing continuity.

The reader will observe that this text contains much material that is included in first-year organic and physical chemistry courses, though in most cases it goes more deeply into each subject and, of course, provides references, which first-year texts do not. It has been my experience that students who have completed the first-year courses often have a hazy recollection of the material and greatly profit from a representation of the material if it is organized in a different way. It is hoped that the organization of the material on reactions and mechanisms will greatly aid the memory and the understanding. In any given course the teacher may want to omit some chapters because students already have an adequate knowledge of the material, or because there are other graduate courses that cover the areas more thoroughly. Chapters 1, 4, and 7 especially may fall into one of these categories.

This book is probably most valuable as a reasonably up-to-date reference work. Students preparing for qualifying examinations and practicing organic chemists will find that Part 2 contains a survey of what is known about the mechanism and scope of a large number of reactions, arranged in an orderly manner based on reaction type and on which bonds are broken and formed. Also valuable for reference purposes are the previously mentioned lists of reactions classified by type of compound prepared (Appendix B) and of all of the *Organic Syntheses* references to each reaction.

Anyone who writes a book such as this is faced with the question of which units to use, in cases where international rules mandate one system, but published papers use another. Two instances are the units used for energies and for bond distances. For energies, IUPAC mandates joules, and many journals do use this unit exclusively. However, organic chemists who publish in United States journals overwhelmingly use calories and this situation shows no signs of changing in the near future. Since previous editions of this book have been used extensively both in this country and abroad, I have now adopted the practice of giving virtually all energy values in both calories and joules. The question of units for bond distances is easier to answer. Although IUPAC does not recommend Ångstrom units, nearly all bond distances published in the literature anywhere in the world, whether in organic or in crystallographic journals, are in these units, though a few papers do use picometers. Therefore, I continue to use only Ångstrom units.

I would like to acknowledge the contributions of those chemists cited and thanked by Professor March in the first four editions. I especially thank George Majetich, Warren Hehre, and Amos B. Smith III for generous contributions to specialized sections in the book as well as reviewing those sections. I also thank the many people who have contributed comments or have pointed out errors in the 5th edition that were invaluable to putting together the 6th edition. I thank CambridgeSoft Inc. for providing *ChemOffice*, with *ChemDraw*, which was used to prepare all reactions and several structures in this book. I thank Dr. Warren Hehre and Wavefunction, Inc. for providing MacSpartan, allowing the incorporation of Spartan 3D models for selected molecules and intermediates.

Special thanks are due to the Interscience division of John Wiley & Sons and to Dr. Darla Henderson without whose support the book would not have been completed. Special thanks are also given to Shirley Thomas and Rebekah Amos at

Wiley for their fine work as editors in turning the manuscript into the finished book. I also thank Ms. Jeannette Stiefel, for an excellent job of copy editing the manuscript. I gratefully acknowledge the work of the late Professor Jerry March, upon whose work this new edition is built, and who is responsible for the concept of this book and for carrying it through four very successful editions.

I encourage those who read and use the sixth edition to contact me directly with comments, errors, and with publications that might be appropriate for future editions. I hope that this new edition will carry on the tradition that Professor March began with the first edition.

My Email address is

michael.smith@uconn.edu

and my homepage is

http://orgchem.chem.uconn.edu/home/mbs-home.html

Finally, I want to thank my wife Sarah for her patience and understanding during the preparation of this manuscript. I also thank my son Steven for his support. Without their support, this work would not have been possible.

Michael B. Smith

June, 2006

5th edition ⟶ 6th edition

10-1 ⟶ 10-1	10-18 ⟶ 10-14	10-35 ⟶ 16-68
10-2 ⟶ 10-2	10-19 ⟶ 10-15	10-36 ⟶ 10-24
10-3 ⟶ 10-3	10-20 ⟶ 10-16	10-37 ⟶ 10-25
10-4 ⟶ 10-4	10-21 ⟶ 16-61	10-38 ⟶ 10-26
10-5 ⟶ 10-5	10-22 ⟶ 16-62	10-39 ⟶ 16-69
10-6 ⟶ 10-6	10-23 ⟶ 16-63	10-40 ⟶ 10-27
10-7 ⟶ 10-7	10-24 ⟶ 16-64	10-41 ⟶ 10-28
10-8 ⟶ 16-57	10-25 ⟶ 16-65	10-42 ⟶ 10-29
10-9 ⟶ 16-58	10-26 ⟶ 10-17	10-43 ⟶ 10-30
10-10 ⟶ 16-59	10-27 ⟶ 10-18	10-44 ⟶ 10-31
10-11 ⟶ 16-60	10-28 ⟶ 10-19	10-46 ⟶ 10-32
10-12 ⟶ 10-8	10-29 ⟶ 16-66	10-47 ⟶ 10-33
10-13 ⟶ 10-9	10-30 ⟶ 16-67	10-48 ⟶ 16-70
10-14 ⟶ 10-10	10-31 ⟶ 10-20	10-49 ⟶ 10-34
10-15 ⟶ 10-11	10-32 ⟶ 10-21	10-50 ⟶ 10-35
10-16 ⟶ 10-12	10-33 ⟶ 10-22	10-51 ⟶ 10-37
10-17 ⟶ 10-13	10-34 ⟶ 10-23	10-52 ⟶ 10-38

10-53 ⟶ 10-39
10-54 ⟶ 10-40
10-55 ⟶ 16-72
10-56 ⟶ 16-73
10-57 ⟶ 16-74
10-58 ⟶ 16-75
10-59 ⟶ 16-76
10-60 ⟶ 16-77
10-61 ⟶ 10-41
10-62 ⟶ 10-42
10-63 ⟶ 10-36
10-64 ⟶ 10-42
10-65 ⟶ 10-43
10-66 ⟶ 10-44
10-67 ⟶ 10-45
10-68 ⟶ 10-46
10-69 ⟶ 10-47
10-70 ⟶ 10-48
10-71 ⟶ 10-49
10-72 ⟶ 10-50
10-73 ⟶ 10-51
10-74 ⟶ 10-52
10-75 ⟶ 10-53
10-76 ⟶ 10-54
10-77 ⟶ 16-79
10-78 ⟶ 16-80
10-79 ⟶ 19-53
10-80 ⟶ 19-57
10-81 ⟶ 19-54
10-82 ⟶ 19-58
10-83 ⟶ 19-66
10-84 ⟶ 19-56
10-85 ⟶ 19-35
10-86 ⟶ 19-59
10-87 ⟶ 19-67
10-88 ⟶ 19-70
10-89 ⟶ 19-39
10-90 ⟶ 19-40
10-91 ⟶ 19-41
10-92 ⟶ 10-55
10-93 ⟶ 10-56
10-94 ⟶ 10-57
10-95 ⟶ 10-58
10-96 ⟶ 10-59
10-98 ⟶ 10-61
10-99 ⟶ 10-63

10-100 ⟶ 10-60
10-101 ⟶ 10-64
10-102 ⟶ 10-65
10-103 ⟶ 10-66
10-104 ⟶ 10-67
10-105 ⟶ 10-68
10-106 ⟶ 10-70
10-107 ⟶ 10-71
10-108 ⟶ 10-72
10-109 ⟶ 10-73
10-110 ⟶ 10-74
10-111 ⟶ 10-75
10-112 ⟶ 10-76
10-113 ⟶ 10-77
10-114 ⟶ 16-81
10-115 ⟶ 16-82
10-116 ⟶ 16-83
10-117 ⟶ 16-84
10-118 ⟶ 16-85
10-119 ⟶ 16-86
10-120 ⟶ 16-87
10-121 ⟶ 16-88
10-122 ⟶ 16-89
10-123 ⟶ 16-90
10-124 ⟶ 16-100
10-125 ⟶ 16-101
10-126 ⟶ 16-102
10-127 ⟶ 16-103
10-128 ⟶ 16-104
10-129 ⟶ 16-105

11-1 ⟶ 11-1
11-2 ⟶ 11-2
11-3 ⟶ 11-3
11-4 ⟶ 11-4
11-5 ⟶ 11-5
11-6 ⟶ 11-6
11-7 ⟶ 11-7
11-8 ⟶ 11-8
11-9
11-10 ⟶ 11-9
11-11 ⟶ 11-10
11-12 ⟶ 11-11
11-13 ⟶ 11-15
11-14 ⟶ 11-17
11-15 ⟶ 11-18
11-19 ⟶ 11-19
11-20 ⟶ 11-20
11-21 ⟶ 11-21
11-22 ⟶ 11-12
11-23 ⟶ 11-13
11-24 ⟶ 11-14
11-25 ⟶ 11-22
11-26 ⟶ 11-23
11-27 ⟶ 11-24
11-28 ⟶ 11-25
11-29 ⟶ 11-26
11-30 ⟶ 11-27
11-31 ⟶ 11-28
11-32 ⟶ 11-29
11-33 ⟶ 11-30
11-34 ⟶ 11-31
11-35 ⟶ 11-32
11-36 ⟶ 11-33
11-37 ⟶ 11-34
11-38 ⟶ 11-35
11-39 ⟶ 11-36
11-40 ⟶ 11-37
11-41 ⟶ 11-38
11-42 ⟶ 11-39
11-43 ⟶ 11-40
11-44 ⟶ 11-41

12-1 ⟶ 12-1
12-2 ⟶ 12-2
12-3 ⟶ 12-3
12-4 ⟶ 12-4
12-5 ⟶ 12-5
12-6 ⟶ 12-6
12-7 ⟶ 12-7
12-8 ⟶ 12-8
12-9 ⟶ 12-10
12-10 ⟶ 12-11
12-11 ⟶ 12-12
12-12 ⟶ 12-13
12-13 ⟶ 12-14
12-14 ⟶ 12-16
12-15 ⟶ 12-18
12-16 ⟶ 12-19
12-17 ⟶ 12-20
12-18 ⟶ 10-69
12-19 ⟶ 12-21

12-20 ⟶ 12-22
12-21 ⟶ 12-23
12-22 ⟶ 12-17
12-23 ⟶ 12-24
12-24 ⟶ 12-25
12-25 ⟶ 12-26
12-26 ⟶ 12-27
12-27 ⟶ 12-30
12-28 ⟶ 12-31
12-29 ⟶ 12-32
12-30 ⟶ 12-33
12-31 ⟶ 12-34
12-32 ⟶ 12-35
12-33 ⟶ 12-36
12-34 ⟶ 12-37
12-36 ⟶ 12-38
12-37 ⟶ 12-39
12-38 ⟶ 12-40
12-39 ⟶ 12-41
12-40 ⟶ 12-42
12-41 ⟶ 12-43
12-42 ⟶ 12-44
12-43 ⟶ 12-45
12-44 ⟶ 12-46
12-45 ⟶ 12-47
12-46 ⟶ 12-48
12-47 ⟶ 13-19
12-48 ⟶ 12-49
12-49 ⟶ 12-50
12-50 ⟶ 13-24
12-51 ⟶ 12-51
12-52 ⟶ 12-52
12-53 ⟶ 12-53

13-1 ⟶ 13-1
13-2 ⟶ 13-2
13-3 ⟶ 13-3
13-4 ⟶ 13-4
13-5 ⟶ 13-5
13-6 ⟶ 13-6
13-7 ⟶ 13-7
13-8 ⟶ 19-55
13-10 ⟶ 13-8
13-11 ⟶ 13-9
13-12 ⟶ 13-14
13-13 ⟶ 13-15
13-14 ⟶ 13-11
13-15 ⟶ 13-17
13-16 ⟶ 13-18
13-17 ⟶ 13-20
13-18 ⟶ 13-21
13-19 ⟶ 13-22
13-20 ⟶ 13-23
13-21 ⟶ 13-30
13-22 ⟶ 13-31
13-23 ⟶ 13-32
13-24 ⟶ 13-33

14-1 ⟶ 14-1
14-2 ⟶ 14-3
14-3 ⟶ 14-4
14-4 ⟶ 19-14
14-5 ⟶ 14-5
14-6 ⟶ 19-23
14-7 ⟶ 14-6
14-8 ⟶ 14-7
14-9 ⟶ 14-8
14-10 ⟶ 14-9
14-11 ⟶ 14-10
14-12 ⟶ 12-9
14-13 ⟶ 14-11
14-14 ⟶ 14-12
14-15 ⟶ 14-14
14-16 ⟶ 14-16
14-17 ⟶ 13-27
14-18 ⟶ 13-26
14-19 ⟶ 13-10
14-20 ⟶ 12-15
14-21 ⟶ 14-17
14-22 ⟶ 14-18
14-23 ⟶ 14-19
14-24 ⟶ 19-69
14-25 ⟶ 14-20
14-26 ⟶ 14-21
14-27 ⟶ 14-22
14-28 ⟶ 13-28
14-29 ⟶ 13-25
14-30 ⟶ 14-23
14-31 ⟶ 14-24
14-32 ⟶ 14-26
14-33 ⟶ 14-25
14-34 ⟶ 14-27
14-35 ⟶ 14-28
14-36 ⟶ 14-29
14-37 ⟶ 14-30
14-38 ⟶ 14-31
14-39 ⟶ 14-32

15-1 ⟶ 15-1
15-2 ⟶ 15-2
15-3 ⟶ 15-3
15-4 ⟶ 15-4
15-5 ⟶ 15-5
15-6 ⟶ 15-6
15-7 ⟶ 15-7
15-8 ⟶ 15-8
15-9 ⟶ 15-9
15-10 ⟶ 15-10
15-11 ⟶ 15-11
15-12 ⟶ 15-12
15-13 ⟶ 15-14
15-14 ⟶ 15-13
15-15 ⟶ 15-15
15-16 ⟶ 15-16
15-17 ⟶ 15-17
15-18 ⟶ 15-18
15-19 ⟶ 15-20
15-20 ⟶ 15-23
15-21 ⟶ 15-24
15-22 ⟶ 15-21
15-23 ⟶ 15-22
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15-25 ⟶ 15-27
15-26 ⟶ 15-28
15-27 ⟶ 15-32
15-28 ⟶ 15-33
15-29 ⟶ 15-36
15-30 ⟶ 15-35
15-31 ⟶ 15-37
15-32 ⟶ 15-34
15-33 ⟶ 15-38
15-34 ⟶ 15-19
15-35 ⟶ 15-29
15-36 ⟶ 15-30
15-37 ⟶ 15-39

15-38 ⟶ 15-41
15-39 ⟶ 15-40
15-40 ⟶ 15-42
15-41 ⟶ 15-43
15-42 ⟶ 15-44
15-43 ⟶ 15-45
15-44 ⟶ 15-46
15-45 ⟶ 15-47
15-46 ⟶ 15-48
15-47 ⟶ 15-49
15-48 ⟶ 15-50
15-49 ⟶ 15-62
15-50 ⟶ 15-51
15-51 ⟶ 15-52
15-52 ⟶ 15-53
15-53 ⟶ 15-54
15-54 ⟶ 15-55
15-55 ⟶ 15-56
15-56 ⟶ 15-57
15-57 ⟶ 15-58
15-58 ⟶ 15-60
15-59 ⟶ 15-61
15-60 ⟶ 15-59
15-61 ⟶ 15-63
15-62 ⟶ 15-64
15-63 ⟶ 15-65
15-64 ⟶ 15-66

16-1 ⟶ 16-1
16-2 ⟶ 16-2
16-3 ⟶ 16-3
16-4 ⟶ 16-4
16-5 ⟶ 16-5
16-6 ⟶ 16-7
16-7 ⟶ 16-8
16-8 ⟶ 16-9
16-9 ⟶ 16-10
16-10 ⟶ 16-11
16-11 ⟶ 16-12
16-12 ⟶ 16-13
16-13 ⟶ 16-18
16-14 ⟶ 16-17
16-15 ⟶ 16-19
16-16 ⟶ 16-20
16-17 ⟶ 16-21
16-18 ⟶ 16-22
16-19 ⟶ 16-14
16-20 ⟶ 16-15
16-21 ⟶ 16-16
16-22 ⟶ 16-23
16-23 ⟶ 19-36
16-24 ⟶ 19-42
16-25 ⟶ 19-43
16-26 ⟶ 19-44
16-27 ⟶ 16-24
16-28 ⟶ 16-25
16-29 ⟶ 16-26
16-30 ⟶ 16-27
16-31 ⟶ 16-28
16-32 ⟶ 16-29
16-33 deleted - combined with 10-115
16-34 ⟶ 16-30
16-35 ⟶ 16-31
16-36 ⟶ 16-32
16-37 ⟶ 16-33
16-38 ⟶ 16-34
16-39 ⟶ 16-35
16-40 ⟶ 16-36
16-41 ⟶ 16-38
16-42 ⟶ 16-41
16-43 ⟶ 16-42
16-44 ⟶ 16-39
16-45 ⟶ 16-40
16-46 ⟶ 16-43
16-47 ⟶ 16-44
16-48 ⟶ 16-45
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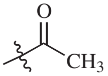
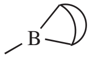
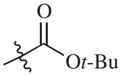
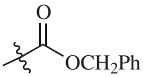
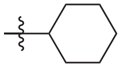
BIOGRAPHICAL NOTE

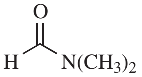
Professor Michael B. Smith was born in Detroit, Michigan in 1946 and lived there until 1957. In 1957, he and his family moved to Madison Heights, Virginia, where he attended high school and then Ferrum Jr. College, where he graduated with an A.A in 1966. Professor Smith then transferred to Virginia Polytechnic Institute (Virginia Tech), and graduated with a B.S in chemistry in 1969. After working as an analytical chemist at the Newport News Shipbuilding and Dry Dock Co. (Tenneco) in Newport News, Virginia for three years, he began graduate studies at Purdue University under the mentorship of Professor Joseph Wolinsky. Professor Smith graduated with a Ph.D. in Organic chemistry in 1977. He then spent one year as a faculty research associate at the Arizona State University, in the Cancer Research Institute directed by Professor George R. Pettit. Professor Smith spent a second year doing postdoctoral work at the Massachusetts Institute of Technology under the mentorship of Professor Sidney Hecht. In 1979 Professor Smith began his independent academic career, where he now holds the rank of full professor.

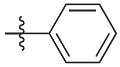
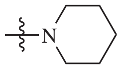
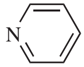
Professor smith is the author of approximately 70 independent research articles, and is the author of 14 published books. The books include the 5th edition of March's Advanced Organic Chemistry (Wiley), volumes 6–11 of the Compendium of Organic Synthetic Methods (Wiley), Organic Chemistry a Two Semester Course (HarperCollins) into its 2nd edition, and Organic Synthesis (McGraw-Hill) through its 2nd edition. The 3rd edition of the Organic Synthesis book is due out in 2007, published by Wavefunction, Inc.

Professor Smith's current research involves the synthesis and structural verification of several bioactive lipids obtained from the dental pathogen *Porphyromonas gingivalis*. Another area of research examines the chemical reactivity of conducting polymers such as poly(ethylenedioxy)thiophene (PEDOT). Such polymers are supposed to be chemically inert but, in fact, induce a variety of chemical reactions, including Friedel-Crafts alkylation of aromatic compounds with alcohols. Another area of research involves the development of a dye-conjugate designed to target and image tumors, as well as the total synthesis of anti-cancer phenanthridone alkaloids such as pancratistatin.

ABBREVIATIONS

Ac	Acetyl	
acac	Acetylacetonato	
AIBN	Azoisobutyronitrile	
aq.	Aqueous	
	9-Borabicyclo[3.3.1]nonylboryl	
9-BBN	9-Borabicyclo[3.3.1]nonane	
BER	Borohydride exchange resin	
BINAP	(*2R*,*3S*),*2*,*2*′-bis(diphenylphosphino)-1,1′-binapthyl	
Bn	Benzyl	
Bz	Benzoyl	
BOC	*tert*-Butoxycarbonyl	
bpy (bipy)	2,2′-Bipyridyl	
Bu	*n*-Butyl	$-CH_2CH_2CH_2CH_3$
CAM	Carboxamidomethyl	
CAN	Ceric ammonium nitrate	$(NH)_2Ce(NO_3)_6$
c-	Cyclo-	
cat.	Catalytic	
Cbz	Carbobenzyloxy	
Chirald	(2*S*,3*R*)-(+)-4-dimethylamino-1,2-diphenyl-3-methylbutan-2-o1	
Cod	1,5-Cyclooctadiene (ligand)	
Cot	1,3,5,7-Cyclooctatetraene (ligand)	
Cp	Cyclopentadienyl	
CSA	Camphorsulfonic acid	
CTAB	Cetyltrimethylammonium bromide	$C_{16}H_{33}NMe_3{}^+Br^-$
Cy (c-C_6H_{11})	Cyclohexyl	
°C	Temperature in degrees Centigrade	
DABCO	1,4-Diazobicyclo[2.2.2]octane	
dba	Dibenzylidene acetone	
DBE	1,2-Dibromoethane	$BrCH_2CH_2Br$
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene	
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene	
DCC	1,3-Dicyclohexylcarbodiimide	c-C_6H_{13}—N=C=N-c-C_6H_{13}
DCE	1,2-Dichloroethane	$ClCH_2CH_2Cl$

DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone	
% de	% Diasteromeric excess	
DEA	Diethylamine	$HN(CH_2CH_3)_2$
DEAD	Diethylazodicarboxylate	$EtO_2C{-}N{=}NCO_2Et$
Dibal-H	Diisobutylaluminum hydride	$(Me_2CHCH_2)_2AlH$
Diphos (dppe)	1,2-bis(Diphenylphosphino)ethane	$Ph_2PCH_2CH_2PPh_2$
Diphos-4 (dppb)	1,4-bis(Diphenylphosphino)butane	$Ph_2P(CH_2)_4PPh_2$
DMAP	4-Dimethylaminopyridine	
DMA	Dimethylacetamide	
DME	1,2-Dimethoxyethane	$MeOCH_2CH_2OMe$
DMF	*N,N'*-Dimethylformamide	
dmp	bis-[1,3-Di(*p*-methoxyphenyl)-1,3-propanedionato]	
DMSO	Dimethyl sulfoxide	
dpm	Dipivaloylmethanato	
dppb	1,4-bis(Diphenylphosphino)butane $Ph_2P(CH_2)_4PPh_2$	
dppe	1,2-bis(Diphenylphosphino)ethane $Ph_2PCH_2CH_2CH_2PPh_2$	
dppf	bis(Diphenylphosphino)ferrocene	
dppp	1,3-bis(Diphenylphosphino)propane	$Ph_2P(CH_2)_3PPh_2$
dvb	Divinylbenzene	
e^-	Electrolysis	
% ee	% Enantiomeric excess	
EE	1-Ethoxyethyl	EtO(Me)HCO—
Et	Ethyl	$-CH_2CH_3$
EDA	Ethylenediamine	$H_2NCH_2CH_2NH_2$
EDTA	Ethylenediaminetetraacetic acid	
FMN	Flavin mononucleotide	
fod	*tris*-(6,6,7,7,8,8,8)-Heptafluoro-2,2-dimethyl-3,5-octanedionate	
Fp	Cyclopentadienyl-bis(carbonyl iron)	
FVP	Flash vacuum pyrolysis	
h	Hour (hours)	
hν	Irradiation with light	
1,5-HD	1,5-Hexadienyl	
HMPA	Hexamethylphosphoramide	$(Me_3N)_3P{=}O$
HMPT	Hexamethylphorous triamide	$(Me_3N)_3P$
*i*Pr	Isopropyl	$-CHMe_2$
IR	Infrared	
LICA (LIPCA)	Lithium cyclohexylisopropylamide	
LDA	Lithium diisopropylamide	LiN(*i*Pr)$_2$
LHMDS	Lithium hexamethyl disilazide	$LiN(SiMe_3)_2$
LTMP	Lithium 2,2,6,6-tetramethylpiperidide	
MABR	Methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide)	

MAD	bis(2,6-Di-*tert*-butyl-4-methylphenoxy)methyl aluminum	
mCPBA	*meta*-Chloroperoxybenzoic acid	
Me	Methyl	$-CH_3$
MEM	β-Methoxyethoxymethyl	$MeOCH_2CH_2OCH_2-$
Mes	Mesityl	2,4,6-tri-Me-C_6H_2
MOM	Methoxymethyl	$MeOCH_2-$
Ms	Methanesulfonyl	CH_3SO_2-
MS	Molecular sieves (3 Å or 4 Å)	
MTM	Methylthiomethyl	CH_3SCH_2-
NAD	Nicotinamide adenine dinucleotide	
NADP	Sodium triphosphopyridine nucleotide	
Napth	Naphthyl ($C_{10}H_8$)	
NBD	Norbornadiene	
NBS	*N*-Bromosuccinimide	
NCS	*N*-Chlorosuccinimide	
NIS	*N*-Iodosuccinimide	
Ni(R)	Raney nickel	
NMP	*N*-Methyl-2-pyrrolidinone	
NY	New York	
NMR	Nuclear magnetic resonance	
Oxone	$2\ KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$	
Ⓟ	Polymeric backbone	
PCC	Pyridinium chlorochromate	
PDC	Pyridinium dichromate	
PEG	Polyethylene glycol	
Ph	Phenyl	
PhH	Benzene	
PhMe	Toluene	
Phth	Phthaloyl	
pic	2-Pyridinecarboxylate	
Pip	Piperidyl	
PMP	4-Methoxyphenyl	
Pr	*n*-Propyl	$-CH_2CH_2CH_3$
Py	Pyridine	
quant.	Quantitative yield	
Red-Al	$[(MeOCH_2CH_2O)_2AlH_2]Na$	
*s*Bu	*sec*-Butyl	$CH_3CH_2CH(CH_3)$
*s*BuLi	*sec*-Butyllithium	$CH_3CH_2CH(Li)CH_3$
Siamyl	Diisoamyl	$(CH_3)_2CHCH(CH_3)$-
TADDOL	α,α,α′α′-Tetraaryl-4,5-dimethoxy-1,3-dioxolane	
TASF	*tris*-(Diethylamino)sulfonium difluorotrimethyl silicate	
TBAF	Tetrabutylammonium fluoride	n-$Bu_4N^+F^-$
TBDMS	*tert*-Butyldimethylsilyl	t-$BuMe_sSi$
TBHP	*tert*-Butylhydroperoxide (*t*-BuOOH)	Me_3COOH

t-Bu	*tert*-Butyl	$-C(CH_3)_3$
TBS	*tert*-Butyl dimethylsilyl	t-BuMe$_2$Si
TEBA	Triethylbenzylammonium	$Bn(CH_3)_3N^+$
TEMPO	Tetramethylpiperdinyloxy free radical	
TFA	Trifluoroacetic acid	CF_3COOH
TFAA	Trifluoroacetic anhydride	$(CF_3CO)_2O$
Tf (OTf)	Triflate	$-SO_2CF_3(-OSO_2CF_3)$
THF	Tetrahydrofuran	
THP	Tetrahydropyran	
TMEDA	Tetramethylethylenediamine	$Me_2NCH_2CH_2NMe_2$
TMG	1,1,3,3-Tetramethylguanidine	
TMS	Trimethylsilyl	$-Si(CH_3)_3$
TMP	2,2,6,6-Tetramethylpiperidine	
TPAP	tetra-*n*-Propylammonium perruthenate	
Tol	Tolyl	$4MeC_6H_4$
Tr	Trityl	$-CPh_3$
TRIS	Triisopropylphenylsulfonyl	
Ts(Tos)	Tosyl = *p*-Toluenesulfonyl	$4\text{-}MeC_6H_4$
UV	Ultraviolet	
X_c	Chiral auxiliary	

PART ONE

This book contains 19 chapters. Chapters 10–19, which make up Part 2, are directly concerned with organic reactions and their mechanisms. Chapters 1–9 may be thought of as an introduction to Part 2. The first five chapters deal with the structure of organic compounds. These chapters discuss the kinds of bonding important in organic chemistry, the three-dimensional structure of organic molecules, and the structure of species in which the valence of carbon is less than 4. Chapters 6–9 are concerned with other topics that help to form a background to Part 2: acids and bases, photochemistry, the relationship between structure and reactivity, and a general discussion of mechanisms and the means by which they are determined.

CHAPTER 1

Localized Chemical Bonding

Localized chemical bonding may be defined as bonding in which the electrons are shared by two and only two nuclei. In Chapter 2, we will consider *delocalized bonding*, in which electrons are shared by more than two nuclei.

COVALENT BONDING[1]

Wave mechanics is based on the fundamental principle that electrons behave as waves (e.g., they can be diffracted) and that consequently a wave equation can be written for them, in the same sense that light waves, sound waves, and so on can be described by wave equations. The equation that serves as a mathematical model for electrons is known as the *Schrödinger equation*, which for a one-electron system is

$$\frac{\delta^2\psi}{\delta x^2} + \frac{\delta^2\psi}{\delta y^2} + \frac{\delta^2\psi}{\delta z^2} + \frac{8\pi^2 m}{h^2}(E - V)\psi = 0$$

where m is the mass of the electron, E is its total energy, V is its potential energy, and h is Planck's constant. In physical terms, the function Ψ expresses the square root of the probability of finding the electron at any position defined by the coordinates x, y, and z, where the origin is at the nucleus. For systems containing more than one electron, the equation is similar, but more complicated.

[1]The treatment of orbitals given here is necessarily simplified. For much fuller treatments of orbital theory as applied to organic chemistry, see Matthews, P.S.C. *Quantum Chemistry of Atoms and Molecules*, Cambridge University Press, Cambridge, ***1986***; Clark, T. *A Handbook of Computational Chemistry*, Wiley, NY, ***1985***; Albright, T.A.; Burdett, J.K.; Whangbo, M. *Orbital Interactions in Chemistry*, Wiley, NY, ***1985***; MacWeeny, R.M. *Coulson's Valence*, Oxford University Press, Oxford, ***1980***; Murrell, J.N.; Kettle, S.F.A; Tedder, J.M. *The Chemical Bond*, Wiley, NY, ***1978***; Dewar, M.J.S.; Dougherty. R.C. *The PMO Theory of Organic Chemistry*, Plenum, NY, ***1975***; Zimmerman, H.E. *Quantum Mechanics for Organic Chemists*, Academic Press, NY, ***1975***; Borden, W.T. *Modern Molecular Orbital Theory for Organic Chemists*, Prentice-Hall, Englewood Cliffs, NJ, ***1975***; Dewar, M.J.S. *The Molecular Orbital Theory of Organic Chemistry*, McGraw-Hill, NY, ***1969***; Liberles, A. *Introduction to Molecular Orbital Theory*, Holt, Rinehart, and Winston, NY, ***1966***.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Sixth Edition, by
Michael B. Smith and Jerry March
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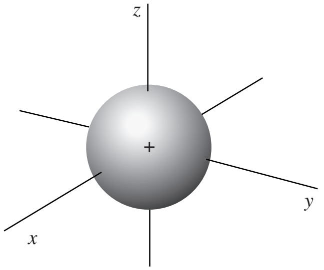


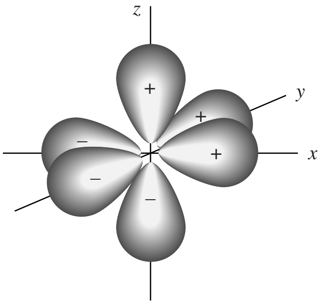


Fig. 1.1. (*a*) The 1*s* orbital. (*b*) The three 2*p* orbitals.

The Schrödinger equation is a differential equation, which means that solutions of it are themselves equations, but the solutions are not differential equations. They are simple equations for which graphs can be drawn. Such graphs, which are three-dimensional (3D) pictures that show the electron density, are called *orbitals* or electron clouds. Most students are familiar with the shapes of the *s* and *p* atomic orbitals (Fig. 1.1). Note that each *p* orbital has a *node*: A region in space where the probability of finding the electron is extremely small.[2] Also note that in Fig. 1.1 some lobes of the orbitals are labeled + and others −. These signs do not refer to positive or negative *charges*, since both lobes of an electron cloud must be negatively charged. They are the signs of the wave function Ψ. When two parts of an orbital are separated by a node, Ψ always has opposite signs on the two sides of the node. According to the Pauli exclusion principle, no more than two electrons can be present in any orbital, and they must have opposite spins.

Unfortunately, the Schrödinger equation can be solved exactly only for one-electron systems, such as the hydrogen atom. If it could be solved exactly for molecules containing two or more electrons,[3] we would have a precise picture of the shape of the orbitals available to each electron (especially for the important ground state) and the energy for each orbital. Since exact solutions are not available, drastic approximations must be made. There are two chief general methods of approximation: the molecular-orbital method and the valence-bond method.

In the molecular-orbital method, bonding is considered to arise from the overlap of atomic orbitals. When any number of atomic orbitals overlap, they combine to

[2]When wave-mechanical calculations are made according to the Schrödinger equation, the probability of finding the electron in a node is zero, but this treatment ignores relativistic considerations. When such considerations are applied, Dirac has shown that nodes do have a very small electron density: Powell, R.E. *J. Chem. Educ.* ***1968***, *45*, 558. See also, Ellison, F.O. and Hollingsworth, C.A. *J. Chem. Educ.* ***1976***, *53*, 767; McKelvey, D.R. *J. Chem. Educ.* ***1983***, *60*, 112; Nelson, P.G. *J. Chem. Educ.* ***1990***, *67*, 643. For a review of relativistic effects on chemical structures in general, see Pyykkö, P. *Chem. Rev.* ***1988***, *88*, 563.
[3]For a number of simple systems containing two or more electrons, such as the H_2 molecule or the He atom, approximate solutions are available that are so accurate that for practical purposes they are as good as exact solutions. See, for example, Roothaan, C.C.J.; Weiss, A.W. *Rev. Mod. Phys.* ***1960***, *32*, 194; Kolos, W.; Roothaan, C.C.J. *Rev. Mod. Phys.* ***1960***, *32*, 219. For a review, see Clark, R.G.; Stewart, E.T. *Q. Rev. Chem. Soc.* ***1970***, *24*, 95.

form an equal number of new orbitals, called *molecular orbitals*. Molecular orbitals differ from atomic orbitals in that they are clouds that surround the nuclei of two or more atoms, rather than just one atom. In localized bonding the number of atomic orbitals that overlap is two (each containing one electron), so that two molecular orbitals are generated. One of these, called a *bonding orbital*, has a lower energy than the original atomic orbitals (otherwise a bond would not form), and the other, called an *antibonding orbital*, has a higher energy. Orbitals of lower energy fill first. Since the two original atomic orbitals each held one electron, both of these electrons can now go into the new molecular *bonding* orbital, since any orbital can hold two electrons. The antibonding orbital remains empty in the ground state. The greater the overlap, the stronger the bond, although total overlap is prevented by repulsion between the nuclei. Figure 1.2 shows the bonding and antibonding orbitals that arise by the overlap of two 1*s* electrons. Note that since the antibonding orbital has a node between the nuclei, there is practically no electron density in that area, so that this orbital cannot be expected to bond very well. Molecular orbitals formed by the overlap of two atomic orbitals when the centers of electron density are on the axis common to the two nuclei are called σ (*sigma*) orbitals, and the bonds are called σ bonds. Corresponding antibonding orbitals are designated σ^*. Sigma orbitals are formed not only by the overlap of two *s* orbitals, but also by the overlap of any of the kinds of atomic orbital (*s, p, d*, or *f*) whether the same or different, but the two lobes that overlap must have the same sign: a positive *s* orbital can form a bond only by overlapping with another positive *s* orbital or with a positive lobe of a *p, d*, or *f* orbital. Any *s* orbital, no matter what kind of atomic orbitals it has arisen from, may be represented as approximately ellipsoidal in shape.

Orbitals are frequently designated by their symmetry properties. The σ orbital of hydrogen is often written ψ_g. The *g* stands for *gerade*. A gerade orbital is one in which the sign on the orbital does not change when it is inverted through its center of symmetry. The σ^* orbital is *ungerade* (designated ψ_u). An ungerade orbital changes sign when inverted through its center of symmetry.

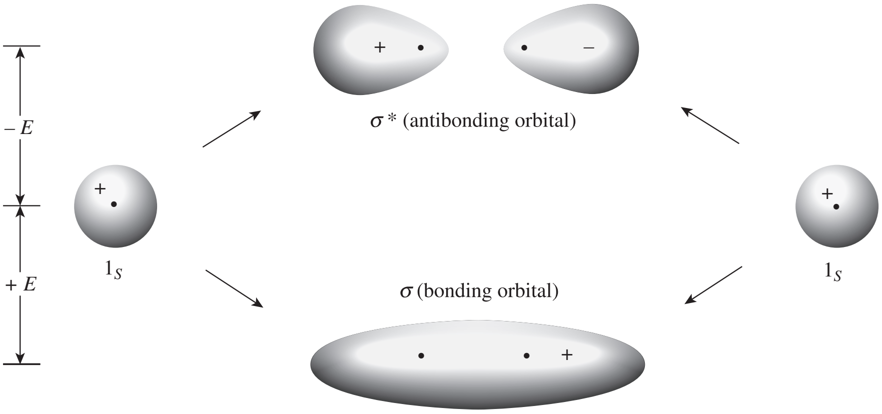


Fig. 1.2. Overlap of two 1*s* orbitals gives rise to a σ and a σ^* orbital.

In molecular-orbital calculations, a wave function is formulated that is a linear combination of the atomic orbitals that have overlapped (this method is often called the *linear combination of atomic orbitals*, or LCAO). Addition of the atomic orbitals gives the bonding molecular orbital:

$$\psi = c_A\psi_A + c_B\psi_B \tag{1-1}$$

The functions ψ_A and ψ_B are the functions for the atomic orbitals of atoms A and B, respectively, and c_A and c_B represent weighting factors. Subtraction is also a linear combination:

$$\psi = c_A\psi_A - c_B\psi_B \tag{1-2}$$

This gives rise to the antibonding molecular orbital.

In the valence-bond method, a wave equation is written for each of various possible electronic structures that a molecule may have (each of these is called a *canonical form*), and the total ψ is obtained by summation of as many of these as seem plausible, each with its weighting factor:

$$\psi = c_1\psi_1 + c_2\psi_2 + \cdots \tag{1-3}$$

This resembles Eq. (1), but here each ψ represents a wave equation for an imaginary canonical form and each c is the amount contributed to the total picture by that form. For example, a wave function can be written for each of the following canonical forms of the hydrogen molecule:[4]

H–H $H:^-$ H^+ ^+H $H:^-$

Values for c in each method are obtained by solving the equation for various values of each c and choosing the solution of lowest energy. In practice, both methods give similar solutions for molecules that contain only localized electrons, and these are in agreement with the Lewis structures long familiar to the organic chemist. Delocalized systems are considered in Chapter 2.

MULTIPLE VALENCE

A univalent atom has only one orbital available for bonding. But atoms with a valence of 2 or more must form bonds by using at least two orbitals. An oxygen atom has two half-filled orbitals, giving it a valence of 2. It forms single bonds by the overlap of these with the orbitals of two other atoms. According to the principle of maximum overlap, the other two nuclei should form an angle of 90° with the oxygen nucleus, since the two available orbitals on oxygen are *p* orbitals, which are perpendicular. Similarly, we should expect that nitrogen, which has three mutually perpendicular *p* orbitals, would have bond angles of 90° when it forms three single bonds. However, these are not the observed bond angles. The bond

[4]In this book, a pair of electrons, whether in a bond or unshared, is represented by a straight line.

angles are,[5] in water, 104°27′, and in ammonia, 106°46′. For alcohols and ethers the angles are even larger (see p. 25). A discussion of this will be deferred to p. 25, but it is important to note that covalent compounds do have definite bond angles. Although the atoms are continuously vibrating, the mean position is the same for each molecule of a given compound.

HYBRIDIZATION

Consider the case of mercury. Its electronic structure is

$$[\mathbf{Xe}\ \text{core}]4f^{14}5d^{10}6s^{2}$$

Although it has no half-filled orbitals, it has a valence of 2 and forms two covalent bonds. We can explain this by imagining that one of the 6*s* electrons is promoted to a vacant 6*p* orbital to give the excited configuration

$$[\mathbf{Xe}\ \text{core}]4f^{14}5d^{10}6s^{1}6p^{1}$$

In this state, the atom has two half-filled orbitals, but they are not equivalent. If bonding were to occur by the overlap of these orbitals with the orbitals of external atoms, the two bonds would not be equivalent. The bond formed from the 6*p* orbital would be more stable than the one formed from the 6*s* orbital, since a larger amount of overlap is possible with the former. A more stable situation is achieved when, in the course of bond formation, the 6*s* and 6*p* orbitals combine to form two new orbitals that *are* equivalent; these are shown in Fig. 1.3.

Since these new orbitals are a mixture of the two original orbitals, they are called *hybrid orbitals*. Each is called an *sp* orbital, since a merger of an *s* and a *p* orbital was required to form it. The *sp* orbitals, each of which consists of a large lobe and a very small one, are atomic orbitals, although they arise only in the bonding process and do not represent a possible structure for the free atom. A mercury atom forms

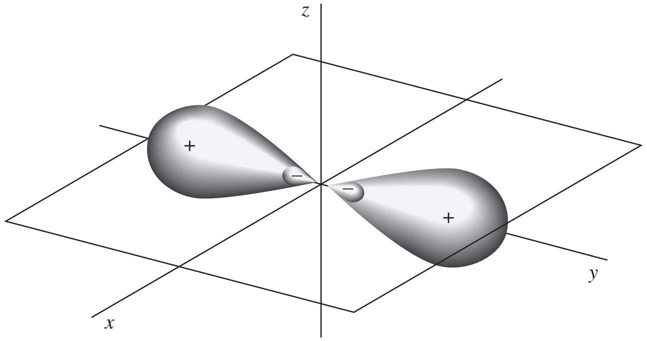


Fig. 1.3. The two *sp* orbitals formed by mercury.

[5]Bent, H.A. *Chem. Rev.* ***1961***, *61*, 275, p. 277.

its two bonds by overlapping each of the large lobes shown in Fig. 1.3 with an orbital from an external atom. This external orbital may be any of the atomic orbitals previously considered (*s, p, d*, or *f*) or it may be another hybrid orbital, although only lobes of the same sign can overlap. In any of these cases, the molecular orbital that arises is called a σ orbital since it fits our previous definition of a σ orbital.

In general, because of mutual repulsion, equivalent orbitals lie as far away from each other as possible, so the two *sp* orbitals form an angle of 180°. This means that $HgCl_2$, for example, should be a linear molecule (in contrast to H_2O), and it is. This kind of hybridization is called *digonal hybridization*. An *sp* hybrid orbital forms a stronger covalent bond than either an *s* or a *p* orbital because it extends out in space in the direction of the other atom's orbital farther than the *s* or the *p* and permits greater overlap. Although it would require energy to promote a 6*s* electron to the 6*p* state, the extra bond energy more than makes up the difference.

Many other kinds of hybridization are possible. Consider boron, which has the electronic configuration

$$1s^2 2s^2 2p^1$$

yet has a valence of 3. Once again we may imagine promotion and hybridization:

$$1s^2 2s^2 2p^1 \xrightarrow{\text{promotion}} 1s^2 2s^1 2p_x^1 2p_y^1 \xrightarrow{\text{hybridization}} 1s^2 (sp^2)^3$$

In this case, there are three equivalent hybrid orbitals, each called sp^2 (*trigonal hybridization)*. This method of designating hybrid orbitals is perhaps unfortunate since nonhybrid orbitals are designated by single letters, but it must be kept in mind that *each* of the three orbitals is called sp^2. These orbitals are shown in Fig. 1.4. The three axes are all in one plane and point to the corners of an equilateral triangle. This accords with the known structure of BF_3, a planar molecule with angles of 120°.

The case of carbon (in forming four single bonds) may be represented as

$$1s^2 2s^2 2p_x^1 2p_y^1 \xrightarrow{\text{promotion}} 1s^2 2s^1 2p_x^1 2p_y^1 2p_z^1 \xrightarrow{\text{hybridization}} 1s^2 (sp^3)^4$$

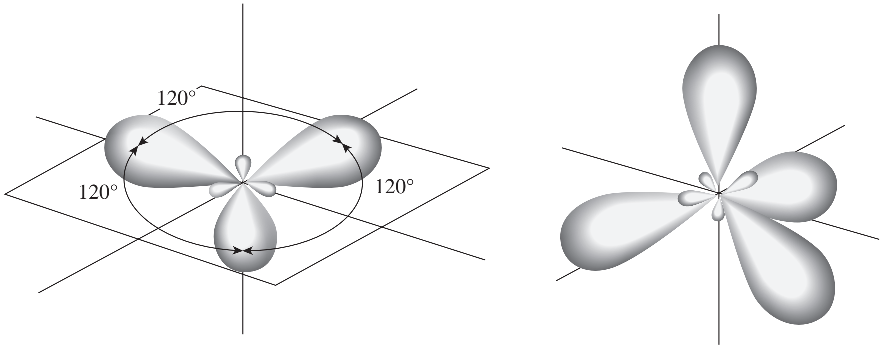


Fig. 1.4. The three sp^2 and the four sp^3 orbitals.

There are four equivalent orbitals, each called sp^3, which point to the corners of a regular tetrahedron (Fig. 1.4). The bond angles of methane would thus be expected to be 109°28′, which is the angle for a regular tetrahedron.

Although the hybrid orbitals discussed in this section satisfactorily account for most of the physical and chemical properties of the molecules involved, it is necessary to point out that the sp^3 orbitals, for example, stem from only one possible approximate solution of the Schrödinger equation. The *s* and the three *p* atomic orbitals can also be combined in many other equally valid ways. As we shall see on p. 13, the four C—H bonds of methane do not always behave as if they are equivalent.

MULTIPLE BONDS

If we consider the ethylene molecule in terms of the molecular-orbital concepts discussed so far, we have each carbon using sp^2 orbitals to form bonds with the three atoms to which it is connected. These sp^2 orbitals arise from hybridization of the $2s^1$, $2p_x^1$, and $2p_y^1$ electrons of the promoted state shown on p. 8. We may consider that any carbon atom that is bonded to only three different atoms uses sp^2 orbitals for this bonding. Each carbon of ethylene is thus bonded by three σ bonds: one to each hydrogen and one to the other carbon. Each carbon therefore has another electron in the $2p_z$ orbital that is perpendicular to the plane of the sp^2 orbitals. The two parallel $2p_z$ orbitals can overlap sideways to generate two new orbitals, a bonding and an antibonding orbital (Fig. 1.5). Of course, in the ground state, both electrons go into the bonding orbital and the antibonding orbital remains vacant. Molecular orbitals formed by the overlap of atomic orbitals whose axes are parallel are called π orbitals if they are bonding and π^* if they are antibonding.

In this picture of ethylene, the two orbitals that make up the double bond are not equivalent.[6] The σ orbital is ellipsoidal and symmetrical about the C—C axis. The π orbital is in the shape of two ellipsoids, one above the plane and one below. The plane itself represents a node for the π orbital. In order for the *p* orbitals to maintain maximum overlap, they must be parallel. This means that free rotation is not possible about the double bond, since the two *p* orbitals would have to reduce their overlap to allow one H—C—H plane to rotate with respect to the other. The six atoms of a double bond are therefore in a plane with angles that should be ~120°. Double bonds are shorter than the corresponding single bonds because maximum stability is obtained when the *p* orbitals overlap as much as possible. Double bonds between carbon and oxygen or nitrogen are similarly represented: they consist of one σ and one π orbital.

In triple-bond compounds, carbon is connected to only two other atoms and hence uses *sp* hybridization, which means that the four atoms are in a straight

[6]The double bond can also be pictured as consisting of two equivalent orbitals, where the centers of electron density point away from the C—C axis. This is the bent-bond or banana-bond picture. Support for this view is found in Pauling. L. *Theoretical Organic Chemistry, The Kekulé Symposium*, Butterworth, London, ***1959***, pp. 2–5; Palke, W.E. *J. Am. Chem. Soc.* ***1986***, *108*, 6543. However, most of the literature of organic chemistry is written in terms of the σ–π picture, and we will use it in this book.

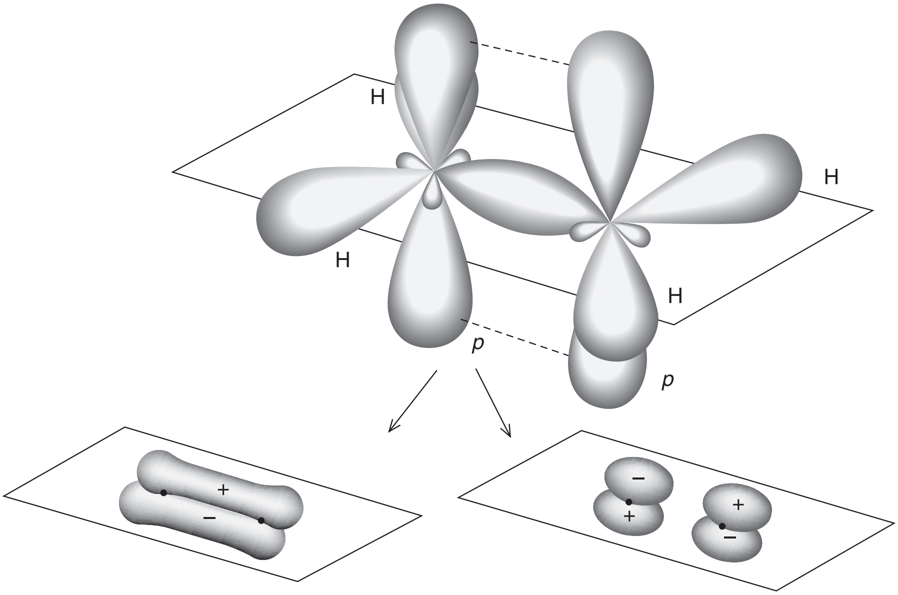


Fig. 1.5. Overlapping *p* orbitals form a π and a π* orbital. The σ orbitals are shown in the upper figure. They are still there in the states represented by the diagrams below, but have been removed from the picture for clarity.

line (Fig. 1.6).[7] Each carbon has two *p* orbitals remaining, with one electron in each. These orbitals are perpendicular to each other and to the C—C axis. They overlap in the manner shown in Fig. 1.7 to form two π orbitals. A triple bond is thus composed of one σ and two π orbitals. Triple bonds between carbon and nitrogen can be represented in a similar manner.

Double and triple bonds are important only for the first-row elements carbon, nitrogen, and oxygen.[8] For second-row elements multiple bonds are rare and

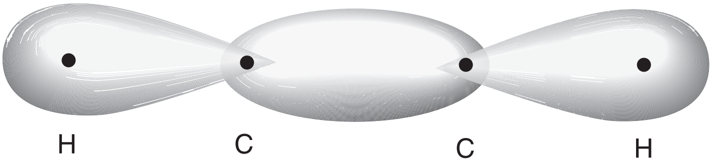


Fig. 1.6. The σ electrons of acetylene.

[7]For reviews of triple bonds, see Simonetta, M.; Gavezzotti, A., in Patai, S. *The Chemistry of the Carbon-Carbon Triple Bond*, Wiley, NY, ***1978***, pp. 1–56; Dale, J., in Viehe, H. G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 3–96.

[8]This statement applies to the representative elements. Multiple bonding is also important for some transition elements. For a review of metal–metal multiple bonds, see Cotton, F.A. *J. Chem. Educ.* ***1983***, *60*, 713.

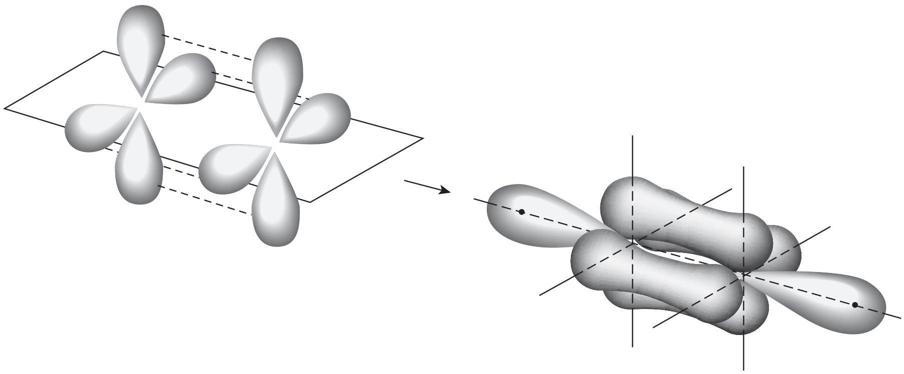


Fig. 1.7. Overlap of *p* orbitals in a triple bond for clarity, the σ orbitals have been removed from the drawing on the left, although they are shown on the right.

compounds containing them are generally less stable[9] because these elements tend to form weaker π bonds than do the first-row elements.[10] The only ones of any importance at all are C=S bonds, and C=S compounds are generally much less stable than the corresponding C=O compounds (however, see *p*π–*d*π bonding, p. $$$). Stable compounds with Si=C and Si=Si bonds are rare, but examples have been reported,[11] including a pair of cis and trans Si=Si isomers.[12]

[9]For a review of double bonds between carbon and elements other than C, N, S, or O, see Jutzi, P. *Angew. Chem. Int. Ed.* ***1975***, *14*, 232. For reviews of multiple bonds involving silicon and germanium, see Barrau, J.; Escudié, J.; Satgé, J. *Chem. Rev.* ***1990***, *90*, 283 (Ge only); Raabe, G.; Michl, J., in Patai, S. and Rappoport, Z. *The Chemistry of Organic Silicon Compounds, part 2*, Wiley: NY, ***1989***, pp. 1015–1142; *Chem. Rev.* ***1985***, *85*, 419 (Si only); Wiberg, N. *J. Organomet. Chem.* ***1984***, *273*, 141 (Si only); Gusel'nikov, L.E.; Nametkin, N.S. *Chem. Rev.* ***1979***, *79*, 529 (Si only). For reviews of C=P and C+P bonds, see Regitz, M. *Chem. Rev.* ***1990***, *90*, 191; Appel, R.; Knoll, F. *Adv. Inorg. Chem.* ***1989***, *33*, 259; Markovski, L.N.; Romanenko, V.D. *Tetrahedron* ***1989***, *45*, 6019. For reviews of other second-row double bonds, see West, R. *Angew. Chem. Int. Ed.* ***1987***, *26*, 1201 (Si=Si bonds); Brook, A.G.; Baines, K.M. *Adv. Organometal. Chem.* ***1986***, *25*, 1 (Si=C bonds); Kutney, G.W.; Turnbull, K. *Chem. Rev.* ***1982***, *82*, 333 (S=S bonds). For reviews of multiple bonds between heavier elements, see Cowley, A.H.; Norman, N.C. *Prog. Inorg. Chem.* ***1986***, *34*, 1; Cowley, A.H. *Polyhedron* ***1984***, *3*, 389; *Acc. Chem. Res.* ***1984***, *17*, 386. For a theoretical study of multiple bonds to silicon, see Gordon, M.S. *Mol. Struct. Energ.* ***1986***, *1*, 101.

[10]For discussions, see Schmidt, M.W.; Truong, P.N.; Gordon, M.S. *J. Am. Chem. Soc.* ***1987***, *109*, 5217; Schleyer, P. von R.; Kost, D. *J. Am. Chem. Soc.* ***1988***, *110*, 2105.

[11]For Si=C bonds, see Brook, A.G.; Nyburg, S.C.; Abdesaken, F.; Gutekunst, B.; Gutekunst, G.; Kallury, R.K.M.R.; Poon, Y.C.; Chang, Y.; Wong-Ng, W. *J. Am. Chem. Soc.* ***1982***, *104*, 5667; Schaefer III, H.F. *Acc. Chem. Res.* ***1982***, *15*, 283; Wiberg, N.; Wagner, G.; Riede, J.; Müller, G. *Organometallics* ***1987***, *6*, 32. For Si=Si bonds, see West, R.; Fink, M.J.; Michl, J. *Science* ***1981***, *214*, 1343; Boudjouk, P.; Han, B.; Anderson, K.R. *J. Am. Chem. Soc.* ***1982***, *104*, 4992; Fink, M.J.; DeYoung, D.J.; West, R.; Michl, J. *J. Am. Chem. Soc.* ***1983***, *105*, 1070; Fink, M.J.; Michalczyk, M.J.; Haller, K.J.; West, R.; Michl, J. *Organometallics* ***1984***, *3*, 793; West, R. *Pure Appl. Chem.* ***1984***, *56*, 163; Masamune, S.; Eriyama, Y.; Kawase, T. *Angew. Chem. Int. Ed.* ***1987***, *26*, 584; Shepherd, B.D.; Campana, C.F.; West, R. *Heteroat. Chem.* ***1990***, *1*, 1. For an Si=N bond, see Wiberg, N.; Schurz, K.; Reber, G.; Müller, G. *J. Chem. Soc. Chem. Commun.* ***1986***, 591.

[12]Michalczyk, M.J.; West, R.; Michl, J. *J. Am. Chem. Soc.* ***1984***, *106*, 821, *Organometallics* ***1985***, *4*, 826.

PHOTOELECTRON SPECTROSCOPY

Although the four bonds of methane are equivalent according to most physical and chemical methods of detection (e.g., neither the nuclear magnetic resonances (NMR) nor the infrared (IR) spectrum of methane contains peaks that can be attributed to different kinds of C—H bonds), there is one physical technique that shows that the eight valence electrons of methane can be differentiated. In this technique, called *photoelectron spectroscopy*,[13] a molecule or free atom is bombarded with vacuum ultraviolet (UV) radiation, causing an electron to be ejected. The energy of the ejected electron can be measured, and the difference between the energy of the radiation used and that of the ejected electron is the *ionization potential* of that electron. A molecule that contains several electrons of differing energies can lose any one of them as long as its ionization potential is less than the energy of the radiation used (a single molecule loses only one electron; the loss of two electrons by any individual molecule almost never occurs). A photoelectron spectrum therefore consists of a series of bands, each corresponding to an orbital of a different energy. The spectrum gives a direct experimental picture of all the orbitals present, in order of their energies, provided that radiation of sufficiently high energy is used.[14] Broad

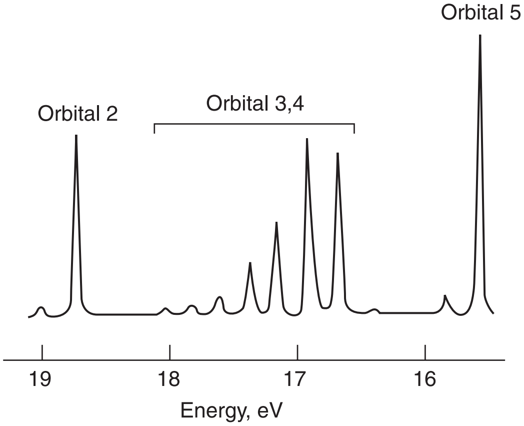


Fig. 1.8. Photoelectron spectrum of N_2.[15]

[13]Only the briefest description of this subject is given here. For monographs, see Ballard, R.E. *Photoelectron Spectroscopy and Molecular Orbital Theory*, Wiley, NY, ***1978***; Rabalais, J.W., *Principles of Ultraviolet Photoelectron Spectroscopy*, Wiley, NY, ***1977***; Baker, A.D.; Betteridge, D. *Photoelectron Spectroscopy*, Pergamon, Elmsford, NY, ***1972***; Turner, D.W.; Baker, A.D..; Baker, C.; Brundle, C.R. *High Resolution Molecular Photoelectron Spectroscopy*, Wiley, NY, ***1970***. For reviews, see Westwood, N.P.C. *Chem. Soc. Rev.* ***1989***, *18*, 317; Carlson, T.A. *Annu. Rev. Phys. Chem.* ***1975***, *26*, 211; Baker, C.; Brundle, C.R.; Thompson, M. *Chem. Soc. Rev.* ***1972***, *1*, 355; Bock, H.; Mollère, P.D. *J. Chem. Educ.* ***1974***, *51*, 506; Bock, H.; Ramsey, B.G. *Angew. Chem. Int. Ed.* ***1973***, *12*, 734; Turner, D.W. *Adv. Phys. Org. Chem.* ***1966***, *4*, 31. For the IUPAC descriptive classification of the electron spectroscopies, see Porter, H.Q.; Turner, D.W. *Pure Appl. Chem.* ***1987***, *59*, 1343.
[14]The correlation is not perfect, but the limitations do not seriously detract from the usefulness of the method. The technique is not limited to vacuum UV radiation. Higher energy radiation can also be used.

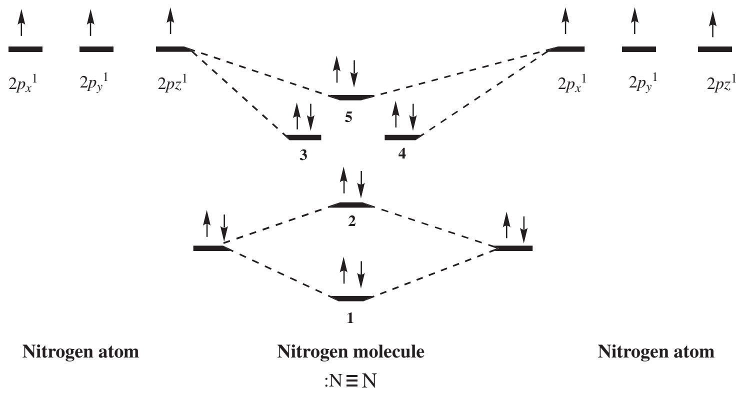


Fig. 1.9. Electronic structure of N_2 (inner-shell electrons omitted).

bands usually correspond to strongly bonding electrons and narrow bands to weakly bonding or nonbonding electrons. A typical spectrum is that of N_2, shown in Fig. 1.8.[15] The N_2 molecule has the electronic structure shown in Fig. 1.9. The two 2*s* orbitals of the nitrogen atoms combine to give the two orbitals marked 1 (bonding) and 2 (antibonding), while the six 2*p* orbitals combine to give six orbitals, three of which (marked 3, 4, and 5) are bonding. The three antibonding orbitals (not indicated in Fig. 1.9) are unoccupied. Electrons ejected from orbital 1 are not found in Fig. 1.8 because the ionization potential of these electrons is greater than the energy of the light used (they can be seen when higher energy light is used). The broad band in Fig. 1.8 (the individual peaks within this band are caused by different vibrational levels; see Chapter 7) corresponds to the four electrons in the degenerate orbitals 3 and 4. The triple bond of N_2 is therefore composed of these two orbitals and orbital 1. The bands corresponding to orbitals 2 and 5 are narrow; hence these orbitals contribute little to the bonding and may be regarded as the two unshared pairs of N̈≡N̈. Note that this result is contrary to that expected from a naive consideration of orbital roverlaps, where it would be expected that the two unshared pairs would be those of orbitals 1 and 2, resulting from the overlap of the filled 2*s* orbitals, and that the triple bond would be composed of orbitals 3, 4, and 5, resulting from overlap of the *p* orbitals. This example is one illustration of the value of photoelectron spectroscopy.

The photoelectron spectrum of methane[16] shows two bands,[17] at ~23 and 14 eV, and not the single band we would expect from the equivalency of the four C—H

[15]From Brundle, C.R.; Robin, M.B., in Nachod, F.C.; Zuckerman, J.J. *Determination of Organic Structures by Physical Methods, Vol. 3*, Academic Press, NY, ***1971***, p. 18.

[16]Brundle, C.R.; Robin, M.B.; Basch, H. *J. Chem. Phys.* ***1970***, *53*, 2196; Baker, A.D.; Betteridge, D.; Kemp, N.R.; Kirby, R.E. *J. Mol. Struct.* ***1971***, *8*, 75; Potts, A.W.; Price, W.C. *Proc. R. Soc. London, Ser A* ***1972***, *326*, 165.

[17]A third band, at 290 eV, caused by the 1*s* electrons of carbon, can also found if radiation of sufficiently high energy is used.

bonds. The reason is that ordinary sp^3 hybridization is not adequate to explain phenomena involving ionized molecules (e.g., the CH_4^+ radical ion, which is left behind when an electron is ejected from methane). For these phenomena it is necessary to use other combinations of atomic orbitals (see p. 9). The band at 23 eV comes from two electrons in a low-energy level (called the a_1 level), which can be regarded as arising from a combination of the 2*s* orbital of carbon with an appropriate combination of hydrogen 1*s* orbitals. The band at 14 eV comes from six electrons in a triply degenerate level (the t_2 level), arising from a combination of the three 2*p* orbitals of carbon with other combinations of 1*s* hydrogen orbitals. As was mentioned above, most physical and chemical processes cannot distinguish these levels, but photoelectron spectroscopy can. The photoelectron spectra of many other organic molecules are known as well,[18] including monocyclic alkenes, in which bands <10 eV are due to π-orbital ionization and those >10 eV originate from ionization of s-orbitals only.[19]

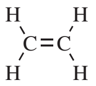
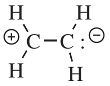
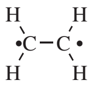
ELECTRONIC STRUCTURES OF MOLECULES

For each molecule, ion, or free radical that has only localized electrons, it is possible to draw an electronic formula, called a *Lewis structure*, that shows the location of these electrons. Only the valence electrons are shown. Valence electrons may be found in covalent bonds connecting two atoms or they may be unshared.[20] The student must be able to draw these structures correctly, since the position of electrons changes in the course of a reaction, and it is necessary to know where the electrons are initially before one can follow where they are going. To this end, the following rules operate:

1. The total number of valence electrons in the molecule (or ion or free radical) must be the sum of all outer-shell electrons "contributed" to the molecule by each atom plus the negative charge or minus the positive charge, for the case of ions. Thus, for H_2SO_4, there are 2 (one for each hydrogen) + 6 (for the sulfur) + 24 (6 for each oxygen) = 32; while for SO_4^{2-}, the number is also 32, since each atom "contributes" 6 plus 2 for the negative charge.
2. Once the number of valence electrons has been ascertained, it is necessary to determine which of them are found in covalent bonds and which are unshared. Unshared electrons (either a single electron or a pair) form part of the outer shell of just one atom, but electrons in a covalent bond are part of the outer shell of both atoms of the bond. *First-row atoms* (B, C, N, O, F) *can have a maximum of eight valence electrons*, and usually have this number, although some cases are known where a first-row atom has only six or seven.

[18]See Robinson, J.W., *Practical Handbook of Spectroscopy*, CRC Press, Boca Raton, FL, ***1991***, p. 178.
[19]Novak, I.; Potts, A.W. *Tetrahedron* ***1997***, *53*, 14713.
[20]It has been argued that although the Lewis picture of two electrons making up a covalent bond may work well for organic compounds, it cannot be successfully applied to the majority of inorganic compounds: Jørgensen, C.K. *Top. Curr. Chem.* ***1984***, *124*, 1.

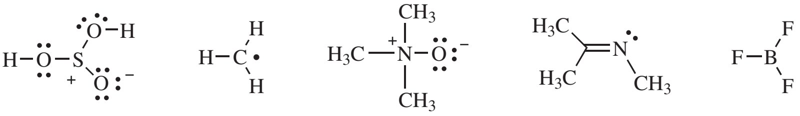
Where there is a choice between a structure that has six or seven electrons around a first-row atom and one in which all such atoms have an octet, it is the latter that generally has the lower energy and that consequently exists. For example, ethylene is

 and not  or 

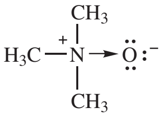
There are a few exceptions. In the case of the molecule O_2, the structure :Ȯ–Ȯ: has a lower energy than :Ö=Ö:. Although first-row atoms are limited to 8 valence electrons, this is not so for second-row atoms, which can accommodate 10 or even 12 because they can use their empty *d* orbitals for this purpose.[21] For example, PCl_5 and SF_6 are stable compounds. In SF_6, one *s* and one *p* electron from the ground state $3s^23p^4$ of the sulfur are promoted to empty *d* orbitals, and the six orbitals hybridize to give six sp^3d^2 orbitals, which point to the corners of a regular octahedron.

3. It is customary to show the formal charge on each atom. For this purpose, an atom is considered to "own" all unshared electrons, but only *one-half of the electrons in covalent bonds*. The sum of electrons that thus "belong" to an atom is compared with the number "contributed" by the atom. An excess belonging to the atom results in a negative charge, and a deficiency results in a positive charge. The total of the formal charges on all atoms equals the charge on the whole molecule or ion. Note that the counting procedure is not the same for determining formal charge as for determining the number of valence electrons. For both purposes, an atom "owns" all unshared electrons, but for outer-shell purposes it "owns" both the electrons of the covalent bond, while for formal-charge purposes it "owns" only one-half of these electrons.

Examples of electronic structures are (as mentioned in Ref. 4, an electron pair, whether unshared or in a bond, is represented by a straight line):



A coordinate-covalent bond, represented by an arrow, is one in which both electrons come from the same atom; that is, the bond can be regarded as being formed by the overlap of an orbital containing two electrons with an empty one. Thus trimethylamine oxide would be represented



[21]For a review concerning sulfur compounds with a valence shell larger than eight, see Salmond, W.G. *Q. Rev. Chem. Soc.* ***1968***, *22*, 235.

For a coordinate-covalent bond the rule concerning formal charge is amended, so that both electrons count for the donor and neither for the recipient. Thus the nitrogen and oxygen atoms of trimethylamine oxide bear no formal charges. However, it is apparent that the electronic picture is exactly the same as the picture of trimethylamine oxide given just above, and we have our choice of drawing an arrowhead or a charge separation. Some compounds, for example, amine oxides, must be drawn one way or the other. It seems simpler to use charge separation, since this spares us from having to consider as a "different" method of bonding a way that is really the same as ordinary covalent bonding once the bond has formed.

ELECTRONEGATIVITY

The electron cloud that bonds two atoms is not symmetrical (with respect to the plane that is the perpendicular bisector of the bond) except when the two atoms are the same and have the same substituents. The cloud is necessarily distorted toward one side of the bond or the other, depending on which atom (nucleus plus electrons) maintains the greater attraction for the cloud. This attraction is called *electronegativity*;[22] and it is greatest for atoms in the upper-right corner of the periodic table and lowest for atoms in the lower-left corner. Thus a bond between fluorine and chlorine is distorted so that there is a higher probability of finding the electrons near the fluorine than near the chlorine. This gives the fluorine a partial negative charge and the chlorine a partial positive charge.

A number of attempts have been made to set up quantitative tables of electronegativity that indicate the direction and extent of electron-cloud distortion for a bond between any pair of atoms. The most popular of these scales, devised by Pauling, is based on bond energies (see p. 27) of diatomic molecules. It is rationalized that if the electron distribution were symmetrical in a molecule A—B, the bond energy would be the mean of the energies of A—A and B—B, since in these cases the cloud must be undistorted. If the actual bond energy of A—B is higher than this (and it usually is), it is the result of the partial charges, since the charges attract each other and make a stronger bond, which requires more energy to break. It is necessary to assign a value to one element arbitrarily (F = 4.0). Then the electronegativity of another is obtained from the difference between the actual energy of A—B and the mean of A—A and B—B (this difference is called Δ) by the formula

$$x_A - x_B = \sqrt{\frac{\Delta}{23.06}}$$

where x_A and x_B are the electronegativities of the known and unknown atoms and 23.06 is an arbitrary constant. Part of the scale derived from this treatment is shown in Table 1.1.

[22]For a collection of articles on this topic, see Sen, K.D.; Jørgensen, C.K. *Electronegativity* (Vol. 6 of *Structure and Bonding*); Springer: NY, ***1987***. For a review, see Batsanov, S.S. *Russ. Chem. Rev.* ***1968***, *37*, 332.

TABLE 1.1. Electronegativities of Some Atoms on the Pauling[23] and Sanderson[24] Scales

Element	Pauling	Sanderson	Element	Pauling	Sanderson
F	4.0	4.000	H	2.1	2.592
O	3.5	3.654	P	2.1	2.515
Cl	3.0	3.475	B	2.0	2.275
N	3.0	3.194	Si	1.8	2.138
Br	2.8	3.219	Mg	1.2	1.318
S	2.5	2.957	Na	0.9	0.835
I	2.5	2.778	Cs	0.7	0.220
C	2.5	2.746			

Other treatments[25] have led to scales that are based on different principles, for example, the average of the ionization potential and the electron affinity,[26] the average one-electron energy of valence-shell electrons in ground-state free atoms,[27] or the "compactness" of an atom's electron cloud.[24] In some of these treatments electronegativities can be calculated for different valence states, for different hybridizations (e.g., *sp* carbon atoms are more electronegative than sp^2, which are still more electronegative than sp^3),[28] and even differently for primary, secondary, and tertiary carbon atoms. Also, electronegativities can be calculated for groups rather than atoms (Table 1.2).[29]

Electronegativity information can be obtained from NMR spectra. In the absence of a magnetically anisotropic group[30] the chemical shift of a ^{1}H or a ^{13}C nucleus is approximately proportional to the electron density around it and hence to the electronegativity of the atom or group to which it is attached. The greater the electronegativity of the atom or group, the lower the electron density around the proton, and the further downfield the chemical shift. An example of the use of this correlation is found in the variation of chemical shift of the *ring* protons in the series

[23]Taken from Pauling, L. *The Nature of the Chemical Bond*, 3rd ed.; Cornell University Press: Ithaca, NY, p. 93, except for the value for Na, which is from Sanderson, R.T. *J. Am. Chem. Soc.* ***1983***, *105*, 2259; *J. Chem. Educ.* ***1988***, *65*, 112, 223.

[24]See Sanderson, R.T. *J. Am. Chem. Soc.* ***1983***, *105*, 2259; *J. Chem. Educ.* ***1988***, *65*, 112, 223.

[25]For several sets of electronegativity values, see Huheey, J.E. *Inorganic Chemistry*, 3rd ed., Harper and Row: NY, ***1983***, pp. 146–148; Mullay, J., in Sen, K.D.; Jørgensen, C.K. *Electronegativity* (Vol. 6 of *Structure and Bonding*), Springer, NY, ***1987***, p. 9.

[26]Mulliken, R.S. *J. Chem. Phys.* ***1934***, *2*, 782; Iczkowski, R.P.; Margrave, J.L. *J. Am. Chem. Soc.* ***1961***, *83*, 3547; Hinze, J.; Jaffé, H.H. *J. Am. Chem. Soc.* ***1962***, *84*, 540; Rienstra-Kiracofe, J.C.; Tschumper, G.S.; Schaefer III, H.F.; Nandi, S.; Ellison, G.B. *Chem. Rev.* ***2002***, *102*, 231.

[27]Allen, L.C. *J. Am. Chem. Soc.* ***1989***, *111*, 9003.

[28]Walsh, A.D. *Discuss. Faraday Soc.* ***1947***, *2*, 18; Bergmann, D.; Hinze, J., in Sen, K.D.; Jørgensen, C.K. *Electronegativity* (Vol. 6 of *Structure and Bonding*), Springer, NY, ***1987***, pp. 146–190.

[29]Inamoto, N.; Masuda, S. *Chem. Lett.* ***1982***, 1003. For a review of group electronegativities, see Wells, P.R. *Prog. Phys. Org. Chem.* ***1968***, *6*, 111. See also Bratsch, S.G. *J. Chem. Educ.*, ***1988***, *65*, 223; Mullay, J. *J. Am. Chem. Soc.* ***1985***, *107*, 7271; Zefirov, N.S.; Kirpichenok, M.A.; Izmailov, F.F.; Trofimov, M.I. *Dokl. Chem.* ***1987***, *296*, 440; Boyd, R.J.; Edgecombe, K.E. *J. Am. Chem. Soc.* ***1988***, *110*, 4182.

[30]A magnetically anisotropic group is one that is not equally magnetized along all three axes. The most common such groups are benzene rings (see p. 55) and triple bonds.

TABLE 1.2. Some Group Electronegativites Relative to H = 2.176.[29]

CH_3	2.472	CCl_3	2.666
CH_3CH_2	2.482	C_6H_5	2.717
CH_2Cl	2.538	CF_3	2.985
CBr_3	2.561	C≡N	3.208
$CHCl_2$	2.602	NO_2	3.421

toluene, ethylbenzene, isopropylbenzene, *tert*-butylbenzene (there is a magnetically anisotropic group here, but its effect should be constant throughout the series). It is found that the electron density surrounding the ring protons decreases[31] in the order given.[32] However, this type of correlation is by no means perfect, since all the measurements are being made in a powerful field, which itself may affect the electron density distribution. Coupling constants between the two protons of a system $-\underset{|}{C}H\underset{|}{C}H-X$ have also been found to depend on the electronegativity of X.[33]

When the difference in electronegativities is great, the orbital may be so far over to one side that it barely covers the other nucleus. This is an *ionic bond*, which is seen to arise naturally out of the previous discussion, leaving us with basically only one type of bond in organic molecules. Most bonds can be considered intermediate between ionic and covalent. We speak of percent ionic character of a bond, which indicates the extent of electron-cloud distortion. There is a continuous gradation from ionic to covalent bonds.

DIPOLE MOMENT

The *dipole moment* is a property of the molecule that results from charge separations like those discussed above. However, it is not possible to measure the dipole moment of an individual bond within a molecule; we can measure only the total moment of the molecule, which is the vectorial sum of the individual bond moments.[34] These individual moments are roughly the same from molecule to molecule,[35] but this constancy is by no means universal. Thus, from the dipole moments of toluene and nitrobenzene (Fig. 1.10)[36] we should expect the moment of *p*-nitrotoluene to be ~4.36 D.

[31]This order is opposite to that expected from the field effect (p. 19). It is an example of the Baker–Nathan order (p. 96).

[32]Moodie, R.B.; Connor, T.M.; Stewart, R. *Can. J. Chem.* ***1960***, *38*, 626.

[33]Williamson, K.L. *J. Am. Chem. Soc.* ***1963***, *85*, 516; Laszlo, P.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1963***, *85*, 2709; Niwa, J. *Bull. Chem. Soc. Jpn.* ***1967***, *40*, 2192.

[34]For methods of determining dipole moments and discussions of their applications, see Exner, O. *Dipole Moments in Organic Chemistry*; Georg Thieme Publishers: Stuttgart, ***1975***. For tables of dipole moments, see McClellan, A.L. *Tables of Experimental Dipole Moments*, Vol. 1; W.H. Freeman: San Francisco, ***1963***; Vol. 2, Rahara Enterprises: El Cerrito, CA, ***1974***.

[35]For example, see Koudelka, J.; Exner, O. *Collect. Czech. Chem. Commun.* ***1985***, *50*, 188, 200.

[36]The values for toluene, nitrobenzene, and *p*-nitrotoluene are from MacClellan, A.L., *Tables of Experimental Dipole Moments*, Vol. 1, W.H. Freeman, San Francisco, ***1963***; Vol. 2, Rahara Enterprises, El Cerrito, CA, ***1974***. The values for phenol and *p*-cresol were determined by Goode, E.V.; Ibbitson, D.A. *J. Chem. Soc.* ***1960***, 4265.

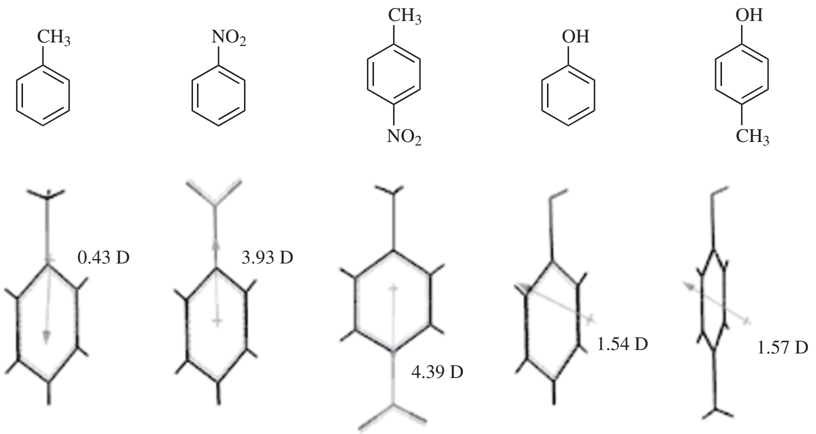


Fig. 1.10. Some dipole moments, in debye units, measured in benzene. In the 3D model, the arrow indicates the direction of the dipole moment for the molecule, pointing to the negative part of the molecule.[36]

The actual value 4.39 D is reasonable. However, the moment of *p*-cresol (1.57 D) is quite far from the predicted value of 1.11 D. In some cases, molecules may have substantial individual bond moments but no total moments at all because the individual moments are canceled out by the overall symmetry of the molecule. Some examples are CCl_4, *trans*-1,2-dibromoethene, and *p*-dinitrobenzene.

Because of the small difference between the electronegativities of carbon and hydrogen, alkanes have very small dipole moments, so small that they are difficult to measure. For example, the dipole moment of isobutane is 0.132 D[37] and that of propane is 0.085 D.[38] Of course, methane and ethane, because of their symmetry, have no dipole moments.[39] Few organic molecules have dipole moments >7 D.

INDUCTIVE AND FIELD EFFECTS

The C—C bond in ethane has no polarity because it connects two equivalent atoms. However, the C—C bond in chloroethane is polarized by the presence of the electronegative chlorine atom. This polarization is actually the sum of two effects. In the first of these, the C-1 atom, having been deprived of some of its electron density by the

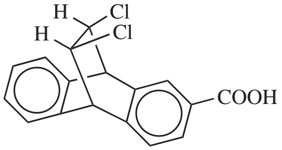
$$\overset{\delta+}{{}^{1}CH_3} \longrightarrow \overset{\delta+}{{}^{2}CH_2} \longrightarrow\!\!\!\!\rightarrow \overset{\delta-}{Cl}$$

[37]Maryott, A.A.; Birnbaum, G. *J. Chem. Phys.* **1956**, *24*, 1022; Lide Jr., D.R.; Mann, D.E. *J. Chem. Phys.* ***1958***, *29*, 914.

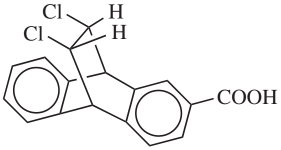
[38]Muenter, J.S.; Laurie, V.W. *J. Chem. Phys.* ***1966***, *45*, 855.

[39]Actually, symmetrical tetrahedral molecules like methane do have extremely small dipole moments, caused by centrifugal distortion effects; these moments are so small that they can be ignored for all practical purposes. For CH_4 μ is $\sim 5.4 \times 10^{-6}$ *D*: Ozier, I. *Phys. Rev. Lett.* ***1971***, *27*, 1329; Rosenberg, A.; Ozier, I.; Kudian, A.K. *J. Chem. Phys.* ***1972***, *57*, 568.

greater electronegativity of Cl, is partially compensated by drawing the C—C electrons closer to itself, resulting in a polarization of this bond and a slightly positive charge on the C-2 atom. This polarization of one bond caused by the polarization of an adjacent bond is called the *inductive effect*. The effect is greatest for adjacent bonds but may also be felt farther away; thus the polarization of the C—C bond causes a (slight) polarization of the three methyl C—H bonds. The other effect operates not through bonds, but directly through space or solvent molecules, and is called the *field effect*.[40] It is often very difficult to separate the two kinds of effect, but it has been done in a number of cases, generally by taking advantage of the fact that the field effect depends on the geometry of the molecule but the inductive effect depends only on the nature of the bonds. For example, in isomers **1** and **2**[41] the inductive effect of the chlorine atoms on the position of the electrons in the COOH group (and hence on the



1
pK_a = 6.07



2
pK_a = 5.67

acidity, see Chapter 8) should be the same since the same bonds intervene; but the field effect is different because the chlorines are closer in space to the COOH in **1** than they are in **2**. Thus a comparison of the acidity of **1** and **2** should reveal whether a field effect is truly operating. The evidence obtained from such experiments is overwhelming that field effects are much more important than inductive effects.[42] In most cases, the two types of effect are considered together; in this book, we will not attempt to separate them, but will use the name *field effect* to refer to their combined action.[43]

Functional groups can be classified as electron-withdrawing ($-I$) or electron-donating ($+I$) groups relative to hydrogen. This means, for example, that NO_2, a $-I$ group, will draw electrons to itself more than a hydrogen atom would if it

[40]Roberts, J.D.; Moreland, Jr., W.T. *J. Am. Chem. Soc.* ***1953***, *75*, 2167.

[41]This example is from Grubbs, E.J.; Fitzgerald, R.; Phillips, R.E.; Petty, R. *Tetrahedron* ***1971***, *27*, 935.

[42]For example, see Dewar, M.J.S.; Grisdale, P.J. *J. Am. Chem. Soc.* ***1962***, *84*, 3548; Stock, L.M. *J. Chem. Educ.*, ***1972***, *49*, 400; Golden, R.; Stock, L.M. *J. Am. Chem. Soc.* ***1972***, *94*, 3080; Liotta, C.; Fisher, W.F.; Greene Jr., G.H.; Joyner, B.L. *J. Am. Chem. Soc.* ***1972***, *94*, 4891; Wilcox, C.F.; Leung, C. *J. Am. Chem. Soc.* ***1968***, *90*, 336; Butler, A.R. *J. Chem. Soc. B* ***1970***, 867; Rees, J.H.; Ridd, J.H.; Ricci, A. *J. Chem. Soc. Perkin Trans. 2* ***1976***, 294; Topsom, R.D. *J. Am. Chem. Soc.* ***1981***, *103*, 39; Grob, C.A.; Kaiser, A.; Schweizer, T. *Helv. Chim. Acta* ***1977***, *60*, 391; Reynolds, W.F. *J. Chem. Soc. Perkin Trans. 2* ***1980*****,** 985, *Prog. Phys. Org. Chem.* ***1983***, *14*, 165-203; Adcock, W.; Butt, G.; Kok, G.B.; Marriott, S.; Topsom, R.D. *J. Org. Chem.* ***1985***, *50*, 2551; Schneider, H.; Becker, N. *J. Phys. Org. Chem.* ***1989***, *2*, 214; Bowden, K.; Ghadir, K.D.F. *J. Chem. Soc. Perkin Trans. 2* ***1990***, 1333. Inductive effects may be important in certain systems. See, for example, Exner, O.; Fiedler, P. *Collect. Czech. Chem. Commun.* ***1980***, *45*, 1251; Li, Y.; Schuster, G.B. *J. Org. Chem.* ***1987***, *52*, 3975.

[43]There has been some question as to whether it is even meaningful to maintain the distinction between the two types of effect: see Grob, C.A. *Helv. Chim. Acta* ***1985***, *68*, 882; Lenoir, D.; Frank, R.M. *Chem. Ber.* ***1985***, *118*, 753; Sacher, E. *Tetrahedron Lett.* ***1986***, *27*, 4683.

TABLE 1.3. Field Effects of Various Groups Relative to Hydrogen[a]

+I		*−I*	
O^-	NR_3^+	COOH	OR
COO^-	SR_2^+	F	COR
CR_3	NH_3^+	Cl	SH
CHR_2	NO_2	Br	SR
CH_2R	SO_2R	I	OH
CH_3	CN	OAr	C≡CR
D	SO_2Ar	COOR	Ar
			$C{\equiv}CR_2$

[a]The groups are listed approximately in order of decreasing strength for both *−I* and *+I* groups.

occupied the same position in the molecule.

$$O_2N \twoheadleftarrow\!\!-\!\!-\, CH_2 \leftarrow\!\!-\!\!-\, Ph$$
$$H \text{———} CH_2 \text{———} Ph$$

Thus, in α-nitrotoluene, the electrons in the N—C bond are farther away from the carbon atom than the electrons in the H—C bond of toluene. Similarly, the electrons of the C—Ph bond are farther away from the ring in α-nitrotoluene than they are in toluene. Field effects are always comparison effects. We compare the *−I* or +I effect of one group with another (usually hydrogen). It is commonly said that, compared with hydrogen, the NO_2 group is electron-withdrawing and the O^- group electron-donating or electron releasing. However, there is no actual donation or withdrawal of electrons, though these terms are convenient to use; there is merely a difference in the position of electrons due to the difference in electronegativity between H and NO_2 or between H and O^-.

Table 1.3 lists a number of the most common *−I* and *+I* groups.[44] It can be seen that compared with hydrogen, most groups are electron withdrawing. The only electrondonating groups are groups with a formal negative charge (but not even all these), atoms of low electronegativity (Si,[45] Mg, etc., and perhaps alkyl groups). Alkyl groups[46] were formerly regarded as electron donating, but many examples of behavior have been found that can be interpreted only by the conclusion that alkyl groups are electron withdrawing compared with hydrogen.[47] In accord with this is the value of 2.472 for the group electronegativity of CH_3 (Table 1.2) compared with 2.176 for H. We will see that when an alkyl group is attached to an unsaturated or trivalent carbon (or other atom), its behavior is best explained by assuming it is *+I* (see, e.g., pp. 239, 251, 388, 669), but when it is connected to a saturated atom, the results are not as clear,

[44]See also Ceppi, E.; Eckhardt, W.; Grob, C.A. *Tetrahedron Lett.* ***1973***, 3627.

[45]For a review of field and other effects of silicon-containing groups, see Bassindale, A.R.; Taylor. P.G., in Patai, S.; Rappoport, Z. *The Chemistry of Organic Silicon Compounds*, pt. 2, Wiley, NY, ***1989***, pp. 893–963.

[46]For a review of the field effects of alkyl groups, see Levitt, L.S.; Widing, H.F. *Prog. Phys. Org. Chem.* ***1976***, *12*, 119.

[47]See Sebastian, J.F. *J. Chem. Educ.* ***1971***, *48*, 97.

and alkyl groups seem to be $+I$ in some cases and $-I$ in others[48] (see also p. 391). Similarly, it is clear that the field-effect order of alkyl groups attached to unsaturated systems is tertiary > secondary > primary > CH_3, but this order is not always maintained when the groups are attached to saturated systems. Deuterium is electron-donating with respect to hydrogen.[49] Other things being equal, atoms with *sp* bonding generally have a greater electron-withdrawing power than those with sp^2 bonding, which in turn have more electron-withdrawing power than those with sp^3 bonding.[50] This accounts for the fact that aryl, vinylic, and alkynyl groups are $-I$. Field effects always decrease with increasing distance, and in most cases (except when a very powerful $+I$ or $-I$ group is involved), cause very little difference in a bond four bonds away or more. There is evidence that field effects can be affected by the solvent.[51]

For discussions of field effects on acid and base strength and on reactivity, see Chapters 8 and 9, respectively.

BOND DISTANCES[52]

The distances between atoms in a molecule are characteristic properties of the molecule and can give us information if we compare the same bond in different molecules. The chief methods of determining bond distances and angles are X-ray diffraction (only for solids), electron diffraction (only for gases), and spectroscopic methods, especially microwave spectroscopy. The distance between the atoms of a bond is not constant, since the molecule is always vibrating; the measurements obtained are therefore average values, so that different methods give different results.[53] However, this must be taken into account only when fine distinctions are made.

Measurements vary in accuracy, but indications are that similar bonds have fairly constant lengths from one molecule to the next, though exceptions are known.[54] The variation is generally less than 1%. Table 1.4 shows

[48]See, for example, Schleyer, P. von.R.; Woodworth, C.W. *J. Am. Chem. Soc.* ***1968***, *90*, 6528; Wahl Jr., G.H.; Peterson Jr., M.R. *J. Am. Chem. Soc.* ***1970***, *92*, 7238. The situation may be even more complicated. See, for example, Minot, C.; Eisenstein, O.; Hiberty, P.C.; Anh, N.T. *Bull. Soc. Chim. Fr.* ***1980***, II-119.

[49]Streitwieser Jr., A.; Klein, H.S. *J. Am. Chem. Soc.* ***1963***, *85*, 2759.

[50]Bent, H.A. *Chem. Rev.* ***1961***, *61*, 275, p. 281.

[51]See Laurence, C.; Berthelot, M.; Lucon, M.; Helbert, M.; Morris, D.G.; Gal, J. *J. Chem. Soc. Perkin Trans. 2* ***1984***, 705.

[52]For tables of bond distances and angles, see Allen, F.H.; Kennard, O.; Watson, D.G.; Brammer, L.; Orpen, A.G.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* ***1987***, S1–S19 (follows p. 1914); Tables of Interatomic Distances and Configurations in Molecules and Ions *Chem. Soc. Spec. Publ.* No. 11, ***1958***; Interatomic Distances Supplement *Chem. Soc. Spec. Publ.* No. 18, ***1965***; Harmony, M.D. Laurie, V.W.; Kuczkowski, R.L.; Schwendeman, R.H.; Ramsay, D.A.; Lovas, F.J.; Lafferty, W.J.; Maki, A.G. *J. Phys. Chem. Ref. Data* ***1979***, *8*, 619–721. For a review of molecular shapes and energies for many small organic molecules, radicals, and cations calculated by molecular-orbital methods, see Lathan, W.A.; Curtiss, L.A.; Hehre, W.J.; Lisle, J.B.; Pople, J.A. *Prog. Phys. Org. Chem.* ***1974***, *11*, 175. For a discussion of substituent effects on bond distances, see Topsom, R.D. *Prog. Phys. Org. Chem.* ***1987***, *16*, 85.

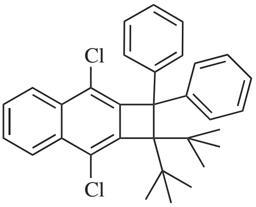
[53]Burkert, U.; Allinger, N.L. *Molecular Mechanics*; ACS Monograph 177, American Chemical Society, Washington, ***1982***, pp. 6–9; Whiffen, D.H. *Chem. Ber.* ***1971***, *7*, 57–61; Stals, J. *Rev. Pure Appl. Chem.* ***1970***, *20*, 1, pp. 2–5.

[54]Schleyer, P.v.R.; Bremer, M. *Angew. Chem. Int. Ed.* ***1989***, *28*, 1226.

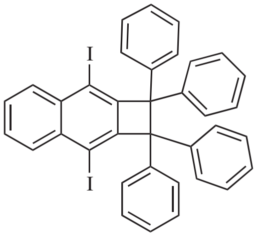
TABLE 1.4. Bond Lengths between *sp*[3] Carbons in Some Compounds

C—C bond in	Reference	Bond length, Å
Diamond	55	1.544
C_2H_6	56	1.5324 ± 0.0011
C_2H_5Cl	57	1.5495 ± 0.0005
C_3H_8	58	1.532 ± 0.003
Cyclohexane	59	1.540 ± 0.015
tert-Butyl chloride	60	1.532
n-Butane to *n*-heptane	61	1.531 − 1.534
Isobutane	62	1.535 ± 0.001

distances for single bonds between two sp^3 carbons. However, an analysis of C—OR bond distances in >2000 ethers and carboxylic esters (all with sp^3 carbon) shows that this distance increases with increasing electron withdrawal in the R group and as the C changes from primary to secondary to tertiary.[63] For these compounds, mean bond lengths of the various types ranged from 1.418 to 1.475 Å. Certain substituents can also influence bond length. The presence of a silyl substituent β- to a C—O (ester) linkage can lengthen the C—O, thereby weakening it.[64] This is believed to result from σ-σ^* interactions in which the C—Si σ-bonding orbital acts as the donor and the C—O σ^* orbitals acts as the receptor.



3



4

Although a typical carbon—carbon single bond has a bond length of ~1.54 Å, certain molecules are known that have significantly longer bond lengths.[65] Calculations

[55]Lonsdale, K. *Phil. Trans. R. Soc. London* ***1947***, *A240*, 219.
[56]Bartell, L.S.; Higginbotham, H.K. *J. Chem. Phys.* ***1965***, *42*, 851.
[57]Wagner, R.S.; Dailey, B.P. *J. Chem. Phys.* ***1957***, *26*, 1588.
[58]Iijima, T. *Bull. Chem. Soc. Jpn.* ***1972***, *45*, 1291.
[59]Tables of Interatomic Distances, Ref. 52.
[60]Momany, F.A.; Bonham, R.A.; Druelinger, M.L. *J. Am. Chem. Soc.* ***1963***, *85*, 3075; also see, Lide, Jr., D.R.; Jen, M. *J. Chem. Phys.* ***1963***, *38*, 1504.
[61]Bonham, R.A.; Bartell, L.S.; Kohl, D.A. *J. Am. Chem. Soc.* ***1959***, *81*, 4765.
[62]Hilderbrandt, R.L.; Wieser, J.D. *J. Mol. Struct.* ***1973***, *15*, 27.
[63]Allen, F.H.; Kirby, A.J. *J. Am. Chem. Soc.* ***1984***, *106*, 6197; Jones, P.G.; Kirby, A.J. *J. Am. Chem. Soc.* ***1984***, *106*, 6207.
[64]White, J.M.; Robertson, G.B. *J. Org. Chem.* ***1992***, *57*, 4638.
[65]Kaupp, G.; Boy, J *Angew. Chem. Int. Ed.* ***1997***, *36*, 48.

have been done for unstable molecules that showed them to have long bond lengths, and an analysis of the X-ray structure for the photoisomer of [2.2]-tetrabenzoparacyclophane (see Chapter 2) showed a C—C bond length of 1.77 Å.[66,65] Long bond lengths have been observed in stable molecules such as benzocyclobutane derivatives.[67] A bond length of 1.729 Å was reliably measured in 1,1-di-*tert*-butyl-2, 2-diphenyl-3,8-dichlorocyclobutan[*b*]naphthalene, **3**.[68] X-ray analysis of several of these derivations confirmed the presence of long C—C bonds, with **4** having a confirmed bond length of 1.734 Å.[69]

Bond distances for some important bond types are given in Table 1.5.[70] As can be seen in this table, carbon bonds are shortened by increasing *s* character.

TABLE 1.5. Bond distances[a]

Bond Type	Length, Å	Typical Compounds
C—C		
sp^3–sp^3	1.53	
sp^3–sp^2	1.51	Acetaldehyde, toluene, propene
sp^3–sp	1.47	Acetonitrile, propyne
sp^2–sp^2	1.48	Butadiene, glyoxal, biphenyl
sp^2–sp	1.43	Acrylonitrile, vinylacetylene
sp–*sp*	1.38	Cyanoacetylene, butadiyne
C=C		
sp^2–sp^2	1.32	Ethylene
sp^2–*sp*	1.31	Ketene, allenes
sp–*sp*[71]	1.28	Butatriene, carbon suboxide
C≡C[72]		
sp–*sp*	1.18	Acetylene
C—H[73]		
sp^3–**H**	1.09	Methane
sp^2–**H**	1.08	Benzene, ethylene
sp–**H**[74]	1.08	**HCN**, acetylene

[66]Ehrenberg, M. *Acta Crystallogr.* ***1966***, *20*, 182.

[67]Toda, F.; Tanaka, K.; Stein, Z.; Goldberg, I *Acta Crystallogr., Sect. C* ***1996***, *52*, 177.

[68]Toda, F.; Tanaka, K.; Watanabe, M.; Taura, K.; Miyahara, I.; Nakai, T.; Hirotsu, K. *J. Org. Chem.* ***1999***, *64*, 3102.

[69]Tanaka, K.; Takamoto, N.; Tezuka, Y.; Kato, M.; Toda, F. *Tetrahedron* ***2001***, *57*, 3761.

[70]Except where noted, values are from Allen, F.H.; Kennard, O.; Watson, D.G.; Brammer, L.; Orpen, A.G.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* ***1987***, S1-S19 (follows p. 1914). In this source, values are given to three significant figures.

[71]Costain, C.C.; Stoicheff, B.P. *J. Chem. Phys.* ***1959***, *30*, 777.

[72]For a full discussion of alkyne bond distances, see Simonetta, M.; Gavezzotti, A, in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond,* Wiley, NY, ***1978***.

[73]For an accurate method of C—H bond distance determination, see Henry, B.R. *Acc. Chem. Res.* ***1987***, *20*, 429.

[74]Bartell, L.S.; Roth, E.A.; Hollowell, C.D.; Kuchitsu, K.; Young, Jr., J.E. *J. Chem. Phys.* ***1965***, *42*, 2683.

TABLE 1.5. (*continued*)

Bond Type	Length, Å	Typical Compounds
C—O		
*sp*³–**O**	1.43	Dimethyl ether, ethanol
*sp*²–**O**	1.34	Formic acid
C=O		
*sp*²–**O**	1.21	Formaldehyde, formic acid
sp–**O**[59]	1.16	**CO_2**
C—N		
*sp*³–**N**	1.47	Methylamine
*sp*²–**N**	1.38	Formamide
C=N		
*sp*²–**N**	1.28	Oximes, imines
C≡N		
sp–**N**	1.14	**HCN**
C—S		
*sp*³–**S**	1.82	Methanethiol
*sp*²–**S**	1.75	Diphenyl sulfide
sp–**S**	1.68	CH_3SCN
C=S		
sp–**S**	1.67	**CS_2**

C—halogen[75]	**F**	**Cl**	**Br**	**I**
*sp*³–halogen	1.40	1.79	1.97	2.16
*sp*²–halogen	1.34	1.73	1.88	2.10
sp–halogen	1.27[76]	1.63	1.79[77]	1.99[77]

[a]The values given are average lengths and do not necessarily apply exactly to the compounds mentioned.[70]

This is most often explained by the fact that, as the percentage of *s* character in a hybrid orbital increases, the orbital becomes more like an *s* orbital and hence is held more tightly by the nucleus than an orbital with less *s* character. However, other explanations have also been offered (see p. 39), and the matter is not completely settled.

Indications are that a C—D bond is slightly shorter than a corresponding C—H bond. Thus, electron-diffraction measurements of C_2H_6 and C_2D_6 showed a C—H bond distance of 1.1122 ± O.0012 Å and a C—D distance of 1.1071 ± 0.0012 Å.[56]

BOND ANGLES

It might be expected that the bond angles of sp^3 carbon would always be the tetrahedral angle 109°28′, but this is so only where the four groups are identical, as in

[75]For reviews of carbon-halogen bonds, see Trotter, J., in Patai, S. *The Chemistry of the Carbon–Halogen Bond*, pt. 1, Wiley, NY, ***1973***, pp. 49–62; Mikhailov, B.M. *Russ. Chem. Rev.* ***1971***, *40*, 983.
[76]Lide, Jr., D.R. *Tetrahedron* ***1962***, *17*, 125.
[77]Rajput, A.S.; Chandra, S. *Bull. Chem. Soc. Jpn.* ***1966***, *39*, 1854.

methane, neopentane, or carbon tetrachloride. In most cases, the angles deviate a little from the pure tetrahedral value. For example, the C—C—Br angle in 2-bromopropane is 114.2°.[78] Similarly, slight variations are generally found from the ideal values of 120 and 180° for sp^2 and *sp* carbon, respectively. These deviations occur because of slightly different hybridizations, that is, a carbon bonded to four other atoms hybridizes one *s* and three *p* orbitals, but the four hybrid orbitals thus formed are generally not exactly equivalent, nor does each contain exactly 25% *s* and 75% *p* character. Because the four atoms have (in the most general case) different electronegativities, each makes its own demand for electrons from the carbon atom.[79] The carbon atom supplies more *p* character when it is bonded to more electronegative atoms, so that in chloromethane, for example, the bond to chlorine has somewhat more than 75% *p* character, which of course requires that the other three bonds have somewhat less, since there are only three *p* orbitals (and one *s*) to be divided among the four hybrid orbitals.[80] Of course, in strained molecules, the bond angles may be greatly distorted from the ideal values (see p. 216).

For oxygen and nitrogen, angles of 90° are predicted from p^2 bonding. However, as we have seen (p. 6), the angles of water and ammonia are much larger than this, as are the angles of other oxygen and nitrogen compounds (Table 1.6); in fact, they are much closer to the tetrahedral angle of 109°28′ than to 90°. These facts have

TABLE 1.6. Oxygen, Sulfur, and Nitrogen Bond Angles in Some Compounds

Angle	Value	Compound	Reference
H—O—H	104°27′	Water	5
C—O—H	107–109°	Methanol	59
C—O—C	111°43′	Dimethyl ether	81
C—O—C	124° ± 5°	Diphenyl ether	82
H—S—H	92.1°	H_2S	82
C—S—H	99.4°	Methanethiol	82
C—S—C	99.1°	Dimethyl sulfide	83
H—N—H	106°46′	Ammonia	5
H—N—H	106°	Methylamine	84
C—N—H	112°	Methylamine	83
C—N—C	108.7°	Trimethylamine	85

[78]Schwendeman, R.H.; Tobiason, F.L. *J. Chem. Phys.* ***1965***, *43*, 201.
[79]For a review of this concept, see Bingel, W.A.; Lüttke, W. *Angew. Chem. Int. Ed.* ***1981***, *20*, 899.
[80]This assumption has been challenged: see Pomerantz, M.; Liebman, J.F. *Tetrahedron Lett.* ***1975***, 2385.
[81]Blukis, V.; Kasai, P.H.; Myers, R.J. *J. Chem. Phys.* ***1963***, *38*, 2753.
[82]Abrahams, S.C. *Q. Rev. Chem. Soc.* ***1956***, *10*, 407.
[83]Iijima, T.; Tsuchiya, S.; Kimura, M. *Bull. Chem. Soc. Jpn.* ***1977***, *50*, 2564.
[84]Lide, Jr., D.R. *J. Chem. Phys.* ***1957***, *27*, 343.
[85]Lide, Jr., D.R.; Mann, D.E. *J. Chem. Phys.* ***1958***, *28*, 572.

led to the suggestion that in these compounds oxygen and nitrogen use sp^3 bonding, that is, instead of forming bonds by the overlap of two (or three) p orbitals with $1s$ orbitals of the hydrogen atoms, they hybridize their $2s$ and $2p$ orbitals to form four sp^3 orbitals and then use only two (or three) of these for bonding with hydrogen, the others remaining occupied by unshared pairs (also called *lone pairs*). If this description is valid, and it is generally accepted by most chemists today,[86] it becomes necessary to explain why the angles of these two compounds are in fact not 109°28′ but a few degrees smaller. One explanation that has been offered is that the unshared pair actually has a greater steric requirement than a pair in a bond, since there is no second nucleus to draw away some of the electron density and the bonds are thus crowded together. However, most evidence is that unshared pairs have smaller steric requirements than bonds[87] and the explanation most commonly accepted is that the hybridization is not pure sp^3. As we have seen above, an atom supplies more p character when it is bonded to more electronegative atoms. An unshared pair may be considered to be an "atom" of the lowest possible electronegativity, since there is no attracting power at all. Consequently, the unshared pairs have more s and the bonds more p character than pure sp^3 orbitals, making the bonds somewhat more like p^2 bonds and reducing the angle. As seen in Table 1.6, oxygen, nitrogen, and sulfur angles generally increase with decreasing electronegativity of the substituents. Note that the explanation given above cannot explain why some of these angles are *greater* than the tetrahedral angle.

BOND ENERGIES[88,89]

There are two kinds of bond energy. The energy necessary to cleave a bond to give the constituent radicals is called the *dissociation energy D*. For example, D for $H_2O \rightarrow HO + H$ is 118 kcal mol^{-1} (494/mol). However, this is not taken as the energy of the O—H bond in water, since D for $H\text{—}O \rightarrow H + O$ is 100 kcal mol^{-1} (418 kJ mol^{-1}). The average of these two values, 109 kcal mol^{-1} (456 kJ mol^{-1}), is taken as the *bond energy E*. In diatomic molecules, of course, $D = E$.

[86]An older theory holds that the bonding is indeed p^2, and that the increased angles come from repulsion of the hydrogen or carbon atoms. See Laing, M., *J. Chem. Educ.* ***1987***, *64*, 124.

[87]See, for example, Pumphrey, N.W.J.; Robinson, M.J.T. *Chem. Ind. (London)* ***1963***, 1903; Allinger, N.L.; Carpenter, J.G.D.; Karkowski, F.M. *Tetrahedron Lett.* ***1964***, 3345; Jones, R.A.Y.; Katritzky, A.R.; Richards, A.C.; Wyatt, R.J.; Bishop, R.J.; Sutton, L.E. *J. Chem. Soc. B* ***1970***, 127; Blackburne, I.D.; Katritzky, A.R.; Takeuchi, Y. *J. Am. Chem. Soc.* ***1974***, *96*, 682; *Acc. Chem. Res.* ***1975***, *8*, 300; Aaron, H.S.; Ferguson, C.P. *J. Am. Chem. Soc.* ***1976***, *98*, 7013; Anet, F.A.L.; Yavari, I. *J. Am. Chem. Soc.* ***1977***, *99*, 2794; Vierhapper, F.W.; Eliel, E.L. *J. Org. Chem.* ***1979***, *44*, 1081; Gust, D.; Fagan, M.W. *J. Org. Chem.* ***1980***, *45*, 2511. For other views, see Lambert, J.B.; Featherman, S.I. *Chem. Rev.* ***1975***, *75*, 611; Crowley, P.J.; Morris, G.A.; Robinson, M.J.T. *Tetrahedron Lett.* ***1976***, 3575; Breuker, K.; Kos, N.J.; van der Plas, H.C.; van Veldhuizen, B. *J. Org. Chem.* ***1982***, *47*, 963.

[88]Blanksby, S.J.; Ellison, G.B. *Acc. Chem. Res.* ***2003***, *36*, 255.

[89]For reviews including methods of determination, see Wayner, D.D.M.; Griller, D. *Adv. Free Radical Chem. (Greenwich, Conn.)* ***1990***, *1*, 159; Kerr, J.A. *Chem. Rev.* ***1966***, *66*, 465; Benson, S.W. *J. Chem. Educ.* ***1965***, *42*, 520; Wiberg, K.B., in Nachod, F.C.; Zuckerman, J.J. *Determination of Organic Structures by Physical Methods*, Vol. 3, Academic Press, NY, ***1971***, pp. 207–245.

				kcal	kJ
$C_2H_{6\,(gas)}$	+ 3.5 O_2	= 2 $CO_{2\,(gas)}$	+ 3 $H_2O_{(liq)}$	+372.9	+1560
	2 $CO_{2\,(gas)}$	= 2 $C_{(graphite)}$	+ 2 $O_{2\,(gas)}$	−188.2	−787
	3 $H_2O_{(liq)}$	= 3 $H_{2\,(gas)}$	+ 1.5 $O_{2\,(gas)}$	−204.9	−857
	3 $H_{2\,(gas)}$	= 6 $H_{(gas)}$		−312/5	−1308
	2 $C_{(graphite)}$	= 2 $C_{(gas)}$		−343.4	−1437
	$C_2H_{6\,(gas)}$	= 6 $H_{(gas)}$	+ 2 $C_{(gas)}$	−676.1 kcal	−2829 kJ

Fig. 1.11. Calculation of the heat of atomization of ethane at 25°C.

The *D* values may be easy or difficult to measure, and they can be estimated by various techniques.[90] When properly applied, "Pauling's original electronegativity equation accurately describes homolytic bond dissociation enthalpies of common covalent bonds, including highly polar ones, with an average deviation of (1.5 kcal mol^{-1} [≈6.3 kJ mol^{-1}] from literature values)."[91] Whether measured or calculated, there is no question as to what *D* values mean. With *E* values the matter is not so simple. For methane, the total energy of conversion from CH_4 to C + 4H (at 0 K) is 393 kcal mol^{-1} (1644 kJ mol^{-1}).[92] Consequently, *E* for the C—H bond in methane is 98 kcal mol^{-1} (411 kJ mol^{-1}) at 0 K. The more usual practice, though, is not to measure the heat of atomization (i.e., the energy necessary to convert a compound to its atoms) directly but to calculate it from the heat of combustion. Such a calculation is shown in Figure 1.11.

Heats of combustion are very accurately known for hydrocarbons.[93] For methane the value at 25°C is 212.8 kcal mol^{-1} (890.4 kJ mol^{-1}), which leads to a heat of atomization of 398.0 kcal mol^{-1} (1665 kJ mol^{-1}) or a value of *E* for the C—H bond at 25°C of 99.5 kcal mol^{-1} (416 kJ mol^{-1}). This method is fine for molecules like methane in which all the bonds are equivalent, but for more complicated molecules assumptions must be made. Thus for ethane, the heat of atomization at 25°C is 676.1 kcal mol^{-1} or 2829 kJ mol^{-1} (Fig. 1.11), and we must decide how much of this energy is due to the C—C bond and how much to the six C—H bonds. Any assumption must be artificial, since there is no way of actually obtaining this information, and indeed the question has no real meaning. If we make the assumption that *E* for each of the C—H bonds is the same as *E* for the C—H bond in methane (99.5 kcal mol^{-1} or 416 kJ mol^{-1}), then 6× 99.5 (or 416) = 597.0 (or 2498), leaving 79.1 kcal mol^{-1} (331 kJ mol^{-1}) for the C—C bond. However, a similar calculation for propane gives a value of 80.3 (or 336) for the

[90]Cohen, N.; Benson, S.W. *Chem. Rev.* ***1993***, *93*, 2419; Korth, H.-G.; Sicking, W. *J. Chem. Soc. Perkin Trans. 2* ***1997***, 715.

[91]Matsunaga, N.; Rogers, D.W.; Zavitsas, A.A. *J. Org. Chem*, ***2003***, *68*, 3158.

[92]For the four steps, *D* values are 101 to 102, 88, 124, and 80 kcal mol^{-1} (423–427, 368, 519, and 335 kJ mol^{-1}), respectively, though the middle values are much less reliable than the other two: Knox, B.E.; Palmer, H.B. *Chem. Rev.* ***1961***, *61*, 247; Brewer, R.G.; Kester, F.L. *J. Chem. Phys.* ***1964***, *40*, 812; Linevsky, M.J. *J. Chem. Phys.* ***1967***, *47*, 3485.

[93]For values of heats of combustion of large numbers of organic compounds: hydrocarbons and others, see Cox, J.D.; Pilcher, G., *Thermochemistry of Organic and Organometallic Compounds*, Academic Press, NY, ***1970***; Domalski, E.S. *J. Phys. Chem. Ref. Data* ***1972***, *1*, 221–277. For large numbers of heats-of-formation values (from which heats of combustion are easily calculated) see Stull, D.R.; Westrum, Jr., E.F.; Sinke, G.C. *The Chemical Thermodynamics of Organic Compounds*, Wiley, NY, ***1969***.

C—C bond, and for isobutane, the value is 81.6 (or 341). A consideration of heats of atomization of isomers also illustrates the difficulty. *E* values for the C—C bonds in pentane, isopentane, and neopentane, calculated from heats of atomization in the same way, are (at 25°C) 81.1, 81.8, and 82.4 kcal mol^{-1} (339, 342, 345 kJ mol^{-1}), respectively, even though all of them have twelve C—H bonds and four C—C bonds.

These differences have been attributed to various factors caused by the introduction of new structural features. Thus isopentane has a tertiary carbon whose C—H bond does not have exactly the same amount of *s* character as the C—H bond in pentane, which for that matter contains secondary carbons not possessed by methane. It is known that *D* values, which *can* be measured, are not the same for primary, secondary, and tertiary C—H bonds (see Table 5.3). There is also the steric factor. Hence, it is certainly not correct to use the value of 99.5 kcal mol^{-1} (416 kJ mol^{-1}) from methane as the *E* value for all C—H bonds. Several empirical equations have been devised that account for these factors; the total energy can be computed[94] if the proper set of parameters (one for each structural feature) is inserted. Of course, these parameters are originally calculated from the known total energies of some molecules which contain the structural feature.

Table 1.7 gives *E* values for various bonds. The values given are averaged over a large series of compounds. The literature contains charts that take account of

TABLE 1.7. Bond Energy *E* Values at 25°C for Some Important Bond Types[95a]

Bond	kcal mol^{-1}	kJ mol^{-1}	Bond	kcal mol^{-1}	kJ mol^{-1}
O—H	110–111	460–464	C—S[96]	61	255
C—H	96–99	400–415	C—I	52	220
N—H	93	390			
S—H	82	340	C≡C	199–200	835
			C=C	146–151	610–630
C—F	—	—	C—C	83–85	345–355
C—H	96–99	400–415			
C—O	85–91	355–380	C≡N	204	854
C—C	83–85	345–355	C=O	173–81	724–757
C—Cl	79	330			
C—N[97]	69–75	290–315	C=N[97]	143	598
C—Br	66	275	O—O[98]	42.9	179.6 ± 4.5

[a]The *E* values are arranged within each group in order of decreasing strength. The values are averaged over a large series of compounds.

[94]For a review, see Cox, J.D.; Pilcher, G. *Thermochemistry of Organic and Organometallic Compounds*, Academic Press, NY, ***1970***, pp. 531–597. See also, Gasteiger, J.; Jacob, P.; Strauss, U. *Tetrahedron* ***1979***, *35*, 139.

[95]These values, except where noted, are from Lovering, E.G.; Laidler, K.J. *Can. J. Chem.* ***1960***, *38*, 2367; Levi, G.I.; Balandin, A.A. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* ***1960***, 149.

[96]Grelbig, T.; Pötter, B.; Seppelt, K. *Chem. Ber.* ***1987***, *120*, 815.

[97]Bedford, A.F.; Edmondson, P.B.; Mortimer, C.T. *J. Chem. Soc.* ***1962***, 2927.

[98]The average of the values obtained was *DH*°(O—O). dos Santos, R.M.B.; Muralha, V.S.F.; Correia, C.F.; Simões, J.A.M. *J. Am. Chem. Soc.* ***2001***, *123*, 12670.

hybridization (thus an sp^3 C—H bond does not have the same energy as an sp^2 C—H bond).[99] Bond dissociation energies, both calculated and experientially determined, are constantly being refined. Improved values are available for the O—O bond of peroxides,[100] the C—H bond in alkyl amines,[101] the N—H bond in aniline derivatives,[102] the N—H bond in protonated amines,[103] the O—H bond in phenols,[104] the C—H bond in alkenes,[105] amides and ketones,[106] and in CH_2X_2 and CH_3X derivatives (X = COOR, C=O, SR, NO_2, etc.),[107] the O—H and S—H bonds of alcohols and thiols,[108] and the C—Si bond of aromatic silanes.[109] Solvent plays a role in the *E* values. When phenols bearing electron-releasing groups are in aqueous media, calculations show that the bond dissociation energies of decrease due to hydrogen-bonding interactions with water molecules, while electron-withdrawing substituents on the phenol increase the bond dissociation energies.[110]

Certain generalizations can be derived from the data in Table 1.7.

1. There is a correlation of bond strengths with bond distances. A comparison of Tables 1.5 and 1.7 shows that, in general, *shorter bonds are stronger bonds*. Since we have already seen that increasing *s* character shortens bonds (p. 24), it follows that bond strengths increase with increasing *s* character. Calculations show that ring strain has a significant effect on bond dissociation energy, particularly the C—H bond of hydrocarbons, because it forces the compound to adopt an undesirable hybridization.[111]
2. Bonds become weaker as we move down the Periodic Table. Compare C—O and C—S, or the carbon–halogen bonds C—F, C—Cl, C—Br, C—I. This is a consequence of the first generalization, since bond distances must increase as we go down the periodic table because the number of inner electrons increases. However, it is noted that "high-level *ab initio* molecular-orbital calculations confirm that the effect of alkyl substituents on R—X bond dissociation energies varies according to the nature of X (the stabilizing

[99]Cox, J.D.; Pilcher, G. *Thermochemistry of Organic and Organometallic Compounds*, Academic Press, NY, ***1970***, pp. 531–597; Cox, J.D. *Tetrahedron* ***1962***, *18*, 1337.

[100]Bach, R.D.; Ayala, P.Y.; Schlegel, H.B. *J. Am. Chem. Soc.* ***1996***, *118*, 12758.

[101]Wayner, D.D.M.; Clark, K.B.; Rauk, A.; Yu, D.; Armstrong, D.A. *J. Am. Chem. Soc.* ***1997***, *119,* 8925. For the α C—H bond of tertiary amines, see Dombrowski, G.W.; Dinnocenzo, J.P.; Farid, S.; Goodman, J.L. Gould, I.R. *J. Org. Chem.* ***1999***, *64*, 427.

[102]Bordwell, F.G.; Zhang, X.-M.; Cheng, J.-P. *J. Org. Chem.* ***1993***, *58*, 6410. See also, Li, Z.; Cheng, J.-P. *J. Org. Chem.* ***2003***, *68*, 7350.

[103]Liu, W.-Z.; Bordwell, F.G. *J. Org. Chem.* ***1996***, *61*, 4778.

[104]Lucarini, M.; Pedrielli, P.; Pedulli, G.F.; Cabiddu, S.; Fattuoni, C. *J. Org. Chem.* ***1996***, *61*, 9259. For the O—H *E* of polymethylphenols, see de Heer, M.I.; Korth, H.-G.; Mulder, P. *J. Org. Chem.* ***1999***, *64*, 6969.

[105]Zhang, X.-M. *J. Org. Chem.* ***1998***, *63*, 1872.

[106]Bordwell, F.G.; Zhang, X.-M.; Filler, R. *J. Org. Chem.* ***1993***, *58*, 6067.

[107]Brocks, J.J.; Beckhaus, H.-D.; Beckwith, A.L.J.; Rüchardt, C. *J. Org. Chem.* ***1998***, *63*, 1935.

[108]Hadad, C.M.; Rablen, P.R.; Wiberg, K.B. *J. Org. Chem.* ***1998***, *63*, 8668.

[109]Cheng, Y.-H.; Zhao, X.; Song, K.-S.; Liu, L.; Guo, Q.-X. *J. Org. Chem.* ***2002***, *67*, 6638.

[110]Guerra, M.; Amorati, R.; Pedulli, G.F. *J. Org. Chem.* ***2004***, *69*, 5460.

[111]Feng, Y.; Liu, L.; Wang, J.-T.; Zhao, S.-W.; Guo, Q.X. *J. Org. Chem.* ***2004***, *69*, 3129; Song, K.-S.; Liu, L.; Guo, Q.X. *Tetrahedron* ***2004***, *60*, 9909.

influence of the ionic configurations to increase in the order Me < Et < *i*-Pr < *t*-Bu, accounting for the *increase* (rather than expected decrease) in the R—X bond dissociation energies with increasing alkylation in the R—OCH_3, R—OH, and R—F molecules. This effect of X can be understood in terms of the increasing contribution of the ionic R^+X^- configuration for electronegative X substituents."[112]

3. Double bonds are both shorter and stronger than the corresponding single bonds, but not twice as strong, because π overlap is less than σ overlap. This means that a σ bond is stronger than a π bond. The difference in energy between a single bond, say C—C, and the corresponding double bond is the amount of energy necessary to cause rotation around the double bond.[113]

[112]Coote, M.L.; Pross, A.; Radom, L. *Org. Lett.* ***2003***, *5*, 4689.

[113]For a discussion of the different magnitdues of the bond energies of the two bonds of the double bond, see Miller, S.I. *J. Chem. Educ.* ***1978***, *55*, 778.

CHAPTER 2

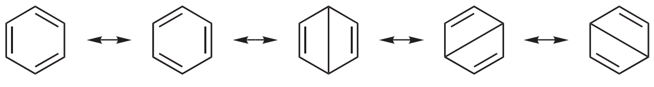
Delocalized Chemical Bonding

Although the bonding of many compounds can be adequately described by a single Lewis structure (p. 14), this is not sufficient for many other compounds. These compounds contain one or more bonding orbitals that are not restricted to two atoms, but that are spread out over three or more. Such bonding is said to be *delocalized*.[1] In this chapter, we will see which types of compounds must be represented in this way.

The two chief general methods of approximately solving the wave equation, discussed in Chapter 1, are also used for compounds containing delocalized bonds.[2] In the valence-bond method, several possible Lewis structures (called *canonical forms*) are drawn and the molecule is taken to be a weighted average of them. Each Ψ in Eq. (1.3), Chapter 1,

$$\Psi = c_1\psi_1 + c_1\psi_1 + \cdots$$

represents one of these structures. This representation of a real structure as a weighted average of two or more canonical forms is called *resonance*. For benzene the canonical forms are **1** and **2**. Double-headed arrows ($\leftrightarrow$) are used to indicate resonance. When the wave equation is solved, it is found that the energy value obtained by considering that **1** and **2** participate equally is lower than that for **1** or **2** alone. If **3**, **4**, and **5** (called *Dewar structures*) are also considered, the value



1 **2** **3** **4** **5**

[1]The classic work on delocalized bonding is Wheland, G.W. *Resonance in Organic Chemistry*; Wiley, NY, ***1955***.

[2]There are other methods. For a discussion of the free-electron method, see Streitwieser Jr., A. *Molecular Orbital Theory for Organic Chemists*; Wiley, NY, ***1961***, pp. 27–29. For the nonpairing method, in which benzene is represented as having three electrons between adjacent carbons, see Hirst, D.M.; Linnett, J.W. *J. Chem. Soc.* ***1962***, 1035; Firestone, R.A. *J. Org. Chem.* ***1969***, *34*, 2621.

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is lower still. According to this method, **1** and **2** each contribute 39% to the actual molecule and the others 7.3% each.[3] The carbon–carbon bond order is 1.463 (not 1.5, which would be the case if only **1** and **2** contributed). In the valence-bond method, the *bond order* of a particular bond is the sum of the weights of those canonical forms in which the bonds is double plus 1 for the single bond that is present in all of them.[4] Thus, according to this picture, each C—C bond is not halfway between a single and a double bond but somewhat less. The energy of the actual molecule is obviously less than that of any one Lewis structure, since otherwise it would have one of those structures. The difference in energy between the actual molecule and the Lewis structure of lowest energy is call the *resonance energy*. Of course, the Lewis structures are not real, and their energies can only be estimated.

Qualitatively, the resonance picture is often used to describe the structure of molecules, but quantitative valence-bond calculations become much more difficult as the structures become more complicated (e.g., naphthalene, and pyridine). Therefore, the molecular-orbital method is used much more often for the solution of wave equations.[5] If we look at benzene by this method (qualitatively), we see that each carbon atom, being connected to three other atoms, uses sp^2 orbitals to form σ bonds, so that all 12 atoms are in one plane. Each carbon has a *p* orbital (containing one electron) remaining and each of these can overlap equally with the two adjacent *p* orbitals. This overlap of six orbitals (see Fig. 2.1) produces six new orbitals, three of which (shown) are bonding. These three (called π orbitals) all occupy approximately the same space.[6] One of the three is of lower energy than the other two, which are degenerate. They each have the plane of the ring as a node and so are in two parts, one above and one below the plane. The two orbitals of higher energy (Fig. 2.1*b* and *c*) also have another node. The six electrons that occupy this torus-shaped cloud are called the *aromatic sextet*. The carbon–carbon bond order for benzene, calculated by the molecular-orbital method, is 1.667.[7]

For planar unsaturated and aromatic molecules, many molecular-orbital calculations (*MO calculations*) have been made by treating the σ and π electrons separately. It is assumed that the σ orbitals can be treated as localized bonds and the

[3]Pullman, A. *Prog. Org. Chem.* ***1958***, *4*, 31, p. 33.

[4]For a more precise method of calculating valence-bond orders, see Clarkson, D.; Coulson, C.A.; Goodwin, T.H. *Tetrahedron* ***1963***, *19*, 2153. See also Herndon, W.C.; Párkányi, C. *J. Chem. Educ.* ***1976***, *53*, 689.

[5]For a review of how MO theory explains localized and delocalized bonding, see Dewar, M.J.S. *Mol. Struct. Energ.*, ***1988***, *5*, 1.

[6]According to the explanation given here, the symmetrical hexagonal structure of benzene is caused by both the σ bonds and the π orbitals. It has been contended, based on MO calculations, that this symmetry is caused by the σ framework alone, and that the π system would favor three localized double bonds: Shaik, S.S.; Hiberty, P.C.; Lefour, J.; Ohanessian, G. *J. Am. Chem. Soc.* ***1987***, *109*, 363; Stanger, A.; Vollhardt, K.P.C. *J. Org. Chem.* ***1988***, *53*, 4889. See also Cooper, D.L.; Wright, S.C.; Gerratt, J.; Raimondi, M. J. *Chem. Soc. Perkin Trans. 2* ***1989***, 255, 263; Jug, K.; Köster, A.M. *J. Am. Chem. Soc.* ***1990***, *112*, 6772; Aihara, J. *Bull. Chem. Soc. Jpn.* ***1990***, *63*, 1956.

[7]The molecular-orbital method of calculating bond order is more complicated than the valence-bond method. See Pullman, A. *Prog. Org. Chem.* ***1958***, *4*, 31, p. 36; Clarkson, D.; Coulson, C.A.; Goodwin, T.H. *Tetrahedron* ***1963***, *19*, 2153.

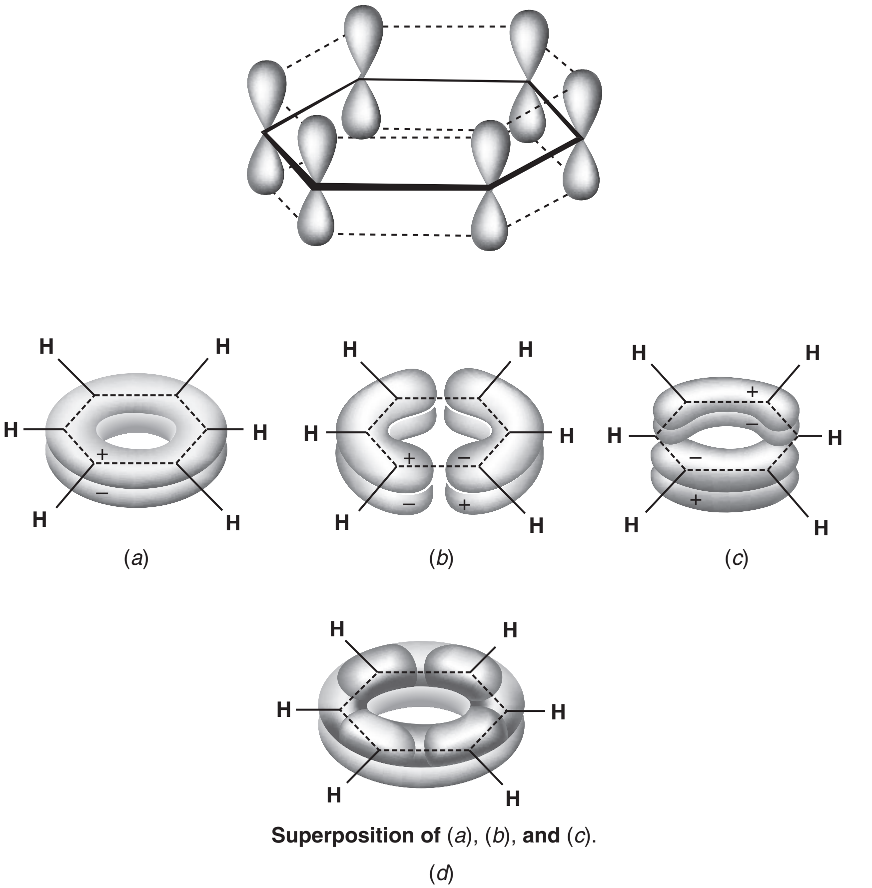


Fig. 2.1. The six *p* orbitals of benzene overlap to form three bonding orbitals, (*a*), (*b*), and (*c*). The three orbitals superimposed are shown in (*d*).

calculations involve only the π electrons. The first such calculations were made by Hückel; such calculations are often called *Hückel molecular-orbital* (HMO) *calculations*.[8] Because electron–electron repulsions are either neglected or averaged out in the HMO method, another approach, the *self-consistent field* (SCF), or *Hartree–Fock*, method, was devised.[9] Although these methods give many useful results for

[8]See Yates, K. *Hückel Molecular Orbital Theory*, Academic Press, NY, ***1978***; Coulson, C.A.; O'Leary, B.; Mallion, R.B. *Hückel Theory for Organic Chemists*, Academic Press, NY, ***1978***; Lowry, T.H.; Richardson, K.S. *Mechanism and Theory in Organic Chemistry*, 3rd ed., Harper and Row, NY, ***1987***, pp. 100–121.
[9]Roothaan, C.C.J. *Rev. Mod. Phys.* ***1951***, *23*, 69; Pariser, R.; Parr, R.G. *J. Chem. Phys.* ***1952***, *21*, 466, 767; Pople, J.A. *Trans. Faraday Soc,.* ***1953***, *49*, 1375, *J. Phys. Chem.* ***1975***, *61*, 6; Dewar, M.J.S. *The Molecular Orbital Theory of Organic Chemistry*; McGraw-Hill, NY, ***1969***; Dewar, M.J.S., in *Aromaticity, Chem. Soc. Spec. Pub.* no. 21, ***1967***, pp. 177–215.

planar unsaturated and aromatic molecules, they are often unsuccessful for other molecules; it would obviously be better if all electrons, both σ and π, could be included in the calculations. The development of modern computers has now made this possible.[10] Many such calculations have been made[11] using a number of methods, among them an extension of the Hückel method (EHMO)[12] and the application of the SCF method to all valence electrons.[13]

One type of MO calculation that includes all electrons is called *ab initio*.[14] Despite the name (which means "from first principles") this type does involve assumptions, though not very many. It requires a large amount of computer time, especially for molecules that contain more than about five or six atoms other than hydrogen. Treatments that use certain simplifying assumptions (but still include all electrons) are called *semiempirical* methods.[15] One of the first of these was called CNDO (Complete Neglect of Differential Overlap),[16] but as computers have become more powerful, this has been superseded by more modern methods, including MINDO/3 (Modified Intermediate Neglect of Differential Overlap),[17] MNDO (Modified Neglect of Diatomic Overlap),[17] and AM1 (Austin Model 1), all of which were introduced by M.J. Dewar and co-workers.[18] Semiempirical calculations are generally regarded as less accurate than *ab initio* methods,[19] but are much faster and cheaper. Indeed, calculations for some very large molecules are possible only with the semiempirical methods.[20]

Molecular-orbital calculations, whether by *ab initio* or semiempirical methods, can be used to obtain structures (bond distances and angles), energies (e.g., heats of formation), dipole moments, ionization energies, and other properties of molecules,

[10]For discussions of the progress made in quantum chemistry calculations, see Ramsden, C.A. *Chem. Ber.* ***1978***, *14*, 396; Hall, G.G. *Chem. Soc. Rev.* ***1973***, *2*, 21.

[11]For a review of molecular-orbital calculatons on saturated organic compounds, see Herndon, W.C. *Prog. Phys. Org. Chem.* ***1972***, *9*, 99.

[12]Hoffmann, R. *J. Chem. Phys.* ***1963***, *39*, 1397. See Yates, K. *Hückel Molecular Orbital Theory*, Academic Press, NY, ***1978***, pp. 190–201.

[13]Dewar, M.J.S. *The Molecular Orbital Theory of Chemistry*, McGraw-Hill, NY, ***1969***; Jaffé, H.H. *Acc. Chem. Res.* ***1969***, *2*, 136; Kutzelnigg, W.; Del Re, G.; Berthier, G. *Fortschr. Chem. Forsch.* ***1971***, *22*, 1.

[14]Hehre, W.J.; Radom, L.; Schleyer, P.v.R.; Pople, J.A. *Ab Initio Molecular Orbital Theory*, Wiley, NY, ***1986***; Clark, T. *A Handbook of Computational Chemistry*, Wiley, NY, ***1985***, pp. 233–317; Richards, W.G.; Cooper, D.L. *Ab Initio Molecular Orbital Calculations for Chemists*, 2nd ed., Oxford University Press: Oxford, ***1983***.

[15]For a review, see Thiel, W. *Tetrahedron* ***1988***, *44*, 7393.

[16]Pople, J.A.; Santry, D.P.; Segal, G.A. *J. Chem. Phys.* ***1965***, *43*, S129; Pople, J.A.; Segal, G.A. *J. Chem. Phys.* ***1965***, *43*, S136; ***1966***, *44*, 3289; Pople, J.A.; Beveridge, D.L. *Approximate Molecular Orbital Theory*; McGraw-Hill, NY, ***1970***.

[17]For a discussion of MNDO and MINDO/3, and a list of systems for which these methods have been used, with references, see Clark, T. *A Handbook of Computational Chemistry*, Wiley, NY, ***1985***, pp. 93–232. For a review of MINDO/3, see Lewis, D.F.V. *Chem. Rev.* ***1986***, *86*, 1111.

[18]First publications are, MINDO/3: Bingham, R.C.; Dewar, M.J.S.; Lo, D.H. *J. Am. Chem. Soc.* ***1975***, *97*, 1285; MNDO: Dewar, M.J.S.; Thiel, W. *J. Am. Chem. Soc.* ***1977***, *99*, 4899; AM1: Dewar, M.J.S.; Zoebisch, E.G.; Healy, E.F.; Stewart, J.J.P. *J. Am. Chem. Soc.* ***1985***, *107*, 3902.

[19]See, however, Dewar, M.J.S.; Storch, D.M. *J. Am. Chem. Soc.* ***1985***, *107*, 3898.

[20]Clark, T. *A Handbook of Computational Chemistry*, Wiley, NY, ***1985***, p. 141.

ions, and radicals: not only of stable ones, but also of those so unstable that these properties cannot be obtained from experimental measurements.[21] Many of these calculations have been performed on transition states (p. 302); this is the only way to get this information, since transition states are not, in general, directly observable. Of course, it is not possible to check data obtained for unstable molecules and transition states against any experimental values, so that the reliability of the various MO methods for these cases is always a question. However, our confidence in them does increase when (*1*) different MO methods give similar results, and (*2*) a particular MO method works well for cases that can be checked against experimental methods.[22]

Both the valence-bond and molecular-orbital methods show that there is delocalization in benzene. For example, each predicts that the six carbon–carbon bonds should have equal lengths, which is true. Since each method is useful for certain purposes, we will use one or the other as appropriate. Recent *ab initio, SCF* calculations confirms that the delocalization effect acts to strongly stabilize symmetric benzene, consistent with the concepts of classical resonance theory.[23]

Bond Energies and Distances in Compounds Containing Delocalized Bonds

If we add the energies of all the bonds in benzene, taking the values from a source like Table 1.7, the value for the heat of atomization turns out to be less than that actually found in benzene (Fig. 2.2). The actual value is 1323 kcal mol^{-1} (5535 kJ mol^{-1}). If we use *E* values for a C=C double bond obtained from cyclohexene (148.8 kcal mol^{-1}; 622.6 kJ mol^{-1}), a C—C single bond from cyclohexane (81.8 kcal mol^{-1}, 342 kJ mol^{-1}), and C–H bonds from methane (99.5 kcal mol^{-1}, 416 kJ mol^{-1}), we get a total of 1289 kcal mol^{-1} (5390 kJ mol^{-1}) for structure **1** or **2**. By this calculation the resonance energy is 34 kcal mol^{-1} (145 kJ mol^{-1}). Of course, this is an arbitrary calculation since, in addition to the fact that we are calculating a heat of atomization for a nonexistent structure (**1**), we are forced to use *E* values that themselves do not have a firm basis in reality. The actual C—H bond energy for benzene has been measured to be 113.5 ± 0.5 kcal mol^{-1} at 300 K and estimated to be 112.0 ± 0.6 kcal mol^{-1} (469 kJ mol^{-1}) at 0 K.[24] The resonance energy can never be measured, only estimated, since we can measure the heat of atomization of the real molecule but can only make an intelligent guess at that of the Lewis structure of lowest energy.

[21]Another method of calculating such properies is molecular mechanics (p. $$$).

[22]Dias, J.R. *Molecular Orbital Calculations Using Chemical Graph Theory*, Spring-Verlag, Berlin, ***1993***.

[23]Glendening, E.D.; Faust, R.; Streitwieser, A.; Vollhardt, K.P.C.; Weinhold, F. *J. Am. Chem.Soc.* ***1993***, *115*, 10952.

[24]Davico, G.E.; Bierbaum, V.M.; DePuy, C.H.; Ellison, G.B.; Squires, R.R. *J. Am. Chem. Soc.* ***1995***, *117*, 2590. See also Barckholtz, C.; Barckholtz, T.A.; Hadad, C.M. *J. Am. Chem. Soc.* ***1999***, *121*, 491; Pratt, D.A.; DiLabio, G.A.; Mulder, P.; Ingold, K.U. *Acc. Chem. Res.* ***2004***, *37*, 334.

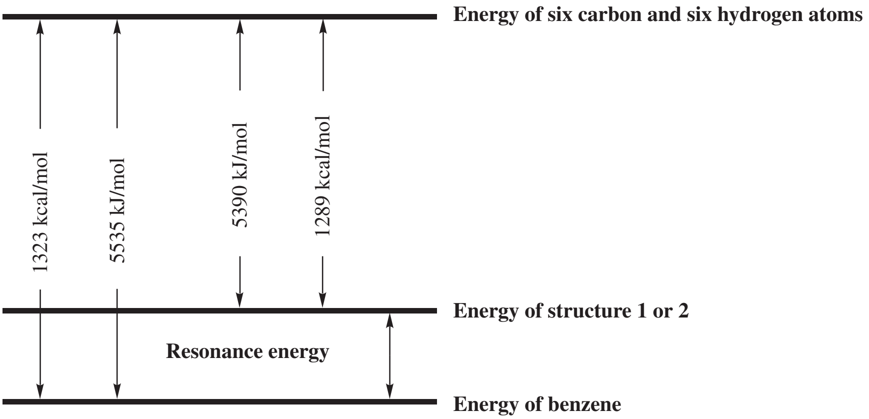


Fig. 2.2. Resonance energy in benzene.

Another method frequently used for estimation of resonance energy involves measurements of heats of hydrogenation.[25] Thus, the heat of hydrogenation of cyclohexene is 28.6 kcal mol^{-1} (120 kJ mol^{-1}), so we might expect a hypothetical **1** or **2** with three double bonds to have a heat of hydrogenation of about 85.8 kcal mol^{-1} (360 kJ mol^{-1}). The real benzene has a heat of hydrogenation of 49.8 kcal mol^{-1} (208 kJ mol^{-1}), which gives a resonance energy of 36 kcal mol^{-1} (152 kJ mol^{-1}). By any calculation the real molecule is more stable than a hypothetical **1** or **2**.

The energies of the six benzene orbitals can be calculated from HMO theory in terms of two quantities, α and β. The parameter α is the amount of energy possessed by an isolated 2*p* orbital before overlap, while β (called the *resonance integral*) is an energy unit expressing the degree of stabilization resulting from π-orbital overlap. A negative value of β corresponds to stabilization, and the energies of the six orbitals are (lowest to highest): $\alpha + 2\beta$, $\alpha + \beta$, $\alpha + \beta$, $\alpha - \beta$, $\alpha - \beta$, and $\alpha - 2\beta$.[26] The total energy of the three occupied orbitals is $6\alpha + 8\beta$, since there are two electrons in each orbital. The energy of an ordinary double bond is $\alpha + \beta$, so that structure **1** or **2** has an energy of $6\alpha + 6\beta$. The resonance energy of benzene is therefore 2β. Unfortunately, there is no convenient way to calculate the value of β from molecular-orbital theory. It is often given for benzene as about 18 kcal mol^{-1} (76 kJ mol^{-1}); this number being one-half of the resonance energy calculated from heats of combustion or hydrogenation. Using modern *ab initio* calculations, bond resonance energies for many aromatic hydrocarbons other than benzene have been reported.[27]

[25]For a review of heats of hydrogenation, with tables of values, see Jensen, J.L. *Prog. Phys. Org. Chem.* ***1976***, *12*, 189.

[26]For the method for calculating these and similar results given in this chapter, see Higasi, K.; Baba, H.; Rembaum, A. *Quantum Organic Chemistry*, Interscience, NY, ***1965***. For values of calculated orbital energies and bond orders for many conjugated molecules, see Coulson, C.A.; Streitwieser, Jr., A. *Dictionary of* π *Electron Calculations*, W.H. Freeman, San Francisco, ***1965***.

[27]Aihara, J-i. *J. Chem. Soc. Perkin Trans 2* ***1996***, 2185.

Isodesmic and homodesmotic reactions are frequently used for the study of aromaticity from the energetic point of view.[28] However, the energy of the reactions used experimentally or in calculations may reflects only the relative aromaticity of benzene and not its absolute aromaticity. A new homodesmotic reactions based on radical systems predict an absolute aromaticity of 29.13 kcal mol^{-1} (121.9 kJ mol^{-1}) for benzene and an absolute antiaromaticity of 40.28 kcal mol^{-1} (168.5 kJ mol^{-1}) for cyclobutadiene at the MP4(SDQ)/6-31G-(*d*,*p*) level.[29]

We might expect that in compounds exhibiting delocalization the bond distances would lie between the values gives in Table 1.5. This is certainly the case for benzene, since the carbon–carbon bond distance is 1.40 Å,[30] which is between the 1.48 Å for an sp^2–sp^2 C—C single bond and the 1.32 Å of the sp^2–sp^2 C=C double bond.[31]

Kinds of Molecules That Have Delocalized Bonds

There are four main types of structure that exhibit delocalization:

1. *Double (or Triple) Bonds in Conjugation.*[32] The double bonds in benzene are conjugated, of course, but the conjugation exists in acyclic molecules such as butadiene. In the molecular orbital picture (Fig. 2.3), the overlap of four orbitals gives two bonding orbitals that contain the four electrons and two vacant antibonding orbitals. It can be seen that each orbital has one more node than the one of next lower energy. The energies of the four orbitals are (lowest to highest): $\alpha + 1.618\beta$, $\alpha + 0.618\beta$, $\alpha - 0.618\beta$, and $\alpha - 1.618\beta$; hence the total energy of the two occupied orbitals is $4\alpha + 4.472\beta$. Since the energy of two isolated double bonds is $4\alpha + 4\beta$, the resonance energy by this calculation is 0.472β.

   In the resonance picture, these structures are considered to contribute:

$$\underset{\mathbf{6}}{CH_2{=}CH{-}CH{=}CH_2} \leftrightarrow \underset{\mathbf{7}}{\overset{\oplus}{C}H_2{-}CH{=}CH{-}\overset{\ominus}{C}H_2} \leftrightarrow \underset{\mathbf{8}}{\overset{\ominus}{C}H_2{-}CH{=}CH{-}\overset{\oplus}{C}H_2}$$

[28]Hehre, W.J.; Ditchfield, R.; Radom, L.; Pople, J.A. *J. Am. Chem.Soc.* ***1970***, *92*, 4796; Hehre, W.J.; Radom, L.; Pople, J.A. *J. Am. Chem. Soc.* ***1971***, *93*, 289; George, P.; Trachtman, M.; Bock, C.W.; Brett, A.M. *Theor. Chim. Acta*, ***1975***, *38*, 121; George, P.; Trachtman, M.; Bock, C.W.; Brett, A.M. *J. Chem. Soc. Perkin Trans. 2* ***1976***, 1222; George, P.; Trachtman, M.; Brett, A.M. Bock, C.W.; *Tetrahedron* ***1976***, *32*, 317; George, P.; Trachtman, M.; Brett, A.M.; Bock, C.W. *J. Chem. Soc. Perkin Trans. 2* ***1977***, 1036.

[29]Suresh, C.H.; Koga, N. *J. Org. Chem.* ***2002***, *67*, 1965.

[30]Bastiansen, O.; Fernholt, L.; Seip, H.M.; Kambara, H.; Kuchitsu, K. *J. Mol. Struct.* ***1973***, *18*, 163; Tamagawa, K.; Iijima, T.; Kimura, M. *J. Mol. Struct.* ***1976***, *30*, 243.

[31]The average C—C bond distance in aromatic rings is 1.38 Å: Allen, F.H.; Kennard, O.; Watson, D.G.; Brammer, L.; Orpen, A.G.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* ***1987***, p. S8.

[32]For reviews of conjugation in open-chain hydrocarbons, see Simmons, H.E. *Prog. Phys. Org. Chem.* ***1970***, *7*, 1; Popov, E.M.; Kogan, G.A. *Russ. Chem. Rev.* ***1968***, *37*, 119.

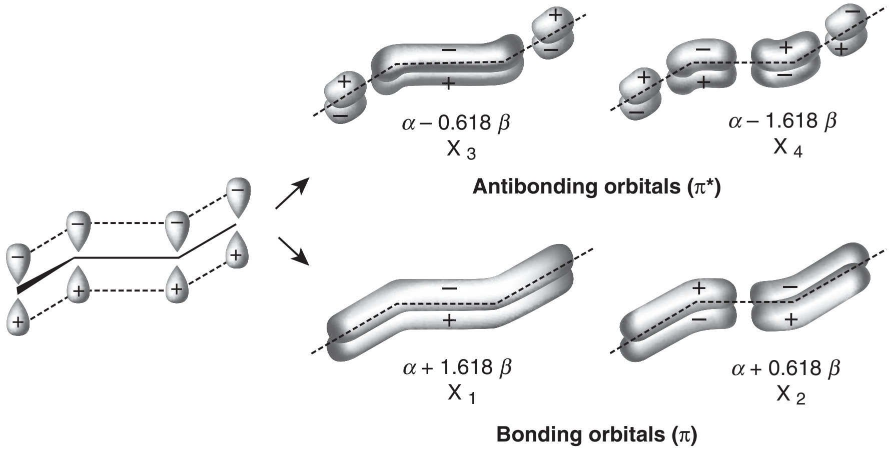


Fig. 2.3. The four π-orbitals of butadiene, formed by overlap of four *p* orbitals.

In either picture, the bond order of the central bond should be >1 and that of the other carbon–carbon bonds <2, although neither predicts that the three bonds have equal electron density. Molecular-orbital bond orders of 1.894 and 1.447 have been calculated.[33]

The existence of delocalization in butadiene and similar molecules has been questoned. The bond lengths in butadiene are 1.34 Å for the double bonds and 1.48 Å for the single bond.[34] Since the typical single-bond distance of a bond that is not adjacent to an unsaturated group is 1.53 Å (p. 26), it has been argued that the shorter single bond in butadiene provides evidence for resonance. However, this shortening can also be explained by hybridization changes (see p. 26); and other explanations have also been offered.[35] Resonance energies for butadienes, calculated from heats of combustion or hydrogenation, are only about 4 kcal mol^{-1} (17 kJ mol^{-1}), and these values may not be entirely attributable to resonance. Thus, a calculation from heat of atomization data gives a resonance energy of 4.6 kcal mol^{-1} (19 kJ mol^{-1}) for *cis*-1,3-pentadiene, and −0.2 kcal mol^{-1} (−0.8 kJ mol^{-1}), for 1,4-pentadiene. These two compounds, each of which possesses two double bonds, two C—C single bonds, and eight C—H bonds, would seem to offer as similar a comparison as we could make of a conjugated with a nonconjugated compound, but they are nevertheless not strictly comparable. The former has three sp^3 C—H and five sp^2 C—H bonds, while the latter has two and six, respectively. Also, the two single C—C bonds

[33]Coulson, C.A. *Proc. R. Soc. London, Ser. A* ***1939***, *169*, 413.

[34]Marais, D.J.; Sheppard, N.; Stoicheff, B.P. *Tetrahedron* ***1962***, *17*, 163.

[35]Bartell, L.S. *Tetrahedron* ***1978***, *34*, 2891, *J. Chem. Educ.* ***1968***, *45*, 754; Wilson, E.B. *Tetrahedron* ***1962***, *17*, 191; Hughes, D.O. *Tetrahedron* ***1968***, *24*, 6423; Politzer, P.; Harris, D.O. *Tetrahedron* ***1971***, *27*, 1567.

of the 1,4-diene are both sp^2–sp^3 bonds, while in the 1,3-diene, one is sp^2–sp^3 and the other sp^2–sp^2. Therefore, it may be that some of the already small value of 4 kcal mol^{-1} (17 kJ mol^{-1}) is not resonance energy but arises from differing energies of bonds of different hybridization.[36]

Although bond distances fail to show it and the resonance energy is low, the fact that butadiene is planar[37] shows that there is some delocalization, even if not as much as previously thought. Similar delocalization is found in other conjugated systems (e.g., C=C–C=O[38] and C=C–C=N), in longer systems with three or more multiple bonds in conjugation, and where double or triple bonds are conjugated with aromatic rings. Diynes such as 1,3-butadiyne (**9**) are another example of conjugated molecules. Based on calculations, Rogers et al. reported that the conjugation stabilization of 1,3-butadiyne is zero.[39] Later calculations concluded that consideration of hyperconjugative interactions provides a more refined measure of conjugative stabilization.[40] When this measure is used, the conjugation energies of the isomerization and hydrogenation reactions considered agree with a conjugative stabilization of 9.3 (0.5 kcal mol^{-1} for diynes and 8.2 (0.1 kcal mol^{-1} for dienes.

H–C≡C–C≡C–H

9

2. *Double (or Triple) Bonds in Conjugation with a p Orbital on an Adjacent Atom.* Where a *p* orbital is on an atom adjacent to a double bond, there are three parallel *p* orbitals that overlap. As previously noted, it is a general rule that the overlap of *n* atomic orbitals creates *n* molecular orbitals, so overlap of a *p* orbital with an adjacent double bond gives rise to three new orbitals, as

[36] For negative views on delocalization in butadiene and similar molecules, see Dewar, M.J.S.; Gleicher, G.J. *J. Am. Chem. Soc.* ***1965***, *87*, 692; Brown, M.G. *Trans. Faraday Soc.* ***1959***, *55*, 694; Somayajulu, G.R. *J. Chem. Phys.* ***1959***, *31*, 919; Mikhailov, B.M. *J. Gen. Chem. USSR* ***1966***, *36*, 379. For positive views, see Miyazaki, T.; Shigetani, T.; Shinoda, H. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 1491; Berry, R.S. *J. Chem. Phys.* ***1962***, *30*, 936; Kogan, G.A.; Popov, E.M. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1964***, 1306; Altmann, J.A.; Reynolds, W.F. *J. Mol. Struct.*, ***1977***, *36*, 149. In general, the negative argument is that resonance involving excited structures, such as **7** and **8**, is unimportant. See rule 6 on p. $$$. An excellent discussion of the controversy is found in Popov, E.M.; Kogan, G.A. *Russ. Chem. Rev.* ***1968***, *37*, 119, pp. 119–124.

[37] Marais, D.J.; Sheppard, N.; Stoicheff, B.P. *Tetrahedron* ***1962***, *17*, 163; Fisher, J.J.; Michl, J. *J. Am. Chem. Soc.* ***1987***, *109*, 1056; Wiberg, K.B.; Rosenberg, R.E.; Rablen, P.R. *J. Am. Chem. Soc.* ***1991***, *113*, 2890.

[38] For a treatise on C=C–C=O systems, see Patai, S.; Rappoport, Z. *The Chemistry of Enones*, two parts; Wiley, NY, ***1989***.

[39] Rogers, D.W.; Matsunaga, N.; Zavitsas, A.A.; McLafferty, F.J.; Liebman, J.F. *Org. Lett.* ***2003***, *5*, 2373; Rogers, D.W.; Matsunaga, N.; McLafferty, F.J.; Zavitsas, A.A.; Liebman, J.F. *J. Org. Chem.* ***2004***, *69*, 7143.

[40] Jarowski, P.D.; Wodrich, M.D.; Wannere, C.S.; Schleyer, P.v.R.; Houk, K.N. *J. Am. Chem. Soc.* ***2004***, *126*, 15036.

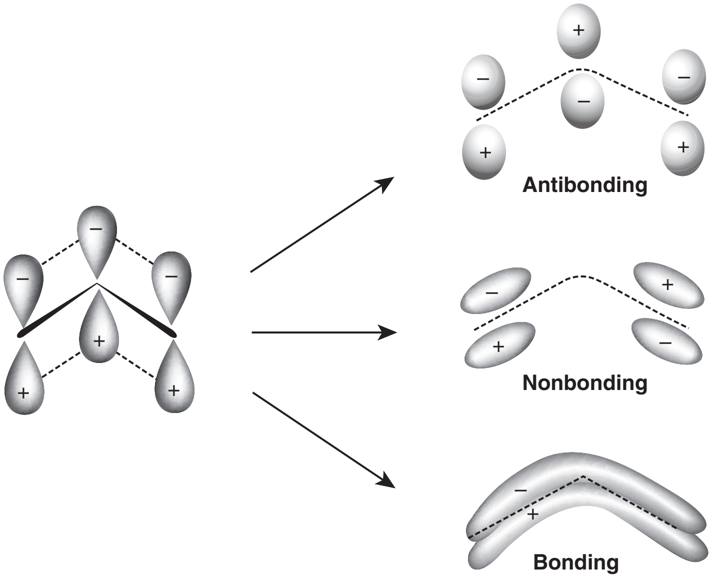
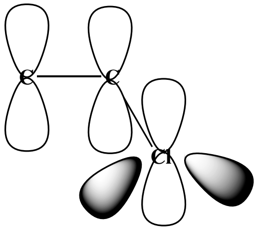


Fig. 2.4. The three orbitals of an allylic carbon, formed by overlap of three *p* orbitals.

shown in Fig. 2.4. The middle orbital is a *nonbonding orbital* of zero bonding energy. The central carbon atom does not participate in the nonbonding orbital.

There are three cases: the original *p* orbital may have contained two, one, or no electrons. Since the original double bond contributes two electrons, the total number of electrons accommodated by the new orbitals is four, three, or two. A typical example of the first situation is vinyl chloride $CH_2{=}CH{-}Cl$. Although the *p* orbital of the chlorine atom is filled, it still overlaps with the double bond (see **10**). The four electrons occupy the two molecular orbitals of lowest energies. This is our first example of resonance involving overlap between unfilled orbitals and a *filled* orbital. Canonical forms for vinyl chloride are shown in **11**.



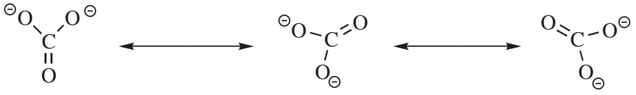
10

$$CH_2{=}CH{-}Cl \longleftrightarrow \overset{\ominus}{C}H_2{-}CH{=}\overset{\oplus}{Cl}$$

11

Any system containing an atom that has an unshared pair and that is directly attached to a multiple-bond atom can show this type of delocalization.

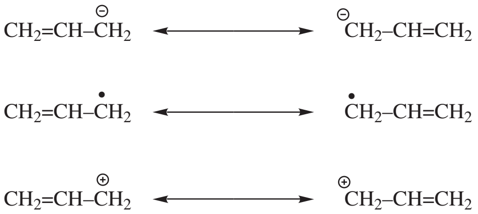
Another example is the carbonate ion:



The bonding in allylic carbanions, for example, $CH_2{=}CH{-}CH_2^-$, is similar.

The other two cases, where the original *p* orbital contains only one or no electron, are generally found only in free radicals and cations, respectively. Allylic free radicals have one electron in the nonbonding orbital. In allylic cations this orbital is vacant and only the bonding orbital is occupied. The orbital structures of the allylic carbanion, free radical, and cation differ from each other, therefore, only in that the nonbonding orbital is filled, half-filled, or empty. Since this is an orbital of zero bonding energy, it follows that the bonding π energies of the three species relative to electrons in the 2*p* orbitals of free atoms are the same. The electrons in the nonbonding orbital do not contribute to the bonding energy, positively or negatively.[41]

By the resonance picture, the three species may be described as having double bonds in conjugation with, respectively, an unshared pair, an unpaired electron, and an empty orbital as in the allyl cation **12** (see Chapter 5).



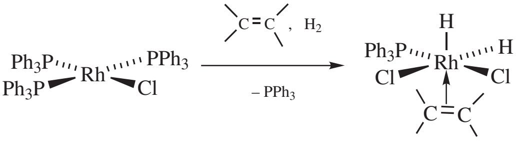
12

3. *π-Allyl and Other η-Complexes*. In the presence of transition metals, delocalized cations are stabilized by donating electrons to the metal.[42] In a C—Metal bond, such as $H_3C{-}Fe$, the carbon donates (shares) one electron with them metal, and is considered to be a one-electron donor. With a π-bond, such as that found in ethylene, both electrons can be donated to the metal to

[41]It has been contended that here too, as with the benzene ring (Ref. 6), the geometry is forced upon allylic systems by the σ framework, and not the π system: Shaik, S.S.; Hiberty, P.C.; Ohanessian, G.; Lefour, J. *Nouv. J. Chim.*, ***1985***, *9*, 385. It has also been suggested, on the basis of ab initio calculations, that while the allyl cation has significant resonance stabilization, the allyl anion has little stabilization: Wiberg, K.B.; Breneman, C.M.; LePage, T.J. *J. Am. Chem. Soc.* ***1990***, *112*, 61.

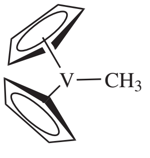
[42]Crabtree, R.H. *The Organometallic Chemistry of the Transition Metals*, Wiley-Interscience, NY, ***2005***; Hill, A.F. *Organotransition Metal Chemistry*, Wiley Interscience, Canberra, ***2002***.

form a complex such as **14** by reaction of Wilkinson's catalyst (**13**) with an alkene and hydrogen gas,[43] and the π-bond is considered to be a two-electron donor. In these two cases, the electron donating ability of the group coordinated to the metal (the ligand) is indicated by terminology η^1, η^2, η^3, and so on, for a one-, two-, and three-electron donor, respectively.



13 **14**

Wilkinson's catalyst



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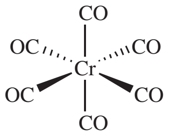

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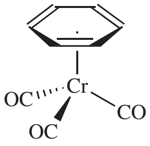

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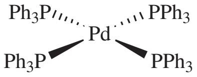


18

Ligands can therefore be categorized as η-ligands according to their electron donation to the metal. A hydrogen atom (as in **14**) or a halogen ligand (as in **13**) are η^1 ligands and an amine (NR_3), a phosphine (PR_3, as in **13**, **14**, and **18**), CO (as in **16** or **17**), an ether (OR_2) or a thioether (SR_2) are η^2 ligands. Hydrocarbon ligands include alkyl (as the methyl in **15**) or aryl with a C—metal bond (η^1), alkenes or carbenes (η^2, see p. 116), π-allyl (η^3), conjugated dienes such as 1,3-butadiene (η^4), cyclopentadienyl (η^5, as in **15** and see p 63), and arenes or benzene (η^6).[44] Note that in the formation of **14** from **13**, the two electron donor alkene displaces a two-electron donor phosphine. Other typical complexes include chromium hexacarbonyl $Cr(CO)_6$ (**16**), with six η^2-CO ligands; η^6-$C_6H_6Cr(CO)_3$ (**18**), and *tetrakis*-triphenylphosphinopalladium (0), **17**, with four η^2-phosphine ligands.

In the context of this section, the electron-delocalized ligand π-allyl (**12**) is an η^3 donor and it is well known that allylic halides react with $PdCl_2$ to form a *bis*-η^3-complex **19** (see the 3D model **20**).[45] Complexes, such as **19**, react with nucleophiles to give the corresponding coupling product (**10–60**).[46] The

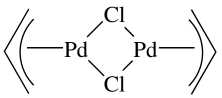
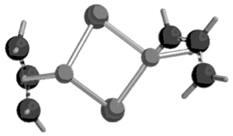
[43]Jardine, F.H., Osborn, J.A.; Wilkinson, G.; Young, G.F. *Chem. Ind. (London)* ***1965***, 560; Imperial Chem. Ind. Ltd., *Neth. Appl. 6,602,062* [*Chem. Abstr., 66*: 10556y ***1967***]; Bennett, M.A.; Longstaff, P.A. *Chem. Ind.* ***1965***, 846.

[44]Davies, S.G. *Organotransition Metal Chemistry*, Pergamon, Oxford, ***1982***, p. 4.

[45]Trost, B.M.; Strege, P.E.; Weber, L.; Fullerton, T.J.; Dietsche, T.J. *J. Am. Chem. Soc.* ***1978***, *100*, 3407.

[46]Trost, B.M.; Weber, L.; Strege, P.E.; Fullerton, T.J.; Dietsche, T.J. *J. Am. Chem. Soc.*, ***1978*** *100*, 3416.

reaction of allylic acetates or carbons and a catalytic amount of palladium (0) compounds also lead to an η^3-complex that can react with nucleophiles.[47]

$[PdCl(\pi\text{-allyl})]_2 = [PdCl(\eta^3C_3H_5)]_2$ =  = 

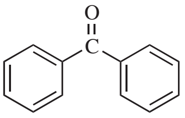
19 **20**

4. *Hyperconjugation*. The type of delocalization called *hyperconjugation*, is discussed on p. 95.

   We will find examples of delocalization that cannot be strictly classified as belonging to any of these types.

Cross Conjugation[48]

In a cross-conjugated compound, three groups are present, two of which are not conjugated with each other, although each is conjugated with the third. Some examples[49] are benzophenone (**21**), triene **22** and divinyl ether **23**. Using the



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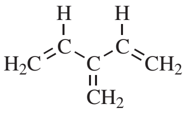

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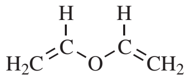


23

molecular-orbital method, we find that the overlap of six *p* orbitals in **22** gives six molecular orbitals, of which the three bonding orbitals are shown in Fig. 2.5, along with their energies. Note that two of the carbon atoms do not participate in the $\alpha + \beta$ orbital. The total energy of the three occupied orbitals is $6\alpha + 6.900\beta$, so the resonance energy is 0.900β. Molecular-orbital bond orders are 1.930 for the C-1,C-2 bond, 1.859 for the C-3,C-6 bond and 1.363 for the C-2,C-3 bond.[49] Comparing these values with those for butadiene (p. 39), we see that the C-1,C-2 bond contains more and the C-3,C-6 bond less double-bond character than the double bonds in butadiene. The resonance picture supports this conclusion, since each C-1,C-2 bond is double in three of the five canonical forms, while the C-3,C-6 bond is double in only one. In most cases, it is easier to treat cross-conjugated

[47]Melpolder, J.B.; Heck, R.F. *J. Org. Chem.* ***1976***, *41*, 265; Trost, B.M.; Verhoeven, T.R. *J. Am. Chem. Soc.*, ***1976***, *98*, 630; ***1978***, *100*, 3435; Takahashi, K.; Miyake, A.; Hata, G. *Bull Chem. Soc. Jpn.* ***1970***, *45*, 230,1183; Trost, B.M.; Verhoeven, T.R. *J. Org. Chem.* ***1976***, *41*, 3215; Trost, B.M.; Verhoeven, T.R. *J. Am. Chem. Soc.* ***1980***, *102*, 4730.

[48]For a discussion, see Phelan, N.F.; Orchin, M. *J. Chem. Educ.* ***1968***, *45*, 633.

[49]Compound **22** is the simplest of a family of cross-conjugated alkenes, called dendralenes. For a review of these compounds, see Hopf, H. *Angew. Chem. Int. Ed.* ***1984***, *23*, 948.

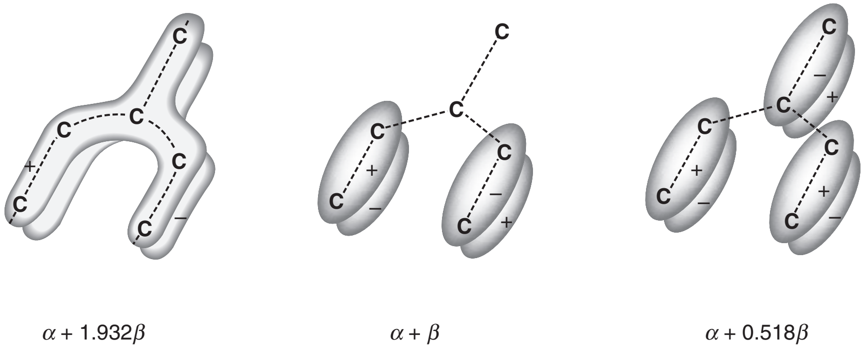
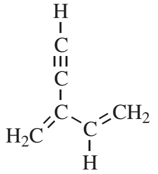


Fig. 2.5. The three bonding orbitals of 3-methylelene-1,4-pentadiene (**22**).

molecules by the molecular-orbital method than by the valence-bond method.



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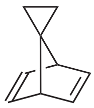


26

One consequence of this phenomenon is that the cross-conjugated C=C unit has a slightly longer bond length that the noncross conjugated bond. In **24**, for example, the cross-conjugated bond is ~0.01 Å longer.[50] The conjugative effect of a C=C or C≡C unit can be measured. An ethenyl substituent on a conjugated enone contributes 4.2 kcal mol^{-1} and an ethynyl substituent has a more variable effect but contributes ~2.3 kcal mol^{-1}.[51]

The phenomenon of homoconjugation is related to cross-conjugation in that there are C=C units in close proximity, but not conjugated one to the other. Homoconjugation arises when the termini of two orthogonal π-systems are held in close proximity by being linked by a spiro-tetrahedral carbon atom.[52] Spiro[4.4]nonatetraene (**25**)[53] is an example and it known that the HOMO (p. 1208) of **25** is raised relative to cyclopentadiene, whereas the LUMO is unaffected[54] Another example

[50]Trætteberg, M.; Hopf, H. *Acta Chem. Scand. B* ***1994***, *48*, 989.

[51]Trætteberg, M.; Liebman, J.F.; Hulce, M.; Bohn, A.A.; Rogers, D.W. *J. Chem. Soc. Perkin Trans. 2* ***1997***, 1925.

[52]Simons, H.E.; Fukunaga, R. *J. Am. Chem. Soc.* ***1967***, *89*, 5208; Hoffmann, R.; Imamura, A.; Zeiss, G.D. *J. Am. Chem. Soc.* ***1967***, *89*, 5215; Durr, H.; Gleiter, R. *Angew. Chem. Int. Ed.* ***1978***, *17*, 559.

[53]For the synthesis of this molecule, see Semmelhack, M.F.; Foos, J.S.; Katz, S. *J. Am. Chem. Soc.* ***1973***, *95*, 7325.

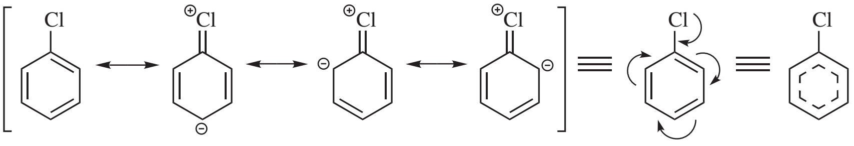
[54]Raman, J.V.; Nielsen, K.E.; Randall, L.H.; Burke, L.A.; Dmitrienko, G.I. *Tetrahedron Lett.* ***1994***, *35*, 5973.

is **26**, where there are bond length distortions caused by electronic interactions between the unsaturated bicyclic moiety and the cyclopropyl moiety.[55] It is assumed that cyclopropyl homoconjugation is responsible for this effect.

The Rules of Resonance

We have seen that one way of expressing the actual structure of a molecule containing delocalized bonds is to draw several possible structures and to assume that the actual molecule is a hybrid of them. These canonical forms have no existence except in our imaginations. The molecule does *not* rapidly shift between them. It is *not* the case that some molecules have one canonical form and some another. All the molecules of the substance have the same structure. That structure is always the same all the time and is a weighted average of all the canonical forms. In drawing canonical forms and deriving the true structures from them, we are guided by certain rules, among them the following:

1. All the canonical forms must be bona fide Lewis structures (see p. 14). For example, none of them may have a carbon with five bonds.
2. The positions of the nuclei must be the same in all the structures. This means that when we draw the various canonical forms, all we are doing is putting in the *electrons* in different ways. For this reason, shorthand ways of representing resonance are easy to devise:



27 **28**

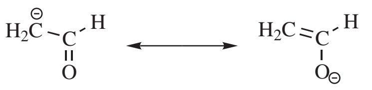
The resonance interaction of chlorine with the benzene ring can be represented as shown in **27** or **28** and both of these representations have been used in the literature to save space. However, we will not use the curved-arrow method of **27** since arrows will be used in this book to express the actual movement of electrons in reactions. We will use representations like **28** or else write out the canonical forms. The convention used in dashed-line formulas like **28** is that bonds that are present in all canonical forms are drawn as solid lines while bonds that are not present in all forms are drawn as dashed lines. In most resonance, σ bonds are not involved, and only the π or unshared electrons are put in, in different ways. This means that if we write one canonical form for a molecule, we can then write the others by merely moving π and unshared electrons.

[55]Haumann, T.; Benet-Buchholz, J.; Klärner, F.-G.; Boese, R. *Liebigs Ann. Chem.* ***1997***, 1429.

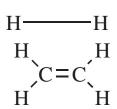
3. All atoms taking part in the resonance, that is, covered by delocalized electrons, must lie in a plane or nearly so (see p. 48). This, of course, does not apply to atoms that have the same bonding in all the canonical forms. The reason for planarity is maximum overlap of the *p* orbitals.
4. All canonical forms must have the same number of unpaired electrons. Thus $^{\bullet}CH_2{-}CH{=}CH{-}CH_2{\bullet}$ is not a valid canonical form for butadiene.
5. The energy of the actual molecule is lower than that of any form, obviously. Therefore, delocalization is a stabilizing phenomenon.[56]
6. All canonical forms do not contribute equally to the true molecule. Each form contributes in proportion to its stability, the most stable form contributing most. Thus, for ethylene, the form $^{+}CH_2{-}CH_2^{-}$ has such a high energy compared to $CH_2{=}CH_2$ that it essentially does not contribute at all. We have seen the argument that such structures do not contribute even in such cases as butadiene.[36] Equivalent canonical forms, such as **1** and **2**, contribute equally. The greater the number of significant structures that can be written and the more nearly equal they are, the greater the resonance energy, other things being equal.

It is not always easy to decide relative stabilities of imaginary structures; the chemist is often guided by intuition.[57] However, the following rules may be helpful:

a. Structures with more covalent bonds are ordinarily more stable than those with fewer (cf. **6** and **7**).
b. Stability is decreased by an increase in charge separation. Structures with formal charges are less stable than uncharged structures. Structures with more than two formal charges usually contribute very little. An especially unfavorable type of structure is one with two like charges on adjacent atoms.
c. Structures that carry a negative charge on a more electronegative atom are more stable than those in which the charge is on a less electronegative atom. Thus, **30** is more stable than **29**. Similarly, positive charges are best carried on atoms of low electronegativity.



29 **30**



31

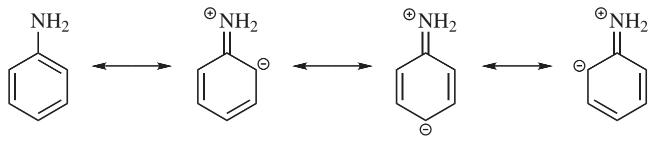
d. Structures with distorted bond angles or lengths are unstable, for example, the structure **31** for ethane.

[56]It has been argued that resonance is not a stabilizing phenomenon in all systems, especially in acyclic ions: Wiberg, K.B. *Chemtracts: Org. Chem.* ***1989***, *2*, 85. See also, Siggel, M.R.; Streitwieser Jr., A.; Thomas, T.D. *J. Am. Chem. Soc.* ***1988***, *110*, 8022; Thomas, T.D.; Carroll, T.X.; Siggel, M.R. *J. Org. Chem.* ***1988***, *53*, 1812.

[57]A quantitative method for weighting canonical forms has been proposed by Gasteiger, J.; Saller, H. *Angew. Chem. Int. Ed.* ***1985***, *24*, 687.

The Resonance Effect

Resonance always results in a different distribution of electron density than would be the case if there were no resonance. For example, if **32** were the actual structure of aniline, the two unshared electrons of the nitrogen would reside



32

entirely on that atom. The structure of **32** can be represented as a hybrid that includes contributions from the canonical forms shown, indicating that the electron density of the unshared pair does not reside entirely on the nitrogen, but is spread over the ring. This decrease in electron density at one position (and corresponding increase elsewhere) is called the *resonance* or *mesomeric effect*. We loosely say that the NH_2 contributes or donates electrons to the ring by a resonance effect, although no actual contribution takes place. The "effect" is caused by the fact that the electrons are in a different place from that we would expect if there were no resonance. In ammonia, where resonance is absent, the unshared pair *is* located on the nitrogen atom. As with the field effect (p. 20), we think of a certain molecule (in this case ammonia) as a substrate and then see what happens to the electron density when we make a substitution. When one of the hydrogen atoms of the ammonia molecule is replaced by a benzene ring, the electrons are "withdrawn" by the resonance effect, just as when a methyl group replaces a hydrogen of benzene, electrons are "donated" by the the field effect of the methyl. The idea of donation or withdrawal merely arises from the comparison of a compound with a closely related one or a real compound with a canonical form.

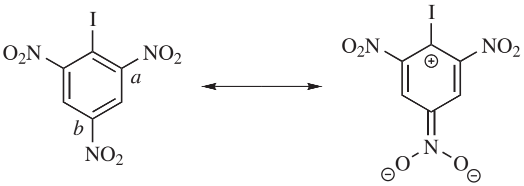
Steric Inhibition of Resonance and the Influences of Strain

Rule 3 states that all the atoms covered by delocalized electrons must lie in a plane or nearly so. Many examples are known where resonance is reduced or prevented because the atoms are sterically forced out of planarity.

Bond lengths for the *o*- and *p*-nitro groups in picryl iodide are quite different.[58] Distance *a* in **33** is 1.45 Å, whereas *b* is 1.35 Å. This phenomenon can be explained if the oxygens of the *p*-nitro group are in the plane of the ring and thus in resonance with it, so that *b* has partial double-bond character, while the oxygens of the *o*-nitro

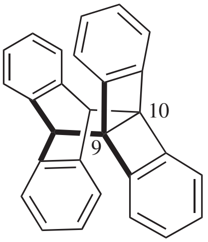
[58]Wepster, B.M. *Prog. Stereochem.* ***1958***, *2*, 99, p. 125. For another example of this type of steric inhibition of resonance, see Exner, O.; Folli, U.; Marcaccioli, S.; Vivarelli, P. *J. Chem. Soc. Perkin Trans. 2* ***1983***, 757.

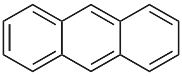
groups are forced out of the plane by the large iodine atom.

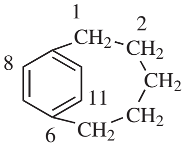


33

The Dewar-type structure for the central ring of the anthracene system in **34** is possible only because the 9,10 substituents prevent the system from being planar.[59] **34** is the actual structure of the molecule and is not in resonance with forms like **35**, although in anthracene itself, Dewar structures and structures like **35** both contribute. This is a consequence of rule 2 (p. 46). In order for a **35**-like structure to contribute to resonance in **34**, the nuclei would have to be in the same positions in both forms.







34 **35** **36**

Even the benzene ring can be forced out of planarity.[60] In [5]paracyclophane (**36**),[61] the presence of a short bridge (this is the shortest para bridge known for a benzene ring) forces the benzene ring to become boat-shaped. The parent **36** has so far not proven stable enough for isolation, but a UV spectrum was obtained and showed that the benzene ring was still aromatic, despite the distorted ring.[62] The 8,11-dichloro analog of **36** is a stable solid, and X-ray diffraction showed

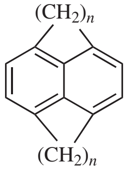
[59]Applequist, D.E.; Searle, R. *J. Am. Chem. Soc.* ***1964***, *86*, 1389.

[60]For a review of planarity in aromatic systems, see Ferguson, G.; Robertson, J.M. *Adv. Phys. Org. Chem.* ***1963***, *1*, 203.

[61]For a monograph, see Keehn, P.M.; Rosenfeld, S.M. *Cyclophanes*, 2 vols., Academic Press, NY, ***1983***. For reviews, see Bickelhaupt, F. *Pure Appl. Chem.* ***1990***, *62*, 373; Vögtle, F.; Hohner, G. *Top. Curr. Chem.* ***1978***, *74*, 1; Cram, D.J.; Cram, J.M. *Acc. Chem. Res.* ***1971***, *4*, 204; Vögtle, F.; Neumann, P. reviews in *Top. Curr. Chem.* ***1983***, *113*, 1; ***1985***, *115*, 1.

[62]Jenneskens, L.W.; de Kanter, F.J.J.; Kraakman, P.A.; Turkenburg, L.A.M.; Koolhaas, W.E.; de Wolf, W.H.; Bickelhaupt, F.; Tobe, Y.; Kakiuchi, K.; Odaira, Y. *J. Am. Chem. Soc.* ***1985***, *107*, 3716. See also Tobe, Y.; Kaneda, T.; Kakiuchi, K.; Odaira, Y. *Chem. Lett.* ***1985***, 1301; Kostermans, G.B.M.; de Wolf, W.E.; Bickelhaupt, F. *Tetrahedron Lett.* ***1986***, *27*, 1095; van Zijl, P.C.M.; Jenneskens, L.W.; Bastiaan, E.W.; MacLean, C.; de Wolf, W.E.; Bickelhaupt, F. *J. Am. Chem. Soc.* ***1986***, *108*, 1415; Rice, J.E.; Lee, T.J.; Remington, R.B.; Allen, W.D.; Clabo Jr., D.A.; Schaefer III, H.F. *J. Am. Chem. Soc.* ***1987***, *109*, 2902.

that the benzene ring is boat-shaped, with one end of the boat bending ~27° out of the plane, and the other ~12°.[63] This compound too is aromatic, as shown by UV and NMR spectra. [6]Paracyclophanes are also bent,[64] but in [7]paracyclophanes the bridge is long enough so that the ring is only moderately distorted. Similarly, [*n,m*]paracyclophanes (**37**), where *n* and *m* are both 3 or less (the smallest yet prepared is [2.2]paracyclophane), have bent (boat-shaped) benzene rings. All these compounds have properties that depart significantly from those of ordinary benzene compounds. Strained paracyclophanes exhibit both π- and σ-strain, and the effect of the two types of strain on the geometry is approximately additive.[65] In "belt" cyclophane **38**,[66] the molecule has a pyramidal structure with C_3 symmetry rather than the planar structure found in [18]-annulene. 1,8-Dioxa[8](2,70-pyrenophane (**39**)[67] is another severely distorted aromatic hydrocarbon, in which the bridge undergoes rapid pseudo-rotation (p. 212). A recent study showed that despite substantial changes in the hybridization of carbon atoms involving changes in the σ-electron structure of pyrenephane, such as **39**, the aromaticity of the system decreases slightly and regularly upon increasing the bend angle θ from 0 to 109.2°.[68] Heterocyclic paracyclophane analogs have been prepared, such as the report of [2.*n*](2,5)pyridinophanes.[69]



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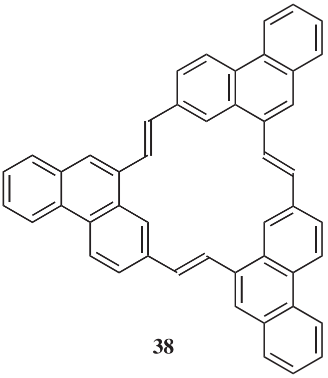

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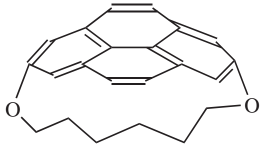


39

[63]Jenneskens, L.W.; Klamer, J.C.; de Boer, H.J.R.; de Wolf, W.H.; Bickelhaupt, F.; Stam, C.H. *Angew. Chem. Int. Ed.* ***1984***, *23*, 238.

[64]See, for example, Liebe, J.; Wolff, C.; Krieger, C.; Weiss, J.; Tochtermann, W. *Chem. Ber.* ***1985***, *118*, 4144; Tobe, Y.; Ueda, K.; Kakiuchi, K.; Odaira, Y.; Kai, Y.; Kasai, N. *Tetrahedron* ***1986***, *42*, 1851.

[65]Stanger, A.; Ben-Mergui, N.; Perl, S. *Eur. J. Org. Chem.* ***2003***, 2709.

[66]Meier, H.; Müller, K. *Angew. Chem. Int. Ed.*, ***1995***, *34*, 1437.

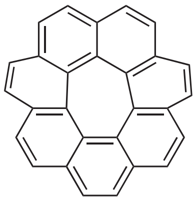
[67]Bodwell, G.J.; Bridson, J.N.; Houghton, T.J.; Kennedy, J.W.J.; Mannion, M.R. *Angew. Chem. Int. Ed.*, ***1996***, *35*, 1320.

[68]Bodwell, G.J.; Bridson, J.N.; Cyranski, M.K.; Kennedy, J.W.J.; Krygowski, T.M.; Mannion, M.R.; Miller, D.O. *J. Org. Chem.* ***2003***, *68*, 2089; Bodwell, G.J.; Miller, D.O.; Vermeij, R.J. *Org. Lett.* ***2001***, *3*, 2093

[69]Funaki, T.; Inokuma, S.; Ida, H.; Yonekura, T.; Nakamura, Y.; Nishimura, J. *Tetrahedron Lett.* ***2004***, *45*, 2393.

There are many examples of molecules in which benzene rings are forced out of planarity, including 7-circulene (**40**),[70] 9,8-diphenyltetrabenz[*a,c,h,j*]anthracene (**41**),[71] and **42**[72] (see also p. 230). These have been called tormented aromatic systems.[73] The "record" for twisting an aromatic π-electron system appears to be 9,10,11,12,13,14,15,16-octaphenyldibenzo[*a,c*]naphthacene (**43**),[74] which has an end-to-end twist of 105°. This is >1.5 times as great as that observed in any previous polyaromatic hydrocarbon.

Perchlorotriphenylene has been reported in the literature and said to show severe molecular twisting, however, recent work suggests this molecule has not actually been isolated with perchlorofluorene-9-spirocyclohexa-2′,5′-diene being formed instead.[75] The X-ray structure of the linear [3]phenylene (benzo[3,4]cyclobuta-[1,2-b]biphenylene, **44**) has been obtained, and it shows a relatively large degree of bond alternation while the center distorts to a cyclic bis-allyl frame.[76]



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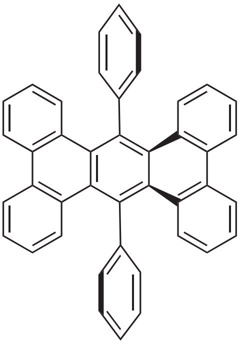

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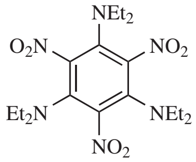

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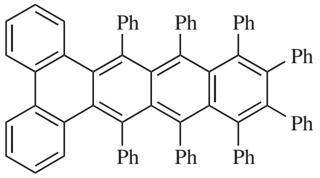


43

[70]Yamamoto, K.; Harada, T.; Okamoto, Y.; Chikamatsu, H.; Nakazaki, M.; Kai, Y.; Nakao, T.; Tanaka, M.; Harada, S.; Kasai, N. *J. Am. Chem. Soc.* ***1988***, *110*, 3578.

[71]Pascal, Jr., R.A.; McMillan, W.D.; Van Engen, D.; Eason, R.G. *J. Am. Chem. Soc.* ***1987***, *109*, 4660.

[72]Chance, J.M.; Kahr, B.; Buda, A.B.; Siegel, J.S. *J. Am. Chem. Soc.* ***1989***, *111*, 5940.

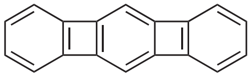
[73]Pascal, Jr., R.A. *Pure Appl. Chem.* ***1993***, *65*, 105.

[74]Qiao, X.; Ho, D.M.; Pascal Jr., R.A. *Angew. Chem. Int. Ed.*, ***1997***, *36*, 1531.

[75]Campbell, M.S.; Humphries, R.E.; Munn, N.M. *J. Org. Chem.* ***1992***, *57*, 641.

[76]Schleifenbaum, A.; Feeder, N.; Vollhardt, K.P.C. *Tetrahedron Lett.* ***2001***, *42*, 7329.

It is also possible to fuse strained rings on benzene, which induces great strain on the benzene ring. In **45**, the benzene ring is compressed by the saturated environment of the tetrahydropyran units. In this case, the strain leads to distortion of the benzene ring in **45** into a *boat* conformation.[77] Benzocyclopropene (**46**) and benzocyclobutene (**47**) are also molecules where the small annellated ring induces great strain on the benzene ring. In these cases, bonds of annellation and those adjacent to it are strained.



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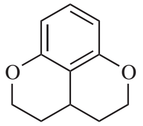

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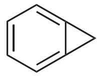

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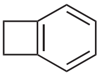


47

Strain-induced bond localization was introduced in 1930 by Mills and Nixon[78] and is commonly referred to as the *Mills–Nixon effect* (see Chapter 11, p. 677). Ortho-fused aromatic compounds, such as **46**, are known as cycloproparenes[79] and are highly strained. Cyclopropabenzene (**46**) is a stable molecule with a strain energy of 68 kcal mol^{-1} (284.5 kJ mol^{-1}).[80] and the annellated bond is always the shortest, although in **47** the adjacent bond is the shortest.[81] In cycloproparenes, there is the expectation of partial aromatic bond localization, with bond length alternation in the aromatic ring.[82] When the bridging units are saturated, the benzene ring current is essentially unchanged, but annelation with one or more cyclobutadieno units disrupts the benzene ring current.[83] The chemistry of the cycloproparenes is dominated by the influence of the high strain energy. When fused to a benzene ring, the bicyclo[1.1.0]butane unit also leads to strain-induced localization of aromatic π-bonds.[84]

*p*π–*d*π Bonding: Ylids

We have mentioned (p. 10) that, in general, atoms of the second row of the Periodic table do not form stable double bonds of the type discussed in Chapter 1

[77]Hall, G.G *J. Chem. Soc. Perkin Trans. 2* ***1993***, 1491.

[78]Mills, W. H.; Nixon, I.G. *J. Chem. Soc.* ***1930***, 2510.

[79]Halton, B. *Chem. Rev.* ***2003***, *103*, 1327; Halton, B. *Chem. Rev.* ***1989***, *89*, 1161, and reviews cited therein.

[80]Billups, W.E.; Chow, W.Y.; Leavell, K.H.; Lewis, E.S.; Margrave, J.L.; Sass, R.L.; Shieh, J.J.; Werness, P.G.; Wood, J.L. *J. Am. Chem. Soc.* ***1973***, *95*, 7878.; Apeloig, Y.; Arad, D. *J. Am. Chem. Soc.* ***1986***, *108*, 3241.

[81]Boese, R.; Bläser, D.; Billups, W.E.; Haley, M.M.; Maulitz, A.H.; Mohler, D.L.; Vollhardt, K.P.C. *Angew. Chem. Int. Ed.*, ***1994***, *33*, 313.

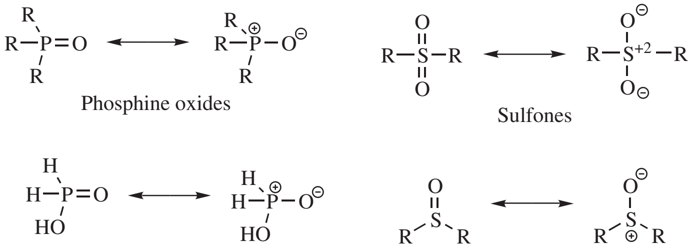
[82]Halton, B. *Pure Appl. Chem.* ***1990***, *62*, 541; Stanger, A. *J. Am. Chem. Soc.* ***1998***, *120*, 12034; Maksić, Z.B.; Eckert-Maksić, M.; Pfeifer, K.-H. *J. Mol. Struct.* ***1993***, *300*, 445; Mó, M.; Yáñez, M.; Eckert-Maksić, M.; Maksić, Z.B. *J. Org. Chem.* ***1995***, *60*, 1638; Eckert-Maksić, M.; Glasovac, Z.; Maksić, Z.B.; Zrinski, I. *J. Mol. Struct. (THEOCHEM)* ***1996***, *366*, 173; Baldridge, K.K.; Siegel, J.S. *J. Am. Chem. Soc.* ***1992***, *114*, 9583.

[83]Soncini, A.; Havenith, R.W.A.; Fowler, P.W.; Jenneskens, L.W.; Steiner, E. *J. Org. Chem.* ***2002***, *67*, 4753

[84]Cohrs, C.; Reuchlein, H.; Musch, P.W.; Selinka, C.; Walfort, B.; Stalke, D.; Christl, M. *Eur. J. Org. Chem.* ***2003***, 901.

(π bonds formed by overlap of parallel *p* orbitals). However, there is another type of double bond that is particularly common for the second-row atoms, sulfur and phosphorus. For example, such a double bond is found in the compound H_2SO_3,

as written on the left. Like an ordinary double bond, this double bond contains one *s* orbital, but the second orbital is not a π orbital formed by overlap of half-filled *p* orbitals; instead it is formed by overlap of a filled *p* orbital from the oxygen with an empty *d* orbital from the sulfur. It is called a *pπ–dπ orbital*.[85] Note that we can represent this molecule by two canonical forms, but the bond is nevertheless localized, despite the resonance. Some other examples of *pπ–dπ* bonding are Nitrogen



Phosphine oxides Sulfones

Hypophorphoros acid Sulfoxides

analogs are known for some of these phosphorus compounds, but they are less stable because the resonance is lacking. For example, amine oxides, analogs of phosphine oxides, can only be written R_3N^+—O^-. The *pπ–dπ* canonical form is impossible since nitrogen is limited to eight outer-shell electrons.

In all the examples given above, the atom that donates the electron pair is oxygen and, indeed, oxygen is the most common such atom. But in another important class of compounds, called *ylids*, this atom is carbon.[86] There are three main types of ylids phosphorus,[87] nitrogen,[88] and sulfur ylids,[89] although

[85]For a monograph, see Kwart, H.; King, K. *d-Orbitals in the Chemistry of Silicon, Phosphorus, and Sulfur*; Springer, NY, ***1977***.

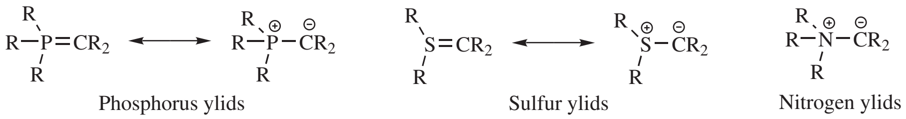
[86]For a monograph, see Johnson, A.W. *Ylid Chemistry*; Academic Press, NY, ***1966***. For reviews, see Morris, D.G., *Surv. Prog. Chem.* ***1983***, *10*, 189; Hudson, R.F. *Chem. Br.*, ***1971***, *7*, 287; Lowe, P.A. *Chem. Ind. (London)* ***1970***, 1070. For a review on the formation of ylids from the reaction of carbenes and carbenoids with heteroatom lone pairs, see Padwa, A.; Hornbuckle, S.F. *Chem. Rev.* ***1991***, *91*, 263.

[87]Although the phosphorus ylid shown has three R groups on the phosphorus atom, other phosphorus ylids are known where other atoms, for example, oxygen, replace one or more of these R groups. When the three groups are all alkyl or aryl, the phosphorus ylid is also called a phosphorane.

[88]For a review of nitrogen ylids, see Musker, W.K. *Fortschr. Chem. Forsch.* ***1970***, *14*, 295.

[89]For a monograph on sulfur ylids, see Trost, B.M.; Melvin Jr., L.S. *Sulfur Ylids*; Academic Press, NY, ***1975***. For reviews, see Fava, A, in Bernardi, F.; Csizmadia, I.G.; Mangini, A. *Organic Sulfur Chemistry*; Elsevier, NY, ***1985***, pp. 299–354; Belkin, Yu.V.; Polezhaeva, N.A. *Russ. Chem. Rev.* ***1981***, *50*, 481; Block, E. in Stirling, C.J.M. *The Chemistry of the Sulphonium Group*, part 2, Wiley, NY, ***1981***, pp. 680–702; Block, E. *Reactions of Organosulfur Compounds*; Academic Press, NY, ***1978***, pp. 91–127.

arsenic,[90] selenium, and so on, ylids are also known. Ylids may be defined as compounds in which a positively charged atom from group 15 or 16 of the Periodic table is connected to a carbon atom carrying an unshared pair of electrons. Because of *pπ–dπ* bonding, two canonical forms can be written for phosphorus and sulfur, but there is only one for nitrogen ylids. Phosphorus ylids are much more stable than nitrogen ylids (see also p. 810). Sulfur ylids also have a low stability.



In almost all compounds that have *pπ–dπ* bonds, the central atom is connected to four atoms or three atoms and an unshared pair and the bonding is approximately tetrahedral. The *pπ–dπ* bond, therefore, does not greatly change the geometry of the molecule in contrast to the normal π bond, which changes an atom from tetrahedral to trigonal. Calculations show that nonstabilized phosphonium ylids have nonplanar ylidic carbon geometries whereas stabilized ylids have planar ylidic carbons.[91]

AROMATICITY[92]

In the nineteenth century, it was recognized that aromatic compounds[93] differ greatly from unsaturated aliphatic compounds,[94] but for many years chemists

[90]For reviews of arsenic ylids, see Lloyd, D.; Gosney, I.; Ormiston, R.A. *Chem. Soc. Rev.* ***1987***, *16*, 45; Yaozeng, H.; Yanchang, S. *Adv. Organomet. Chem.* ***1982***, *20*, 115.
[91]Bachrach, S.M. *J. Org. Chem.* ***1992***, *57*, 4367.
[92]Krygowski, T.M.; Cyrañski, M.K.; Czarnocki, Z.; Häfelinger, G.; Katritzky, A.R. *Tetrahedron* ***2000***, *56*, 1783; Simkin, B.Ya.; Minkin, V.I.; Glukhovtsev, M.N., in *Advances in Heterocyclic Chemistry*, Vol. 56, Katritzky, A.R., Ed., Academic Press, San Diego, ***1993***, pp 303–428; Krygowski, T.M.; Cyranski, M.K. *Chem. Rev.* ***2001***, *101*, 1385; Katritzky, A.R.; Jug, K.; Oniciu, D.C. *Chem. Rev.* ***2001***, *101*, 1421; Katritzky, A.R.; Karelson, M.; Wells, A.P. *J. Org. Chem.* ***1996***, *61*, 1619. See also Cyranski, M.K.; Krygowski, T.M.; Katritzky, A.R.; Schleyer, P.v.R. *J. Org. Chem.* ***2002***, *67*, 1333.
[93]For books on Aromaticity, see Lloyd, D. *The Chemistry of Conjugated Cyclic Compounds*, Wiley, NY, ***1989***; *Non-Benzenoid Conjugated Carbocyclic Compounds*, Elsevier, NY, ***1984***; Garratt, P.J. *Aromaticity*, Wiley, NY, ***1986***; Balaban, A.T.; Banciu, M.; Ciorba, V. *Annulenes, Benzo-, Hetero-, Homo-Derivatives and their Valence Isomers*, 3 vols., CRC Press, Boca Raton, FL ***1987***; Badger, G.M. *Aromatic Character and Aromaticity*, Cambridge University Press, Cambridge, ***1969***; Snyder, J.P. *Nonbenzenoid Aromatics*, 2 vols., Academic Press, NY, ***1969–1971***; Bergmann, E.D.; Pullman, B. *Aromaticity, Pseudo-Aromaticity, and Anti-Aromaticity*, Israel Academy of Sciences and Humanities, Jerusalem, ***1971***; *Aromaticity*; *Chem. Soc. Spec. Pub.* No. 21, ***1967***. For reviews, see Gorelik, M.V. *Russ. Chem. Rev.* ***1990***, *59*, 116; Stevenson, G.R. *Mol. Struct. Energ.*, ***1986***, *3*, 57; Sondheimer, F. *Chimia*, ***1974***, *28*, 163; Cresp, T.M.; Sargent, M.V. *Essays Chem.* ***1972***, *4*, 91; Figeys, H.P. *Top. Carbocyclic Chem.* ***1969***, *1*, 269; Garratt, P.J.; Sargent, M.V. papers in, *Top. Curr. Chem.* ***1990***, 153 and *Pure Appl. Chem.* ***1980***, *52*, 1397.
[94]For an account of the early history of Aromaticity, see Snyder, J.P., in Snyder, J.P. *Nonbenzenoid Aromatics*, Vol. 1, Academic Press, NY, ***1971***, pp. 1–31. See also Balaban, A.T. *Pure Appl. Chem.* ***1980***, *52*, 1409.

were hard pressed to arrive at a mutually satisfactory definition of aromatic character.[95] Qualitatively, there has never been real disagreement. Definitions have taken the form that aromatic compounds are characterized by a special stability and that they undergo substitution reactions more easily than addition reactions. The difficulty arises because these definitions are vague and not easy to apply in borderline cases. Definitions of aromaticity must encompass molecules ranging form polycyclic conjugated hydrocarbons,[96] to heterocyclic compounds[97] of various ring sizes, to reactive intermediates. In 1925 Armit and Robinson,[98] recognized that the aromatic properties of the benzene ring are related to the presence of a closed loop of electrons, the *aromatic sextet* (aromatic compounds are thus the arch examples of delocalized bonding), but it still was not easy to determine whether rings other than the benzene ring possessed such a loop. With the advent of magnetic techniques, most notably NMR, it is possible to determine experimentally whether or not a compound has a closed ring of electrons; aromaticity can now be defined as the *ability to sustain an induced ring current*. A compound with this ability is called ***diatropic***. Although this definition also has its flaws,[99] it is the one most commonly accepted today. There are several methods of determining whether a compound can sustain a ring current, but the most important one is based on NMR chemical shifts.[100] In order to understand this, it is necessary to remember that, as a general rule, the value of the chemical shift of a proton in an NMR spectrum depends on the electron density of its bond; the greater the density of the electron cloud surrounding or partially surrounding a proton, the more upfield is its chemical shift (a lower value of δ). However, this rule has several exceptions; one is for protons in the vicinity of an aromatic ring. When an external magnetic field is imposed upon an aromatic ring (as in an NMR instrument), the closed loop of aromatic electrons circulates in a diamagnetic ring current, which sends out a field of its own. As can be seen in Fig. 2.6, this induced field curves around and in the area of the proton is parallel to the external field, so the field "seen" by the aromatic protons is greater than it would have been in the absence of the diamagnetic ring current. The protons are moved downfield (to higher δ) compared to where they would be if electron

[95]For a review of the criteria used to define aromatic character, see Jones, A.J. *Pure Appl. Chem.* ***1968***, *18*, 253. For methods of assigning Aromaticity, see Jug, K.; Köster, A.M. *J. Phys. Org. Chem.* ***1991***, *4*, 163; Zhou, Z.; Parr, R.G. *J. Am. Chem. Soc.* ***1989***, *111*, 7371; Katritzky, A.R.; Barczynski, P.; Musumarra, G.; Pisano, D.; Szafran, M. *J. Am. Chem. Soc.* ***1989***, *111*, 7; Schaad, L.J.; Hess, Jr., B.A. *J. Am. Chem. Soc.* ***1972***, *94*, 3068, *J. Chem. Educ.* ***1974***, *51*, 640. See also, Bird, C.W. *Tetrahedron* ***1985***, *41*, 1409; ***1986***, *42*, 89; ***1987***, *43*, 4725.

[96]Randic, M. *Chem. Rev.* ***2003***, *103*, 3449.

[97]Balaban, A.T.; Oniciu, D.C.; Katritzky, A.R. *Chem. Rev.* ***2004***, *104*, 2777.

[98]Armit, J.W.; Robinson; R. *J. Chem. Soc.* ***1925***, *127*, 1604.

[99]Jones, A.J. *Pure Appl. Chem.* ***1968***, *18*, 253, pp. 266–274; Mallion, R.B. *Pure Appl. Chem.* **1980**, 52, 1541. Also see, Schleyer, P.v.R.; Jiao, H. *Pure Appl. Chem.* ***1996***, *68*, 209.

[100]For a review of NMR and other magnetic properties with respect to aromaticity, see Haddon, R.C.; Haddon, V.R.; Jackman, L.M. *Fortschr. Chem. Forsch.* ***1971***, *16*, 103. For an example of a magentic method other than NMR, see Dauben Jr., H.J.; Wilson, J.D.; Laity, J.L., in Snyder, J.P. *Nonbenzenoid Aromatics*, Vol. 2, Academic Press, NY, ***1971***, pp. 167–206.

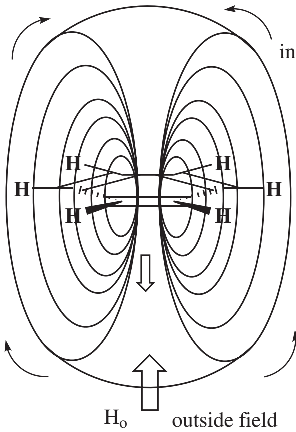
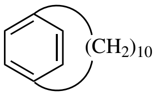
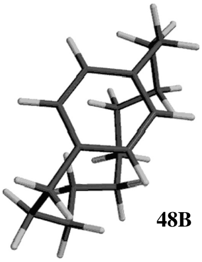


Fig. 2.6. Ring current in benzene.

density were the only factor. Thus ordinary alkene hydrogens are found at ~5–6 δ, while the hydrogens of benzene rings are located at ~7–8 δ. However, if there



48A



48B

were protons located above or within the ring, they would be subjected to a *decreased* field and should appear at lower δ values than normal CH_2 groups (normal δ for CH_2 is ~1–2). The nmr spectrum of [10]paracyclophane (**48A**) showed that this was indeed the case[101] and that the CH_2 peaks were shifted to lower δ the closer they were to the middle of the chain. Examination of **48B** shows that a portion of the methylene chain is positioned directly over the benzene ring, making it subject to the anisotropy shift mentioned above.

It follows that aromaticity can be determined from an NMR spectrum. If the protons attached to the ring are shifted downfield from the normal alkene region, we can conclude that the molecule is diatropic, and hence aromatic. In addition, if the compound has protons above or within the ring (we shall see an example of the latter on p. 90), then if the compound is diatropic, these will be shifted upfield.

[101]Waugh, J.S.; Fessenden, R.W. *J. Am. Chem. Soc.* ***1957***, *79*, 846. See also, Shapiro, B.L.; Gattuso, M.J.; Sullivan, G.R. *Tetrahedron Lett.* ***1971***, 223; Pascal, Jr., R.A.; Winans, C.G.; Van Engen, D. *J. Am. Chem. Soc.* ***1989***, *111*, 3007.

One drawback to this method is that it cannot be applied to compounds that have no protons in either category, for example, the dianion of squaric acid (p. 92). Unfortunately, ^{13}C NMR is of no help here, since these spectra do not show ring currents.[102]

Antiaromatic systems exhibit a *paramagnetic* ring current,[103] which causes protons on the outside of the ring to be shifted *upfield* while any inner protons are shifted *downfield*, in sharp contrast to a diamagnetic ring current, which causes shifts in the opposite directions. Compounds that sustain a paramagnetic ring current are called *paratropic*; and are prevalent in four- and eight-electron systems. As with aromaticity, we expect that antiaromaticity will be at a maximum when the molecule is planar and when bond distances are equal. The diamagnetic and paramagnetic effects of the ring currents associated with aromatic and antiaromatic compounds (i.e., shielding and deshielding of nuclei) can be measured by a simple and efficient criterion known as nucleus independent chemical shift (NICS).[104] The aromatic–antiaromatic ring currents reflect the extra π-effects that the molecules experience. The unique near zero value of NICS at the cyclobutadiene ring center is due to cancelation by large and opposite anistropic components.[105]

There are at least four theoretical models for aromaticity, which have recently been compared and evaluated for predictive ability.[106] The *Hess–Schaad model*[107] is good for predicting aromatic stability of benzenoid hydrocarbons, but does not predict reactivity. The *Herndon model*[108] is also good for predicting aromatic stability, but is unreliable for benzenoidicity and does not predict reactivity. The *conjugated-circuit model*[109] is very good for predicting aromatic stability, but not reactivity, and the *hardness model*[110] is best for predicting kinetic stability. Delocalization energy of π-electrons has also been used as an index for aromaticity in polycyclic aromatic hydrocarbons.[111] The claims for linear relationships between aromaticity and energetics, geometries, and magnetic criteria were said to be *invalid* for any representative set of heteroaromatics in which the number of heteroatoms varies.[112]

It should be emphasized that the old and new definitions of aromaticity are not necessarily parallel. If a compound is diatropic and therefore aromatic under the

[102]For a review of ^{13}C NMR spectra of aromatic compounds, see Günther, H.; Schmickler, H. *Pure Appl. Chem.* ***1975***, *44*, 807.

[103]Pople, J.A.; Untch, K.G. *J. Am. Chem. Soc.* ***1966***, *88*, 4811; Longuet-Higgins, H.C. in Garratt, P.J. *Aromaticity*, Wiley, NY, ***1986***, pp. 109–111.

[104]Schleyer, P.v.R.; Maerker, C.; Dransfeld, A.; Jiao, H.; Hommes, N.J.R.v.E. *J. Am. Chem. Soc.* ***1996***, *118*, 6317.

[105]Schleyer, P.v.R.; Manoharan, M.; Wang, Z.-X.; Kiran, B.; Jiao, H.; Puchta, R.; Hommes, N.J.R.v.E. *Org. Lett.* ***2001***, *3*, 2465

[106]Plavić, D.; Babić, D.; Nikolić, S.; Trinajstić, N. *Gazz. Chim. Ital.*, ***1993***, *123*, 243.

[107]Hess, Jr., B.A.; Schaad, L.J. *J. Am. Chem. Soc.* ***1971***, *93*, 305.

[108]Herndon, W.C. *Isr. J. Chem.* ***1980***, *20*, 270.

[109]Randić,M. *Chem.Phys.Lett.* ***1976***, *38*, 68.

[110]Zhou, Z.; Parr, R.G. *J. Am. Chem. Soc.* ***1989***, *111*, 7371; Zhou, Z.; Navangul, H.V. *J. Phys. Org. Chem.* ***1990***, *3*, 784.

[111]Behrens, S.; Köster, A.M.; Jug, K. *J. Org. Chem.* ***1994***, *59*, 2546.

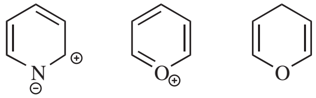
[112]Katritzky, A.R.; Karelson, M.; Sild, S.; Krygowski, T.M.; Jug, K. *J. Org. Chem.* ***1998***, *63*, 5228.

new definition, it is more stable than the canonical form of lowest energy, but this does not mean that it will be stable to air, light, or common reagents, since *this* stability is determined not by the resonance energy, but by the difference in free energy between the molecule and the transition states for the reactions involved; and these differences may be quite small, even if the resonance energy is large. A unified theory has been developed that relates ring currents, resonance energies, and aromatic character.[113] Note that aromaticity varies in magnitude relatively and sometimes absolutely with the molecular environment, which includes the polarity of the medium.[114]

The vast majority of aromatic compounds have a closed loop of six electrons in a ring (the aromatic sextet), and we consider these compounds first.[115] Note that a "formula Periodic table" for the benzenoid polyaromatic hydrocarbons has been developed.[116]

Six-Membered Rings

Not only is the benzene ring aromatic, but so are many heterocyclic analogs in which one or more heteroatoms replace carbon in the ring.[117] When nitrogen is the heteroatom, little difference is made in the sextet and the unshared pair of the nitrogen does not participate in the aromaticity. Therefore, derivatives such as *N*-oxides or pyridinium ions are still aromatic. However, for nitrogen heterocycles there are more significant canonical forms (e.g., **49**) than for benzene. Where oxygen or sulfur is the heteroatom, it must be present in its ionic form (**50**) in order to possess the valence of 3 that participation in such a system demands. Thus, pyran (**51**) is not aromatic, but the pyrylium ion (**49**) is.[118]



49 **50** **51**

[113]Haddon, R.C. *J. Am. Chem. Soc.* ***1979***, *101*, 1722; Haddon, R.C.; Fukunaga, T. *Tetrahedron Lett.* ***1980***, *21*, 1191.

[114]Katritzky, A.R.; Karelson, M.; Wells, A.P. *J. Org. Chem.* ***1996***, *61*, 1619.

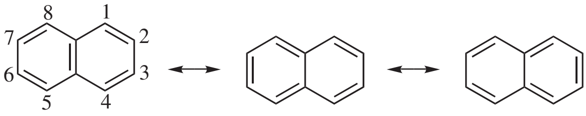
[115]Values of molecular-orbital energies for many aromatic systems, calculated by the HMO method, are given in Coulson, C.A.; Streitwieser, Jr., A. *A Dictonary of* π *Electron Calculations*, W.H. Freeman, San Francisco, ***1965***. Values calculated by a variation of the SCF method are given by Dewar, M.J.S.; Trinajstic, N. *Collect. Czech. Chem. Commun.* ***1970***, *35*, 3136, 3484.

[116]Dias, J.R. *Chem. Br.* ***1994***, 384.

[117]For reviews of Aromaticity of heterocycles, see Katritzky, A.R.; Karelson, M.; Malhotra, N. *Heterocycles* ***1991***, *32*, 127.

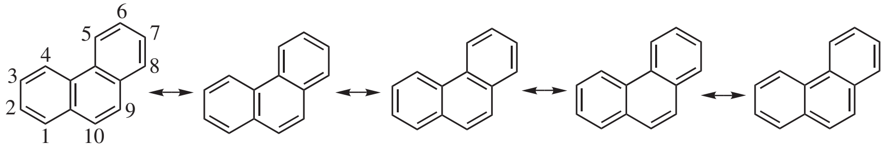
[118]For a review of pyrylium salts, see Balaban, A.T.; Schroth, W.; Fischer, G. *Adv. Heterocycl. Chem.* ***1969***, *10*, 241.

In systems of fused six-membered aromatic rings,[119] the principal canonical forms are usually not all equivalent. Compound **52** has a central double bond and is thus different from the other two canonical forms of naphthalene, which are equivalent to each other.[120] For naphthalene, these are the only forms that can be drawn



52

without consideration of Dewar forms or those with charge separation.[121] If we assume that the three forms contribute equally, the 1,2 bond has more double-bond character than the 2,3 bond. Molecular-orbital calculations show bond orders of 1.724 and 1.603, respectively, (cf. benzene, 1.667). In agreement with these predictions, the 1,2 and 2,3 bond distances are 1.36 and 1.415 Å, respectively,[122] and ozone preferentially attacks the 1,2 bond.[123] This nonequivalency of bonds, called *partial bond fixation*,[124] is found in nearly all fused aromatic systems. In phenanthrene, where the 9,10 bond is a single bond in only one of five forms (**53**), bond fixation becomes extreme and this bond is readily attacked by many reagents:[125] It has been observed that increased steric crowding leads to an increase in Dewar-benzene type structures.[126]



53

[119]For books on this subject, see Gutman, I.; Cyvin, S.J. *Introduction to the Theory of Benzenoid Hydrocarbons*, Springer, NY, ***1989***; Dias, J.R. *Handbook of Polycyclic Hydrocarbons, Part A: Benzenoid Hydrocarbons*, Elsevier, NY, ***1987***; Clar, E. *Polycyclic Hydrocarbons*, 2 vols., Academic Press, NY, ***1964***. For a "Periodic table" that systematizes fused aromatic hydrocarbons, see Dias, J.R. *Acc. Chem. Res.* ***1985***, *18*, 241; *Top. Curr. Chem.* ***1990***, *253*, 123; *J. Phys. Org. Chem.* ***1990***, *3*, 765.

[120]As the size of a given fused ring system increases, it becomes more difficult to draw all the canonical forms. For discussions of methods for doing this, see Herndon, W.C. *J. Chem. Educ.* ***1974***, *51*, 10; Cyvin, S.J.; Cyvin, B.N.; Brunvoll, J.; Chen, R. *Monatsh. Chem.* ***1989***, *120*, 833; Fuji, Z.; Xiaofeng, G.; Rongsi, C. *Top. Curr. Chem.* ***1990***, *153*, 181; Wenchen, H.; Wenjie, H. *Top. Curr. Chem.* ***1990***, *153*, 195; Sheng, R. *Top. Curr. Chem.* ***1990***, *153*, 211; Rongsi, C.; Cyvin, S.J.; Cyvin, B.N.; Brunvoll, J.; Klein, D.J. *Top. Curr. Chem.* ***1990***, *153*, 227, and references cited in these papers. For a monograph, see Cyvin, S.J.; Gutman, I. *Kekulé Structures in Benzenoid Hydrocarbons*; Springer, NY, ***1988***.

[121]For a modern valence bond description of naphthalene, see Sironi, M.; Cooper, D.L.; Gerratt, J.; Raimondi, M. *J. Chem. Soc. Chem. Commun.* ***1989***, 675.

[122]Cruickshank, D.W.J. *Tetrahedron* ***1962***, *17*, 155.

[123]Kooyman, E.C. *Recl. Trav. Chim. Pays-Bas*, ***1947***, *66*, 201.

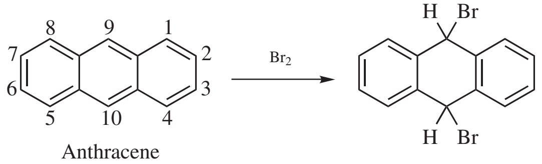
[124]For a review, see Efros, L.S. *Russ. Chem. Rev.* ***1960***, *29*, 66.

[125]See also Lai, Y. *J. Am. Chem. Soc.* ***1985***, *107*, 6678.

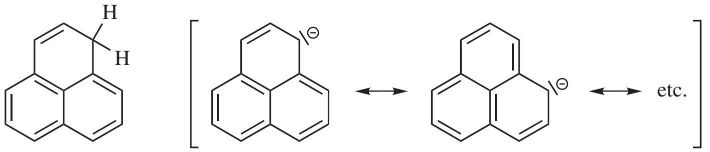
[126]Zhang, J.; Ho, D.M.; Pascal Jr., R.A. *J. Am. Chem. Soc.* ***2001***, *123*, 10919.

In general, there is a good correlation between bond distances in fused aromatic compounds and bond orders. Another experimental quantity that correlates well with the bond order of a given bond in an aromatic system is the NMR coupling constant for coupling between the hydrogens on the two carbons of the bond.[127]

The resonance energies of fused systems increase as the number of principal canonical forms increases, as predicted by rule 6 (p. 47).[128] Thus, for benzene, naphthalene, anthracene, and phenanthrene, for which we can draw, respectively, two, three, four, and five principal canonical forms, the resonance energies are, respectively, 36, 61, 84, and 92 kcal mol^{-1} (152, 255, 351, and 385 kJ mol^{-1}), calculated from heat-of-combustion data.[129] Note that when phenanthrene, which has a total resonance energy of 92 kcal mol^{-1} (385 kJ mol^{-1}), loses the 9,10 bond by attack of a reagent, such as ozone or bromine, two complete benzene rings remain, each with 36 kcal mol^{-1} (152 kJ mol^{-1}) that would be lost if benzene was similarly attacked. The fact that anthracene undergoes many reactions across the 9,10 positions can be explained in a similar manner. Resonance energies for fused systems can be estimated by counting canonical forms.[130]



Not all fused systems can be fully aromatic. Thus for phenalene (**54**) there is no way double bonds can be distributed so that each carbon has one single and one double bond.[131] However, phenalene is acidic and reacts with potassium methoxide to give the corresponding anion (**55**), which is completely aromatic. So are the corresponding radical and cation, in which the resonance energies are the same (see p. 68).[132]



54 **55**

[127]Jonathan, N.; Gordon, S.; Dailey, B.P. *J. Chem. Phys.* ***1962***, *36*, 2443; Cooper, M.A.; Manatt, S.L. *J. Am. Chem. Soc.* ***1969***, *91*, 6325.

[128]See Herndon, W.C.; Ellzey Jr., M.L. *J. Am. Chem. Soc.* ***1974***, *96*, 6631.

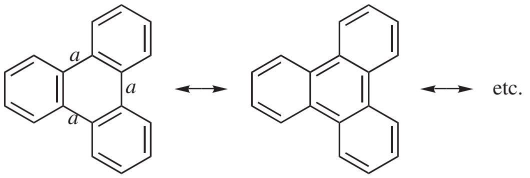
[129]Wheland, G.W. *Resonance in Organic Chemistry*, Wiley, NY, ***1955***, p. 98.

[130]Swinborne-Sheldrake, R.; Herndon, W.C. *Tetrahedron Lett.* ***1975***, 755.

[131]For reviews of phenalenes, see Murata, I. *Top. Nonbenzenoid Aromat. Chem.* ***1973***, *1*, 159; Reid, D.H. *Q. Rev. Chem. Soc.* ***1965***, *19*, 274.

[132]Pettit, R. *J. Am. Chem. Soc.* ***1960***, *82*, 1972.

Molecules that contain fused rings, such as phenanthrene or anthracene, are generally referred to as linear or angular polyacenes. In a fused system, there are not six electrons for each ring.[133] In naphthalene, if one ring is to have six, the other must have only four. One way to explain the greater reactivity of the ring system of naphthalene compared with benzene is to regard one of the naphthalene rings as aromatic and the other as a butadiene system.[134] This effect can become extreme, as in the case of triphenylene.[135] For this compound, there are eight canonical forms like **56**, in which none of the three bonds marked *a* is a double bond and only one form (**57**) in which at least one of them is double. Thus the molecule behaves as if the 18 electrons were distributed so as to give each of the outer rings a sextet, while the middle ring is "empty." Since none of the outer rings need share



56 **57**

any electrons with an adjacent ring, they are as stable as benzene; triphenylene, unlike most fused aromatic hydrocarbons, does not dissolve in concentrated sulfuric acid and has a low reactivity.[136] This phenomenon, whereby some rings in fused systems give up part of their aromaticity to adjacent rings, is called *annellation* and can be demonstrated by UV spectra[119] as well as reactivities. In general, an increase of size of both linear and angular polyacenes is associated with a substantial edecrease in their aromaticity, with a greater decrease for the linear polyacenes.[137]

A six-membered ring with a circle is often used to indicate an aromatic system, and this will be used from time to time. Kekulé structures, those having the C=C units rather than a circle, are used most often in this book. Note that one circle can be used for benzene, but it would be misleading to use two circles for naphthalene, for example, because that would imply 12 aromatic electrons, although naphthalene has only 10.[138]

Five-, Seven-, and Eight-Membered Rings

Aromatic sextets can also be present in five- and seven-membered rings. If a five-membered ring has two double bonds, and the fifth atom possesses an unshared pair

[133]For discussions of how the electrons in fused aromatic systems interact to form $4n + 2$ systems, see Glidewell, C.; Lloyd, D. *Tetrahedron* ***1984***, *40*, 4455, *J. Chem. Educ.* ***1986***, *63*, 306; Hosoya, H. *Top. Curr. Chem.* ***1990***, *153*, 255.

[134]Meredith, C.C.; Wright, G.F. *Can. J. Chem.* ***1960***, *38*, 1177.

[135]For a review of triphenylenes, see Buess, C.M.; Lawson, D.D. *Chem. Rev.* ***1960***, *60*, 313.

[136]Clar, E.; Zander, M. *J. Chem. Soc.* ***1958***, 1861.

[137]Cyrań ski, M.K.; Stępień, B.T.; Krygowski, T.M. *Tetrahedron* ***2000***, *56*, 9663.

[138]See Belloli, R. *J. Chem. Educ.* ***1983***, *60*, 190.

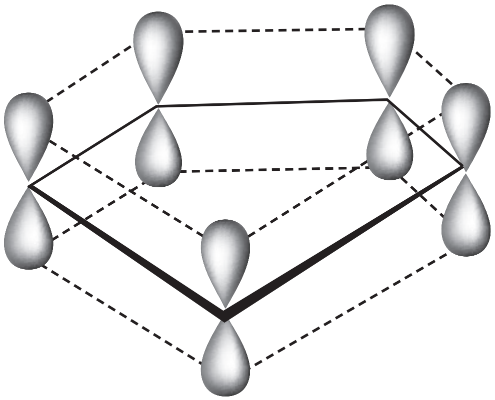
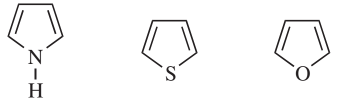
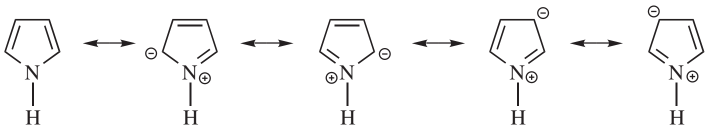


Fig. 2.7. Overlap of five *p* orbitals in molecules such as pyrrole, thiophene, and the cyclopentadienide ion

of electrons, the ring has five *p* orbitals that can overlap to create five new orbitals: three bonding and two antibonding (Fig. 2.7). There are six electrons for these orbitals: the four *p* orbitals of the double bonds each contribute one and the filled orbital contributes the other two. The six electrons occupy the bonding orbitals and



constitute an aromatic sextet. The heterocyclic compounds pyrrole, thiophene, and furan are the most important examples of this kind of aromaticity, although furan has a lower degree of aromaticity than the other two.[139] Resonance energies for these three compounds are, respectively, 21, 29, and 16 kcal mol^{-1} (88, 121, and 67 kJ mol^{-1}).[140] The aromaticity can also be shown by canonical forms, for example, for pyrrole:



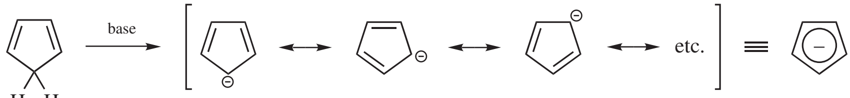
A

[139]The order of aromaticity of these compounds is benzene > thiophene > pyrrole > furan, as calculated by an Aromaticity index based on bond distance measurements. This index has been calculated for five- and six-membered monocyclic and bicyclic heterocycles: Bird, C.W. *Tetrahedron* ***1985***, *41*, 1409; ***1986***, *42*, 89; ***1987***, *43*, 4725.

[140]Wheland, G.W. *Resonance in Organic Chemistry*, Wiley, NY, ***1955***, p 99. See also, Calderbank, K.E.; Calvert, R.L.; Lukins, P.B.; Ritchie, G.L.D. *Aust. J. Chem.* ***1981***, *34*, 1835.

In contrast to pyridine, the unshared pair in canonical structure **A** in pyrrole is needed for the aromatic sextet. This is why pyrrole is a much weaker base than pyridine.

The fifth atom may be carbon if it has an unshared pair. Cyclopentadiene has unexpected acidic properties ($pK_a \approx 16$) since on loss of a proton, the resulting carbanion is greatly stabilized by resonance although it is quite reactive. The cyclopentadienide ion is usually represented as in **58**. Resonance in this ion is greater than in pyrrole, thiophene, and furan, since all five forms are equivalent. The resonance energy for **58** has been estimated to be 24–27 kcal mol^{-1} (100–113 kJ mol^{-1}).[141]



58

That all five carbons are equivalent has been demonstrated by labeling the starting compound with ^{14}C and finding all positions equally labeled when cyclopentadiene was regenerated[142] As expected for an aromatic system, the cyclopentadienide ion is diatropic[143] and aromatic substitutions on it have been successfully carried out.[144] Average bond order has been proposed as a parameter to evaluate the aromaticity of these rings, but there is poor correlation with non-aromatic and antiaromatic systems.[145] A model that relies on calculating relative aromaticity from appropriate molecular fragments has also been developed.[146] Bird devised the aromatic index (I_A, or aromaticity index),[147] which is a statistical evaluation of the extent of ring bond order, and this has been used as a criterion of aromaticity. Another bond-order index was proposed by Pozharskii,[148] which goes back to the work of Fringuelli and co-workers.[149] Absolute hardness (see p. 377), calculated from molecular refractions for a range of aromatic and heteroaromatic compounds, shows good linear correlation with aromaticity.[150] Indene and fluorene are also acidic ($pK_a \approx 20$ and 23, respectively), but less so than cyclopentadiene, since annellation causes the electrons to be less available to the five-membered ring. On the other hand, the acidity of 1,2,3,4,5-pentakis(trifluoromethyl)cyclopentadiene (**59**) is greater than that of nitric acid,[151] because of the electron-

[141]Bordwell, F.G.; Drucker, G.E.; Fried, H.E. *J. Org. Chem.* ***1981***, *46*, 632.

[142]Tkachuk, R.; Lee, C.C. *Can. J. Chem.* ***1959***, *37*, 1644.

[143]Bradamante, S.; Marchesini, A.; Pagani, G. *Tetrahedron Lett.* ***1971***, 4621.

[144]Webster, O.W. *J. Org. Chem.* ***1967***, *32*, 39; Rybinskaya, M.I.; Korneva, L.M. *Russ. Chem. Rev.* ***1971***, *40*, 247.

[145]Jursic, B.S. *J. Heterocycl. Chem.* ***1997***, *34*, 1387.

[146]Hosmane, R.S.; Liebman, J.F. *Tetrahedron Lett.* ***1992***, *33*, 2303.

[147]Bird, C.W. *Tetrahedron* ***1985***, *41*, 1409; *Tetrahedron* ***1992***, *48*, 335; *Tetrahedron* ***1996***, *52*, 9945.

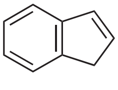
[148]Pozharskii, A.F. *Khimiya Geterotsikl Soedin* ***1985***, 867.

[149]Fringuelli, F. Marino, G.; Taticchi, A.; Grandolini, G. J. *Chem. Soc. Perkin Trans. 2* ***1974***, 332.

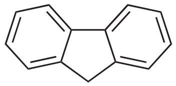
[150]Bird, C.W. *Tetrahedron* ***1997***, *53*, 3319; *Tetrahedron* ***1998***, *54*, 4641.

[151]Laganis, E.D.; Lemal, D.M. *J. Am. Chem. Soc.* ***1980***, *102*, 6633.

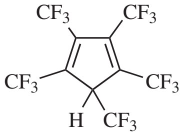
withdrawing effects of the trifluoromethyl groups (see p. 381). Modifications of the Bird and Pozharskii systems have been introduced that are particularly useful for five-membered ring heterocycles.[152] Recent work introduced a new local aromaticity measure, defined as the mean of Bader's electron delocalization index (DI)[153] of para-related carbon atoms in six-membered rings.[154]



Indene

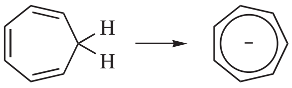


Fluorene

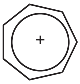


59

As seen above, acidity of compounds can be used to study the aromatic character of the resulting conjugate base. In sharp contrast to cyclopentadiene (see p. 63) is cycloheptatriene (**60**), which has no unusual acidity. This would be hard to explain without the aromatic sextet theory, since, on the basis of resonance forms or a simple



60 **61**



62

consideration of orbital overlaps, **61** should be as stable as the cyclopentadienyl anion (**58**). While **61** has been prepared in solution,[155] it is less stable than **58** and far less stable than **62**, in which **60** has lost not a proton, but a hydride ion. The six double-bond electrons of **62** overlap with the empty orbital on the seventh carbon and there is a sextet of electrons covering seven carbon atoms. The cycloheptatrienyl cations (known as the *tropylium ion*, **62**) is quite stable.[156] Tropylium bromide (**63**), which could be completely covalent if the electrons of the bromine were sufficiently attracted to the ring, is actually an ionic compound:[157] Many substituted tropylium ions have been prepared to probe the aromaticity, structure, and reactivity of such systems.[158] Just as with **58**, the equivalence of the carbons

[152]Kotelevskii, S.I.; Prezhdo, O.V. *Tetahedron* ***2001***, *57*, 5715.

[153]See Bader, R.F.W. *Atoms in Molecules: A Quantum Theory*, Clarendon, Oxford, ***1990***; Bader, R.F.W. *Acc. Chem. Res.* ***1985***, *18*, 9; Bader, R.F.W. *Chem. Rev.* ***1991***, *91*, 893.

[154]Poater, J.; Fradera, X.; Duran, M.; Solà, M. *Chem. Eur. J.* ***2003***, *9*, 400; 1113.

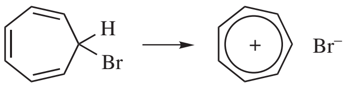
[155]Dauben Jr., H.J.; Rifi, M.R. *J. Am. Chem. Soc.* ***1963***, *85*, 3041; also see Breslow, R.; Chang, H.W. *J. Am Chem. Soc.* ***1965***, *87*, 2200.

[156]For reviews, see Pietra, F. *Chem. Rev.* ***1973***, *73*, 293; Bertelli, D.J. *Top. Nonbenzenoid Aromat. Chem.* ***1973***, *1*, 29; Kolomnikova, G.D.; Parnes, Z.N. *Russ. Chem. Rev.* ***1967***, *36*, 735; Harmon, K.H., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 4, Wiley, NY, 1973, pp. 1579–1641.

[157]Doering, W. von E.; Knox, L.H. *J. Am. Chem. Soc.* ***1954***, *76*, 3203.

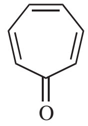
[158]Pischel, U.; Abraham, W.; Schnabel, W.; Müller, U. *Chem. Commun.* ***1997***, 1383. See Komatsu, K.; Nishinaga, T.; Maekawa, N.; Kagayama, A.; Takeuchi, K. *J. Org. Chem.* ***1994***, *59*, 7316 for a tropylium dication.

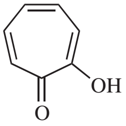
in **62** has been demonstrated by isotopic labeling.[159] The aromatic cycloheptatrienyl cations $C_7Me_7^+$ and $C_7Ph_7^+$ are known,[160] although their coordination complexes with transition metals have been problematic, possibly because they assume a boat-like rather than a planar conformation[161]



63

Another seven-membered ring that shows some aromatic character is tropone (**64**). This molecule would have an aromatic sextet if the two C=O electrons stayed away from the ring and resided near the electronegative oxygen atom. In fact, tropones are stable compounds, and tropolones (**65**) are found in nature.[162] However, analyses of dipole moments, NMR spectra, and X-ray diffraction measurements show that tropones and tropolones display appreciable bond alternations.[163]





64 **65**

These molecules must be regarded as essentially non-aromatic, although with some aromatic character. Tropolones readily undergo aromatic substitution, emphasizing that the old and the new definitions of aromaticity are not always parallel. In sharp contrast to **64**, cyclopentadienone (**66**) has been isolated only in an argon matrix <38 K.[164] Above this temperature it dimerizes. Many earlier attempts to prepare it were unsuccessful.[165] As in **64**, the electronegative oxygen atom draws electron to itself, but in this case it leaves only four electrons and the molecule is

[159]Vol'pin, M.E.; Kursanov, D.N.; Shemyakin, M.M.; Maimind, V.I.; Neiman, L.A. *J. Gen. Chem. USSR* ***1959***, *29*, 3667.

[160]Takeuchi, K.; Yokomichi, Y.; Okamoto, K. *Chem. Lett.* ***1977***,1177; Battiste, M.A. *J. Am. Chem. Soc.* ***1961***, *83*, 4101.

[161]Tamm, M.; Dreßel, B.; Fröhlich, R. *J. Org. Chem.* ***2000***, *65*, 6795.

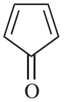
[162]For reviews of tropones and tropolones, see Pietra, F. *Acc. Chem. Res.* ***1979***, *12*, 132; Nozoe, T. *Pure Appl. Chem.* ***1971***, *28*, 239.

[163]Bertelli, D.J.; Andrews, Jr., T.G. *J. Am. Chem. Soc.* ***1969***, *91*, 5280; Bertelli, D.J.; Andrews Jr., T.G.; Crews, P.O. *J. Am. Chem. Soc.* ***1969***, *91*, 5286; Schaefer, J.P.; Reed, L.L. *J. Am. Chem. Soc.* ***1971***, *93*, 3902; Watkin, D.J.; Hamor, T.A. *J. Chem. SOc. B* ***1971***, 2167; Barrow, M.J.; Mills, O.S.; Filippini, G. *J. Chem. Soc. Chem. Commun.* ***1973***, 66.

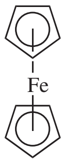
[164]Maier, G.; Franz, L.H.; Lanz, K.; Reisenauer, H.P. *Chem. Ber.* ***1985***, *118*, 3196.

[165]For a review of cyclopentadienone derivatives and of attempts to prepare the parent compound, see Ogliaruso, M.A.; Romanelli, M.G.; Becker, E.I. *Chem. Rev.* ***1965***, *65*, 261.

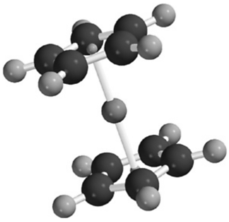
unstable. Some derivatives of **66** have been prepared.[130]



66



Ferrocene



67

Another type of five-membered aromatic compound is the *metallocenes* (also called *sandwich compounds*), in which two cyclopentadienide rings form a sandwich around a metallic ion. The best known of these is ferrocene, where the η^5-coordination of the two cyclopentadienyl rings to iron is apparent in the 3D model **67**. Other sandwich compounds have been prepared with Co, Ni, Cr, Ti, V, and many other metals.[166] As a reminder (see p. 43), the η terminology refers to π-donation of electrons to the metal (η^3 for π-allyl systems, η^6 for coordination to a benzene ring, etc.), and η^5 refers to donation of five π-electrons to the iron. Ferrocene is quite stable, subliming >100°C and unchanged at 400°C. The two rings rotate freely.[167] Many aromatic substitutions have been carried out on metallocenes.[168] Metallocenes containing two metal atoms and three cyclopentadienyl rings have also been prepared and are known as *triple-decker sandwiches*.[169] Even tetradecker, pentadecker, and hexadecker sandwiches have been reported.[170]

The bonding in ferrocene may be looked upon in simplified molecular-orbital terms as follows.[171] Each of the cyclopentadienide rings has five molecular orbitals: three filled bonding and two empty antibonding orbitals (p. 62). The outer

[166]For a monograph on metallocenes, see Rosenblum, M. *Chemistry of the Iron Group Metallocenes*, Wiley, NY, ***1965***. For reviews, see Lukehart, C.M. *Fundamental Transition Metal Organometallic Chemistry*, Brooks/Cole, Monterey, CA, ***1985***, pp. 85–118; Lemenovskii, D.A.; Fedin, V.P. *Russ. Chem. Rev.* ***1986***, *55*, 127; Sikora, D.J.; Macomber, D.W.; Rausch, M.D. *Adv. Organomet. Chem.* ***1986***, *25*, 317; Pauson, P.L. *Pure Appl. Chem.* ***1977***, *49*, 839; Nesmeyanov, A.N.; Kochetkova, N.S. *Russ. Chem. Rev.* ***1974***, *43*, 710; Shul'pin, G.B.; Rybinskaya, M.I. *Russ. Chem. Rev.* ***1974***, *43*, 716; Perevalova, E.G.; Nikitina, T.V. *Organomet. React.*, ***1972***, *4*, 163; Bublitz, D.E.; Rinehart Jr., K.L. *Org. React.*, ***1969***, *17*, 1; Leonova, E.V.; Kochetkova, N.S. *Russ. Chem. Rev.* ***1973***, *42*, 278; Rausch, M.D. *Pure Appl. Chem.* ***1972***, *30*, 523. For a bibliography of reviews on metallocenes, see Bruce, M.I. *Adv. Organomet. Chem.* ***1972***, *10*, 273, pp. 322–325.

[167]For a discussion of the molecular structure, see Haaland, A. *Acc. Chem. Res.* ***1979***, *12*, 415.

[168]For a review on aromatic substitution on ferrocenes, see Plesske, K. *Angew. Chem. Int. Ed.* ***1962***, *1*, 312, 394.

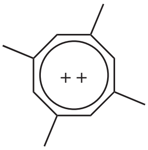
[169]For a review, see Werner, H. *Angew. Chem. Int. Ed.* ***1977***, *16*, 1.

[170]See, for example, Siebert, W. *Angew. Chem. Int. Ed.* ***1985***, *24*, 943.

[171]Rosenblum, M. *Chemistry of the Iron Group Metallocnes*, Wiley, NY, ***1965***, pp. 13–28; Coates, G.E.; Green, M.L.H.; Wade, K. *Organometallic Compounds*, 3rd ed., Vol. 2, Methuene, London, ***1968***, pp. 97–104; Grebenik, P.; Grinter, R.; Perutz, R.N. *Chem. Soc. Rev.* ***1988***, *17*, 453; 460.

shell of the Fe atom possesses nine atomic orbitals, that is, one 4*s*, three 4*p*, and five 3*d* orbitals. The six filled orbitals of the two cyclopentadienide rings overlap with the *s*, three *p*, and two of the *d* orbitals of the Fe to form twelve new orbitals, six of which are bonding. These six orbitals make up two ring-to-metal triple bonds. In addition, further bonding results from the overlap of the empty antibonding orbitals of the rings with additional filled *d* orbitals of the iron. All told, there are 18 electrons (10 of which may be considered to come from the rings and 8 from iron in the zero oxidation state) in nine orbitals; six of these are strongly bonding and three weakly bonding or nonbonding.

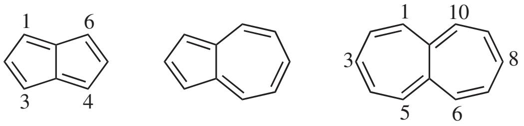
The tropylium ion has an aromatic sextet spread over seven carbon atoms. An analogous ion, with the sextet spread over eight carbon atoms, is 1,3,5,7-tetramethylcyclooctatetraene dictation (**68**). This ion, which is stable in solution at −50°C, is diatropic and approximately planar. The dication **68** is not stable above about −30°C.[172]



68

Other Systems Containing Aromatic Sextets

Simple resonance theory predicts that pentalene (**69**), azulene (**70**), and heptalene (**71**) should be aromatic, although no nonionic canonical form can have a double bond at the ring junction. Molecular-orbital calculations show that azulene should be stable but not the other two, and this is borne out by experiment. Heptalene has been prepared,[173] but reacts readily with oxygen, acids, and bromine, is easily hydrogenated, and polymerizes on standing. Analysis of its NMR spectrum shows

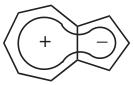


69 **70** **71**

[172]This and related ions were prepared by Olah, G.A.; Staral, J.S.; Liang, G.; Paquette, L.A.; Melega, W.P.; Carmody, M.J. *J. Am. Chem. Soc.* ***1977***, *99*, 3349. See also Radom, L.; Schaefer III, H.F. *J. Am. Chem. Soc.* ***1977***, *99*, 7522; Olah, G.A.; Liang, G. *J. Am. Chem. Soc.* ***1976***, *98*, 3033; Willner, I.; Rabinovitz, M. *Nouv. J. Chim.*, ***1982***, *6*, 129.

[173]Dauben, Jr., H.J.; Bertelli, D.J. *J. Am. Chem. Soc.* ***1961***, *83*, 4659; Vogel, E.; Königshofen, H.; Wassen, J.; Müllen, K.; Oth, J.F.M. *Angew. Chem. Int. Ed.* ***1974***, *13*, 732; Paquette, L.A.; Browne, A.R.; Chamot, E. *Angew. Chem. Int. Ed.* ***1979***, *18*, 546. For a review of heptalenes, see Paquette, L.A. *Isr. J. Chem.* ***1980***, *20*, 233.

that it is not planar.[174] The 3,8-dibromo and 3,8-dicarbomethoxy derivatives of **71** are stable in air at room temperature but are not diatropic.[175] A number of methylated heptalenes and dimethyl 1,2-heptalenedicarboxylates have also been prepared and are stable nonaromatic compounds.[176] Pentalene has not been prepared,[177] but the hexaphenyl[178] and 1,3,5-tri-*tert*-butyl derivatives[179] are known. The former is air sensitive in solution. The latter is stable, but X-ray diffraction and photoelectron spectral data show bond alternation.[180] Pentalene and its methyl and dimethyl derivatives have been formed in solution, but they dimerize before they can be isolated.[181] Many other attempts to prepare these two systems have failed.



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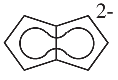
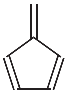


73



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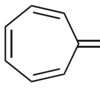

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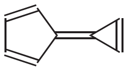


76

In sharp contrast to **69** and **71**, azulene, a blue solid, is quite stable and many of its derivatives are known.[182] Azulene readily undergoes aromatic substitution. Azulene may be regarded as a combination of **58** and **62** and, indeed, possesses a dipole moment of 0.8 *D* (see **72**).[183] Interestingly, if two electrons are added to pentalene, a stable dianion (**73**) results.[184] It can be concluded that an aromatic system of electrons will be spread over two rings only if 10 electrons (not 8 or 12) are available for aromaticity. $[n, m]$-Fluvalenes ($n \neq m$, where fulvalene is **74**) as well as azulene are known to shift their π-electrons due to the influence of dipolar aromatic resonance structures.[185] However, calculations showed that

[174]Bertelli, D.J., in Bergmann, E.D.; Pullman, B. *Aromaticity, Pseudo-Aromaticity, and Anti-Aromaticity*, Israel Academy of Sciences and Humanities, Jerusalem, ***1971***, p. 326. See also Stegemann, J.; Lindner, H.J. *Tetrahedron Lett.* ***1977***, 2515.

[175]Vogel, E.; Ippen, J. *Angew. Chem. Int. Ed.* ***1974***, *13*, 734; Vogel, E.; Hogrefe, F. *Angew. Chem. Int. Ed.* ***1974***, *13*, 735.

[176]Hafner, K.; Knaup, G.L.; Lindner, H.J. *Bull. Soc. Chem. Jpn.* ***1988***, *61*, 155.

[177]Metal complexes of pentalene have been prepared: Knox, S.A.R.; Stone, F.G.A. *Acc. Chem. Res.* ***1974***, *7*, 321.

[178]LeGoff, E. *J. Am. Chem. Soc.* ***1962***, *84*, 3975. See also Hafner, K.; Bangert, K.F.; Orfanos, V. *Angew. Chem. Int. Ed.* ***1967***, *6*, 451; Hartke, K.; Matusch, R. *Angew. Chem. Int. Ed.* ***1972***, *11*, 50.

[179]Hafner, K.; Süss, H.U. *Angew. Chem. Int. Ed.* ***1973***, *12*, 575. See also Hafner, K.; Suda, M. *Angew. Chem. Int. Ed.* ***1976***, *15*, 314.

[180]Kitschke, B.; Lindner, H.J. *Tetrahedron Lett.* ***1977***, 2511; Bischof, P.; Gleiter, R.; Hafner, K.; Knauer, K.H.; Spanget-Larsen, J.; Süss, H.U. *Chem. Ber.* ***1978***, *111*, 932.

[181]Bloch, R.; Marty, R.A.; de Mayo, P. *J. Am. Chem. Soc.* ***1971***, *93*, 3071; *Bull. Soc. Chim. Fr.*, ***1972***, 2031; Hafner, K.; Dönges, R.; Goedecke, E.; Kaiser, R. *Angew. Chem. Int. Ed.* ***1973***, *12*, 337.

[182]For a review on azulene, see Mochalin, V.B.; Porshnev, Yu.N. *Russ. Chem. Rev.* ***1977***, *46*, 530.

[183]Tobler, H.J.; Bauder, A.; Günthard, H.H. *J. Mol. Spectrosc.*, ***1965***, *18*, 239.

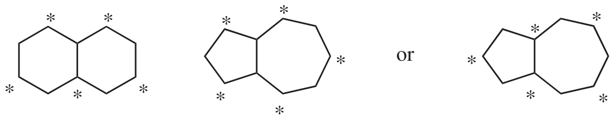
[184]Katz, T.J.; Rosenberger, M.; O'Hara, R.K. *J. Am. Chem. Soc.* ***1964***, *86*, 249. See also, Willner, I.; Becker, J.Y.; Rabinovitz, M. *J. Am. Chem. Soc.* ***1979***, *101*, 395.

[185]Möllerstedt, H.; Piqueras, M.C.; Crespo, R.; Ottosson, H. *J. Am. Chem. Soc.* ***2004***, *126*, 13938.

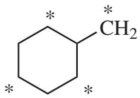
dipolar resonance structures contribute only 5% to the electronic structure of heptafulvalene (**75**), although 22–31% to calicene (**76**).[186] Based on Baird's theory,[187] these molecules are influenced by aromaticity in both the ground and excited states, therefore acting as aromatic "chameleons." This premise was confirmed in work by Ottosson and co-workers.[185] Aromaticity indexes for various substituted fulvalene compounds has been reported.[188]

Alternant and Nonalternant Hydrocarbons[189]

Aromatic hydrocarbons can be divided into alternant and nonalternant hydrocarbons. In alternant hydrocarbons, the conjugated carbon atoms can be divided into two sets such that no two atoms of the same set are directly linked. For convenience, one set may be starred. Naphthalene is an alternant and azulene a nonalternant hydrocarbon:



In alternant hydrocarbons, the bonding and antibonding orbitals occur in pairs; that is, for every bonding orbital with an energy $-E$ there is an antibonding one with energy $+E$ (Fig. 2.8[190]). Even-alternant hydrocarbons are those with an even number of conjugated atoms, that is, an equal number of starred and unstarred atoms. For these hydrocarbons, all the bonding orbitals are filled and the π electrons are uniformly spread over the unsaturated atoms.



As with the allylic system, odd-alternant hydrocarbons (which must be carbocations, carbanions, or radicals) in addition to equal and opposite bonding and antibonding orbitals also have a nonbonding orbital of zero energy. When an odd number of orbitals overlap, an odd number is created. Since orbitals of alternant hydrocarbons occur in $-E$ and $+E$ pairs, one orbital can have no partner and must therefore have zero bonding energy. For example, in the benzylic system the cation has an unoccupied nonbonding orbital, the free radical has one electron there and the carbanion two (Fig. 2.9). As with the allylic system, all three species have the same bonding energy. The charge distribution (or unpaired-electron distribution)

[186]Scott, A.P.; Agranat, A.; Biedermann, P.U.; Riggs, N.V.; Radom, L. *J. Org. Chem.* ***1997***, *62*, 2026.
[187]Baird, N.C. *J. Am. Chem. Soc.* ***1972***, *94*, 4941.
[188]Stepien, B.T.; Krygowski, T.M.; Cyranski, M.K. *J. Org. Chem.* ***2002***, *67*, 5987.
[189]For discussions, see Jones, R.A.Y. *Physical and Mechanistic Organic Chemistry*, 2nd ed.; Cambridge University Press, Cambridge, ***1984***, pp. 122–129; Dewar, M.J.S. *Prog. Org. Chem.* ***1953***, *2*, 1.
[190]Taken from Dewar, M.J.S *Prog. Org. Chem.* ***1953***, *2*, 1, p. 8.

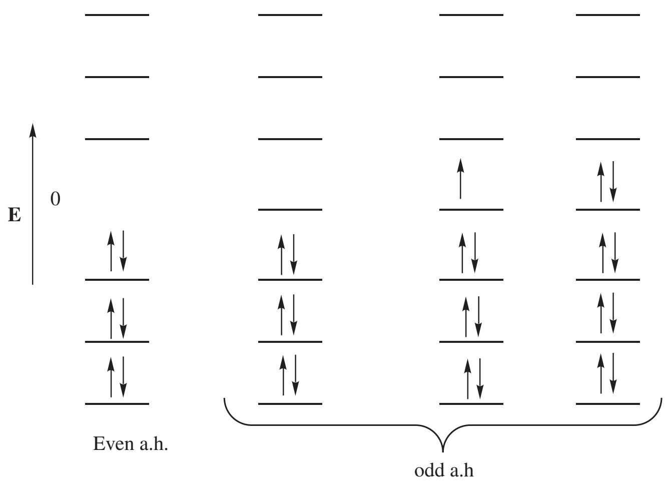


Fig. 2.8. Energy levels in odd- and even-alternant hydrocarbons.[190] The arrows represent electrons. The orbitals are shown as having different energies, but some may be degenerate.

over the entire molecule is also the same for the three species and can be calculated by a relatively simple process.[189]

For nonalternant hydrocarbons the energies of the bonding and antibonding orbitals are not equal and opposite and charge distributions are not the same in cations, anions, and radicals. Calculations are much more difficult but have been carried

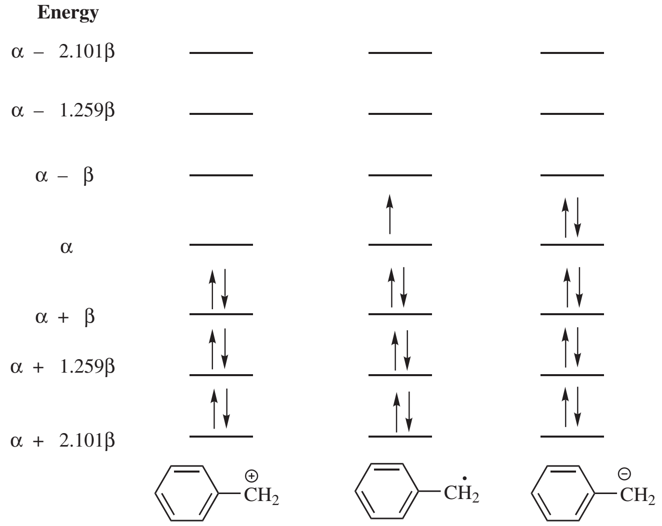
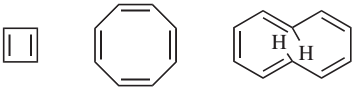


Fig. 2.9. Energy levels for the benzyl cation, free radical, and carbanion. Since α is the energy of a *p*-orbital (p. 36), the nonbonding orbital has no bonding energy.

out.[191] Theoretical approaches to calculate topological polarization and reactivity of these hydrocarbons have been reported.[192]

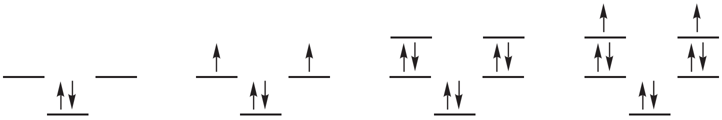
Aromatic Systems with Electron Numbers Other Than Six

Ever since the special stability of benzene was recognized, chemists have been thinking about homologous molecules and wondering whether this stability is also associated with rings that are similar but of different sizes, such as cyclobutadiene (**77**), cyclooctatetraene (**78**), cyclodecapentaene (**79**)[193], and so on. The general



77 **78** **79**

name *annulene* is given to these compounds, benzene being [6]annulene, and **77–79** being called, respectively, [4], [8], and [10]annulene. By a naïve consideration of resonance forms, these annulenes and higher ones should be as aromatic as benzene. Yet they proved remarkably elusive. The ubiquitous benzene ring is found in thousands of natural products, in coal and petroleum, and is formed by strong treatment of many noncyclic compounds. None of the other annulene ring systems has ever been found in nature and, except for cyclooctatetraene, their synthesis is not simple. Obviously, there is something special about the number six in a cyclic system of electrons.



Duet (aromatic) Quartet (diradical) Sextet (aromatic) Octet (diradical)

Hückel's rule, based on molecular-orbital calculations,[194] predicts that electron rings will constitute an aromatic system only if the number of electrons in the ring is of the form $4n + 2$, where n is zero or any position integer. Systems that contain $4n$ electrons are predicted to be nonaromatic. The rule predicts that

[191]Peters, D. *J. Chem. Soc.* ***1958***, 1023, 1028, 1039; Brown, R.D.; Burden, F.R.; Williams, G.R. *Aust. J. Chem.* ***1968***, *21*, 1939. For reviews, see Zahradnik, R., in Snyder, J.P. *Nonbenzenoid Aromatics* vol. 2, Academic Press, NY, ***1971***, pp. 1–80; Zahradnik, R. *Angew. Chem. Int. Ed.* ***1965***, *4*, 1039.

[192]Langler, R.F. *Aust. J. Chem.* ***2000***, *53*, 471; Fredereiksen, M.U.; Langler, R.F.; Staples, M.A.; Verma, S.D. *Aust. J. Chem.* ***2000***, *53*, 481.

[193]The cyclodecapentaene shown here is the cis–trans–cis–cis–trans form. For other stereoisomers, see p. 79.

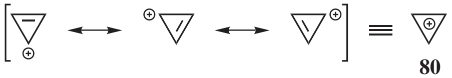
[194]For reviews of molecular-orbital calculations of nonbenzenoid cyclic conjugated hydrocarbons, see Nakajima, T. *Pure Appl. Chem.* ***1971***, *28*, 219; *Fortschr. Chem. Forsch.* ***1972***, *32*, 1.

rings of 2, 6, 10, 14, and so on, electrons will be aromatic, while rings of 4, 8, 12, and so on, will not be. This is actually a consequence of Hund's rule. The first pair of electrons in an annulene goes into the π orbital of lowest energy. After that the bonding orbitals are degenerate and occur in pairs of equal energy. When there is a total of four electrons, Hund's rule predicts that two will be in the lowest orbital but the other two will be unpaired, so that the system will exist as a diradical rather than as two pairs. The degeneracy can be removed if the molecule is distorted from maximum molecular symmetry to a structure of lesser symmetry. For example, if **77** assumes a rectangular rather than a square shape, one of the previously degenerate orbitals has a lower energy than the other and will be occupied by two electrons. In this case, of course, the double bonds are essentially separate and the molecule is still not aromatic. Distortions of symmetry can also occur when one or more carbons are replaced by heteroatoms or in other ways.[195]

In the following sections systems with various numbers of electrons are discussed. When we look for aromaticity we look for (*1*) the presence of a diamagnetic ring current; (*2*) equal or approximately equal bond distances, except when the symmetry of the system is disturbed by a heteroatom or in some other way; (*3*) planarity; (*4*) chemical stability; (*5*) the ability to undergo aromatic substitution.

Systems of Two Electrons[196]

Obviously, there can be no ring of two carbon atoms though a double bond may be regarded as a degenerate case. However, in analogy to the tropylium ion, a three-membered ring with a double bond and a positive charge on the third atom (the *cyclopropenyl cation*) is a $4n + 2$ system and hence is expected to show aromaticity. The unsubstituted **80** has been prepared,[197] as well as several derivatives, e.g.,



80

the trichloro, diphenyl, and dipropyl derivatives, and these are stable despite the angles of only 60°. In fact, the tripropylcyclopropenyl,[198] tricyclopropylcyclopropenyl,[199] chlorodipropylcyclopropenyl,[200] and chloro-bisdialkylaminocyclopropenyl[201] cations are among the most stable carbocations known, being stable

[195]For a discussion, see Hoffmann, R. *Chem. Commun.* ***1969***, 240.

[196]For reviews, see Billups, W.E.; Moorehead, A.W., in Rappoport *The Chemistry of the Cyclopropyl Group*, pt. 2, Wiley, NY, ***1987***, pp. 1533–1574; Potts, K.T.; Baum, J.S. *Chem. Rev.* ***1974***, *74*, 189; Yoshida, Z. *Top. Curr. Chem.* ***1973***, *40*, 47; D'yakonov, I.A.; Kostikov, R.R. *Russ. Chem. Rev.* ***1967***, *36*, 557; Closs, G.L. *Adv. Alicyclic Chem.* ***1966***, *1*, 53, pp. 102–126; Krebs, A.W. *Angew. Chem. Int. Ed.* ***1965***, *4*, 10.

[197]Farnum, D.G.; Mehta, G.; Silberman, R.G. *J. Am. Chem. Soc.* ***1967***, *89*, 5048; Breslow, R.; Groves, J.T. *J. Am. Chem. Soc.* ***1970***, *92*, 984.

[198]Breslow, R.; Höver, H.; Chang, H.W. *J. Am. Chem. Soc.* ***1962***, *84*, 3168.

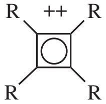
[199]Komatsu, K.; Tomioka, K.; Okamoto, K. *Tetrahedron Lett.* ***1980***, *21*, 947; Moss, R.A.; Shen, S.; Krogh-Jespersen, K.; Potenza, J.A.; Schugar, H.J.; Munjal, R.C. *J. Am. Chem. Soc.* ***1986***, *108*, 134.

[200]Ito, S.; Morita, N.; Asao, T. *Tetrahedron Lett.* ***1992***, *33*, 3773.

[201]Taylor, M.J.; Surman, P.W.J.; Clark, G.R. *J. Chem. Soc. Chem. Commun.* ***1994***, 2517.

even in water solution. The tri-*tert*-butylcyclopropenyl cation is also very stable.[202] In addition, cyclopropenone and several of its derivatives are stable

Cyclopropenone



81

compounds,[203] in accord with the corresponding stability of the tropones.[204] The ring system **80** is nonalternant and the corresponding radical and anion (which do not have an aromatic duet) have electrons in antibonding orbitals, so that their energies are much higher. As with **58** and **62**, the equivalence of the three carbon atoms in the triphenylcyclopropenyl cation has been demonstrated by ^{14}C labeling experiments.[205] The interesting dications **81** (R = Me or Ph) have been prepared,[206] and they too should represent aromatic systems of two electrons.[207]

Systems of Four Electrons: Antiaromaticity

The most obvious compound in which to look for a closed loop of four electrons is cyclobutadiene (**77**).[208] Hückel's rule predicts no aromatic character here, since 4 is not a number of the form $4n + 2$. There is a long history of attempts to prepare this compound and its simple derivatives, and those experiments fully bear out Hückel's prediction. Cyclobutadienes display none of the characteristics that would lead us to call them aromatic, and there is evidence that a closed loop of four electrons is actually *antiaromatic*.[209] If such compounds simply lacked aromaticity, we would expect

[202]Ciabattoni, J.; Nathan III, E.C. *J. Am. Chem. Soc.* ***1968***, *90*, 4495.

[203]See, for example, Kursanov, D.N.; Vol'pin, M.E.; Koreshkov, Yu.D. *J. Gen. Chem. USSR* ***1960***, *30*, 2855; Breslow, R.; Oda, M. *J. Am. Chem. Soc.* ***1972***, *94*, 4787; Yoshida, Z.; Konishi, H.; Tawara, Y.; Ogoshi, H. *J. Am. Chem. Soc.* ***1973***, *95*, 3043; Ciabattoni, J.; Nathan III, E.C. *J. Am. Chem. Soc.* ***1968***, *90*, 4495.

[204]For a reveiw of cyclopropenones, see Eicher, T.; Weber, J.L. *Top. Curr. Chem. Soc.* ***1975***, *57*, 1. For discussions of cyclopropenone structure, see Shäfer, W.; Schweig, A.; Maier, G.; Sayrac, T.; Crandall, J.K. *Tetrahedron Lett.* ***1974***, 1213; Tobey, S.W., in Bergmann, E.D.; Pullman, B. *Aromaticity, Pseudo-Aromaticity, and Anti-Aromaticity*, Israel Academy of Sciences and Humanities, Jerusalem, ***1971***, pp. 351–362; Greenberg, A.; Tomkins, R.P.T.; Dobrovolny, M.; Liebman, J.F. *J. Am. Chem. Soc.* ***1983***, *105*, 6855.

[205]D'yakonov, I.A.; Kostikov, R.R.; Molchanov, A.P. *J. Org. Chem. USSR* ***1969***, *5*, 171; ***1970***, *6*, 304.

[206]Freedman, H.H.; Young, A.E. *J. Am. Chem. Soc.* ***1964***, *86*, 734; Olah, G.A.; Staral, J.S. *J. Am. Chem. Soc.* ***1976***, *98*, 6290. See also Lambert, J.B.; Holcomb, A.G. *J. Am. Chem. Soc.* ***1971***, *93*, 2994; Seitz, G.; Schmiedel, R.; Mann, K. *Synthesis*, ***1974***, 578.

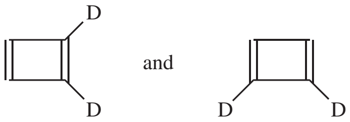
[207]See Pittman Jr., C.U.; Kress, A.; Kispert, L.D. *J. Org. Chem.* ***1974***, *39*, 378. See, however, Krogh-Jespersen, K.; Schleyer, P.v.R.; Pople, J.A.; Cremer, D. *J. Am. Chem. Soc.* ***1978***, *100*, 4301.

[208]For a monograph, see Cava, M.P.; Mitchell, M.J. *Cyclobutadiene and Related Compounds*; Academic Press, NY, ***1967***. For reviews, see Maier, G. *Angew. Chem. Int. Ed.* ***1988***, *27*, 309; ***1974***, *13*, 425–438; Bally, T.; Masamune, S. *Tetrahedron* ***1980***, *36*, 343; Vollhardt, K.P.C. *Top. Curr. Chem.* ***1975***, *59*, 113.

[209]For reviews of antiaromaticity, see Glukhovtsev, M.N.; Simkin, B.Ya.; Minkin, V.I. *Russ. Chem. Rev.* ***1985***, *54*, 54; Breslow, R. *Pure Appl. Chem.* ***1971***, *28*, 111; *Acc. Chem. Res.* ***1973***, *6*, 393.

them to be about as stable as similar nonaromatic compounds, but both theory and experiment show that they are *much less stable*.[210] An antiaromatic compound may be defined as a compound that is destabilized by a closed loop of electrons.

After years of attempts to prepare cyclobutadiene, the goal was finally reached by Pettit and co-workers.[211] It is now clear that **77** and its simple derivatives are extremely unstable compounds with very short lifetimes (they dimerize by a Diels–Alder reaction; see **15–60**) unless they are stabilized in some fashion, either at ordinary temperatures embedded in the cavity of a hemicarcerand[212] (see the structure of a carcerand on p. 128), or in matrices at very low temperatures (generally under 35 K). In either of these cases, the cyclobutadiene molecules are forced to remain apart from each other, and other molecules cannot get in. The structures of **77** and some of its derivatives have been studied a number of times using the low-temperature matrix technique.[213] The ground-state structure of **77** is a rectangular diene (not a diradical) as shown by the ir spectra of **77** and deuterated **77** trapped in matrices,[214] as well as by a photoelectron spectrum.[215] Molecular-orbital calculations agree.[216] The same conclusion was also reached in an elegant experiment in which 1,2-dideuterocyclobutadiene was generated. If **77** is a rectangular diene, the dideutero compound should exist as two isomers:



The compound was generated (as an intermediate that was not isolated) and two isomers were indeed found.[217] The cyclobutadiene molecule is not static, even in the matrices. There are two forms (**77a** and **77b**), which rapidly interconvert.[218]

[210]For a discussion, see Bauld, N.L.; Welsher, T.L.; Cessac, J.; Holloway, R.L. *J. Am. Chem. Soc.* ***1978***, *100*, 6920.

[211]Watts, L.; Fitzpatrick, J.D.; Pettit, R. *J. Am. Chem. Soc.* ***1965***, *87*, 3253, ***1966***, *88*, 623. See also, Cookson, R.C.; Jones, D.W. *J. Chem. Soc.* ***1965***, 1881.

[212]Cram, D.J.; Tanner, M.E.; Thomas, R. *Angew. Chem. Int. Ed.* ***1991***, *30*, 1024.

[213]See, for example, Lin, C.Y.; Krantz, A. *J. Chem. Soc. Chem. Commun.* ***1972***, 1111; Chapman, O.L.; McIntosh, C.L.; Pacansky, J. *J. Am. Chem. Soc.* ***1973***, *95*, 614; Maier, G.; Mende, U. *Tetrahedron Lett.* ***1969***, 3155. For a review, see Sheridan, R.S. *Org. Photochem.* ***1987***, *8*, 159; pp. 167–181.

[214]Masamune, S.; Souto-Bachiller, F.A.; Machiguchi, T.; Bertie, J.E. *J. Am. Chem. Soc.* ***1978***, *100*, 4889.

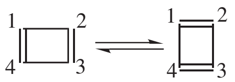
[215]Kreile, J.; Münzel, N.; Schweig, A.; Specht, H. *Chem. Phys. Lett.* ***1986***, *124*, 140.

[216]See, for example, Borden, W.T.; Davidson, E.R.; Hart, P. *J. Am. Chem. Soc.* ***1978***, *100*, 388; Kollmar, H.; Staemmler, V. *J. Am. Chem. Soc.* ***1978***, *100*, 4304; Jafri, J.A.; Newton, M.D. *J. Am. Chem. Soc.* ***1978***, *100*, 5012; Ermer, O.; Heilbronner, E. *Angew. Chem. Int. Ed.* ***1983***, *22*, 402; Voter, A.F.; Goddard III, W.A. *J. Am. Chem. Soc.* ***1986***, *108*, 2830.

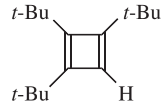
[217]Whitman, D.W.; Carpenter, B.K. *J. Am. Chem. Soc.* ***1980***, *102*, 4272. See also Whitman, D.W.; Carpenter, B.K. *J. Am. Chem. Soc.* ***1982***, *104*, 6473.

[218]Carpenter, B.K. *J. Am. Chem. Soc.* ***1983***, *105*, 1700; Huang, M.; Wolfsberg, M. *J. Am. Chem. Soc.* ***1984***, *106*, 4039; Dewar, M.J.S.; Merz, Jr., K.M.; Stewart, J.J.P. *J. Am. Chem. Soc.* ***1984***, *106*, 4040; Orendt, A.M.; Arnold, B.R.; Radziszewski, J.G.; Facelli, J.C.; Malsch, K.D.; Strub, H.; Grant, D.M.; Michl, J. *J. Am. Chem. Soc.* ***1988***, *110*, 2648. See, however, Arnold, B.R.; Radziszewski, J.G.; Campion, A.; Perry, S.S.; Michl, J. *J. Am. Chem. Soc.* ***1991***, *113*, 692.

Note that there is experimental evidence that the aromatic and antiaromatic characters of neutral and dianionic systems are measurably increased via deuteration.[219]

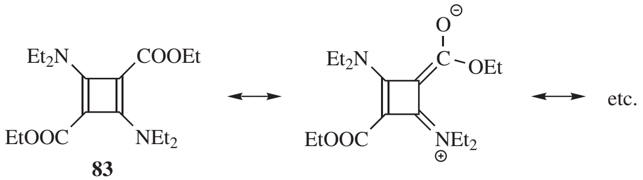


77a **77b**



82

There are some simple cyclobutadienes that are stable at room temperature for varying periods of time. These either have bulky substituents or carry certain other stabilizing substituents such as seen in tri-*tert*-butylcyclobutadiene (**83**).[220] Such compounds are relatively stable because dimerization is sterically hindered. Examination of the NMR spectrum of **83** showed that the ring proton ($\delta = 5.38$) was shifted *upfield*, compared with the position expected for a nonaromatic proton, for example, cyclopentadiene. As we will see (pp. 89–90), this indicates that the compound is antiaromatic.



83

The other type of stable cyclobutadiene has two electron-donating and two electron-withdrawing groups,[221] and is stable in the absence of water.[222] An example is **58**. The stability of these compounds is generally attributed to the resonance shown, a type of resonance stabilization called the *push–pull or captodative effect*,[223] although it has been concluded from a photoelectron spectroscopy study that second-order bond fixation is more important.[224] An X-ray crystallographic study of **83** has shown[225] the ring to be a distorted square with bond lengths of 1.46 Å and angles of 87° and 93°.

[219]For experiments with [16]-annulene (see p 82), see Stevenson, C.D.; Kurth, T.L. *J. Am. Chem. Soc.* ***1999***, *121*, 1623

[220]Masamune, S.; Nakamura, N.; Suda, M.; Ona, H. *J. Am. Chem. Soc.* ***1973***, *95*, 8481; Maier, G.; Alzérreca, A. *Angew. Chem. Int. Ed.* ***1973***, *12*, 1015. For a discussion, see Masamune, S. *Pure Appl. Chem.* ***1975***, *44*, 861.

[221]The presence of electron-donating and -withdrawing groups on the same ring stabilizes $4n$ systems and destabilizes $4n + 2$ systems. For a review of this concept, see Gompper, R.; Wagner, H. *Angew. Chem. Int. Ed.* ***1988***, *27*, 1437.

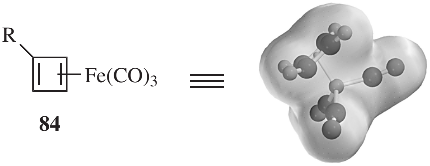
[222]Neuenschwander, M.; Niederhauser, A. *Chimia*, ***1968***, *22*, 491, *Helv. Chim. Acta*, ***1970***, *53*, 519; Gompper, R.; Kroner, J.; Seybold, G.; Wagner, H. *Tetrahedron* ***1976***, *32*, 629.

[223]Manatt, S.L.; Roberts, J.D. *J. Org. Chem.* ***1959***, *24*, 1336; Breslow, R.; Kivelevich, D.; Mitchell, M.J.; Fabian, W.; Wendel, K. *J. Am. Chem. Soc.* ***1965***, *87*, 5132; Hess Jr., B.A.; Schaad, L.J. *J. Org. Chem.* ***1976***, *41*, 3058.

[224]Gompper, R.; Holsboer, F.; Schmidt, W.; Seybold, G. *J. Am. Chem. Soc.* ***1973***, *95*, 8479.

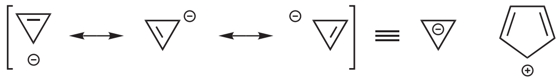
[225]Lindner, H.J.; von Ross, B. *Chem. Ber.* ***1974***, *107*, 598.

It is clear that simple cyclobutadienes, which could easily adopt a square planar shape if that would result in aromatic stabilization, do not in fact do so and are not aromatic. The high reactivity of these compounds is not caused merely by steric strain, since the strain should be no greater than that of simple cyclopropenes, which are known compounds. It is probably caused by antiaromaticity.[226]



84

The cyclobutadiene system can be stabilized as a η^4-complex with metals,[227] as with the iron complex **84** (see Chapter 3), but in these cases electron density is withdrawn from the ring by the metal and there is no aromatic quartet. In fact, these cyclobutadiene–metal complexes can be looked upon as systems containing an aromatic duet. The ring is square planar,[228] the compounds undergo aromatic substitution,[229] and nmr spectra of monosubstituted derivatives show that the C-2 and C-4 protons are equivalent.[229]



85 **86** **87**

Other systems that have been studied as possible aromatic or antiaromatic four-electron systems include the cyclopropenyl anion (**86**), the cyclopentadienyl cation (**87**).[230] With respect to **86**, HMO theory predicts that an unconjugated **85** (i.e., a single canonical form) is more stable than a conjugated **86**,[231] so that **85** would actually lose stability by forming a closed loop of four electrons. The HMO theory

[226]For evidence, see Breslow, R.; Murayama, D.R.; Murahashi, S.; Grubbs, R. *J. Am. Chem. Soc.* ***1973***, *95*, 6688; Herr, M.L. *Tetrahedron* ***1976***, *32*, 2835.

[227]For reviews, see Efraty, A. *Chem. Rev.* ***1977***, *77*, 691; Pettit, R. *Pure Appl. Chem.* ***1968***, *17*, 253; Maitlis, P.M. *Adv. Organomet. Chem.* ***1966***, *4*, 95; Maitlis, P.M.; Eberius, K.W., in Snyder, J.P. *Nonbenzenoid Aromatics*, vol. 2, Academic Press, NY, ***1971***, pp. 359–409.

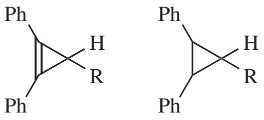
[228]Dodge, R.P.; Schomaker, V. *Acta Crystallogr.* ***1965***, *18*, 614; *Nature* (*London*) ***1960***, *186*, 798; Dunitz, J.D.; Mez, H.C.; Mills, O.S.; Shearer, H.M.M. *Helv. Chim. Acta*, ***1962***, *45*, 647; Yannoni, C.S.; Ceasar, G.P.; Dailey, B.P. *J. Am. Chem. Soc.* ***1967***, *89*, 2833.

[229]Fitzpatrick, J.D.; Watts, L.; Emerson, G.F.; Pettit, R. *J. Am. Chem. Soc.* ***1965***, *87*, 3255. For a discussion, see Pettit, R. *J. Organomet. Chem.* ***1975***, *100*, 205.

[230]For a review of cyclopentadienyl cations, see Breslow, R. *Top. Nonbenzenoid Aromat. Chem.* ***1973***, *1*, 81.

[231]Clark, D.T. *Chem. Commun.* ***1969***, 637; Glukhovtsev, M.N.; Simkin, B.Ya.; Minkin, V.I. *Russ. Chem. Rev.* ***1985***, *54*, 54; Breslow, R. *Pure Appl. Chem.* ***1971***, *28*, 111; *Acc. Chem. Res.* ***1973***, *6*, 393.

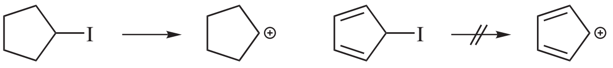
is supported by experiment. Among other evidence,



88 **89**

it has been shown that **88** (R = COPh) loses its proton in hydrogen-exchange reactions ~6000 times more slowly than **89** (R = COPh).[232] Where R = CN, the ratio is ~10,000.[233] This indicates that **88** are much more reluctant to form carbanions (which would have to be cyclopropenyl carbanions) than **89**, which form ordinary carbanions. Thus the carbanions of **88** are less stable than corresponding ordinary carbanions. Although derivatives of cyclopropenyl anion have been prepared as fleeting intermediates (as in the exchange reactions mentioned above), all attempts to prepare the ion or any of its derivatives as relatively stable species have so far met with failure.[234]

In the case of **87**, the ion has been prepared and has been shown to be a diradical in the ground state,[235] as predicted by the discussion on p. 73.[236] Evidence that **87** is not only nonaromatic, but also antiaromatic comes from studies on **90** and **92**.[237] When **90** is treated with silver perchlorate in propionic acid, the molecule is rapidly solvolyzed (a reaction in which the intermediate **91** is formed; see Chapter 5). Under the same conditions, **92** undergoes no solvolysis at all; that is, **87** does not form. If **87** were merely nonaromatic, it should be about as stable as **91** (which of course has no resonance stabilization at all). The fact that it is so much more reluctant to form indicates that **87** is much less stable than **91**. It is noted that under certain conditions, **91** can be generated solvolytically.[238]



90 **91** **92** **87**

[232]Breslow, R.; Brown, J.; Gajewski, J.J. *J. Am. Chem. Soc.* ***1967***, *89*, 4383.

[233]Breslow, R.; Douek, M. *J. Am. Chem. Soc.* ***1968***, *90*, 2698.

[234]See, for example, Breslow, R.; Cortés, D.A.; Juan, B.; Mitchell, R.D. *Tetrahedron Lett.* ***1982***, *23*, 795. A triphenylcyclopropyl anion has been prepared in the gas phase, with a lifetime of 1–2 s: Bartmess, J.E.; Kester, J.; Borden, W.T.; Köser, H.G. *Tetrahedron Lett.* ***1986***, *27*, 5931.

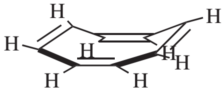
[235]Saunders, M.; Berger, R.; Jaffe, A.; McBride, J.M.; O'Neill, J.; Breslow, R.; Hoffman Jr., J.M.; Perchonock, C.; Wasserman, E.; Hutton, R.S.; Kuck, V.J. *J. Am. Chem. Soc.* ***1973***, *95*, 3017.

[236]Derivatives of **87** show similar behavior. Volz, H. *Tetrahedron Lett.* ***1964***, 1899; Breslow, R.; Chang, H.W.; Hill, R.; Wasserman, E. *J. Am. Chem. Soc.* ***1967***, *89*, 1112; Gompper, R.; Glöckner, H. *Angew. Chem. Int. Ed.* ***1984***, *23*, 53.

[237]Breslow, R.; Mazur, S. *J. Am. Chem. Soc.* ***1973***, *95*, 584. For further evidence, see Lossing, F.P.; Treager, J.C. *J. Am. Chem. Soc.* ***1975***, *97*, 1579. See also, Breslow, R.; Canary, J.W. *J. Am. Chem. Soc.* ***1991***, *113*, 3950.

[238]Allen, A.D.; Sumonja, M.; Tidwell, T.T. *J. Am. Chem. Soc.* ***1997***, *119*, 2371.

It is strong evidence for Hückel's rule that **86** and **87** are not aromatic while the cyclopropenyl cation (**80**) and the cyclopentadienyl anion (**58**) are, since simple resonance theory predicts no difference between **86** and **80** or **87** and **58** (the same number of equivalent canonical forms can be drawn for **86** as for **80** and for **87** as for **58**).



78a

Systems of Eight Electrons

Cyclooctatetraene[239] ([8]annulene, **78a**) is not planar, but tub-shaped.[240] Therefore we would expect that it is neither aromatic nor antiaromatic, since both these conditions require overlap of parallel *p* orbitals. The reason for the lack of planarity is that a regular octagon has angles of 135°, while sp^2 angles are most stable at 120°. To avoid the strain, the molecule assumes a nonplanar shape, in which orbital overlap is greatly diminished.[241] Single- and double-bond distances in **78** are, respectively, 1.46 and 1.33 Å, which is expected for a compound made up of four individual double bonds.[240] The reactivity is also what would be expected for a linear polyene. Reactive intermediates can be formed in solution. Dehydrohalogenation of bromocyclooctatetraene at −100°C has been reported, for example, and trapping by immediate electron transfer gave a stable solution of the [8]annulyne anion radical.[242]

The cyclooctadiendiynes **93** and **94** are planar conjugated eight-electron systems (the four extra triple-bond electrons do not participate), which nmr evidence show to be antiaromatic.[243] There is evidence that part of the reason for the lack of planarity in **78** itself is that a planar molecular would have to be antiaromatic.[244] The cycloheptatrienyl anion (**61**) also has eight electrons, but does not behave like an aromatic system.[151] The bond lengths for a series of molecules containing the cycloheptatrienide anion have recently been published.[245] The NMR spectrum

[239]For a monograph, see Fray, G.I.; Saxton, R.G. *The Chemistry of Cyclooctatetraene and its Derivatives*; Cambridge University Press: Cambridge, ***1978***. For a review, see Paquette, L.A. *Tetrahedron* ***1975***, *31*, 2855. For reviews of heterocyclic 8π systems, see Kaim, W. *Rev. Chem. Intermed.* ***1987***, *8*, 247; Schmidt, R.R. *Angew. Chem. Int. Ed.* ***1975***, *14*, 581.

[240]Bastiansen, O.; Hedberg, K.; Hedberg, L. *J. Chem. Phys.* ***1957***, *27*, 1311.

[241]The compound perfluorotetracyclobutacyclooctatetraene has been found to have a planar cyclooctatetraene ring, although the corresponding tetracyclopenta analog is nonplanar: Einstein, F.W.B.; Willis, A.C.; Cullen, W.R.; Soulen, R.L. *J. Chem. Soc. Chem. Commun.* ***1981***, 526. See also, Paquette, L.A.; Wang, T.; Cottrell, C.E. *J. Am. Chem. Soc.* ***1987***, *109*, 3730.

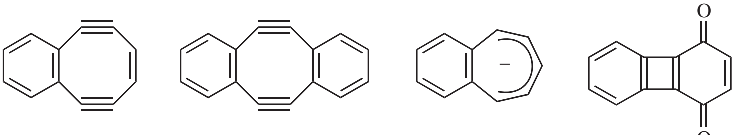
[242]Peters, S.J.; Turk, M.R.; Kiesewetter, M.K.; Stevenson, C.D. *J. Am. Chem. Soc.* ***2003***, *125*, 11264.

[243]For a review, see Huang, N.Z.; Sondheimer, F. *Acc. Chem. Res.* ***1982***, *15*, 96. See also, Dürr, H.; Klauck, G.; Peters, K.; von Schnering, H.G. *Angew. Chem. Int. Ed.* ***1983***, *22*, 332; Chan, T.; Mak, T.C.W.; Poon, C.; Wong, H.N.C.; Jia, J.H.; Wang, L.L. *Tetrahedron* ***1986***, *42*, 655.

[244]Figeys, H.P.; Dralants, A. *Tetrahedron Lett.* ***1971***, 3901; Buchanan, G.W. *Tetrahedron Lett.* ***1972***, 665.

[245]Dietz, F.; Rabinowitz, M.; Tadjer, A.; Tyutyulkov, N. *J. Chem. Soc. Perkin Trans. 2* ***1995***, 735.

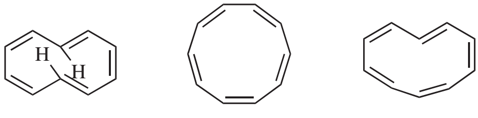
of the benzocycloheptatrienyl anion (**95**) shows that, like **82**, **93**, and **94**, this compound is antiaromatic.[246] A new antiaromatic compound 1,4-biphenylene quinone (**96**) was prepared, but it rapidly dimerizes due to instability.[247]



93 **94** **95** **96**

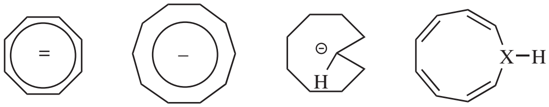
Systems of Ten Electrons[248]

There are three geometrically possible isomers of [10]annulene: the all-*cis* (**97**), the mono-*trans* (**98**), and the *cis–trans–cis–cis–trans* (**79**). If Hückel's rule applies, they should be planar. But it is far from obvious that the molecules would adopt a planar



79 **97** **98**

shape, since they must overcome considerable strain to do so. For a regular decagon (**97**) the angles would have to be 144°, considerably larger than the 120° required for sp^2 angles. Some of this strain would also be present in **98**, but this kind of strain is eliminated in **79** since all the angles are 120°. However, it was pointed out by Mislow[249] that the hydrogens in the 1 and 6 positions should interfere with each other and force the molecule out of planarity.



99 **100** **101** **102**

Compounds **97** and **98** have been prepared[250] as crystalline solids at −80°C. The NMR spectra show that all the hydrogens lie in the alkene region and it was concluded that neither compound is aromatic. Calculations on **98** suggest that

[246]Staley, S.W.; Orvedal, A.W. *J. Am. Chem. Soc.* ***1973***, *95*, 3382.

[247]Kiliç, H.; Balci, M. *J. Org. Chem.* ***1997***, *62*, 3434.

[248]For reviews, see Kemp-Jones, A.V.; Masamune, S. *Top. Nonbenzenoid Aromat. Chem.* ***1973***, *1*, 121; Masamune, S.; Darby, N. *Acc. Chem. Res.* ***1972***, *5*, 272; Burkoth, T.L.; van Tamelen, E.E., in Snyder,J.P. *Nonbenzenoid Aromaticity*, Vol. 1, Academic Press, NY, ***1969***, pp. 63–116; Vogel, E., in Garratt, P.J. Aromaticity, Wiley, NY, ***1986***, pp. 113–147.

[249]Mislow, K. *J. Chem. Phys.* ***1952***, *20*, 1489.

[250]Masamune,S.; Hojo, K.; Bigam, G.; Rabenstein, D.L. *J. Am. Chem. Soc.* ***1971***, *93*, 4966. [10]Annulenes had previously been prepared, but it was not known which ones: van Tamelen, E.E.; Greeley, R.H. *Chem. Commun.* ***1971***, 601; van Tamelen, E.E.; Burkoth, T.L.; Greeley, R.H. *J. Am. Chem. Soc.* ***1971***, *93*, 6120.

it may indeed be aromatic, although the other isomers are not.[251] It is known that the Hartree–Fock (HF) method incorrectly favors bond-length-alternating structures for [10]annulene, and aromatic structures are incorrectly favored by density functional theory. Improved calculations predict that the twist conformation is lowest in energy, and the naphthalene-like and heart-shaped conformations lie higher than the twist by 1.40 and 4.24 kcal mol^{-1}, respectively.[252] From ^{13}C and proton (H^1) nmr spectra it has been deduced that neither is planar. However, that the angle strain is not insurmountable has been demonstrated by the preparation of several compounds that have large angles, but that are definitely planar 10-electron aromatic systems. Among these are the dianion **99**, the anions **100** and **101**, and the azonine **102**.[253] Compound **99**[254] has angles of ~135°, while **100**[255] and **101**[256] have angles of ~140°, which are not very far from 144°. The inner proton in **101**[257] (which is the mono-trans isomer of the all-cis **100**) is found far upfield in the NMR (−3.5 δ). For **97** and **98**, the cost in strain energy to achieve planarity apparently outweighs the extra stability that would come from an aromatic ring. To emphasize the delicate balance between these factors, we may mention that the oxygen analog of **102** (X = O, oxonin) and the *N*-carbethoxy derivative of **102** (X = CH) are nonaromatic and nonplanar, while **102** (X = N) is aromatic and planar.[258] Other azaannulenes are known, including Vogel's 2,7-methanoazaannulene,[259] as well

[251]Sulzbach, H.M.; Schleyer, P.v.R.; Jiao, H.; Xie, Y.; Schaefer III, H.F. *J. Am. Chem. Soc.* ***1995***, *117*, 1369. Also see, Sulzbach, H.M.; Schaefer III, H.F.; Klopper, W.; Lüthi, H.P. *J. Am. Chem. Soc.* ***1996***, *118*, 3519 for a discussion of Aromaticity calculations for [10]annulene.

[252]King, R.A.; Crawford, T.D.; Stanton, J.F.; Schaefer, III, H.F. *J. Am. Chem. Soc.* ***1999***, *121*, 10788.

[253]For reviews of **102** (X = N) and other nine-membered rings containing four double bonds and a hetero atom (heteronins), see Anastassiou, A.G. *Acc. Chem. Res.* ***1972***, *5*, 281, *Top. Nonbenzenoid Aromat. Chem.* ***1973***, *1*, 1, *Pure Appl. Chem.* ***1975***, *44*, 691. For a review of heteroannulenes in general, see Anastassiou; Kasmai, H.S. *Adv. Heterocycl. Chem.* ***1978***, *23*, 55.

[254]Katz, T.J. *J. Am. Chem. Soc.* ***1960***, *82*, 3784, 3785; Goldstein, M.J.; Wenzel, T.T. *J. Chem. Soc. Chem. Commun.* ***1984***, 1654; Garkusha, O.G.; Garbuzova, I.A.; Lokshin, B.V.; Todres, Z.V. *J. Organomet. Chem.* ***1989***, *371*, 279. See also, Noordik, J.H.; van den Hark, T.E.M.; Mooij, J.J.; Klaassen, A.A.K. *Acta Crystallogr. Sect. B.* ***1974***, *30*, 833; Goldberg, S.Z.; Raymond, K.N.; Harmon, C.A.; Templeton, D.H. *J. Am. Chem. Soc.* ***1974***, *96*, 1348; Evans, W.J.; Wink, D.J.; Wayda, A.L.; Little, D.A. *J. Org. Chem.* ***1981***, *46*, 3925; Heinz, W.; Langensee, P.; Müllen, K. *J. Chem. Soc. Chem. Commun.* ***1986***, 947.

[255]Katz, T.J.; Garratt, P.J. *J. Am. Chem. Soc.* ***1964***, *86*, 5194; LaLancette, E.A.; Benson, R.E. *J. Am. Chem. Soc.* ***1965***, *87*, 1941; Simmons, H.E.; Chesnut, D.B.; LaLancette, E.A. *J. Am. Chem. Soc.* ***1965***, *87*, 982; Paquette, L.A.; Ley, S.V.; Meisinger, R.H.; Russell, R.K.; Oku, M. *J. Am. Chem. Soc.* ***1974***, *96*, 5806; Radlick, P.; Rosen, W. *J. Am. Chem. Soc.* ***1966***, *88*, 3461.

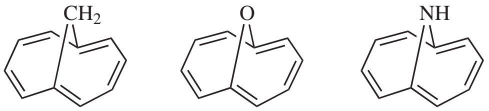
[256]Anastassiou, A.G.; Gebrian, J.H. *Tetrahedron Lett.* ***1970***, 825.

[257]Boche, G.; Weber, H.; Martens, D.; Bieberbach, A. *Chem. Ber.* ***1978***, *111*, 2480. See also, Anastassiou, A.G.; Reichmanis, E. *Angew. Chem. Int. Ed.* ***1974***, *13*, 728; Boche, G.; Bieberbach, A. *Tetrahedron Lett.* ***1976***, 1021.

[258]Anastassiou, A.G.; Gebrian, J.H. *J. Am. Chem. Soc.* ***1969***, *91*, 4011; Chiang, C.C.; Paul, I.C.; Anastassiou, A.G.; Eachus, S.W. *J. Am. Chem. Soc.* ***1974***, *96*, 1636.

[259]Vogel, E.; Roth, H.D. *Angew. Chem. Int. Ed.* ***1964***, *3*, 228; Vogel, E.; Biskup, M.; Pretzer, W.; Böll, W.A. *Angew. Chem. Int. Ed.* ***1964***, *3*, 642.; Vogel, E.; Meckel, M.; Grimme, W. *Angew. Chem. Int. Ed.* ***1964***, *3*, 643; Vogel, E.; Pretzer, W.; Böll, W.A. *Tetrahedron Lett.* ***1965***, 3613; Sondheimer, F.; Shani, A. *J. Am. Chem. Soc.* ***1964***, *86*, 3168; Shani, A.; Sondheimer, F. *J. Am. Chem. Soc.* ***1967***, *89*, 6310; Bailey, N.A.; Mason, R. *J. Chem. Soc. Chem. Commun.* ***1967***, 1039.

as 3,8-methanoaza[10]annulene,[260] and their alkoxy derivatives.[261] Calculations for aza[10]annulene concluded that the best olefinic twist isomer is 2.1 kcal mol^{-1} (8.8 kJ mol^{-1}) more stable than the aromatic form,[262] and is probably the more stable form.



103 **104** **105**

So far, **79** has not been prepared despite many attempts. However, there are various ways of avoiding the interference between the two inner protons. The approach that has been most successful involves bridging the 1 and 6 positions.[263] Thus, 1,6-methano[10]annulene (**103**)[264] and its oxygen and nitrogen analogs, **104**[265] and **105**,[266] have been prepared and are stable compounds that undergo aromatic substitution and are diatropic.[267] For example, the perimeter protons of **103** are found at 6.9–7.3 δ, while the bridge protons are at −0.5 δ. The crystal structure of **103** shows that the perimeter is nonplanar, but the bond distances are in the range 1.37–1.42 Å.[268] It has therefore been amply demonstrated that a closed loop of 10 electrons is an aromatic system, although some molecules that could conceivably have such a system are too distorted from planarity to be aromatic. A small distortion from planarity (as in **103**) does not prevent aromaticity, at least in part because the s orbitals so distort themselves as to maximize the favorable (parallel) overlap

[260]Schäfer-Ridder, M.; Wagner, A.; Schwamborn, M.; Schreiner, H.; Devrout, E.; Vogel, E. *Angew. Chem. Int. Ed.* ***1978***, *17*, 853.; Destro, R.; Simonetta, M.; Vogel, E. *J. Am. Chem. Soc.* ***1981***, *103*, 2863.

[261]Vogel, E. Presented at the 3rd International Symposium on Novel Aromatic Compounds (ISNA 3), San Francisco, Aug ***1977***; Gölz, H.-J.; Muchowski, J.M.; Maddox, M.L. *Angew. Chem. Int. Ed.* ***1978***, *17*, 855; Schleyer, P.v.R.; Jiao, H.; Sulzbach, H.M.; Schaefer III H.F. *J. Am. Chem. Soc.* ***1996***, *118*, 2093.

[262]Bettinger, H.F.; Sulzbach, H.M.; Schleyer, P.v.R.; Schaefer III, H.F. *J. Org. Chem.* ***1999***, *64*, 3278.

[263]For reviews of bridged [10]-, [14]-, and [18]annulenes, see Vogel, E. *Pure Appl. Chem.* ***1982***, *54*, 1015; *Isr. J. Chem.* ***1980***, *20*, 215; *Chimia*, ***1968***, *22*, 21; Vogel, E.; Günther, H. *Angew. Chem. Int. Ed.* ***1967***, *6*, 385.

[264]Vogel, E.; Roth, H.D. *Angew. Chem. Int. Ed.* ***1964***, *3*, 228; Vogel, E.; Böll, W.A. *Angew. Chem. Int. Ed.* ***1964***, *3*, 642; Vogel, E.; Böll, W.A.; Biskup, M. *Tetrahedron Lett.* ***1966***, 1569.

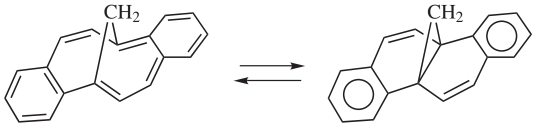
[265]Vogel, E.; Biskup, M.; Pretzer, W.; Böll, W.A. *Angew. Chem. Int. Ed.* ***1964***, *3*, 642; Shani, A.; Sondheimer, F. *J. Am. Chem. Soc.* ***1967***, *89*, 6310; Bailey, N.A.; Mason, R. *Chem. Commun.* ***1967***, 1039.

[266]Vogel, E.; Pretzer, W.; Böll, W.A. *Tetrahedron Lett.* ***1965***, 3613. See also, Vogel, E.; Biskup, M.; Pretzer, W.; Böll, W.A. *Angew. Chem. Int. Ed.* ***1964***, *3*, 642.

[267]For another type of bridged diatropic [10]annulene, see Lidert, Z.; Rees, C.W. *J. Chem. Soc. Chem. Commun.* ***1982***, 499; Gilchrist, T.L.; Rees, C.W.; Tuddenham, D. *J. Chem. Soc. Perkin Trans. 1* ***1983***, 83; McCague, R.; Moody, C.J.; Rees, C.W. *J. Chem. Soc. Perkin Trans. 1* ***1984***, 165, 175; Gibbard, H.C.; Moody, C.J.; Rees, C.W. *J. Chem. Soc. Perkin Trans. 1* ***1985***, 731, 735.

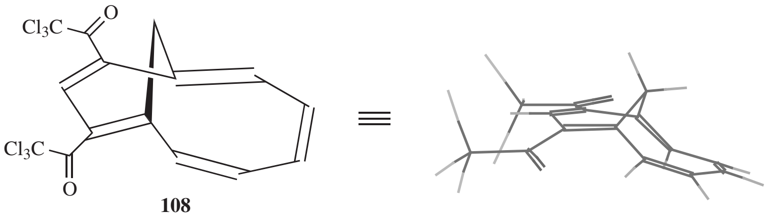
[268]Bianchi, R.; Pilati, T.; Simonetta, M. *Acta Crystallogr., Sect. B* ***1980***, *36*, 3146. See also Dobler, M.; Dunitz, J.D. *Helv. Chim Acta*, ***1965***, *48*, 1429.

of *p* orbitals to form the aromatic 10-electron loop.[269]



106 **107**

In **106**, where **103** is fused to two benzene rings in such a way that no canonical form can be written in which both benzene rings have six electrons, the aromaticity is reduced by annellation, as shown by the fact that the molecule rapidly converts to the more stable **107**, in which both benzene rings can be fully aromatic[270] (this is similar to the cycloheptatriene–norcaradiene conversions discussed on p. 1664).



108

Molecules can sustain significant distortion from planarity and retain their aromatic character. 1,3-Bis(trichloroacetyl)homoazulene (**108**) qualifies as aromatic using the geometric criterion that there is only a small average deviation from the C—C bond length in the [10]annulene perimeter.[271] X-ray crystal structure shows that the 1,5-bridge distorts the [10]-annulene π-system away from planarity (see the 3D model) with torsion angles as large as 42.2° at the bridgehead position, but **108** does not lose its aromaticity.

Systems of More than Ten Electrons: $4n + 2$ Electrons[272]

Extrapolating from the discussion of [10]annulene, we expect larger $4n + 2$ systems to be aromatic if they are planar. Mislow[249] predicted that [14]annulene (**109**)

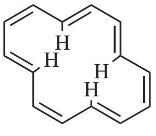
[269]For a discussion, see Haddon, R.C. *Acc. Chem. Res.* ***1988***, *21*, 243.

[270]Hill, R.K.; Giberson, C.B.; Silverton, J.V. *J. Am. Chem. Soc.* ***1988***, *110*, 497. See also, McCague, R.; Moody, C.J.; Rees, C.W.; Williams, D.J. *J. Chem. Soc. Perkin Trans. 1* ***1984***, 909.

[271]Scott, L.T.; Sumpter, C.A.; Gantzel, P.K.; Maverick, E.; Trueblood, K.N. *Tetrahedron* ***2001***, *57*, 3795.

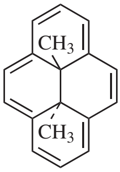
[272]For reviews of annulenes, with particular attention to their nmr spectra, see Sondheimer, F. *Acc. Chem. Res.* ***1972***, *5*, 81–91, *Pure Appl. Chem.* ***1971***, *28*, 331, *Proc. R. Soc. London. Ser. A*, ***1967***, *297*, 173; Sondheimer, F.; Calder, I.C.; Elix, J.A.; Gaoni, Y; Garratt, P.J.; Grohmann, K.; di Maio, G.; Mayer, J.; Sargent, M.V.; Wolovsky, R. in Garratt, P.G. *Aromaticity*, Wiley, NY, ***1986***, pp. 75–107; Haddon, R.C.; Haddon, V.R.; Jackman, L.M. *Fortschr. Chem. Forsch.* ***1971***, *16*, 103. For a review of annulenoannulenes (two annulene rings fused together), see Nakagawa, M. *Angew. Chem. Int. Ed.* ***1979***, *18*, 202. For a review of reduction and oxidation of annulenes; that is, formation of radical ions, dianions, and dications, see Müllen, K. *Chem. Rev.* ***1984***, *84*, 603. For a review of annulene anions, see Rabinovitz, M. *Top. Curr. Chem.* ***1988***, *146*, 99. Also see Cyvin, S.J.; Brunvoll, J.; Chen, R.S.; Cyvin, B.N.; Zhang, F.J. *Theory of Coronoid Hydrocarbons II*, Springer-Verlag, Berlin, ***1994***.

would possess the same type of interference as **79**, although in lesser degree. This is

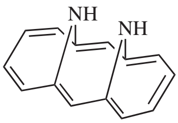


109

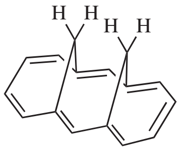
borne out by experiment. Compound **109** is aromatic (it is diatropic; inner protons at 0.00 δ, outer protons at 7.6 δ),[273] but is completely destroyed by light and air in 1 day. X-ray analysis shows that although there are no alternating single and double bonds, the molecule is not planar.[274] A number of stable bridged [14]annulenes have been prepared,[275] for example, *trans*-15,16-dimethyldihydropyrene (**110**),[276] *syn*-1,6:8,13-diimino[14]annulene (**111**),[277] and *syn*- and *anti*-1,6:8,13-bis(methano[14]annulene) (**112** and **113**).[278] The dihydropyrene **110**



110



111



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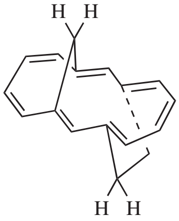


113

(and its diethyl and dipropyl homologs) is undoubtedly aromatic: the π perimeter is approximately planar;[279] the bond distances are all 1.39–1.40 Å; and the

[273]Gaoni, Y.; Melera, A.; Sondheimer, F.; Wolovsky, R. *Proc. Chem. Soc.* ***1964***, 397.

[274]Bregman, J. *Nature (London)* ***1962***, *194*, 679; Chiang, C.C.; Paul, I.C. *J. Am. Chem. Soc. 1972*, ***94***, 4741. Another 14-electron system is the dianion of [12]annulene, which is also apparently aromatic though not planar: Oth, J.F.M.; Schröder, G. *J. Chem. Soc. B*, ***1971***, 904. See also Garratt, P.J.; Rowland, N.E.; Sondheimer, F. *Tetrahedron* ***1971***, *27*, 3157; Oth, J.F.M.; Müllen, K.; Königshofen, H.; Mann, M.; Sakata, Y.; Vogel, E. *Angew. Chem. Int. Ed.* ***1974***, *13*, 284. For some other 14-electron aromatic systems, see Anastassiou, A.G.; Elliott, R.L.; Reichmanis, E. *J. Am. Chem. Soc.* ***1974***, *96*, 7823; Wife, R.L.; Sondheimer, F. *J. Am. Chem. Soc.* ***1975***, *97*, 640; Ogawa, H.; Kubo, M.; Saikachi, H.*Tetrahedron Lett.* ***1971***, 4859; Oth, J.F.M.; Müllen, K.; Königshofen, H.; Wassen, J.; Vogel, E. *Helv. Chim. Acta*, ***1974***, *57*, 2387; Willner, I.; Gutman, A.L.; Rabinovitz, M. *J. Am. Chem. Soc.* ***1977***, *99*, 4167; Röttele, H.; Schröder, G. *Chem. Ber.* ***1982***, *115*, 248.

[275]For a review, see Vogel, E. *Pure Appl. Chem.* ***1971***, *28*, 355.

[276]Boekelheide, V.; Phillips, J.B. *J. Am. Chem. Soc.* ***1967***, *89*, 1695; Boekelheide, V.; Miyasaka, T. *J. Am. Chem. Soc.* ***1967***, *89*, 1709. For reviews of dihydropyrenes, see Mitchell, R.H. *Adv. Theor. Interesting Mol.* ***1989***, *1*, 135; Boekelheide, V. *Top. Nonbenzoid Arom. Chem.* ***1973***, *1*, 47; *Pure Appl. Chem.* ***1975***, *44*, 807.

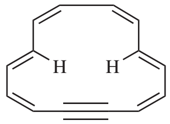
[277]Vogel, E.; Kuebart, F.; Marco, J.A.; Andree, R.; Günther, H.; Aydin, R. *J. Am. Chem. Soc.* ***1983***, *105*, 6982; Destro, R.; Pilati, T.; Simonetta, M.; Vogel, E. *J. Am. Chem. Soc.* ***1985***, *107*, 3185, 3192. For the di-*O*- analog of **102**, see Vogel, A.; Biskup, M.; Vogel, E.; Günther, H. *Angew. Chem. Int. Ed.* ***1966***, *5*, 734.

[278]Vogel, E.; Sombroek, J.; Wagemann, W. *Angew. Chem. Int. Ed.* ***1975***, *14*, 564.

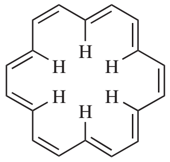
[279]Hanson, A.W. *Acta Crystallogr.* ***1965***, *18*, 599, 1967, 23, 476.

molecule undergoes aromatic substitution[276] and is diatropic.[280] The outer protons are found at 8.14–8.67 δ, while the CH_3 protons are at −4.25 δ. Other nonplanar aromatic dihydropyrenes are known.[281] Annulenes **111** and **112** are also diatropic,[282] although X-ray crystallography indicates that the π periphery in at least **111** is not quite planar.[283] However, **113**, in which the geometry of the molecule greatly reduces the overlap of the *p* orbitals at the bridgehead positions with adjacent *p* orbitals, is definitely not aromatic,[284] as shown by NMR spectra[278] and X-ray crystallography, from which bond distances of 1.33–1.36 Å for the double bonds and 1.44–1.49 Å for the single bonds have been obtained.[285] In contrast, all the bond distances in **111** are ∼1.38–1.40 Å.[283]

Another way of eliminating the hydrogen interferences of [14]annulene is to introduce one or more triple bonds into the system, as in dehydro[14]annulene (**114**).[286] All five known dehydro[14]annulenes are diatropic, and **87** can be nitrated or sulfonated.[287] The extra electrons of the triple bond do not form part of the aromatic system, but simply



114



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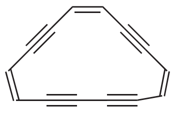


116

exist as a localized bond. There has been a debate concerning the extent of delocalization in dehydrobenzoannulenes,[288] but there is evidence for a weak, but discernible ring current.[289] 3,4,7,8,9,10,13,14-Octahydro[14]annulene (**116**) has been

[280]A number of annellated derivatives of **110** are less diatropic, as would be expected from the discussion on p. $$$: Mitchell, R.H.; Williams, R.V.; Mahadevan, R.; Lai, Y.H.; Dingle, T.W. *J. Am. Chem. Soc.* ***1982***, *104*, 2571 and other papers in this series.

[281]Bodwell, G.J.; Bridson, J.N.; Chen, S.-L.; Poirier, R.A. *J. Am. Chem. Soc.* ***2001***, *123*, 4704; Bodwell, G.J.; Fleming, J.J.; Miller, D.O. *Tetrahedron* ***2001***, *57*, 3577.

[282]As are several other similarly bridged [14]annulenes; see, for example, Flitsch, W.; Peeters, H. *Chem. Ber.* ***1973***, *106*, 1731; Huber, W.; Lex, J.; Meul, T.; Müllen, K. *Angew. Chem. Int. Ed.* ***1981***, *20*, 391; Vogel, E.; Nitsche, R.; Krieg, H. *Angew. Chem. Int. Ed.* ***1981***, *20*, 811; Mitchell, R.H.; Anker, W. *Tetrahedron Lett.* ***1981***, *22*, 5139; Vogel, E.; Wieland, H.; Schmalstieg, L.; Lex, J. *Angew. Chem. Int. Ed.* ***1984***, *23*, 717; Neumann, G.; Müllen, K. *J. Am. Chem. Soc.* ***1986***, *108*, 4105.

[283]Ganis, P.; Dunitz, J.D. *Helv. Chim. Acta*, ***1967***, *50*, 2369.

[284]For another such pair of molecules, see Vogel, E.; Nitsche, R.; Krieg, H. *Angew. Chem. Int. Ed.* ***1981***, *20*, 811. See also, Vogel, E.; Schieb, T.; Schulz, W.H.; Schmidt, K.; Schmickler, H.; Lex, J. *Angew. Chem. Int. Ed.* ***1986***, *25*, 723.

[285]Gramaccioli, C.M.; Mimun, A.; Mugnoli, A.; Simonetta, M. *Chem. Commun.* ***1971***, 796. See also, Destro, R.; Simonetta, M. *Tetrahedron* ***1982***, *38*, 1443.

[286]For a review of dehydroannulenes, see, Nakagawa, M. *Top. Nonbenzenoid Aromat. Chem.* ***1973***, *1*, 191.

[287]Gaoni, Y.; Sondheimer, F. *J. Am. Chem. Soc.* ***1964***, *86*, 521.

[288]Balaban, A.T.; Banciu, M.; Ciorba, V. *Annulenes, Benzo-, Hetero-, Homo- Derivatives and their Valence Isomers*, Vols. 1–3, CRC Press, Boca Raton, FL, ***1987***; Garratt, P.J. *Aromaticity*, Wiley, NY, ***1986***; Minkin, V.I.; Glukhovtsev, M.N.; Simkin, B.Ya. *Aromaticity and Antiaromaticity*, Wiley, NY, ***1994***.

[289]Kimball, D.B.; Wan, W.B.; Haley, M.M. *Tetrahdron Lett.* ***1998***, *39*, 6795; Bell, M.L.; Chiechi, R.C.; Johnson, C.A.; Kimball, D.B.; Matzger, A.J.; Wan, W.B.; Weakley, T.J.R.; Haley, M.M. *Tetahedron* ***2001***, *57*, 3507; Wan, W.B.; Chiechi, R.C.; Weakley, T.J.R.; Haley, M.M. *Eur. J. Org. Chem.* ***2001***, 3485.

prepared, for example, and the evidence supported its aromaticity.[290] This study suggested that increasing benzoannelation of the parent, **116**, led to a step-down in aromaticity, a result of competing ring currents in the annulenic system.

[18]Annulene (**115**) is diatropic:[291] the 12 outer protons are found at $\sim\delta = 9$ and the 6 inner protons at $\sim\delta = -3$. X-ray crystallography[292] shows that it is nearly planar, so that interference of the inner hydrogens is not important in annulenes this large. Compound **115** is reasonably stable, being distillable at reduced pressures, and undergoes aromatic substitutions.[293] The C—C bond distances are not equal, but they do not alternate. There are 12 inner bonds of ~1.38 Å and 6 outer bonds of ~1.42 Å.[292] Compound **115** has been estimated to have a resonance energy of ~37 kcal mol^{-1} (155 kJ mol^{-1}), similar to that of benzene.[294]

The known bridged [18]annulenes are also diatropic[295] as are most of the known dehydro[18]annulenes.[296] The dianions of open and bridged [16]annulenes[297] are also 18-electron aromatic systems,[298] and there are dibenzo[18]annulenes.[299]

[22]Annulene[300] and dehydro[22]annulene[301] are also diatropic. A dehydrobenzo[22]annulene has been prepared that has eight C≡C units, is planar and possesses a weak induced ring current.[302] In the latter compound there are 13 outer protons at 6.25–8.45 δ and 7 inner protons at 0.70–3.45 δ. Some aromatic bridged

[290]Bodyston, A.J.; Haley, M.M. *Org. Lett.* ***2001***, *3*, 3599; Boydston, A.J.; Haley, M.M.; Williams, R.V.; Armantrout, J.R. *J. Org. Chem.* ***2002***, *67*, 8812.

[291]Jackman, L.M.; Sondheimer, F.; Amiel, Y.; Ben-Efraim, D.A.; Gaoni, Y.; Wolovsky, R.; Bothner-By, A.A. *J. Am. Chem. Soc.* ***1962***, *84*, 4307; Gilles, J.; Oth, J.F.M.; Sondheimer, F.; Woo, E.P. *J. Chem. Soc. B*, ***1971***, 2177. For a thorough discussion, see Baumann, H.; Oth, J.F.M. *Helv. Chim. Acta*, ***1982***, *65*, 1885.

[292]Bregman, J.; Hirshfeld, F.L.; Rabinovich, D.; Schmidt, G.M.J. *Acta Crystallogr.*, ***1965***, *19*, 227; Hirshfeld, F.L.; Rabinovich, D. *Acta Crystallogr.*, ***1965***, *19*, 235.

[293]Sondheimer, F. *Tetrahedron* ***1970***, *26*, 3933.

[294]Oth, J.F.M.; Bünzli, J.; de Julien de Zélicourt, Y. *Helv. Chim. Acta*, ***1974***, *57*, 2276.

[295]For some examples, see DuVernet, R.B.; Wennerström, O.; Lawson, J.; Otsubo, T.; Boekelheide, V. *J. Am. Chem. Soc.* ***1978***, *100*, 2457; Ogawa, H.; Sadakari, N.; Imoto, T.; Miyamoto, I.; Kato, H.; Taniguchi, Y. *Angew. Chem. Int. Ed.* ***1983***, *22*, 417; Vogel, E.; Sicken, M.; Röhrig, P.; Schmickler, H.; Lex, J.; Ermer, O. *Angew. Chem. Int. Ed.* ***1988***, *27*, 411.

[296]Okamura, W.H.; Sondheimer, F. *J. Am. Chem. Soc.* ***1967***, *89*, 5991; Ojima, J.; Ejiri, E.; Kato, T.; Nakamura, M.; Kuroda, S.; Hirooka, S.; Shibutani, M. *J. Chem. Soc. Perkin Trans. 1* ***1987***, 831; Sondheimer, F. *Acc. Chem. Res.* ***1972***, *5*, 81. For two that are not, see Endo, K.; Sakata, Y.; Misumi, S. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 2465.

[297]For a review of this type of polycyclic ion, see Rabinovitz, M.; Willner, I.; Minsky, A. *Acc. Chem. Res.* ***1983***, *16*, 298.

[298]Mitchell, R.H.; Boekelheide, V. *Chem. Commun.* ***1970***, 1557; Oth, J.F.M.; Baumann, H.; Gilles, J.; Schröder, G. *J. Am. Chem. Soc.* ***1972***, *94*, 3948. See also Brown, J.M.; Sondheimer, F. *Angew. Chem. Int. Ed.* ***1974***, *13*, 337; Cresp, T.M.; Sargent, M.V. *J. Chem. Soc. Chem. Commun.* ***1974***, 101; Schröder, G.; Plinke, G.; Smith, D.M.; Oth, J.F.M. *Angew. Chem. Int. Ed.* ***1973***, *12*, 325; Rabinovitz, M.; Minsky, A. *Pure Appl. Chem.* ***1982***, *54*, 1005.

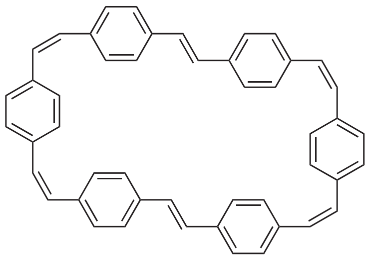
[299]Michels, H.P.; Nieger, M.; Vögtle, F. *Chem. Ber.* ***1994***, *127*, 1167.

[300]McQuilkin, R.M.; Metcalf, B.W.; Sondheimer, F. *Chem. Commun.* ***1971***, 338.

[301]McQuilkin, R.M.; Sondheimer, F. *J. Am. Chem. Soc.* ***1970***, *92*, 6341; Iyoda, M.; Nakagawa, M. *J. Chem. Soc. Chem. Commun.* ***1972***, 1003. See also, Akiyama, S.; Nomoto, T.; Iyoda, M.; Nakagawa, M. *Bull. Chem. Soc. Jpn.* ***1976***, *49*, 2579.

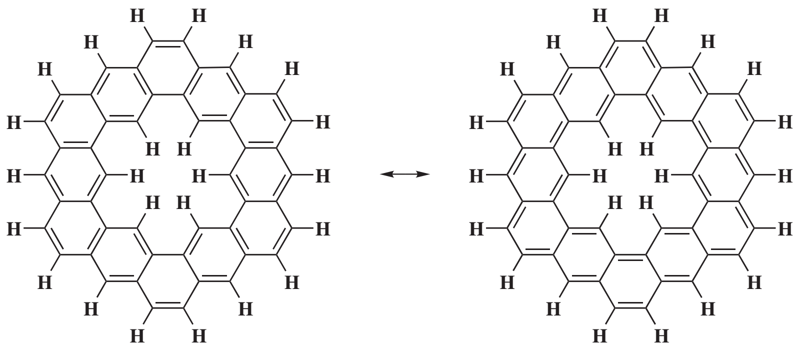
[302]Wan, W.B.; Kimball, D.B.; Haley, M.M. *Tetrahedron Lett.* ***1998***, *39*, 6795.

[22]annulenes are also known.[303] [26]Annulene has not yet been prepared, but several dehydro[26]annulenes are aromatic.[304] Furthermore, the dianion of 1,3,7,9,13,-15,19,21-octadehydro[24]annulene is another 26-electron system that is aromatic.[305] Ojima and co-workers have prepared bridged dehydro derivatives of [26], [30], and [34] annulenes.[306] All of these are diatropic. The same workers prepared a bridged tetradehydro[38]annulene,[306] which showed no ring current. On the other hand, the dianion of the cyclophane, **117**, also has 38 perimeter electrons, and this species is diatropic.[307]



117

There is now no doubt that $4n + 2$ systems are aromatic if they can be planar, although **97** and **113** among others, demonstrate that not all such systems are in fact planar enough for aromaticity. The cases of **109** and **111** prove that absolute planarity is not required for aromaticity, but that aromaticity decreases with decreasing planarity.



118a **118b**

[303]For example see Broadhurst, M.J.; Grigg, R.; Johnson, A.W. *J. Chem. Soc. Perkin Trans. 1* ***1972***, 2111; Ojima, J.; Ejiri, E.; Kato, T.; Nakamura, M.; Kuroda, S.; Hirooka, S.; Shibutani, M. *J. Chem. Soc. Perkin Trans. 1* ***1987***, 831; Yamamoto, K.; Kuroda, S.; Shibutani, M.; Yoneyama, Y.; Ojima, J.; Fujita, S.; Ejiri, E.; Yanagihara, K. *J. Chem. Soc. Perkin Trans. 1* ***1988***, 395.

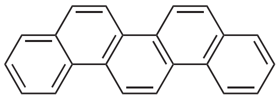
[304]Metcalf, B.W.; Sondheimer, F. *J. Am. Chem. Soc.* ***1971***, *93*, 5271; Iyoda, M.; Nakagawa, M. *Tetrahedron Lett.* ***1972***, 4253; Ojima, J.; Fujita, S.; Matsumoto, M.; Ejiri, E.; Kato, T.; Kuroda, S.; Nozawa, Y.; Hirooka, S.; Yoneyama, Y.; Tatemitsu, H. *J. Chem. Soc. Perkin Trans. 1* ***1988***, 385.

[305]McQuilkin, R.M.; Garratt, P.J.; Sondheimer, F. *J. Am. Chem. Soc.* ***1970***, *92*, 6682. See also, Huber, W.; Müllen, K.; Wennerström, O. *Angew. Chem. Int. Ed.* ***1980***, *19*, 624.

[306]Ojima, J.; Fujita, S.; Matsumoto, M.; Ejiri, E.; Kato, T.; Kuroda, S.; Nozawa, Y.; Hirooka, S.; Yoneyama, Y.; Tatemitsu, H. *J. Chem. Soc., Perkin Trans. 1* ***1988***, 385.

[307]Müllen, K.; Unterberg, H.; Huber, W.; Wennerström, O.; Norinder, U.; Tanner, D.; Thulin, B. *J. Am. Chem. Soc.* ***1984***, *106*, 7514.

The proton NMR (^{1}H NMR) spectrum of **118** (called kekulene) showed that in a case where electrons can form either aromatic sextets or larger systems, the sextets are preferred.[308] There was initial speculation that kekulene might be *superaromatic*, that is, it would show enhanced aromatic stabilization. Recent calculations suggest that there is no enhanced stabilization.[309] The 48 π electrons of **118** might, in theory, prefer structure **118a**, where each ring is a fused benzene ring, or **118b**, which has a [30]annulene on the outside and an [18]annulene on the inside. The ^{1}H NMR spectrum of this compound shows three peaks at $\delta = 7.94$, 8.37, and 10.45 in a ratio of 2:1:1. It is seen from the structure that **118** contains three groups of protons. The peak at 7.94 δ is attributed to the 12 ortho protons and the peak at 8.37 δ to the six external para protons. The remaining peak comes from the six inner protons. If the molecule preferred **118b**, we would expect to find this peak upfield, probably with a negative δ, as in the case of **115**. The fact that this peak is far downfield indicates that the electrons prefer to be in benzenoid rings. Note that in the case of the dianion of **117**, we have the opposite situation. In this ion, the 38-electron system is preferred even though 24 of these must come from the six benzene rings, which therefore cannot have aromatic sextets.



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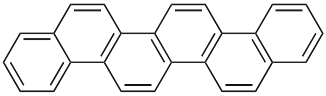
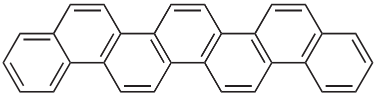


120



121

Phenacenes are a family of "graphite ribbons," where benzene rings are fused together in an alternating pattern. Phenanthrene is the simplest member of this family and other members include the 22-electron system picene (**119**); the 26-electron system fulminene (**120**); and the larger member of this family, the 30 electron [7]-phenancene, with seven rings (**121**).[310] In the series benzene to heptacene, reactivity increases although acene resonance energies per π electron are nearly constant. The inner rings of the "acenes" are more reactive, and calculations shown that those rings are more aromatic than the outer rings, and even more aromatic than benzene itself.[311]

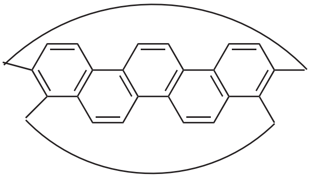
[308]Staab, H.A.; Diederich, F. *Chem. Ber.* ***1983***, *116*, 3487; Staab, H.A.; Diederich, F.; Krieger, C.; Schweitzer, D. *Chem. Ber.* ***1983***, *116*, 3504. For a similar molecule with 10 instead of 12 rings, see Funhoff, D.J.H.; Staab, H.A. *Angew. Chem. Int. Ed.* ***1986***, *25*, 742.

[309]Jiao, H.; Schleyer, P.v.R. *Angew. Chem. Int. Ed.*, ***1996***, *35*, 2383.

[310]Mallory, F.B.; Butler, K.E.; Evans, A.C.; Mallory, C.W. *Tetrahedron Lett.* ***1996***, *37*, 7173.

[311]Schleyer, P.v.R.; Manoharan, M.; Jiao, H.; Stahl, F. *Org. Lett.* ***2001***, *3*, 3643.

A super ring molecule is formed by rolling a polyacene molecule into one ring with one edge benzene ring folding into the other. These are called cyclopolyacenes or cyclacenes.[312] Although the *zigzag* cyclohexacenes (**122**) are highly aromatic (this example is a 22-electron system), the linear cyclohexacenes (e.g., the 24 electron **123**) are much less aromatic.[313]



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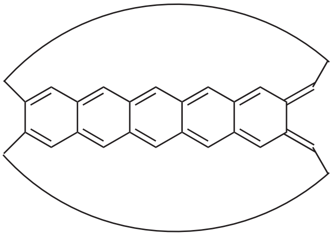
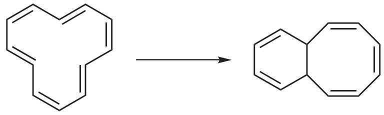


123

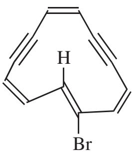
Systems of More Than Ten Electrons: 4*n* Electrons[224]

As we have seen (p. 74), these systems are expected to be not only nonaromatic, but actually antiaromatic.



124 **125**

The [12]annulene **124** has been prepared.[314] In solution, **124** undergoes rapid conformational mobility (as do many other annulenes),[315] and above −150°C in this partiuclar case, all protons are magnetically equivalent. However, at −170°C the mobility is greatly slowed and the three inner protons are found at ~8 δ while the nine outer protons are at ~6 δ. Interaction of the "internal" hydrogens in annulene **124** leads to nonplanarity. Above −50°C, **124** is unstable and rearranges to **125**. Several bridged



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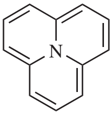

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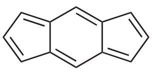

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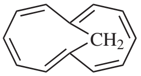

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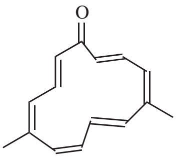


130

[312]Ashton, P.R.; Issacs, N.S.; Kohnke, F.H.; Slawin, A.M.Z.; Spencer, C.M.; Stoddart, J.F.; Williams, D.J. *Angew. Chem. Int. Ed.* ***1988***, *27*, 966; Ashton, P.R.; Brown, G.R.; Issacs, N.S.; Giuffrida, D.; Kohnke, F.H.; Mathias, J.P.; Slawin, A.M.Z.; Smith, D.R.; Stoddart, J.F.; Williams, D.J. *J. Am. Chem. Soc.* ***1992***, *114*, 6330; Ashton, P.R.; Girreser, U.; Giuffrida, D.; Kohnke, F.H.; Mathias, J.P.; Raymo, F.M.; Slawin, A.M.Z.; Stoddart, J.F.; Williams, D.J. *J. Am. Chem. Soc.* ***1993***, *115*, 5422.

[313]Aihara, J-i. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 971.

[314]Oth, J.F.M.; Röttele, H.; Schröder, G. *Tetrahedron Lett.* ***1970***, 61; Oth, J.F.M.; Gilles, J.; Schröder, G. *Tetrahedron Lett.* ***1970***, 67.

[315]For a review of conformational mobility in annulenes, see Oth, J.F.M. *Pure Appl. Chem.* ***1971***, *25*, 573.

and dehydro[12]annulenes are known, for example, 5-bromo-1,9-didehydro[12]annulene (**126**),[316] cycl[3.3.3]azine (**127**),[317] *s*-indacene (**128**),[318] and 1,7-methano[12]annulene (**129**).[319] *s*-Indacene is a planar, conjugated system perturbed by two cross-links, and studies showed that the low-energy structure has *localized* double bonds. In these compounds, both hydrogen interference and conformational mobility are prevented. In **127**–**129**, the bridge prevents conformational changes, while in **126** the bromine atom is too large to be found inside the ring. The NMR spectra show that all four compounds are paratropic, the inner proton of **126** being found at 16.4 δ. The dication of **112**[320] and the dianion of **103**[321] are also 12-electron paratropic species. An interesting 12-electron [13]-annulenone has recently been reported. 5,10-Dimethyl[13]annulenone (**130**) is the first monocyclic annulene larger than tropane,[322] and a linearly fused benzodehydro[12]annulene system has been reported.[323]

The results for [16]annulene are similar. The compound was synthesized in two different ways,[324] both of which gave **131**, which in solution is in equilibrium with **132**. Above −50°C there is conformational mobility, resulting in the magnetic equivalence of all protons, but at −130°C the compound is clearly paratropic: there are 4 protons at 10.56 δ and 12 at 5.35 δ. In the solid state, where the compound exists entirely as **131**, X-ray crystallography[325] shows that the molecules are nonplanar with almost complete bond alternation: the single bonds are 1.44–1.47 Å and the double bonds 1.31–1.35 Å. A number of dehydro and bridged [16]annulenes are also paratropic,[326] as are [20]annulene[327] and

[316]Untch, K.G.; Wysocki, D.C. *J. Am. Chem. Soc.* ***1967***, *89*, 6386.

[317]Farquhar, D.; Leaver, D. *Chem. Commun.* ***1969***, 24. For a review, see Matsuda, Y.; Gotou, H. *Heterocycles* ***1987***, *26*, 2757.

[318]Hertwig, R.H.; Holthausen, M.C.; Koch, W.; Maksić, Z.B. *Angew. Chem. Int. Ed.* ***1994***, *33*, 1192.

[319]Vogel, E.; Königshofen, H.; Müllen, K.; Oth, J.F.M. *Angew. Chem. Int. Ed.* ***1974***, *13*, 281. See also, Mugnoli, A.; Simonetta, M. *J. Chem. Soc. Perkin Trans. 2* ***1976***, 822; Scott, L.T.; Kirms, M.A.; Günther, H.; von Puttkamer, H. *J. Am. Chem. Soc.* ***1983***, *105*, 1372; Destro, R.; Ortoleva, E.; Simonetta, M.; Todeschini, R. *J. Chem. Soc. Perkin Trans. 2* ***1983***, 1227.

[320]Müllen, K.; Meul, T.; Schade, P.; Schmickler, H.; Vogel, E. *J. Am. Chem. Soc.* ***1987***, *109*, 4992. This paper also reports a number of other bridged paratropic 12-, 16-, and 20-electron dianions and dications. See also Hafner, K.; Thiele, G.F. *Tetrahedron Lett.* ***1984***, *25*, 1445.

[321]Schmalz, D.; Günther, H. *Angew. Chem. Int. Ed.* ***1988***, *27*, 1692.

[322]Higuchi, H.; Hiraiwa, N.; Kondo, S.; Ojima, J.; Yamamoto, G. *Tetrahedron Lett.* ***1996***, *37*, 2601.

[323]Gallagher, M.E.; Anthony, J.E. *Tetrahedron Lett.* ***2001***, *42*, 7533.

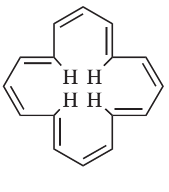
[324]Schröder, G.; Oth, J.F.M. *Tetrahedron Lett.* ***1966***, 4083; Oth, J.F.M.; Gilles, J. *Tetrahedron Lett.* ***1968***, 6259; Calder, I.C.; Gaoni, Y.; Sondheimer, F. *J. Am. Chem. Soc.* ***1968***, *90*, 4946. For monosubstituted [16]annulenes, see Schröder, G.; Kirsch, G.; Oth, J.F.M. *Chem. Ber.* ***1974***, *107*, 460.

[325]Johnson, S.M.; Paul, I.C.; King, G.S.D. *J. Chem. Soc. B* ***1970***, 643.

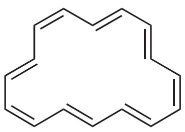
[326]For example, see Calder, I.C.; Garratt, P.J.; Sondheimer, F. *J. Am. Chem. Soc.* ***1968***, *90*, 4954; Murata, I.; Okazaki, M.; Nakazawa, T. *Angew. Chem. Int. Ed.* ***1971***, *10*, 576; Ogawa, H.; Kubo, M.; Tabushi, I. *Tetrahedron Lett.* ***1973***, 361; Nakatsuji, S.; Morigaki, M.; Akiyama, S.; Nakagawa, M. *Tetrahedron Lett.* ***1975***, 1233; Elix, J.A. *Aust. J. Chem.* ***1969***, *22*, 1951; Vogel, E.; Kürshner, U.; Schmickler, H.; Lex, J.; Wennerström, O.; Tanner, D.; Norinder, U.; Krüger, C. *Tetrahedron Lett.* ***1985***, *26*, 3087.

[327]Metcalf, B.W.; Sondheimer, F. *J. Am. Chem. Soc.* ***1971***, *93*, 6675. See also Oth, J.F.M.; Woo, E.P.; Sondheimer, F. *J. Am. Chem. Soc.* ***1973***, *95*, 7337; Nakatsuji, S.; Nakagawa, M. *Tetrahedron Lett.* ***1975***, 3927; Wilcox, Jr., C.F.; Farley, E.N. *J. Am. Chem. Soc.* *1984*, ***106***, 7195.

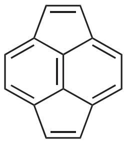
[24]annulene.[328] However, a bridged tetradehydro[32]annulene was atropic.[306]



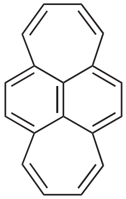
131



132



133



134

Both pyracyclene (**133**)[329] (which because of strain is stable only in solution) and dipleiadiene (**134**)[330] are paratropic, as shown by NMR spectra. These molecules might have been expected to behave like naphthalenes with outer bridges, but the outer π frameworks (12 and 16 electrons, respectively) constitute antiaromatic systems with an extra central double bond. With respect to **133**, the $4n+2$ rule predicts pyracylene to be "aromatic" if it is regarded as a 10-π-electron naphthalene unit connected to two 2-π-electron etheno systems, but "antiaromatic" if it is viewed as a 12-π-electron cyclododecahexaene periphery perturbed by an internal cross-linked etheno unit.[331] Recent studies have concluded on energetic grounds that **133** is a "borderline" case, in terms of aromaticity–antiaromaticity character.[329] Dipleiadiene appears to be antiaromatic.[330]

The fact that many $4n$ systems are paratropic, even though they may be nonplanar and have unequal bond distances, indicates that if planarity were enforced, the ring currents might be even greater. That this is true is dramatically illustrated by the NMR spectrum of the dianion of **110**[332] (and its diethyl and dipropyl homologs).[333] We may recall that in **110**, the outer protons were found at 8.14–8.67 δ with the methyl protons at −4.25 δ. For the dianion, however, which is forced to have approximately the same planar geometry, but now has 16 electrons, the outer protons are shifted to about −3 δ while the methyl protons are found at ~21 δ, a shift of ~25 δ! We have already seen where the converse shift was made, when [16]annulenes that were antiaromatic were converted to 18-electron dianions that were aromatic.[254] In these cases, the changes in nmr chemical shifts were almost

[328]Calder, I.C.; Sondheimer, F. *Chem. Commun.* ***1966***, 904. See also, Stöckel, K.; Sondheimer, F. *J. Chem. Soc. Perkin Trans. 1* ***1972***, 355; Nakatsuji, S.; Akiyama, S.; Nakagawa, M. *Tetrahedron Lett.* ***1976***, 2623; Yamamoto, K.; Kuroda, S.; Shibutani, M.; Yoneyama, Y.; Ojima, J.; Fujita, S.; Ejiri, E.; Yanagihara, K. *J. Chem. Soc., Perkin Trans. 1* ***1988***, 395.

[329]Trost, B.M.; Herdle, W.B. *J. Am. Chem. Soc.* ***1976***, *98*, 4080.

[330]Vogel, E.; Neumann, B.; Klug, W.; Schmickler, H.; Lex, J. *Angew. Chem. Int. Ed.* ***1985***, *24*, 1046.

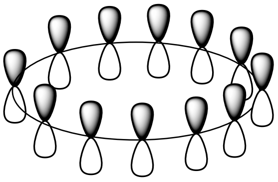
[331]Diogo, H.P.; Kiyobayashi, T.; Minas da Piedade, M.E.; Burlak, N.; Rogers, D.W.; McMasters, D.; Persy, G.; Wirz, J.; Liebman, J.F. *J. Am. Chem. Soc.* ***2002***, *124*, 2065.

[332]For a review of polycyclic dianions, see Rabinovitz, M.; Cohen, Y. *Tetrahedron* ***1988***, *44*, 6957.

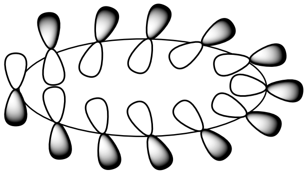
[333]Mitchell, R.H.; Klopfenstein, C.E.; Boekelheide, V. *J. Am. Chem. Soc.* ***1969***, *91*, 4931. For another example, see Deger, H.M.; Müllen, K.; Vogel, E. *Angew. Chem. Int. Ed.* ***1978***, *17*, 957.

as dramatic. Heat-of-combustion measures also show that [16]annulene is much less stable than its dianion.[334]

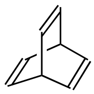
We can therefore conclude that 4*n* systems will be at a maximum where a molecule is constrained to be planar (as in **86** or the dianion of **110**) but, where possible, the molecule will distort itself from planarity and avoid equal bond distances in order to reduce. In some cases, such as cyclooctatraene, the distortion and bond alternation are great enough to be completely avoided. In other cases, for example, **124** or **131**, it is apparently not possible for the molecules to avoid at least some *p*-orbital overlap. Such molecules show evidence of paramagnetic ring currents, although the degree of is not as great as in molecules such as **86** or the dianion of **110**.



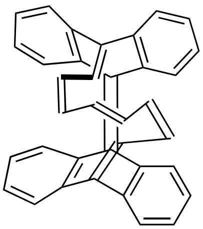
Hückel



Möbius



135



136

The concept of "Möbius aromaticity" was conceived by Helbronner in 1964[335] when he suggested that large cyclic [4*n*]annulenes might be stabilized if the π-orbitals were twisted gradually around a Möbius strip. This concept is illustrated by the diagrams labeled Hückel, which is a destabilized [4*n*] system, in contrast to the Möbius model, which is a stabilized [4*n*] system.[336] Zimmerman generalized this idea and applied the "Hückel–Möbius concept" to the analysis of ground-state systems, such as barrelene (**135**).[337] In 1998, a computational reinterpretation of existing experimental evidence for $(CH)_9^+$ as a Möbius

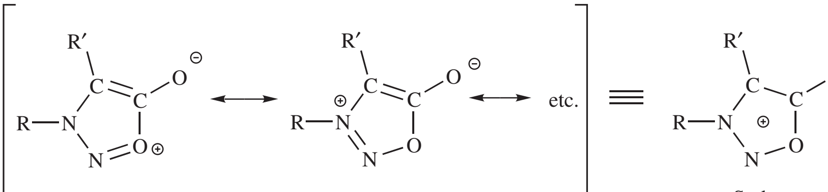
[334]Stevenson, G.R.; Forch, B.E. *J. Am. Chem. Soc.* ***1980***, *102*, 5985.
[335]Heilbronner, E. *Tetrahedron Lett.* ***1964***, 1923.
[336]Kawase, T; Oda, M. *Angew. Chem. Int. Ed.*, ***2004***, *43*, 4396.
[337]Zimmerman, H.E. *J. Am. Chem. Soc.* ***1966***, *88*, 1564.; Zimmerman, H.E. *Acc. Chem. Res.* ***1972***, *4*, 272.

aromatic cyclic annulene with 4*n* π-electrons was reported.[338] A recent computational study predicted several Möbius local minima for [12]-, [16]-, and [20]annulenes.[339] A twisted [16]annulene has been prepared and calculations suggested it should show Möbius aromaticity.[340] High-performance liquid chromatography (HPLC) separation of isomers gave **136**, which the authors concluded is Möbius aromatic.

Other Aromatic Compounds

We will briefly mention three other types of aromatic compounds.

1. *Mesoionic Compounds.*[341] These compounds cannot be satisfactorily represented by Lewis structures not involving charge separation. Most of them contain five-membered rings. The most common are the *sydnones*, stable aromatic compounds that undergo aromatic substitution when R′ is hydrogen.



2. *The Dianion of Squaric Acid.*[342] The stability of this system is illustrated by the fact that the pK_1 of squaric acid[343] is ~1.5 and the pK_2 is ~3.5,[344] which means that even the second proton is given up much more readily than the proton of acetic acid, for example.[345] The analogous three-,[346]

[338]Mauksch, M.; Gogonea, V.; Jiao, H.; Schleyer, P.v.R. *Angew. Chem. Int. Ed.*, ***1998***, *37*, 2395.

[339]Castro, C.; Isborn, C.M.; Karney, W.L.; Mauksch, M.; Schleyer, P.v.R. *Org. Lett.* ***2002***, *4*, 3431.

[340]Ajami, D.; Oeckler, O.; Simon, A.; Herges, R. *Nature (London)* ***2003***, *426*, 819.

[341]For reviews, see Newton, C.G.; Ramsden, C.A. *Tetrahedron* ***1982***, *38*, 2965; Ollis, W.D.; Ramsden, C.A. *Adv. Heterocycl. Chem.* ***1976***, *19*, 1; Ramsden, C.A. *Tetrahedron* ***1977***, *33*, 3203; Yashunskii, V.G.; Kholodov, L.E. *Russ. Chem. Rev.* ***1980***, *49*, 28; Ohta, M.; Kato, H., in Snyder, J.P. *Nonbenzenoid Aromaticity*, Vol. 1, Academic Press, NY, ***1969***, pp. 117–248.

[342]West, R.; Powell, D.L. *J. Am. Chem. Soc.* ***1963***, *85*, 2577; Ito, M.; West, R. *J. Am. Chem. Soc.* ***1963***, *85*, 2580.

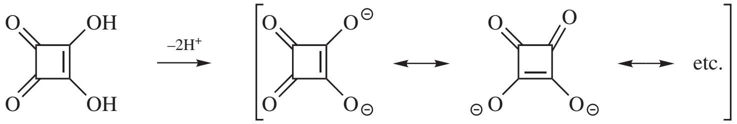
[343]For a review of squaric acid and other nonbenzenoid quinones, see Wong, H.N.C.; Chan, T.; Luh, T., in Patai, S.; Rappoport, Z. *The Chemistry of the Quinonoid Compounds*, Vol. 2, pt. 2, Wiley, NY, ***1988***, pp. 1501–1563.

[344]Ireland, D.T.; Walton, H.F. *J. Phys. Chem.* ***1967***, *71*, 751; MacDonald, D.J. *J. Org. Chem.* ***1968***, *33*, 4559.

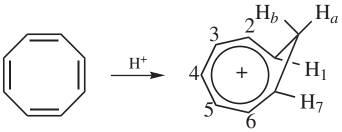
[345]There has been a controversy as to whether this dianion is in fact aromatic. See Aihara, J. *J. Am. Chem. Soc.* ***1981***, *103*, 1633.

[346]Eggerding, D.; West, R. *J. Am. Chem. Soc.* ***1976***, *98*, 3641; Pericás, M.A.; Serratosa, F. *Tetrahedron Lett.* ***1977***, 4437; Semmingsen, D.; Groth, P. *J. Am. Chem. Soc.* ***1987***, *109*, 7238.

five-, and six-membered ring compounds are also known.[347]



3. *Homoaromatic Compounds*. When cyclooctatetraene is dissolved in concentrated H_2SO_4, a proton adds to one of the double bonds to form the homotropylium ion **137**.[348] In this species, an aromatic sextet is spread over seven carbons, as in the tropylium ion. The eighth carbon is an sp^3 carbon and so cannot take part in the aromaticity. The NMR spectra show the presence of a diatropic ring current: H_b is found at $\delta = -0.3$; H_a at 5.1 δ; H_1 and H_7 at 6.4 δ; H_2–H_6 at 8.5 δ. This ion is an example of a *homoaromatic* compound, which may be defined as a compound that contains one or more[349] sp^3-hybridized carbon atoms in an otherwise conjugated cycle.[350]



137

In order for the orbitals to overlap most effectively so as to close a loop, the sp^3 atoms are forced to lie almost vertically above the plane of the

[347]For a monograph, see West, R. *Oxocarbons*; Academic Press, NY, ***1980***. For reviews, see Serratosa, F. *Acc. Chem. Res.* ***1983***, *16*, 170; Schmidt, A.H. *Synthesis* ***1980***, 961; West, R. *Isr. J. Chem.* ***1980***, *20*, 300; West, R.; Niu, J., in Snyder, J.P. *Nonbenzenoid Aromaticity*, Vol. 1, Academic Press, NY, ***1969***, pp. 311–345, and in Zabicky, J. *The Chemistry of the Carbonyl Group*, Vol. 2, Wiley, NY, ***1970***, pp. 241–275; Maahs, G.; Hegenberg, P. *Angew. Chem. Int. Ed.* ***1966***, *5*, 888.

[348]Rosenberg, J.L.; Mahler, J.E.; Pettit, R. *J. Am. Chem. Soc.* ***1962***, *84*, 2842; Keller, C.E.; Pettit, R. *J. Am. Chem. Soc.* ***1966***, *88*, 604, 606; Winstein, S.; Kreiter, C.G.; Brauman, J.I. *J. Am. Chem. Soc.* ***1966***, *88*, 2047; Haddon, R.C. *J. Am. Chem. Soc.* ***1988***, *110*, 1108. See also, Childs, R.F.; Mulholland, D.L.; Varadarajan, A.; Yeroushalmi, S. *J. Org. Chem.* ***1983***, *48*, 1431. See also, Alkorta, I.; Elguero, J.; Eckert-Maksić, M.; Maksić, Z.B. *Tetrahedron* ***2004***, *60*, 2259.

[349]If a compound contains two such atoms it is bishomoaromatic; if three, trishomoaromatic, and so on. For examples see Paquette, L.A. *Angew. Chem. Int. Ed.* ***1978***, *17*, 106.

[350]For reviews, see Childs, R.F. *Acc. Chem. Res.* ***1984***, *17*, 347; Paquette, L.A. *Angew. Chem. Int. Ed.* ***1978***, *17*, 106; Winstein, S. *Q. Rev. Chem. Soc.* ***1969***, *23*, 141; Garratt, P.J. *Aromaticity*, Wiley, NY, ***1986***, pp. 5–45; and in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Wiley, NY, Vol. 3, ***1972***, the reviews by Story, P.R.; Clark, Jr., B.C. 1007–1098, pp. 1073–1093; Winstein, S. 965–1005. (The latter is a reprint of the *Q. Rev. Chem. Soc.* review mentioned above.)

aromatic atoms.[351] In **137**, H_b is directly above the aromatic sextet, and so is shifted far upfield in the nmr. All homoaromatic compounds so far discovered are ions, and it is questionable[352] as to whether homoaromatic character can exist in uncharged systems.[353] Homoaromatic ions of 2 and 10 electrons are also known.

New conceptual applications to 3D homoaromatic systems with cubane, dodecahedrane, and adamantane frameworks has been presented.[354] This concept includes families of spherical homoaromatics with both 2 and 8 mobile electrons. Each set has complete *spherical homoaromaticity*, that is, all the sp^2 carbon atoms in a highly symmetrical frameworks are separated by one or two sp^3-hybridized atoms.

4. *Fullerenes.* Fullerenes are a family of aromatic hydrocarbons based on the parent buckminsterfullerene (**138**; C_{60})[355] that have a variety of very interesting properties.[356] Molecular-orbital calculations showed that "fullerene aromaticity lies within 2 kcal mol^{-1} (8.4 kJ mol^{-1}) per carbon of a hypothetical ball of rolled up graphite.[357] Another class of polynuclear aromatic hydrocarbons are the *buckybowls*, which are essentially fragments of **138**. Corannulene (**139**)[358] (also called 5-circulene), for example, is the simplest curved-surface hydrocarbon possessing a carbon framework that is identified with the buckminsterfullerene

[351]Calculations show that only ~60% of the chemical shift difference between H_a and H_b is the result of the aromatic ring current, and that even H_a is shielded; it would appear at δ ~ 5.5 without the ring current: Childs, R.F.; McGlinchey, M.J.; Varadarajan, A. *J. Am. Chem. Soc.* ***1984***, *106*, 5974.

[352]Houk, K.N.; Gandour, R.W.; Strozier, R.W.; Rondan, N.G.; Paquette, L.A. *J. Am. Chem. Soc.* ***1979***, *101*, 6797; Paquette, L.A.; Snow, R.A.; Muthard, J.L.; Cynkowski, T. *J. Am. Chem. Soc.* ***1979***, *101*, 6991. See however, Liebman, J.F.; Paquette, L.A.; Peterson, J.R.; Rogers, D.W. *J. Am. Chem. Soc.* ***1986***, *108*, 8267.

[353]Examples of uncharged homoantiaromatic compounds have been claimed: Wilcox, Jr., C.F.; Blain, D.A.; Clardy, J.; Van Duyne, G.; Gleiter, R.; Eckert-Maksic, M. *J. Am. Chem. Soc.* ***1986***, *108*, 7693; Scott, L.T.; Cooney, M.J.; Rogers, D.W.; Dejroongruang, K. *J. Am. Chem. Soc.* ***1988***, *110*, 7244.

[354]Chen, Z.; Haijun Jiao, H.; Andreas Hirsch, A.; Schleyer, P.v.R. *Angew. Chem. Int. Ed.*, ***2002***, *41*, 4309

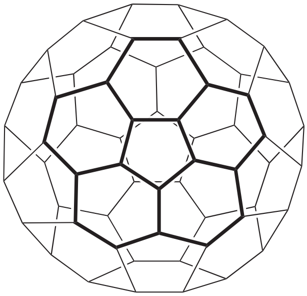
[355]Billups, W.E.; Ciufolini, M.A. *Buckminsterfullerenes*, VCH, NY, ***1993***; Taylor, R. *The Chemistry of Fullerenes*, World Scientific, River Edge, NJ, Singapore, ***1995***; Aldersey-Williams, H. *The Most Beautiful Molecule: The Discovery of the Buckyball*, Wiley, NY, ***1995***; Baggott, J.E. *Perfect Symmetry: the Accidental Discovery of Buckminsterfullerene*, Oxford University Press, Oxford, NY, ***1994***. Also see Kroto, H.W.; Heath, J.R.; O'Brien, S.C.; Curl, R.F.; Smalley, R.E. *Nature (London)* ***1985***, *318*, 162.

[356]Smalley, R.E. *Acc. Chem. Res.* ***1992***, *25*, 98; Diederich, F.; Whetten, R.L. *Acc. Chem. Res.* ***1992***, *25*, 119; Hawkins, J.M. *Acc. Chem. Res.* ***1992***, *25*, 150; Wudl, F. *Acc. Chem. Res.* ***1992***, *25*, 157; McElvany, S.W.; Ross, M.M.; Callahan, J.H. *Acc. Chem. Res.* ***1992***, *25*, 162; Johnson, R.D.; Bethune, D.S.; Yannoni, C.S. *Acc. Chem. Res.* ***1992***, *25*, 169.

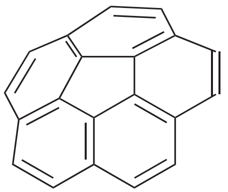
[357]Warner, P.M. *Tetrahedron Lett.* ***1994***, *35*, 7173.

[358]Barth, W.E.; Lawton, R.G. *J. Am. Chem. Soc.* ***1971***, *93*, 1730; Scott, L.T.; Hashemi, M.M.; Meyer, D.T.; Warren, H.B. *J. Am. Chem. Soc.* ***1991***, *113*, 7082.

surface. It has been synthesized by Scott,[352] and several other groups.[359] Corannulene is a flexible molecule, with a bowl-to-bowl inversion barrier of ~10–11 kcal mol^{-1} (41.8–46.0 kJ mol^{-1}).[360] Benzocorannulenes are known,[361] and other bowl-shaped hydrocarbons include acenaphtho[3,2,1,8-*ijklm*]diindeno[4,3,2,1-*cdef*-1′,2′,3′,4′*pqra*]triphenylene.[362] The inversion barrier to buckybowl inversion has been lowered by such benzannelation of the rim.[363] Other semibuckminsterfullerenes include C_{2v}-$C_{30}H_{12}$ and C_3-$C_{30}H_{12}$.[358] Larger fullerenes include C_{60},C_{80}, C_{84}, and fullerenes are known that contain an endohedral metal, such as scandium or even Sc_3N.[364] Synthetic methods often generate mixtures of fullerenes that must be separated, as in the report of new methods for separating C_{84}-fullerenes.[365] A homofullerene has been prepared.[366]



138



139

HYPERCONJUGATION

All of the delocalization discussed so far involves π electrons. Another type, called *hyperconjugation*, involves σ electrons.[367] When a carbon attached

[359]Borchardt, A.; Fuchicello, A.; Kilway, K.V.; Baldridge, K.K.; Siegel, J.S. *J. Am. Chem. Soc.* ***1992***, *114*, 1921; Liu, C.Z.; Rabideau, P.W. *Tetrahedron Lett.* ***1996***, *37*, 3437.

[360]Biedermann, P.U.; Pogodin, S.; Agranat, I. *J. Org. Chem.* ***1999***, *64*, 3655; Rabideau, P.W.; Sygula, A. *Acc. Chem. Res.* ***1996***, *29*, 235; Mehta, G.; Panda, G. *Chem. Comm.*, ***1997***, 2081; Rabideau, P.W.; Abdourazak, A.H.; Folsom, H.E.; Marcinow, Z.; Sygula, A.; Sygula, R. *J. Am. Chem. Soc.* ***1994***, *116*, 7891; Hagan, S.; Bratcher, M.S.; Erickson, M.S.; Zimmermann, G.; Scott, L.T. *Angew. Chem. Int. Ed.*, ***1997***, *36*, 406. See also, Dinadayalane, T.C.; Sastry, G.N. *Tetrahedron* ***2003***, *59*, 8347.

[361]Dinadayalane, T.C.; Sastry, G.N. *J. Org. Chem.* ***2002***, *67*, 4605.

[362]Marcinow, Z.; Grove, D.I.; Rabideau, P.W. *J. Org. Chem.* ***2002***, *67*, 3537.

[363]Marcinow, Z.; Sygula, A.; Ellern, D.A.; Rabideau, P.W. *Org. Lett.* ***2001***, *3*, 3527.

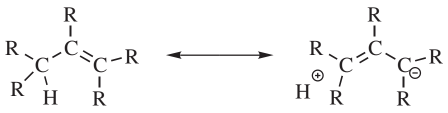
[364]Stevenson, S.; Rice, G.; Glass, T.; Harich, K.; Cromer, F.; Jordan, M.R.; Craft, J.; Hadju, E.; Bible, R.; Olmstead, M.M.; Maitra, K.; Fisher, A.J.; Balch, A.L.; Dorn, H.C. *Nature (London)* ***1999***, *401*, 55.

[365]Wang, G.-W.; Saunders, M.; Khong, A.; Cross, R.J. *J. Am. Chem. Soc.* ***2000***, *122*, 3216.

[366]Kiely, A.F.; Haddon, R.C.; Meier, M.S.; Selegue, J.P.; Brock, C.P.; Patrick, B.O.; Wang, G.-W.; Chen, Y. *J. Am. Chem. Soc.* ***1999***, *121*, 7971.

[367]For monographs, see Baker, J.W. *Hyperconjugation*, Oxford University Press, Oxford, ***1952***; Dewar, M.J.S. *Hyperconjugation*, Ronald Press, NY, ***1962***. For a review, see de la Mare, P.B.D. *Pure Appl. Chem.* ***1984***, *56*, 1755.

forms there is no bond at all between the carbon and hydrogen. The effect of **140** on the actual molecule is that the electrons in the C—H bond are closer to the carbon than they would be if **140** did not contribute at all.

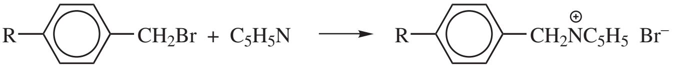


140

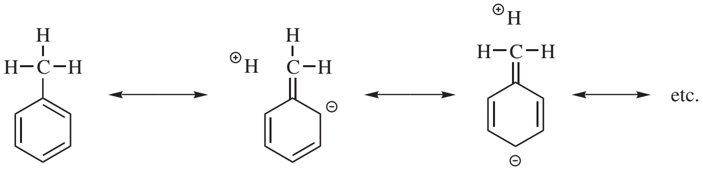
Hyperconjugation in the above case may be regarded as an overlap of the σ orbital of the C—H bond and the π orbital of the C—C bond, analogous to the π–π orbital overlap previously considered. As might be expected, those who reject the idea of resonance in butadiene (p. 39) believe it even less likely when it involves no-bond structures.

The concept of hyperconjugation arose from the discovery of apparently anomalous electron-release patterns for alkyl groups. By the field effect alone, the order of electron release for simple alkyl groups connected to an unsaturated system is *tert*-butyl > isopropyl > ethyl > methyl, and this order is observed in many phenomena. Thus, the dipole moments in the gas phase of $PhCH_3$, PhC_2H_5, $PhCH(CH_3)_2$, and $PhC(CH_3)_3$ are, respectively, 0.37, 0.58, 0.65, and 0.70 D.[368]

However, Baker and Nathan[369] observed that the rates of reaction with pyridine of *para*-substituted benzyl bromides (see reaction **10-31**) were opposite that expected from electron release by the field effect. That is, the methyl-substituted compound reacted fastest and the *tert*-butyl-substituted compounded reacted slowest.



This came to be called the *Baker–Nathan effect* and has since been found in many processes. Baker and Nathan explained it by considering that hyperconjugative forms contribute to the actual structure of toluene:

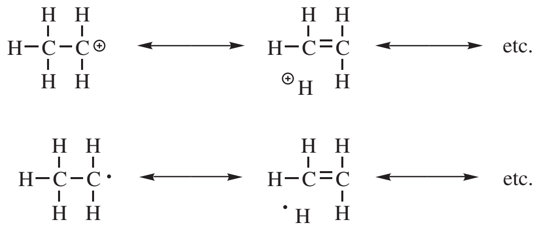


For the other alkyl groups, hyperconjugation is diminished because the number of C—H bonds is diminished and in *tert*-butyl there are none; hence, with

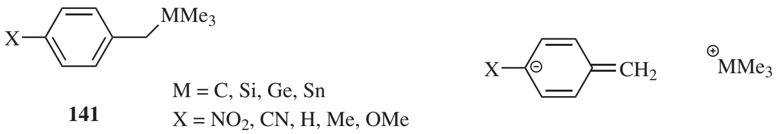
[368]Baker, J.W.; Groves, L.G. *J. Chem. Soc.* ***1939***, 1144.
[369]Baker, J.W.; Nathan, W.S. *J. Chem. Soc.* ***1935***, 1840, 1844.

respect to this effect, methyl is the strongest electron donor and *tert*-butyl is the weakest.

However, the Baker–Nathan effect has now been shown not to be caused by hyperconjugation, but by differential solvation.[370] This was demonstrated by the finding that in certain instances where the Baker–Nathan effect was found to apply in solution, the order was completely reversed in the gas phase.[371] Since the molecular structures are unchanged in going from the gas phase into solution, it is evident that the Baker–Nathan order in these cases is not caused by a structural feature (hyperconjugation), but by the solvent. That is, each alkyl group is solvated to a different extent.[372]



There is a large body of evidence against hyperconjugation in the ground states of neutral molecules.[373] A recent study of the one-bond coupling constants for the aromatic system **141**, however, appears to provide the first structural evidence for hyperconjugation in a neutral ground state.[374] In hyperconjugation



141

in the ground state of neutral molecules, which Muller and Mulliken call *sacrificial hyperconjugation*,[375] the canonical forms involve not only no-bond resonance, but also a charge separation not possessed by the main form (see **141**). For carbocations and free radicals[376] and for excited states of molecules,[377] there is evidence that hyperconjugation is important. In free radicals and carbocations, the canonical

[370]This idea was first suggested by Schubert, W.M.; Sweeney, W.A. *J. Org. Chem.* ***1956***, *21*, 119.

[371]Hehre,W.J.; McIver, Jr., R.T.; Pople, J.A.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1974***, *96*, 7162; Arnett, E.M.; Abboud, J.M. *J. Am. Chem. Soc.* ***1975***, *97*, 3865; Glyde, E.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* ***1977***, 678. See also, Taylor, R. *J. Chem. Res. (S)*, ***1985***, 318.

[372]For an opposing view, see Cooney, B.T.; Happer, D.A.R. *Aust. J. Chem.* ***1987***, *40*, 1537.

[373]For some evidence in favor, see Laube, T.; Ha, T. *J. Am. Chem. Soc.* ***1988***, *110*, 5511.

[374]Lambert, J.B.; Singer, R.A. *J. Am. Chem. Soc.* ***1992***, *114*, 10246.

[375]Muller, N.; Mulliken, R.S. *J. Am. Chem. Soc.* ***1958***, *80*, 3489.

[376]Symons, M.C.R. *Tetrahedron* ***1962***, *18*, 333.

[377]Rao, C.N.R.; Goldman, G.K.; Balasubramanian, A. *Can. J. Chem.* ***1960***, *38*, 2508.

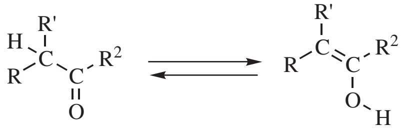
forms display no more charge separation than the main form. Muller and Mulliken call this *isovalent hyperconjugation*: Even here the main form contributes more to the hybrid than the others.

TAUTOMERISM[378]

There remains one topic to be discussed in our survey of chemical bonding in organic compounds. For most compounds, all the molecules have the same structure, whether or not this structure can be satisfactorily represented by a Lewis formula. But for many other compounds there is a mixture of two or more structurally distinct compounds that are in rapid equilibrium. When this phenomenon, called *tautomerism*,[379] exists, there is a rapid shift back and forth among the molecules. In most cases, it is a proton that shifts from one atom of a molecule to another.

Keto–Enol Tautomerism[380]

A very common form of tautomerism is that between a carbonyl compound containing an a hydrogen and its enol form:[381] Such equilibria are pH dependent, as in the case of 2-acetylcyclohexanone.[382]



Keto form **Enol form**

In simple cases (R^2 = H, alkyl, OR, etc.) the equilibrium lies well to the left (Table 2.1). The reason can be seen by examining the bond energies in Table 1.7.

[378]Baker, J.W. *Tautomerism*; D. Van Nostrand Company, Inc., New York, ***1934***; Minkin, V.I.; Olekhnovich, L.P.; Zhdanov, Y.A. *Molecular Design of Tautomeric Compounds*, D. Reidel Publishing Co.: Dordrecht, Holland, ***1988***.

[379]For reviews, see Toullec, J. *Adv. Phys. Org. Chem.* ***1982***, *18*, 1; Kołsov, A.I.; Kheifets, G.M. *Russ. Chem. Rev.* ***1971***, *40*, 773; ***1972***, *41*, 452–467; Forsén, S.; Nilsson, M., in Zabicky, J. *The Chemistry of the Carbonyl Group*, Vol. 2, Wiley, NY, ***1970***, pp. 157–240.

[380]The mechanism for conversion of one tautomer to another is discussed in Chapter 12 (reaction **12-3**).

[381]Capponi, M.; Gut, I.G.; Hellrung, B.; Persy, G.; Wirz, J. *Can. J. Chem.* ***1999***, *77*, 605. For a treatise, see Rappoport, Z. *The Chemistry of Enols*, Wiley, NY, ***1990***.

[382]Iglesias, E. *J. Org. Chem*, ***2003***, *68*, 2680.

TABLE 2.1. The Enol Content of Some Carbonyl Compounds

Compound	Enol Content, %	References
Acetone	6×10^{-7}	383
$PhCOCH_3$	1.1×10^{-6}	384
Cyclopentanone	1×10^{-6}	385
CH_3CHO	6×10^{-5}	386
Cyclohexanone	4×10^{-5}	385
Butanal	5.5×10^{-4}	387
$(CH_3)_2CHCHO$	1.4×10^{-2}	388,387
Ph_2CHCHO	9.1	389
CH_3COOEt	No enol found[a]	385
CH_3COCH_2COOEt	8.4	390
$CH_3COCH_2COCH_3$	80	322
$PhCOCH_2COCH_3$	89.2	385
$EtOOCCH_2COOEt$	7.7×10^{-3}	385
$N{\equiv}C{-}CH_2COOEt$	2.5×10^{-1}	385
Indane-1-one	3.3×10^{-8}	391
Malonamide	No enol found	392

[a]Less than 1 part in 10 million.

The keto form differs from the enol form in possessing a C—H, a C—C, and a C=O bond, where the enol has a C=C, a C—O, and an O—H bond. The approximate sum of the first three is 359 kcal mol^{-1} (1500 kJ mol^{-1}) and of the second three is 347 kcal mol^{-1} (1452 kJ mol^{-1}). The keto form is therefore thermodynamically more stable by ~12 kcal mol^{-1} (48 kJ mol^{-1}) and enol forms cannot normally be isolated.[393] In certain cases, however, a larger amount of the enol form is present,

[383]Tapuhi, E.; Jencks, W.P. *J. Am. Chem. Soc.* **1982**, *104*, 5758; Chiang, Y.; Kresge, A.J.; Tang, Y.S.; Wirz, J. *J. Am. Chem. Soc.* **1984**, *106*, 460. See also, Hine, J.; Arata, K. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3089; Guthrie, J.P. *Can. J. Chem.* 1979, *57*, 797, 1177; Dubois, J.E.; El-Alaoui, M.; Toullec, J. *J. Am. Chem. Soc.* 1981, *103*, 5393; Toullec, J. *Tetrahedron Lett.* 1984, *25*, 4401; Chiang, Y.; Kresge, A.J.; Schepp, N.P. *J. Am. Chem. Soc.* **1989**, *111*, 3977.

[384]Keeffe, J.R.; Kresge, A.R.; Toullec, J. *Can. J. Chem.* **1986**, *64*, 1224.

[385]Gero, A. *J. Org. Chem.* **1954**, *19*, 469, 1960; Keeffe, J.R., Kresge, A.J.; Schepp, N.P. *J. Am. Chem. Soc.* **1990**, *112*, 4862; Iglesias, E. *J. Chem. Soc. Perkin Trans. 2* **1997**, 431. See these papers for values for other simple compounds.

[386]Chiang, Y.; Hojatti, M.; Keeffe, J.R.; Kresge, A.J.; Schepp, N.P.; Wirz, J. *J. Am. Chem. Soc.* **1987**, *109*, 4000.

[387]Bohne, C.; MacDonald, I.D.; Dunford, H.B. *J. Am. Chem. Soc.* **1986**, *108*, 7867.

[388]Chiang, Y.; Kresge, A.J.; Walsh, P.A. *J. Am. Chem. Soc.* **1986**, *108*, 6314.

[389]Chiang, Y.; Kresge, A.J.; Krogh, E.T. *J. Am. Chem. Soc.* **1988**, *110*, 2600.

[390]Moriyasu, M.; Kato, A.; Hashimoto, Y. *J. Chem. Soc. Perkin Trans. 2* 1986, 515. For enolization of β-ketoamides, see Hynes, M.J.; Clarke, E.M. *J. Chem. Soc. Perkin Trans. 2* **1994**, 901.

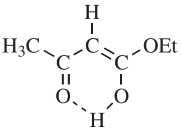
[391]Jefferson, E.A.; Keeffe, J.R.; Kresge, A.J. *J. Chem. Soc. Perkin Trans. 2* **1995**, 2041.

[392]Williams, D.L.H.; Xia, L. *J. Chem. Soc. Chem. Commun.* **1992**, 985.

[393]For reviews on the generation of unstable enols, see Kresge, A.J. *Pure Appl. Chem.* ***1991***, *63*, 213; Capon, B., in Rappoport, Z. *The Chemistry of Enols*, Wiley, NY, ***1990***, pp. 307–322.

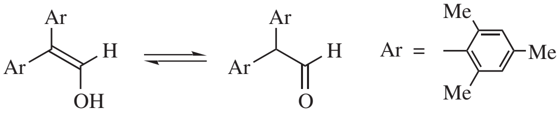
and it can even be the predominant form.[394] There are three main types of the more stable enols:[395]

1. Molecules in which the enolic double bond is in conjugation with another double bond. Some of these are shown in Table 2.1. As the table shows, carboxylic esters have a much smaller enolic content than ketones. In molecules like acetoacetic ester (**142**), the enol is also stabilized by internal hydrogen bonding, which is unavailable to the keto form:



142

2. Molecules that contain two or three bulky aryl groups.[396] An example is 2,2-dimesitylethenol (**143**). In this case the keto content at equilibrium is only 5%.[397] In cases such as this, steric hindrance (p. 230) destabilizes the keto form. In **143**, the two aryl groups are ~120° apart, but in **144** they must move closer together (~109.5°). Such compounds are often called *Fuson-type enols*.[398] There is one example of an amide with a bulky aryl group [*N*-methyl bis(2,4,6-triisopropylphenyl)acetamide] that has a measurable enol content, in sharp contrast to most amides.[399]



143 **144**

[394]For reviews of stable enols, see Kresge, A.J. *Acc. Chem. Res.* ***1990***, *23*, 43; Hart, H.; Rappoport, Z.; Biali, S.E., in Rappoport, Z. *The Chemistry of Enols*, Wiley, NY, ***1990***, pp. 481–589; Hart, H. *Chem. Rev*, ***1979***, *79*, 515; Hart, H.; Sasaoka, M. *J. Chem. Educ.* ***1980***, *57*, 685.

[395]For some examples of other types, see Pratt, D.V.; Hopkins, P.B. *J. Am. Chem. Soc.* ***1987***, *109*, 5553; Nadler, E.B.; Rappoport, Z.; Arad, D.; Apeloig, Y. *J. Am. Chem. Soc.* ***1987***, *109*, 7873.

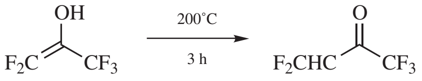
[396]For a review, see Rappoport, Z.; Biali, S.E. *Acc. Chem. Res.* ***1988***, *21*, 442. For a discussion of their structures, see Kaftory, M.; Nugiel, D.A.; Biali, D.A.; Rappoport, Z. *J. Am. Chem. Soc.* ***1989***, *111*, 8181.

[397]Biali, S.E.; Rappoport, Z. *J. Am. Chem. Soc.* ***1985***, *107*, 1007. See also, Kaftory, M.; Biali, S.E.; Rappoport, Z. *J. Am. Chem. Soc.* ***1985***, *107*, 1701; Nugiel, D.A.; Nadler, E.B.; Rappoport, Z. *J. Am. Chem. Soc.* ***1987***, *109*, 2112; O'Neill, P.; Hegarty, A.F. *J. Chem. Soc. Chem. Commun.* ***1987***, 744; Becker, H.; Andersson, K. *Tetrahedron Lett.* ***1987***, *28*, 1323.

[398]First synthesized by Fuson, R.C.; see, for example, Fuson, R.C.; Southwick, P.L.; Rowland, S.P. *J. Am. Chem. Soc.* ***1944***, *66*, 1109.

[399]Frey, J.; Rappoport, Z. *J. Am. Chem. Soc.* ***1996***, *118*, 3994.

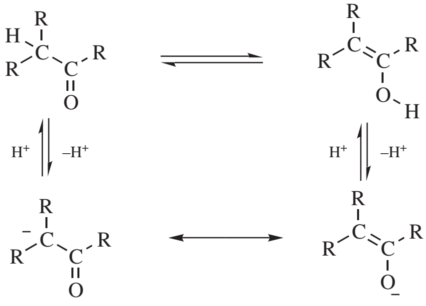
3. Highly fluorinated enols, such as **145**.[400]



145 **146**

In this case, the enol form is not more stable than the keto form (**146**). The enol form is less stable, and converts to the keto form upon prolonged heating). It can, however, be kept at room temperature for long periods of time because the tautomerization reaction (**12-3**) is very slow, owing to the electron-withdrawing power of the fluorines.

Frequently, when the enol content is high, both forms can be isolated. The pure keto form of acetoacetic ester melts at −39°C, while the enol is a liquid even at −78°C. Each can be kept at room temperature for days if catalysts, such as acids or bases, are rigorously excluded.[401] Even the simplest enol, vinyl alcohol $CH_2{=}CHOH$, has been prepared in the gas phase at room temperature, where it has a half-life of ~30 min.[402] The enol $Me_2C{=}CCHOH$ is indefinitely stable in the solid state at −78°C and has a half-life of ~24 h in the liquid state at 25°C.[403] When both forms cannot be isolated, the extent of enolization is often measured by NMR.[404]



147 **148**

[400]For a review, see Bekker, R.A.; Knunyants, I.L. *Sov. Sci. Rev. Sect. B* ***1984***, *5*, 145.

[401]For an example of particularly stable enol and keto forms, which could be kept in the solid state for more than a year without significant interconversion, see Schulenberg, J.W. *J. Am. Chem. Soc.* ***1968***, *90*, 7008.

[402]Saito, S. *Chem. Phys. Lett.* ***1976***, *42*, 399. See also, Capon, B.; Rycroft, D.S.; Watson, T.W.; Zucco, C. *J. Am. Chem. Soc.* ***1981***, *103*, 1761; Holmes, J.L.; Lossing, F.P. *J. Am. Chem. Soc.* ***1982***, *104*, 2648; McGarrity, J.F.; Cretton, A.; Pinkerton, A.A.; Schwarzenbach, D.; Flack, H.D. *Angew. Chem. Int. Ed.* ***1983***, *22*, 405; Rodler, M.; Blom, C.E.; Bauder, A. *J. Am. Chem. Soc.* ***1984***, *106*, 4029; Capon, B.; Guo, B.; Kwok, F.C.; Siddhanta, A.K.; Zucco, C. *Acc. Chem. Res.* ***1988***, *21*, 135.

[403]Chin, C.S.; Lee, S.Y.; Park, J.; Kim, S. *J. Am. Chem. Soc.* ***1988***, *110*, 8244.

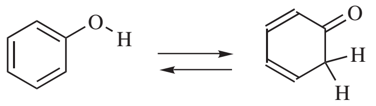
[404]Cravero, R.M.; González-Sierra, M.; Olivieri, A.C. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 1067.

The extent of enolization[405] is greatly affected by solvent,[406] concentration, and temperature. Lactone enols, for example, have been shown to be stable in the gas phase, but unstable in solution.[407] Thus, acetoacetic ester has an enol content of 0.4% in water and 19.8% in toluene.[408] In this case, water reduces the enol concentration by hydrogen bonding with the carbonyl, making this group less available for internal hydrogen bonding. As an example of the effect of temperature, the enol content of pentan-2,4-dione, $CH_3COCH_2COCH_3$, was found to be 95, 68, and 44%, respectively, at 22, 180, and 275°C.[409] When a strong base is present, both the enol and the keto form can lose a proton. The resulting anion (the *enolate ion*) is the same in both cases. Since **147** and **148** differ only in placement of electrons, *they* are not tautomers, but canonical forms. The true structure of the enolate ion is a hybrid of **147** and **148** although **148** contributes more, since in this form the negative charge is on the more electronegative atom.

Other Proton-Shift Tautomerism

In all such cases, the anion resulting from removal of a proton from either tautomer is the same because of resonance. Some examples are:[410]

1. *Phenol–Keto Tautomerism.*[411]



Phenol **Cyclohexadienone**

For most simple phenols, this equilibrium lies well to the side of the phenol, since only on that side is there aromaticity. For phenol itself, there is no evidence for the existence of the keto form.[412] However, the keto form

[405]For a review of keto–enol equilibrium constants, see Toullec, J. in Rappoport, Z. *The Chemistry of Enols*, Wiley, NY, ***1990***, pp. 323–398.

[406]For an extensive study, see Mills, S.G.; Beak, P. *J. Org. Chem.* ***1985***, *50*, 1216. For keto–enol tautomerism in aqueous alcohol solutions, see Blokzijl, W.; Engberts, J.B.F.N.; Blandamer, M.J. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 455; For theoretical calculations of keto–enol tautomerism in aqueous solutions, see Karelson, M.; Maran, U.; Katritzky, A.R. *Tetrahedron* ***1996***, *52*, 11325.

[407]Tureč ek, F.; Vivekananda, S.; Sadílek, M.; Polás̆ ek, M. *J. Am. Chem. Soc,.* ***2002***, *124*, 13282.

[408]Meyer, K.H. *Leibigs Ann. Chem.* ***1911***, *380*, 212. See also, Moriyasu, M.; Kato, A.; Hashimoto, Y. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 515.

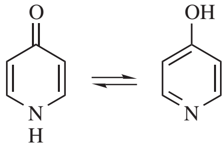
[409]Hush, N.S.; Livett, M.K.; Peel, J.B.; Willett, G.D. *Aust. J. Chem.* ***1987***, *40*, 599.

[410]For a review of the use of X-ray crystallography to determine tautomeric forms, see Furmanova, N.G. *Russ. Chem. Rev.* ***1981***, *50*, 775.

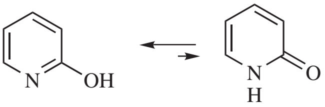
[411]For reviews, see Ershov, V.V.; Nikiforov, G.A. *Russ. Chem. Rev.* ***1966***, *35*, 817; Forsén, S.; Nilsson, M., in Zabicky, J. *The Chemistry of the Carbonyl Group*, Vol. 2, Wiley, NY, ***1970***, pp. 168–198.

[412]Keto forms of phenol and some simple derivatives have been generated as intermediates with very short lives, but long enough for spectra to be taken at 77 K. Lasne, M.; Ripoll, J.; Denis, J. *Tetrahedron Lett.* ***1980***, *21*, 463. See also, Capponi, M.; Gut, I.; Wirz, J. *Angew. Chem. Int. Ed.* ***1986***, *25*, 344.

becomes important and may predominate: (*1*) where certain groups, such as a second OH group or an N=O group, are present;[413] (*2*) in systems of fused aromatic rings;[414] (*3*) in heterocyclic systems. In many heterocyclic compounds in the liquid phase or in solution, the keto form is more stable,[415] although in the vapor phase the positions of many of these equilibria are reversed.[416] For example, in the equilibrium between 4-pyridone (**149**) and 4-hydroxypyridine (**150**), **149** is the only form detectable in ethanolic solution, while **150** predominates in the vapor phase.[416] In other heterocycles, the hydroxy-form predominates. 2-Hydroxypyridone (**151**) and pyridone-2-thiol (**153**)[417] are in equilibrium with their tautomers, 2-pyridone **152** and pyridine-2-thione **154**, respectively. In both cases, the most stable form is the hydroxy tautomer, **151** and **153**.[418]



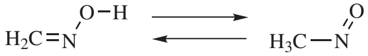
149 **150**



151 **152**

153 **154**

2. *Nitroso–Oxime Tautomerism.*



The equiblirum shown for formaldhyde oxime and nitrosomethane illustrates this process.[419] In molecules where the products are stable, the equilibrium lies far to the right, and as a rule nitroso compounds are stable only when there is not a hydrogen.

[413]Ershov, V.V.; Nikiforov, G.A. *Russ. Chem. Rev.* ***1966***, *35*, 817. See also, Highet, R.J.; Chou, F.E. *J. Am. Chem. Soc.* ***1977***, *99*, 3538.

[414]See, for example, Majerski, Z.; Trinajstić, N. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 2648.

[415]For a monograph on tautomerism in heterocyclic compounds, see Elguero, J.; Marzin, C.; Katritzky, A.R.; Linda, P. *The Tautomerism of Heterocycles*, Academic Press, NY, ***1976***. For reviews, see Katritzky, A.R.; Karelson, M.; Harris, P.A. *Heterocycles* ***1991***, *32*, 329; Beak, P. *Acc. Chem. Res.* ***1977***, *10*, 186; Katritzky, A.R. *Chimia*, ***1970***, *24*, 134.

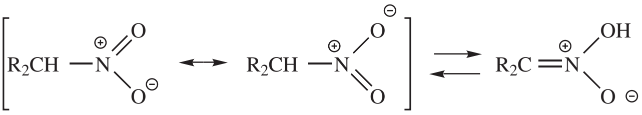
[416]Beak, P.; Fry, Jr., F.S.; Lee, J.; Steele, F. *J. Am. Chem. Soc.* ***1976***, *98*, 171.

[417]Moran, D.; Sukcharoenphon, K.; Puchta, R.; Schaefer III, H.F.; Schleyer, P.v.R.; Hoff, C.D. *J. Org. Chem.* ***2002***, *67*, 9061.

[418]Parchment, O.G.; Burton, N.A.; Hillier, I.H.; Vincent, M.A. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 861.

[419]Long, J.A.; Harris, N.J.; Lammertsma, K. *J. Org. Chem.* ***2001***, *66*, 6762.

3. *Aliphatic Nitro Compounds Are in Equilibrium with Aci Forms.*



Nitro form — Aci form

The nitro form is much more stable than the aci form in sharp contrast to the parallel case of nitroso–oxime tautomerism, undoubtedly because the nitro form has resonance not found in the nitroso case. Aci forms of nitro compounds are also called nitronic acids and azinic acids.

4. *Imine–Enamine Tautomerism.*[420]

$$R_2CH{-}CR{=}NR \rightleftharpoons R_2C{=}CR{-}NHR$$

Imine — Enamine

Enamines are normally stable only when there is no hydrogen on the nitrogen ($R_2C{=}CR{-}NR_2$). Otherwise, the imine form predominates.[421] The energy of various imine–enamine tautomers has been calculated.[422] In the case of 6-aminofulvene-1-aldimines, tautomerism was observed in the solid state, as well as in solution.[423]

5. *Ring-Chain Tautomerism.* Ring-chain tautomerism[424] occurs in sugars (aldehyde vs. the pyranose or furanose structures), and in γ-oxocarboxylic acids.[425] In benzamide carboxaldehyde, **156**, whose ring-chain tautomer is **155**, the equilibrium favors the cyclic form (**156**).[426] Similarly, benzoic acid 2-carboxyaldehyde (**157**) exists largely as the cyclic form (**158**).[427] In these latter cases, and in many others, this tautomerism influences chemical reactivity. Conversion of **157** to an ester, for example, is difficult since most standard methods lead to the OR derivative of **158** rather than the ester of **157**. Ring-chain tautomerism also occurs in sprioxathianes,[428] and in

[420]For reviews, see Shainyan, B.A.; Mirskova, A.N. *Russ. Chem. Rev.* ***1979***, *48*, 107; Mamaev, V.P.; Lapachev, V.V. *Sov. Sci. Rev. Sect. B.* ***1985***, *7*, 1. The second review also includes other closely related types of tautomerization.

[421]For examples of the isolation of primary and secondary enamines, see Shin, C.; Masaki, M.; Ohta, M. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 1657; de Jeso, B.; Pommier, J. *J. Chem. Soc. Chem. Commun.* ***1977***, 565.

[422]Lammertsma, K.; Prasad, B.V. *J. Am. Chem. Soc.* ***1994***, *116*, 642.

[423]Sanz, D.; Perez-Torralba, M.; Alarcon, S.H.; Claramunt, R.M.; Foces-Foces, C.; Elguero, J. *J. Org. Chem.* ***2002***, *67*, 1462.

[424]For a monograph, see Valters, R.E.; Flitsch, W. *Ring-Chain Tautomerism*, Plenum, NY, ***1985***. For reviews, see Valters, R.E. *Russ. Chem. Rev.* ***1973***, *42*, 464; ***1974***, *43*, 665; Escale, R.; Verducci, J. *Bull. Soc. Chim. Fr.*, ***1974***, 1203.

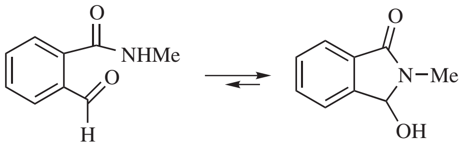
[425]Fabian, W.M.F.; Bowden, K. *Eur. J. Org. Chem.* ***2001***, 303.

[426]Bowden, K.; Hiscocks, S.P.; Perjéssy, A. *J. Chem. Soc. Perkin Trans. 2* ***1998***, 291.

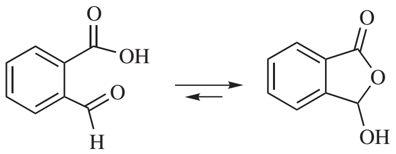
[427]Ring chain tautomer of benzoic acid 2-carboxaldehdye.

[428]Terec, A.; Grosu, I.; Muntean, L.; Toupet, L.; Plé, G.; Socaci, C.; Mager, S. *Tetrahedron* ***2001***, *57*, 8751; Muntean, L.; Grosu, I.; Mager, S.; Plé, G.; Balog, M. *Tetrahedron Lett.* ***2000***, *41*, 1967.

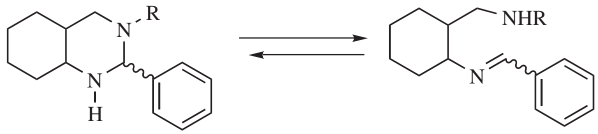
decahydroquinazolines, such as **159** and **160**,[429] as well as other 1,3-heterocycles.[430]



155 **156**

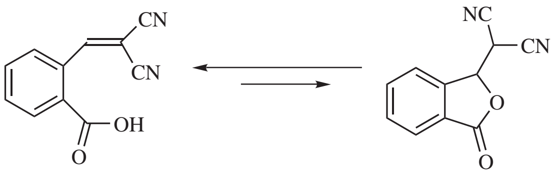


157 **158**



159 **160**

There are many other highly specialized cases of proton-shift tautomerism, including an internal Michael reaction (see **15-24**) in which 2-(2,2-dicyano-1-methylethenyl)benzoic acid (**161**) exists largely in the open chain form rather an its tautomer (**162**) in the solid state, but in solution there is an increasing amount of **162** as the solvent becomes more polar.[431]



161 **162**

Valence Tautomerism

This type of tautomerism is discussed on p. 105.

[429]Lazar, L.; Goblyos, A.; Martinek, T.A.; Fulop, F. *J. Org. Chem.* ***2002***, *67*, 4734.
[430]Lázár, L.; Fülöp, F. *Eur. J. Org. Chem.* ***2003***, 3025.
[431]Kolsaker, P.; Arukwe, J.; Barcóczy, J.; Wiberg, A.; Fagerli, A.K. *Acta Chem. Scand. B* ***1998***, *52*, 490.

CHAPTER 3

Bonding Weaker than Covalent

In the first two chapters, we discussed the structure of molecules each of which is an aggregate of atoms in a distinct three-dimensional (3D) arrangement held together by bonds with energies on the order of 50–100 kcal mol^{-1} (200–400 kJ mol^{-1}). There are also very weak attractive forces *between* molecules, on the order of a few tenths of a kilocalorie per mole. These forces, called van der Waals forces, are caused by electrostatic attractions, such as those between dipole and dipole, induced dipole, and induced dipole, and are responsible for liquefaction of gases at sufficiently low temperatures. The bonding discussed in this chapter has energies of the order of 2–10 kcal mol^{-1} (9–40 kJ mol^{-1}), intermediate between the two extremes, and produces clusters of molecules. We will also discuss compounds in which portions of molecules are held together without any attractive forces at all.

HYDROGEN BONDING

A *hydrogen bond* is a bond between a functional group A—H and an atom or group of atoms B in the same or a different molecule.[1] With exceptions to be noted later, hydrogen bonds are *assumed to form only when A is oxygen, nitrogen, or fluorine and when B is oxygen, nitrogen, or fluorine*.[2] The oxygen may be singly or doubly

[1]For a treatise, see Schuster, P.; Zundel, G.; Sandorfy, C. *The Hydrogen Bond*, 3 vols., North-Holland Publishing Co.: Amsterdam, The Netherlands, ***1976***. For a monograph, see Joesten, M.D.; Schaad, L.J. *Hydrogen Bonding*; Marcel Dekker, NY, ***1974***. For reviews, see Meot-Ner, M. *Mol. Struct. Energ.* ***1987***, *4*, 71; Deakyne, C.A. *Mol. Struct. Energ.* ***1987***, *4*, 105; Joesten, M.D. *J. Chem. Educ.* ***1982***, *59*, 362; Gur'yanova, E.N.; Gol'dshtein, I.P.; Perepelkova, T.I. *Russ. Chem. Rev.* ***1976***, *45*, 792; Pimentel, G.C.; McClellan, A.L. *Annu. Rev. Phys. Chem.* ***1971***, *22*, 347; Kollman, P.A.; Allen, L.C. *Chem. Rev.* ***1972***, *72*, 283; Huggins, M.L. *Angew. Chem. Int. Ed.* ***1971***, *10*, 147; Rochester, C.H., in Patai, S. The Chemistry of the Hydroxyl Group, pt. 1; Wiley, NY, ***1971***, pp. 327–392, 328–369. See also Hamilton, W.C.; Ibers, J.A. *Hydrogen Bonding in Solids*, W.A. Benjamin, NY, ***1968***. Also see, Chen, J.; McAllister, M.A.; Lee, J.K.; Houk, K.N. *J. Org. Chem.* ***1998***, *63*, 4611 for a discussion of short, strong hydrogen bonds.

[2]The ability of functional groups to act as hydrogen bond acids and bases can be obtained from either equilibrium constants for 1:1 hydrogen bonding or overall hydrogen bond constants. See Abraham, M.H.; Platts, J.A. *J. Org. Chem.* ***2001***, *66*, 3484.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Sixth Edition, by Michael B. Smith and Jerry March
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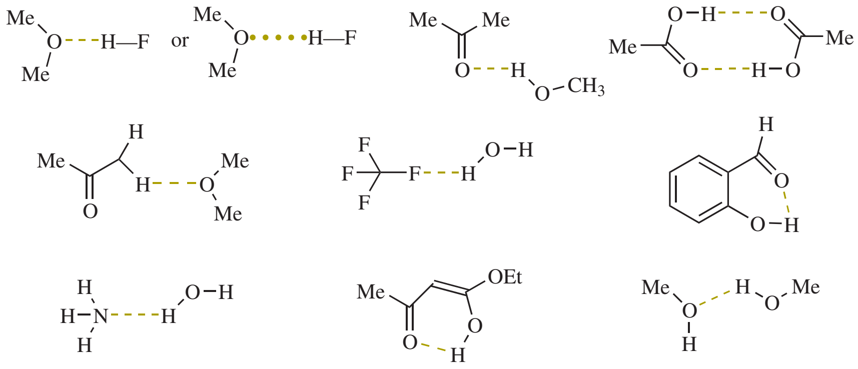
bonded and the nitrogen singly, doubly, or triply bonded. The bonds are usually represented by dotted or dashed lines, as shown in the following examples:



Hydrogen bonds can exist in the solid[3] and liquid phases and in solution.[4] Many organic reactions that will be discussed in later chapters can be done in aqueous media,[5] and their efficacy is due, in part, to the hydrogen bonding nature of aqueous media.[6] Even in the gas phase, compounds that form particularly strong hydrogen bonds may remain associated.[7] Acetic acid, for example, exists in the gas phase as a dimer, as shown above, except at very low pressures.[8] In solution and in the liquid phase, hydrogen bonds rapidly form and break. The mean lifetime of the $NH_3 \cdots H_2O$ bond is 2×10^{-12} s.[9] Except for a few very strong hydrogen bonds,[10] such as the $FH \cdots F^-$ bond (which has an energy of ~50 kcal mol^{-1} or 210 kJ mol^{-1}), the strongest hydrogen bonds are the FH•••F bond and the bonds connecting one carboxylic acid with another. The energies of these bonds are in the range of 6–8 kcal mol^{-1} or 25–30 kJ mol^{-1} (for carboxylic acids, this refers to the energy of each bond). In general, short contact hydrogen bonds between fluorine and HO or NH are rare.[11] Other OH•••O and NH•••N bonds[12] have energies of 3–6 kcal mol^{-1} (12–25 kJ mol^{-1}).

[3]Steiner, T. *Angew. Chem. Int. Ed.* ***2002***, *41*, 48. See also Damodharan, L.; Pattabhi, V. *Tetrahedron Lett.* ***2004***, *45*, 9427.

[4]See Nakahara, M.; Wakai, C. *Chem. Lett.* ***1992***, 809 for a discussion of monomeric and cluster states of water molecules in organic solvents due to hydrogen bonding.

[5]Li, C.-J.; Chen, T.-H. *Organic Reactions in Aqueous Media*, Wiley, NY, ***1997***.

[6]Li, C.-J. *Chem. Rev.* ***1993***, *93*, 2023.

[7]For a review of energies of hydrogen bonds in the gas phase, see Curtiss, L.A.; Blander, M. *Chem. Rev.* ***1988***, *88*, 827.

[8]For a review of hydrogen bonding in carboxylic acids and acid derivatives, see Hadži, D.; Detoni, S., in Patai, S. *The Chemistry of Acid Derivatives*, pt. 1, Wiley, NY, ***1979***, pp. 213–266.

[9]Emerson, M.T.; Grunwald, E.; Kaplan, M.L.; Kromhout, R.A. *J. Am. Chem. Soc.* ***1960***, *82*, 6307.

[10]For a review of very strong hydrogen bonding, see Emsley, J. *Chem. Soc. Rev.* ***1980***, *9*, 91.

[11]Howard, J.A.K.; Hoy, V.J.; O'Hagan, D.; Smith, G.T. *Tetrahedron* ***1996***, *52*, 12613.

[12]For an *ab initio* study of diamine hydrogen bonds see Sorensen, J.B.; Lewin, A.H.; Bowen, J.P. *J. Org. Chem.* ***2001***, *66*, 4105.

The intramolecular O–H•••N hydrogen bond in hydroxy amines is also rather strong.[13]

To a first approximation, the strength of hydrogen bonds increases with increasing acidity of A—H and basicity of B, but the parallel is far from exact.[14] A quantitative measure of the strengths of hydrogen bonds has been established, involving the use of an α scale to represent hydrogen-bond donor acidities and a β scale for hydrogen-bond acceptor basicities.[15] The use of the β scale, along with another parameter, ξ, allows hydrogen-bond basicities to be related to proton-transfer basicities (p*K* values).[16] A database has been developed to locate all possible occurrences of bimolecular cyclic hydrogen-bond motifs in the Cambridge Structural Database,[17] and donor–acceptor as well as polarity parameters have been calculated for hydrogen-bonding solvents.[18]

When two compounds whose molecules form hydrogen bonds with each other are both dissolved in water, the hydrogen bond between the two molecules is usually greatly weakened or completely removed,[19] because the molecules generally form hydrogen bonds with the water molecules rather than with each other, especially since the water molecules are present in such great numbers. In amides, the oxygen atom is the preferred site of protonation or complexation with water.[20] In the case of dicarboxylic acids, arguments have been presented that there is little or no evidence for strong hydrogen bonding in aqueous solution,[21] although recent studies concluded that strong, intramolecular hydrogen bonding can exist in aqueous acetone solutions (0.31 mole-fraction water) of hydrogen maleate and hydrogen *cis*-cyclohexane-1,2-dicarboxylate.[22]

Many studies have been made of the geometry of hydrogen bonds,[23] and the evidence shows that in most (though not all) cases, the hydrogen is on or near the

[13]Grech, E.; Nowicka-Scheibe, J.; Olejnik, Z.; Lis, T.; Pawêka, Z.; Malarski, Z.; Sobczyk, L. *J. Chem. Soc., Perkin Trans. 2* ***1996***, 343. See Steiner, T. *J. Chem. Soc., Perkin Trans. 2* ***1995***, 1315 for a discussion of hydrogen bonding in the crystal structure of α-amino acids.

[14]For reviews of the relationship between hydrogen-bond strength and acid-base properties, see Pogorelyi, V.K.; Vishnyakova, T.B. *Russ. Chem. Rev.* ***1984***, *53*, 1154; Epshtein, L.M. *Russ. Chem. Rev.* ***1979***, *48*, 854.

[15]For reviews, see Abraham, M.H.; Doherty, R.M.; Kamlet, M.J.; Taft, R.W. *Chem. Br.* ***1986***, 551; Kamlet, M.J.; Abboud, J.M.; Taft, R.W. *Prog. Phys. Org. Chem.* ***1981***, *13*, 485. For a comprehensive table and α and β values, see Kamlet, M.J.; Abboud, J.M.; Abraham, M.H.; Taft, R.W. *J. Org. Chem.* ***1983***, *48*, 2877. For a criticism of the β scale, see Laurence, C.; Nicolet, P.; Helbert, M. *J. Chem. Soc., Perkin Trans. 2* ***1986***, 1081. See also Nicolet, P.; Laurence, C.; Luçon, M. *J. Chem. Soc., Perkin Trans. 2* ***1987***, 483; Abboud, J.M.; Roussel, C.; Gentric, E.; Sraidi, K.; Lauransan, J.; Guihéneuf, G.; Kamlet, M.J.; Taft, R.W. *J. Org. Chem.* ***1988***, *53*, 1545; Abraham, M.H.; Grellier, P.L.; Prior, D.V.; Morris, J.J.; Taylor, P.J. *J. Chem. Soc., Perkin Trans. 2* ***1990***, 521.

[16]Kamlet, M.J.; Gal, J.; Maria, P.; Taft, R.W. *J. Chem. Soc., Perkin Trans. 2* ***1985***, 1583.

[17]Allen, F.H.; Raithby, P.R.; Shields, G.P.; Taylor, R. *Chem. Commun.* ***1998***, 1043.

[18]Joerg, S.; Drago, R.S.; Adams, J. *J. Chem. Soc., Perkin Trans. 2* ***1997***, 2431.

[19]Stahl, N.; Jencks, W.P. *J. Am. Chem. Soc.* ***1986***, *108*, 4196.

[20]Scheiner, S.; Wang, L. *J. Am. Chem. Soc.* ***1993***, *115*, 1958.

[21]Perrin, C.L. *Annu. Rev. Phys. Org. Chem.* ***1997***, *48*, 511.

[22]Lin, J.; Frey, P.A. *J. Am. Chem. Soc.* ***2000***, *122*, 11258.

[23]For reviews, see Etter, M.C. *Acc. Chem. Res.* ***1990***, *23*, 120; Taylor, R.; Kennard, O. *Acc. Chem. Res.* ***1984***, *17*, 320.

straight line formed by A and B.[24] This is true both in the solid state (where X-ray crystallography and neutron diffraction have been used to determine structures),[25] and in solution.[26] It is significant that the vast majority of intramolecular hydrogen bonding occurs where *six-membered rings* (counting the hydrogen as one of the six) can be formed, in which linearity of the hydrogen bond is geometrically favorable, while five-membered rings, where linearity is usually not favored (though it is known), are much rarer. A novel nine-membered intramolecular hydrogen bond has been reported.[27]

In certain cases, X-ray crystallography has shown that a single H–A can form simultaneous hydrogen bonds with two B atoms (*bifurcated* or *three-center hydrogen bonds*). An example is an adduct (**1**) formed from pentane-2,4-dione (in its enol form; see p. 98) and diethylamine, in which the O–H hydrogen simultaneously bonds[28] to an O and an N (the N–H hydrogen forms a hydrogen bond with the O of another pentane-2,4-dione molecule).[29] On the other hand, in the adduct (**2**) formed from 1,8-biphenylenediol and hexamethylphosphoramide (HMPA), the B atom (in this case oxygen) forms simultaneous hydrogen bonds with two A•••H hydrogens.[30] Another such case is found in methyl hydrazine carboxylate **3**.[31] Except for the special case of FH•••F^- bonds (see p. 107), the hydrogen is not equidistant between A and B. For example, in ice the O–H distance is 0.97 Å, while the H•••O distance is 1.79 Å.[32] A theoretical study of the vinyl alcohol–vinyl alcoholate system concluded the hydrogen bonding is strong, but asymmetric.[33] The hydrogen bond in the enol of malonaldehyde, in organic solvents, is asymmetric with the hydrogen atom closer to the basic oxygen atom.[34] There is recent evidence, however, that symmetrical hydrogen bonds to carboxylates should be regarded as two-center rather than three-center hydrogen bonds, since the criteria traditionally used to infer three-center hydrogen bonding are inadequate for carboxylates.[35] There is

[24]See Stewart, R. *The Proton: Applications to Organic Chemistry*; Academic Press, NY, ***1985***, pp. 148–153.

[25]A statisical analysis of X-ray crystallographic data has shown that most hydrogen bonds in crystals are nonlinear by ~10–15°: Kroon, J.; Kanters, J.A.; van Duijneveldt-van de Rijdt, J.G.C.M.; van Duijneveldt, F.B.; Vliegenthart, J.A. *J. Mol. Struct.* ***1975***, *24*, 109. See also, Ceccarelli, C.; Jeffrey, G.A.; Taylor, R. *J. Mol. Struct.* ***1981***, *70*, 255; Taylor, R.; Kennard, O.; Versichel, W. *J. Am. Chem. Soc.* ***1983***, *105*, 5761; ***1984***, *106*, 244.

[26]For reviews of a different aspect of hydrogen-bond geometry: the angle between A•••H•••B and the rest of the molecule, see Legon, A.C.; Millen, D.J. *Chem. Soc. Rev.* ***1987***, *16*, 467, *Acc. Chem. Res.* ***1987***, *20*, 39.

[27]Yoshimi, Y.; Maeda, H.; Sugimoto, A.; Mizuno, K. *Tetrahedron Lett.* ***2001***, *42*, 2341.

[28]Emsley, J.; Freeman, N.J.; Parker, R.J.; Dawes, H.M.; Hursthouse, M.B. *J. Chem. Soc., Perkin Trans. 1* ***1986***, 471.

[29]For some other three-center hydrogen bonds, see Taylor, R.; Kennard, O.; Versichel, W. *J. Am. Chem. Soc.* ***1984***, *106*, 244; Jeffrey, G.A.; Mitra, J. *J. Am. Chem. Soc.* ***1984***, *106*, 5546; Staab, H.A.; Elbl, K.; Krieger, C. *Tetrahedron Lett.* ***1986***, *27*, 5719.

[30]Hine, J.; Hahn, S.; Miles, D.E. *J. Org. Chem.* ***1986***, *51*, 577.

[31]Caminati, W.; Fantoni, A.C.; Schäfer, L.; Siam, K.; Van Alsenoy, C. *J. Am. Chem. Soc.* ***1986***, *108*, 4364.

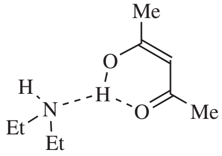
[32]Pimentel, G.C.; McClellan, A.L. *The Hydrogen Bond*; W.H. Freeman: San Francisco, ***1960***, p. 260.

[33]Chandra, A.K.; Zeegers-Huyskens, T., *J. Org. Chem.* ***2003***, *68*, 3618.

[34]Perrin, C.L.; Kim, Y.-J. *J. Am. Chem. Soc.* ***1998***, *120*, 12641.

[35]Görbitz, C.H.; Etter, M.C. *J. Chem. Soc., Perkin Trans. 2* ***1992***, 131.

also an example of cooperative hydrogen bonding (O–H•••C≡C–H•••Ph) in crystalline 2-ethynyl-6,8-diphenyl-7*H*-benzocyclohepten-7-ol (**4**).[36]



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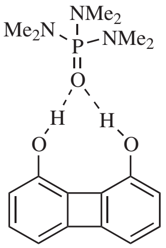

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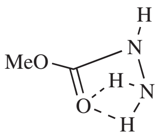

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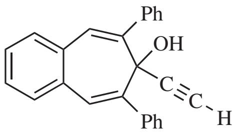


4

Hydrogen bonding has been detected in many ways, including measurements of dipole moments, solubility behavior, freezing-point lowering, and heats of mixing, but one important way is by the effect of the hydrogen bond on IR.[37] The IR frequencies of groups, such as O–H or C=O, are shifted when the group is hydrogen bonded. Hydrogen bonding always moves the peak toward lower frequencies, for both the A—H and the B groups, though the shift is greater for the former. For example, a free OH group of an alcohol or phenol absorbs at ~3590–3650 cm^{-1}, while a hydrogen-bonded OH group is found ~50–100 cm^{-1} lower.[38] In many cases, in dilute solution, there is partial hydrogen bonding, that is, some OH groups are free and some are hydrogen bonded. In such cases, two peaks appear. Infrared spectroscopy can also distinguish between inter- and intramolecular hydrogen bonding, since intermolecular peaks are intensified by an increase in concentration while intramolecular peaks are unaffected. Other types of spectra that have been used for the detection of hydrogen bonding include Raman, electronic,[39] and NMR.[40] Since hydrogen bonding involves a rapid movement of protons from one atom to another, nmr records an average value. Hydrogen bonding can be detected because it usually produces a chemical shift to a lower field. For example, carboxylic acid–carboxylate systems arising from either mono- or diacids generally exhibit a downfield resonance (16–22 ppm), which indicates "strong" hydrogen bonding

[36]Steiner, T.; Tamm, M.; Lutz, B.; van der Maas, J. *Chem. Commun.* ***1996***, 1127.

[37]For reviews of the use of ir spectra to detect hydrogen bonding, see Symons, M.C.R. *Chem. Soc. Rev.* ***1983***, *12*, 1; Egorochkin, A.N.; Skobeleva, S.E. *Russ. Chem. Rev.* ***1979***, *48*, 1198; Tichy, M. *Adv. Org. Chem.* ***1965***, *5*, 115; Ratajczak, H.; Orville-Thomas, W.J. *J. Mol. Struct.* ***1968***, *1*, 449. For a review of studies by ir of the shapes of intramolecular hydrogen-bonded compounds, see Aaron, H.S. *Top. Stereochem.* ***1979***, *11*, 1. For a review of the use of rotational spectra to study hydrogen bonding, see Legon, A.C. *Chem. Soc. Rev.* ***1990***, *19*, 197.

[38]Tichy, M. *Adv. Org. Chem.* ***1965***, *5*, 115 contains a lengthy table of free and intramolecularly hydrogen-bonding peaks.

[39]For a discussion of the effect of hydrogen bonding on electronic spectra, see Lees, W.A.; Burawoy, A. *Tetrahedron* ***1963***, *19*, 419.

[40]For a review of the use of nmr to detect hydrogen bonding, see Davis, Jr., J.C.; Deb, K.K. *Adv. Magn. Reson.* ***1970***, *4*, 201. Also see, Kumar, G.A.; McAllister, M.A. *J. Org. Chem.* ***1998***, *63*, 6968, which shows the relationship between ^{1}H NMR chemical shift and hydrogen bond strength.

in anhydrous, aprotic solvents.[41] Hydrogen bonding changes with temperature and concentration, and comparison of spectra taken under different conditions also serves to detect and measure it. As with IR spectra, intramolecular hydrogen bonding can be distinguished from intermolecular by its constancy when the concentration is varied. The spin–spin coupling constant across a hydrogen bond, obtained by NMR studies, has been shown to provide a "fingerprint" for hydrogen-bond type.[42]

Hydrogen bonds are important because of the effects they have on the properties of compounds, among them:

1. Intermolecular hydrogen bonding raises boiling points and frequently melting points.
2. If hydrogen bonding is possible between solute and solvent, this greatly increases solubility and often results in large or even infinite solubility where none would otherwise be expected.
3. Hydrogen bonding causes lack of ideality in gas and solution laws.
4. As previously mentioned, hydrogen bonding changes spectral absorption positions.
5. Hydrogen bonding, especially the intramolecular variety, changes many chemical properties. For example, it is responsible for the large amount of enol present in certain tautomeric equilibria (see p. 98). Also, by influencing the conformation of molecules (see Chapter 4), it often plays a significant role in determining reaction rates.[43] Hydrogen bonding is also important in maintaining the 3D structures of protein and nucleic acid molecules.

Besides oxygen, nitrogen, and fluorine, there is evidence that weaker hydrogen bonding exists in other systems.[44] Although many searches have been made for hydrogen bonding where A is carbon,[45] only three types of C–H bonds have been found that are acidic enough to form weak hydrogen bonds.[46] These are found in terminal alkynes, RC≡CH,[47] chloroform and some other halogenated alkanes, and HCN. Sterically unhindered C–H groups ($CHCl_3$, CH_2Cl_2, RC≡CH) form short contact hydrogen bonds with carbonyl acceptors, where there is a significant preference for coordination with the conventional carbonyl lone-pair direction.[48]

[41]Bruck, A.; McCoy, L.L.; Kilway, K.V. *Org. Lett.* ***2000***, *2*, 2007.

[42]Del Bene, J.E.; Perera, S.A.; Bartlett, R.J. *J. Am. Chem. Soc.* ***2000***, *122*, 3560.

[43]For reviews of the effect of hydrogen bonding on reactivity, see Hibbert, F.; Emsley, J. *Adv. Phys. Org. Chem.* ***1990***, *26*, 255; Sadekov, I.D.; Minkin, V.I.; Lutskii, A.E. *Russ. Chem. Rev.* ***1970***, *39*, 179.

[44]For a review, see Pogorelyi, V.K. *Russ. Chem. Rev.* ***1977***, *46*, 316.

[45]For a monograph on this subject, see Green, R.D. *Hydrogen Bonding by C–H Groups*; Wiley, NY, ***1974***. See also Taylor, R.; Kennard, O. *J. Am. Chem. Soc.* ***1982***, *104*, 5063; Harlow, R.L.; Li, C.; Sammes, M.P. *J. Chem. Soc., Perkin Trans. 1* ***1984***, 547; Nakai, Y.; Inoue, K.; Yamamoto, G.; Ō ki, M. *Bull. Chem. Soc. Jpn.* ***1989***, *62*, 2923; Seiler, P.; Dunitz, J.D. *Helv. Chim. Acta* ***1989***, *72*, 1125.

[46]For a theoretical study of weak hydrogen-bonds, see Calhorda, M.J. *Chem. Commun.* ***2000***, 801.

[47]For a review, see Hopkinson, A.C., in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, pt. 1, Wiley, NY, ***1978***, pp. 75–136. See also DeLaat, A.M.; Ault, B.S. *J. Am. Chem. Soc.* ***1987***, *109*, 4232.

[48]Streiner, T.; Kanters, J.A.; Kroon, J. *Chem. Commun.* ***1996***, 1277.

Weak hydrogen bonds are formed by compounds containing S–H bonds.[49] There has been much speculation regarding other possibilities for B. There is evidence that Cl can form weak hydrogen bonds,[50] but Br and I form very weak bonds if at all.[51] However, the *ions* Cl^-, Br^-, and I^- form hydrogen bonds that are much stronger than those of the covalently bonded atoms.[52] As we have already seen, the FH•••F^- bond is especially strong. In this case, the hydrogen is equidistant from the fluorines.[53] Similarly, a sulfur atom[49] can be the B component in weak hydrogen bonds,[54] but the ^-SH ion forms much stronger bonds.[55] There are theoretical studies of weak hydrogen bonding.[56] Hydrogen bonding has been directly observed (by NMR and IR) between a negatively charged carbon (see Carbanions, Chapter 5) and an OH group in the same molecule.[57] Another type of molecule in which carbon is the B component are isocyanides, $R{-}^+N{\equiv}C^-$ which form rather strong hydrogen bonds.[58] There is evidence that double and triple bonds, aromatic rings,[59] and even cyclopropane rings[60] may be the B component of hydrogen bonds, but these bonds are very weak. An interesting case is that of the *in*-bicyclo[4.4.4]-1-tetradecyl cation **5** (see in–out isomerism, p. 189). The NMR and IR spectra show that the actual structure of this ion is **6**, in which both the A and the B component of the hydrogen bond is a carbon.[61] These are sometimes

[49]For reviews of hydrogen bonding in sulfur-containing compounds, see Zuika, I.V.; Bankovskii, Yu.A. *Russ. Chem. Rev.* ***1973***, *42*, 22; Crampton, M.R., in Patai, S. *The Chemistry of the Thiol Group*, pt. 1; Wiley, NY, ***1974***, pp. 379–396; Pogorelyi, V.K. *Russ. Chem. Rev.* ***1977***, *46*, 316.

[50]For a review of hydrogen bonding to halogens, see Smith, J.W., in Patai, S. *The Chemistry of the Carbon-Halogen Bond*, pt. 1; Wiley, NY, ***1973***, pp. 265–300. See also, Bastiansen, O.; Fernholt, L.; Hedberg, K.; Seip, R. *J. Am. Chem. Soc.* ***1985***, *107*, 7836.

[51]West, R.; Powell, D.L.; Whatley, L.S.; Lee, M.K.T.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1962***, *84*, 3221; Fujimoto, E.; Takeoka, Y.; Kozima, K. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 991; Azrak, R.G.; Wilson, E.B. *J. Chem. Phys.* ***1970***, *52*, 5299.

[52]Allerhand, A.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1963***, *85*, 1233; McDaniel, D.H.; Valleé, R.E. *Inorg. Chem.* ***1963***, *2*, 996; Fujiwara, F.Y.; Martin, J.S. *J. Am. Chem. Soc.* ***1974***, *96*, 7625; French, M.A.; Ikuta, S.; Kebarle, P. *Can. J. Chem.* ***1982***, *60*, 1907.

[53]A few exceptions have been found, where the presence of an unsymmetrical cation causes the hydrogen to be closer to one fluorine than to the other: Williams, J.M.; Schneemeyer, L.F. *J. Am. Chem. Soc.* ***1973***, *95*, 5780.

[54]Vogel, G.C.; Drago, R.S. *J. Am. Chem. Soc.* ***1970***, *92*, 5347; Mukherjee, S.; Palit, S.R.; De, S.K. *J. Phys. Chem.* ***1970***, *74*, 1389; Schaefer, T.; McKinnon, D.M.; Sebastian, R.; Peeling, J.; Penner, G.H.; Veregin, R.P. *Can. J. Chem.* ***1987***, *65*, 908; Marstokk, K.; Møllendal, H.; Uggerrud, E. *Acta Chem. Scand.* ***1989***, *43*, 26.

[55]McDaniel, D.H.; Evans, W.G. *Inorg. Chem.* ***1966***, *5*, 2180; Sabin, J.R. *J. Chem. Phys.* ***1971***, *54*, 4675.

[56]Calhorda, M.J. *Chem. Commun.* ***2000***, 801.

[57]Ahlberg, P.; Davidsson, O.; Johnsson, B.; McEwen, I.; Rönnqvist, M. *Bull. Soc. Chim. Fr.* ***1988***, 177.

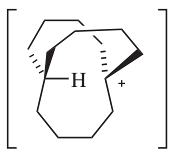
[58]Ferstandig, L.L. *J. Am. Chem. Soc.* ***1962***, *84*, 3553; Allerhand, A.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1963***, *85*, 866.

[59]For example, see Bakke, J.M.; Chadwick, D.J. *Acta Chem. Scand. Ser. B* ***1988***, *42*, 223: Atwood, J.L.; Hamada, F.; Robinson, K.D.; Orr, G.W.; Vincent, R.L. *Nature (London)* ***1991***, *349*, 683.

[60]Joris, L.; Schleyer, P.v.R.; Gleiter, R. *J. Am. Chem. Soc.* ***1968***, *90*, 327; Yoshida, Z.; Ishibe, N.; Kusumoto, H. *J. Am. Chem. Soc.* ***1969***, *91*, 2279.

[61]McMurry, J.E.; Lectka, T.; Hodge, C.N. *J. Am. Chem. Soc.* ***1989***, *111*, 8867. See also, Sorensen, T.S.; Whitworth, S.M. *J. Am. Chem. Soc.* ***1990***, *112*, 8135.

called 3-center–2-electron C–H–C bonds.[62] A technique called generalized population analysis has been developed to study this type of multicenter bonding.[63]



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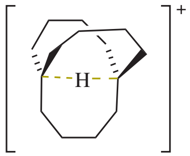
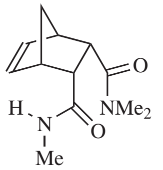


6

A weak (~1.5 kcal mol^{-1}) and rare C–H•••O=C hydrogen bond has been reported in a class of compounds known as a [6]semirubin (a dipyrrinone).[64] There is also evidence for a C–H•••N/CH•••OH bond in the crystal structures of α,β-unsaturated ketones carrying a terminal pyridine subunit,[65] and for R_3N^+–C–H•••O=C hydrogen bonding.[66]

Deuterium also forms hydrogen bonds; in some systems these seem to be stronger than the corresponding hydrogen bonds; in others, weaker.[67]



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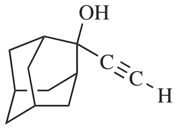


8

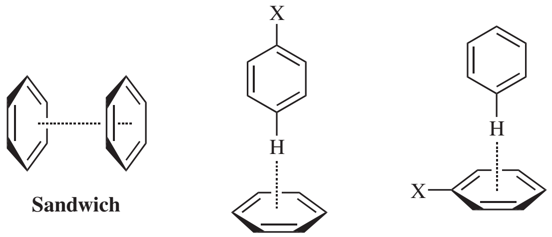
Weak hydrogen bonds can be formed between an appropriate hydrogen and a π bond, both with alkenes and with aromatic compounds. For example, IR data in dilute dichloromethane suggests that the predominant conformation for bis (amide) **7** contains an N–H•••π hydrogen bond involving the C=C unit.[68] The strength of an intramolecular π-facial hydrogen bond between an NH group and an aromatic ring in chloroform has been estimated to have a lower limit of -4.5 ± 0.5 kcal mol^{-1}(-18.8 kJ mol^{-1}).[69] A neutron diffraction study of crystalline 2-ethynyladamantan-2-ol (**8**) shows the presence of an unusual O–H•••π

[62]McMurry, J.E.; Lectka, T. *Acc. Chem. Res.* ***1992***, *25*, 47.
[63]Ponec, R.; Yuzhakov, G.; Tantillo, D.J. *J. Org. Chem.* ***2004***, *69*, 2992.
[64]Huggins, M.T.; Lightner, D.A. *J. Org. Chem.* ***2001***, *66*, 8402.
[65]Mazik, M.; Bläser, D.; Boese, R. *Tetrahedron* ***2001***, *57*, 5791.
[66]Cannizzaro, C.E.; Houk, K.N. *J. Am. Chem. Soc.* ***2002***, *124*, 7163.
[67]Dahlgren Jr., G.; Long, F.A. *J. Am. Chem. Soc.* ***1960***, *82*, 1303; Creswell, C.J.; Allred, A.L. *J. Am. Chem. Soc.* ***1962***, *84*, 3966; Singh, S.; Rao, C.N.R. *Can. J. Chem.* ***1966***, *44*, 2611; Cummings, D.L.; Wood, J.L. *J. Mol. Struct.* ***1974***, *23*, 103.
[68]Gallo, E.A.; Gelman, S.H. *Tetrahedron Lett.* ***1992***, *33*, 7485.
[69]Adams, H.; Harris, K.D.M.; Hembury, G.A.; Hunter, C.A.; Livingstone, D.; McCabe, J.F. *Chem. Commun.* ***1996***, 2531. See Steiner, T.; Starikov, E.B.; Tamm, M. *J. Chem. Soc., Perkin Trans. 2* ***1996***, 67 for a related example with 5-ethynyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ol.

hydrogen bond, which is short and linear, as well as the more common O–H•••O and C–H•••O hydrogen bonds.[70]

π–π INTERACTIONS

The π–π interactions are fundamental to many supramolecular organization and recognition processes.[71] There are many theoretical and experimental studies that clearly show the importance of π–π interactions.[72] Perhaps the simplest prototype of aromatic π–π interactions is the benzene dimer.[73] Within dimeric aryl systems such as this, possible π–π interactions are the sandwich and T-shaped interactions shown. It has been shown that all substituted sandwich dimers bind more strongly than benzene dimer, whereas the T-shaped configurations bind more or less favorably depending on the substituent.[74] Electrostatic, dispersion, induction, and exchange-repulsion contributions are all significant to the overall binding energies.[74]



Sandwich **T-shaped (1)** **T-shaped (2)**

The π-electrons of aromatic rings can interact with charged species, yielding strong cation–π interactions dominated by electrostatic and polarization effects.[75] Interactions with CH units is also possible. For CH–π interactions in both alkyl- and aryl-based model systems, dispersion effects dominate the interaction, but the electrostatics term is also relevant for aryl CH–π interactions.[76]

[70]Allen, F.H.; Howard, J.A.K.; Hoy, V.J.; Desiraju, G.R.; Reddy, D.S.; Wilson, C.C. *J. Am. Chem. Soc.* ***1996***, *118*, 4081.
[71]Meyer, E.A.; Castellano, R.K.; Diederich, F. *Angew. Chem. Int. Ed.* ***2003***, *42*, 1210.
[72]Tsuzuki, T.; Uchimaru, T.; Tanabe, K. *J. Mol. Struct.* (*THEOCHEM*) ***1994***, *307*, 107; Hobza, P.; Selzle, H.L.; Schlag, E.W. *J. Phys. Chem.* ***1996***, *100*, 18790; Tsuzuki, S.; Lüthi, H.P. *J. Chem. Phys.* ***2001***, *114*, 3949; Steed, J.M.; Dixon, T.A.; Klemperer, W. *J. Chem. Phys.* ***1979***, *70*, 4940.; Arunan, E.; Gutowsky, H.S. *J. Chem. Phys.* ***1993***, *98*, 4294; Law, K.S.; Schauer, M.; Bernstein, E.R. *J. Chem. Phys.* ***1984***, *81*, 4871; Felker, P.M.; Maxton, P.M.; Schaeffer, M.W. *Chem. Rev.* ***1994***, *94*, 1787; Venturo, V.A.; Felker, P.M. *J. Chem. Phys.* ***1993***, *99*, 748; Tsuzuki, S.; Honda, K.; Uchimaru, T.; Mikami, M.; Tanabe, K. *J. Am. Chem. Soc.* ***2002***, *124*, 104; Hobza, P.; Jurečka, P. *J. Am. Chem. Soc.* ***2003***, *125*, 15608.
[73]Sinnokrot, M.O.; Valeev, E.F.; Sherrill, C.D. *J. Am. Chem. Soc.* ***2002***, *124*, 10887.
[74]Sinnokrot, M.O.; Sherrill, C.D. *J. Am. Chem. Soc.* ***2004***, *126*, 7690
[75]Lindeman, S.V.; Kosynkin, D.; Kochi, J.K. *J. Am. Chem. Soc.* ***1998***, *120*, 13268; Ma, J.C.; Dougherty, D.A. *Chem. Rev.* ***1997***, *97*, 1303; Dougherty, D.A. *Science* ***1996***, *271*, 163; Cubero, E.; Luque, F.J.; Orozco, M. *Proc. Natl. Acad. Sci. U.S.A.* ***1998***, *95*, 5976.
[76]Ribas, J.; Cubero, E.; Luque, F. J.; Orozco, M. *J. Org. Chem.* ***2002***, *67*, 7057.

Detection of π–π interactions has largely relied on NMR-based techniques, such as chemical shifts variations,[77] and Nuclear Overhauser Effect Spectroscopy (NOESY) or Rotating-Frame NOE Spectroscopy (ROESY).[78] Diffusion-ordered NMR spectroscopy (DOSY) has also been used to detect π–π stacked complexes.[79]

ADDITION COMPOUNDS

When the reaction of two compounds results in a product that contains all the mass of the two compounds, the product is called an *addition compound*. There are several kinds. In the rest of this chapter, we will discuss addition compounds in which the molecules of the starting materials remain more or less intact and weak bonds hold two or more molecules together. We can divide them into four broad classes: electron donor–acceptor complexes, complexes formed by crown ethers and similar compounds, inclusion compounds, and catenanes.

Electron Donor–Acceptor (EDA) Complexes[80]

In *EDA complexes*,[81] there is always a donor and an acceptor molecule. The donor may donate an unshared pair (an *n* donor) or a pair of electrons in a π orbital of a double bond or aromatic system (a π donor). One test for the presence of an EDA complex is the electronic spectrum. These complexes generally exhibit a spectrum (called a *charge-transfer spectrum*) that is not the same as the sum of the spectra of the two individual molecules.[82] Because the first excited state of the complex is relatively close in energy to the ground state, there is usually a peak in the visible or near-uv region and EDA complexes are often colored. Many EDA complexes are unstable and exist only in solutions in equilibrium with their components, but others are stable solids. In most EDA complexes the donor and acceptor molecules are present in an integral ratio, most often 1:1, but complexes with nonintegral ratios are also known. There are several types of acceptor molecules; we will discuss complexes formed by two of them.

[77]Petersen, S.B.; Led, J.J.; Johnston, E.R.; Grant, D.M. *J. Am. Chem. Soc.* ***1982***, *104*, 5007.

[78]Wakita, M.; Kuroda, Y.; Fujiwara, Y.; Nakagawa, T. *Chem. Phys. Lipids* ***1992***, *62*, 45.

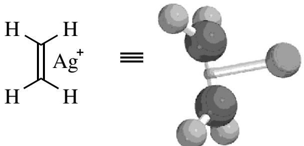
[79]Viel, S.; Mannina, L.; Segre, A. *Tetrahedron Lett.* ***2002***, *43*, 2515. See also, Ribas, J.; Cubero, E.; Luque, F.J.; Orozco, M. *J. Org. Chem.* ***2002***, *67*, 7057.

[80]For monographs, see Foster, R. *Organic Charge-Transfer Complexes*, Academic Press, NY, ***1969***; Mulliken, R.S.; Person, W.B. *Molecular Complexes*, Wiley, NY, ***1969***; Rose, J. *Molecular Complexes*, Pergamon, Elmsford, NY, ***1967***. For reviews, see Poleshchuk, O.Kh.; Maksyutin, Yu.K. *Russ. Chem. Rev.* ***1976***, *45*, 1077; Banthorpe, D.V. *Chem. Rev.* ***1970***, *70*, 295; Kosower, E.M. *Prog. Phys. Org. Chem.* ***1965***, *3*, 81; Foster, R. *Chem. Br.* ***1976***, *12*, 18.

[81]These have often been called *charge-transfer complexes*, but this term implies that the bonding involves charge transfer, which is not always the case, so that the more neutral name EDA complex is preferable. See Mulliken, R.S.; Person, W.B. *J. Am. Chem. Soc.* ***1969***, *91*, 3409.

[82]For examples of EDA complexes that do not show charge-transfer spectra, see Bentley, M.D.; Dewar, M.J.S. *Tetrahedron Lett.* ***1967***, 5043.

1. *Complexes in Which the Acceptor Is A Metal Ion and the Donor an Alkene or an Aromatic Ring* (*n* donors do not give EDA complexes with metal ions but form covalent bonds instead).[83] Many metal ions form complexes, that are often stable solids, with alkenes, dienes (usually conjugated, but not always), alkynes, and aromatic rings. The donor (or ligand) molecules in these complexes are classified by the prefix *hapto*[84] and/or the descriptor η^n (the Greek letter eta), where *n* indicates how many atoms the ligand uses to bond with the metal.[85] The generally accepted picture of the bonding in these complexes,[86] first proposed by Dewar,[87] can be



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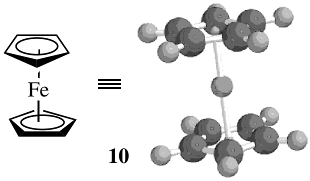


10

illustrated by the ethylene complex with silver, **9**, in which the alkene unit forms an η^2-complex with the silver ion (the alkene functions as a 2-electron donating ligand to the metal). There is evidence of π-complexation of Na^+ by C=C.[88]

[83]For monographs, see Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed, University Science Books, Mill Valley, CA, ***1987***; Alper, H. *Transition Metal Organometallics in Organic Synthesis*, 2 vols., Academic Press, NY, ***1976***, ***1978***; King, R.B. *Transition-Metal Organic Chemistry*, Academic Press, NY, ***1969***; Green, M.L.H. *Organometallic Compounds*, Vol. 2, Methuen, London, ***1968***; For general reviews, see Churchill, M.R.; Mason, R. *Adv. Organomet. Chem.* **1967**, *5*, 93; Cais, M., in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, ***1964***, pp. 335–385. Among the many reviews limited to certain classes of complexes are transition metals–dienes, Nakamura, A. *J. Organomet. Chem.* ***1990***, *400*, 35; metals-cycloalkynes and arynes, Bennett, M.A.; Schwemlein, H.P. *Angew. Chem. Int. Ed.* ***1989***, *28*, 1296; metals-pentadienyl ions, Powell, P. *Adv. Organomet. Chem.* ***1986***, *26*, 125; complexes of main-group metals, Jutzi, P. *Adv. Organomet. Chem.* ***1986***, *26*, 217; intramolecular complexes, Omae, I. *Angew. Chem. Int. Ed.* ***1982***, *21*, 889; transition metals–olefins and acetylenes, Pettit, L.D.; Barnes, D.S. *Fortschr. Chem. Forsch.* ***1972***, *28*, 85; Quinn, H.W.; Tsai, J.H. *Adv. Inorg. Chem. Radiochem.* ***1969***, *12*, 217; Pt- and Pd-olefins and acetylenes, Hartley, F.R. *Chem. Rev.* ***1969***, *69*, 799; silver ions-olefins and aromatics, Beverwijk, C.D.M.; van der Kerk, G.J.M.; Leusink, J.; Noltes, J.G. *Organomet. Chem. Rev. Sect. A* ***1970***, *5*, 215; metals-substituted olefins, Jones, R. *Chem. Rev.* ***1968***, *68*, 785; transition metals-allylic compounds, Clarke, H.L. *J. Organomet. Chem.* ***1974***, *80*, 155; transition metals–arenes, Silverthorn, W.E. *Adv. Organomet. Chem.* ***1976***, *14*, 47; metals-organosilicon compounds, Haiduc, I.; Popa, V. *Adv. Organomet. Chem.* ***1977***, *15*, 113; metals–carbocations, Pettit, L.D.; Haynes, L.W., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 5, Wiley, NY, ***1976***, pp. 2263–2302; metals-seven-and eight-membered rings, Bennett, M.A. *Adv. Organomet. Chem.* ***1966***, *4*, 353. For a list of review articles on this subject, see Bruce, M.I. *Adv. Organomet. Chem.* ***1972***, *10*, 273, pp. 317–321.

[84]For a discussion of how this system originated, see Cotton, F.A. *J. Organomet. Chem.* ***1975***, *100*, 29.

[85]Another prefix used for complexes is μ (mu), which indicates that the ligand bridges two metal atoms.

[86]For reviews, see Pearson, A.J. *Metallo-organic Chemistry*, Wiley, NY, ***1985***; Ittel, S.D.; Ibers, J.A. *Adv. Organomet. Chem.* ***1976***, *14*, 33; Hartley, F.R. *Chem. Rev.* ***1973***, *73*, 163; *Angew. Chem. Int. Ed.* ***1972***, *11*, 596.

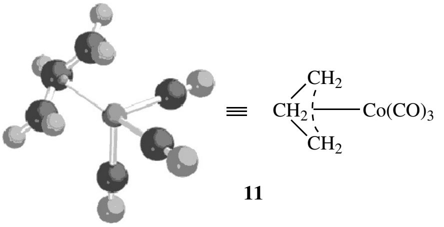
[87]Dewar, M.J.S. *Bull. Soc. Chim. Fr.* ***1951***, *18*, C79.

[88]Hu, J.; Gokel, G.W.; Barbour, L.J. *Chem. Commun.* ***2001***, 1858.

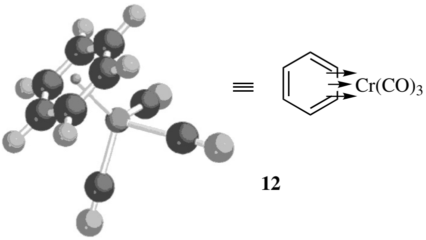
In the case of the silver complex, the bond is not from one atom of the C=C unit to the silver ion, but from the π center such that two electrons are transferred from the alkene to the metal ion.[89] Ethene has two π-electrons and is a dihapto or η^2 ligand, as are other simple alkenes. Similarly, benzene has six π-electrons and is a hexahapto or η^6 ligand. Ferrocene (**10**) has two cyclopentadienyl ligands (each is a five-electron donor or an η^5 ligand), and ferrocene is properly called bis(η^5-cyclopentadienyl)iron(II). This system can be extended to compounds in which only a single σ bond connects the organic group to the metal, for example, C_6H_5–Li (a monohapto or η^1 ligand), and to complexes in which the organic group is an ion, for example, π-allyl complexes, such as **11**, in which the allyl ligand is trihapto or η^3. Note that in a compound such as allyllithium, where a σ bond connects the carbon to the metal, the allyl group is referred to as monohapto or η^1.

$CH_2{=}CH{-}CH_2{-}Li$

Allyllithium



11



12

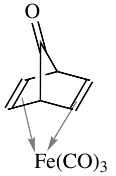
As mentioned, benzene is an η^6 ligand that forms complexes with silver and other metals.[90] When the metal involved has a coordination number >1, more than one donor molecule (ligand) participates. The CO group is a common ligand (a two-electron donating or η^2 ligand), and in metal complexes the CO group is classified as a metal carbonyl. Benzenechromium tricarbonyl (**12**) is a stable compound[91] that illustrates both benzene and carbonyl ligands. Three arrows are shown to represent the six-electron donation (an η^6 ligand), but the accompanying model gives a clearer picture of the bonding. Cyclooctatetraene is an eight-electron donating or η^8 ligand that also forms complexes with metals. Metallocenes (see **10**) may be considered a special case of this type of complex, although the bonding in

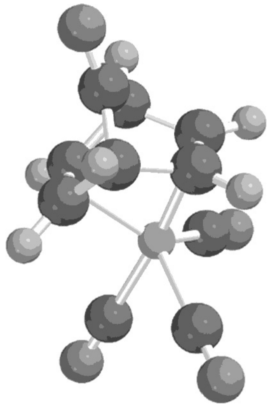
[89]For a discussion of how the nature of the metal ion affects the stability of the complex, see p. $$$.

[90]For a monograph, see Zeiss, H.; Wheatley, P.J.; Winkler, H.J.S. *BenzenoidMetal Complexes*; Ronald Press, NY, ***1966***.

[91]Nicholls, B.; Whiting, M.C. *J. Chem. Soc.* ***1959***, 551. For reviews of arene–transition-metal complexes, see Uemura, M. *Adv. Met.-Org. Chem.* ***1991***, *2*, 195; Silverthorn, W.E. *Adv. Organomet. Chem.* ***1975***, *13*, 47.

metallocenes is much stronger.

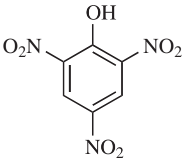




13

In a number of cases, alkenes that are too unstable for isolation have been isolated in the form of metal complexes. As example is norbornadienone, which was isolated in the form of its iron–tricarbonyl complex (**13**),[92] where the norbornadiene unit is an η^4 ligand, and each of the carbonyl units are η^2 ligands. The free dienone spontaneously decomposes to carbon monoxide and benzene (see reaction **17-28**).

2. *Complexes in Which the Acceptor Is an Organic Molecule*. Picric acid, 1,3,5-trinitrobenzene, and similar polynitro compounds are the most important of these.[93] Picric acid forms addition compounds with many



Picric acid

aromatic hydrocarbons, aromatic amines, aliphatic amines, alkenes, and other compounds. These addition compounds are usually solids with definite melting points and are often used as derivatives of the compounds in question. They are called picrates, though they are not salts of picric acid, but addition compounds. Unfortunately, salts of picric acid are also called picrates. Similar complexes are formed between phenols and quinones (quinhydrones).[94]

[92]Landesberg, J.M.; Sieczkowski, J. *J. Am. Chem. Soc.* ***1971***, *93*, 972.

[93]For a review, see Parini, V.P. *Russ. Chem. Rev.* ***1962***, *31*, 408; for a review of complexes in which the acceptor is an organic cation, see Kampar, V.E. *Russ. Chem. Rev.* ***1982***, *51*, 107; also see Ref. 80.

[94]For a review of quinone complexes, see Foster, R.; Foreman, M.I., in Patai, S. *The Chemistry of the Quinonoid Compounds*, pt. 1, Wiley, NY, ***1974***, pp. 257–333.

Alkenes that contain electron-withdrawing substituents also act as acceptor molecules, as do carbon tetrahalides[95] and certain anhydrides.[96] A particularly strong alkene acceptor is tetracyanoethylene.[97]

The bonding in these cases is more difficult to explain than in the previous case, and indeed no really satisfactory explanation is available.[98] The difficulty is that although the donor has a pair of electrons to contribute (both n and π donors are found here), the acceptor does not have a vacant orbital. Simple attraction of the dipole-induced dipole type accounts for some of the bonding,[99] but is too weak to explain the bonding in all cases;[100] for example, nitromethane, with about the same dipole moment as nitrobenzene, forms much weaker complexes. Some other type of bonding clearly must also be present in many EDA complexes. The exact nature of this bonding, called *charge-transfer bonding*, is not well understood, but it presumably involves some kind of donor–acceptor interaction.

Crown Ether Complexes and Cryptates[101]

Crown ethers are large-ring compounds containing several oxygen atoms, usually in a regular pattern. Examples are 12-crown-4 (**14**; where 12 is the size of the ring

[95]See Blackstock, S.C.; Lorand, J.P.; Kochi, J.K. *J. Org. Chem.* ***1987***, *52*, 1451.

[96]For a review of anhydrides as acceptors, see Foster, R., in Patai, S. *The Chemistry of Acid Derivatives*, pt. 1, Wiley, NY, ***1979***, pp. 175–212.

[97]For a review of complexes formed by tetracyanoethylene and other polycyano compounds, see Melby, L.R., in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 639–669. See also, Fatiadi, A.J. *Synthesis* ***1987***, 959.

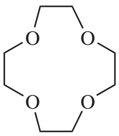
[98]For reviews, see Bender, C.J. *Chem. Soc. Rev.* ***1986***, *15*, 475; Kampar, E.; Neilands, O. *Russ. Chem. Rev.* ***1986***, *55*, 334; Bent, H.A. *Chem. Rev.* ***1968***, *68*, 587.

[99]See, for example, Le Fevre, R.J.W.; Radford, D.V.; Stiles, P.J. *J. Chem. Soc. B* ***1968***, 1297.

[100]Mulliken, R.S.; Person, W.B. *J. Am. Chem. Soc.* ***1969***, *91*, 3409.

[101]For a treatise, see Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, 3 vols.; Academic Press, NY, ***1984***. For monographs, see Weber, E. et al., *Crown Ethers and Analogs*, Wiley, NY, ***1989***; Vögtle, F. *Host Guest Complex Chemistry I, II, and III* (*Top. Curr. Chem. 98, 101, 121*); Springer, Berlin, ***1981***, ***1982***, ***1984***; Vögtle, F.; Weber, E. *Host Guest Complex Chemistry/Macrocycles*, Springer, Berlin, ***1985*** [this book contains nine articles from the *Top. Curr. Chem.* vols. just mentioned]; Hiraoka, M. *Crown Compounds*, Elsevier, NY, ***1982***; De Jong, F.; Reinhoudt, D.N. *Stability and Reactivity of Crown-Ether Complexes*, Academic Press, NY, ***1981***; Izatt, R.M.; Christensen, J.J. *Synthetic Multidentate Macrocyclic Compounds*, Academic Press, NY, ***1978***. For reviews, see McDaniel, C.W.; Bradshaw, J.S.; Izatt, R.M. *Heterocycles*, ***1990***, *30*, 665; Sutherland, I.O. *Chem. Soc. Rev.* ***1986***, *15*, 63; Sutherland, I.O., in Takeuchi, Y.; Marchand, A.P. *Applications of NMR Spectroscopy to Problems in Stereochemistry and Conformational Analysis*, VCH, NY, ***1986***; Franke, J.; Vögtle, F. *Top. Curr. Chem.* ***1986***, *132*, 135; Cram, D.J. *Angew. Chem. Int. Ed.* ***1986***, *25*, 1039; Gutsche, C.D. *Acc. Chem. Res.* ***1983***, *16*, 161; Tabushi, I.; Yamamura, K. *Top. Curr. Chem.* ***1983***, *113*, 145; Stoddart, J.F. *Prog. Macrocyclic Chem.* ***1981***, *2*, 173; De Jong, F.; Reinhoudt, D.N. *Adv. Phys. Org. Chem.* ***1980***, *17*, 279; Vögtle, E.; Weber, E., in Patai, S. *The Chemistry of Functional Groups, Supplement E*, Wiley, NY, ***1980***, pp. 59–156; Poonia, N.S. *Prog. Macrocyclic Chem.* ***1979***, *1*, 115; Reinhoudt, D.N.; De Jong, F. *Prog. Macrocyclic Chem.* ***1979***, *1*, 157; Cram, D.J.; Cram, J.M. *Acc. Chem. Res.* ***1978***, *11*, 8, *Science* ***1974***, *183*, 803; Knipe, A.C. *J. Chem. Educ.* ***1976***, *53*, 618; Gokel, G.W.; Durst, H.D. *Synthesis* ***1976***, 168; *Aldrichimica Acta* ***1976***, *9*, 3; Lehn, J.M. *Struct. Bonding* (*Berlin*) ***1973***, *16*, 1; Christensen, J.J.; Eatough, D.J.; Izatt, R.M. *Chem. Rev.* ***1974***, *74*, 351; Pedersen, C.J.; Frensdorff, H.K. *Angew. Chem. Int. Ed.* ***1972***, *11*, 16.

and 4 represents the number of coordinating atoms, here oxygen),[102] dicyclohexano-18-crown-6 (**15**), and 15-crown-5 (**16**). These compounds have the property[103] of forming complexes with positive ions, generally metallic ions (though not usually ions of transition metals) or ammonium and substituted ammonium ions.[104] The crown ether is called the *host* and the ion is the *guest*. In most cases, the ions are held tightly in the center of the cavity.[105] Each crown ether binds different ions, depending on the size of the cavity. For example, **14** binds Li^+[106] but not K^+,[107] while **15** binds K^+ but not Li^+.[108] Similarly, **15** binds Hg^{2+}, but not Cd^{2+} or Zn^{2+}, and Sr^{2+} but not Ca^{2+}.[109] 18-Crown-5 binds alkali and ammonium cations >1000 times weaker than 18-crown-6, presumably because the larger 18-crown-6 cavity involves more hydrogen bonds.[110] The complexes can frequently be prepared as well-defined sharp-melting solids.



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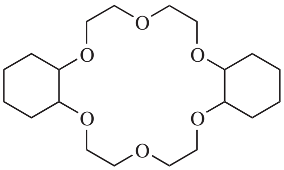

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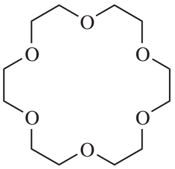

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For a monograph on the synthesis of crown ethers, see Gokel, G.W.; Korzeniowski, S.H. *Macrocyclic Polyether Synthesis*, Springer, NY, ***1982***. For reviews, see Krakowiak, K.E.; Bradshaw, J.S.; Zamecka-Krakowiak, D.J. *Chem. Rev.* ***1989***, *89*, 929; Jurczak, J.; Pietraszkiewicz, M. *Top. Curr. Chem.* ***1986***, *130*, 183; Gokel, G.W.; Dishong, D.M.; Schultz, R.A.; Gatto, V.J. *Synthesis* ***1982***, 997; Bradshaw, J.S.; Stott, P.E. *Tetrahedron* ***1980***, *36*, 461; Laidler, D.A.; Stoddart, J.F., in Patai, S. *The Chemistry of Functional Groups, Supplement E*, Wiley, NY, ***1980***, pp. 3–42. For reviews of acyclic molecules with similar properties, see Vögtle, E. *Chimia* ***1979***, *33*, 239; Vögtle, E.; Weber, E. *Angew. Chem. Int. Ed.* ***1979***, *18*, 753. For a review of cryptands that hold two positive ions, see Lehn, J.M. *Pure Appl. Chem.* ***1980***, *52*, 2441. The 1987 Nobel Prize in Chemistry was awarded to Charles J. Pedersen, Donald J. Cram, and Jean-Marie Lehn for their work in this area. The three Nobel lectures were published in two journals (respectively, CJP, DJC, J-ML): *Angew. Chem. Int. Ed.* ***1988***, *27* pp. 1021, 1009, 89; and *Chem. Scr.* ***1988***, *28*, pp. 229, 263, 237. See also the series *Advances in Supramolecular Chemistry*.

[102]Cook, F.L.; Caruso, T.C.; Byrne, M.P.; Bowers, C.W.; Speck, D.H.; Liotta, C. *Tetrahedron Lett.* ***1974***, 4029.

[103]Discovered by Pedersen, C.J. *J. Am. Chem. Soc.* ***1967***, *89*, 2495, 7017. For an account of the discovery, see Schroeder, H.E.; Petersen, C.J. *Pure Appl. Chem.* ***1988***, *60*, 445.

[104]For a monograph, see Inoue, Y.; Gokel, G.W. *Cation Binding by Macrocycles*, Marcel Dekker, NY, ***1990***.

[105]For reviews of thermodynamic and kinetic data for this type of interaction, see Izatt, R.M.; Bradshaw, J.S.; Nielsen, S.A.; Lamb, J.D.; Christensen, J.J.; Sen, D. *Chem. Rev.* ***1985***, *85*, 271; Parsonage, N.G.; Staveley, L.A.K., in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 3, Academic Press, NY, ***1984***, pp. 1–36.

[106]Anet, F.A.L.; Krane, J.; Dale, J.; Daasvatn, K.; Kristiansen, P.O. *Acta Chem. Scand.* ***1973***, *27*, 3395.

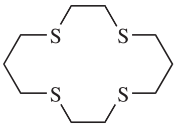
[107]Certain derivatives of 14-crown-4 and 12-crown-3 show very high selectivity for Li^+ compared to the other alkali metal ions. See Bartsch, R.A.; Czech, B.P.; Kang, S.I.; Stewart, L.E.; Walkowiak, W.; Charewicz, W.A.; Heo, G.S.; Son, B. *J. Am. Chem. Soc.* ***1985***, *107*, 4997; Dale, J.; Eggestad, J.; Fredriksen, S.B.; Groth, P. *J. Chem. Soc., Chem. Commun.* ***1987***, 1391; Dale, J.; Fredriksen, S.B. *Pure Appl. Chem.* ***1989***, *61*, 1587.

[108]Izatt, R.M.; Nelson, D.P.; Rytting, J.H.; Haymore, B.L.; Christensen, J.J. *J. Am. Chem. Soc.* ***1971***, *93*, 1619.

[109]Kimura, Y.; Iwashima, K.; Ishimori, T.; Hamaguchi, H. *Chem. Lett.* ***1977***, 563.

[110]Raevsky, O.A.; Solov'ev, V.P.; Solotnov, A.F.; Schneider, H.-J.; Rüdiger, V. *J. Org. Chem.* ***1996***, *61*, 8113.

Apart from their obvious utility in separating mixtures of cations,[111] crown ethers have found much use in organic synthesis (see the discussion on p. 510). Chiral crown ethers have been used for the resolution of racemic mixtures (p. 138). Although crown ethers are most frequently used to complex cations, amines, phenols, and other neutral molecules have also been complexed[112] (see p. 189 for the complexing of anions).[113] Macrocycles containing nitrogen (aza-crown ethers) or sulfur atoms (thiacrown ethers),[114] such as **17** and **18**,[115] have complexing properties similar to other crown ethers, as do mixed heteroatom crown ethers such as **19**,[116] **20**,[117] or **21**.[118]



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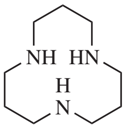

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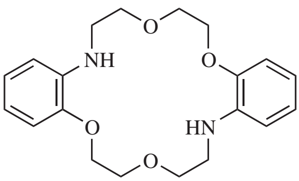

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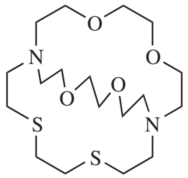

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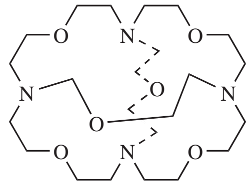

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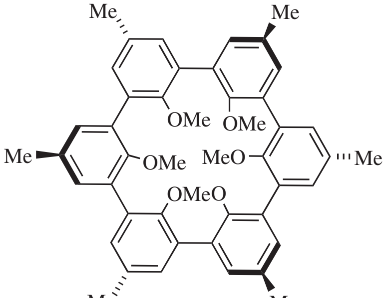

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[111]Crown ethers have been used to separate isotopes of cations, for example, ^{44}Ca from ^{40}Ca. For a review, see Heumann, K.G. *Top. Curr. Chem.* ***1985***, *127*, 77.

[112]For reviews, see Vögtle, F.; Müller, W.M.; Watson, W.H. *Top. Curr. Chem.* ***1984***, *125*, 131; Weber, E. *Prog. Macrocycl. Chem.* ***1987***, *3*, 337; Diederich, F. *Angew. Chem. Int. Ed.* ***1988***, *27*, 362.

[113]A neutral molecule (e.g., urea) and a metal ion (e.g., Li^+) were made to be joint guests in a macrocyclic host, with the metal ion acting as a bridge that induces a partial charge on the urea nitrogens: van Staveren, C.J.; van Eerden, J.; van Veggel, F.C.J.M.; Harkema, S.; Reinhoudt, D.N. *J. Am. Chem. Soc.* ***1988***, *110*, 4994. See also, Rodrigue, A.; Bovenkamp, J.W.; Murchie, M.P.; Buchanan, G.W.; Fortier, S. *Can. J. Chem.* ***1987***, *65*, 2551; Fraser, M.E.; Fortier, S.; Markiewicz, M.K.; Rodrigue, A.; Bovenkamp, J.W. *Can. J. Chem.* ***1987***, *65*, 2558.

[114]For reviews of sulfur-containing macroheterocycles, see Voronkov, M.G.; Knutov, V.I. *Sulfur Rep.* ***1986***, *6*, 137, *Russ. Chem. Rev.* ***1982***, *51*, 856. For a review of those containing S and N, see Reid, G.; Schröder, M. *Chem. Soc. Rev.* ***1990***, *19*, 239.

[115]For a review of **17** and its derivatives, see Chaudhuri, P.; Wieghardt, K. *Prog. Inorg. Chem.* ***1987***, *35*, 329. *N*-Aryl-azacrown ethers are known, see Zhang, X.-X.; Buchwald, S.L. *J. Org. Chem.* ***2000***, *65*, 8027.

[116]Gersch, B.; Lehn, J.-M.; Grell, E. *Tetrahedron Lett.* ***1996***, *37*, 2213.

[117]Newcomb, M.; Gokel, G.W.; Cram, D.J. *J. Am. Chem. Soc.* ***1974***, *96*, 6810.

[118]Graf, E.; Lehn, J.M. *J. Am. Chem. Soc.* ***1975***, *97*, 5022; Ragunathan, K.G.; Shukla, R.; Mishra, S.; Bharadwaj, P.K. *Tetrahedron Lett.* ***1993***, *34*, 5631.

Bicyclic molecules like **20** can surround the enclosed ion in three dimensions, binding it even more tightly than the monocyclic crown ethers. Bicyclics and cycles of higher order[119] are called *cryptands* and the complexes formed are called *cryptates* (monocyclic compunds are sometimes called cryptands). When the molecule contains a cavity that can accommodate a guest molecule, usually through hydrogen-bonding interactions, it is sometimes called a cavitand.[120] The tricyclic cryptand **21** has 10 binding sites and a spherical cavity.[93] Another molecule with a spherical cavity (though not a cryptand) is **22**, which complexes Li^+ and Na^+ (preferentially Na^+), but not K^+, Mg^{2+}, or Ca^{2+}.[121] Molecules such as these, whose cavities can be occupied only by spherical entities, have been called *spherands*.[77] Other types are *calixarenes*,[122] for example, **23**.[123] Spherand-type calixarenes are known.[124] There is significant hydrogen bonding involving the phenolic OH units in [4]calixarenes, but this diminishes as the size of the cavity increases in larger ring calixarenes.[125] There are also calix[6]arenes,[126] which have been shown to have conformational isomers (see p. 195) in equilibrium (cone vs. alternate) that can sometimes be isolated:[127] calix[8]arenes,[128] azacalixarenes,[129] homooxacalixarenes,[130]

[119]For reviews, see Potvin, P.G.; Lehn, J.M. *Prog. Macrocycl. Chem.* ***1987***, *3*, 167; Kiggen, W.; Vögtle, F. *Prog. Macrocycl. Chem.* ***1987***, *3*, 309; Dietrich, B., in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 2, Academic Press, NY, ***1984***, pp. 337–405; Parker, D. *Adv. Inorg. Radichem.* ***1983***, *27*, 1; Lehn, J.M. *Acc. Chem. Res.* ***1978***, *11*, 49, *Pure Appl. Chem.* ***1977***, *49*, 857.

[120]Shivanyuk, A.; Spaniol, T.P.; Rissanen, K.; Kolehmainen, E.; Böhmer, V. *Angew. Chem. Int. Ed.* ***2000***, *39*, 3497.

[121]Cram, D.J.; Doxsee, K.M. *J. Org. Chem.* ***1986***, *51*, 5068; Cram, D.J. *CHEMTECH* ***1987***, 120, *Chemtracts: Org. Chem.* ***1988***, *1*, 89; Bryany, J.A.; Ho, S.P.; Knobler, C.B.; Cram, D.J. *J. Am. Chem. Soc.* ***1990***, *112*, 5837.

[122]Shinkai, S. *Tetrahedron* ***1993***, *49*, 8933.

[123]For monographs, see Vicens, J.; Böhmer, V. *Calixarenes: A Versatile Class of Macrocyclic Compounds*, Kluver, Dordrecht, ***1991***; Gutsche, C.D. *Calixarenes*; Royal Society of Chemistry: Cambridge, ***1989***. For reviews, see Gutsche, C.D. *Prog. Macrocycl. Chem.* ***1987***, *3*, 93, *Top. Curr. Chem.* ***1984***, *123*, 1. Also see Geraci, C.; Piatelli, M.; Neri, P. *Tetrahedron Lett.* ***1995***, *36*, 5429; Deng, G.; Sakaki, T.; Kawahara, Y.; Shinkai, S. *Tetrahedron Lett.* ***1992***, *33*, 2163; Zhong, Z.-L.; Chen, Y.-Y.; Lu, X.-R. *Tetrahedron Lett.* ***1995***, *36*, 6735; No, K.; Kim, J.E.; Kwon, K.M. *Tetrahedron Lett.* ***1995***, *36*, 8453.

[124]Agbaria, K.; Aleksiuk, O.; Biali, S.E.; Böhmer, V.; Frings, M.; Thondorf, I. *J. Org. Chem.* ***2001***, *66*, 2891. For the stereochemistry of such compounds, see Agbaria, K.; Biali, S.E.; Böhmer, V.; Brenn, J.; Cohen, S.; Frings, M., Grynszpan, F.; Harrowfield, J.Mc B.; Sobolev, A.N.; Thondorf, I. *J. Org. Chem.* ***2001***, *66*, 2900.

[125]Cerioni, G.; Biali, S.E.; Rappoport, Z. *Tetrahedron Lett.* ***1996***, *37*, 5797. For a synthesis of calix[4]arene see Molard, Y.; Bureau, C.; Parrot-Lopez, H.; Lamartine, R.; Regnourf-de-Vains, J.-B. *Tetrahedron Lett.* ***1999***, *40*, 6383.

[126]Otsuka, H.; Araki, K.; Matsumoto, H.; Harada, T.; Shinkai, S. *J. Org. Chem.* ***1995***, *60*, 4862.

[127]Neri, P.; Rocco, C.; Consoli, G.M.L.; Piatelli; M. *J. Org. Chem.* ***1993***, *58*, 6535; Kanamathareddy, S.; Gutsche, C.D. *J. Org. Chem.* ***1994***, *59*, 3871.

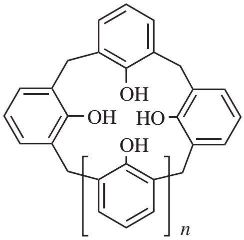
[128]Cunsolo, F.; Consoli, G.M.L.; Piatelli; M.; Neri, P. *Tetrahedron Lett.* ***1996***, *37*, 715; Geraci, C.; Piatelli, M.; Neri, P. *Tetrahedron Lett.* ***1995***, *36*, 5429.

[129]Miyazaki, Y.; Kanbara, T.; Yamamoto, T. *Tetrahedron Lett.* ***2002***, *43*, 7945; Khan, I.U.; Takemura, H.; Suenaga, M.; Shinmyozu, T.; Inazu, T. *J. Org. Chem.* ***1993***, *58*, 3158.

[130]Masci, B. *J. Org. Chem.* ***2001***, *66*, 1497. For dioxocalix[4]arenes, see Seri, N.; Thondorf, I.; Biali, S.E. *J. Org. Chem.* ***2004***, *69*, 4774. For tetraoxacalix[3]arenes, see Tsubaki, K.; Morimoto, T.; Otsubo, T.; Kinoshita, T.; Fuji, K. *J. Org. Chem.* ***2001***, *66*, 4083.

and calix[9–20]arenes.[131] Note that substitution of the unoccupied "meta" positions immobilizes calix[4]arenes and substantially reduces the conformational mobility (see p. 211) in calix[8]arenes.[132] Amide-bridged calix[4]arenes[133] calix[4]azulene,[134] and quinone-bridged calix[6]arenes[135] are known, and diammoniumcalix[4]arene has been prepared.[136] Enantiopure calix[4]resorcinarene derivatives are known,[137] and water soluble calix[4]arenes have been prepared.[138] There are also a variety of calix[*n*]-crown ethers,[139] some of which are cryptands.[140]

calix[4]arene, *n* = 1
calix[6]arene, *n* = 3
calix[8]arene, *n* = 5



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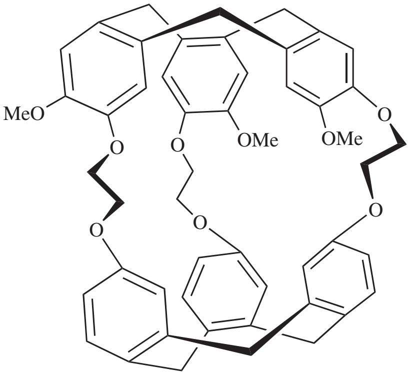

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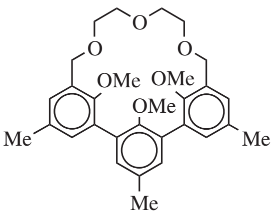
Other molecules include *cryptophanes*, for example, **24**,[141] *hemispherands* (an example is **25**[142]), and *podands*.[143] The last-named are host compounds in which two or more arms come out of a central structure. Examples are **26**[144] and **27**[145] and the latter molecule binds simple cations, such as Na^+, K^+, and Ca^{2+}. *Lariat ethers* are compounds containing a crown ether ring with one or more side chains

[131]Stewart, D.R.; Gutsche, C.D. *J. Am. Chem. Soc.* ***1999***, *121*, 4136.
[132]Mascal, M.; Naven, R.T.; Warmuth, R. *Tetrahedron Lett.* ***1995***, *36*, 9361.
[133]Wu, Y.; Shen, X.-P.; Duan, C.-y.; Liu, Y.-i.; Xu, Z. *Tetrahedron Lett.* ***1999***, *40*, 5749.
[134]Colby, D.A.; Lash, T.D. *J. Org. Chem.* ***2002***, *67*, 1031.
[135]Akine, S.; Goto, K.; Kawashima, T. *Tetrahedron Lett.* ***2000***, *41*, 897.
[136]Aeungmaitrepirom, W.; Hagège, A.; Asfari, Z.; Bennouna, L.; Vicens, J.; Leroy, M. *Tetrahedron Lett.* ***1999***, *40*, 6389.
[137]Page, P.C.B.; Heaney, H.; Sampler, E.P. *J. Am. Chem. Soc.* ***1999***, *121*, 6751.
[138]Shimizu, S.; Shirakawa, S.; Sasaki, Y.; Hirai, C. *Angew. Chem. Int. Ed.* ***2000***, *39*, 1256.
[139]Stephan, H.; Gloe, K.; Paulus, E.F.; Saadioui, M.; Böhmer, V. *Org. Lett.* ***2000***, *2*, 839; Asfari, Z.; Thuéry, P.; Nierlich, M.; Vicens, J. *Tetrahedron Lett.* ***1999***, *40*, 499; Geraci, C.; Piattelli, M.; Neri, P. *Tetrahedron Lett.* ***1996***, *37*, 3899; Pappalardo, S.; Petringa, A.; Parisi, M.F.; Ferguson, G. *Tetrahedron Lett.* ***1996***, *37*, 3907.
[140]Pulpoka, B.; Asfari, Z.; Vicens, J. *Tetrahedron Lett.* ***1996***, *37*, 6315.
[141]For reviews, see Collet, A. *Tetrahedron* ***1987***, *43*, 5725, in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 1, Academic Press, NY, ***1984***, pp. 97–121.
[142]Lein, G.M.; Cram, D.J. *J. Am. Chem. Soc.* ***1985***, *107*, 448.
[143]For reviews, see Kron, T.E.; Tsvetkov, E.N. *Russ. Chem. Rev.* ***1990***, *59*, 283; Menger, F.M. *Top. Curr. Chem.* ***1986***, *136*, 1.
[144]Tümmler, B.; Maass, G.; Weber, E.; Wehner, W.; Vögtle, F. *J. Am. Chem. Soc.* ***1977***, *99*, 4683.
[145]Vögtle, F.; Weber, E. *Angew. Chem. Int. Ed.* ***1974***, *13*, 814.

that can also serve as ligands, for example, **28**.[146] There is also a class of ortho cyclophanes that are crown ethers (see **29**) and have been given the name *starands*.[147]



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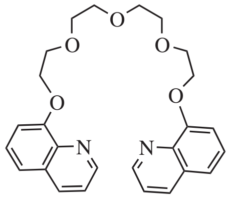

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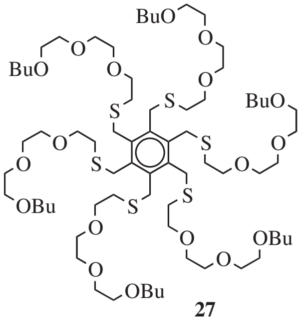

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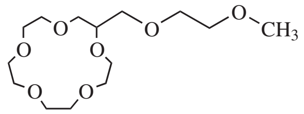

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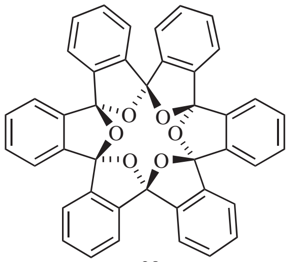


29

The bonding in these complexes is the result of ion-dipole attractions between the heteroatoms and the positive ions. The parameters of the host–guest interactions can sometimes be measured by NMR.[148]

As we have implied, the ability of these host molecules to bind guests is often very specific, often linked to the hydrogen-bonding ability of the host,[149] enabling the host to pull just one molecule or ion out of a mixture. This is called *molecular recognition*.[150] In general, cryptands, with their well-defined 3D cavities, are better for this than monocyclic crown ethers or ether derivatives. An example is the host **30**, which selectively binds the dication **31** ($n = 5$) rather than **31** ($n = 4$), and **31** ($n = 6$) rather than **31** ($n = 7$).[151] The host **32**, which is water soluble, forms 1:1 complexes with neutral aromatic hydrocarbons, such as pyrene and fluoranthene,

[146]See Gatto, V.J.; Dishong, D.M.; Diamond, C.J. *J. Chem. Soc., Chem. Commun.* ***1980***, 1053; Gatto, V.J.; Gokel, G.W. *J. Am. Chem. Soc.* ***1984***, *106*, 8240; Nakatsuji, Y.; Nakamura, T.; Yonetani, M.; Yuya, H.; Okahara, M. *J. Am. Chem. Soc.* ***1988***, *110*, 531.

[147]Lee, W.Y.; Park, C.H. *J. Org. Chem.* ***1993***, *58*, 7149.

[148]Wang, T.; Bradshaw, J.S.; Izatt, R.M. *J. Heterocylic Chem.* ***1994***, *31*, 1097.

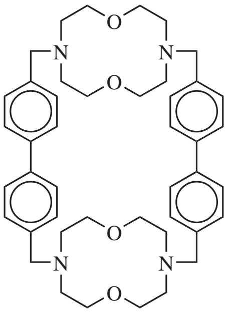
[149]Fujimoto, T.; Yanagihara, R.; Koboyashi, K.; Aoyama, Y. *Bull. Chem. Soc. Jpn.* ***1995***, *68*, 2113.

[150]For reviews, see Rebek Jr., J. *Angew. Chem. Int. Ed.* ***1990***, *29*, 245; *Acc. Chem. Res.* ***1990***, *23*, 399; *Top. Curr. Chem.* ***1988***, *149*, 189; Diederich, F. *J. Chem. Educ.* ***1990***, *67*, 813; Hamilton, A.D. *J. Chem. Educ.* ***1990***, *67*, 821; Raevskii, O.A. *Russ. Chem. Rev.* ***1990***, *59*, 219.

[151]Mageswaran, R.; Mageswaran, S.; Sutherland, I.O. *J. Chem. Soc., Chem. Commun.* ***1979***, 722.

and even (though more weakly) with biphenyl and naphthalene, and is able to transport them through an aqueous phase.[152]

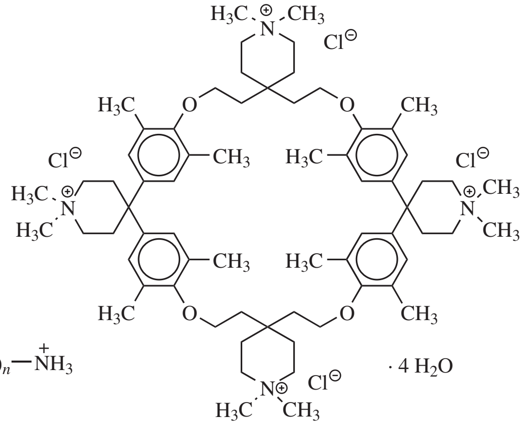
Of course, it has long been known that molecular recognition is very important in biochemistry. The action of enzymes and various other biological molecules is extremely specific because these molecules also have host cavities that are able to recognize only one or a few particular types of guest molecules. It is only in recent years that organic chemists have been able to synthesize nonnatural hosts that can also perform crude (compared to biological molecules) molecular recognition. The macrocycle **33** has been used as a catalyst, for the hydrolysis of acetyl phosphate and the synthesis of pyrophosphate.[153]



30

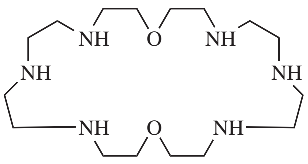
$H_3\overset{+}{N}—(CH_2)_n—\overset{+}{N}H_3$

31



32

No matter what type of host, the strongest attractions occur when combination with the guest causes the smallest amount of distortion of the host.[154] That is, a fully preorganized host will bind better than a host whose molecular shape must change in order to accommodate the guest.



33

[152]Diederich, F.; Dick, K. *J. Am. Chem. Soc.* ***1984***, *106*, 8024; Diederich, F.; Griebe, D. *J. Am. Chem. Soc.* ***1984***, *106*, 8037. See also Vögtle, F.; Müller, W.M.; Werner, U.; Losensky, H. *Angew. Chem. Int. Ed.* ***1987***, *26*, 901.

[153]Hosseini, M.W.; Lehn, J.M. *J. Am. Chem. Soc.* ***1987***, *109*, 7047. For a discussion, see Mertes, M.P.; Mertes, K.B. *Acc. Chem. Res.* ***1990***, *23*, 413.

[154]See Cram, D.J. *Angew. Chem. Int. Ed.* ***1986***, *25*, 1039.

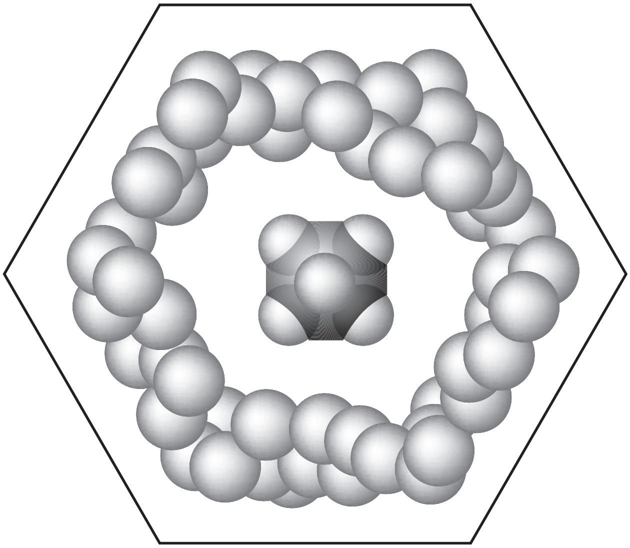


Fig. 3.1. Guest molecule in a urea lattice.[157]

Inclusion Compounds

This type of addition compound is different from either the EDA complexes or the crown ether type of complexes previously discussed. Here, the host forms a crystal lattice that has spaces large enough for the guest to fit into. There is no bonding between the host and the guest except van der Waals forces. There are two main types, depending on the shape of the space.[155] The spaces in *inclusion compounds* are in the shape of long tunnels or channels, while the other type, often called *clathrate*,[156] or *cage compounds* have spaces that are completely enclosed. In both types, the guest molecule must fit into the space and potential guests that are too large or too small will not go into the lattice, so that the addition compound will not form.[157]

One important host molecule among the inclusion compounds is urea.[158] Ordinary crystalline urea is tetragonal, but when a guest is present, urea crystallizes in a hexagonal lattice, containing the guest in long channels (Fig. 3.1).[157]

[155]For a treatise that includes both types, see Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vols. 1–3, Academic Press, NY, ***1984***. For reviews, see Weber, E. *Top. Curr. Chem.* ***1987***, *140*, 1; Gerdil, R. *Top. Curr. Chem.* ***1987***, *140*, 71; Mak, T.C.W.; Wong, H.N.C. *Top. Curr. Chem.* ***1987***, *140*, 141. For a review of channels with helical shapes, see Bishop, R.; Dance, I.G. *Top. Curr. Chem.* ***1988***, *149*, 137.

[156]For reviews, see Goldberg, I. *Top. Curr. Chem.* ***1988***, *149*, 1; Weber, E.; Czugler, M. *Top. Curr. Chem.* ***1988***, *149*, 45; MacNicol, D.D.; McKendrick, J.J.; Wilson, D.R. *Chem. Soc. Rev.* ***1978***, *7*, 65.

[157]This picture is taken from a paper by Montel, G. *Bull. Soc. Chim. Fr.* ***1955***, 1013.

[158]For a review of urea and thiourea inclusion compounds, see Takemoto, K.; Sonoda, N., in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 2, Academic Press, NY, ***1984***, pp. 47–67.

The hexagonal type of lattice can form only when a guest molecule is present, showing that van der Waals forces between the host and the guest, while small, are essential to the stability of the structure. The diameter of the channel is ~5 Å, and which molecules can be guests is dependent only on their shapes and sizes and not on any electronic or chemical effects. For example, octane and 1-bromooctane are suitable guests for urea, but 2-bromooctane, 2-methylheptane, and 2-methyloctane are not. Also both dibutyl maleate and dibutyl fumarate are guests; neither diethyl maleate or diethyl fumarate is a guest, but dipropyl fumarate is a guest and dipropyl maleate is not.[159] In these complexes, there is usually no integral molar ratio (though by chance there may be). For example, the octane/urea ratio is 1:6.73.[160] A deuterium quadrupole echo spectroscopy study of a urea complex showed that the urea molecules do not remain rigid, but undergo 180° flips about the C=O axis at the rate of $>10^6$ sec^{-1} at 30°C.[161]

The complexes are solids, but are not useful as derivatives, since they melt with decomposition of the complex at the melting point of urea. They are useful, however, in separating isomers that would be quite difficult to separate otherwise. Thiourea also forms inclusion compounds though with channels of larger diameter, so that *n*-alkanes cannot be guests but, for example, 2-bromooctane, cyclohexane, and chloroform readily fit.

The most important host for clathrates is hydroquinone.[162] Three molecules, held together by hydrogen bonding, make a cage in which fits one molecule of guest. Typical guests are methanol (but not ethanol), SO_2, CO_2, and argon (but not neon). One important use is the isolation of anhydrous hydrazine as complex.[163] Its highly explosive nature makes the preparation of anhydrous hydrazine by distillation of aqueous hydrazine solutions difficult and dangerous. The inclusion complex can be readily isolated and reactions done in the solid state, such as the reaction with esters to give hydrazides (reaction **16-75**).[163] In contrast to the inclusion compounds, the crystal lattices here can exist partially empty. Another host is water. Usually six molecules of water form the cage and many guest molecules, among them Cl_2, propane, and methyl iodide, can fit. The water clathrates, which are solids, can normally be kept only at low temperatures; at room temperature, they decompose.[164] Another inorganic host is sodium chloride (and some other alkali halides), which can encapsulate organic molecules, such as benzene, naphthalene, and diphenylmethane.[165]

[159]Radell, J.; Connolly, J.W.; Cosgrove Jr., W.R. *J. Org. Chem.* ***1961***, *26*, 2960.

[160]Redlich, O.; Gable, C.M.; Dunlop, A.K.; Millar, R.W. *J. Am. Chem. Soc.* ***1950***, *72*, 4153.

[161]Heatom, N.J.; Vold, R.L.; Vold, R.R. *J. Am. Chem. Soc.* ***1989***, *111*, 3211.

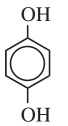
[162]For a review, see MacNicol, D.D., in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 2, Academic Press, NY, ***1984***, pp. 1–45.

[163]Toda, F.; Hyoda, S.; Okada, K.; Hirotsu, K. *J. Chem. Soc., Chem. Commun.* ***1995***, 1531.

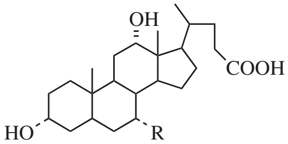
[164]For a monograph on water clathrates, see Berecz, E.; Balla-Achs, M. *Gas Hydrates*; Elsevier, NY, ***1983***. For reviews, see Jeffrey, G.A., in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 1, Academic Press, NY, ***1984***, pp. 135–190; Cady, G.H. *J. Chem. Educ.* ***1983***, *60*, 915; Byk, S.Sh.; Fomina, V.I. *Russ. Chem. Rev.* ***1968***, *37*, 469.

[165]Kirkor, E.; Gebicki, J.; Phillips, D.R.; Michl, J. *J. Am. Chem. Soc.* ***1986***, *108*, 7106.

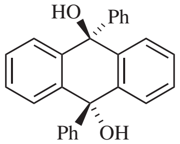
Among other hosts[166] for inclusion and/or clathrate compounds are deoxycholic acid,[167] cholic acid,[168] anthracene compounds, such as **34**,[169] dibenzo-24-crown-8,[170] and the compound **35**, which has been called a *carcerand*.[171] When carcerand-type molecules trap ions or other molecules (called guests), the resulting complex is called a carciplex.[172] It has been shown that in some cases, the motion of the guest within the carciplex is restricted.[173]



Hydroquinone



cholic acid (R = OH)
deoxycholic acid (R = H)



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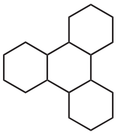
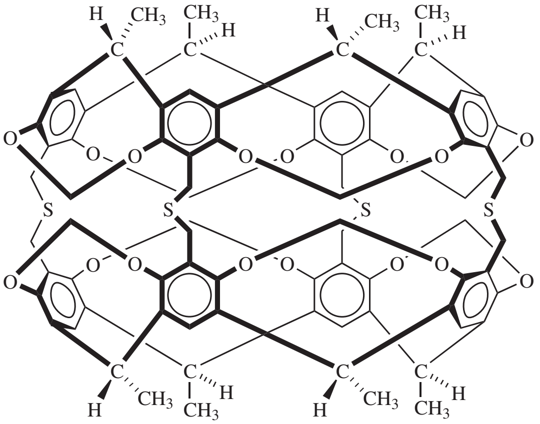


Perhydrotriphenylene



35

[166]See also Toda, F. *Pure App. Chem.* ***1990***, *62*, 417, *Top. Curr. Chem.* ***1988***, *149*, 211; ***1987***, *140*, 43; Davies, J.E.; Finocchiaro, P.; Herbstein, F.H., in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 2, Academic Press, NY, ***1984***, pp. 407–453.

[167]For a review, see Giglio, E., in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 2, Academic Press, NY, ***1984***, pp. 207–229.

[168]See Miki, K.; Masui, A.; Kasei, N.; Miyata, M.; Shibakami, M.; Takemoto, K. *J. Am. Chem. Soc.* ***1988***, *110*, 6594.

[169]Barbour, L.J.; Caira, M.R.; Nassimbeni, L.R. *J. Chem. Soc., Perkin Trans. 2* ***1993***, 2321. Also see, Barbour, L.J.; Caira, M.R.; Nassimbeni, L.R. *J. Chem. Soc., Perkin Trans. 2* ***1993***, 1413 for a dihydroanthracene derivative that enclathrates diethyl ether.

[170]Lämsä, M.; Suorsa, T.; Pursiainen, J.; Huuskonen, J.; Rissanen, K. *Chem. Commun.* ***1996***, 1443.

[171]Sherman, J.C.; Knobler, C.B.; Cram, D.J. *J. Am. Chem. Soc.* ***1991***, *113*, 2194.

[172]Kurdistani, S.K.; Robbins, T.A.; Cram, D.J. *J. Chem. Soc., Chem. Commun.* ***1995***, 1259; Timmerman, P.; Verboom, W.; van Veggel, F.C.J.M.; van Duynhoven, J.P.M.; Reinhoudt, D.N. *Angew. Chem. Int. Ed.* ***1994***, *33*, 2345; van Wageningen, A.M.A.; Timmerman, P.; van Duynhoven, J.P.M.; Verboom, W.; van Veggel, F.C.J.M.; Reinhoudt, D.N. *Chem. Eur. J.* ***1997***, *3*, 639; Fraser, J.R.; Borecka, B.; Trotter, J.; Sherman, J.C. *J. Org. Chem.* ***1995***, *60*, 1207; Place, D.; Brown, J.; Deshayes, K. *Tetrahedron Lett.* ***1998***, *39*, 5915. See also: Jasat, A.; Sherman, J.C. *Chem. Rev.* ***1999***, *99*, 931.

[173]Chapman, R.G.; Sherman, J.C. *J. Org. Chem.* ***2000***, *65*, 513.

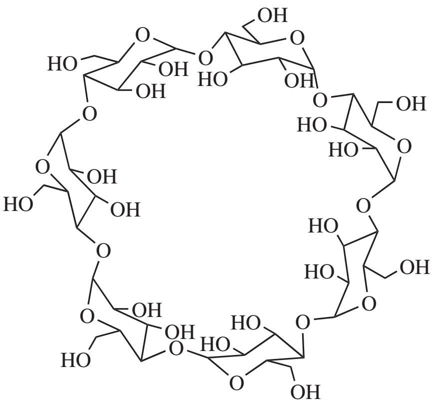


Fig. 3.2. β-Cyclodextrin.

Cyclodextrins

There is one type of host that can form both channel and cage complexes. This type is called *cyclodextrins* or *cycloamyloses*.[174] The host molecules are made up of six, seven, or eight glucose units connected in a large ring, called, respectively, α-, β-, or γ-cyclodextrin (Fig. 3.2 shows the β or seven-membered ring compound). The three molecules are in the shape of hollow truncated cones (Fig. 3.3) with primary OH groups projecting from the narrow side of the cones and secondary OH group from the wide side. As expected for carbohydrate molecules, all of them are soluble in water and the cavities normally fill with water molecules held in place by hydrogen bonds (6, 12, and 17 H_2O molecules for the α, β, and γ forms, respectively), but the insides of the cones are less polar than the outsides, so that nonpolar organic molecules readily displace the water. Thus the cyclodextrins form 1:1 cage complexes with many guests, ranging in size from the noble gases to large organic molecules. A guest molecule must not be too large or it will not fit, though many stable complexes are known in which one end of the guest molecule protrudes from the cavity (Fig. 3.4). On the other hand, if the guest is too small, it may go through the bottom hole (though some small polar molecules, e.g., methanol, do form complexes in which the cavity also contains some water molecules). Since the cavities of the three cyclodextrins are of different sizes (Fig. 3.3), a large variety of guests can be

[174]For a monograph, see Bender, M.L.; Komiyama, M. *Cyclodextrin Chemistry*, Springer, NY, ***1978***. For reviews, see, in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Academic Press, NY, ***1984***, the reviews, by Saenger, W. Vol. 2, 231–259, Bergeron, R.J. Vol. 3, 391–443, Tabushi, I. Vol. 3, 445–471, Breslow, R. Vol. 3, 473–508; Croft, A.P.; Bartsch, R.A. *Tetrahedron* ***1983***, *39*, 1417; Tabushi, I.; Kuroda, Y. *Adv. Catal.*, ***1983***, *32*, 417; Tabushi, I. *Acc. Chem. Res.* ***1982***, *15*, 66; Saenger, W. *Angew. Chem. Int. Ed.* ***1980***, *19*, 344; Bergeron, R. *J. Chem. Ed.* ***1977***, *54*, 204; Griffiths, D.W.; Bender, M.L. *Adv. Catal.* ***1973***, *23*, 209.

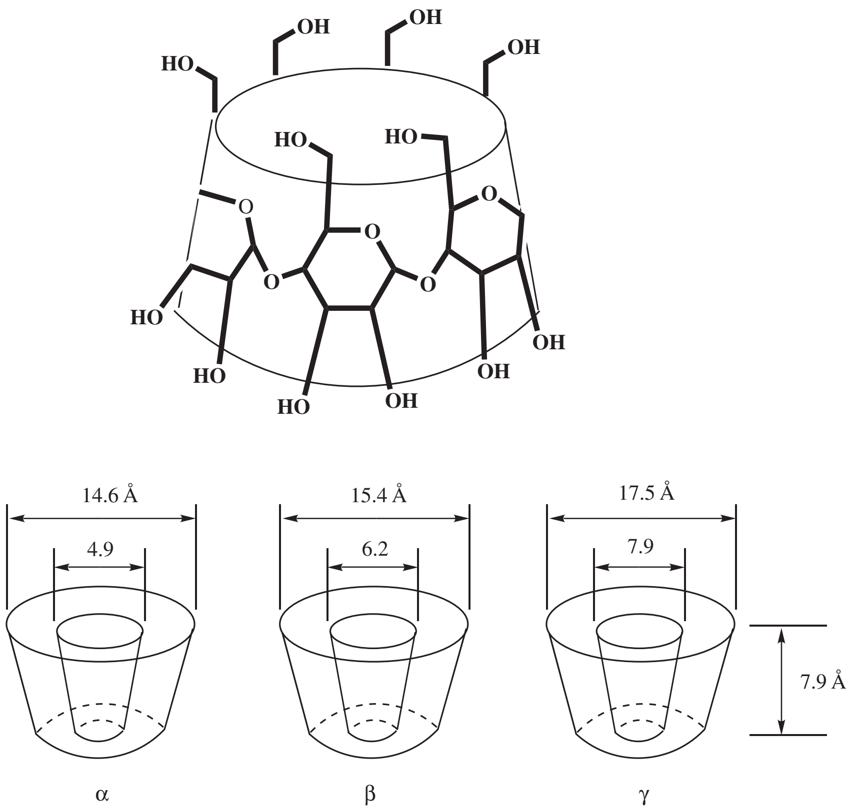


Fig. 3.3. Shape and dimensions of the α-, β-, and γ-cyclodextrin molecules.[175]

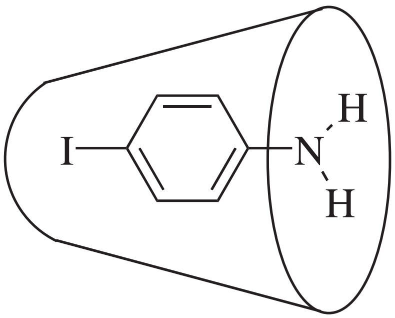


Fig. 3.4. Schematic drawing of the complex of α-cyclodextrin and *p*-iodoaniline.[176]

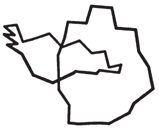
[175]Szejtli, J., in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 3, Academic Press, NY, ***1984***, p. 332; Nickon, A.; Silversmith, E.F. *The Name Game*, Pergamon, Elmsford, NY, p. 235.
[176]Modified from Saenger, W.; Beyer, K.; Manor, P.C. *Acta Crystallogr. Sect. B* ***1976***, *32*, 120.

accommodated. Since cyclodextrins are nontoxic (they are actually small starch molecules), they are now used industrially to encapsulate foods and drugs.[177]

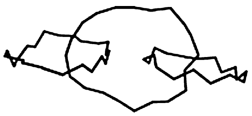
The cyclodextrins also form channel-type complexes, in which the host molecules are stacked on top of each other, like coins in a row.[178] For example, α-cyclodextrin (cyclohexaamylose) forms cage complexes with acetic, propionic, and butyric acids, but channel complexes with valeric and higher acids. Capped cyclodextrins are known.[179]

Catenanes and Rotaxanes[180]

These compounds contain two or more independent portions that are not bonded to each other by any valence forces but nevertheless must remain linked. [*n*]-*Catenanes* (where *n* corresponds to the number of linked rings) are made up of two or more rings held together as links in



A [2]-catenane



A [3]-catenane

A rotaxane

a chain, while in *rotaxanes* a linear portion is threaded through a ring and cannot get away because of bulky end groups. Among several types of bulky molecular units, porphyrin units have been used to cap rotaxanes[181] as have C_{60} fullerenes.[182] [2]-Rotaxanes and [2]-catenanes are quite common, and [3]-catenanes are known having rather robust amide linkages.[183] More intricate variants, such as oligocatenanes,[184] molecular necklaces (a cyclic oligorotaxane in which a number of small rings are threaded onto a large ring),[185] and cyclic daisy chains (an interwoven chain in which each monomer unit acts as a donor and an acceptor for a threading

[177]For reviews, see Pagington, J.S. *Chem. Br.* ***1987***, *23*, 455; Szejtli, J., in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 3, Academic Press, NY, ***1984***, pp. 331–390.

[178]See Saenger, W. *Angew. Chem. Int. Ed.* ***1980***, *19*, 344.

[179]Engeldinger, E.; Armspach, D.; Matt, D. *Chem. Rev.* ***2003***, *103*, 4147.

[180]For a monograph, see Schill, *G. Catenanes, Rotaxanes, and Knots*, Academic Press, NY, ***1971***. For a review, see Schill, G., in Chiurdoglu, G. *Conformational Analysis*, Academic Press, NY, ***1971***, pp. 229–239.

[181]Solladié, N.; Chambron, J.-C.; Sauvage, J.-P. *J. Am. Chem. Soc.* ***1999***, *121*, 3684.

[182]Sasabe, H.; Kihara, N.; Furusho, Y.; Mizuno, K.; Ogawa, A.; Takata, T. *Org. Lett.* ***2004***, *6*, 3957.

[183]Safarowsky, O.; Vogel, E.; Vögtle, F. Eur. *J. Org. Chem.* ***2000***, 499.

[184]Amabilino, D.B.; Ashton, P.R.; Boyd, S.E.; Lee, J.Y.; Menzer, S.; Stoddart, J.F.; Williams, D.J. *Angew. Chem. Int. Ed.* ***1997***, *36*, 2070; Amabilino, D.B.; Ashton, P.R.; Balzani, V.; Boyd, S.E.; Credi, A.; Lee, J.Y.; Menzer, S.; Stoddart, J.F.; Venturi, M.; Williams, D.J. *J. Am. Chem. Soc.* ***1998***, *120*, 4295.

[185]Chiu, S.-H.; Rowan, S.J.; Cantrill, S.J.; Ridvan, L.; Ashton, R.P.; Garrell, R.L.; Stoddart, J.-F. *Tetrahedron* ***2002***, *58*, 807; Whang, D.; Park, K.-M.; Heo, J.; Ashton, P.R.; Kim, K. *J. Am. Chem. Soc.* ***1998***, *120*, 4899; Roh, S.-G.; Park, K.-M.; Park, G.-J.; Sakamoto, S.; Yamaguchi, K.; Kim, K. *Angew. Chem. Int. Ed.* ***1999***, *38*, 638.

interaction)[186] are known. Ring-in-ring complexes have also been reported.[187] Molecular thread, ribbon, and belt assemblies have been synthesized.[188] Rotaxanes have been used as the basis for molecular switches,[189] and a rotaxane eciplex has been generated that may have applications to molecular-scale photonic devices.[190]

Transitional isomers are possible in [2]-rotaxanes.[191] Catenanes and rotaxanes can be prepared by statistical methods or directed syntheses.[192] Catenanes can contain heteroatoms and heterocyclic units. In some cases, the catenane exists in equilibrium with the cyclic-non-catenane structures and in some cases this exchange is thought to proceed by ligand exchange and a Möbius strip mechanism.[193] An example of a statistical synthesis of a rotaxane is a reaction where a compound **A** is bonded at two positions to another compound **B** in the presence of a large ring **C**. It is hoped that some **A** molecules would by chance be threaded through **C** before combining with the two **B** molecules, so that some rotaxane (**D**) would be formed along with the normal product **E**.[194] In a directed synthesis,[195] the separate parts of the molecule are held together by other bonds that are later cleaved.

B **A** **B** **C** **D** **E** **C**

Rotation of one unit through the other catenanes is complex, often driven by making and breaking key hydrogen bonds or π–π interactions. In the case of the

[186]For example, see Ashton, P.R.; Baxter, I.; Cantrill, S.J.; Fyfe, M.C.T.; Glink, P.T.; Stoddart, J.F.; White, A.J.P.; Williams, D.J. *Angew. Chem. Int. Ed.* ***1998***, *37*, 1294; Hoshino, T.; Miyauchi, M.; Kawaguchi, Y.; Yamaguchi, H.; Harada, A. *J. Am. Chem. Soc.* ***2000***, *122*, 9876; Onagi, H.; Easton, C.J.; Lincoln, S.F. *Org. Lett.* ***2001***, *3*, 1041; Cantrill, S.J.; Youn, G.J.; Stoddart, J.F.; Williams, D.J. *J. Org. Chem.* ***2001***, *66*, 6857.

[187]Chiu, S.-H.; Pease, A.R.; Stoddart, J.F.; White, A.J.P.; Williams, D.J. *Angew. Chem. Int. Ed.* ***2002***, *41*, 270.

[188]Schwierz, H.; Vögtle, F. *Synthesis* ***1999***, 295.

[189]Jun, S.I.; Lee, J.W.; Sakamoto, S.; Yamaguchi, K.; Kim, K. *Tetrahedron Lett.* ***2000***, *41*, 471; Elizarov, A.M.; Chiu, S.-H.; Stoddart, J.-F. *J. Org. Chem.* ***2002***, *67*, 9175.

[190]MacLachlan, M.J.; Rose, A.; Swager, T.M. *J. Am. Chem. Soc.* ***2001***, *123*, 9180.

[191]Amabilino, D.B.; Ashton, P.R.; Boyd, S.E.; Gómez-López, M.; Hayes, W.; Stoddart, J.F. *J. Org. Chem.* ***1997***, *62*, 3062.

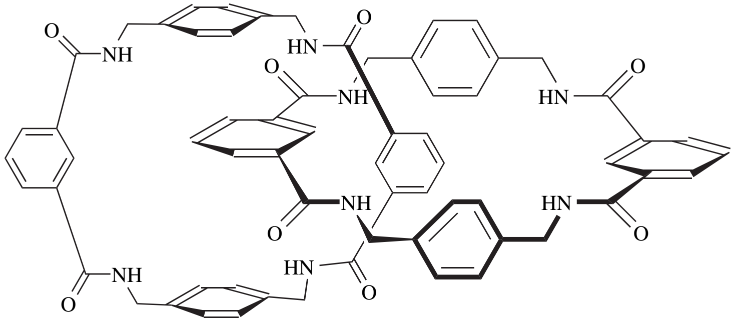
[192]For discussions, see Schill, G. *Catenanes, Rotaxanes, and Knots*, Academic Press, NY, ***1971***. For a review, see Schill, G., in Chiurdoglu, G. *Conformational Analysis*, Academic Press, NY, ***1971***, pp. 229–239; Walba, D.M. *Tetrahedron* ***1985***, *41*, 3161.

[193]Fujita, M.; Ibukuro, F.; Seki, H.; Kamo, O.; Imanari, M.; Ogura, K. *J. Am. Chem. Soc.* ***1996***, *118*, 899.

[194]Schemes of this type were carried out by Harrison, I.T.; Harrison, S. *J. Am. Chem. Soc.* ***1967***, *89*, 5723; Ogino, H. *J. Am. Chem. Soc.* ***1981***, *103*, 1303. For a different kind of statistical syntheszis of a rotaxane, see Harrison, I.T. *J. Chem. Soc., Perkin Trans. 1* ***1974***, 301; Schill, G.; Beckmann, W.; Schweikert, N.; Fritz, H. *Chem. Ber.* ***1986***, *119*, 2647. See also Agam, G.; Graiver, D.; Zilkha, A. *J. Am. Chem. Soc.* ***1976***, *98*, 5206.

[195]For a directed synthesis of a rotaxane, see Schill, G.; Zürcher, C.; Vetter, W. *Chem. Ber.* ***1973***, *106*, 228.

isophthaloyl [2]-catenane, **36**, the rate-determining steps do not necessarily correspond to the passage of the bulkiest groups.[196]



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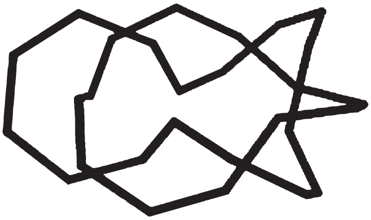
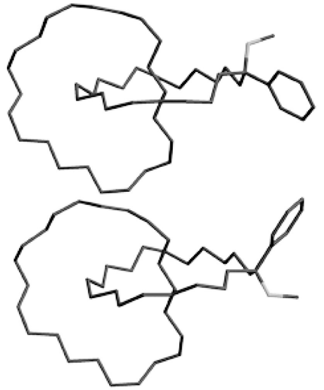




37 **38**

Singly and doubly interlocked [2]-catenanes[197] can exist as *topological stereoisomers*[198] (see p. 163 for a discussion of diastereomers). Catenanes **37** and **38** are such stereoisomers, and would be expected to have identical mass spectra. Analysis showed that **37** is more constrained and cannot readily accommodate an excess of energy during the mass spectrometry ionization process and, hence, breaks more easily.

Catenanes, molecular knots, and other molecules in these structural categories can exist as enantiomers. In other words, stereoisomers can be generated in some cases. This phenomenon was first predicted by Frisch and Wassermann,[199] and the

[196]Deleuze, M.S.; Leigh, D.A; Zerbetto, F. *J. Am. Chem. Soc.* ***1999***, *121*, 2364.

[197]For the synthesis of a doubly interlocking [2]-catenane, see Ibukuro, F.; Fujita, M.; Yamaguchi, K.; Sauvage, J.-P. *J. Am. Chem. Soc.* ***1999***, *121*, 11014.

[198]See Lukin, O.; Godt, A.; Vögtle, F. *Chem. Eur. J.* ***2004***, *10*, 1879.

[199]Frisch, H.L.; Wasserman, E. *J. Am. Chem. Soc.* ***1961***, *83*, 3789.

first stereoisomeric catenanes and molecular knots were synthesized by Sauvage et al.[200] [2, 3]-Enantiomeric resolution has been achieved.[201] A chiral [3]-rotaxane containing two achiral wheels, mechanically bonded has been reported,[202] generating a cyclodiastereomeric compound,[8], and the enantiomers were separated using chiral HPLC. The terms cycloenantiomerism and cyclodiastereomerism were introduced by Prelog et al.[203] This stereoisomerism occurs in cyclic arrangements of several centrally chiral elements in combination with an orientation of the macrocycle.[202]

A rotaxane can also be an inclusion compound.[204] The molecule contains bulky end groups (or "stoppers," such as triisopropylsilyl groups, iPr$_3$Si–) and a chain that consists of a series of –O–CH_2CH_2–O– groups, but also contains two benzene rings. The ring (or bead) around the chain is a macrocycle containing two benzene rings and four pyridine rings, and is preferentially attracted to one of the benzene rings in the chain. The benzene moiety serves as a "station" for the "bead." However, symmetry of the chain can make the two "stations" equivalent, so that the "bead" is equally attracted to them, and the "bead" actually moves back and forth rapidly between the two "stations," as shown by the temperature dependence of the NMR spectrum.[205] This molecule has been called a *molecular shuttle*. A copper(I) complexed rotaxane has been prepared with two fullerene (see p. 94) stoppers.[206]

Another variation of these molecules are called molecular knots, such as **39**, where the ● represents a metal [in this case, copper(I)].[207] This is particularly interesting since knotted forms of deoxyribonuclic acid (DNA) have been reported.[208]

[200] *Molecular Catenanes, Rotaxanes and Knots* (Eds.: Sauvage, J.-P.; Dietrich-Buchecker, C.O, Wiley-VCH, Weinheim, ***1999***; Ashton, P.R.; Bravo, J.A.; Raymo, F.M.; Stoddart, J.F.; White, A.J.P.; Williams, D. *J. Eur. J. Org. Chem.* ***1999***, 899; Mitchell, D.K.; Sauvage, J.-P. *Angew. Chem. Int. Ed.* ***1988***, *27*, 930; Nierengarten, J.-F.; Dietrich-Buchecker, C.O.; Sauvage, J.-P. *J. Am. Chem. Soc.* ***1994***, *116*, 375; Walba, D.M. *Tetrahedron* ***1985***, *41*, 3161; Chen, C.-T.; Gantzel, P.; Siegel, J.S.; Baldridge, K.K.; English, R.B.; Ho, D.M. *Angew. Chem. Int. Ed.* ***1995***, *34*, 2657.

[201] Kaida, T.; Okamoto, Y.; Chambron, J.-C.; Mitchell, D.K.; Sauvage, J.-P. *Tetrahedron Lett.* ***1993***, *34*, 1019.

[202] Schmieder, R.; Hübner, G.; Seel, C.; Vögtle, F. *Angew. Chem. Int. Ed.* ***1999***, *38*, 3528.

[203] Prelog, V.; Gerlach, H. *Helv. Chim. Acta* ***1964***, *47*, 2288; Gerlach, H.; Owtischinnkow, J.A.; Prelog, V. *Helv. Chim. Acta* ***1964***, *47*, 2294; Eliel, E.L. *Stereochemie der Kohlenstoffverbindungen*, Verlag Chemie, Weinheim, ***1966***; Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley, NY, ***1994***, pp. 1176–1181; Chorev, M.; Goodman, M. *Acc. Chem. Res.* ***1993***, *26*, 266 ; Mislow, K. *Chimia*, ***1986***, *40*, 395.

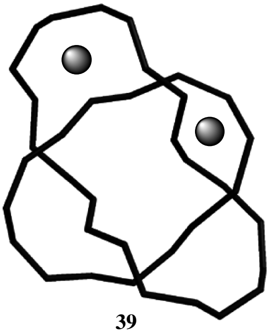
[204] For an example, see Anelli, P.L.; Spencer, N.; Stoddart, J.F. *J. Am. Chem. Soc.* ***1991***, *113*, 5131.

[205] Anelli, P.L.; Spencer, N.; Stoddart, J.F. *J. Am. Chem. Soc.* ***1991***, *113*, 5131. For a review of the synthesis and properties of molecules of this type, see Philp, D.; Stoddart, J.F. *Synlett* ***1991***, 445.

[206] Diederich, F.; Dietrich-Buchecker, C.O.; Nierengarten, S.-F.; Sauvage, J.-P. *J. Chem. Soc., Chem. Commun.* ***1995***, 781.

[207] Dietrich-Buchecker, C.O.; Nierengarten, J.-F.; Sauvage, J.-P. *Tetrahedron Lett.* ***1992***, *33*, 3625. See Dietrich-Buchecker, C.O.; Sauvage, J.-P. *Angew. Chem. Int. Ed.* ***1989***, *28*, 189 and Dietrich-Buchecker, C.O.; Guilhem, J.; Pascard, C.; Sauvage, J.-P. *Angew. Chem. Int. Ed.* ***1990***, *29*, 1154 for the synthesis of other molecular knots.

[208] Liu, L.F.; Depew, R.E.; Wang, J.C. *J. Mol. Biol.* ***1976***, *106*, 439.

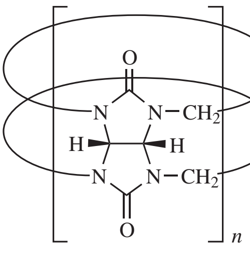


● = Cu(I)

39

Cucurbit[*n*]uril-Based Gyroscane

A new molecule known as gyroscane has been prepared, and proposed as a new supramolecular form.[209] The class of compounds known as cucurbit[*n*]urils, abbreviated Q_n (**40**),[210] are condensation products of glycoluril and formaldehyde. These macrocycles can act as molecular hosts. The new "supramolecular form is one in which a smaller macrocycle, Q5, is located inside a larger macrocycle, Q10, with facile rotation of one relative to the other in solution (see **41**).[210] The image of a ring rotating independently inside another ring, which resembles a gyroscope, suggests the name gyroscane for this new class of supramolecular system."[210]



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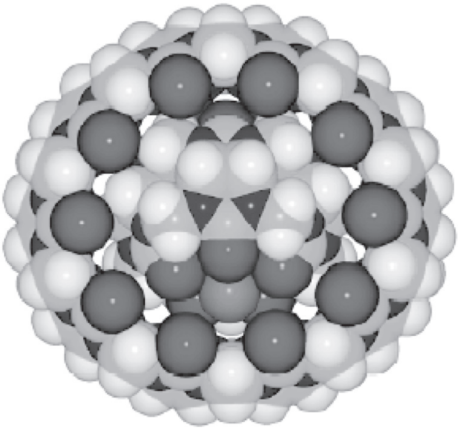

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[209]Day, A.I.; Blanch, R.J.; Arnold, A.P.; Lorenzo, S.; Lewis, G.R.; Dance, I. *Angew. Chem. Int. Ed.* ***2002***, *41*, 275.

[210]Freeman, W.A.; Mock, W.L.; Shih, N.Y. *J. Am. Chem. Soc.* ***1981***, *103*, 7367; Cintas, P. *J. Inclusion Phenom.* ***1994***, *17*, 205; Mock, W.L. *Top. Curr. Chem.* ***1995***, *175*, 1; Mock, W.L., in *Comprehensive Supramolecular Chemistry*, Vol. 2, Atwood, J.L.; Davies, J.E.D.; MacNicol, D.D.; Vogtle, F. (Eds.), Pergamon, Oxford, ***1996***, pp. 477–493; Day, A.; Arnold, A.P.; Blanch, R.J.; Snushall, B. *J. Org. Chem.* ***2001***, *66*, 8094; Kim, J.; Jung, I.-S.; Kim, S.-Y.; Lee, E.; Kang, J.-L.; Sakamoto, S.; Yamaguchi, K.; Kim, K. *J. Am. Chem. Soc.* ***2000***, *122*, 540.

CHAPTER 4

Stereochemistry

In Chapters 1–3, we discussed electron distribution in organic molecules. In this chapter, we discuss the 3D structure of organic compounds.[1] The structure may be such that *stereoisomerism*[2] is possible. Stereoisomers are compounds made up of the same atoms bonded by the same sequence of bonds, but having different 3D structures that are not interchangeable. These 3D structures are called *configurations*.

OPTICAL ACTIVITY AND CHIRALITY

Any material that rotates the plane of polarized light is said to be *optically active*. If a pure compound is optically active, the molecule is nonsuperimposable on its mirror image. If a molecule is superimposable on its mirror image, the compound does not rotate the plane of polarized light; it is *optically inactive*. The property

[1]For books on this subject, see Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***; Sokolov, V.I. *Introduction to Theoretical Stereochemistry*, Gordon and Breach, NY, ***1991***; Bassindale, A. *The Third Dimension in Organic Chemistry*, Wiley, NY, ***1984***; Nógrádi, M. *Sterochemistry*, Pergamon, Elmsford, NY, ***1981***; Kagan, H. *Organic Sterochemistry*, Wiley, NY, ***1979***; Testa, B. *Principles of Organic Stereochemistry*, Marcel Dekker, NY, ***1979***; Izumi, Y.; Tai, A. *Stereo-Differentiating Reactions*, Academic Press, NY, Kodansha Ltd., Tokyo, ***1977***; Natta, G.; Farina, M. *Stereochemistry*, Harper and Row, NY, ***1972***; Eliel, E.L. *Elements of Stereochemistry*, Wiley, NY, ***1969***; Mislow, K. *Introduction to Stereochemistry*, W. A. Benjamin, NY, ***1965***. Two excellent treatments of stereochemistry that, though not recent, contain much that is valid and useful, are Wheland, G.W. *Advanced Organic Chemistry*, 3rd ed., Wiley, NY, ***1960***, pp. 195–514; Shriner, R.L.; Adams, R.; Marvel, C.S. in Gilman, H. *Advanced Organic Chemistry*; Vol. 1, 2nd ed., Wiley, NY, ***1943***, pp. 214–488. For a historical treatment, see Ramsay, O.B. *Stereochemistry*, Heyden & Son, Ltd., London, ***1981***.

[2]The IUPAC 1974 Recommendations, Section E, Fundamental Stereochemistry, give definitions for most of the terms used in this chapter, as well as rules for naming the various kinds of stereoisomers. They can be found in *Pure Appl. Chem.* ***1976***, *45*, 13 and in *Nomenclature of Organic Chemistry*, Pergamon, Elmsford, NY, ***1979*** (the "Blue Book").

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Sixth Edition, by Michael B. Smith and Jerry March
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of nonsuperimposability of an object on its mirror image is called *chirality*. If a molecule is not superimposable on its mirror image, it is *chiral*. If it is superimposable on its mirror image, it is *achiral*. The relationship between optical activity and chirality is absolute. No exceptions are known, and many thousands of cases have been found in accord with it (however, see p. 141). The ultimate criterion, then, for optical activity is chirality (nonsuperimposability on the mirror image). This is both a necessary and a sufficient condition.[3] This fact has been used as evidence for the structure determination of many compounds, and historically the tetrahedral nature of carbon was deduced from the hypothesis that the relationship might be true. Note that parity violation represents an essential property of particle and atomic handedness, and has been related to chirality.[4]

If a molecule is nonsuperimposable on its mirror image, the mirror image must be a different molecule, since superimposability is the same as identity. In each case of optical activity of a pure compound there are two and only two isomers, called *enantiomers* (sometimes *enantiomorphs*), which differ in structure only in the left and right handedness of their orientations (Fig. 4.1). Enantiomers have identical[5] physical and chemical properties except in two important respects:

1. They rotate the plane of polarized light in opposite directions, although in equal amounts. The isomer that rotates the plane to the left (counterclockwise)

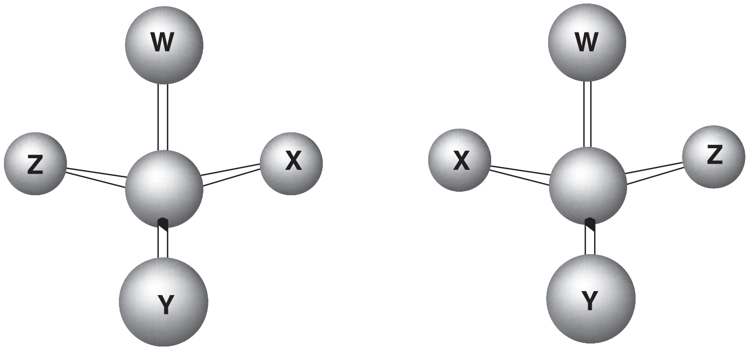


Fig. 4.1. Enantiomers.

[3]For a discussion of the conditions for optical activity in liquids and crystals, see O'Loane, J.K. *Chem. Rev.* ***1980***, *80*, 41. For a discussion of chirality as applied to molecules, see Quack, M. *Angew. Chem. Int. Ed.* ***1989***, *28*, 571.

[4]Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J.L.; Palacios, J.C. *Tetrahedron Asymmetry* ***2000***, *11*, 2845.

[5]Interactions between electrons, nucleons, and certain components of nucleons (e.g., bosons), called *weak interactions*, violate parity; that is, mirror-image interactions do not have the same energy. It has been contended that interactions of this sort cause one of a pair of enantiomers to be (slightly) more stable than the other. See Tranter, G.E. *J. Chem. Soc. Chem. Commun. 1986*, 60, and references cited therein. See also Barron, L.D. *Chem. Soc. Rev.* ***1986***, *15*, 189.

is called the *levo isomer* and is designated (−), while the one that rotates the plane to the right (clockwise) is called the *dextro isomer* and is designated (+). Because they differ in this property they are often called *optical antipodes.*

2. They react at different rates with other chiral compounds. These rates may be so close together that the distinction is practically useless, or they may be so far apart that one enantiomer undergoes the reaction at a convenient rate while the other does not react at all. This is the reason that many compounds are biologically active while their enantiomers are not. Enantiomers react at the same rate with achiral compounds.[6]

In general, it may be said that enantiomers have identical properties in a symmetrical environment, but their properties may differ in an unsymmetrical environment.[7] Besides the important differences previously noted, enantiomers may react at different rates with achiral molecules if an optically active *catalyst* is present; they may have different solubilities in an optically active *solvent*; they may have different indexes of refraction or absorption spectra *when examined with circularly polarized light*, and so on. In most cases, these differences are too small to be useful and are often too small to be measured.

Although pure compounds are always optically active if they are composed of chiral molecules, mixtures of equal amounts of enantiomers are optically inactive since the equal and opposite rotations cancel. Such mixtures are called *racemic mixtures*[8] or *racemates.*[9] Their properties are not always the same as those of the individual enantiomers. The properties in the gaseous or liquid state or in solution usually are the same, since such a mixture is nearly ideal, but properties involving the solid state,[10] such as melting points, solubilities, and heats of fusion, are often different. Thus racemic tartaric acid has a melting point of 204–206°C and a solubility in water at 20°C of $206\,g\,L^{-1}$, while for the (+) or the (−) enantiomer, the corresponding figures are 170°C and $1390\,g\,L^{-1}$. The separation of a racemic mixture into its two optically active components is called *resolution*. The presence of optical activity always proves that a given compound is chiral, but its absence does not prove that the compound is achiral. A compound that is optically inactive may be achiral, or it may be a racemic mixture (see also, p. 142).

[6]For a reported exception, see Hata, N. *Chem. Lett.* ***1991***, 155.

[7]For a review of discriminating interactions between chiral molecules, see Craig, D.P.; Mellor, D.P. *Top. Curr. Chem.* ***1976***, *63*, 1.

[8]Strictly speaking, the term *racemic mixture* applies only when the mixture of molecules is present as separate solid phases, but in this book we shall use this expression to refer to any equimolar mixture of enantiomeric molecules, liquid, solid, gaseous, or in solution.

[9]For a monograph on the properties of racemates and their resolution, see Jacques, J.; Collet, A.; Wilen, S.H. *Enantiomers, Racemates, and Resolutions*, Wiley, NY, ***1981***.

[10]For a discussion, see Wynberg, H.; Lorand, J.P. *J. Org. Chem.* ***1981***, *46*, 2538, and references cited therein.

Dependence of Rotation on Conditions of Measurement

The *amount* of rotation α is not a constant for a given enantiomer; it depends on the length of the sample vessel, the temperature, the solvent[11] and concentration (for solutions), the pressure (for gases), and the wavelength of light.[12] Of course, rotations determined for the same compound under the same conditions are identical. The length of the vessel and the concentration or pressure determine the number of molecules in the path of the beam and a is linear with this. Therefore, a number is defined, called the *specific rotation* [α], which is

$$[\alpha] = \frac{\alpha}{lc} \quad \text{for solutions} \qquad [\alpha] = \frac{\alpha}{ld} \quad \text{for pure compounds}$$

where α is the observed rotation, l is the cell length in decimeters, c is the concentration in grams per milliliter, and d is the density in the same units. The specific rotation is usually given along with the temperature and wavelength, in this manner: $[\alpha]_{546}^{25}$. These conditions must be duplicated for comparison of rotations, since there is no way to put them into a simple formula. The expression $[\alpha]_D$ means that the rotation was measured with sodium D light; that is, $\lambda = 589$ nm. The molar rotation $[M]_\lambda^t$ is the specific rotation times the molecular weight divided by 100.

It must be emphasized that although the value of a changes with conditions, the molecular structure is unchanged. This is true even when the changes in conditions are sufficient to change not only the amount of rotation, but even the direction. Thus one of the enantiomers of aspartic acid, when dissolved in water, has $[\alpha]_D$ equal to +4.36° at 20°C and −1.86° at 90°C, although the molecular structure is unchanged. A consequence of such cases is that there is a temperature at which there is *no* rotation (in this case 75°C). Of course, the other enantiomer exhibits opposite behavior. Other cases are known in which the direction of rotation is reversed by changes in wavelength, solvent, and even concentration.[13] In theory, there should be no change in [α] with concentration, since this is taken into account in the formula, but associations, dissociations, and solute–solvent interactions often cause nonlinear behavior. For example, $[\alpha]_D^{24}$ for (−)-2-ethyl-2-methylsuccinic acid in $CHCl_3$ is −5.0° at $c = 16.5\ \text{g}\ 100\ \text{mL}^{-1}$ ($0.165\ \text{g mL}^{-1}$), −0.7° at $c = 10.6$, +1.7° at $c = 8.5$, and +18.9° at $c = 2.2$.[14] Note that the concentration is sometimes reported in $\text{g}\ 100\ \text{mL}^{-1}$ (as shown) or as g dL^{-1} (decaliters) rather than the standard grams per milliliter (g mL^{-1}). One should always check the concentration term to be certain. Noted that calculation of the optical rotation of (*R*)-(−)-3-chloro-1-butene found a remarkably large dependence on the C=C–C–C torsional angle.[15]

[11]A good example is found, in Kumata, Y.; Furukawa, J.; Fueno, T. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 3920.

[12]For a review of polarimetry, see Lyle, G.G.; Lyle, R.E., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, ***1983***, pp. 13–27.

[13]For examples, see Shriner, R.L.; Adams, R.; Marvel, C.S., in Gilman, H. *Advanced Organic Chemistry*, Vol. 1, 2nd ed. Wiley, NY, ***1943***, pp. 291–301.

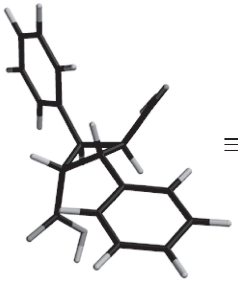
[14]Krow, G.; Hill, R.K. *Chem. Commun.* ***1968***, 430.

[15]Wiberg, K. B.; Vaccaro, P. H.; Cheeseman, J. R. *J. Am. Chem. Soc.* ***2003***, *125*, 1888.

However, the observed rotations are a factor of 2.6 smaller than the calculated values, independent of both conformation and wavelength from 589 to 365 nm.

What Kinds of Molecules Display Optical Activity?

Although the ultimate criterion is, of course, nonsuperimposability on the mirror image (chirality), other tests may be used that are simpler to apply but not always accurate. One such test is the presence of a *plane of symmetry*.[16] A plane of symmetry[17] (also called a *mirror plane*) is a plane passing through an object such that the part on one side of the plane is the exact reflection of the part on the other side (the plane acting as a mirror). *Compounds possessing such a plane are always optically inactive*, but there are a few cases known in which compounds lack a plane of symmetry and are nevertheless inactive. Such compounds possess a *center of symmetry*, such as in α-truxillic acid, or an *alternating axis of symmetry* as in **1**.[18] A center of symmetry[17] is a point within an object such that a straight line drawn from any part or element of the object to the center and extended an equal distance on the other side encounters an equal part or element. An alternating axis of symmetry[17] of order n is an axis such that when an object containing such an axis is rotated by 360°/n about the axis and then reflection is effected across a plane at right angles to the axis, a new object is obtained that is indistinguishable from the original one. Compounds that lack an alternating axis of symmetry are always chiral.



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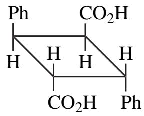
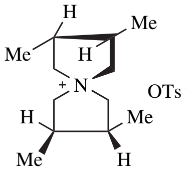


α-Truxillic acid



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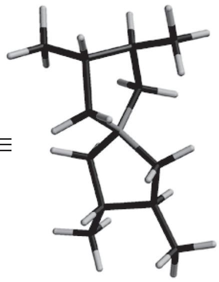


A molecule that contains just one *chiral (stereogenic) carbon atom* (defined as a carbon atom connected to four different groups; also called an *asymmetric carbon atom*) is always chiral, and hence optically active.[19] As seen in Fig. 4.1, such a

[16]For a theoretical discussion of the relationship between symmetry and chirality, including parity violation (Ref. 5), see Barron L.D. *Chem. Soc. Rev.* ***1986***, *15*, 189.

[17]The definitions of plane, center, and alternating axis of symmetry are taken from Eliel, E.L. *Elements of Stereochemistry*, Wiley, NY, ***1969***, pp. 6,7. See also Lemière, G.L.; Alderweireldt, F.C. *J. Org. Chem.* ***1980***, *45*, 4175.

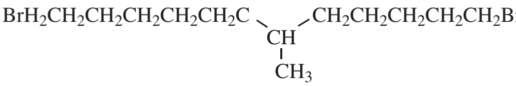
[18]McCasland, G.E.; Proskow, S. *J. Am. Chem. Soc.* ***1955***, *77*, 4688.

[19]For discussions of the relationship between a chiral carbon and chirality, see Mislow, K.; Siegel, J. *J. Am. Chem. Soc.* ***1984***, *106*, 3319; Brand, D.J.; Fisher, J. *J. Chem. Educ.* ***1987***, *64*, 1035.

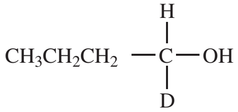
molecule cannot have a plane of symmetry, whatever the identity of W, X, Y, and Z, as long as they are all different. However, the presence of a chiral carbon is neither a necessary nor a sufficient condition for optical activity, since optical activity may be present in molecules with no chiral atom[20] and since some molecules with two or more chiral carbon atoms are superimposable on their mirror images, and hence inactive. Examples of such compounds will be discussed subsequently.

Optically active compounds may be classified into several categories.

1. *Compounds with a Stereogenic Carbon Atom.* If there is only one such atom, the molecule must be optically active. This is so no matter how slight the differences are among the four groups. For example, optical activity is present in



Optical activity has been detected even in cases,[21] such as 1-butanol-1-*d*, where one group is hydrogen and another deuterium.[22]



However, the amount of rotation is greatly dependent on the nature of the four groups, in general increasing with increasing differences in polarizabilities among the groups. Alkyl groups have very similar polarizabilities[23] and the optical activity of 5-ethyl-5-propylundecane is too low to be measurable at any wavelength between 280 and 580 nm.[24]

2. *Compounds with Other Quadrivalent Stereogenic Atoms.*[25] Any molecule containing an atom that has four bonds pointing to the corners of a tetrahedron will be optically active if the four groups are different. Among atoms in this category are Si,[26] Ge, Sn,[27] and N (in quaternary salts or

[20]For a review of such molecules, see Nakazaki, M. *Top. Stereochem.* ***1984***, *15*, 199.

[21]For reviews of compounds where chirality is due to the presence of deuterium or tritium, see Barth, G.; Djerassi, C. *Tetrahedron* ***1981***, *24*, 4123; Arigoni, D.; Eliel, E.L. *Top. Stereochem.* ***1969***, *4*, 127; Verbit, L. *Prog. Phys. Org. Chem.* ***1970***, *7*, 51. For a review of compounds containing chiral methyl groups, see Floss, H.G.; Tsai, M.; Woodard, R.W. *Top. Stereochem.* ***1984***, *15*, 253.

[22]Streitwieser, Jr., A.; Schaeffer, W.D. *J. Am. Chem. Soc.* ***1956***, *78*, 5597.

[23]For a discussion of optical activity in paraffins, see Brewster, J.H. *Tetrahedron* ***1974***, *30*, 1807.

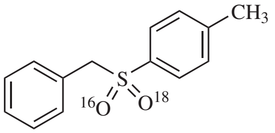
[24]Ten Hoeve, W.; Wynberg, H. *J. Org. Chem.* ***1980***, *45*, 2754.

[25]For reviews of compounds with asymmetric atoms other than carbon, see Aylett, B.J. *Prog. Stereochem.* ***1969***, *4*, 213; Belloli, R. *J. Chem. Educ.* ***1969***, *46*, 640; Sokolov, V.I.; Reutov, O.A. *Russ. Chem. Rev.* ***1965***, *34*, 1.

[26]For reviews of stereochemistry of silicon, see Corriu, R.J.P.; Guérin, C.; Moreau, J.J.E., in Patai, S.; Rappoport, Z. *The Chemistry of Organic Silicon Compounds*, pt. 1, Wiley, NY, ***1989***, pp. 305–370, *Top. Stereochem.* ***1984***, *15*, 43; Maryanoff, C.A.; Maryanoff, B.E., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 4, Academic Press, NY, ***1984***, pp. 355–374.

[27]For reviews of the stereochemistry of Sn and Ge compounds, see Gielen, M. *Top. Curr. Chem.* ***1982***, *104*, 57; *Top. Stereochem.* ***1981***, *12*, 217.

N-oxides).[28] In sulfones, the sulfur bonds with a tetrahedral array, but since two of the groups are always oxygen, no chirality normally results. However, the preparation[29] of an optically active sulfone (**2**) in which one oxygen is ^{16}O and the other ^{18}O illustrates the point that slight differences in groups are all that is necessary. This has been taken even further with the preparation of the ester **3**, both enantiomers of which have been prepared.[30] Optically active chiral phosphates **4** have similarly been made.[31]



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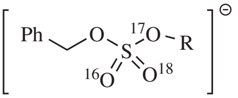

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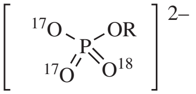

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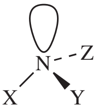
3. *Compounds with Tervalent Stereogenic Atoms*. Atoms with pyramidal bonding[32] might be expected to give rise to optical activity if the atom is connected to three different groups, since the unshared pair of electrons is analogous to a fourth group, necessarily different from the others. For example, a secondary or tertiary amine where X, Y, and Z are different would be expected to be chiral and thus resolvable. Many attempts have been made to resolve such compounds, but until 1968 all of them failed because of *pyramidal inversion*, which is a rapid oscillation of the unshared pair from



one side of the XYZ plane to the other, thus converting the molecule into its enantiomer.[33] For ammonia, there are 2×10^{11} inversions every second. The inversion is less rapid in substituted ammonia derivatives[34] (amines,

[28]For a review, see Davis, F.A.; Jenkins, Jr., R.H., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 4, Academic Press, NY, ***1984***, pp. 313–353. The first resolution of a quaternary ammonium salt of this type was done by Pope, W, J.; Peachey, S.J. *J. Chem. Soc.* ***1899***, *75*, 1127.

[29]Stirling, C.J.M. *J. Chem. Soc.* ***1963***, 5741; Sabol, M.A.; Andersen, K.K. *J. Am. Chem. Soc.* ***1969***, *91*, 3603; Annunziata, R.; Cinquini, M.; Colonna, S. *J. Chem. Soc. Perkin Trans. 1* ***1972***, 2057.

[30]Lowe, G.; Parratt, M.J. *J. Chem. Soc. Chem. Commun.* ***1985***, 1075.

[31]Abbott, S.J.; Jones, S.R.; Weinman, S.A.; Knowles, J.R. *J. Am. Chem. Soc.* ***1978***, *100*, 2558; Cullis, P.M.; Lowe, G. *J. Chem. Soc. Chem. Commun.* ***1978***, 512. For a review, see Lowe, G. *Acc. Chem. Res.* ***1983***, *16*, 244.

[32]For a review of the stereochemistry at trivalent nitrogen, see Raban, M.; Greenblatt, J., in Patai, S. *The Chemistry of Functional Groups*, *Supplement F*, pt. 1, Wiley, NY, ***1982***, pp. 53–83.

[33]For reviews of the mechanism of, and the effect of structure on, pyramidal inversion, see Lambert, J.B. *Top. Stereochem.* ***1971***, *6*, 19; Rauk, A.; Allen, L.C.; Mislow, K. *Angew. Chem. Int. Ed.* ***1970***, *9*, 400; Lehn, J.M. *Fortschr. Chem. Forsch.* ***1970***, *15*, 311.

[34]For example, see Stackhouse, J.; Baechler, R.D.; Mislow, K. *Tetrahedron Lett.* ***1971***, 3437, 3441.

amides, etc.). The interconversion barrier for endo vesus exo methyl in *N*-methyl-2-azabicyclo[2.2.1]heptane, for example, is 0.3 kcal.[35] In this case, torsional strain plays a significant role, along with angle strain, in determining inversion barriers. Two types of nitrogen atom invert particularly slowly, namely, a nitrogen atom in a three-membered ring and a nitrogen atom connected to another atom bearing an unshared pair. Even in such compounds, however, for many years pyramidal inversion proved too rapid to permit isolation of separate isomers. This goal was accomplished[28] only when compounds were synthesized in which both features are combined: a nitrogen atom in a three-membered ring connected to an atom containing an unshared pair. For example, the two isomers of 1-chloro-2-methylaziridine (**5** and **6**) were separated and do not interconvert at room temperature.[36] In suitable cases this barrier to inversion can result in compounds that are optically active solely because of a chiral tervalent nitrogen atom. For example, **7** has been resolved into its separate enantiomers.[37] Note that in this case too, the nitrogen is connected to an atom with an unshared pair. Conformational stability has also been demonstrated for oxaziridines,[38] diaziridines (e.g., **8**)[39] triaziridines (e.g., **9**),[40] and 1,2-oxazolidines (e.g., **10**)[41] even although in this case the ring is five membered. However, note that the nitrogen atom in **10** is connected to two oxygen atoms.

Another compound in which nitrogen is connected to two oxygens is **11**. In this case, there is no ring at all, but it has been resolved into (+) and (−) enantiomers ($[\alpha]_D^{20} \approx \pm 3°$).[42] This compound and

[35]Forsyth, D.A.; Zhang, W.; Hanley, J.A. *J. Org. Chem.* ***1996***, *61*, 1284. Also see Adams, D.B. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 567.

[36]Brois, S.J. *J. Am. Chem. Soc.* ***1968***, *90*, 506, 508. See also Shustov, G.V.; Kadorkina, G.K.; Kostyanovsky, R.G.; Rauk, A. *J. Am. Chem. Soc.* ***1988***, *110*, 1719; Lehn, J.M.; Wagner, J. *Chem. Commun.* ***1968***, 148; Felix, D.; Eschenmoser, A. *Angew. Chem. Int. Ed.* ***1968***, *7*, 224; Kostyanovsky, R.G.; Samoilova, Z.E.; Chervin, I.I. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1968***, 2705, *Tetrahedron Lett.* ***1969***, 719. For a review, see Brois, S.J. *Trans. N.Y. Acad. Sci.* ***1969***, *31*, 931.

[37]Schurig, V.; Leyrer, U. *Tetrahedron: Asymmetry* ***1990***, *1*, 865.

[38]Boyd, D.R. *Tetrahedron Lett.* ***1968***, 4561; Boyd, D.R.; Spratt, R.; Jerina, D.M. *J. Chem. Soc. C* ***1969***, 2650; Montanari, F.; Moretti, I.; Torre, G. *Chem. Commun.* ***1968***, 1694; ***1969***, 1086; Bucciarelli, M.; Forni, A.; Moretti, I.; Torre, G.; Brückner, S.; Malpezzi, L. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 1595. See also Mannschreck, A.; Linss, J.; Seitz, W. *Liebigs Ann. Chem.* ***1969***, *727*, 224; Forni, A.; Moretti, I.; Torre, G.; Brückner, S.; Malpezzi, L.; Di Silvestro, G.D. *J. Chem. Soc. Perkin Trans. 2* ***1984***, 791. For a review of oxaziridines, see Schmitz, E. *Adv. Heterocycl. Chem.* ***1979***, *24*, 63.

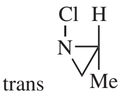
[39]Shustov, G.V.; Denisenko, S.N.; Chervin, I.I.; Asfandiarov, N.L.; Kostyanovsky, R.G. *Tetrahedron* ***1985***, *41*, 5719 and cited references. See also Mannschreck, A.; Radeglia, R.; Gründemann, E.; Ohme, R. *Chem. Ber.* ***1967***, *100*, 1778.

[40]Hilpert, H.; Hoesch, L.; Dreiding, A.S. *Helv. Chim. Acta* ***1985***, *68*, 1691, ***1987***, *70*, 381.

[41]Müller, K.; Eschenmoser, A. *Helv. Chim. Acta* ***1969***, *52*, 1823; Dobler, M.; Dunitz, J.D.; Hawley, D.M. *Helv. Chim. Acta* ***1969***, *52*, 1831.

[42]Kostyanovsky, R.G.; Rudchenko, V.F.; Shtamburg, V.G.; Chervin, I.I.; Nasibov, S.S. *Tetrahedron* ***1981***, *37*, 4245; Kostyanovsky, R.G.; Rudchenko, V.F. *Doklad. Chem.* ***1982***, *263*, 121. See also Rudchenko, V.F.; Ignatov, S.M.; Chervin, I.I.; Kostyanovsky, R.G. *Tetrahedron* ***1988***, *44*, 2233.

several similar ones reported in the same paper are the first examples of



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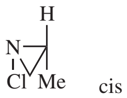

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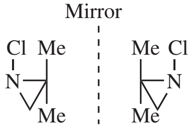

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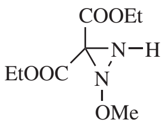

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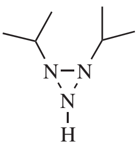

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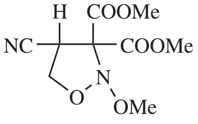

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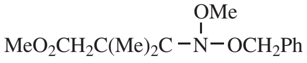
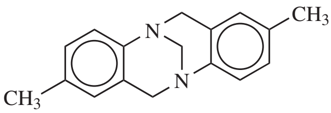


11

compounds whose optical activity is solely due to an acyclic tervalent chiral nitrogen atom. However, **11** is not optically stable and racemizes at 20°C with a half-life of 1.22 h. A similar compound (**11**, with OCH_2Ph replaced by OEt) has a longer half-life, 37.5 h at 20°C.



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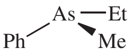
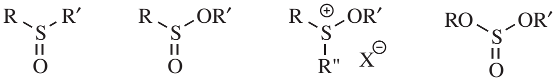


13

In molecules in which the nitrogen atom is at a bridgehead, pyramidal inversion is of course prevented. Such molecules, if chiral, can be resolved even without the presence of the two structural features noted above. For example, optically active **12** (Tröger's base) has been prepared.[43] Phosphorus inverts more slowly and arsenic still more slowly.[44] Nonbridgehead phosphorus,[45] arsenic, and antimony compounds have also been resolved, for example, **13**.[46] Sulfur exhibits pyramidal bonding in sulfoxides, sulfinic

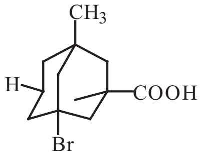


[43]Prelog, V.; Wieland, P. *Helv. Chim. Acta* ***1944***, *27*, 1127.
[44]For reviews, see Yambushev, F.D.; Savin, V.I. *Russ. Chem. Rev.* ***1979***, *48*, 582; Gallagher, M.J.; Jenkins, I.D. *Top. Stereochem.* ***1968***, *3*, 1; Kamai, G.; Usacheva, G.M. *Russ. Chem. Rev.* ***1966***, *35*, 601.
[45]For a review of chiral phosphorus compounds, see Valentine, Jr., D.J., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 4, Academic Press, NY, ***1984***, pp. 263–312.
[46]Horner, L.; Fuchs, H. *Tetrahedron Lett.* ***1962***, 203.

esters, sulfonium salts, and sulfites. Examples of each of these have been resolved.[47] An interesting example is (+)-$Ph^{12}CH_2SO^{13}CH_2Ph$, a sulfoxide in which the two alkyl groups differ only in ^{12}C versus ^{13}C, but which has $[\alpha]280 = +0.71°$.[48] A computational study indicates that base-catalyzed inversion at sulfur in sulfoxides is possible via a tetrahedral intermediate.[49]

4. *Suitably Substituted Adamantanes*. Adamantanes bearing four different substituents at the bridgehead positions are chiral and optically active and **14**, for example, has been resolved.[50] This type of molecule is a kind of expanded tetrahedron and has the same symmetry properties as any other tetrahedron.

5. *Restricted Rotation Giving Rise to Perpendicular Disymmetric Planes*. Certain compounds that do not contain asymmetric atoms are nevertheless chiral because they contain a structure that can be schematically represented as in Fig. 4.2. For these compounds, we can draw two perpendicular planes neither of which can be bisected by a plane of symmetry. If either plane could be so bisected, the



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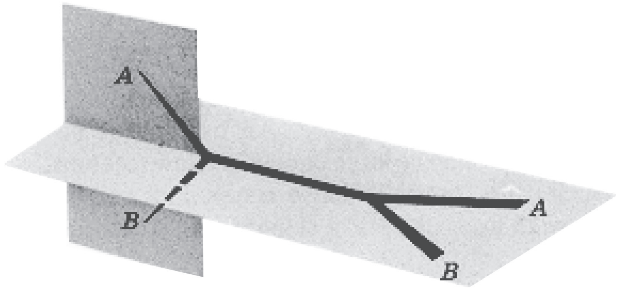


Fig. 4.2. Perpendicular disymmetric planes.

[47]For reviews of chiral organosulfur compounds, see Andersen, K.K., in Patai, S. Rappoport, Z. Stirling, C. *The Chemistry of Sulphones and Sulphoxides*, Wiley, NY, ***1988***, pp. 55–94; and, in Stirling, C.J.M. *The Chemistry of the Sulphonium Group*, pt. 1, Wiley, NY, ***1981***, pp. 229–312; Barbachyn, M.R.; Johnson, C.R., in Morrison, J.D. *Asymmetric Synthesis* Vol. 4, Academic Press, NY, ***1984***, pp. 227–261; Cinquini, M.; Cozzi, F.; Montanari, F., in Bernardi, F.; Csizmadia, I.G.; Mangini, A. *Organic Sulfur Chemistry*; Elsevier, NY, ***1985***, pp. 355–407; Mikoł ajczyk, M.; Drabowicz, J. *Top. Stereochem.* ***1982***, *13*, 333.

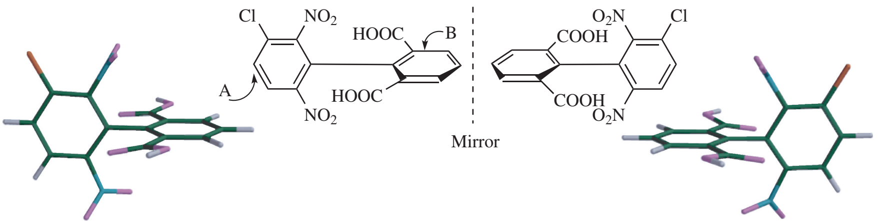
[48]Andersen, K.K.; Colonna, S.; Stirling, C.J.M. *J. Chem. Soc. Chem. Commun.* ***1973***, 645.

[49]Balcells, D.; Maseras, F.; Khiar, N. *Org. Lett.* ***2004***, *6*, 2197.

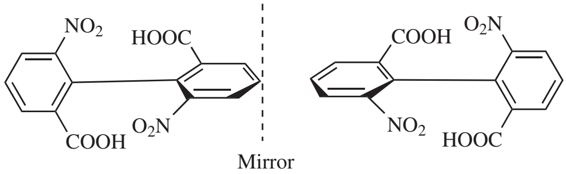
[50]Hamill, H.; McKervey, M.A. *Chem. Commun.* ***1969***, 864; Applequist, J.; Rivers, P.; Applequist, D.E. *J. Am. Chem. Soc.* ***1969***, *91*, 5705.

molecule would be superimposable on its mirror image, since such a plane would be a plane of symmetry. These points will be illustrated by examples.

Biphenyls containing four large groups in the ortho positions cannot freely rotate about the central bond because of steric hindrance.[51] For example, the activation energy (rotational barrier) for the enantiomerization process was determined, $\Delta G^{\ddagger} = 21.8 \pm 0.1\ \text{kcal mol}^{-1}$, for the chiral 2-carboxy-2′-methoxy-6-nitrobiphenyl.[52] In such compounds, the two rings are in perpendicular planes. If either ring is symmetrically substituted, the molecule has a plane of symmetry. For example, consider the biaryls:



Ring B is symmetrically substituted. A plane drawn perpendicular to ring B contains all the atoms and groups in ring A; hence, it is a plane of symmetry and the compound is achiral. On the other hand, consider:



There is no plane of symmetry and the molecule is chiral; many such compounds have been resolved. Note that groups in the para position cannot cause lack of symmetry. Isomers that can be separated only because rotation about single bonds is prevented or greatly slowed are called *atropisomers*.[53] 9,9′-Bianthryls also show hindered rotation and exhibit atropisomers.[54]

It is not always necessary for four large ortho groups to be present in order for rotation to be prevented. Compounds with three and even two groups, if large enough, can have hindered rotation and, if suitably substituted, can be resolved. An example is biphenyl-2,2′-bis-sulfonic acid.[55] In some cases, the groups may be large enough to slow rotation greatly but not to prevent it

[51]When the two rings of a biphenyl are connected by a bridge, rotation is of course impossible. For a review of such compounds, see Hall, D.M. *Prog. Stereochem.* ***1969***, *4*, 1.

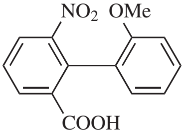
[52]Ceccacci, F.; Mancini, G.; Mencarelli, P.; Villani, C. *Tetrahedron Asymmetry* ***2003***, *14*, 3117.

[53]For a review, see Ō ki, M. *Top. Stereochem.* ***1983***, *14*, 1.

[54]Becker, H.-D.; Langer, V.; Sieler, J.; Becker, H.-C. *J. Org. Chem.* ***1992***, *57*, 1883.

[55]Patterson, W.I.; Adams, R. *J. Am. Chem. Soc.* ***1935***, *57*, 762.

completely. In such cases, optically active compounds can be prepared that



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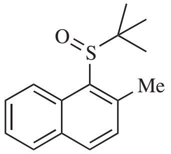

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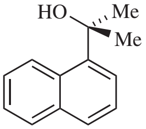
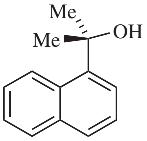
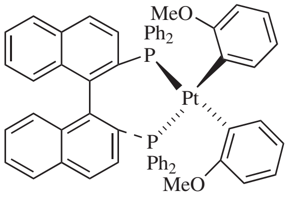


17a



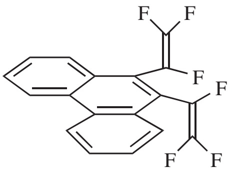
17b



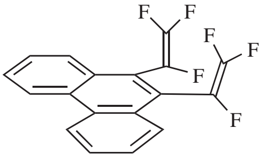
18

slowly racemize on standing. Thus, **15** loses its optical activity with a half-life of 9.4 min in ethanol at 25°C.[56] Compounds with greater rotational stability can often be racemized if higher temperatures are used to supply the energy necessary to force the groups past each other.[57]

Atropisomerism occurs in other systems as well, including monopyrroles.[58] Sulfoxide **16**, for example, forms atropisomers with an interconversion barrier with its atropisomer of 18–19 kcal mol^{-1}.[59] The atropisomers of hindered naphthyl alcohols, such as **17** exist as the *sp*-atropisomer (**17a**) and the *ap*-atropisomer (**17b**).[60] Atropisomers can also be formed in organometallic compounds, such as the bis(phosphinoplatinum) complex (see **18**), generated by reaction with R-BINAP (see p. 1801).[61]



19a

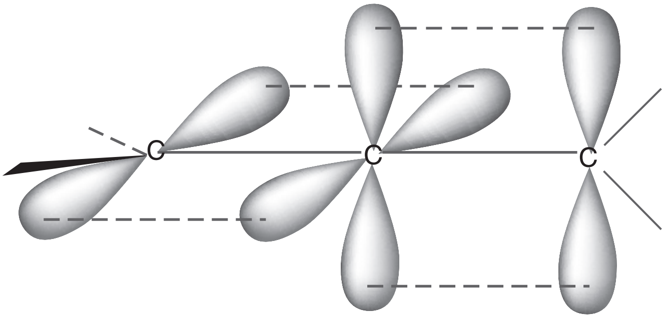


19b

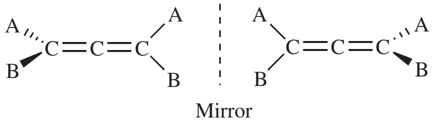
[56]Stoughton, R.W.; Adams, R. *J. Am. Chem. Soc.* ***1932***, *54*, 4426.
[57]For a monograph on the detection and measurement of restricted rotations, see Ō ki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, ***1985***.
[58]Boiadjiev, S.E.; Lightner, S.A. *Tetrahedron Asymmetry* ***2002***, *13*, 1721.
[59]Casarini, D.; Foresti, E.; Gasparrini, F.; Lunazzi, L.; Macciantelli, D.; Misiti, D.; Villani, C. *J. Org. Chem.* ***1993***, *58*, 5674.
[60]Casarini, D.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem.* ***1997***, *62*, 3315.
[61]Alcock, N.W.; Brown, J.M.; Pérez-Torrente, J.J. *Tetrahedron Lett.* ***1992***, *33*, 389. See also, Mikami, K.; Aikawa, K.; Yusa, Y.; Jodry, J.J.; Yamanaka, M. *Synlett* ***2002***, 1561.

It is possible to isolate isomers in some cases, often due to restricted rotation. In 9,10-bis(trifluorovinyl)phenanthrene (**19**) torsional diastereomers (see p. 163) are formed. The value of K for interconversion of **19a** and **19b** is 0.48, with $\Delta G^\circ = 15.1\ \text{kcal mol}^{-1}$.[62] The ability to isolate atropisomers can depend on interactions with solvent, as in the isolation of atropisomeric colchicinoid alkaloids, which have been isolated, characterized, and their dichroic behavior described.[63]

In allenes, the central carbon is *sp* bonded. The remaining two *p* orbitals are perpendicular to each other and each overlaps with the *p* orbital of one adjacent carbon atom, forcing the two remaining bonds of each carbon into perpendicular planes. Thus allenes fall into the category represented by Fig. 4.2: Like biphenyls, allenes are chiral only if both sides are unsymmetrically substituted.[64] For example,



These cases are completely different from the cis–trans isomerism of compounds with one double bond (p. 182). In the latter cases, the four groups are all in one plane, the isomers are not enantiomers, and neither is chiral, while in allenes the groups are in two perpendicular planes and the isomers are a pair of optically active enantiomers.



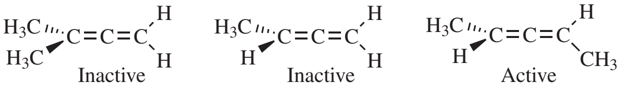
When three, five, or any *odd* number of cumulative double bonds exist, orbital overlap causes the four groups to occupy one plane and cis–trans isomerism is observed. When four, six, or any *even* number of cumulative double bonds

[62]Dolbier Jr., W.R.; Palmer, K.W. *Tetrahedron Lett.* ***1992***, *33*, 1547.

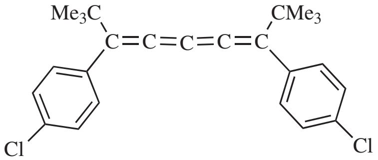
[63]Cavazza, M.; Zandomeneghi, M.; Pietra, F. *Tetrahedron Lett.* ***2000***, *41*, 9129.

[64]For reviews of allene chirality, see Runge, W., in Landor, S.R. *The Chemistry of the Allenes*, Vol. 3, Academic Press, NY, ***1982***, pp. 579–678, and, in Patai, S. *The Chemistry of Ketenes, Allenes, and Related Compounds*, pt. 1, Wiley, NY, ***1980***, pp. 99–154; Rossi, R.; Diversi, P. *Synthesis* ***1973***, 25.

exist, the situation is analogous to that in the allenes and optical activity is possible. Compound **20** has been resolved.[65]



Among other types of compounds that contain the system illustrated in Fig. 4.2 and that are similarly chiral if both sides are dissymmetric are spiranes (e.g., **21**) and compounds with exocyclic double bonds (e.g., **22**). Atropisomerism exists in (1,5)-bridgedcalix[8]arenes (see p. 123).[66]



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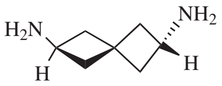

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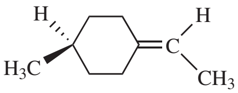


22

6. *Chirality Due to a Helical Shape.*[67] Several compounds have been prepared that are chiral because they have a shape that is actually helical and can therefore be left or right handed in orientation. The entire molecule is usually less than one full turn of the helix, but this does not alter the possibility of left and right handedness. An example is hexahelicene,[68] in which one side of the molecule must lie above the other because of crowding.[69] The rotational barrier for helicene is ~22.9 kcal mol^{-1}, and is significantly higher when substituents are present.[70] It has been shown that the dianion of helicene retains its chirality.[71] Chiral discrimination of helicenes is possible.[72] 1,16-Diazo[6]helicene has also been prepared and, interestingly, does not act as a proton sponge (see p. 386) because the helical structure leaves the basic nitrogen atoms too far apart. Heptalene is another compound that is not planar (p. 67). Its twisted structure makes it

[65]Nakagawa, M.; Shing ū, K.; Naemura, K. *Tetrahedron Lett.* ***1961***, 802.

[66]Consoli, G.M.L.; Cunsolo, F.; Geraci, C.; Gavuzzo, E.; Neri, P. *Org. Lett.* ***2002***, *4*, 2649.

[67]For a review, see Meurer, K.P.; Vögtle, F. *Top. Curr. Chem.* ***1985***, *127*, 1. See also Laarhoven, W.H.; Prinsen, W.J.C. *Top. Curr. Chem.* ***1984***, *125*, 63; Martin, R.H. *Angew. Chem. Int. Ed.* ***1974***, *13*, 649.

[68]Newman, M.S.; Lednicer, D. *J. Am. Chem. Soc.* ***1956***, *78*, 4765. Optically active heptahelicene has also been prepared, as have higher helicenes: Martin, R.H.; Baes, M. *Tetrahedron* ***1975***, *31*, 2135; Bernstein, W.J.; Calvin, M.; Buchardt, O. *J. Am. Chem. Soc.* ***1972***, *94*, 494, ***1973***, *95*, 527; Defay, N.; Martin, R.H. *Bull. Soc. Chim. Belg.* ***1984***, *93*, 313. Even pentahelicene is crowded enough to be chiral: Goedicke, C.; Stegemeyer, H. *Tetrahedron Lett.* ***1970***, 937: Bestmann, H.J.; Roth, W. *Chem. Ber.* ***1974***, *107*, 2923.

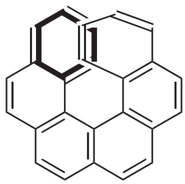
[69]For reviews of the helicenes, see Laarhoven, W.H.; Prinsen, W.J.C. *Top. Curr. Chem.* ***1984***, *125*, 63; Martin, R.H. *Angew. Chem. Int. Ed.* ***1974***, *13*, 649.

[70]Janke, R.H.; Haufe, G.; Würthwein, E.-U.; Borkent, J.H. *J. Am. Chem. Soc.* ***1996***, *118*, 6031.

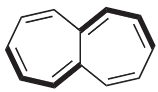
[71]Frim, R.; Goldblum, A.; Rabinovitz, M. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 267.

[72]Murguly, E.; McDonald, R.; Branda, N.R. *Org. Lett.* ***2000***, *2*, 3169.

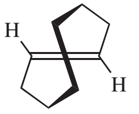
chiral, but the enantiomers rapidly interconvert.[73]



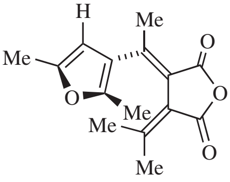
Hexahelicene



Heptalene



trans-Cyclooctene



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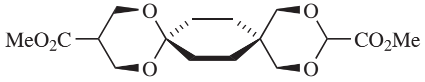
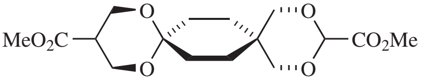


24a



24b

trans-Cyclooctene (see also, p. 184) also exhibits helical chirality because the carbon chain must lie above the double bond on one side and below it on the other.[74] Similar helical chirality also appears in fulgide **23**[75] and dispiro-1,3-dioxane, **24**, shows two enantiomers, **24a** and **24b**.[76]

7. *Optical Activity Caused by Restricted Rotation of Other Types*. Substituted paracyclophanes may be optically active[77] and **25**, for example, has been resolved.[78] In this case, chirality results because the benzene ring cannot rotate in such a way that the carboxyl group goes through the alicyclic ring. Many chiral layered cyclophanes, (e.g., **26**) have been prepared.[79] Another cyclophane[80] with a different type of chirality is [12][12]paracyclophane (**27**), where the chirality arises from the relative orientation of the two rings attached to the central benzene ring.[81] An aceytlenic cyclophane was shown to have helical chirality.[82] Metallocenes substituted with at least two different groups on one ring are also chiral.[83]

[73]Staab, H.A.; Diehm, M.; Krieger, C. *Tetrahedron Lett.* ***1994***, *35*, 8357.

[74]Cope, A.C.; Ganellin, C.R.; Johnson Jr., H.W.; Van Auken, T.V.; Winkler, H.J.S. *J. Am. Chem. Soc.* ***1963***, *85*, 3276. Also see Levin, C.C.; Hoffmann, R. *J. Am. Chem. Soc.* ***1972***, *94*, 3446.

[75]Yokoyama, Y.; Iwai, T.; Yokoyama, Y.; Kurita, Y. *Chem. Lett.* ***1994***, 225.

[76]Grosu, I.; Mager, S.; Plé, G.; Mesaros, E. *Tetrahedron* ***1996***, *52*, 12783.

[77]For an example, see Rajakumar, P.; Srisailas, M. *Tetrahedron* ***2001***, *57*, 9749.

[78]Blomquist, A.T.; Stahl, R.E.; Meinwald, Y.C.; Smith, B.H. *J. Org. Chem.* ***1961***, *26*, 1687. For a review of chiral cyclophanes and related molecules, see Schlögl, K. *Top. Curr. Chem.* ***1984***, *125*, 27.

[79]Nakazaki, M.; Yamamoto, K.; Tanaka, S.; Kametani, H. *J. Org. Chem.* ***1977***, *42*, 287. Also see Pelter, A.; Crump, R.A.N.C.; Kidwell, H. *Tetrahedron Lett.* ***1996***, *37*, 1273. for an example of a chiral [2.2]paracyclophane.

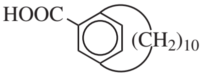
[80]For a treatise on the quantitative chirality of helicenes, see Katzenelson, O.; Edelstein, J.; Avnir, D. *Tetrahedron Asymmetry* ***2000***, *11*, 2695.

[81]Chan, T.-L.; Hung, C.-W.; Man, T.-O.; Leung, M.-k. *J. Chem. Soc. Chem. Commun.* ***1994***, 1971.

[82]Collins, S.K.; Yap, G.P.A.; Fallis, A.G. *Org. Lett.* ***2000***, *2*, 3189.

[83]For reviews on the stereochemistry of metallocenes, see Schlögl, K. *J. Organomet. Chem.* ***1986***, *300*, 219, *Top. Stereochem.* ***1967***, *1*, 39; *Pure Appl. Chem.* ***1970***, *23*, 413.

Several hundred such compounds have been resolved, one example



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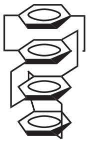

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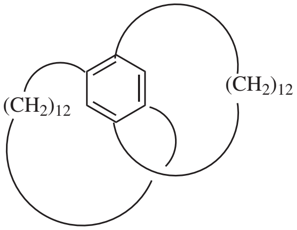

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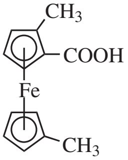

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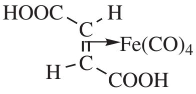

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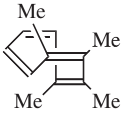
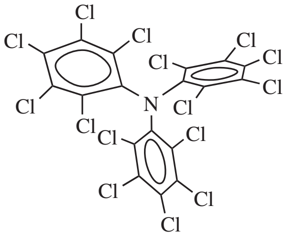
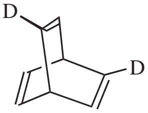


30

being **28**. Chirality is also found in other metallic complexes of suitable geometry.[84] For example, fumaric acid–iron tetracarbonyl (**29**) has been resolved.[85] 1,2,3,4-Tetramethylcyclooctatetraene (**30**) is also chiral.[86] This molecule, which exists in the tub form (p. 71), has



Perchlorotriphenylamine



31

neither a plane nor an alternating axis of symmetry. Another compound that is chiral solely because of hindered rotation is the propeller-shaped perchlorotriphenylamine, which has been resolved.[87] The 2,5-dideuterio

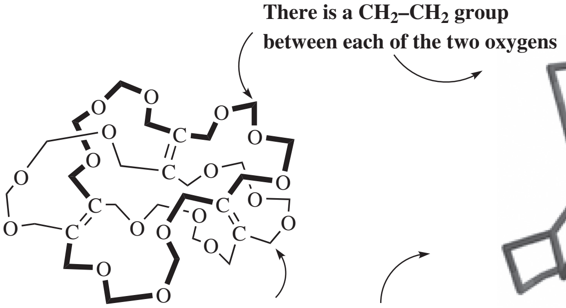
[84]For reviews of such complexes, see Paiaro, G. *Organomet. Chem. Rev. Sect. A* ***1970***, *6*, 319.

[85]Paiaro, G.; Palumbo, R.; Musco, A.; Panunzi, A. *Tetrahedron Lett.* ***1965***, 1067; also see Paiaro, G.; Panunzi, A. *J. Am. Chem. Soc.* ***1964***, *86*, 5148.

[86]Paquette, L.A.; Gardlik, J.M.; Johnson, L.K.; McCullough, K.J. *J. Am. Chem. Soc.* ***1980***, *102*, 5026.

[87]Okamoto, Y.; Yashima, E.; Hatada, K.; Mislow, K. *J. Org. Chem.* ***1984***, *49*, 557. For a conformational study concerning stereomutation of the helical enantiomers of trigonal carbon diaryl-substituted compounds by dynamic NMR, see Grilli, S.; Lunazzi, L.; Mazzanti, A.; Casarini, D.; Femoni, C. *J. Org. Chem.* ***2001***, *66*, 488.

derivative (**31**) of barrelene is chiral, although the parent hydrocarbon and the monodeuterio derivative are not. Compound **25** has been prepared in optically active form[88] and is another case where chirality is due to isotopic substitution.



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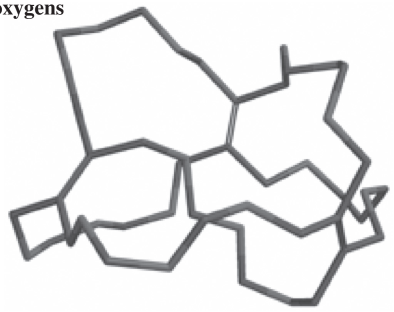
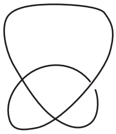


33

The main molecular chain in compound **32** has the form of a Möbius strip (see Fig. 15.7 and 3D model **33**).[89] This molecule has no stereogenic carbons, nor does it have a rigid shape a plane nor an alternating axis of symmetry. However, **32** has been synthesized and has been shown to be chiral.[90] Rings containing 50 or more members should be able to exist as knots (**34**, and see **39** on p. 133 in Chapter 3). Such a knot would be nonsuperimposable on its mirror image. Calixarenes,[91] crown ethers,[92] catenanes, and rotaxanes (see p. 131) can also be chiral if suitably substituted.[93] For example, **40** and **41** are nonsuperimposable mirror images.



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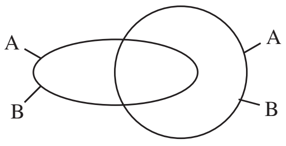

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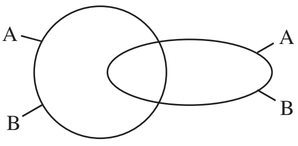

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[88]Lightner, D.A.; Paquette, L.A.; Chayangkoon, P.; Lin, H.; Peterson, J.R.*J. Org. Chem.* ***1988***, *53*, 1969.
[89]For a review of chirality in Möbius-strip molecules catenanes, and knots, see Walba, D.M. *Tetrahedron* ***1985***, *41*, 3161.
[90]Walba, D.M.; Richards, R.M.; Haltiwanger, R.C. *J. Am. Chem. Soc.* ***1982***, *104*, 3219.
[91]Iwanek, W.; Wolff, C.; Mattay, J. *Tetrahedron Lett.* ***1995***, *36*, 8969.
[92]de Vries, E.F.J.; Steenwinkel, P.; Brussee, J.; Kruse, C.G.; van der Gen, A. *J. Org. Chem.* ***1993***, *58*, 4315; Pappalardo, S.; Palrisi, M.F. *Tetrahedron Lett.* ***1996***, *37*, 1493; Geraci, C.; Piattelli, M.; Neri, P. *Tetrahedron Lett.* ***1996***, *37*, 7627.
[93]For a discussion of the stereochemistry of these compounds, see Schill, G. *Catenanes, Rotaxanes, and Knots*; Academic Press, NY, ***1971***, pp. 11–18.

Creation of a Stereogenic Center

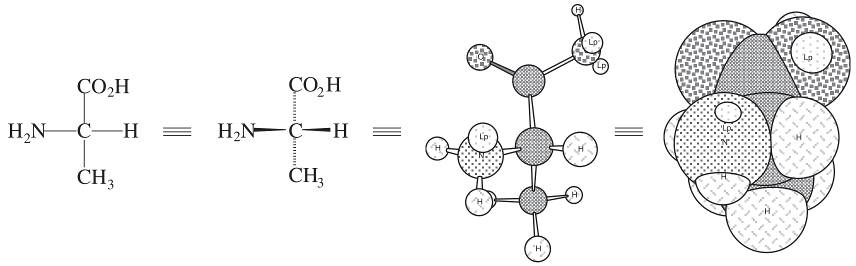
Any structural feature of a molecule that gives rise to optical activity may be called a *stereogenic center* (the older term is chiral center) In many reactions, a new chiral center is created, for example,

$$CH_3CH_2COOH + Br_2 \xrightarrow{P} CH_3CHBrCOOH$$

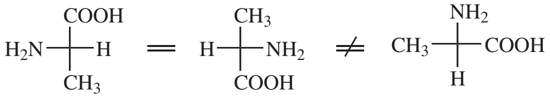
If the reagents and reaction conditions are all symmetrical, the product must be a racemic mixture. No optically active material can be created if all starting materials and conditions are optically inactive.[94] This statement also holds when one begins with a racemic mixture. Thus racemic 2-butanol, treated with HBr, must give racemic 2-bromobutane.

The Fischer Projection

For a thorough understanding of stereochemistry it is useful to examine molecular models (like those depicted in Fig. 4.1). However, this is not feasible when writing on paper or a blackboard. In 1891, Emil Fischer greatly served the interests of chemistry by inventing the Fischer projection, a method of representing tetrahedral carbons on paper. By this convention, the model is held so that the two bonds in front of the paper are horizontal and those behind the paper are vertical.

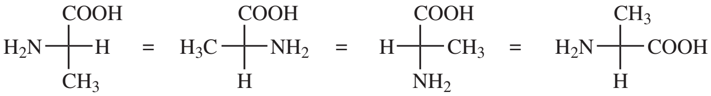


In order to obtain proper results with these formulas, it should be remembered that they are projections and must be treated differently from the models in testing for superimposability. Every plane is superimposable on its mirror image; hence with these formulas there must be added the restriction that they may not be taken out of the plane of the blackboard or paper. Also, they may not be rotated 90°, although 180° rotation is permissible:



[94]There is one exception to this statement. In a very few cases, racemic mixtures may crystalize from solution in such a way that all the (+) molecules go into one crystal and the (−) molecules into another. If one of the crystals crystallizes before the other, a rapid filtration results in optically active material. For a discussion, see Pincock, R.E.; Wilson, K.R. *J. Chem. Educ.* ***1973***, *50*, 455.

It is also permissible to keep any one group fixed and to rotate the other three clockwise or counterclockwise (because this can be done with models):

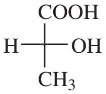


However, the *interchange* of any two groups results in the conversion of an enantiomer into its mirror image (this applies to models as well as to the Fischer projections).

With these restrictions Fischer projections may be used instead of models to test whether a molecule containing asymmetric carbons is superimposable on its mirror image. However, there are no such conventions for molecules whose chirality arises from anything other than chiral atoms; when such molecules are examined on paper, 3D pictures must be used. With models or 3D pictures there are no restrictions about the plane of the paper.

Absolute Configuration

Suppose we have two test tubes, one containing (−)-lactic acid and the other the (+) enantiomer. One test tube contains **37** and the other **38**. How do we know which is which? Chemists in the early part of the twentieth century pondered this problem and



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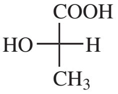

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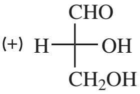

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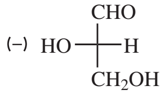
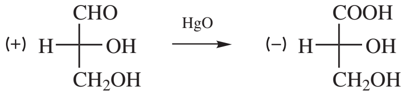


40

decided that they could not know: for lactic acid or any other compound. Therefore Rosanoff proposed that one compound be chosen as a standard and a configuration be arbitrarily assigned to it. The compound chosen was glyceraldehyde because of its relationship to the sugars. The (+) isomer was assigned the configuration shown in **39** and given the label D. The (−) isomer, designated to be **39**, was given the label L. Once a standard was chosen, other compounds could then be related to it. For example, (+)-glyceraldehyde, oxidized with mercuric oxide, gives (−)-glyceric acid:



Since it is highly improbable that the configuration at the central carbon changed, it can be concluded that (−)-glyceric acid has the same configuration as (+)-glyceraldehyde and therefore (−)-glyceric acid is also called D. This example emphasizes that molecules with the same configuration need not rotate the plane of polarized light in the same direction. This fact should not surprise us when we remember that the same compound can rotate the plane in opposite directions under different conditions.

Once the configuration of the glyceric acids was known (in relation to the glyceraldehydes), it was then possible to relate other compounds to either of these, and each time a new compound was related, others could be related to *it*. In this way, many thousands of compounds were related, indirectly, to D- or L-glyceraldehyde, and it was determined that **37**, which has the D configuration, is the isomer that rotates the plane of polarized light to the left. Even compounds without asymmetric atoms, such as biphenyls and allenes, have been placed in the D or L series.[95] When a compound has been placed in the D or L series, its *absolute configuration* is said to be known.[96]

In 1951, it became possible to determine whether Rosanoff's guess was right. Ordinary X-ray crystallography cannot distinguish between a D and a L isomer, but by use of a special technique, Bijvoet was able to examine sodium rubidium tartrate and found that Rosanoff had made the correct choice.[97] It was perhaps historically fitting that the first true absolute configuration should have been determined on a salt of tartaric acid, since Pasteur made his great discoveries on another salt of this acid.

In spite of the former widespread use of D and L to denote absolute configuration, the method is not without faults. The designation of a particular enantiomer as D or L can depend on the compounds to which it is related. Examples are known where an enantiomer can, by five or six steps, be related to a known D compound, and by five or six other steps, be related to the L enantiomer of the same compound. In a case of this sort, an arbitrary choice of D or L must be used. Because of this and other flaws, the DL system is no longer used, except for certain groups of compounds, such as carbohydrates and amino acids.

The Cahn–Ingold–Prelog System

The system that has replaced the DL system is the *Cahn–Ingold–Prelog* system, in which the four groups on an asymmetric carbon are ranked according to a set of sequence rules.[98] For our purposes, we confine ourselves to only a few

[95]The use of small *d* and *l* is now discouraged, since some authors used it for rotation, and some for configuration. However, a racemic mixture is still a *dl* mixture, since there is no ambiguity here.

[96]For lists of absolute configurations of thousands of compounds, with references, mostly expressed as (*R*) or (*S*) rather than D or L, see Klyne, W.; Buckingham, J. *Atlas of Stereochemistry*, 2nd ed., 2 vols., Oxford University Press: Oxford, ***1978***; Jacques, J.; Gros, C.; Bourcier, S.; Brienne, M.J.; Toullec, J. *Absolute Configurations* (Vol. 4 of Kagan *Stereochemistry*), Georg Thieme Publishers, Stuttgart, ***1977***.

[97]Bijvoet, J.M.; Peerdeman, A.F.; van Bommel, A.J. *Nature (London)* ***1951***, *168*, 271. For a list of organic structures whose absolute configurations have been determined by this method, see Neidle, S.; Rogers, D.; Allen, F.H. *J. Chem. Soc. C* ***1970***, 2340.

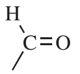
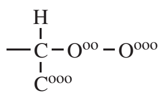
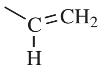
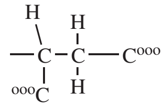
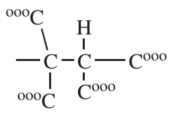
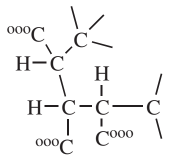
[98]For descriptions of the system and sets of sequence rules, see *Pure Appl. Chem.* ***19767***, *45*, 13; *Nomenclature of Organic Chemistry*, Pergamon, Elmsford, NY, ***1979*** (the Blue Book); Cahn, R.S.; Ingold, C.K.; Prelog, V. *Angew. Chem. Int. Ed.* ***1966***, *5*, 385; Cahn, R.S. *J. Chem. Educ.* ***1964***, *41*, 116; Fernelius, W.C.; Loening, K.; Adams, R.M. *J. Chem. Educ.* ***1974***, *51*, 735. See also, Prelog, V.; Helmchen, G. *Angew. Chem. Int. Ed.* ***1982***, *21*, 567. Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***, pp. 101–147. Also see, Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY, ***2001***, pp. 13–20.

of these rules, which are sufficient to deal with the vast majority of chiral compounds.

1. Substituents are listed in order of decreasing atomic number of the atom directly joined to the carbon.
2. Where two or more of the atoms connected to the asymmetric carbon are the same, the atomic number of the second atom determines the order. For example, in the molecule Me_2CH–CHBr–CH_2OH, the CH_2OH group takes precedence over the Me_2CH group because oxygen has a higher atomic number than carbon. Note that this is so even although there are two carbons in Me_2CH and only one oxygen in CH_2OH. If two or more atoms connected to the second atom are the same, the third atom determines the precedence, and so on.
3. All atoms except hydrogen are formally given a valence of 4. Where the actual valence is less (as in nitrogen, oxygen, or a carbanion), phantom atoms (designated by a subscript $_0$) are used to bring the valence up to four. These phantom atoms are assigned an atomic number of zero and necessarily rank lowest. Thus the ligand $-HNHMe_2$ ranks higher than $-NMe_2$.
4. A tritium atom takes precedence over deuterium, which in turn takes precedence over ordinary hydrogen. Similarly, any higher isotope (e.g., ^{14}C) takes precedence over any lower one.
5. Double and triple bonds are counted as if they were split into two or three single bonds, respectively, as in the examples in Table 4.1 (note the treatment of the phenyl group). Note that in a C=C double bond, the two carbon atoms are *each* regarded as being connected to two carbon atoms and that one of the latter is counted as having three phantom substituents.

As an exercise, we shall compare the four groups in Table 4.1. The first atoms are connected, respectively, to (H, O, O), (H, C, C), (C, C, C), and (C, C, C). That is enough to establish that —CHO ranks first and $-CH=CH_2$ last, since even one

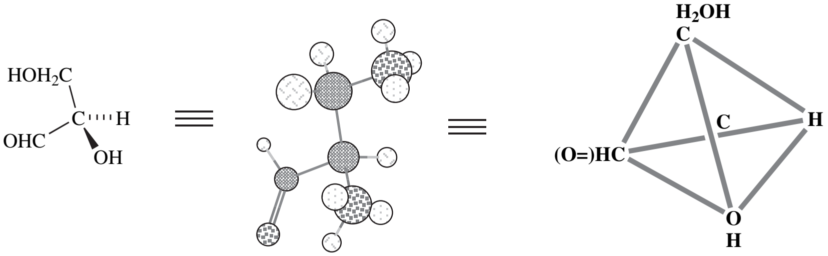
TABLE 4.1. How Four Common Groups Are Treated in the Cahn–Ingold–Prelog System

Group	Treated as If It Were	Group	Treated as If It Were
			
—C≡C—H		$-C_6H_5$	

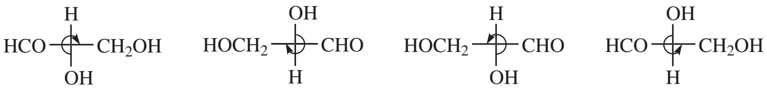
oxygen outranks three carbons and three carbons outrank two carbons and a hydrogen. To classify the remaining two groups we must proceed further along the chains. We note that $-C_6H_5$ has two of its (C, C, C) carbons connected to (C, C, H), while the third is $({}_{000})$ and is thus preferred to $-C{\equiv}CH$, which has only one (C, C, H) and two $({}_{000})$s.

By application of the above rules, some groups in descending order of precedence are COOH, COPh, COMe, CHO, $CH(OH)_2$, *o*-tolyl, *m*-tolyl, *p*-tolyl, phenyl, $C{\equiv}CH$, *tert*-butyl, cyclohexyl, vinyl, isopropyl, benzyl, neopentyl, allyl, *n*-pentyl, ethyl, methyl, deuterium, and hydrogen. Thus the four groups of glyceraldehyde are arranged in the sequence: OH, CHO, CH_2OH, H.

Once the order is determined, the molecule is held so that the lowest group in the sequence is pointed away from the viewer. Then if the other groups, in the order listed, are oriented clockwise, the molecule is designated (*R*), and if counterclockwise, (*S*). For glyceraldehyde, the (+) enantiomer is (*R*):

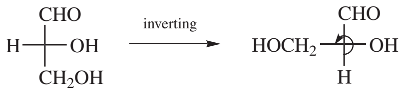


Note that when a compound is written in the Fischer projection, the configuration can easily be determined without constructing the model.[99] If the lowest ranking group is either at the top or the bottom (because these are the two positions pointing away from the viewer), the (*R*) configuration is present if the other three groups in descending order are clockwise, for example,



(*R*)-Glyceraldehyde (*S*)-Glyceraldehyde

If the lowestranking group is not at the top or bottom, one can simply interchange it with the top or bottom group, bearing in mind that in so doing, one is inverting the configuration, for example:

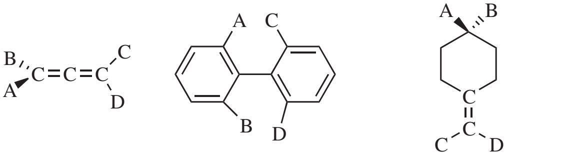


(*S*)-Glyceraldehyde

Therefore the original compound was (*R*)-glyceraldehyde.

[99]For a discussion of how to determine (*R*) or (*S*) from other types of formula, see Eliel, E.L. *J. Chem. Educ.* ***1985***, *62*, 223.

The Cahn–Ingold–Prelog system is unambiguous and easily applicable in most cases. Whether to call an enantiomer (*R*) or (*S*) does not depend on correlations, but the configuration must be known before the system can be applied and this does depend on correlations. The Cahn–Ingold–Prelog system has also been extended to chiral compounds that do not contain stereogenic centers, but have a chiral axis.[100] Compounds having a chiral axis include unsymmetrical allenes, biaryls that exhibit atropisomerism (see p. 146), and alkylidene cyclohexane derivatives, molecular propellers and gears, helicenes, cyclophanes, annulenes, *trans*-cycloalkenes, and metallocenes. A series of rules have been proposed to address the few cases where the rules can be ambiguous, as in cyclophanes and other systems.[101]

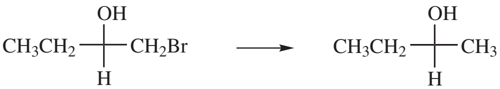


Allenes Biaryls Alkylidenecyclohexanes

Methods of Determining Configuration[102]

In all the methods,[103] it is necessary to relate the compound of unknown configuration to another whose configuration is known. The most important methods of doing this are

1. Conversion of the unknown to, or formation of the unknown from, a compound of known configuration without disturbing the chiral center. See the glyceraldehyde–glyceric acid example above (p. 154). Since the chiral



(*R*) (*S*)

[100]Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley, NY, ***1994***, pp. 1119–1190. For a discussion of these rules, as well as for a review of methods for establishing configurations of chiral compounds not containing a stereogenic center, see Krow, G. *Top. Stereochem.* ***1970***, *5*, 31.

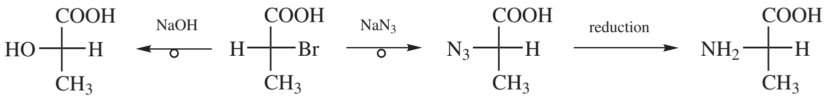
[101]Dodziuk, H.; Mirowicz, M. *Tetrahedron Asymmetry* ***1990***, *1*, 171; Mata, P.; Lobo, A.M.; Marshall, C.; Johnson, A.P. *Tetrahedron Asymmetry* ***1993***, *4*, 657; Perdih, M.; Razinger, M. *Tetrahedron Asymmetry* ***1994***, *5*, 835.

[102]For a monograph, see Kagan, H.B. *Determination of Configuration by Chemical Methods* (Vol. 3 of Kagan, H.B. *Stereochemistry*), Georg Thieme Publishers: Stuttgart, ***1977***. For reviews, see Brewster, J.H., in Bentley, K.W.; Kirby, G.W. *Elucidation of Organic Structures by Physical and Chemical Methods*, 2nd ed. (Vol. 4 of Weissberger, A. *Techniques of Chemistry*), pt. 3, Wiley, NY, ***1972***, pp. 1–249; Klyne, W.; Scopes, P.M. *Prog. Stereochem.* ***1969***, *4*, 97; Schlenk Jr., W. *Angew. Chem. Int. Ed.* ***1965***, *4*, 139. For a review of absolute configuration of molecules in the crystalline state, see Addadi, L.; Berkovitch-Yellin, Z.; Weissbuch, I.; Lahav, M.; Leiserowitz, L. *Top. Stereochem.* ***1986***, *16*, 1.

[103]Except the X-ray method of Bijvoet.

center was not disturbed, the unknown obviously has the same configuration as the known. This does not necessarily mean that if the known is (*R*), the unknown is also (*R*). This will be so if the sequence is not disturbed, but not otherwise. For example, when (*R*)-1-bromo-2-butanol is reduced to 2-butanol without disturbing the chiral center, the product is the (*S*) isomer, even although the configuration is unchanged, because CH_3CH_2 ranks lower than $BrCH_2$, but higher than CH_3.

2. Conversion at the chiral center if the mechanism is known. Thus, the S_N2 mechanism proceeds with inversion of configuration at an asymmetric carbon (see p. 426) It was by a series of such transformations that lactic acid was related to alanine:



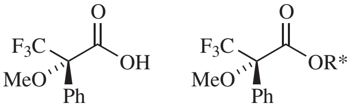
(*S*)-(+)-Lactic acid (*R*) (*S*) (*S*)-(+)-Alanine

See also, the discussion on p. 427.

3. Biochemical methods. In a series of similar compounds, such as amino acids or certain types of steroids, a given enzyme will usually attack only molecules with one kind of configuration. If the enzyme attacks only the L form of eight amino acids, say, then attack on the unknown ninth amino acid will also be on the L form.

4. Optical comparison. It is sometimes possible to use the sign and extent of rotation to determine which isomer has which configuration. In a homologous series, the rotation usually changes gradually and in one direction. If the configurations of enough members of the series are known, the configurations of the missing ones can be determined by extrapolation. Also certain groups contribute more or less fixed amounts to the rotation of the parent molecule, especially when the parent is a rigid system, such as a steroid.

5. The special X-ray method of Bijvoet gives direct answers and has been used in a number of cases.[86]

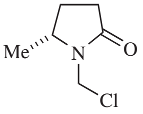


41 **42**

6. One of the most useful methods for determining enantiomeric composition is to derivatize the alcohol with a chiral nonracemic reagent and examine the ratio of resulting diastereomers by gas chromatography (gc).[104] There are many derivatizing agents available, but the most widely used are derivatives of α-methoxy-α-trifluoromethylphenyl acetic acid (MTPA, Mosher's acid,

[104]Parker, D. *Chem. Rev.* ***1991***, *91*, 1441.

41).[105] Reaction with a chiral nonracemic alcohol (R*OH, where R* is a group containing a stereogenic center) generates a Mosher's ester (**42**) that can be analyzed for diastereomeric composition by ^{1}H or ^{19}F NMR, as well as by chromatographic techniques.[106] Alternatively, complexation with lanthanide shift reagents allow the signals of the MTPA ester to be resolved and used to determine enantiomeric composition.[107] This nmr method, as well as other related methods,[108] are effective for determining the absolute configuration of an alcohol of interest (R*OH).[109] Two, of many other reagents that have been developed to allow the enantiopurity of alcohols and amines to be determined include **43** and **44**. Chloromethyl lactam **43** reacts with R*OH or R*NHR (R*NH_2),[110] forming derivatives that allow analysis by ^{1}H NMR and **44** reacts with alkoxides (R*O^-)[111] to form a derivative that can be analyzed by ^{31}P NMR. For a more detailed discussion of methods to determine optical purity (see p. 179).



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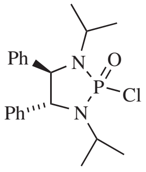


44

7. Other methods have also been used for determining absolute configuration in a variety of molecules, including optical rotatory dispersion,[112] circular dichroism,[113,114] and asymmetric synthesis (see p. 166). Optical rotatory dispersion (ORD) is a measurement of specific rotation, [α], as a function of wavelength.[115] The change of specific rotation [α] or molar rotation [Φ]

[105]Dale, J. A.; Dull, D.L.; Mosher, H. S. *J. Org. Chem.* ***1969***, 34, 2543; Dale, J.A.; Mosher, H.S. *J. Am. Chem. Soc.* ***1973***, *95*, 512.

[106]See Mori, K.; Akao, H. *Tetrahedron Lett.* ***1978***, 4127; Plummer, E.L.; Stewart, T.E.; Byrne, K.; Pearce, G.T.; Silverstein, R.M. *J. Chem. Ecol.* ***1976***, *2*, 307. See also Seco, J.M.; Quiñoá, E.; Riguera, R. *Tetrahedron Asymmetry* ***2000***, *11*, 2695.

[107]Yamaguchi, S.; Yasuhara, F.; Kabuto, K. *Tetrahedron* ***1976***, *32*, 1363; Yasuhara, F.; Yamaguchi, S. *Tetrahedron Lett.* ***1980***, *21*, 2827; Yamaguchi, S.; Yasuhara, F. *Tetrahedron Lett.* ***1977***, 89.

[108]Latypov, S.K.; Ferreiro, M.J.; Quiñoá, E.; Riguera, R. *J. Am. Chem. Soc.* ***1998***, *120*, 4741; Latypov, S.K.; Seco, J.M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* ***1995***, *60*, 1538.

[109]Seco, J.M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* ***2004***, *104*, 17.

[110]Smith, M.B.; Dembofsky, B.T.; Son, Y.C. *J. Org. Chem.* ***1994***, *59*, 1719; Latypov, S.K.; Riguera, R.; Smith, M.B.; Polivkova, J. *J. Org. Chem.* ***1998***, *63*, 8682.

[111]Alexakis, A.; Mutti, S.; Mangeney, P. *J. Org. Chem.* ***1992***, *57*, 1224.

[112]See Ref. 268 for books and reviews on optical rotatory dispersion and CD. For predictions about anomalous ORD, see Polavarapu, P.L.; Zhao, C. *J. Am. Chem. Soc.* ***1999***, *121*, 246.

[113]Gawroński, J.; Grajewski, J. *Org. Lett.* ***2003***, *5*, 3301. See Ref. 268.

[114]For a determination of the absolute configuration of chiral sulfoxides by vibrational circular dichroism spectroscopy, see Stephens, P.J.; Aamouche, A.; Devlin, F.J.; Superchi, S.; Donnoli, M.I.; Rosini, C. *J. Org. Chem.* ***2001***, *66*, 3671.

[115]Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley, NY, ***1994***, pp. 1203, 999–1003.

with wavelength is measured, and a plot of either versus wavelength is often related to the sense of chirality or the substance under consideration. In general, the absolute value of the rotation increases as the wavelength decreases. The plot of circular dichroism (CD) is the differential absorption of left and right circularly polarized radiation by a nonracemic sample, taking place only in spectral regions in which absorption bands are found in the isotropic or visible electronic spectrum.[116] The primary application of both ORD and CD is for the assignment of configuration or conformation.[117] Configurational and conformational analysis have been carried out using infrared and vibrational circular dichroism (VCD) spectroscopies.[118]

In one example of the use of these techniques, one of the more effective methods for derivatizing 1,2-diols is the method employing dimolybdenum tetraacetate [$Mo_2(AcO)_4$] developed by Snatzke and Frelek.[119] Exposure of the resulting complex to air leads, in most cases, to a significant induced CD spectrum (known as ICD). The method can be used for a variety of 1,2-diols.[120]

8. Kishi and co-worker's[121] developed an NMR database of various molecules in chiral solvents, for the assignment of relative and absolute stereochemistry without derivatization or degradation. Kishi referred to this database as a “universal NMR database.”[122] The diagram provided for diols **45** illustrates the method. The graph presents the difference in carbon chemical shifts between the average and the values for **45** (100 MHz) in DMBA (*N*,α-dimethylbenzylamine). Spectra were recorded in both enantiomers of the solvent, where the solid bar was recorded in (*R*)-DMBA and the shaded bar in (*S*)-DMBA. The *X*- and *Y*-axes represent carbon number and $\Delta\delta$ ($\delta_{\mathbf{45a\text{-}h}} - \delta_{ave}$ in ppm), respectively. The graphs are taken from “the ^{13}C NMR database in (*R*)- and (*S*)-DMBA as a deviation in chemical shift for each carbon of a given diastereomer from the average chemical shift of the carbon in question. Each diastereomer exhibits an almost identical NMR profile for (*R*)- and (*S*)-DMBA but shows an NMR profile distinct and differing from the other diastereomers, demonstrating that the database in (*R*)- and/or (*S*)-DMBA can

[116]Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley, NY, ***1994***, pp. 1195, 1003–1007.

[117]Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley, NY, ***1994***, pp. 1007–1071; Nakanishi, K.; Berova, N.; Woody, R.W. *Circular Dichroism: Principles and Applications*, VCH, NY, ***1994***; Purdie, N.; Brittain, H.G. *Analytical Applications of Circular Dichroism*, Elsevier, Amsterdam, The Netherlands, ***1994***.

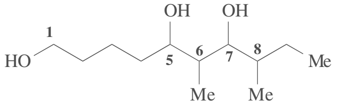
[118]Devlin, F.J.; Stephens, P.J.; Osterle, C.; Wiberg, K.B.; Cheeseman, J.R.; Frisch, M.J. *J. Org. Chem.* ***2002***, *67*, 8090.

[119]Frelek, J.; Geiger, M.; Voelter, W. *Curr. Org. Chem.* ***1999***, *3*, 117–146 and references cited therein.; Snatzke, G.; Wagner, U.; Wolff, H. P. *Tetrahedron* ***1981***, *37*, 349; Frelek, J.; Snatzke, G. *Fresenius̆ J. Anal. Chem.* ***1983***, *316*, 261; Frelek, J.; Pakulski, Z.; Zamojski, A. *Tetrahedron: Asymmetry* ***1996***, *7*, 1363; Frelek, J.; Ikekawa, N.; Takatsuto, S.; Snatzke, G. *Chirality* ***1997***, *9*, 578.

[120]Di Bari, L.; Pescitelli, G.; Pratelli, C.; Pini, D.; Salvadori, P. *J. Org. Chem.* ***2001***, *66*, 4819.

[121]Kobayashi, Y.; Hayashi, N.; Tan, C.-H.; Kishi, Y. *Org. Lett.* ***2001***, *3*, 2245; Hayashi, N.; Kobayashi, Y.; Kishi, Y. *Org. Lett.* ***2001***, *3*, 2249; Kobayashi, Y.; Hayashi, N.; Kishi, Y. *Org. Lett.* ***2001***, *3*, 2253.

[122]Kobayashi, Y.; Tan, C.-H.; Kishi, Y. *J. Am. Chem. Soc.* ***2001***, *123*, 2076.



45
(a) C5(*S*), C6(*R*), C7(*S*), C8(*R*)
(b) C5(*S*), C6(*R*), C7(*R*), C8(*S*)
(c) C5(*S*), C6(*R*), C7(*S*), C8(*S*)
(d) C5(*S*), C6(*R*), C7(*R*), C8(*R*)
(e) C5(*S*), C6(*S*), C7(*R*), C8(*S*)
(f) C5(*R*), C6(*S*), C7(*R*), C8(*S*)
(g) C5(*R*), C6(*S*), C7(*S*), C8(*S*)
(h) C5(*R*), C6(*S*), C7(*R*), C8(*R*)

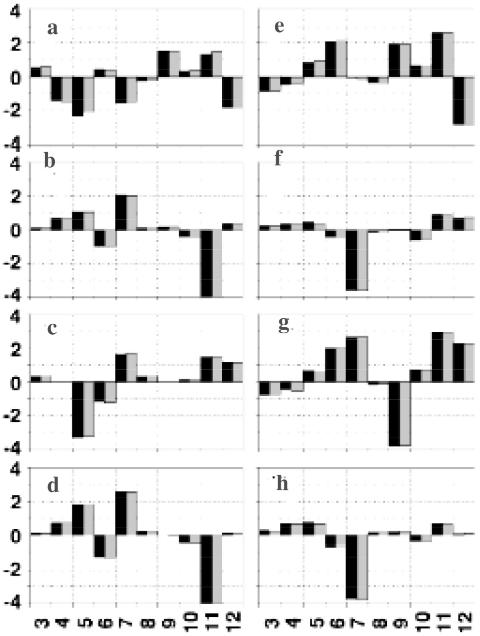


Fig. 4.3. Proton NMR analysis for assignment of stereochemistry.

be used for prediction of the relative stereochemistry of structural motifs in an intact form."[123]

A ^{1}H NMR analysis method has been developed that leads to the assignment of the stereochemistry of β-hydroxy ketones, by visual inspection of the ABX patterns for the (*R*)-methylene unit of the β-hydroxyketones.[124] Since β-hydroxy ketones are derived from the aldol reaction (see p. 1339), this new method is particularly useful in organic synthesis. A method has also been developed that uses ^{13}C NMR to determine the relative stereochemistry of 2,3-dialkylpentenoic acids.[125]

The Cause of Optical Activity

The question may be asked: Just why does a chiral molecule rotate the plane of polarized light? Theoretically, the answer to this question is known and in a greatly simplified form may be explained as follows.[126]

[123]Kobayashi, Y.; Hayashi, N.; Tan, C.-H.; Kishi, Y. *Org. Lett.* ***2001***, *3*, 2245.

[124]Roush, W.R.; Bannister, T.D.; Wendt, M.D.; VanNieuwenhze, M.S.; Gustin, D.J.; Dilley, G.J.; Lane, G.C.; Scheidt, K.A.; Smith III, W.J. *J. Org. Chem.* ***2002***, *67*, 4284.

[125]Hong, S.-p.; McIntosh, M.C. *Tetrahedron* ***2002***, *57*, 5055.

[126]For longer, nontheoretical discussions, see Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***, pp. 93–94, 992–999; Wheland, G.W. *Advanced Organic CHemistry*, 3rd ed., Wiley, NY, ***1960***, pp. 204–211. For theoretical discussions, see Caldwell, D.J.; Eyring, H. *The Theory of Optical Activity* Wiley, NY, ***1971***; Buckingham, A.D.; Stiles, P.J. *Acc. Chem. Res.* ***1974***, *7*, 258; Mason, S.F. *Q. Rev. Chem. Soc.* ***1963***, *17*, 20.

Whenever any light hits any molecule in a transparent material, the light is slowed because of interaction with the molecule. This phenomenon on a gross scale is responsible for the refraction of light and the decrease in velocity is proportional to the refractive index of the material. The extent of interaction depends on the polarizability of the molecule. Plane-polarized light may be regarded as being made up of two kinds of circularly polarized light. Circularly polarized light has the appearance (or would have, if one could see the wave) of a helix propagating around the axis of light motion, and one kind is a left- and the other is a right-handed helix. As long as the plane-polarized light is passing through a symmetrical region, the two circularly polarized components travel at the same speed. However, a chiral molecule has a different polarizability depending on whether it is approached from the left or the right. One circularly polarized component approaches the molecule, so to speak, from the left and sees a different polarizability (hence on a gross scale, a different refractive index) than the other and is slowed to a different extent. This would seem to mean that the left- and right-handed circularly polarized components travel at different velocities, since each has been slowed to a different extent. However, it is not possible for two components of the same light to be traveling at different velocities. What actually takes place, therefore, is that the faster component "pulls" the other toward it, resulting in rotation of the plane. Empirical methods for the prediction of the sign and amount of rotation based on bond refractions and polarizabilities of groups in a molecule have been devised,[127] and have given fairly good results in many cases.

In liquids and gases, the molecules are randomly oriented. A molecule that is optically inactive because it has a plane of symmetry will very seldom be oriented so that the plane of the polarized light coincides with the plane of symmetry. When it is so oriented, that particular molecule does not rotate the plane, but all others not oriented in that manner do rotate the plane, even though the molecules are achiral. There is no net rotation because, even though the molecules are present in large numbers and randomly oriented, there will always be another molecule later on in the path of the light that is oriented exactly opposite and will rotate the plane back again. Even although nearly all molecules rotate the plane individually, the total rotation is zero. For chiral molecules, however (if there is no racemic mixture), no opposite orientation is present and there is a net rotation.

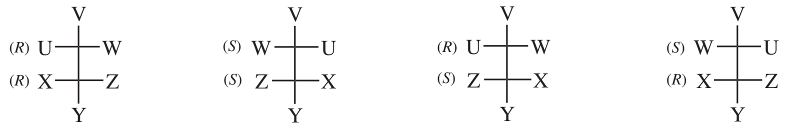
An interesting phenomenon was observed when the CD of chiral molecules was measured in achiral solvents. The chiral solvent contributed as much as 10–20% to the CD intensity in some cases. Apparently, the chiral compound can induce a solvation structure that is chiral, even when the solvent molecules themselves are achiral.[128]

[127]Brewster, J.H. *Top. Stereochem.* ***1967***, *2*, 1, *J. Am. Chem. Soc.* ***1959***, *81*, 5475, 5483, 5493; Davis, D.D.; Jensen, F.R. *J. Org. Chem.* ***1970***, *35*, 3410; Jullien, F.R.; Requin, F.; Stahl-Larivière, H. *Nouv. J. Chim.*, ***1979***, *3*, 91; Sathyanarayana, B.K.; Stevens, E.S. *J. Org. Chem.* ***1987***, *52*, 3170; Wroblewski, A.E.; Applequist, J.; Takaya, A.; Honzatko, R.; Kim, S.; Jacobson, R.A.; Reitsma, B.H.; Yeung, E.S.; Verkade, J.G. *J. Am. Chem. Soc.* ***1988***, *110*, 4144.

[128]Fidler, J.; Rodger, P.M.; Rodger, A. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 235.

MOLECULES WITH MORE THAN ONE STEREOGENIC CENTER

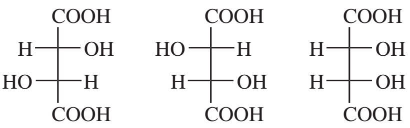
When a molecule has two stereogenic centers, each has its own configuration and can be classified (*R*) or (*S*) by the Cahn–Ingold–Prelog method. There are a total of four isomers, since the first center may be (*R*) or (*S*) and so may the second. Since a molecule can have only one mirror image, only one of the other three can be the enantiomer of **A**. This is **B** [the mirror image of an (*R*) center is *always* an (*S*) center]. Both **C** and **D** are a second pair of enantiomers and the relationship of **C** and **D**



A **B** **C** **D**

to **A** and **B** is designated by the term *diastereomer*. Diastereomers may be defined as *stereoisomers that are not enantiomers*. Since **C** and **D** are enantiomers, they must have identical properties, except as noted on p. 138; the same is true for **A** and **B**. However, the properties of **A** and **B** are not identical with those of **C** and **D**. They have different melting points, boiling points, solubilities, reactivity, and all other physical, chemical, and spectral properties. The properties are usually *similar*, but not *identical*. In particular, diastereomers have different specific rotations; indeed one diastereomer may be chiral and rotate the plane of polarized light while another may be achiral and not rotate at all (an example is presented below).

It is now possible to see why, as mentioned on p. 138, enantiomers react at different rates with other chiral molecules, but at the same rate with achiral molecules. In the latter case, the activated complex formed from the (*R*) enantiomer and the other molecule is the mirror image of the activated complex formed from the (*S*)



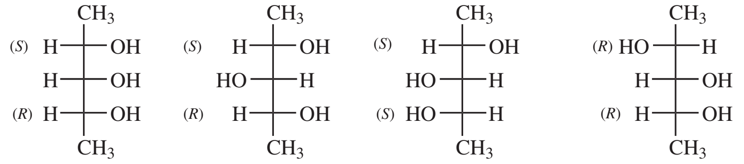
dl Pair meso

The three stereoisomers of tartaric acid

enantiomer and the other molecule. Since the two activated complexes are enantiomeric, their energies are the same and the rates of the reactions in which they are formed must be the same (see Chapter 6). However, when an (*R*) enantiomer reacts with a chiral molecule that has, say, the (*R*) configuration, the activated complex has two chiral centers with configurations (*R*) and (*R*), while the activated complex formed from the (*S*) enantiomer has the configurations (*S*) and (*R*). The two activated complexes are diastereomeric, do not have the same energies, and consequently are formed at different rates.

Although four is the maximum possible number of isomers when the compound has two stereogenic centers (chiral compounds without a chiral carbon, or with one chiral carbon and another type of stereogenic center, also follow the rules described

here), some compounds have fewer. When the three groups on one chiral atom are the same as those on the other, one of the isomers (called a *meso* form) has a plane of symmetry, and hence is optically inactive, even though it has two chiral carbons. Tartaric acid is a typical case. There are only three isomers of tartaric acid: a pair of enantiomers and an inactive meso form. For compounds that have two chiral atoms, meso forms are found only where the four groups on one of the chiral atoms are the same as those on the other chiral atom.



meso meso *dl* Pair

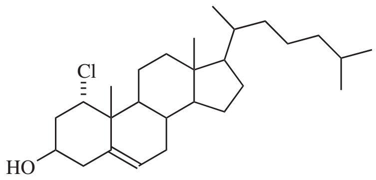
In most cases with more than two stereogenic centers, the number of isomers can be calculated from the formula 2^n, where n is the number of chiral centers, although in some cases the actual number is less than this, owing to meso forms.[129] An interesting case is that of 2,3,4-pentanetriol (or any similar molecule). The middle carbon is not asymmetric when the 2- and 4-carbons are both (*R*) (or both *S*), but is asymmetric when one of them is (*R*) and the other is (*S*). Such a carbon is called a *pseudoasymmetric* carbon. In these cases, there are four isomers: two meso forms and one *dl* pair. The student should satisfy themselves, remembering the rules governing the use of the Fischer projections, that these isomers are different, that the *meso* forms are superimposable on their mirror images, and that there are no other stereoisomers. Two diastereomers that have a different configuration at only one chiral center are called *epimers*.

In compounds with two or more chiral centers, the absolute configuration must be separately determined for each center. The usual procedure is to determine the configuration at one center by the methods discussed on pp. 158–162 and then to relate the configuration at that center to the others in the molecule. One method is X-ray crystallography, which, as previously noted, cannot be used to determine the absolute configuration at any stereogenic center, but which does give relative configurations of all the stereogenic centers in a molecule and hence the absolute configurations of all once the first is independently determined. Other physical and chemical methods have also been used for this purpose.

The problem arises how to name the different stereoisomers of a compound when there are more than two.[2] Enantiomers are virtually always called by the same name, being distinguished by (*R*) and (*S*) or D and L or (+) or (−). In the early days of organic chemistry, it was customary to give each pair of enantiomers a different name or at least a different prefix (such as *epi*-, *peri*-, etc.). Thus the aldohexoses are called glucose, mannose, idose, and so on, although they are all 2,3,4,5,6-pentahydroxyhexanal (in their open-chain forms). This practice was partially due to lack of knowledge

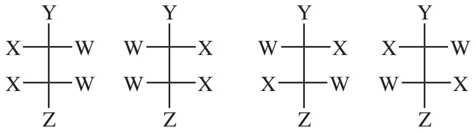
[129]For a method of generating all stereoisomers consistent with a given empirical formula, suitable for computer use, see Nourse, J.G.; Carhart, R.E.; Smith, D.H.; Djerassi, C. *J. Am. Chem. Soc.* ***1979***, *101*, 1216; ***1980***, *102*, 6289.

about which isomers had which configurations.[130] Today it is customary to describe *each chiral position* separately as either (*R*) or (*S*) or, in special fields, to use other symbols. Thus, in the case of steroids, groups above the "plane" of the ring system are designated β, and those below it α. Solid lines are often used to depict β groups and dashed lines for a groups. An example is



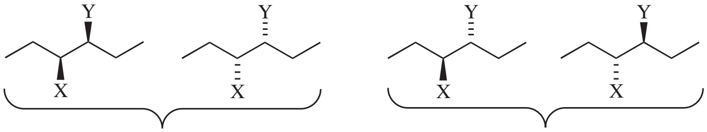
1α-Chloro-5-cholesten-3β-ol

For many open-chain compounds, prefixes are used that are derived from the names of the corresponding sugars and that describe the whole system rather than each chiral center separately. Two such common prefixes are erythro- and threo-, which are applied to systems containing two asymmetric carbons when two of the groups



Erythro *dl* pair   Threo *dl* pair

are the same and the third is different.[131] The erythro pair has the identical groups on the same side when drawn in the Fischer convention, and if Y were changed to Z, it would be meso. The threo pair has them on opposite sides, and if Y were changed to Z, it would still be a *dl* pair. Another system[132] for designating stereoisomers[133] uses the terms syn and anti. The "main chain" of the molecule is drawn in the common zigzag manner. Then, if two non-hydrogen substituents are on the same side of the plane defined by the main chain, the designation is syn; otherwise it is anti.



syn *dl* Pair   anti *dl* Pair

[130]A method has been developed for the determination of stereochemistry in six-membered chairlike rings using residual dipolar couplings. See Yan, J.; Kline, A. D.; Mo, H.; Shapiro, M. J.; Zartler, E. R. *J. Org. Chem.* ***2003***, *68*, 1786.

[131]For more general methods of designating diastereomers, see Carey, F.A.; Kuehne, M.E. *J. Org. Chem.* ***1982***, *47*, 3811; Boguslavskaya, L.S. *J. Org. Chem. USSR* ***1986***, *22*, 1412; Seebach, D.; Prelog, V. *Angew. Chem. Int. Ed.* ***1982***, *21*, 654; Brewster, J.H. *J. Org. Chem.* ***1986***, *51*, 4751. See also Tavernier, D. *J. Chem. Educ.* ***1986***, *63*, 511; Brook, M.A. *J. Chem. Educ.* ***1987***, *64*, 218.

[132]For still another system, see Seebach, D.; Prelog, V. *Angew. Chem. Int. Ed.* ***1982***, *21*, 654.

[133]Masamune, S.; Kaiho, T.; Garvey, D.S. *J. Am. Chem. Soc.* ***1982***, *104*, 5521.

Asymmetric Synthesis

Organic chemists often wish to synthesize a chiral compound in the form of a single enantiomer or diastereomer, rather than as a mixture of stereoisomers. There are two basic ways in which this can be done.[134] The first way, which is more common, is to begin with a single stereoisomer, and to use a synthesis that does not affect the stereogenic center (or centers), as in the glyceraldehyde–glyceric acid example on p. 154. The optically active starting compound can be obtained by a previous synthesis, or by resolution of a racemic mixture (p. 172), but it is often more convenient to obtain it from Nature, since many compounds, such as amino acids, sugars, and steroids, are present in Nature in the form of a single enantiomer or diastereomer. These compounds are regarded as a *chiral pool;* that is, readily available compounds that can be used as starting materials.[135]

The other basic method is called *asymmetric synthesis*,[136] or *stereoselective synthesis*. As mentioned earlier, optically active materials cannot be created from

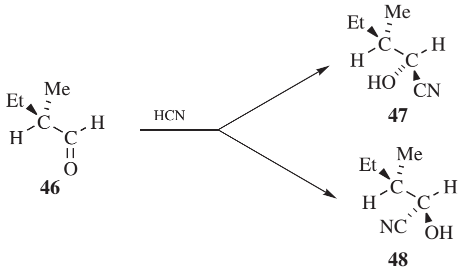
[134]For a monograph that covers both ways, including a list of commercially available optically active starting compounds, see Morrison, J.D.; Scott, J.W. *Asymmetric Synthesis* Vol. 4, Academic Press, NY, ***1984***. For a monograph covering a more limited area, see Williams, R.M. *Synthesis of Optically Active α-Amino Acids*, Pergamon, Elmsford, NY, ***1989***. For reviews on both ways, see Crosby, J. *Tetrahedron* ***1991***, *47*, 4789; Mori, K. *Tetrahedron* ***1989***, *45*, 3233.

[135]For books on the synthesis of optically active compounds starting from natural products, see Coppola, G.M.; Schuster, H.F. *Asymmetric Synthesis*, Wiley, NY, ***1987*** (amino acids as starting compounds); Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*, Pergamon, Elmsford, NY, ***1983*** (mostly carbohydrates as starting compounds). For reviews, see Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* ***1986***, *42*, 447; Hanessian, S. *Aldrichimica Acta* ***1989***, *22*, 3; Jurczak, J.; Gotebiowski, A. *Chem. Rev.* ***1989***, *89*, 149.

[136]For a treatise on this subject, see Morrison, J.D. *Asymmetric Synthesis* 5 vols. [Vol. 4 coedited by Scott, J.W.], Academic Press, NY, ***1983–1985***. For books, see Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, ***1986***; Eliel, E.L.; Otsuka, S. *Asymmetric Reactions and Processes in Chemistry*, American Chemical Society, Washington, ***1982***; Morrison, J.D.; Mosher, H.S. *Asymmetric Organic Reactions*, Prentice-Hall, Englewood Cliffs, NJ, ***1971***, paperback reprint, American Chemical Society, Washington, ***1976***; Izumi,Y.; Tai, A. *Stereo-Differentiating Reactions*, Academic Press, NY, Kodansha Ltd. Tokyo, ***1977***. For reviews, see Ward, R.S. *Chem. Soc. Rev.* ***1990***, *19*, 1; Whitesell, J.K. *Chem. Rev.* ***1989***, *89*, 1581; Fujita, E.; Nagao, Y. *Adv. Heterocycl. Chem.* ***1989***, *45*, 1; Kochetkov, K.A.; Belikov, V.M. *Russ. Chem. Rev.* ***1987***, *56*, 1045; Oppolzer, W. *Tetrahedron* ***1987***, *43*, 1969; Seebach, D.; Imwinkelried, R.; Weber, T. *Mod. Synth. Methods* ***1986***, *4*, 125; ApSimon, J.W.; Collier, T.L. *Tetrahedron* ***1986***, *42*, 5157; Mukaiyama, T.; Asami, M. *Top. Curr. Chem.* ***1985***, *127*, 133; Martens, J. *Top. Curr. Chem.* ***1984***, *125*, 165; Duhamel, L.; Duhamel, P.; Launay, J.; Plaquevent, J. *Bull. Soc. Chim. Fr.* ***1984***, II-421; Mosher, H.S.; Morrison, J.D. *Science*, ***1983***, *221*, 1013; Schöllkopf, U. *Top. Curr. Chem.* ***1983***, *109*, 65; Quinkert, G.; Stark, H. *Angew. Chem. Int. Ed.* ***1983***, *22*, 637; Tramontini, M. *Synthesis* ***1982***, 605; Drauz, K.; Kleeman, A.; Martens, J. *Angew. Chem. Int. Ed.* ***1982***, *21*, 584; Wynberg, H. *Recl. Trav. Chim. Pays-Bas* ***1981***, *100*, 393; Bartlett, P.A. *Tetrahedron* ***1980***, *36*, 2; Valentine, Jr., D.; Scott, J.W. *Synthesis* ***1978***, 329; Kagan, H.B.; Fiaud, J.C. *Top. Stereochem.* ***1978***, *10*, 175; ApSimon, J., in Bentley, K.W.; Kirby, G.W. *Elucidation of Organic Structures by Physical and Chemical Methods*, 2nd ed. (Vol. 4 of Weissberger, A. *Techniques of Chemistry*), pt. 3, Wiley, NY, ***1972***, pp. 251–408; Boyd, D.R.; McKervey, M.A. *Q. Rev. Chem. Soc*, ***1968***, *22*, 95; Goldberg, S.I. *Sel. Org. Transform.* ***1970***, *1*, 363; Klabunovskii, E.I.; Levitina, E.S. *Russ. Chem. Rev.* ***1970***, *39*, 1035; Inch, T.D. *Synthesis* ***1970***, 466; Mathieu, J.; Weill-Raynal, J. *Bull. Soc. Chim. Fr.* ***1968***, 1211; Amariglio, A.; Amariglio, H.; Duval, X. *Ann. Chim. (Paris) [14]* ***1968***, *3*, 5; Pracejus, H. *Fortschr. Chem. Forsch.* ***1967***, *8*, 493; Velluz, L.; Valls, J.; Mathieu, J. *Angew. Chem. Int. Ed.* ***1967***, *6*, 778.

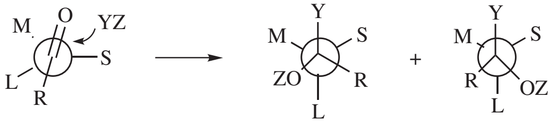
inactive starting materials and conditions, except in the manner previously noted.[94] However, when a new stereogenic center is created, the two possible configurations need not be formed in equal amounts if anything is present that is not symmetric. We discuss asymmetric synthesis under four headings:

1. *Active Substrate*. If a new chiral center is created in a molecule that is already optically active, the two diastereomers are not (except fortuitously) formed in equal amounts. The reason is that the direction of attack by the reagent is determined by the groups already there. For certain additions to the carbon–oxygen double bond of ketones containing an asymmetric α carbon, *Cram's rule* predicts which of two diastereomers will predominate (diastereoselectivity).[137,138] The reaction of **46**, which has a stereogenic center at the α-carbon, and HCN can generate two possible diastereomers,



46 **47** **48**

47 and **48**. If **46** is observed along its axis, it may be represented as in **49** (see p. 197), where S, M, and L stand for small, medium, and large, respectively. The oxygen of the carbonyl orients itself between the small- and the medium-sized groups. The rule is that the incoming group preferentially attacks on the side of the plane containing the small group. By this rule, it can be predicted that **48** will be formed in larger amounts than **47**.



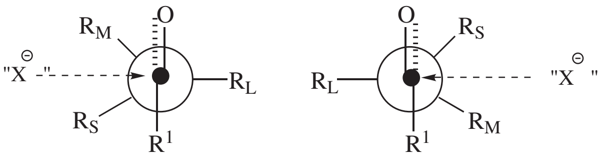
49 Major product Minor product

Another model can be used to predict diastereoselectivity, which assumes reactant-like transition states and that the separation of the incoming group

[137]Leitereg, T.J.; Cram, D.J. *J. Am. Chem. Soc.* ***1968***, *90*, 4019. For discussions, see Salem, L. *J. Am. Chem. Soc.* ***1973***, *95*, 94; Anh, N.T. *Top. Curr. Chem*, ***1980***, *88*, 145, 151–161; Eliel, E.L., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 2, Academic Press, NY, ***1983***, pp. 125–155. See Smith, R.J.; Trzoss, M.; Bühl, M.; Bienz, S. *Eur. J. Org. Chem.* ***2002***, 2770.

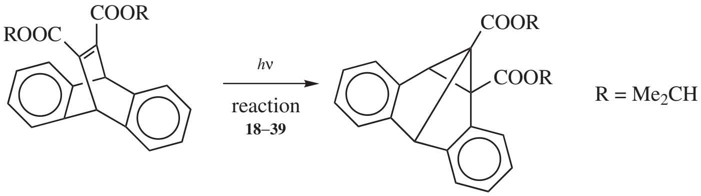
[138]For reviews, see Eliel, E.L. *The Stereochemistry of Carbon Compounds*, McGraw-Hill, NY, ***1962***, pp. 68–74. For reviews of the stereochemistry of addition to carbonyl compounds, see Bartlett, P.A. *Tetrahedron* ***1980***, *36*, 2, pp. 22–28; Ashby, E.C.; Laemmle, J.T. *Chem. Rev.* ***1975***, *75*, 521; Goller, E.J. *J. Chem. Educ.* ***1974***, *51*, 182; Toromanoff, E. *Top. Stereochem.* ***1967***, *2*, 157.

and any electronegative substituent at the α-carbon is greatest. Transition state models **50** and **51** are used to predict diastereoselectivity in what is known as the *Felkin–Ahn Model*.[139] The so-called Cornforth model has also been presented as a model for carbonyl addition.[140]



50 **51**

Many reactions of this type are known, and in some the extent of favoritism approaches 100% (for an example see reaction **12-12**).[141] The farther away the reaction site is from the chiral center, the less influence the latter has and the more equal the amounts of diastereomers formed.



52 Not chiral **53** Optically active

In a special case of this type of asymmetric synthesis, a compound (**52**) with achiral molecules, but whose crystals are chiral, was converted by UV light to a single enantiomer of a chiral product (**53**).[142]

It is often possible to convert an achiral compound to a chiral compound by (*1*) addition of a chiral group; (*2*) running an asymmetric synthesis, and (*3*) cleavage of the original chiral group. An example is conversion of the achiral 2-pentanone to the chiral 4-methyl-3-heptanone, **55**.[143] In this case, >99% of the product was the (*S*) enantiomer. Compound **54** is called a *chiral auxiliary* because it is used to induce asymmetry and is then removed.

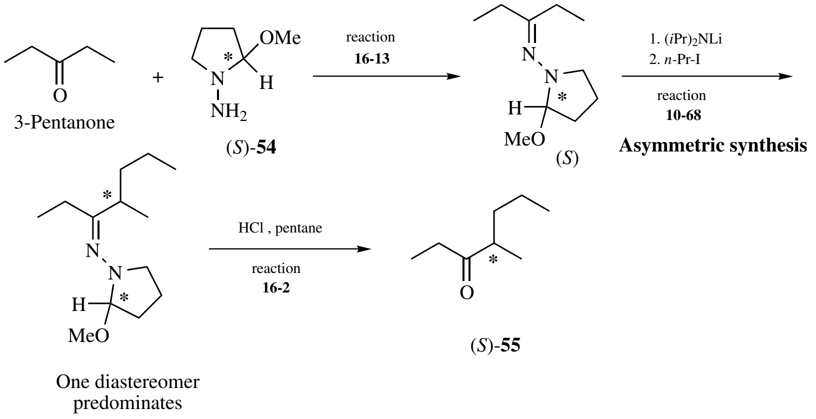
[139]Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* ***1968***, 2199.

[140]Evans, D.A.; Siska, S.J.; Cee, V.J. *Angew. Chem. Int. Ed.* ***2003***, *42*, 1761.

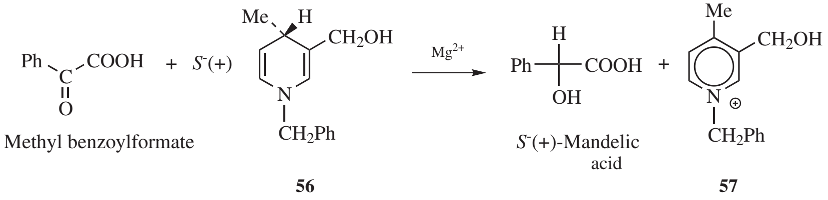
[141]For other examples and references to earlier work, see Eliel, E.L., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 2, Academic Press, NY, ***1983***, pp. 125–155; Eliel, E.L.; Koskimies, J.K.; Lohri, B. *J. Am. Chem. Soc.* ***1978***, *100*, 1614; Still, W.C.; McDonald, J.H. *Tetrahedron Lett.* ***1980***, *21*, 1031; Still, W.C.; Schneider, J.A. *Tetrahedron Lett.* ***1980***, *21*, 1035.

[142]Evans, S.V.; Garcia-Garibay, M.; Omkaram, N.; Scheffer, J.R.; Trotter, J.; Wireko, F. *J. Am. Chem. Soc.* ***1986***, *108*, 5648; Garcia-Garibay, M.; Scheffer, J.R.; Trotter, J.; Wireko, F. *Tetrahedron Lett.* ***1987***, *28*, 4789. For an earlier example, see Penzien, K.; Schmidt, G.M.J. *Angew. Chem. Int. Ed.* ***1969***, *8*, 608.

[143]Enders, D.; Eichenauer, H.; Baus, U.; Schubert, H.; Kremer, K.A.M. *Tetrahedron* ***1984***, *40*, 1345.



2. *Active Reagent.* A pair of enantiomers can be separated by an active reagent that reacts faster with one of them than it does with the other (this is also a method of resolution). If the absolute configuration of the reagent is known, the configuration of the enantiomers can often be determined by a knowledge of the mechanism and by seeing which diastereomer is preferentially



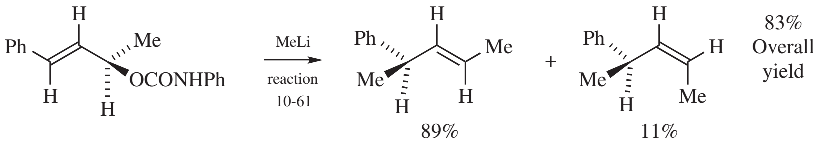
formed.[144] Creation of a new chiral center in an inactive molecule can also be accomplished with an active reagent, although it is rare for 100% selectivity to be observed. An example[145,146] is the reduction of methyl benzoylformate

[144]See, for example, Horeau, A. *Tetrahedron Lett.* ***1961***, 506; Marquet, A.; Horeau, A. *Bull. Soc. Chim. Fr.* ***1967***, 124; Brockmann Jr., H.; Risch, N. *Angew. Chem. Int. Ed.* ***1974***, *13*, 664; Potapov, V.M.; Gracheva, R.A.; Okulova, V.F. *J. Org. Chem. USSR* ***1989***, *25*, 311.

[145]Meyers, A.I.; Oppenlaender, T. *J. Am. Chem. Soc.* ***1986***, *108*, 1989. For reviews of asymmetric reduction, see Morrison, J.D. *Surv. Prog. Chem.* ***1966***, *3*, 147; Yamada, S.; Koga, K. *Sel. Org. Transform.* ***1970***, *1*, 1. See also, Morrison, J.D. *Asymmetric Synthesis*, Vol. 2, Academic Press, NY, ***1983***.

[146]For reviews, see, in Morrison, J.D. *Asymmetric Synthesis* Vol. 5, Academic Press, NY, ***1985***, the reviews by Halpern, J. pp. 41–69, Koenig, K.E. pp. 71–101, Harada, K. pp. 345–383; Ojima, I.; Clos, N.; Bastos, C. *Tetrahedron* ***1989***, *45*, 6901, pp. 6902–6916; Jardine, F.H. in Hartley, F.R. *The Chemistry of the Metal-Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 751–775; Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, ***1986***, pp. 53–87; Knowles, W.S. *Acc. Chem. Res.* ***1983***, *16*, 106; Brunner, H. *Angew. Chem. Int. Ed.* ***1983***, *22*, 897; Klabunovskii, E.I. *Russ. Chem. Rev.* ***1982***, *51*, 630; Čaplar, V.; Comisso, G.; Šunjić, V. *Synthesis* ***1981***, 85; Morrison, J.D.; Masler, W.F.; Neuberg, M.K. *Adv. Catal.* ***1976***, *25*, 81; Kagan, H.B. *Pure Appl. Chem.* ***1975***, *43*, 401; Bogdanović, B. *Angew. Chem. Int. Ed.* ***1973***, *12*, 954. See also Brewster, J.H. *Top. Stereochem.* ***1967***, *2*, 1, *J. Am. Chem. Soc.* ***1959***, *81*, 5475, 5483, 5493; Davis, D.D.; Jensen, F.R. *J. Org. Chem.* ***1970***, *35*, 3410; Jullien, F.R.; Requin, F.; Stahl-Larivière, H. *Nouv. J. Chim.* ***1979***, *3*, 91; Sathyanarayana, B.K.; Stevens, E.S. *J. Org. Chem.* ***1987***, *52*, 3170; Wroblewski, A.E.; Applequist, J.; Takaya, A.; Honzatko, R.; Kim, S.; Jacobson, R.A.; Reitsma, B.H.; Yeung, E.S.; Verkade, J.G. *J. Am. Chem. Soc.* ***1988***, *110*, 4144.

with optically active *N*-benzyl-3-(hydroxymethyl)-4-methyl-1,4-dihydropyridine (**56**) to produce mandelic acid that contained ~97.5% of the (*S*)-(+) isomer and 2.5% of the (*R*)-(−) isomer (for another example, see p. 1079). Note that the other product, **57**, is not chiral. Reactions like this, in which one reagent (in this case **56**) gives up its chirality to another, are called *self-immolative*. In this intramolecular example:



chirality is transferred from one atom to another in the same molecule.[147]

A reaction in which an inactive substrate is converted selectively to one of two enantiomers is called an *enantioselective* reaction, and the process is called *asymmetric induction*. These terms apply to reactions in this category and in categories 3 and 4.

When an optically active substrate reacts with an optically active reagent to form two new stereogenic centers, it is possible for both centers to be created in the desired sense. This type of process is called *double asymmetric synthesis*[148] (for an example, see p. 1349).

3. *Active Catalyst or Solvent.*[149] Many such examples are present in the literature, among them reduction of ketones and substituted alkenes to optically active (though not optically pure) secondary alcohols and substituted alkanes by treatment with hydrogen and a chiral homogeneous hydrogenation catalyst (reactions **16-23** and **15-11**),[150] the treatment of aldehydes or ketones with organometallic compounds in the presence of a chiral catalyst (see reaction **16-24**), and the conversion of alkenes to optically active epoxides by treatment with a hydroperoxide and a chiral catalyst (see reaction **15-50**). In some instances, notably in the homogeneous catalytic hydrogenation of alkenes (reaction **15-11**), the ratio of enantiomers prepared in this way is as high as 98:2.[151] Other examples of the use of a chiral catalyst or solvent are

[147]Goering, H.L.; Kantner, S.S.; Tseng, C.C. *J. Org. Chem.* ***1983***, *48*, 715.

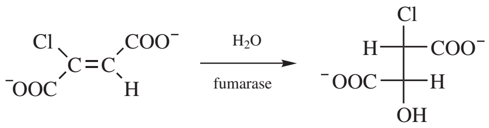
[148]For a review, see Masamune, S.; Choy, W.; Petersen, J.S.; Sita, L.R. *Angew. Chem. Int. Ed.* ***1985***, *24*, 1.

[149]For a monograph, see Morrison, J.D. *Asymmetric Synthesis*, Vol. 5, Academic Press, NY, ***1985***. For reviews, see Tomioka, K. *Synthesis* ***1990***, 541; Consiglio, G.; Waymouth, R.M. *Chem. Rev.* ***1989***, *89*, 257; Brunner, H., in Hartley, F.R. *The Chemistry of the Metal-Carbon Bond*, Vol. 5, Wiley, NY, ***1989***, pp. 109–146; Noyori, R.; Kitamura, M. *Mod. Synth. Methods* ***1989***, *5*, 115; Pfaltz, A. *Mod. Synth. Methods* ***1989***, *5*, 199; Kagan, H.B. *Bull. Soc. Chim. Fr.* ***1988***, 846; Brunner, H. *Synthesis* ***1988***, 645; Wynberg, H. *Top. Stereochem.* ***1986***, *16*, 87.

[150]For reviews of these and related topics, see Zief, M.; Crane, L.J. *Chromatographic Separations*, Marcel Dekker, NY, ***1988***; Brunner, H. *J. Organomet. Chem.* ***1986***, *300*, 39; Bosnich, B.; Fryzuk, M.D. *Top. Stereochem.* ***1981***, *12*, 119.

[151]See Vineyard, B.D.; Knowles, W.S.; Sabacky, M.J.; Bachman, G.L.; Weinkauff, D.J. *J. Am. Chem. Soc.* ***1977***, *99*, 5946; Fryzuk, M.D.; Bosnich, B. *J. Am. Chem. Soc.* ***1978***, *100*, 5491.

the conversion of chlorofumaric acid (in the form of its diion) to the (−)-*threo* isomer of the di-ion of chloromalic acid by treatment with H_2O and the enzyme fumarase,[152] and the preparation of optically active aldols (aldol condensation, see reaction **16-35**) by the condensation of enolate anions with optically active substrates.[153]



(−)-*threo* Isomer

4. *Reactions in the Presence of Circularly Polarized Light.*[154] If the light used to initiate a photochemical reaction (Chapter 7) of achiral reagents is circularly polarized, then, in theory, a chiral product richer in one enantiomer might be obtained. However, such experiments have not proved fruitful. In certain instances, the use of left and right circularly polarized light *has* given products with opposite rotations[155] (showing that the principle is valid), but up to now the extent of favoritism has always been $<1\%$.

Methods of Resolution[156]

A pair of enantiomers can be separated in several ways, of which conversion to diastereomers and separation of these by fractional crystallization is the most often used. In this method and in some of the others, both isomers can be recovered, but in some methods it is necessary to destroy one.

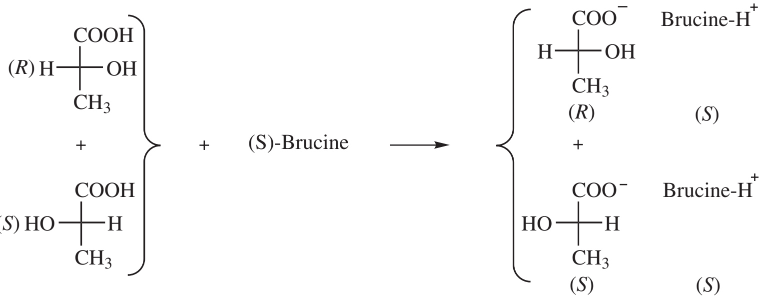
[152]Findeis, M.A.; Whitesides, G.M. *J. Org. Chem.* ***1987***, *52*, 2838. For a monograph on enzymes as chiral catalysts, see Réty, J.; Robinson, J.A. *Stereospecificity in Organic Chemistry and Enzymology*, Verlag Chemie: Deerfield Beach, FL, ***1982***. For reviews, see Klibanov, A.M. *Acc. Chem. Res.* ***1990***, *23*, 114; Jones, J.B., *Tetrahedron* ***1986***, *42*, 3351; Jones, J.B., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 5, Academic Press, NY, ***1985***, pp. 309–344; Svedas, V.; Galaev, I.U. *Russ. Chem. Rev.* ***1983***, *52*, 1184. See also, Simon, H.; Bader, J.; Günther, H.; Neumann, S.; Thanos, J. *Angew. Chem. Int. Ed.* ***1985***, *24*, 539.

[153]Heathcock, C.H.; White, C.T. *J. Am. Chem. Soc.* ***1979***, *101*, 7076.

[154]For a review, See Buchardt, O. *Angew. Chem. Int. Ed.* ***1974***, *13*, 179. For a discussion, see Barron L.D. *J. Am. Chem. Soc.* ***1986***, *108*, 5539.

[155]See, for example, Bernstein, W.J.; Calvin, M.; Buchardt, O. *J. Am. Chem. Soc.* ***1972***, *94*, 494; ***1973***, *95*, 527, *Tetrahedron Lett.* ***1972***, 2195; Nicoud, J.F.; Kagan, J.F. *Isr. J. Chem.* ***1977***, *15*, 78. See also Zandomeneghi, M.; Cavazza, M.; Pietra, F. *J. Am. Chem. Soc.* ***1984***, *106*, 7261.

[156]For a monograph, see Jacques, J.; Collet, A.; Wilen, S.H. *Enantiomers, Racemates, aand Resolutions*, Wiley, NY, ***1981***. For reviews, see Wilen, S.H.; Collet, A.; Jacques, J. *Tetrahedron* ***1977***, *33*, 2725; Wilen, S.H. *Top. Stereochem.* ***1971***, *6*, 107; Boyle, P.H. *Q. Rev. Chem. Soc.* ***1971***, *25*, 323; Buss, D.R.; Vermeulen, T. *Ind. Eng. Chem.* ***1968***, *60* (8), 12. Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***, pp. 297–424.



1. *Conversion to Diastereomers*. If the racemic mixture to be resolved contains a carboxyl group (and no strongly basic group), it is possible to form a salt with an optically active base. Since the base used is, say, the (*S*) form, there will be a mixture of two salts produced having the configurations (*SS*) and (*RS*). Although the acids are enantiomers, the salts are diastereomers and have different properties. The property most often used for separation is differential solubility. The mixture of diastereomeric salts is allowed to crystallize from a suitable solvent. Since the solubilities are different, the initial crystals formed will be richer in one diastereomer. Filtration at this point will already have achieved a partial resolution. Unfortunately, the difference in solubilities is rarely if ever great enough to effect total separation with one crystallization. Usually, fractional crystallizations must be used and the process is long and tedious. Fortunately, naturally occurring optically active bases (mostly alkaloids) are readily available. Among the most commonly used are brucine, ephedrine, strychnine, and morphine. Once the two diastereomers have been separated, it is easy to convert the salts back to the free acids and the recovered base can be used again.

Most resolution is done on carboxylic acids and often, when a molecule does not contain a carboxyl group, it is converted to a carboxylic acid before resolution is attempted. However, the principle of conversion to diastereomers is not confined to carboxylic acids, and other functional groups[157] may be coupled to an optically active reagent.[158] Racemic bases can be converted to diastereomeric salts with active acids. Alcohols[159] can be converted to diastereomeric esters, aldehydes to diastereomeric hydrazones, and so on. Amino alcohols have been resolved using boric acid and chiral

[157]For summaries of methods used to resolve particular types of compounds, see Boyle, P.H. *Q. Rev. Chem. Soc.* ***1971***, *25*, 323; Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***, pp. 322–424.

[158]For an extensive list of reagents that have been used for this purpose and of compounds resolved, see Wilen, S.H. *Tables of Resolving Agents and Optical Resolutions*, University of Notre Dame Press, Notre Dame, IN, ***1972***.

[159]For a review of resolution of alcohols, see Klyashchitskii, B.A.; Shvets, V.I. *Russ. Chem. Rev.* ***1972***, *41*, 592.

bipaphthols.[160] Phosphine oxides[161] and chiral calix[4]arenes[162] have been resolved. Chiral crown ethers have been used to separate mixtures of enantiomeric alkyl- and arylammonium ions, by the formation of diastereomeric complexes[163] (see also category 3, below). Even hydrocarbons can be converted to diastereomeric inclusion compounds,[164] with urea. Urea is not chiral, but the cage structure is.[165] Racemic unsaturated hydrocarbons have been resolved as inclusion complex crystals with a chiral host compound derived from tartaric acid.[166] *trans*-Cyclooctene (p. 150) was resolved by conversion to a platinum complex containing an optically active amine.[167]

Fractional crystallization has always been the most common method for the separation of diastereomers. When it can be used, binary phase diagrams for the diastereomeric salts have been used to calculate the efficiency of optical resolution.[168] However, it is tediousness and the fact that it is limited to solids prompted a search for other methods. Fractional distillation has given only limited separation, but GC[169] and preparative

[160]Periasamy, M.; Kumar, N. S.; Sivakumar, S.; Rao, V. D.; Ramanathan, C. R.; Venkatraman, L. *J. Org. Chem.* ***2001***, *66*, 3828.

[161]Andersen, N.G.; Ramsden, P.D.; Che, D.; Parvez, M.; Keay, B.A. *Org. Lett.* ***1999***, *1*, 2009; Andersen, N.G.; Ramsden, P.D.; Che, D.; Parvez, M.; Keay, B.A. *J. Org. Chem.* ***2001***, *66*, 7478.

[162]Caccamese, S.; Bottino, A.; Cunsolo, F.; Parlato, S.; Neri, P. *Tetrahedron Asymmetry* ***2000***, *11*, 3103.

[163]See, for example, Kyba, E.B.; Koga, K.; Sousa, L.R.; Siegel, M.G.; Cram, D.J. *J. Am. Chem. Soc.* ***1973***, *95*, 2692; Slingenfelter, D.S.; Helgeson, R.C.; Cram, D.J. *J. Org. Chem.* ***1981***, *46*, 393; Pearson, D.P.J.; Leigh, S.J.; Sutherland, I.O. *J. Chem. Soc. Perkin Trans. 1* ***1979***, 3113; Bussman, W.; Lehn, J.M.; Oesch, U.; Plumeré, P.; Simon, W. *Helv. Chim. Acta* ***1981***, *64*, 657; Davidson, R.B.; Bradshaw, J.S.; Jones, B.A.; Dalley, N.K.; Christensen, J.J.; Izatt, R.M.; Morin, F.G.; Grant, D.M. *J. Org. Chem.* ***1984***, *49*, 353. See also Toda, F.; Tanaka, K.; Omata, T.; Nakamura, K.; Ōshima, T. *J. Am. Chem. Soc.* ***1983***, *105*, 5151.

[164]For reviews of chiral inclusion compounds, including their use for resolution, see Prelog, V.; Kovaćević, M.; Egli, M. *Angew. Chem. Int. Ed.* ***1989***, *28*, 1147; Worsch, D.; Vögtle, F. *Top. Curr. Chem.* ***1987***, *140*, 21; Toda, F. *Top. Curr. Chem.* ***1987***, *140*, 43; Stoddart, J.F. *Top. Stereochem.* ***1987***, *17*, 207; Sirlin, C. *Bull. Soc. Chim. Fr.* ***1984***, II-5–40; Arad-Yellin, R.; Green, B.S.; Knossow, M.; Tsoucaris, G., in Atwood; Davies; MacNicol *Inclusion Compounds*, Vol. 3; Academic Press, NY, ***1984***, pp. 263–295; Stoddart, J.F. *Prog. Macrocyclic Chem.* ***1981***, *2*, 173; Cram, D.J.; Helgeson, R.C.; Sousa, L.R.; Timko, J.M.; Newcomb, M.; Moreau, P.; DeJong, F.; Gokel, G.W.; Hoffman, D.H.; Domeier, L.A.; Peacock, S.C.; Madan, K.; Kaplan, L. *Pure Appl. Chem.* ***1975***, *43*, 327.

[165]See Schlenk Jr., W. *Liebigs Ann. Chem.* ***1973***, 1145, 1156, 1179, 1195. Inclusion complexes of tri-*o*-thymotide can be used in a similar manner: see Arad-Yellin, R.; Green, B.S.; Knossow, M.; Tsoucaris, G. *J. Am. Chem. Soc.* ***1983***, *105*, 4561.

[166]Miyamoto, H.; Sakamoto, M.; Yoskioka, K.; Takaoka, R.; Toda, F. *Tetrahedron Asymmetry* ***2000***, *11*, 3045.

[167]Cope, A.C.; Ganellin, C.R.; Johnson, Jr., H.W.; Van Auken, T.V.; Winkler, H.J.S. *J. Am. Chem. Soc.* ***1963***, *85*, 3276. For a review, see Tsuji, J. *Adv. Org. Chem.* ***1969***, *6*, 109, see p. 220.

[168]Amos, R.D.; Handy, N.C.; Jones, P.G.; Kirby, A.J.; Parker, J.K.; Percy, J.M.; Su, M.D. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 549.

[169]See, for example, Casanova, J.; Corey, E.J. *Chem. Ind. (London)* ***1961***, 1664; Gil-Av, E.; Nurok, D. *Proc. Chem. Soc.* ***1962***, 146; Gault, Y.; Felkin, H. *Bull. Soc. Chim. Fr.* ***1965***, 742; Vitt, S.V.; Saporovskaya, M.B.; Gudkova, I.P.; Belikov, V.M. *Tetrahedron Lett.* ***1965***, 2575; Westley, J.W.; Halpern, B.; Karger, B.L. *Anal. Chem.* ***1968***, *40*, 2046; Kawa, H.; Yamaguchi, F.; Ishikawa, N.*Chem. Lett.* ***1982***, 745.

liquid chromatography[170] have proved more useful. In many cases, they have supplanted fractional crystallization, especially where the quantities to be resolved are small.[171]

2. *Differential Absorption*. When a racemic mixture is placed on a chromatographic column, if the column consists of chiral substances, then in principle the enantiomers should move along the column at different rates and should be separable without having to be converted to diastereomers.[171] This has been successfully accomplished with paper, column, thin-layer,[172] and gas and liquid chromatography.[173] For example, racemic mandelic acid has been almost completely resolved by column chromatography on starch.[174] Many workers have achieved separations with gas and liquid chromatography by the use of columns packed with chiral absorbents.[175] Columns packed with chiral materials are now commercially available and are capable of separating the enantiomers of certain types of compounds.[176]
3. *Chiral Recognition*. The use of chiral hosts to form diastereomeric inclusion compounds was mentioned above. But in some cases it is possible for a host to form an inclusion compound with one enantiomer of a racemic guest, but not the other. This is called *chiral recognition*. One enantiomer fits into the chiral host cavity, the other does not. More often, both diastereomers are formed, but one forms more rapidly than the other, so that if the guest is

[170]For example, See Pirkle, W.H.; Hauske, J.R. *J. Org. Chem.* ***1977***, *42*, 1839; Helmchen, G.; Nill, G. *Angew. Chem. Int. Ed.* ***1979***, *18*, 65; Meyers, A.I.; Slade, J.; Smith, R.K.; Mihelich, E.D.; Hershenson, F.M.; Liang, C.D. *J. Org. Chem.* ***1979***, *44*, 2247; Goldman, M.; Kustanovich, Z.; Weinstein, S.; Tishbee, A.; Gil-Av, E. *J. Am. Chem. Soc.* ***1982***, *104*, 1093.

[171]For monographs on the use of liquid chromatography to effect resolutions, see Lough, W.J. *Chiral Liquid Chromatography*; Blackie and Sons: London, ***1989***; Krstulović, A.M. *Chiral Separations by HPLC*; Ellis Horwood: Chichester, ***1989***; Zief, M.; Crane, L.J. *Chromatographic Separations*, Marcel Dekker, NY, ***1988***. For a review, see Karger, B.L. *Anal. Chem.* ***1967***, *39* (8), 24A.

[172]Weinstein, S. *Tetrahedron Lett.* ***1984***, *25*, 985.

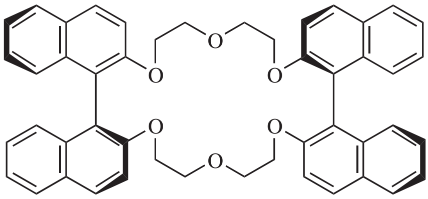
[173]For monographs, see Allenmark, S.G. *Chromatographic Enantioseparation*, Ellis Horwood, Chichester, ***1988***; König, W.A. *The Practice of Enantiomer Separation by Capillary Gas Chromatography*, Hüthig, Heidelberg, ***1987***. For reviews, see Schurig, V.; Nowotny, H. *Angew. Chem. Int. Ed.* ***1990***, *29*, 939; Pirkle, W.H.; Pochapsky, T.C. *Chem. Rev.* ***1989***, *89*, 347, *Adv. Chromatogr.*, ***1987***, *27*, 73; Okamoto, Y. *CHEMTECH* ***1987***, 176; Blaschke, G. *Angew. Chem. Int. Ed.* ***1980***, *19*, 13; Rogozhin, S.V.; Davankov, V.A. *Russ. Chem. Rev.* ***1968***, *37*, 565. See also many articles in the journal *Chirality*.

[174]Ohara, M.; Ohta, K.; Kwan, T. *Bull. Chem. Soc. Jpn.* ***1964***, *37*, 76. See also, Blaschke, G.; Donow, F. *Chem. Ber.* ***1975***, *108*, 2792; Hess, H.; Burger, G.; Musso, H. *Angew. Chem. Int. Ed.* ***1978***, *17*, 612.

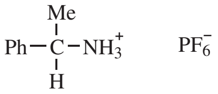
[175]See, for example, Gil-Av, E.; Tishbee, A.; Hare, P.E. *J. Am. Chem. Soc.* ***1980***, *102*, 5115; Hesse, G.; Hagel, R. *Liebigs Ann. Chem.* ***1976***, 996; Schlögl, K.; Widhalm, M. *Chem. Ber.* ***1982***, *115*, 3042; Koppenhoefer, B.; Allmendinger, H.; Nicholson, G. *Angew. Chem. Int. Ed.* ***1985***, *24*, 48; Dobashi, Y.; Hara, S. *J. Am. Chem. Soc.* ***1985***, *107*, 3406, *J. Org. Chem.* ***1987***, *52*, 2490; Konrad, G.; Musso, H. *Liebigs Ann. Chem.* ***1986***, 1956; Pirkle, W.H.; Pochapsky, T.C.; Mahler, G.S.; Corey, D.E.; Reno, D.S.; Alessi, D.M. *J. Org. Chem.* ***1986***, *51*, 4991; Okamoto, Y.; Aburatani, R.; Kaida, Y.; Hatada, K. *Chem. Lett.* ***1988***, 1125; Ehlers, J.; König, W.A.; Lutz, S.; Wenz, G.; tom Dieck, H. *Angew. Chem. Int. Ed.* ***1988***, *27*, 1556; Hyun, M.H.; Park, Y.; Baik, I. *Tetrahedron Lett.* ***1988***, *29*, 4735; Schurig, V.; Nowotny, H.; Schmalzing, D. *Angew. Chem. Int. Ed.* ***1989***, *28*, 736; Ôi, S.; Shijo, M.; Miyano, S. *Chem. Lett. 1990*, 59; Erlandsson, P.; Marle, I.; Hansson, L.; Isaksson, R.; Pettersson, C.; Pettersson, G. *J. Am. Chem. Soc.* ***1990***, *112*, 4573.

[176]See, for example, Pirkle, W.H.; Welch, C.J. *J. Org. Chem.* ***1984***, *49*, 138.

removed it is already partially resolved (this is a form of kinetic resolution, see category 6). An example is use of the chiral crown ether **58** partially to resolve the racemic amine salt **59**.[177] When an aqueous solution of **59** was



58



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mixed with a solution of optically active **58** in chloroform, and the layers separated, the chloroform layer contained about twice as much of the complex between **58** and (*R*)-**59** as of the diastereomeric complex. Many other chiral crown ethers and cryptands have been used, as have been cyclodextrins,[178] cholic acid,[179] and other kinds of hosts.[164] Of course, enzymes are generally very good at chiral recognition, and much of the work in this area has been an attempt to mimic the action of enzymes.

4. *Biochemical Processes*.[180] Biological molcules may react at different rates with the two enantiomers. For example, a certain bacterium may digest one enantiomer, but not the other. Pig liver esterase has been used for the selective cleavage of one enantiomeric ester.[181] This method is limited, since it is necessary to find the proper organism and since one of the enantiomers is destroyed in the process. However, when the proper organism is found, the method leads to a high extent of resolution since biological processes are usually very stereoselective.
5. *Mechanical Separation*.[182] This is the method by which Pasteur proved that racemic acid was actually a mixture of (+)- and (−)-tartaric acids.[183] In the case of racemic sodium ammonium tartrate, the enantiomers crystallize

[177]Cram, D.J.; Cram, J.M. *Science* ***1974***, *183*, 803. See also, Yamamoto, K.; Fukushima, H.; Okamoto, Y.; Hatada, K.; Nakazaki M. *J. Chem. Soc. Chem. Commun.* ***1984***, 1111; Kanoh, S.; Hongoh, Y.; Katoh, S.; Motoi, M.; Suda, H. *J. Chem. Soc. Chem. Commun.* ***1988***, 405; Bradshaw, J.S.; Huszthy, P.; McDaniel, C.W.; Zhu, C.Y.; Dalley, N.K.; Izatt, R.M.; Lifson, S. *J. Org. Chem.* ***1990***, *55*, 3129.

[178]See, for example, Hamilton, J.A.; Chen, L. *J. Am. Chem. Soc.* ***1988***, *110*, 5833.

[179]See Miyata, M.; Shibakana, M.; Takemoto, K. *J. Chem. Soc. Chem. Commun.* ***1988***, 655.

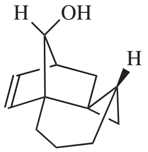
[180]For a review, see Sih, C.J.; Wu, S. *Top. Stereochem.* ***1989***, *19*, 63.

[181]For an example, see Gais, H.-J.; Jungen, M.; Jadhav, V. *J. Org. Chem.* ***2001***, *66*, 3384.

[182]For reviews, see Collet, A.; Brienne, M.; Jacques, J. *Chem. Rev.* ***1980***, *80*, 215; *Bull. Soc. Chim. Fr.* ***1972***, 127; ***1977***, 494. For a discussion, see Curtin, D.Y.; Paul, I.C. *Chem. Rev.* ***1981***, *81*, 525 pp. 535–536.

[183]Besides discovering this method of resolution, Pasteur also discovered the method of conversion to diastereomers and separation by fractional crystallization and the method of biochemical separation (and, by extension, kinetic resolution).

separately: all the (+) molecules going into one crystal and all the (−) into another. Since the crystals too are nonsuperimposable, their appearance is not identical and a trained crystallographer can separate them with tweezers.[184] However, this is seldom a practical method, since few compounds crystallize in this manner. Even sodium ammonium tartrate does so only when it is crystallized <27°C. A more useful variation of the method, although still not very common, is the seeding of a racemic solution with something that will cause only one enantiomer to crystallize.[185] An interesting example of the mechanical separation technique was reported in the isolation of heptahelicene (p. 150). One enantiomer of this compound, which incidentally has the extremely high rotation of $[\alpha]_D^{20} = +6200°$, spontaneously crystallizes from benzene.[186] In the case of 1,1′-binaphthyl, optically active crystals can be formed simply by heating polycrystalline racemic samples of the compound at 76–150°C. A phase change from one crystal form to another takes place.[187] Note that 1,1′-binaphthyl is one of the few compounds that can be resolved by the Pasteur tweezer method. In some cases resolution can be achieved by enantioselective crystallization in the presence of a chiral additive.[188]



60

Spontaneous resolution has also been achieved by sublimation. In the case of the norborneol derivative **60**, when the racemic solid is subjected to sublimation, the (+) molecules condense into one crystal and the (−)

[184]This is a case of optically active materials arising from inactive materials. However, it may be argued that an optically active investigator is required to use the tweezers. Perhaps a hypothetical human being constructed entirely of inactive molecules would be unable to tell the difference between left- and right-handed crystals.

[185]For a review of the seeding method, see Secor, R.M. *Chem. Rev.* ***1963***, *63*, 297.

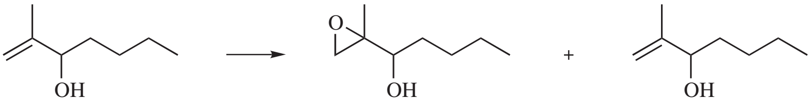
[186]Martin, R.H; Baes, M. *Tetrahedron* ***1975***, *31*, 2135. See also, Wynberg, H.; Groen, M.B. *J. Am. Chem. Soc.* ***1968***, *90*, 5339. For a discussion of other cases, see McBride, J.M.; Carter, R.L. *Angew. Chem. Int. Ed.* ***1991***, *30*, 293.

[187]Wilson, K.R.; Pincock, R.E. *J. Am. Chem. Soc.* ***1975***, *97*, 1474; Kress, R.B.; Duesler, E.N.; Etter, M.C.; Paul, I.C.; Curtin, D.Y. *J. Am. Chem. Soc.* ***1980***, *102*, 7709. See also, Lu, M.D.; Pincock, R.E. *J. Org. Chem.* ***1978***, *43*, 601; Gottarelli, G.; Spada, G.P. *J. Org. Chem.* ***1991***, *56*, 2096. For a discussion and other examples, see Agranat, I.; Perlmutter-Hayman, B.; Tapuhi, Y. *Nouv. J. Chem.* ***1978***, *2*, 183.

[188]Addadi, L.; Weinstein, S.; Gati, E.; Weissbuch, I.; Lahav, M. *J. Am. Chem. Soc.* ***1982***, *104*, 4610. See also, Weissbuch, I.; Addadi, L.; Berkovitch-Yellin, Z.; Gati, E.; Weinstein, S.; Lahav, M.; Leiserowitz, L. *J. Am. Chem. Soc.* ***1983***, *105*, 6615.

molecules into another.[189] In this case, the crystals are superimposable, unlike the situation with sodium ammonium tartrate, but the investigators were able to remove a single crystal, which proved optically active.

6. *Kinetic Resolution*.[190] Since enantiomers react with chiral compounds at different rates, it is sometimes possible to effect a partial separation by stopping the reaction before completion. This method is very similar to the asymmetric syntheses discussed on p. 147. A method has been developed to evaluate the enantiomeric ratio of kinetic resolution using only the extent of substrate conversion.[191] An important application of this method is the resolution of racemic alkenes by treatment with optically active diisopinocampheylborane,[192] since alkenes do not easily lend themselves to conversion to diastereomers if no other functional groups are present. Another example



is the resolution of allylic alcohols, such as **61** with one enantiomer of a chiral epoxidation agent (see **15-50**).[193] In the case of **61**, the discrimination was extreme. One enantiomer was converted to the epoxide and the other was not, the rate ratio (hence the selectivity factor) being >100. Of course, in this method only one of the enantiomers of the original racemic mixture is obtained, but there are at least two possible ways of getting the other: (*1*) use of the other enantiomer of the chiral reagent; (*2*) conversion of the product to the starting compound by a reaction that preserves the stereochemistry.

[189]Paquette, L.A.; Lau, C.J. *J. Org. Chem.* ***1987***, *52*, 1634.

[190]For reviews, see Kagan, H.B.; Fiaud, J.C. *Top. Stereochem.* ***1988***, *18*, 249; Ward, R.S. *Tetrahedron Asymmetry* ***1995***, *6*, 1475; Pellissier, H. *Tetrahedron* ***2003***, *59*, 8291.

[191]Lu, Y.; Zhao, X.; Chen, Z.-N. *Tetrahedron Asymmetry* ***1995***, *6*, 1093.

[192]Brown, H.C.; Ayyangar, N.R.; Zweifel, G. *J. Am. Chem. Soc.* ***1964***, *86*, 397.

[193]Martin, V.S.; Woodard, S.S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1981***, *103*, 6237. See also, Kobayashi, Y.; Kusakabe, M.; Kitano,Y.; Sato, F. *J. Org. Chem.* ***1988***, *53*, 1586; Kitano, Y.; Matsumoto, T.; Sato, F. *Tetrahedron* ***1988***, *44*, 4073; Carlier, P.R.; Mungall, W.S.; Schröder, G.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1988***, *110*, 2978; Discordia, R.P.; Dittmer, D.C. *J. Org. Chem.* ***1990***, *55*, 1414. For other examples, see Miyano, S.; Lu, L.D.; Viti, S.M.; Sharpless, K.B. *J. Org. Chem.* ***1985***, *50*, 4350; Paquette, L.A.; DeRussy, D.T.; Cottrell, C.E. *J. Am. Chem. Soc.* ***1988***, *110*, 890; Weidert, P.J.; Geyer, E.; Horner, L. *Liebigs Ann. Chem.* ***1989***, 533; Katamura, M.; Ohkuma, T.; Tokunaga, M.; Noyori, R. *Tetrahedron: Assymetry* ***1990***, *1*, 1; Hayashi, M.; Miwata, H.; Oguni, N. *J. Chem. Soc. Perkin Trans. 2* ***1991***, 1167.

Kinetic resolution of racemic allylic acetates[194] has been accomplished via asymmetric dihydroxylation (p. 1166), and 2-oxoimidazolidine-4-carboxylates have been developed as new chiral auxiliaries for the kinetic resolution of amines.[195] Reactions catalyzed by enzymes can be utilized for this kind of resolution.[196]

7. *Deracemization*. In this type of process, one enantiomer is converted to the other, so that a racemic mixture is converted to a pure enantiomer, or to a mixture enriched in one enantiomer. This is not quite the same as the methods of resolution previously mentioned, although an outside optically active substance is required. To effect the deracemization two conditions are necessary: (*1*) the enantiomers must complex differently with the optically active substance; (*2*) they must interconvert under the conditions of the experiment. When racemic thioesters were placed in solution with a specific optically active amide for 28 days, the solution contained 89% of one enantiomer and 11% of the other.[197] In this case, the presence of a base (Et_3N) was necessary for the interconversion to take place. Biocatalytic deracemization processes induce deracemization of chiral secondary alcohols.[198] In a specific example, *Sphingomonas paucimobilis* NCIMB 8195 catalyzes the efficient deracemization of many secondary alcohols in up to 90% yield of the (*R*)-alcohol.[199]

Optical Purity[200]

Suppose we have just attempted to resolve a racemic mixture by one of the methods described in the previous section. How do we know that the two enantiomers we have obtained are pure? For example, how do we know that the (+) isomer is not contaminated by, say, 20% of the (−) isomer and vice versa? If we knew the value of [α] for the pure material ($[\alpha]_{max}$), we could easily determine the purity of our sample by measuring its rotation. For example, if $[\alpha]_{max}$ is +80° and our (+) enantiomer contains 20% of the (−) isomer, [α] for the sample will be +48°.[201]

[194]Lohray, B.B.; Bhushan, V. *Tetrahedron Lett.* ***1993***, *34*, 3911.

[195]Kubota, H.; Kubo, A.; Nunami, K. *Tetrahedron Lett.* ***1994***, *35*, 3107.

[196]For example, see Nakamura, K.; Inoue, Y.; Ohno, A. *Tetrahedron Lett.* ***1994***, *35*, 4375; Mohr, P. Rösslein, L.; Tamm, C. *Tetrahedron Lett.* ***1989***, *30*, 2513; Kazlauskas, R.J. *J. Am. Chem. Soc.* ***1989***, *111*, 4953; Schwartz, A.; Madan, P.; Whitesell, J.K.; Lawrence, R.M. *Org. Synth.*, ***69***, 1; Francalanci, F.; Cesti, P.; Cabri, W.; Bianchi, D.; Martinengo, T.; Foá, M. *J. Org. Chem.* ***1987***, *52*, 5079.

[197]Pirkle, W.H.; Reno, D.S. *J. Am. Chem. Soc.* ***1987***, *109*, 7189. For another example, see Reider, P.J.; Davis, P.; Hughes, D.L.; Grabowski, E.J.J. *J. Org. Chem.* ***1987***, *52*, 955.

[198]Stecher, H.; Faber, K. *Synthesis* ***1997***, 1.

[199]Allan, G. R.; Carnell, A. J. *J. Org. Chem.* ***2001***, *66*, 6495.

[200]For a review, see Raban, M.; Mislow, K. *Top. Stereochem.* ***1967***, *2*, 199.

[201]If a sample contains 80% (+) and 20% (−) isomer, the (−) isomer cancels an equal amount of (+) isomer and the mixture behaves as if 60% of it were (+) and the other 40% inactive. Therefore the rotation is 60% of 80° or 48°. This type of calculation, however, is not valid for cases in which [α] is dependent on concentration (p. 139); see Horeau, A.*Tetrahedron Lett.* ***1969***, 3121.

We define *optical purity* as

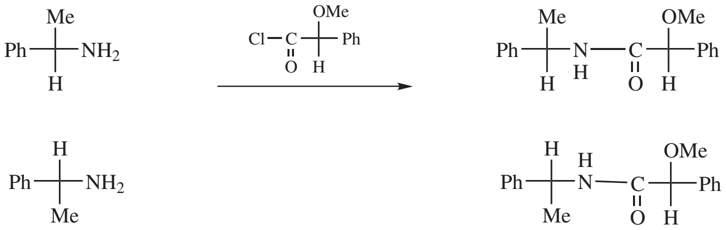
$$\text{Percent optical purity} = \frac{[\alpha]_{obs}}{[\alpha]_{max}} \times 100$$

Assuming a linear relationship between [α] and concentration, which is true for most cases, the optical purity is equal to the percent excess of one enantiomer over the other:

$$\text{Optical purity} = \text{percent enantiomeric excess} = \frac{[R] - [S]}{[R] + [S]} \times 100 = (\%R) - (\%S)$$

But how do we determine the value of $[\alpha]_{max}$? It is plain that we have two related problems here; namely, what are the optical purities of our two samples and what is the value of $[\alpha]_{max}$. If we solve one, the other is also solved. Several methods for solving these problems are known.

One of these methods involves the use of NMR[202] (see p. 161). Suppose we have a nonracemic mixture of two enantiomers and wish to know the proportions. We convert the mixture into a mixture of diastereomers with an optically pure reagent and look at the NMR spectrum of the resulting mixture, for example,



If we examined the NMR spectrum of the starting mixture, we would find only one peak (split into a doublet by the C—H) for the Me protons, since enantiomers give identical NMR spectra.[203] But the two amides are not enantiomers and each Me gives its own doublet. From the intensity of the two peaks, the relative proportions of the two diastereomers (and hence of the original enantiomers) can be determined. Alternatively, the "unsplit" OMe peaks could have been used. This method was satisfactorily used to determine the optical purity of a sample of 1-phenylethylamine (the case shown above),[204] as well as other cases, but it is obvious that

[202]Raban, M.; Mislow, K. *Tetrahedron Lett.* ***1965***, 4249, **1966**, 3961; Jacobus, J.; Raban, M. *J. Chem. Educ.* ***1969***, *46*, 351; Tokles, M.; Snyder, J.K. *Tetrahedron Lett.* ***1988***, *29*, 6063. For a review, see Yamaguchi, S., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, ***1983***, pp. 125–152. See also Raban, M.; Mislow, K. *Top. Stereochem.* ***1967***, *2*, 199.

[203]Though enantiomers give identical nmr spectra, the spectrum of a single enantiomer may be different from that of the racemic mixture, even in solution. See Williams, T.; Pitcher, R.G.; Bommer, P.; Gutzwiller, J.; Uskoković, M. *J. Am. Chem. Soc.* ***1969***, *91*, 1871.

[204]Raban, M.; Mislow, K. *Top. Stereochem.* ***1967***, *2*, 199, see pp. 216–218.

sometimes corresponding groups in diastereomeric molecules will give NMR signals that are too close together for resolution. In such cases, one may resort to the use of a different optically pure reagent. The ^{13}C NMR can be used in a similar manner.[205] It is also possible to use these spectra to determine the absolute configuration of the original enantiomers by comparing the spectra of the diastereomers with those of the original enantiomers.[206] From a series of experiments with related compounds of known configurations it can be determined in which direction one or more of the ^{1}H or ^{13}C NMR peaks are shifted by formation of the diastereomer. It is then assumed that the peaks of the enantiomers of unknown configuration will be shifted the same way.

A closely related method does not require conversion of enantiomers to diastereomers, but relies on the fact that (in principle, at least) enantiomers have different NMR spectra *in a chiral solvent*, or when mixed with a chiral molecule (in which case transient diastereomeric species may form). In such cases, the peaks may be separated enough to permit the proportions of enantiomers to be determined from their intensities.[207] Another variation, which gives better results in many cases, is to use an achiral solvent but with the addition of a *chiral lanthanide shift reagent* such as *tris*[3-trifluoroacetyl-*d*-camphorato]europium(III).[208] Lanthanide shift reagents have the property of spreading NMR peaks of compounds with which they can form coordination compounds, for example, alcohols, carbonyl compounds, and amines. Chiral lanthanide shift reagents shift the peaks of the two enantiomers of many such compounds to different extents.

Another method, involving GC,[209] is similar in principle to the NMR method. A mixture of enantiomers whose purity is to be determined is converted by means of an optically pure reagent into a mixture of two diastereomers. These diastereomers are then separated by GC (p. 172) and the ratios determined from the peak areas.

[205]For a method that relies on diastereomer formation without a chiral reagent, see Feringa, B.L.; Strijtveen, B.; Kellogg, R.M. *J. Org. Chem.* ***1986***, *51*, 5484. See also, Pasquier, M.L.; Marty, W. *Angew. Chem. Int. Ed.* ***1985***, *24*, 315; Luchinat, C.; Roelens, S. *J. Am. Chem. Soc.* ***1986***, *108*, 4873.

[206]See Dale, J.A.; Mosher, H.S. *J. Am. Chem. Soc.* ***1973***, *95*, 512; Rinaldi, P.L. *Prog. NMR Spectrosc.*, ***1982***, *15*, 291; Faghih, R.; Fontaine, C.; Horibe, I.; Imamura, P.M.; Lukacs, G.; Olesker, A.; Seo, S. *J. Org. Chem.* ***1985***, *50*, 4918; Trost, B.M.; Belletire, J.L.; Godleski, S.; McDougal, P.G.; Balkovec, J.M.; Baldwin, J.J.; Christy, M.E.; Ponticello, G.S.; Varga, S.L.; Springer, J.P. *J. Org. Chem.* ***1986***, *51*, 2370.

[207]For reviews of nmr chiral solvating agents, see Weisman, G.R., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, ***1983***, pp. 153–171; Pirkle, W.H.; Hoover, D.J. *Top. Stereochem.* ***1982***, *13*, 263. For literature references, see Sweeting, L.M.; Anet, F.A.L. *Org. Magn. Reson.* ***1984***, *22*, 539. See also, Pirkle, W.H.; Tsipouras, A. *Tetrahedron Lett.* ***1985***, *26*, 2989; Parker, D.; Taylor, R.J. *Tetrahedron* ***1987***, *43*, 5451.

[208]Sweeting, L.M.; Crans, D.C.; Whitesides, G.M. *J. Org. Chem.* ***1987***, *52*, 2273. For a monograph on chiral lanthanide shift reagents, see Morrill, T.C. *Lanthanide Shift Reagents in Stereochemical Analysis*, VCH, NY, ***1986***. For reviews, see Fraser, R.R., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, ***1983***, pp. 173–196; Sullivan, G.R. *Top. Stereochem.* ***1978***, *10*, 287.

[209]Charles, R.; Fischer, G.; Gil-Av, E. *Isr. J. Chem.* ***1963***, *1*, 234; Halpern, B.; Westley, J.W. *Chem. Commun.* ***1965***, 246; Vitt, S.V.; Saporovskaya, M.B.; Gudkova, I.P.; Belikov, V.M. *Tetrahedron Lett.* ***1965***, 2575; Guetté, J.; Horeau, A. *Tetrahedron Lett.* ***1965***, 3049; Westley, J.W.; Halpern, B. *J. Org. Chem.* ***1968***, *33*, 3978.

Once again, the ratio of diastereomers is the same as that of the original enantiomers. High-pressure liquid chromatography has been used in a similar manner and has wider applicability.[210] The direct separation of enantiomers by gas or liquid chromatography on a chiral column has also been used to determine optical purity.[211]

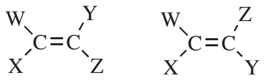
Other methods[212] involve isotopic dilution,[213] kinetic resolution,[214] ^{13}C NMR relaxation rates of diastereomeric complexes,[215] and circular polarization of luminescence.[216]

CIS–TRANS ISOMERISM

Compounds in which rotation is restricted may exhibit cis–trans isomerism.[217] These compounds do not rotate the plane of polarized light (unless they also happen to be chiral), and the properties of the isomers are not identical. The two most important types are isomerism resulting from double bonds and that resulting from rings.

Cis–Trans Isomerism Resulting from Double Bonds

It has been mentioned (p. 10) that the two carbon atoms of a C=C double bond and the four atoms directly attached to them are all in the same plane and that rotation around the double bond is prevented. This means that in the case of a molecule WXC=CYZ, stereoisomerism exists when W ≠ X and Y ≠ Z. There are two and



62 **63**

only two isomers (**62** and **63**), each superimposable on its mirror image unless one of the groups happens to carry a stereogenic center. Note that **62** and **63** are diastereomers, by the definition given on p. 155. There are two ways to name

[210]For a review, see Pirkle, W.H.; Finn, J., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, ***1983***, pp. 87–124.

[211]For reviews, see in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, ***1983***, the articles by Schurig, V. pp. 59–86 and Pirkle, W.H.; Finn, J. pp. 87–124.

[212]See also Leitich, J. *Tetrahedron Lett.* ***1978***, 3589; Hill, H.W.; Zens, A.P.; Jacobus, J. *J. Am. Chem. Soc.* ***1979***, *101*, 7090; Matsumoto, M.; Yajima, H.; Endo, R. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 4139.

[213]Berson, J.A.; Ben-Efraim, D.A. *J. Am. Chem. Soc.* ***1959***, *81*, 4083. For a review, see Andersen, K.K.; Gash, D.M.; Robertson, J.D. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, ***1983***, pp. 45–57.

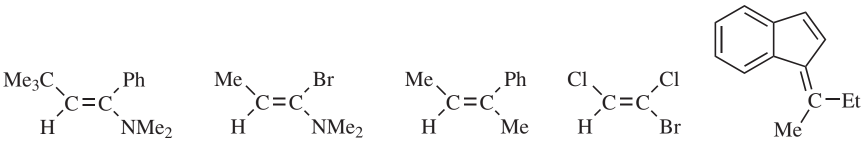
[214]Horeau, A.; Guetté, J.; Weidmann, R. *Bull. Soc. Chim. Fr.* ***1966***, 3513. For a review, see Schoofs, A.R.; Guetté, J., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, ***1983***, pp. 29–44.

[215]Hofer, E.; Keuper, R. *Tetrahedron Lett.* ***1984***, *25*, 5631.

[216]Eaton, S.S. *Chem. Phys. Lett.* ***1971***, *8*, 251; Schippers, P.H.; Dekkers, H.P.J.M. *Tetrahedron* ***1982***, *38*, 2089.

[217]Cis-trans isomerism was formerly called *geometrical isomerism.*

such isomers. In the older method, one isomer is called cis and the other trans. When W = Y, **62** is the cis and **63** the trans isomer. Unfortunately, there is no easy way to apply this method when the four groups are different. The newer method, which can be applied to all cases, is based on the Cahn–Ingold–Prelog system (p. 155). The two groups at each carbon are ranked by the sequence rules. Then that isomer with the two higher ranking groups on the same side of the double bond is called (*Z*) (for the German word *zusammen* meaning *together*); the other is (*E*) (for *entgegen* meaning *opposite*).[218] A few examples are shown. Note that the (*Z*) isomer is not necessarily the one that would be called cis under the older system (e.g., **64**, and **65**). Like *cis* and *trans*, (*E*) and (*Z*) are used as prefixes; for example, **65** is called (*E*)-1-bromo-1,2-dichloroethene.



(*E*) (*Z*) (*Z*) **64** (*E*) **65** (*E*)

This type of isomerism is also possible with other double bonds, such as C=N,[219] N=N, or even C=S,[220] although in these cases only two or three groups are connected to the double-bond atoms. In the case of imines, oximes, and other C=N compounds, if W = Y, **66** may be called syn and **67** anti, although (*E*) and (*Z*) are often used here too.[221] In azo compounds, there is no ambiguity. Compound **68** is always *syn* or (*Z*) regardless of the nature of W and Y.

(*Z*) (*E*)

66 **67** **68**

If there is more than one double bond[222] in a molecule and if W $\neq$ X and Y $\neq$ Z for each, the number of isomers in the most general case is 2^n, although this number may be decreased if some of the substituents are the same, as in

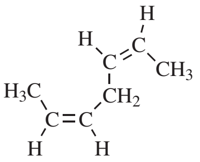
[218]For a complete description of the system, see *Pure Appl. Chem.* ***19767***, *45*, 13; *Nomenclature of Organic Chemistry*, Pergamon, Elmsford, NY, ***1979*** (the Blue Book).

[219]For reviews of isomerizations about C=N bonds, see, in Patai, S. *The Chemistry of the Carbon–Nitrogen Double Bond*; Wiley, NY, ***1970***, the articles by McCarty, C.G., 363–464 (pp. 364–408), and Wettermark, G. 565–596 (pp. 574–582).

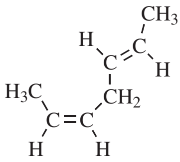
[220]King, J.F.; Durst, T. *Can. J. Chem.* ***1966***, *44*, 819.

[221]A mechanism has been reported for the acid-catalyzed (*Z/E*) isomerization of imines. See Johnson, J.E.; Morales, N.M.; Gorczyca, A.M.; Dolliver, D.D.; McAllister, M.A. *J. Org. Chem.* ***2001***, *66*, 7979.

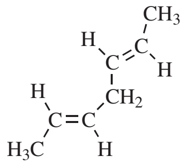
[222]This rule does not apply to allenes, which do not show cis–trans isomerism at all (see p. 148).



cis–cis or
(*Z*, *Z*)

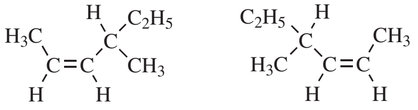


cis–trans or
(*Z*, *E*)

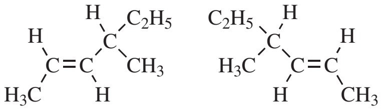


trans–trans or
(*E*, *E*)

When a molecule contains a double bond and an asymmetric carbon, there are four isomers, a cis pair of enantiomers and a trans pair:

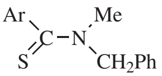


(*Z*) or cis *dl* pair



(*E*) or trans *dl* pair

Double bonds in small rings are so constrained that they must be cis. From cyclopropene (a known system) to cycloheptene, double bonds in a stable ring cannot be trans. However, the cyclooctene ring is large enough to permit trans double bonds to exist (see p. 151), and for rings larger than 10- or 11-membered, trans isomers are more stable[223] (see also, p. 225).



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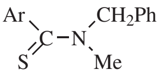

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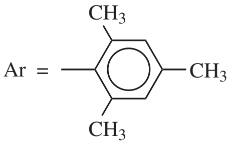
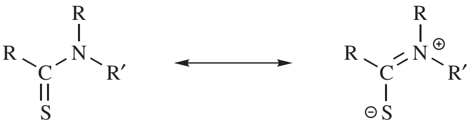


In a few cases, single-bond rotation is so slowed that cis and trans isomers can be isolated even where no double bond exists[224] (see also p. 230). One example is *N*-methyl-*N*-benzylthiomesitylide (**69** and **70**),[225] the isomers of which are stable in the crystalline state but interconvert with a half-life of ~25 h in $CDCl_3$ at 50°C.[226] This type of isomerism is rare; it is found chiefly in certain amides and thioamides, because resonance gives the single bond some double-bond character and slows rotation.[53] (For other examples of restricted rotation about single bonds, see pp. 230–233).



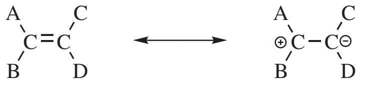
[223]Cope, A.C.; Moore, P.T.; Moore, W.R. *J. Am. Chem. Soc.* ***1959***, *81*, 3153.

[224]For a review, see Ōki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, ***1985***, pp. 41–71.

[225]Mannschreck, A. *Angew. Chem. Int. Ed.* ***1965***, *4*, 985. See also, Toldy, L.; Radics, L. *Tetrahedron Lett.* ***1966***, 4753; Völter, H.; Helmchen, G. *Tetrahedron Lett.* ***1978***, 1251; Walter, W.; Hühnerfuss, H. *Tetrahedron Lett.* ***1981***, *22*, 2147.

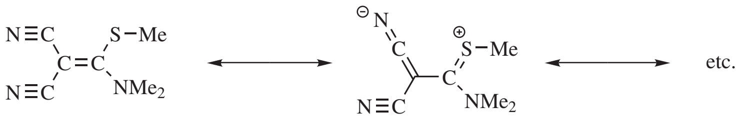
[226]This is another example of atropisomerism (p. 145).

Conversely, there are compounds in which nearly free rotation is possible around what are formally C=C double bonds. These compounds, called *push–pull* or *captodative* ethylenes, have two electron-withdrawing groups on one carbon and two electron-donating groups on the other (**71**).[227] The contribution of di-ionic



71 A, B = electron withdrawing
C, D = electron donating

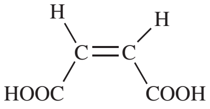
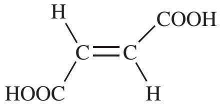
canonical forms, such as the one shown decreases the double-bond character and allows easier rotation. For example, compound **72** has a barrier to rotation of 13 kcal mol^{-1} (55 kJ mol^{-1}),[228] compared to a typical value of ~62–65 kcal mol^{-1} (260–270 kJ mol^{-1}) for simple alkenes.



72

Since they are diastereomers, cis–trans isomers always differ in properties; the differences may range from very slight to considerable. The properties of maleic acid are so different from those of fumaric acid (Table 4.2) that it is not surprising that they have different names. Since they generally have more symmetry than cis isomers, trans isomers in most cases have higher melting points and lower

TABLE 4.2. Some Properties of Maleic and Fumaric Acids

	 Maleic acid	 Fumaric acid
Property	Maleic Acid	Fumaric Acid
Melting point, °C	130	286
Solubility in water at 25°C, g L^{-1}	788	7
K_1 (at 25°C)	1.5×10^{-2}	1×10^{-3}
K_2 (at 25°C)	2.6×10^{-7}	3×10^{-5}

[227]For reviews, see Sandström, J. *Top. Stereochem.* ***1983***, *14*, 83; Ōki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, ***1985***, pp. 111–125.
[228]Sandström, J.; Wennerbeck, I. *Acta Chem. Scand. Ser. B*, ***1978***, *32*, 421.

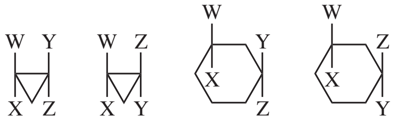
solubilities in inert solvents. The *cis* isomer usually has a higher heat of combustion, which indicates a lower thermochemical stability. Other noticeably different properties are densities, acid strengths, boiling points, and various types of spectra, but the differences are too involved to be discussed here.

It is also important to note that *trans*-alkenes are often more stable than *cis*-alkenes due to diminished steric hindrance (p. 232), but this is not always the case. It is known, for example, that *cis*-1,2-difluoroethene is thermodynamically more stable than *trans*-1,2-difluoroethene. This appears to be due to delocalization of halogen lone-pair electrons and an antiperiplanar effect between vicinal antiperiplanar bonds.[229]

Cis–Trans Isomerism of Monocyclic Compounds

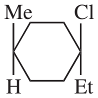
Although rings of four carbons and larger are not generally planar (see p. 211), they will be treated as such in this section, since the correct number of isomers can be determined when this is done[230] and the principles are easier to visualize (see p. 204).

The presence of a ring, like that of a double bond, prevents rotation. Cis and trans isomers are possible whenever there are two carbons on a ring, each of which is substituted by two different groups. The two carbons need not be adjacent. Examples are



In some cases, the two stereoisomers can interconvert. In *cis*- and *trans*-disubstituted cyclopropanones, for example, there is reversible interconversion that favors the more stable trans isomer. This fluxional isomerization occurs via ring opening to an unseen oxyallyl *valence bond* isomer.[231]

As with double bonds, cis and trans isomers are possible, but the restrictions are that W may equal Y and X may equal Z, but W may not equal X and Y may not equal Z. There is an important difference from the double-bond case: The



73

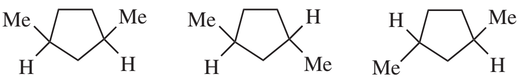
substituted carbons are sterogenic carbons. This means that there are not *only* two isomers. In the most general case, where W, X, Y, and Z are all different,

[229]Yamamoto, T.; Tomoda, S. *Chem. Lett.* ***1997***, 1069.

[230]For a discussion of why this is so, see Leonard, J.E.; Hammond, G.S.; Simmons, H.E. *J. Am. Chem. Soc.* ***1975***, *97*, 5052.

[231]Sorensen, T.S.; Sun, F. *J. Chem. Soc. Perkin Trans. 2* ***1998***, 1053.

there are four isomers since neither the cis nor the trans isomer is superimposable on its mirror image. This is true regardless of ring size or which carbons are involved, except that in rings of even-numbered size when W, X, Y, and Z are at opposite corners, no chirality is present, for example, **73**. In this case, the substituted carbons are *not* chiral carbons. Note also that a plane of symmetry exists in such compounds. When W = Y and X = Z, the cis isomer is always superimposable on its mirror image, and hence is a meso compound, while the trans isomer consists of a *dl* pair, except in the case noted above. Again, the cis isomer has a plane of symmetry while the trans does not.

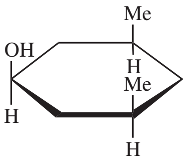


cis meso trans *dl* pair

Rings with more than two differently substituted carbons can be dealt with on similar principles. In some cases, it is not easy to tell the number of isomers by inspection.[105] The best method for the student is to count the number n of differently substituted carbons (these will usually be asymmetric, but not always, e.g., in **73**), and then to draw 2^n structures, crossing out those that can be superimposed on others (usually the easiest method is to look for a plane of symmetry). By this means, it can be determined that for 1,2,3-cyclohexanetriol there are two meso compounds and a *dl* pair; and for 1,2,3,4,5,6-hexachlorocyclohexane there are seven meso compounds and a *dl* pair. The drawing of these structures is left as an exercise for the student.

Similar principles apply to heterocyclic rings as long as there are carbons (or other ring atoms) containing two different groups.

Cyclic stereoisomers containing only two differently substituted carbons are named either cis or trans, as previously indicated. The (*Z*, *E*) system is not used for cyclic compounds. However, cis–trans nomenclature will not suffice for compounds with more than two differently substituted atoms. For these compounds, a system is used in which the configuration of each group is given with respect to a reference group, which is chosen as the group attached to the lowest numbered ring member bearing a substituent giving rise to cis–trans isomerism. The reference group is indicated by the symbol *r*. Three stereoisomers named according to this system are *c*-3,*c*-5-dimethylcyclohexan-*r*-1-ol (**74**), *t*-3,*t*-5-dimethylcyclohexan-*r*-1-ol (**75**), and *c*-3,*t*-5-dimethylcyclohexan-*r*-1-ol (**76**). The last example demonstrates the rule that when there are two otherwise equivalent ways of going around the ring, one chooses the path that gives the cis designation to the first substituent after the reference. Another example is *r*-2,*c*-4-dimethyl-*t*-6-ethyl-1,3-dioxane (**77**).



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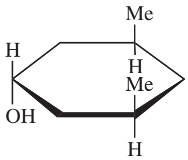

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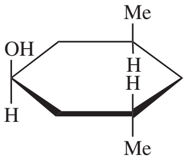

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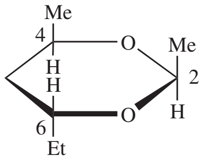
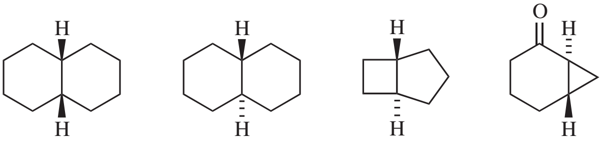


77

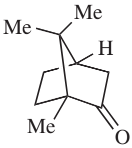
Cis–Trans Isomerism of Fused and Bridged Ring Systems

Fused bicyclic systems are those in which two rings share two and only two atoms. In such systems, there is no new principle. The fusion may be cis or trans, as illustrated by *cis*- and *trans*-decalin. However, when the rings are small enough, the trans configuration is impossible and the junction must be cis. The smallest trans junction that has been prepared when one ring is four membered is a four–five junction; *trans*-bicyclo[3.2.0]heptane (**78**) is known.[232] For the bicyclo[2.2.0] system



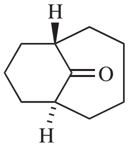
cis-Decalin *trans*-Decalin **78** **79**

(a four–four fusion), only cis compounds have been made. The smallest known trans junction when one ring is three-membered is a six–three junction (a bicyclo[4.1.0] system). An example is **79**.[233] When one ring is three membered and the other eight membered (an eight–three junction), the *trans*-fused isomer is more stable than the corresponding *cis*-fused isomer.[234]



Camphor

In *bridged* bicyclic ring systems, two rings share more than two atoms. In these cases, there may be fewer than 2^n isomers because of the structure of the system. For example, there are only two isomers of camphor (a pair of enantiomers), although it has two chiral carbons. In both isomers, the methyl and hydrogen are *cis*. The *trans* pair of enantiomers is impossible in this case, since the bridge *must*



80

be *cis*. The smallest bridged system so far prepared in which the bridge is trans is the [4.3.1] system; the trans ketone **80** has been prepared.[235] In this case there

[232]Meinwald, J.; Tufariello, J.J.; Hurst, J.J. *J. Org. Chem.* ***1964***, *29*, 2914.

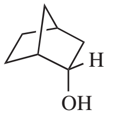
[233]Paukstelis, J.V.; Kao, J. *J. Am. Chem. Soc.* ***1972***, *94*, 4783. For references to other examples, see Dixon, D.A.; Gassman, P.G. *J. Am. Chem. Soc.* ***1988***, *110*, 2309.

[234]Corbally, R.P.; Perkins, M.J.; Carson, A.S.; Laye, P.G.; Steele, W.V. *J. Chem. Soc. Chem. Commun.* ***1978***, 778.

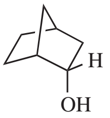
[235]Winkler, J.D.; Hey, J.P.; Williard, P.G. *Tetrahedron Lett.* ***1988***, *29*, 4691.

are four isomers, since both the *trans* and the *cis* (which has also been prepared) are pairs of enantiomers.

When one of the bridges contains a substituent, the question arises as to how to name the isomers involved. When the two bridges that do *not* contain the substituent are of unequal length, the rule generally followed is that the prefix endo- is used when the substituent is closer to the longer of the two unsubstituted bridges; the prefix exo- is used when the substituent is closer to the shorter bridge; for example,

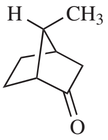


exo-2-Norborneol

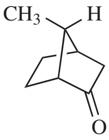


endo-2-Norborneol

When the two bridges not containing the substituent are of equal length, this convention cannot be applied, but in some cases a decision can still be made; for example, if one of the two bridges contains a functional group, the endo isomer is the one in which the substituent is closer to the functional group:



endo-7-Methyl-2-norcamphor



exo-7-Methyl-2-norcamphor

Out–In Isomerism

Another type of stereoisomerism, called *out–in* isomerism (or *in–out*),[236] is found in salts of tricyclic diamines with nitrogen at the bridgeheads. In medium-sized bicyclic ring systems, *in–out* isomerisim is possible,[237] and the bridgehead nitrogen atoms adopt whichever arangement is more stable.[238] If we focus attention on the nitrogne lone pairs, 1,4-diazabicyclo[2.2.2]octane (**81**) favors the *out–out* isomer, 1,6-diazabicyclo[4.4.4]tetradecane (**82**) the *in,in*,[239] 1,5-diazabicyclo[3.3.3]undecane (**83**) has nearly planar nitrogen atoms,[240] and 1,9-diazabicyclo[7.3.1]tridecane (**84**) is *in,out*.[241] One can also focus on the NH unit in the case of ammonium salts.

[236]See Alder, R. *Acc. Chem. Res.* ***1983***, *16*, 321.

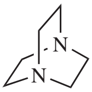
[237]Alder, R.W.; East, S.P. *Chem. Rev.* ***1996***, *96*, 2097.

[238]Alder, R.W. *Tetrahedron* ***1990***, *46*, 683.

[239]Alder, R.W.; Orpen, A.G.; Sessions, R.B. *J. Chem. Soc., Chem. Commun.* ***1983***, 999.

[240]Alder, R.W.; Goode, N.C.; King, T.J.; Mellor, J.M.; Miller, B.W. *J. Chem. Soc., Chem. Commun.* ***1976***, 173; Alder, R.W.; Arrowsmith, R.J.; Casson, A.; Sessions, R.B.; Heilbronner, E.; Kovac, B.; Huber, H.; Taagepera, M. *J. Am. Chem. Soc.* ***1981***, *103*, 6137.

[241]Alder, R.W.; Heilbronner, E.; Honegger, E.; McEwen, A.B.; Moss, R.E.; Olefirowicz, E.; Petillo, P.A.; Sessions, R.B.; Weisman, G.R.; White, J.M.; Yang, Z.-Z. *J. Am. Chem. Soc.* ***1993***, *115*, 6580.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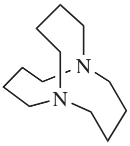
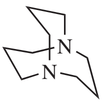

82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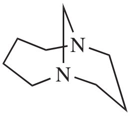
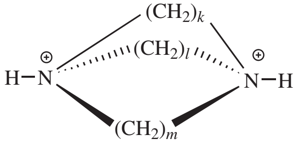

84

In the examples **85**–**87**, when *k*, *l*, and $m > 6$, the N—H bonds can be inside the molecular cavity or outside, giving rise to three isomers, as shown. Simmons and Park[242] isolated several such isomers with *k*, *l*, and *m* varying from 6 to 10. In the 9,9,9 compound, the cavity of the in-in isomer is large enough to encapsulate a

out–out isomer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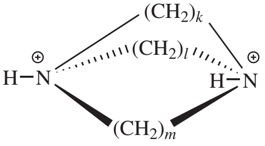
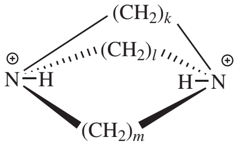
out–in isomer


86

in–in isomer


87

chloride ion that is hydrogen bonded to the two N—H groups. The species thus formed is a cryptate, but differs from the cryptates discussed at p. 119 in that there is a negative rather than a positive ion enclosed.[243] Even smaller ones (e.g., the 4,4,4 compound) have been shown to form mono-inside-protonated ions.[244] In compound **88**, which has four quaternary nitrogens, a halide ion has been encapsulated without a hydrogen being present on a nitrogen.[245] This ion does not display *in–out* isomerism. *Out–in* and *in–in* isomers have also been prepared in analogous all-carbon tricyclic systems.[246]

It is known that chiral phosphanes are more pyramidal and that inversion is more difficult, usually requiring temperatures well over 100°C for racemization.[247] Alder

[242]Simmons, H.E.; Park, C.H. *J. Am. Chem. Soc.* ***1968***, *90*, 2428; Park, C.H.; Simmons, H.E. *J. Am. Chem. Soc.* ***1968***, *90*, 2429, 2431; Simmons, H.E.; Park, C.H.; Uyeda, R.T.; Habibi, M.F. *Trans. N.Y. Acad. Sci.* ***1970***, *32*, 521. See also, Dietrich, B.; Lehn, J.M.; Sauvage, J.P. *Tetrahedron* ***1973***, *29*, 1647; Dietrich, B.; Lehn, J.M.; Sauvage, J.P.; Blanzat, J.*Tetrahedron* ***1973***, *29*, 1629.

[243]For reviews, see Schmidtchen, F.P.; Gleich, A.; Schummer, A. *Pure. Appl. Chem.* ***1989***, *61*, 1535; Pierre, J.; Baret, P. *Bull. Soc. Chim. Fr.* ***1983***, II-367. See also, Hosseini, M.W.; Lehn, J. *Helv. Chim. Acta* ***1988***, *71*, 749.

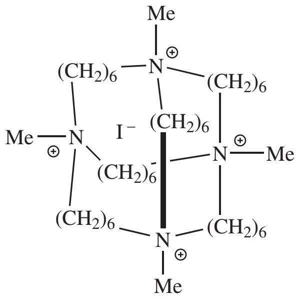
[244]Alder, R.W.; Moss, R.E.; Sessions, R.B. *J. Chem. Soc. Chem. Commun.* ***1983***, 997, 1000; Alder, R.W.; Orpen, A.G.; Sessions, R.B. *J. Chem. Soc. Chem. Commun.* ***1983***, 999; Dietrich, B.; Lehn, J.M.; Guilhem, J.; Pascard, C. *Tetrahedron Lett.* ***1989***, *30*, 4125; Wallon, A.; Peter-Katalinić, J.; Werner, U.; Müller, W.M.; Vögtle, F. *Chem. Ber.* ***1990***, *123*, 375.

[245]Schmidtchen, F.P.; Müller, G. *J. Chem. Soc. Chem. Commun.* ***1984***, 1115. See also, Schmidtchen, F.P. *J. Am. Chem. Soc.* ***1986***, *108*, 8249, *Top. Curr. Chem.* ***1986***, *132*, 101.

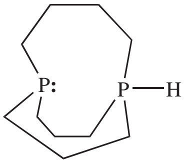
[246]Park, C.H.; Simmons, H.E. *J. Am. Chem. Soc.* ***1972***, *94*, 7184; Gassman, P.G.; Hoye, R.C. *J. Am. Chem. Soc.* ***1981***, *103*, 215; McMurry, J.E.; Hodge, C.N. *J. Am. Chem. Soc.* ***1984***, *106*, 6450; Winkler, J.D.; Hey, J.P.; Williard, P.G. *J. Am. Chem. Soc.* ***1986***, *108*, 6425.

[247]See Baechler, R.D.; Mislow, K. *J. Am. Chem. Soc.* ***1970***, *92*, 3090; Rauk, A.; Allen, L.C.; Mislow, K. *Angew. Chem. Int. Ed.* ***1970***, *9*, 400.

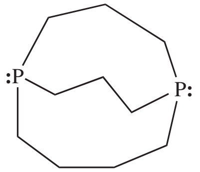
and Read found that deprotonation of bis(phosphorane) **89** (which is known to have an *in–out* structure with significant P—P bonding) leads to a rearrangement and the *out–out* diphosphane **90**.[248] Reprotonation gives **89**,[249] with inversion at the non-protonated phosphorus atom occurring at room temperature.



88



89



90

Enantiotopic and Diastereotopic Atoms, Groups, and Faces[250]

Many molecules contain atoms or groups that appear to be equivalent, but with a close inspection will show to be actually different. We can test whether two atoms are equivalent by replacing each of them in turn with some other atom or group. If the new molecules created by this process are identical, the original atoms are equivalent; otherwise they are not. We can distinguish three cases.

1. In the case of malonic acid $CH_2(COOH)_2$, propane CH_2Me_2, or any other molecule of the form CH_2Y_2,[251] if we replace either of the CH_2 hydrogens by a group Z, the identical compound results. The two hydrogens are thus equivalent. Equivalent atoms and groups need not, of course, be located on the same carbon atom. For example, all the chlorine atoms of hexachlorobenzene are equivalent as are the two bromine atoms of 1,3-dibromopropane.
2. In the case of ethanol CH_2MeOH, if we replace one of the CH_2 hydrogens by a group Z, we get one enantiomer of the compound ZCHMeOH (**91**), while replacement of the other hydrogen gives the *other* enantiomer (**92**). Since the

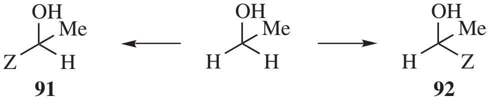
[248]Alder, R.W.; Read, D. *Angew. Chem. Int. Ed.* ***2000***, *39*, 2879.

[249]Alder, R.W.; Ellis, D.D.; Gleiter, R.; Harris, C.J.; Lange, H.; Orpen, A.G.; Read, D.; Taylor, P.N. *J. Chem. Soc., Perkin Trans. 1* ***1998***, 1657.

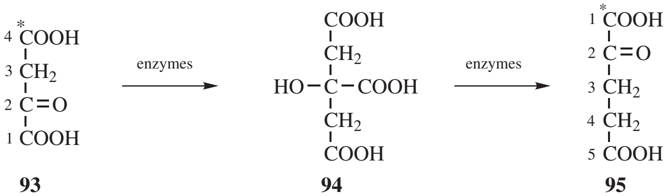
[250]These terms were coined by Mislow. For lengthy discussions of this subject, see Eliel, E.L. *Top. Curr. Chem.* ***1982***, *105*, 1, *J. Chem. Educ.* ***1980***, *57*, 52; Mislow, K.; Raban, M. *Top. Stereochem.* ***1967***, *1*, 1. See also, Ault, A. *J. Chem. Educ.* ***1974***, *51*, 729; Kaloustian, S.A.; Kaloustian, M.K. *J. Chem. Educ.* ***1975***, *52*, 56; Jennings, W.B. *Chem. Rev.* ***1975***, *75*, 307.

[251]In the case where Y is itself a chiral group, this statement is only true when the two Y groups have the same configuration.

two compounds that result upon replacement of H by Z (**91** and **92**) are not



identical but enantiomeric, the hydrogens are *not* equivalent. We define as *enantiotopic* two atoms or groups that upon replacement with a third group give enantiomers. In any symmetrical environment the two hydrogens behave as equivalent, but in a dissymmetrical environment they may behave differently. For example, in a reaction with a chiral reagent they may be attacked at different rates. This has its most important consequences in enzymatic reactions,[252] since enzymes are capable of much greater discrimination than ordinary chiral reagents. An example is found in the Krebs cycle, in biological organisms, where oxaloacetic acid (**93**) is converted to α-oxoglutaric



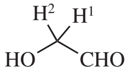
acid (**95**) by a sequence that includes citric acid (**94**) as an intermediate. When **93** is labeled with ^{14}C at the 4 position, the label is found only at C-1 of **95**, despite the fact that **94** is not chiral. The two CH_2COOH groups of **94** are enantiotopic and the enzyme easily discriminates between them.[253] Note that the X atoms or groups of any molecule of the form CX_2WY are always enantiotopic if neither W nor Y is chiral, although enantiotopic atoms and groups may also be found in other molecules, for example, the hydrogen atoms in 3-fluoro-3-chlorocyclopropene (**96**). In this case, substitution of an H by a group Z makes the C-3 atom asymmetric and substitution at C-1 gives the opposite enantiomer from substitution at C-2.

96

[252]For a review, see Benner, S.A.; Glasfeld, A.; Piccirilli, J.A. *Top. Stereochem.* ***1989***, *19*, 127. For a nonenzymatic example, see Job, R.C.; Bruice, T.C. *J. Am. Chem. Soc.* ***1974***, *96*, 809.

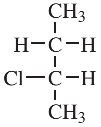
[253]The experiments were carried out by Evans, Jr., E.A.; Slotin, L. *J. Biol. Chem.* ***1941***, *141*, 439; Wood, H.G.; Werkman, C.H.; Hemingway, A.; Nier, A.O. *J. Biol. Chem.* ***1942***, *142*, 31. The correct interpretation was given by Ogston, A.G. *Nature (London)* ***1948***, *162*, 963. For discussion, see Hirschmann, H., in Florkin, M.; Stotz, E.H. *Comprehensive Biochemistry*, Vol. 12, pp. 236–260, Elsevier, NY, ***1964***; Cornforth, J.W. *Tetrahedron* ***1974***, *30*, 1515; Vennesland, B. *Top. Curr. Chem.* ***1974***, *48*, 39; Eliel, E.L. *Top. Curr. Chem.*, ***1982***, *105*, 1, pp. 5–7, 45–70.

The term *prochiral*[254] is used for a compound or group that has two enantiotopic atoms or groups, for example, CX_2WY. That atom or group X that would lead to an R compound if preferred to the other is called *pro*-(*R*). The other is *pro*-(*S*); for example,



H² = *pro*-(*S*)
H¹ = *pro*-(*R*)

3. Where two atoms or groups in a molecule are in such positions that replacing each of them in turn by a group Z gives rise to diastereomers, the atoms or groups are called *diastereotopic*. Some examples are the CH_2 groups of 2-chlorobutane (**97**), vinyl chloride (**98**), and chlorocyclopropane (**99**) and the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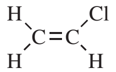
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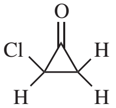
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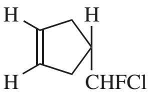
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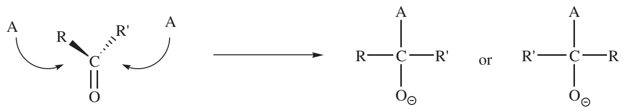
two alkenyl hydrogens of **100**. Diastereotopic atoms and groups are different in any environment, chiral or achiral. These hydrogens react at different rates with achiral reagents, but an even more important consequence is that in nmr spectra, diastereotopic hydrogens theoretically give different peaks and split each other. This is in sharp contrast to equivalent or enantiotopic hydrogens, which are indistinguishable in the NMR, except when chiral solvents are used, in which case enantiotopic (but not equivalent) protons give different peaks.[255] The term *isochronous* is used for hydrogens that are indistinguishable in the NMR.[256] In practice, the NMR signals from diastereotopic protons are often found to be indistinguishable, but this is merely because they are very close together. Theoretically they are distinct, and they have been resolved in many cases. When they appear together, it is sometimes possible to resolve them by the use of lanthanide shift reagents (p. 181) or by changing the solvent or concentration. Note that X atoms or groups CX_2WY are diastereotopic if either W or Y is chiral.

101

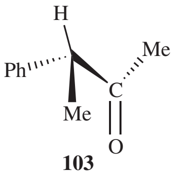

102

[254]Hirschmann, H.; Hanson, K.R. *Tetrahedron* ***1974***, *30*, 3649.

[255]Pirkle, W.H. *J. Am. Chem. Soc.* ***1966***, *88*, 1837; Burlingame, T.G.; Pirkle, W.H. *J. Am. Chem. Soc.* ***1966***, *88*, 4294; Pirkle, W.H.; Burlingame, T.G. *Tetrahedron Lett.* ***1967***, 4039.

[256]For a review of isochronous and nonisochronous nuclei in the nmr, see van Gorkom, M.; Hall, G.E. *Q. Rev. Chem. Soc.* ***1968***, *22*, 14. For a discussion, see Silverstein, R.M.; LaLonde, R.T. *J. Chem. Educ.* ***1980***, *57*, 343.

Just as there are enantiotopic and diastereotopic atoms and groups, so we may distinguish *enantiotopic and diastereotopic faces* in trigonal molecules. Again, we have three cases: (*1*) In formaldehyde or acetone (**101**), attack by an achiral reagent A from either face of the molecule gives rise to the same transition state and product; the two faces are thus equivalent. (*2*) In butanone or acetaldehyde (**102**), attack by an achiral A at one face gives a transition state and product that are the enantiomers of those arising from attack at the other face. Such faces are enantiotopic. As we have already seen (p. 153), a



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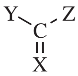
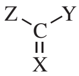
racemic mixture must result in this situation. However, attack at an enantiotopic face by a chiral reagent gives diastereomers, which are not formed in equal amounts. (*3*) In a case like **103**, the two faces are obviously not equivalent and are called diastereotopic. Enantiotopic and diastereotopic faces can be named by an extension of the Cahn–Ingold–Prelog system.[210] If the three groups as arranged by the sequence rules have the order X > Y > Z, that face in which the groups in this sequence are clockwise (as in **104**) is the *Re* face (from Latin *rectus*), whereas **105** shows the *Si* face (from Latin *sinister*).





104 **105**

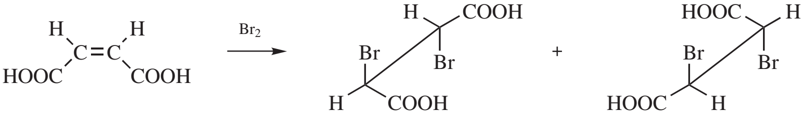
Note that new terminology has been proposed.[257] The concept of sphericity is used, and the terms homospheric, enantiospheric, and hemispheric have been coined to specify the nature of an orbit (an equivalent class) assigned to a coset representation.[258] Using these terms, prochirality can be defined: if a molecule has at least one enantiospheric orbit, the molecule is defined as being prochiral.[258]

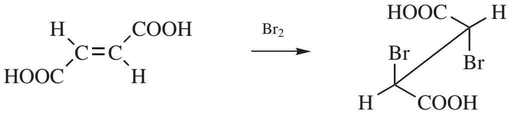
Stereospecific and Stereoselective Syntheses

Any reaction in which only one of a set of stereoisomers is formed exclusively or predominantly is called a *stereoselective* synthesis.[259] The same term is used when a mixture of two or more stereoisomers is exclusively or predominantly formed at

[257]Fujita, S. *J. Org. Chem.* ***2002***, *67*, 6055.
[258]Fujita, S. *J. Am. Chem. Soc.* ***1990***, *112*, 3390.
[259]For a further discussion of these terms and of stereoselective reactions in general, see Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***, pp. 835–990.

the expense of other stereoisomers. In a *stereospecific* reaction, a given isomer leads to one product while another stereoisomer leads to the opposite product. All stereospecific reactions are necessarily stereoselective, but the converse is not true. These terms are best illustrated by examples. Thus, if maleic acid treated with bromine gives the *dl* pair of 2,3-dibromosuccinic acid while fumaric acid gives the meso isomer (this is the case), the reaction is stereospecific as well as stereoselective because two opposite isomers give two opposite isomers:





However, if both maleic and fumaric acid gave the *dl* pair or a mixture in which the *dl* pair predominated, the reaction would be stereoselective, but not stereospecific. If more or less equal amounts of *dl* and meso forms were produced in each case, the reaction would be nonstereoselective. A consequence of these definitions is that if a reaction is carried out on a compound that has no stereoisomers, it cannot be stereospecific, but at most stereoselective. For example, addition of bromine to methylacetylene could (and does) result in preferential formation of *trans*-1,2-dibromopropene, but this can be only a stereoselective, not a stereospecific reaction.

CONFORMATIONAL ANALYSIS

If two different 3D arrangements in space of the atoms in a molecule are interconvertible merely by free rotation about bonds, they are called *conformations*.[260] If they are not interconvertible, they are called *configurations*.[261] Configurations represent *isomers* that can be separated, as previously discussed in this chapter. Conformations represent *conformers*, which are rapidly interconvertible and thus

[260]For related discussions see Bonchev, D.; Rouvray, D.H. *Chemical Topology*, Gordon and Breach, Australia, ***1999***.

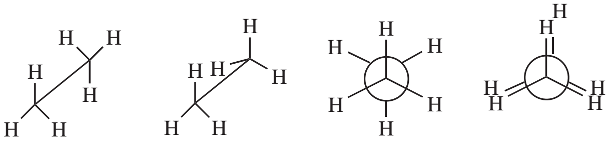
[261]For books on conformational analysis see Dale, J. *Stereochemistry and Conformational Analysis*; Verlag Chemie: Deerfield Beach, FL, ***1978***; Chiurdoglu, G. *Conformational Analysis*; Academic Press, NY, ***1971***; Eliel, E.L.; Allinger, N.L.; Angyal, S.J.; Morrison, G.A. *Conformational Analysis*; Wiley, NY, ***1965***; Hanack, M. *Conformation Theory*; Academic Press, NY, ***1965***. For reviews, see Dale, J. *Top. Stereochem.* ***1976***, *9*, 199; Truax, D.R.; Wieser, H. *Chem. Soc. Rev.* ***1976***, *5*, 411; Eliel, E.L. *J. Chem. Educ.* ***1975***, *52*, 762; Bastiansen, O.; Seip, H.M.; Boggs, J.E. *Perspect. Struct. Chem.* ***1971***, *4*, 60; Bushweller, C.H.; Gianni, M.H., in Patai, S. *The Chemistry of Functional Groups, Supplement E*; Wiley, NY, ***1980***, pp. 215–278.

nonseparable. The terms "conformational isomer" and "rotamer"[262] are sometimes used instead of "conformer." A number of methods have been used to determine conformations.[263] These include X-ray and electron diffraction, IR, Raman, UV, NMR,[264] and microwave spectra,[265] photoelectron spectroscopy,[266] supersonic molecular jet spectroscopy,[267] and optical rotatory dispersion and CD measurements.[268] Ring current NMR anisotropy has been applied to conformational analysis,[269] as has chemical shift simulation.[270] Some of these methods are useful only for solids. It must be kept in mind that the conformation of a molecule in the solid state is not necessarily the same as in solution.[271] Conformations can be *calculated* by a method called molecular mechanics (p. 213). A method was reported that characterized six-membered ring conformations as a linear combination of ideal basic conformations.[272] The term absolute conformation has been introduced for molecules for which one conformation is optically inactive but, by internal rotation about a C(sp^3)—C(sp^3) bond, optically active conformers are produced.[273]

[262]Ōki, M. *The Chemistry of Rotational Isomers*, Springer-Verlag, Berlin, ***1993***.
[263]For a review, see Eliel, E.L.; Allinger, N.L.; Angyal, S.J.; Morrison, G.A. *Conformational Analysis*, Wiley, NY, ***1965***, pp. 129–188.
[264]For monographs on the use of NMR to study conformational questions, see Ōki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, ***1985***; Marshall, J.L. *Carbon–Carbon and Carbon–Proton NMR Couplings*, VCH, NY, ***1983***. For reviews, see Anet, F.A.L.; Anet, R., in Nachod, F.C.; Zuckerman, J.J. *Determination of Organic Structures by Physical Methods*, Vol. 3, Academic Press, NY, ***1971***, pp. 343–420; Kessler, H. *Angew. Chem. Int. Ed.* ***1970***, *9*, 219; Ivanova, T.M.; Kugatova-Shemyakina, G.P. *Russ. Chem. Rev.* ***1970***, *39*, 510; Anderson, J.E. *Q. Rev. Chem. Soc.* ***1965***, *19*, 426; Franklin, N.C.; Feltkamp, H. *Angew. Chem. Int. Ed.* ***1965***, *4*, 774; Johnson, Jr., C.S. *Adv. Magn. Reson.* ***1965***, *1*, 33. See also, Whitesell, J.K.; Minton, M. *Stereochemical Analysis of Alicyclic Compounds by C-13 NMR Spectroscopy*, Chapman and Hall, NY, ***1987***.
[265]For a review see Wilson, E.B. *Chem. Soc. Rev.* ***1972***, *1*, 293.
[266]For a review, see Klessinger, M.; Rademacher, P. *Angew. Chem. Int. Ed.* ***1979***, *18*, 826.
[267]Breen, P.J.; Warren, J.A.; Bernstein, E.R.; Seeman, J.I. *J. Am. Chem. Soc.* ***1987***, *109*, 3453.
[268]For monographs, see Kagan, H.B. *Determination of Configurations by Dipole Moments, CD, or ORD* (Vol. 2 of Kagan, *Stereochemistry*), Georg Thieme Publishers, Stuttgart, ***1977***; Crabbé, P. *ORD and CD in Chemistry and Biochemistry*, Academic Press, NY, ***1972***, *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*, Holden-Day, San Francisco, ***1965***; Snatzke, G. *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*, Sadtler Research Laboratories, Philadelphia, ***1967***; Velluz, L.; Legrand, M.; Grosjean, M. *Optical Circular Dichroism*, Academic Press, NY, ***1965***. For reviews, see Smith, H.E. *Chem. Rev.* ***1983***, *83*, 359; Håkansson, R., in Patai, S. *The Chemistry of Acid Derivatives*, pt. 1, Wiley, NY, ***1979***, pp. 67–120; Hudec, J.; Kirk, D.N. *Tetrahedron* ***1976***, *32*, 2475; Schellman, J.A. *Chem. Rev.* ***1975***, *75*, 323; Velluz, L.; Legrand, M. *Bull. Soc. Chim. Fr.* ***1970***, 1785; Barrett, G.C., in Bentley, K.W.; Kirby, G.W. *Elucidation of Organic Structures by Physical and Chemical Methods*, 2nd ed. (Vol. 4 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, ***1972***, pp. 515–610; Snatzke, G. *Angew. Chem. Int. Ed.* ***1968***, *7*, 14; Crabbé, P., in Nachod, F.C.; Zuckerman, J.J. *Determination of Organic Structures by Physical Methods*, Vol. 3, Academic Press, NY, ***1971***, pp. 133–205; Crabbé, P.; Klyne, W. *Tetrahedron* ***1967***, *23*, 3449; Crabbé, P. *Top. Stereochem.* ***1967***, *1*, 93–198; Eyring, H.; Liu, H.; Caldwell, D. *Chem. Rev.* ***1968***, *68*, 525.
[269]Chen, J.; Cammers-Goodwin, A. *Eur. J. Org. Chem.* ***2003***, 3861.
[270]Iwamoto, H.; Yang, Y.; Usui, S.; Fukazawa, Y. *Tetrahedron Lett.* ***2001***, *42*, 49.
[271]See Kessler, H.; Zimmermann, G.; Förster, H.; Engel, J.; Oepen, G.; Sheldrick, W.S. *Angew. Chem. Int. Ed.* ***1981***, *20*, 1053.
[272]Bérces, A.; Whitfield, D.M.; Nukada, T. *Tetrahedron* ***2001***, *57*, 477.
[273]Ōki, M.; Toyota, S. *Eur. J. Org. Chem.* ***2004***, 255.

Conformation in Open-Chain Systems[274]

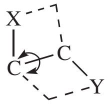
For any open-chain single bond that connects two sp^3 carbon atoms, an infinite number of conformations are possible, each of which has a certain energy associated with it. As a practical matter, the number of conformations is much less. If one ignores duplications due to symmetry, the number of conformations can be *estimated* as being greater than 3^n, where $n =$ the number of internal C—C bonds. *n*-Pentane, for example, has 11, *n*-hexane 35, *n*-heptane 109, *n*-octane 347, *n*-nonane 1101, and *n*-decane 3263.[275] For ethane there are two extremes, a conformation of highest and one of lowest potential energy, depicted in two ways as:



Staggered Eclipsed Staggered Eclipsed

In *Newman projection formulas* (the two figures on the right), the observer looks at the C—C bond head on. The three lines emanating from the center of the circle represent the bonds coming from the front carbon, with respect to the observer.

The staggered conformation is the conformation of lowest potential energy for ethane. As the bond rotates, the energy gradually increases until the eclipsed conformation is reached, when the energy is at a maximum. Further rotation decreases the energy again. Fig. 4.4 illustrates this. The *angle of torsion*, which is a dihedral angle, is the angle between the X—C—C and the C—C—Y planes, as shown:



For ethane, the difference in energy is ~2.9 kcal mol^{-1} (12 kJ mol^{-1}).[276] This difference is called the *energy barrier*, since in free rotation about a single bond there must be enough rotational energy present to cross the barrier every time two hydrogen atoms are opposite each other. There has been much speculation about the cause of the barriers and many explanations have been suggested.[277] It

[274]For a review, see Berg, U.; Sandström, J. *Adv. Phys. Org. Chem.* ***1989***, *25*, 1. Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***, pp. 597–664. Also see, Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY, ***2001***, pp. 32–37.

[275]Gotō, H.; Ō sawa, E.; Yamato, M. *Tetrahedron* ***1993***, *49*, 387.

[276]Lide, Jr., D.R. *J. Chem. Phys.* ***1958***, *29*, 1426; Weiss, S.; Leroi, G.E. *J. Chem. Phys.* ***1968***, *48*, 962; Hirota, E.; Saito, S.; Endo, Y. *J. Chem. Phys.* ***1979***, *71*, 1183.

[277]For a review of methods of measuring barriers, of attempts to explain barriers, and of values of barriers, see Lowe, J.P. *Prog. Phys. Org. Chem.* ***1968***, *6*, 1. For other reviews of this subject, see Oosterhoff, L.J. *Pure Appl. Chem.* ***1971***, *25*, 563; Wyn-Jones, E.; Pethrick, R.A. *Top. Stereochem.* ***1970***, *5*, 205; Pethrick, R.A.; Wyn-Jones, E. *Q. Rev. Chem. Soc.* ***1969***, *23*, 301; Brier, P.N. *J. Mol. Struct.* ***1970***, *6*, 23; Lowe, J.P. *Science* , ***1973***, *179*, 527.

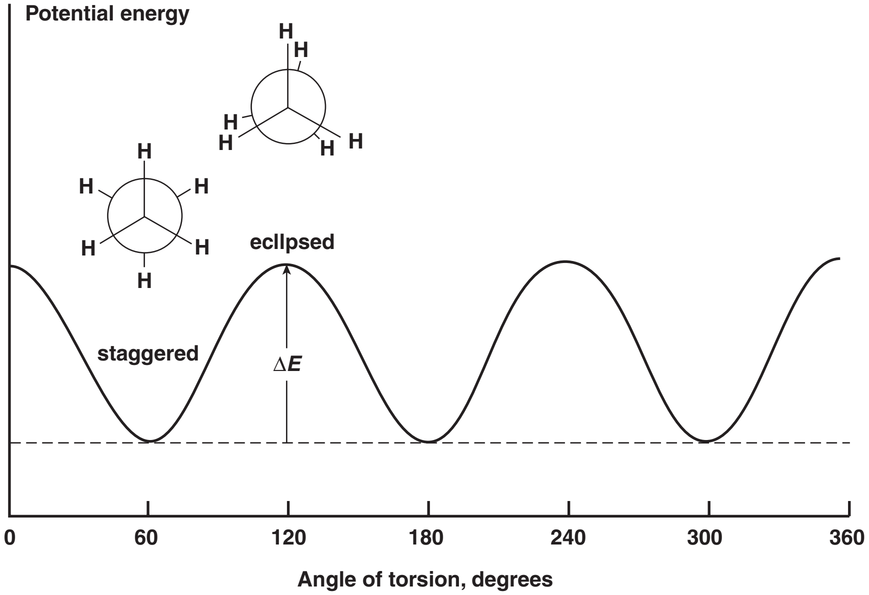


Fig. 4.4. Conformational energy diagram for ethane.

was concluded from molecular-orbital calculations that the barrier is caused by repulsion between overlapping filled molecular orbitals.[278] That is, the ethane molecule has its lowest energy in the staggered conformation because in this conformation the orbitals of the C—H bonds have the least amount of overlap with the C—H orbitals of the adjacent carbon.

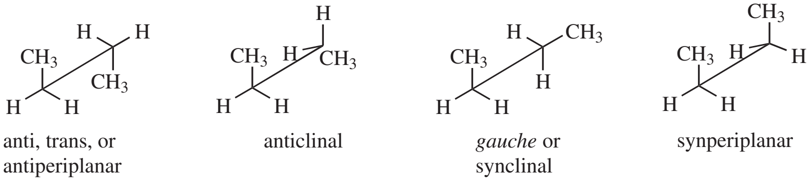
At ordinary temperatures, enough rotational energy is present for the ethane molecule rapidly to rotate, although it still spends most of its time at or near the energy minimum. Groups larger than hydrogen cause larger barriers. When the barriers are large enough, as in the case of suitably substituted biphenyls (p. 146) or the diadamantyl compound mentioned on p. 201, rotation at room temperature is completely prevented and we speak of configurations, not conformations. Even for compounds with small barriers, cooling to low temperatures may remove enough rotational energy for what would otherwise be conformational isomers to become configurational isomers.

A slightly more complicated case than ethane is that of a 1,2-disubstituted ethane (YCH_2—CH_2Y or YCH_2—CH_2X),[279] such as *n*-butane, for which there are four extremes: a fully staggered conformation, called anti, trans, or antiperiplanar; another

[278]See Pitzer, R.M. *Acc. Chem. Res.* ***1983***, *16*, 207. See, however, Bader, R.F.W.; Cheeseman, J.R.; Laidig, K.E.; Wiberg, K.B.; Breneman, C.*J. Am. Chem. Soc.* ***1990***, *112*, 6350.

[279]For discussions of the conformational analysis of such systems, see Kingsbury, C.A. *J. Chem. Educ.* ***1979***, *56*, 431; Wiberg, K.B.; Murcko, M.A. *J. Am. Chem. Soc.* ***1988***, *110*, 8029; Allinger, N.L.; Grev, R.S.; Yates, B.F.; Schaefer III, H.F. *J. Am. Chem. Soc.* ***1990***, *112*, 114.

staggered conformation, called *gauche* or *synclinal*; and two types of eclipsed



106

conformations, called synperiplanar and anticlinal. An energy diagram for this system is given in Fig. 4.5. Although there is constant rotation about the central bond, it is possible to estimate what percentage of the molecules are in each conformation at a given time. For example, it was concluded from a consideration of dipole moment and polarizability measurements that for 1,2-dichloroethane in CCl_4 solution at 25°C ~70% of the molecules are in the anti and ~30% in the gauche conformation.[280] The corresponding figures for 1,2-dibromoethane are 89% *anti* and 11% *gauche*.[281] The eclipsed conformations are unpopulated and serve only as pathways from one staggered conformation to another. Solids normally consist of a single conformer.

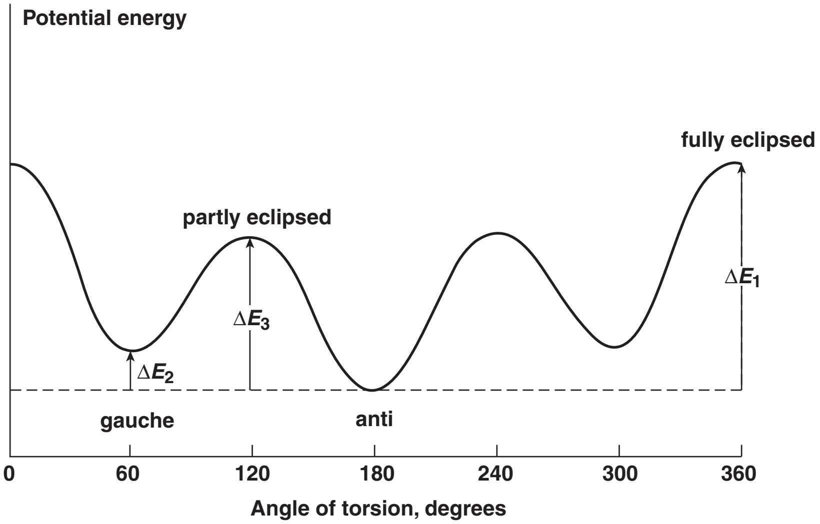


Fig. 4.5. Conformational energy for YCH_2—CH_2Y or YCH_2—CH_2X. For *n*-butane, $\Delta E_1 = 4$–6, $\Delta E_2 = 0.9$, and $\Delta E_3 = 3.4\,\text{kcal mol}^{-1}$ (17–25, 3.8, 14 kL mol^{-1}, respectively).

[280]Aroney, M.; Izsak, D.; Le Fèvre, R.J.W. *J. Chem. Soc.* ***1962***, 1407; Le Fèvre, R.J.W.; Orr, B.J. *Aust. J. Chem.* ***1964***, *17*, 1098.

[281]The *anti* form of butane itself is also more stable than the *gauche* form: Schrumpf, G. *Angew. Chem. Int. Ed.* ***1982***, *21*, 146.

It may be observed that the *gauche* conformation of butane (**106**) or any other similar molecule is chiral. The lack of optical activity in such compounds arises from the fact that **106** and its mirror image are always present in equal amounts and interconvert too rapidly for separation.

For butane and for most other molecules of the forms YCH_2—CH_2Y and YCH_2—CH_2X, the *anti* conformer is the most stable, but exceptions are known. One group of exceptions consists of molecules containing small electronegative atoms, especially fluorine and oxygen. Thus 2-fluoroethanol,[282] 1,2-difluoroethane,[283] and 2-fluoroethyl trichloroacetate ($FCH_2CH_2OCOCCl_3$)[284] exist predominantly in the *gauche* form and compounds, such as 2-chloroethanol and 2-bromoethanol,[282] also prefer the *gauche* form. It has been proposed that the preference for the *gauche* conformation in these molecules is an example of a more general phenomenon, known as the *gauche effect*, that is, a tendency to adopt that structure that has the maximum number of *gauche* interactions between adjacent electron pairs or polar bonds.[285] It was believed that the favorable *gauche* conformation of 2-fluoroethanol was the result of intramolecular hydrogen bonding, but this explanation does not do for molecules like 2-fluoroethyl trichloroacetate and has in fact been ruled out for 2-fluoroethanol as well.[286] The effect of β-substituents in Y—C—C—OX systems, where Y = F or SiR_3 has been examined and there is a small bond shortening effect on C—OX that is greatest when OX is a good leaving group. Bond lengthening was also observed with the β-silyl substituent.[287] Other exceptions are known, where small electronegative atoms are absent. For example, 1,1,2,2-tetrachloroethane and 1,1,2,2-tetrabromoethane both prefer the *gauche* conformation,[288] even although 1,1,2,2-tetrafluoroethane prefers the anti.[289] Also, both 2,3-dimethylpentane and 3,4-dimethylhexane prefer the *gauche* conformation,[290] and 2,3-dimethylbutane shows no preference for either.[291] Furthermore, the solvent can exert a powerful

[282]Wyn-Jones, E.; Orville-Thomas, W.J. *J. Mol. Struct.* ***1967***, *1*, 79; Buckley, P.; Giguère, P.A.; Yamamoto, D. *Can. J. Chem.* ***1968***, *46*, 2917; Davenport, D.; Schwartz, M. *J. Mol. Struct.* ***1978***, *50*, 259; Huang, J.; Hedberg, K. *J. Am. Chem. Soc.* ***1989***, *111*, 6909.

[283]Klaboe, P.; Nielsen, J.R. *J. Chem. Phys.* ***1960***, *33*, 1764; Abraham, R.J.; Kemp, R.H. *J. Chem. Soc. B* ***1971***, 1240; Bulthuis, J.; van den Berg, J.; MacLean, C. *J. Mol. Struct.* ***1973***, *16*, 11; van Schaick, E.J.M.; Geise, H.J.; Mijlhoff, F.C.; Renes, G. *J. Mol. Struct.* ***1973***, *16*, 23; Friesen, D.; Hedberg, K. *J. Am. Chem. Soc.* ***1980***, *102*, 3987; Fernholt, L.; Kveseth, K. *Acta Chem. Scand. Ser. A* ***1980***, *34*, 163.

[284]Abraham, R.J.; Monasterios, J.R. *Org. Magn. Reson.* ***1973***, *5*, 305.

[285]This effect is ascribed to nuclear electron attactive forces between the groups or unshared pairs: Wolfe, S.; Rauk, A.; Tel, L.M.; Csizmadia, I.G. *J. Chem. Soc. B* ***1971***, 136; Wolfe, S. *Acc. Chem. Res.* ***1972***, *5*, 102. See also, Phillips, L.; Wray, V. *J. Chem. Soc. Chem. Commun.* ***1973***, 90; Radom, L.; Hehre, W.J.; Pople, J.A. *J. Am. Chem. Soc.* ***1972***, *94*, 2371; Zefirov, N.S. *J. Org. Chem. USSR* ***1974***, *10*, 1147; Juaristi, E. *J. Chem. Educ.* ***1979***, *56*, 438.

[286]Griffith, R.C.; Roberts, J.D. *Tetrahedron Lett.* ***1974***, 3499.

[287]Amos, R.D.; Handy, N.C.; Jones, P.G.; Kirby, A.J.; Parker, J.K.; Percy, J.M.; Su, M.D. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 549.

[288]Kagarise, R.E. *J. Chem. Phys.* ***1956***, *24*, 300.

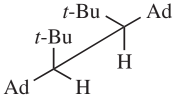
[289]Brown, D.E.; Beagley, B. *J. Mol. Struct.* ***1977***, *38*, 167.

[290]Ritter, W.; Hull, W.; Cantow, H. *Tetrahedron Lett.* ***1978***, 3093.

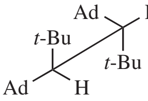
[291]Lunazzi, L.; Macciantelli, D.; Bernardi, F.; Ingold, K.U. *J. Am. Chem. Soc.* ***1977***, *99*, 4573.

effect. For example, the compound 2,3-dinitro-2,3-dimethylbutane exists entirely in the gauche conformation in the solid state, but in benzene, the *gauche*/*anti* ratio is 79:21; while in CCl_4 the anti form is actually favored (*gauche*/*anti* ratio 42:58).[292] In many cases, there are differences in the conformation of these molecules between the gas and the liquid phase (as when X = Y = OMe) because of polar interactions with the solvent.[293]

In one case, two conformational isomers of a single aliphatic hydrocarbon, 3,4-di(1-adamantyl)-2,2,5,5-tetramethylhexane, have proven stable enough for isolation at room temperature.[294] The two isomers **107** and **108** were separately crystallized, and the structures proved by X-ray crystallography. (The actual dihedral angles are distorted from the 60° angles shown in the drawings, owing to steric hindrance between the large groups.)

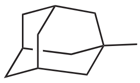


107



108

Ad =



All the conformations so far discussed have involved rotation about sp^3–sp^3 bonds. Many studies were also made of compounds with sp^3–sp^2 bonds.[295] For example, propanal (or any similar molecule) has four extreme conformations, two of which are called *eclipsing* and the other two *bisecting*. For propanal the eclipsing conformations have lower energy than the other two, with **109** favored over **110** by ~1 kcal mol^{-1} (4 kJ mol^{-1}).[296] As has already been pointed out (p. 184), for a few of these compounds, rotation is slow enough to permit cis–trans isomerism, although for simple compounds rotation is rapid. The cis conformer of acetic acid was produced in solid Ar,[297] and it was reported that acetaldehyde has a lower rotational barrier (~1 kcal mol^{-1} or 4 kJ mol^{-1}) than ethane.[298] Calculations have examined the rotational barriers around the CO and CC bonds

[292]Tan, B.; Chia, L.H.L.; Huang, H.; Kuok, M.; Tang, S. *J. Chem. Soc. Perkin Trans. 2* ***1984***, 1407.

[293]Smith, G.D.; Jaffe, R.L.; Yoon, D.Y. *J. Am. Chem. Soc.* ***1995***, *117*, 530. For an analysis of *N,N*-dimethylacetamide see Mack, H.-G.; Oberhammer, H. *J. Am. Chem. Soc.* ***1997***, *119*, 3567.

[294]Flamm-ter Meer; Beckhaus, H.; Peters, K.; von Schnering, H.; Fritz, H.; Rüchardt, C. *Chem. Ber.* ***1986***, *119*, 1492; Rüchardt, C.; Beckhaus, H. *Angew. Chem. Int. Ed.* ***1985***, *24*, 529.

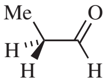
[295]For reviews, see Sinegovskaya, L.M.; Keiko, V.V.; Trofimov, B.A. *Sulfur Rep.* ***1987***, *7*, 337 (for enol ethers and thioethers); Karabatsos, G.J.; Fenoglio, D.J. *Top. Stereochem.* ***1970***, *5*, 167; Jones, G.I.L.; Owen, N.L. *J. Mol. Struct.* ***1973***, *18*, 1 (for carboxylic esters). See also, Schweizer, W.B.; Dunitz, J.D. *Helv. Chim. Acta* ***1982***, *65*, 1547; Chakrabarti, P.; Dunitz, J.D. *Helv. Chim. Acta* ***1982***, *65*, 1555; Cossé-Barbi, A.; Massat, A.; Dubois, J.E. *Bull. Soc. Chim. Belg.* ***1985***, *94*, 919; Dorigo, A.E.; Pratt, D.W.; Houk, K.N. *J. Am. Chem. Soc.* ***1987***, *109*, 6591.

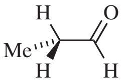
[296]Butcher, S.S.; Wilson Jr., E.B. *J. Chem. Phys.* ***1964***, *40*, 1671; Allinger, N.L.; Hickey, M.J. *J. Mol. Struct.* ***1973***, *17*, 233; Gupta, V.P. *Can. J. Chem.* ***1985***, *63*, 984.

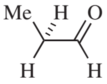
[297]Macoas, E. M. S.; Khriachtchev, L.; Pettersson, M.; Fausto, R.; Rasanen, M. J. *Am. Chem. Soc.* ***2003***, *125*, 16188.

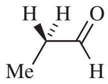
[298]Davidson, R.B.; Allen, L.C. *J. Chem. Phys.* ***1971***, *54*, 2828.

in formic acid, ethanedial and glycolaldedyde molecules.[299]

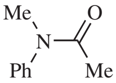

Eclipsing
109

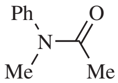

Eclipsing
110

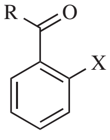

Bisecting


Bisecting

Other carbonyl compounds exhibit rotation about sp^3–sp^3 bonds, including amides.[300] In *N*-acetyl-*N*-methylaniline, the cis conformation (**111**) is more stable than the *trans*- (**112**) by 3.5 kcal mol^{-1} (14.6 kJ mol^{-1}).[301] This is due to destabilization of (*S*) due to steric hindrance between two methyl groups, and to electronic repulsion between the carbonyl lone-pair electrons and the phenyl π-electrons in the twisted phenyl orientation.[301]


111


112


113

A similar conformational analysis has been done with formamide derivatives,[302] with secondary amides,[303] and for hydroxamide acids.[304] It is known that thioformamide has a larger rotational barrier than formamide, which can be explained by a traditional picture of amide ‘‘resonance’ that is more appropriate for the thioformamide than formamide itself.[305] Torsional barriers in α-keto amides have been reported,[306] and the C—N bond of acetamides,[307] thioamides,[308] enamides[309] carbamates (R_2N—CO_2R'),[310,311] and enolate anions derived

[299]Ratajczyk, T.; Pecul, M.; Sadlej, J. *Tetrahedron* ***2004***, *60*, 179.
[300]Avalos, M.; Babiano, R.; Barneto, J.L.; Bravo, J.L.; Cintas, P.; Jiménez, J.L.; Palcios, J.C. *J. Org. Chem.* ***2001***, *66*, 7275.
[301]Saito, S.; Toriumi, Y.; Tomioka, A.; Itai, A. *J. Org. Chem.* ***1995***, *60*, 4715.
[302]Axe, F.U.; Renugopalakrishnan, V.; Hagler, A.T. *J. Chem. Res.* ***1998***, 1. For an analysis of DMF see Wiberg, K.B.; Rablen, P.R.; Rush, D.J.; Keith, T.A. *J. Am. Chem. Soc.* ***1995***, *117*, 4261.
[303]Avalos, M.; Babiano, R.; Barneto, J.L.; Cintas, P.; Clemente, F.R.; Jiménez, J.L.; Palcios, J.C. *J. Org. Chem.* ***2003***, *68*, 1834.
[304]Kakkar, R.; Grover, R.; Chadha, P. *Org. Biomol. Chem.* ***2003***, *1*, 2200.
[305]Wiberg, K.B.; Rablen, P.R. *J. Am. Chem. Soc.* ***1995***, *117*, 2201.
[306]Bach, R.D.; Mintcheva, I.; Kronenberg, W.J.; Schlegel, H.B. *J. Org. Chem.* ***1993***, *58*, 6135.
[307]Ilieva, S.; Hadjieva, B.; Galabov, B. *J. Org. Chem.* ***2002***, *67*, 6210.
[308]Wiberg, K. B.; Rush, D. J. *J. Am. Chem. Soc.* **2001**, 123, 2038; *J. Org. Chem.* ***2002***, *67*, 826.
[309]Rablen, P.R.; Miller, D.A.; Bullock, V.R.; Hutchinson, P.H.; Gorman, J.A. *J. Am. Chem. Soc.* ***1999***, *121*, 218.
[310]Menger, F.M.; Mounier, C.E. *J. Org. Chem.* ***1993***, *58*, 1655.
[311]Deetz, M.J.; Forbes, C.C.; Jonas, M.; Malerich, J.P.; Smith, B.D.; Wiest, O. *J. Org. Chem.* ***2002***, *67*, 3949.

from amides[312] have been examined. It is known that substituents influence rotational barriers.[313]

On p. 146, atropisomerism was possible when ortho substituents on biphenyl derivatives and certain other aromatic compounds prevented rotation about the Csp^3—Csp^3 bond. The presence of ortho substituents can also influence the conformation of certain groups. In **113**, R = alkyl the carbonyl unit is planar with the trans C=O•••F conformer more stable when X = F. When X = CF_3, the cis and trans are planar and the trans predominates.[314] When R = alkyl there is one orthogonal conformation, but there are two interconverting nonplanar conformations when R = O-alkyl.[314] In 1,2-diacylbenzenes, the carbonyl units tend to adopt a twisted conformation to minimize steric interactions.[315]

Conformation in Six-Membered Rings[316]

For cyclohexane there are two extreme conformations in which all the angles are tetrahedral.[317] These are called the *boat* and the *chair* conformations and in each the ring is said to be *puckered*. The chair conformation is a rigid structure, but the boat form is flexible[318] and can easily pass over to a somewhat more stable form

Boat Chair Twist

known as the *twist* conformation. The twist form is ~1.5 kcal mol^{-1} (6.3 kJ mol^{-1}) more stable than the boat because it has less eclipsing interaction (see p. 224).[319] The chair form is more stable than the twist form by ~5 kcal mol^{-1} (21 kJ mol^{-1}).[320] In the vast majority of compounds containing a cyclohexane ring, the molecules exist almost entirely in the chair form.[321] Yet, it

[312]Kim, Y.-J.; Streitwieser, A.; Chow, A.; Fraenkel, G. *Org. Lett.* ***1999***, *1*, 2069.

[313]Smith, B.D.; Goodenough-Lashua, D.M.; D'Souza, C.J.E.; Norton, K.J.; Schmidt, L.M.; Tung, J.C. *Tetrahedron Lett.* ***2004***, *45*, 2747.

[314]Abraham, R.J.; Angioloni, S.; Edgar, M.; Sancassan, F. *J. Chem. Soc. Perkin Trans. 2* ***1997***, 41.

[315]Casarini, D.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem.* ***1997***, *62*, 7592.

[316]For reviews, see Jensen, F.R.; Bushweller, C.H. *Adv. Alicyclic Chem.* ***1971***, *3*, 139; Robinson, D.L.; Theobald, D.W. *Q. Rev. Chem. Soc.* ***1967***, *21*, 314; Eliel, E.L. *Angew. Chem. Int. Ed.* ***1965***, *4*, 761. Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***, pp. 686–753. Also see, Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY, ***2001***, pp. 46–57.

[317]The C—C—C angles in cyclohexane are actually 111.5° [Davis, M.; Hassel, O. *Acta Chem. Scand.* ***1963***, *17*, 1181; Geise, H.J.; Buys, H.R.; Mijlhoff, F.C. *J. Mol. Struct.* ***1971***, *9*, 447; Bastiansen, O.; Fernholt, L.; Seip, H.M.; Kambara, H.; Kuchitsu, K. *J. Mol. Struct.* ***1973***, *18*, 163], but this is within the normal tetrahedral range (see p. 26).

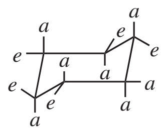
[318]See Dunitz, J.D. *J. Chem. Educ.* ***1970***, *47*, 488.

[319]For a review of nonchair forms, see Kellie, G.M.; Riddell, F.G. *Top. Stereochem.* ***1974***, *8*, 225.

[320]Margrave, J.L.; Frisch, M.A.; Bautista, R.G.; Clarke, R.L.; Johnson, W.S. *J. Am. Chem. Soc.* ***1963***, *85*, 546; Squillacote, M.; Sheridan, R.S.; Chapman, O.L.; Anet, F.A.L. *J. Am. Chem. Soc.* ***1975***, *97*, 3244.

[321]For a study of conformations in the cyclohexane series, see Wiberg, K. B.; Hammer, J. D.; Castejon, H.; Bailey, W. F.; DeLeon, E. L.; Jarret, R. M. *J. Org. Chem.* ***1999***, *64*, 2085; Wiberg, K.B.; Castejon, H.; Bailey, W.F.; Ochterski, J. *J. Org. Chem.* ***2000***, *65*, 1181.

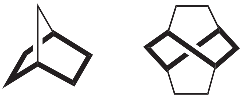
is known that the boat or twist form exists transiently. An inspection of the chair form shows that six of its bonds are directed differently from the other six:



a = axial group
e = equatorial group

On each carbon, one bond is directed up or down and the other more or less in the "plane" of the ring. The up or down bonds are called *axial* and the others *equatorial*. The axial bonds point alternately up and down. If a molecule were frozen into a chair form, there would be isomerism in mono-substituted cyclohexanes. For example, there would be an equatorial methylcyclohexane and an axial isomer. However, it has never been possible to isolate isomers of this type at room temperature.[322] This proves the transient existence of the boat or twist form, since in order for the two types of methylcyclohexane to be nonseparable, there must be rapid interconversion of one chair form to another (in which all axial bonds become equatorial and vice versa) and this is possible only through a boat or twist conformation. Conversion of one chair form to another requires an activation energy of $\sim$10 kcal mol^{-1} (42 kJ mol^{-1})[323] and is very rapid at room temperature.[324] However, by working at low temperatures, Jensen and Bushweller were able to obtain the pure equatorial conformers of chlorocyclohexane and trideuteriomethoxycyclohexane as solids and in solution.[325] Equatorial chlorocyclohexane has a half-life of 22 years in solution at -160°C.

In some molecules, the twist conformation is actually preferred.[326] Of course, in certain bicyclic compounds, the six-membered ring is forced to maintain a boat or twist conformation, as in norbornane or twistane.



Norbornane Twistane

In mono-substituted cyclohexanes, the substituent normally prefers the equatorial position because in the axial position there is interaction between the substituent

[322]Wehle, D.; Fitjer, L. *Tetrahedron Lett.* ***1986***, *27*, 5843, have succeeded in producing two conformers that are indefinitely stable in solution at room temperature. However, the other five positions of the cyclohexane ring in this case are all spirosubstituted with cyclobutane rings, greatly increasing the barrier to chair-chair interconversion.

[323]Jensen, F.R.; Noyce, D.S.; Sederholm, C.H.; Berlin, A.J. *J. Am. Chem. Soc.* ***1962***, *84*, 386; Bovey, F.A.; Hood, F.P.; Anderson, E.W.; Kornegay, R.L. *J. Chem. Phys.* ***1964***, *41*, 2041; Anet, F.A.L.; Bourn, A.J.R. *J. Am. Chem. Soc.* ***1967***, *89*, 760. See also Strauss, H.L. *J. Chem. Educ.* ***1971***, *48*, 221.

[324]For reviews of chair–chair interconversions, see Ōki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, ***1985***, pp. 287–307; Anderson, J.E. *Top. Curr. Chem.* ***1974***, *45*, 139.

[325]Jensen, F.R.; Bushweller, C.H. *J. Am. Chem. Soc.* ***1966***, *88*, 4279; Paquette, L.A.; Meehan, G.V.; Wise, L.D. ***1969***, *91*, 3223.

[326]Weiser, J.; Golan, O.; Fitjer, L.; Biali, S.E. *J. Org. Chem.* ***1996***, *61*, 8277.

and the axial hydrogens in the 3 and 5 positions, but the extent of this preference depends greatly on the nature of the group.[327] Alkyl groups have a greater preference for the equatorial postion than polar groups. For alkyl groups, the preference increases with size, although size seems to be unimportant for polar groups. Both the large HgBr[328] and HgCl[329] groups and the small F group have been reported to have little or no conformational preference (the HgCl group actually shows a slight preference for the axial position). Table 4.3 gives approximate values of the free energy required for various groups to go from the equatorial position to the axial (these are called *A* values),[330] although it must be kept in mind that they vary somewhat with physical state, temperature, and solvent.[331]

In disubstituted compounds, the rule for alkyl groups is that the conformation is such that as many groups as possible adopt the equatorial position. How far it is possible depends on the configuration. In a *cis*-1,2-disubstituted cyclohexane, one substituent must be axial and the other equatorial. In a *trans*-1,2 compound both may be equatorial or both axial. This is also true for 1,4-disubstituted cyclohexanes, but the reverse holds for 1,3 compounds: the trans isomer must have the *ae* conformation and the cis isomer may be *aa* or *ee*. For alkyl groups, the *ee* conformation predominates over the *aa*, but for other groups this is not necessarily so. For example, both *trans*-1,4-dibromocyclohexane and the corresponding dichloro compound have the *ee* and *aa* conformations about equally populated[332] and most *trans*-1,2-dihalocyclohexanes exist predominantly in the *aa* conformation.[333] Note that in the latter case the two halogen atoms are anti in the *aa* conformation, but *gauche* in the *ee* conformation.[334]

Since compounds with alkyl equatorial substituents are generally more stable, trans-1,2 compounds, which can adopt the *ee* conformation, are thermodynamically more stable than their cis-1,2 isomers, which must exist in the *ae* conformation. For the 1,2-dimethylcyclohexanes, the difference in stability is ~2 kcal mol^{-1}

[327]For a study of thioether, sulfoxide and sulfone substituents, see Juaristi, E.; Labastida, V.; Antúnez, S. *J. Org. Chem.* ***2000***, *65*, 969.

[328]Jensen, F.R.; Gale, L.H. *J. Am. Chem. Soc.* ***1959***, *81*, 6337.

[329]Anet, F.A.L.; Krane, J.; Kitching, W.; Dodderel, D.; Praeger, D. *Tetrahedron Lett.* ***1974***, 3255.

[330]Except where otherwise indicated, these values are from Jensen, F.R.; Bushweller, C.H. *Adv. Alicyclic Chem.* ***1971***, *3*, 139. See also Schneider, H.; Hoppen, V. *Tetrahedron Lett.* ***1974***, 579 and see Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY, ***2001***, pp. 46–57.

[331]See, for example, Ford, R.A.; Allinger, N.L. *J. Org. Chem.* ***1970***, *35*, 3178. For a critical review of the methods used to obtain these values, see Jensen, F.R.; Bushweller, C.H. *Adv. Alicyclic Chem.* ***1971***, *3*, 139.

[332]Atkinson, V.A.; Hassel, O. *Acta Chem. Scand.* ***1959***, *13*, 1737; Abraham, R.J.; Rossetti, Z.L. *Tetrahedron Lett.* ***1972***, 4965, *J. Chem. Soc. Perkin Trans. 2* ***1973***, 582. See also, Hammarström, L.; Berg, U.; Liljefors, T. *Tetrahedron Lett.* ***1987***, *28*, 4883.

[333]Hageman, H.J.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* ***1969***, *88*, 97; Klaeboe, P. *Acta Chem. Scand.* ***1971***, *25*, 695; Abraham, M.H.; Xodo, L.E.; Cook, M.J.; Cruz, R. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 1503; Samoshin, V.V.; Svyatkin, V.A.; Zefirov, N.S. *J. Org. Chem. USSR* ***1988***, *24*, 1080, and references cited therein. *trans*-1,2-Difluorocyclohexane exists predominantly in the ee conformation: see Zefirov, N.S.; Samoshin, V.V.; Subbotin, O.A.; Sergeev, N.M. *J. Org. Chem. USSR* ***1981***, *17*, 1301.

[334]For a case of a preferential diaxial conformation in 1,3 isomers, see Ochiai, M.; Iwaki, S.; Ukita, T.; Matsuura, Y.; Shiro, M.; Nagao, Y. *J. Am. Chem. Soc.* ***1988***, *110*, 4606.

TABLE 4.3. Free-Energy Differences between Equatorial and Axial Substituents on a Cyclohexane Ring (*A* Values)[330]

	Approximate $-\Delta G°$,			Approximate $-\Delta G°$	
Group	kcal mol^{-1}	kJ mol^{-1}	Group	kcal mol^{-1}	kJ mol^{-1}
HgCl[330]	−0.25	−1.0	NO_2	1.1	4.6
HgBr	0	0	COOEt	1.1–1.2	4.6–5.0
D[335]	0.008	0.03	COOMe	1.27–1.31	5.3–5.5
CN	0.15–0.25	0.6–1.0	COOH	1.35–1.46	5.7–6.1
F	0.25	1.0	NH_2[336]	1.4	5.9
C≡CH	0.41	1.7	$CH{=}CH_2$[337]	1.7	7.1
I	0.46	1.9	CH_3[338]	1.74	7.28
Br	0.48–0.62	2.0–2.6	C_2H_5	~1.75	~7.3
OTs	0.515	2.15	*i*-Pr	~2.15	~9.0
Cl	0.52	2.2	C_6H_{11}[339]	2.15	9.0
OAc	0.71	3.0	$SiMe_3$[340]	2.4–2.6	10–11
OMe[341]	0.75	3.1	C_6H_5[342]	2.7	11
OH	0.92–0.97	3.8–4.1	*t*-Bu[343]	4.9	21

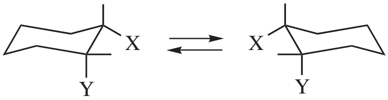
(8 kJ mol^{-1}). Similarly, *trans*-1,4 and *cis*-1,3 compounds are more stable than their stereoisomers.

An interesting anomaly is *all-trans*-1,2,3,4,5,6-hexaisopropylcyclohexane, in which the six isopropyl groups prefer the axial position, although the six ethyl groups of the corresponding hexaethyl compound prefer the equatorial position.[344] The alkyl groups of these compounds can of course only be all axial or all equatorial, and it is likely that the molecule prefers the all-axial conformation because of unavoidable strain in the other conformation.

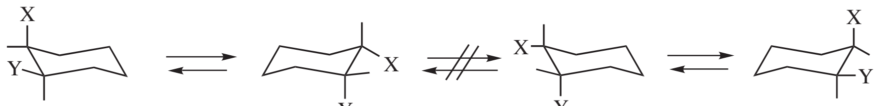
Incidentally, we can now see, in one case, why the correct number of stereoisomers could be predicted by assuming planar rings, even although they are not planar (p. 186). In the case of both a *cis*-1,2-X,X-disubstituted and a *cis*-1,2-X,Y-disubstituted cyclohexane, the molecule is nonsuperimposable on its mirror image;

[335]Anet, F.A.L.; O'Leary, D.J. *Tetrahedron Lett.* ***1989***, *30*, 1059.
[336]Buchanan, G.W.; Webb, V.L. *Tetrahedron Lett.* ***1983***, *24*, 4519.
[337]Eliel, E.L.; Manoharan, M. *J. Org. Chem.* ***1981***, *46*, 1959.
[338]Booth, H.; Everett, J.R. *J. Chem. Soc. Chem. Commun.* ***1976***, 278.
[339]Hirsch, J.A. *Top. Stereochem.* ***1967***, *1*, 199.
[340]Kitching, W.; Olszowy, H.A.; Drew, G.M.; Adcock, W. *J. Org. Chem.* ***1982***, *47*, 5153.
[341]Schneider, H.; Hoppen, V. *Tetrahedron Lett.* ***1974***, 579.
[342]Squillacote, M.E.; Neth, J.M. *J. Am. Chem. Soc.* ***1987***, *109*, 198. Values of 2.59–2.92 kcal mol^{-1} were determined for 4-X-C_6H_4- substituents (X = NO_2, Cl, MeO) - see Kirby, A.J.; Williams, N.H. *J. Chem. Soc. Chem. Commun.* ***1992***, 1285, 1286.
[343]Manoharan, M.; Eliel, E.L. *Tetrahedron Lett.* ***1984***, *25*, 3267.
[344]Golan, O.; Goren, Z.; Biali, S.E. *J. Am. Chem. Soc.* ***1990***, *112*, 9300.

neither has a plane of symmetry. However, in the former case (**114**) conversion of one chair form to the other (which of course happens rapidly) turns the molecule into its mirror image, while in the latter case (**115**) rapid interconversion does not give the mirror image but merely the conformer in which the original axial and equatorial substituents exchange places. Thus the optical inactivity of **114** is not due to a plane of symmetry, but to a rapid interconversion of the molecule and its mirror image. A similar situation holds for cis-1,3 compounds. However, for cis-1,4 isomers (both X,X and X,Y) optical inactivity arises from a plane of symmetry in both conformations. All-trans-1,2- and trans-1,3-disubstituted cyclohexanes are chiral (whether X,X or X,Y), while trans-1,4 compounds (both X,X and X,Y) are achiral, since all conformations have a plane of symmetry. It has been shown that the equilibrium is very dependent on both the solvent and the concentration of the disubstituted cyclohexane.[345] A theoretical study of the 1,2-dihalides showed a preference for the diaxial form with X = Cl, but predicted that the energy difference between diaxial and diequatorial was small when X = F.[346]



114



115

The conformation of a group can be frozen into a desired position by putting into the ring a large alkyl group (most often *tert*-butyl), which greatly favors the equatorial position.[347] It is known that silylated derivatives of *trans*-1,4- and *trans*-1,2-dihydroxycyclohexane, some monosilyloxycyclohexanes and some silylated sugars have unusually large populations of chair conformations with axial substituents.[348] Adjacent silyl groups in the 1,2-disubstituted series show a stabilizing interaction in all conformations, and this leads generally to unusually large axial populations.

[345]Abraham, R.J.; Chambers, E.J.; Thomas, W.A. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 1061.

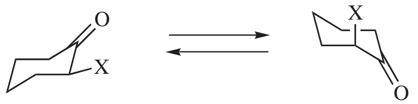
[346]Wiberg, K. B. *J. Org. Chem.* ***1999***, *64*, 6387.

[347]This idea was suggested by Winstein, S.; Holness, N.J. *J. Am. Chem. Soc.* ***1955***, *77*, 5561. There are a few known compounds in which a *tert*-butyl group is axial. See, for example, Vierhapper, F.W. *Tetrahedron Lett.* ***1981***, *22*, 5161.

[348]Marzabadi, C. H.; Anderson, J.E.; Gonzalez-Outeirino, J.; Gaffney, P.R.J.; White, C.G.H.; Tocher, D.A.; Todaro, L.J. *J. Am. Chem. Soc.* ***2003***, *125*, 15163.

The principles involved in the conformational analysis of six-membered rings containing one or two trigonal atoms, for example, cyclohexanone and cyclohexene, are similar.[349–351] The barrier to interconversion in cyclohexane has been calculated to be 8.4–12.1 kcal mol^{-1}.[352] Cyclohexanone derivatives also assume a chair-conformation. Substituents at C-2 can assume an axial or equatorial position depending on steric and electronic influences. The proportion of the conformation with an axial X group is shown in Table 4.4 for a variety of substituents (X) in 2-substituted cyclohexanones.[353]

TABLE 4.4. Proportion of Axial Conformation in 2-Substituted Cyclohexanones, in $CDCl_3$.[353]



X	% Axial Conformation
F	17 ± 3
Cl	45 ± 4
Br	71 ± 4
I	88 ± 5
MeO	28 ± 4
MeS	85 ± 7
MeSe	(92)
Me_2N	44 ± 3
Me	(26)

[349]For a monograph, see Rabideau, P.W. *The Conformational Analysis of Cyclohexenes, Cyclohexadienes, and Related Hydroaromatic Compounds*, VCH, NY, ***1989***. For reviews, see Vereshchagin, A.N. *Russ. Chem. Rev.* ***1983***, *52*, 1081; Johnson, F. *Chem. Rev.* ***1968***, *68*, 375. See also, Lambert, J.B.; Clikeman, R.R.; Taba, K.M.; Marko, D.E.; Bosch, R.J.; Xue, L. *Acc. Chem. Res.* ***1987***, *20*, 454.

[350]For books on conformational analysis see Dale, J. *Stereochemistry and Conformational Analysis*, Verlag Chemie, Deerfield Beach, FL, ***1978***; Chiurdoglu, G. *Conformational Analysis*, Academic Press, NY, ***1971***; Eliel, E.L.; Allinger, N.L.; Angyal, S.J.; Morrison, G.A. *Conformational Analysis*, Wiley, NY, ***1965***; Hanack, M. *Conformation Theory*, Academic Press, NY, ***1965***. For reviews, see Dale, J. *Top. Stereochem.* ***1976***, *9*, 199; Truax, D.R.; Wieser, H. *Chem. Soc. Rev.* ***1976***, *5*, 411; Eliel, E.L. *J. Chem. Educ.* ***1975***, *52*, 762; Bastiansen, O.; Seip, H.M.; Boggs, J.E. *Perspect. Struct. Chem.* ***1971***, *4*, 60; Bushweller, C.H.; Gianni, M.H., in Patai, S. *The Chemistry of Functional Groups, Supplement E*, Wiley, NY, ***1980***, pp. 215–278.

[351]For reviews, see Jensen, F.R.; Bushweller, C.H. *Adv. Alicyclic Chem.* ***1971***, *3*, 139; Robinson, D.L.; Theobald, D.W. *Q. Rev. Chem. Soc.* ***1967***, *21*, 314; Eliel, E.L. *Angew. Chem. Int. Ed.* ***1965***, *4*, 761. Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***, pp. 686–753. Also see Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY, ***2001***, pp. 53–55.

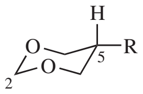
[352]Laane, J.; Choo, J. *J. Am. Chem. Soc.* ***1994***, *116*, 3889.

[353]Basso, E.A.; Kaiser, C.; Rittner, R.; Lambert, J.B. *J. Org. Chem.* ***1993***, *58*, 7865.

Conformation in Six-Membered Rings Containing Heteroatoms

In six-membered rings containing heteroatoms,[354] the basic principles are the same; that is, there are chair, twist, and boat forms, axial, and equatorial groups. The conformational equilibrium for tetrahydropyridines, for example, has been studied.[355] In certain compounds a number of new factors enter the picture. We deal with only two of these.[356]

1. In 5-alkyl-substituted 1,3-dioxanes, the 5-substituent has a much smaller preference for the equatorial position than in cyclohexane derivatives;[357] the *A* values are much lower. This indicates that the lone pairs on the oxygens have a smaller steric requirement than the C—H bonds in the corresponding cyclohexane derivatives. There is some evidence of an homoanomeric interaction in these systems.[358]



   Similar behavior is found in the 1,3-dithianes,[359] and 2,3-disubstituted-1,4-dithianes have also been examined.[360] With certain non-alkyl substituents (e.g., F, NO_2, SOMe,[361] NMe_3^+) the axial position is actually preferred.[362]

2. An alkyl group located on a carbon α to a heteroatom prefers the equatorial position, which is of course the normally expected behavior, but a *polar* group in such a location prefers the *axial* position. An example of this

[354]For monographs, see Glass, R.S. *Conformational Analysis of Medium-Sized Heterocycles*, VCH, NY, ***1988***; Riddell, F.G. *The Conformational Analysis of Heterocyclic Compounds*, Academic Press, NY, ***1980***. For reviews, see Juaristi, E. *Acc. Chem. Res.* ***1989***, *22*, 357; Crabb, T.A.; Katritzky, A.R. *Adv. Heterocycl. Chem.* ***1984***, *36*, 1; Eliel, E.L. *Angew. Chem. Int. Ed.* ***1972***, *11*, 739; *Pure Appl. Chem.* ***1971***, *25*, 509; *Acc. Chem. Res.* ***1970***, *3*, 1; Lambert, J.B. *Acc. Chem. Res.* ***1971***, *4*, 87; Romers, C.; Altona, C.; Buys, H.R.; Havinga, E. *Top. Stereochem.* ***1969***, *4*, 39; Bushweller, C.H.; Gianni, M.H., in Patai, S. *The Chemistry of Functional Groups, Supplement E*, Wley, NY, ***1980***, pp. 232–274.

[355]Bachrach, S.M.; Liu, M. *Tetrahedron Lett.* ***1992***, *33*, 6771.

[356]These factors are discussed by Eliel, E.L. *Angew. Chem. Int. Ed.* ***1972***, *11*, 739.

[357]Riddell, F.G.; Robinson, M.J.T. *Tetrahedron* ***1967***, *23*, 3417; Eliel, E.L.; Knoeber, M.C. *J. Am. Chem. Soc.* ***1968***, *90*, 3444. See also Eliel, E.L.; Alcudia, F. *J. Am. Chem. Soc.* ***1974***, *96*, 1939. See Cieplak, P.; Howard, A.E.; Powers, J.P.; Rychnovsky, S.D.; Kollman, P.A. *J. Org. Chem.* ***1996***, *61*, 3662 for conformational energy differences in 2,2,6-trimethyl-4-alkyl-1,3-dioxane.

[358]Cai, J.; Davies, A.G.; Schiesser, C.H. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 1151.

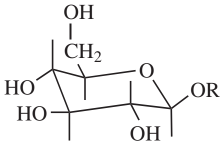
[359]Hutchins, R.O.; Eliel, E.L. *J. Am. Chem. Soc.* ***1969***, *91*, 2703. See also, Juaristi, E.; Cuevas, G. *Tetrahedron* ***1999***, *55*, 359.

[360]Strelenko, Y.A.; Samoshin, V.V.; Troyansky, E.I.; Demchuk, D.V.; Dmitriev, D.E.; Nikishin, G.I.; Zefirov, N.S. *Tetrahedron* ***1994***, *50*, 10107.

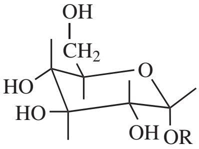
[361]Gordillo, B.; Juaristi, E.; Matínez, R.; Toscano, R.A.; White, P.S.; Eliel, E.L. *J. Am. Chem. Soc.* ***1992***, *114*, 2157.

[362]Kaloustian, M.K.; Dennis, N.; Mager, S.; Evans, S.A.; Alcudia, F.; Eliel, E.L. *J. Am. Chem. Soc.* ***1976***, *98*, 956. See also Eliel, E.L.; Kandasamy, D.; Sechrest, R.C. *J. Org. Chem.* ***1977***, *42*, 1533.

phenomenon, known as the *anomeric effect*,[363] is the greater stability of α-glucosides over β-glucosides. A number of explanations have been offered

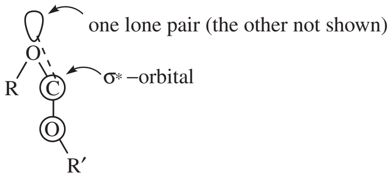


A β-glucoside
116

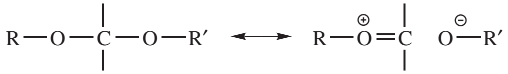


An α-glucoside
117

for the anomeric effect.[364] The one[365] that has received the most acceptance[366] is that one of the lone pairs of the polar atom connected to the carbon (an oxygen atom in the case of **117**) can be stabilized by overlapping with an antibonding orbital of the bond between the carbon and the other polar atom:



This can happen only if the two orbitals are in the positions shown. The situation can also be represented by this type of hyperconjugation (called "negative hyperconjugation"):



It is possible that simple repulsion between parallel dipoles in **116** also plays a part in the greater stability of **117**. It has been shown that aqueous solvation effects reduce anomeric stabilization in many systems, particularly for tetrahydropyranosyls.[367] In contrast to cyclic acetals, simple acyclic acetlas

[363]For books on this subject, see Kirby, A.J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer, NY, ***1983***; Szarek, W.A.; Horton, D. *Anomeric Effect*, American Chemical Society, Washington, ***1979***. For reviews see Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*, Pergamon, Elmsford, NY, ***1983***, pp. 4–26; Zefirov, N.S. *Tetrahedron* ***1977***, *33*, 3193; Zefirov, N.S.; Shekhtman, N.M. *Russ. Chem. Rev.* ***1971***, *40*, 315; Lemieux, R.U. *Pure Appl. Chem.* ***1971***, *27*, 527; Angyal, S.J. *Angew. Chem. Int. Ed.* ***1969***, *8*, 157; Martin, J. *Ann. Chim. (Paris) [14]*, ***1971***, *6*, 205.

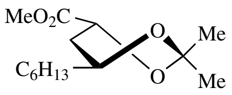
[364]Juaristi, E.; Cuevas, G. *Tetrahedron* ***1992***, *48*, 5019.

[365]See Romers, C.; Altona, C.; Buys, H.R.; Havinga, E. *Top. Stereochem.* ***1969***, *4*, 39, see pp. 73–77; Wolfe, S.; Whangbo, M.; Mitchell, D.J. *Carbohydr. Res.* ***1979***, *69*, 1.

[366]For some evidence for this explanation, see Fuchs, B.; Ellencweig, A.; Tartakovsky, E.; Aped, P. *Angew. Chem. Int. Ed.* ***1986***, *25*, 287; Praly, J.; Lemieux, R.U. *Can. J. Chem.* ***1987***, *65*, 213; Booth, H.; Khedhair, K.A.; Readshaw, S.A. *Tetrahedron* ***1987***, *43*, 4699. For evidence against it, see Box, V.G.S. *Heterocycles* ***1990***, *31*, 1157.

[367]Cramer, C.J. *J. Org. Chem.* ***1992***, *57*, 7034; Booth, H.; Dixon, J.M.; Readshaw, S.A. *Tetrahedron* ***1992***, *48*, 6151.

rarely adopt the anomeric conformation, apparently because the eclipsed conformation better accommodates steric interactions of groups linked by relatively short carbon–oxygen bonds.[368] In all-cis-2,5-di-*tert*-butyl-1,4-cyclohexanediol, hydrogen bonding stabilizes the otherwise high-energy form[369] and 1,3-dioxane (**118**) exists largely as the twist conformation shown.[370] The conformational preference of 1-methyl-1-silacyclohexane (**121**) has been studied.[371] A strongly decreased activation barrier in silacyclohexane was observed, as compared to that in the parent ring, and is explained by the longer endocyclic Si—C bonds.



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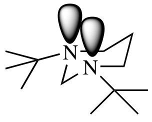

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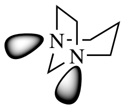
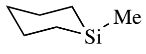


120



121

Second-row heteroatoms are known to show a substantial anomeric effect.[372] There appears to be evidence for a reverse anomeric effect in 2-aminotetrahydropyrans.[373] It has been called into question whether a reverse anomeric effect exists at all.[374] In **119**, the lone-pair electrons assume an axial conformation and there is an anomeric effect.[375] In **120**, however, the lone-pair electron orbitals are oriented gauche to both the axial and equatorial α-CH bond and there is no anomeric effect.[375]

Conformation in Other Rings[376]

Three-membered saturated rings are usually planar, but other three-membered rings can have some flexibility. Cyclobutane[377] is not planar but exists as in **122**, with an

[368]Anderson, J.E. *J. Org. Chem.* ***2000***, *65*, 748.

[369]Stolow, R.D. *J. Am. Chem. Soc.* ***1964***, *86*, 2170; Stolow, R.D.; McDonagh, P.M.; Bonaventura, M.M. *J. Am. Chem. Soc.* ***1964***, *86*, 2165. For some other examples, see Camps, P.; Iglesias, C. *Tetrahedron Lett.* ***1985***, *26*, 5463; Fitjer, L.; Scheuermann, H.; Klages, U.; Wehle, D.; Stephenson, D.S.; Binsch, G. *Chem. Ber.* ***1986***, *119*, 1144.

[370]Rychnovsky, S.D.; Yang, G.; Powers, J.P. *J. Org. Chem.* ***1993***, *58*, 5251.

[371]Arnason, I.; Kvaran, A.; Jonsdottir, S.; Gudnason, P. I.; Oberhammer, H. *J. Org. Chem.* ***2002***, *67*, 3827.

[372]Juaristi, E.; Cuevas, G. *Tetrahedron* ***1992***, *48*, 5109; Juaristi, E.; Tapia, J.; Mendez, R. *Tetrahedron* ***1986***, *42*, 1253; Zefirov, N.S.; Blagoveschenskii, V.S.; Kazimirchik, I.V.; Yakovleva, O.P. *J. Org. Chem. USSR* ***1971***, *7*, 599; Salzner, U.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1993***, *115*, 10231; Aggarwal, V.K.; Worrall, J.M.; Adams, H.; Alexander, R.; Taylor, B.F. *J. Chem. Soc. Perkin Trans. 1* ***1997***, 21.

[373]Salzner, U.; Schleyer, P.v.R. *J. Org. Chem.* ***1994***, *59*, 2138.

[374]Perrin, C.L. *Tetrahedron* ***1995***, *51*, 11901.

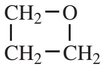
[375]Anderson, J.E.; Cai, J.; Davies, A.G. *J. Chem. Soc. Perkin Trans. 2* ***1997***, 2633. For some controversy concerning the anomeric effect a related system, see Perrin, C.L.; Armstrong, K.B.; Fabian, M.A. *J. Am. Chem.Soc.* ***1994***, *116*, 715 and Salzner, U. *J. Org. Chem.* ***1995***, *60*, 986.

[376]Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***, pp. 675–685 and 754–770.

[377]For reviews of the stereochemistry of four-membered rings, see Legon, A.C. *Chem. Rev.* ***1980***, *80*, 231; Moriarty, R.M. *Top. Stereochem.* ***1974***, *8*, 271; Cotton, F.A.; Frenz, B.A. *Tetrahedron* ***1974***, *30*, 1587.

angle between the planes of ~35°.[378] The deviation from planarity is presumably caused by eclipsing in the planar form (see p. 219). Oxetane, in which eclipsing is

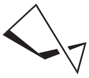
122



Oxetane

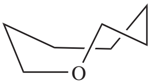
less, is closer to planarity, with an angle between the planes of ~10°.[379] Cyclopentane might be expected to be planar, since the angles of a regular pentagon are 108°, but it is not so, also because of eclipsing effects.[380] There are two puckered conformations, the *envelope* and the *half-chair*. There is little energy difference between these two forms and many five-membered ring systems have conformations somewhere in between them.[381] Although in the envelope conformation one carbon is shown above the others, ring motions cause each of the carbons in

Envelope



Half-chair

rapid succession to assume this position. The puckering rotates around the ring in what may be called a *pseudorotation*.[382] In substituted cyclopentanes and five-membered rings in which at least one atom does not contain two substituents [e.g., tetrahydrofuran (THF), cyclopentanone, C_3 and C_7-mono- and disubstituted hexahydroazepin-2-ones (caprolactams),[383] and tetrahydrothiophene *S*-oxide[384]], one conformer may be more stable than the others. The barrier to planarity in cyclopentane has been reported to be 5.2 kcal mol^{-1} (22 kJ mol^{-1}).[385] Contrary to previous reports, there is only weak stabilization (<2 kcal mol^{-1}; <8 kJ mol^{-1}) of 3-, 4-, and 5-membered rings by *gem*–dialkoxycarbonyl substituents (e.g., COOR).[386]



123

[378]Dows, D.A.; Rich, N. *J. Chem. Phys.* ***1967***, *47*, 333; Stone, J.M.R.; Mills, I.M. *Mol. Phys.* ***1970***, *18*, 631; Miller, F.A.; Capwell, R.J.; Lord, R.C.; Rea, D.G. *Spectrochim. Acta Part A*, ***1972***, *28*, 603. However, some cyclobutane derivatives are planar, at least in the solid state: for example, see Margulis, T.N. *J. Am. Chem. Soc.* ***1971***, *93*, 2193.

[379]Luger, P.; Buschmann, J. *J. Am. Chem. Soc.* ***1984***, *106*, 7118.

[380]For reviews of the conformational analysis of five-membered rings, see Fuchs, B. *Top. Stereochem.* ***1978***, *10*, 1; Legon, A.C. *Chem. Rev.* ***1980***, *80*, 231.

[381]Willy, W.E.; Binsch, G.; Eliel, E.L. *J. Am. Chem. Soc.* ***1970***, *92*, 5394; Lipnick, R.L. *J. Mol. Struct.* ***1974***, *21*, 423.

[382]Kilpatrick, J.E.; Pitzer, K.S.; Spitzer, R. *J. Am. Chem. Soc.* ***1947***, *69*, 2438; Pitzer, K.S.; Donath, W.E. *J. Am. Chem. Soc.* ***1959***, *81*, 3213; Durig, J.R.; Wertz, D.W. *J. Chem. Phys.* ***1968***, *49*, 2118; Lipnick, R.L. *J. Mol. Struct.* ***1974***, *21*, 411; Poupko, R.; Luz, Z.; Zimmermann, H. *J. Am. Chem. Soc.* ***1982***, *104*, 5307; Riddell, F.G.; Cameron K.S.; Holmes, S.A.; Strange, J.H. *J. Am. Chem. Soc.* ***1997***, *119*, 7555.

[383]Matallana, A.; Kruger, A.W.; Kingsbury, C.A. *J. Org. Chem.* ***1994***, *59*, 3020.

[384]Abraham, R.J.; Pollock, L.; Sancassan, F. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 2329.

[385]Carreira, L.A.; Jiang, G.J.; Person, W.B.; Willis, Jr., J.N. *J. Chem. Phys.* ***1972***, *56*, 1440.

[386]Verevkin, S.P.; Kümmerlin, M.; Beckhaus, H.-D.; Galli, C.; Rüchardt, C. *Eur. J. Org. Chem.* ***1998***, 579.

Rings larger than six-membered are always puckered[387] unless they contain a large number of sp^2 atoms (see the section on strain in medium rings, p. 223). The energy and conformations of the alkane series cycloheptane to cyclodecane has been reported.[388] The conformation shown for oxacyclooctane (**123**), for example, appears to be the most abundant one.[389] The conformations of other large ring compounds have been studied, including 11-membered ring lactones,[390] 10- and 11-membered ring ketones,[391] and 11- and 14-membered ring lactams.[392] Dynamic NMR was used to determine the conformation large-ring cycloalkenes and lactones.[393] Note that axial and equatorial hydrogens are found only in the chair conformations of six-membered rings. In rings of other sizes the hydrogens protrude at angles that generally do not lend themselves to classification in this way,[394] although in some cases the terms "pseudo-axial" and "pseudo-equatorial" have been used to classify hydrogens in rings of other sizes.[395]

Molecular Mechanics[396]

Molecular mechanics Molecular Mechanics[397] describes a molecule in terms of a collection of bonded atoms that have been distorted from some idealized geometry due to non-bonded van der Waals (steric) and coulombic (charge–charge)

[387]For reviews of conformations in larger rings, see Arshinova, R.P. *Russ. Chem. Rev.* ***1988***, *57*, 1142; Ounsworth, J.P.; Weiler, L. *J. Chem. Educ.* ***1987***, *64*, 568; Ōki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, ***1985***, pp. 307–321; Casanova, J.; Waegell, B. *Bull. Soc. Chim. Fr.* ***1975***, 911; Anet, F.A.L. *Top. Curr. Chem.* ***1974***, *45*, 169; Dunitz, J.D. *Pure Appl. Chem.* ***1971***, *25*, 495; *Perspect. Struct. Chem.* ***1968***, *2*, 1; Tochtermann, W. *Fortchr. Chem. Forsch.* ***1970***, *15*, 378; Dale, J. *Angew. Chem. Int. Ed.* ***1966***, *5*, 1000. For a monograph, see Glass, R.S. *Conformational Analysis of Medium-Sized Heterocycles*, VCH, NY, ***1988***. Also see the monographs by Eliel, E.L.; Allinger, N.L.; Angyal, S.J.; Morrison, G.A. *Conformational Analysis*; Wiley, NY, ***1965***; Hanack, M. *Conformation Theory*, Academic Press, NY, ***1965***.

[388]Wiberg, K.B. *J. Org. Chem* ***2003***, *68*, 9322.

[389]Meyer, W.L.; Taylor, P.W.; Reed, S.A.; Leister, M.C.; Schneider, H.-J.; Schmidt, G.; Evans, F.E.; Levine, R.A. *J. Org. Chem.* ***1992***, *57*, 291.

[390]Spracklin, D.K.; Weiler, L. *J. Chem. Soc. Chem. Commun.* ***1992***, 1347; Ogura, H.; Furuhata, K.; Harada, Y.; Iitaka, Y. *J. Am. Chem. Soc.* ***1978***, *100*, 6733; Ounsworth, J.P.; Weiler, L. *J. Chem. Ed.*, ***1987***, *64*, 568; Keller, T.H.; Neeland, E.G.; Rettig, S.; Trotter, J.; Weiler, L. *J. Am. Chem. Soc.* ***1988***, *110*, 7858.

[391]Pawar, D.M.; Smith, S.V.; Moody, E.M.; Noe, E.A. *J. Am. Chem. Soc.* ***1998***, *120*, 8241.

[392]Borgen, G.; Dale, J.; Gundersen, L.-L.; Krivokapic, A.; Rise, F.; Øverås, A.T. *Acta Chem. Scand. B*, ***1998***, *52*, 1110.

[393]Pawar, D.M.; Davids, K.L.; Brown, B.L.; Smith, S.V.; Noe, E.A. *J. Org. Chem.* ***1999***, *64*, 4580; Pawar, D.M.; Moody, E.M.; Noe, E.A. *J. Org. Chem.* ***1999***, *64*, 4586.

[394]For definitions of axial, equatorial, and related terms for rings of any size, see Anet, F.A.L.*Tetrahedron Lett.* ***1990***, *31*, 2125.

[395]For a discussion of the angles of the ring positions, see Cremer, D. *Isr. J. Chem.* ***1980***, *20*, 12.

[396]Thanks to Dr. Warren Hehre, Wavefunction, Inc., Irvine, CA. Personal communication. See Hehre, W.J. *A Guide to Molecular Mechanics and Quantum Chemical Calculations*, Wavefunction, Inc., Irvine, CA, ***2003***, pp. 56–57.

[397]For a review, see Rappe, A.K.; Casewit, C.J. *Molecular Mechanics Across Chemistry*, University Science Books, Sausalito, CA, ***1997***.

interactions. This approach is fundamentally different from molecular-orbital theory that is based on quantum mechanics and that make no reference whatsoever to chemical bonding. The success of molecular mechanics depends on the ability to represent molecules in terms of unique valence structures, on the notion that bond lengths and angles may be transferred from one molecule to another and on a predictable dependence of geometrical parameters on the local atomic environment.

The molecular mechanics energy of a molecule is given as a sum of contributions arising from distortions from ideal bond distances (stretch contributions), bond angles (bend contributions) and torsion angles (torsion contributions), together with contributions from nonbonded interactions. This energy is commonly referred to as a strain energy, meaning that it reflects the inherent strain in a real molecule relative to a hypothetical idealized (strain-free) form.

$$\boldsymbol{E}^{\text{strain}} = \boldsymbol{E}_{\text{A}}^{\text{stretch}} + \boldsymbol{E}_{\text{A}}^{\text{bend}} + \boldsymbol{E}_{\text{A}}^{\text{torsion}} + \boldsymbol{E}_{\text{AB}}^{\text{nonbonded}} \tag{1}$$

Stretch and bend terms are most simply given in terms of quadratic (Hooke's law) forms:

$$\boldsymbol{E}^{\text{stretch}}\ (\text{r}) = \frac{1}{2} k^{\text{stretch}}\ (r - r^{\text{eq}})^2 \tag{2}$$

$$\boldsymbol{E}^{\text{bend}}\ (\alpha) = \frac{1}{2} k^{\text{bend}}\ (r - r^{\text{eq}})^2 \tag{3}$$

r and α are the bond distance and angle, respectively, and r^{eq} and α^{eq} are the ideal bond length and angle, respectively.

Torsion terms need to properly reflect the inherent periodicity of the particular bond involved in a rotation. For example, the threefold periodicity of the carbon-carbon bond in ethane may be represented by a simple cosine form.

$$\boldsymbol{E}^{\text{torsion}}(\omega) = k^{\text{torsion3}}[1 - \cos 3(\omega - \omega^{\text{eq}})] \tag{4}$$

Ω is the torsion angle, ω^{eq} is the ideal torsion angle and k^{torsion} is a parameter. Torsion contributions to the strain energy will also usually need to include contributions that are onefold and twofold periodic. These can be represented in the same manner as the threefold term.

$$\begin{aligned} \boldsymbol{E}^{\text{torsion}}(\omega) = {} & k^{\text{torsion1}}[1 - \cos\ (\omega - \omega^{\text{eq}})] + k^{\text{torsion2}}[1 - \cos 2\ (\omega - \omega^{\text{eq}})] \\ & + k^{\text{torsion3}}[1 - \cos 3\ (\omega - \omega^{\text{eq}})] \end{aligned} \tag{5}$$

Nonbonded interacations invovle a sum of van der Waals (VDW) interactions and coulombic interactions. The coulombic term accounts for charge–charge interactions.

$$\boldsymbol{E}^{\text{nonbonded}}\ (r) = E^{\text{VDW}}\ (r) + \boldsymbol{E}^{\text{coulombic}}\ (r) \tag{6}$$

The VDW is made up of two parts, the first to account for strong repulsion on nonbonded atoms as the closely approach, and the second to account for weak long-range attraction, r is the nonbonded distance.

Molecular mechanics methods differ both in the form of the terms that make up the strain energy and in their detailed parameterization. Older methods, such as SYBYL,[398] use very simple forms and relatively few parameters, while newer methods such as MM3,[399] MM4,[400] and MMFF[401] use more complex forms and many more parameters. In general, the more complex the form of the strain energy terms and the more extensive the parameterization, the better will be the results. Of course, more parameters mean that more (experimental) data will be needed in their construction. Because molecular mechanics is not based on "physical fundamentals," but rather is essentially an interpolation scheme, its success depends on the availability of either experimental or high-quality theoretical data for parameterization. A corollary is that molecular mechanics would not be expected to lead to good results for "new" molecules, that is, molecules outside the range of their parameterization.

The two most important applications of molecular mechanics are geometry calculations on very large molecules, for example, on proteins, and conformational analysis on molecules for which there may be hundreds, thousands, or even tens of thousands of distinct structures. It is here that methods based on quantum mechanics are simply not (yet) practical. It should be no surprise that equilibrium geometries obtained from molecular mechanics are generally in good accord with experimental values. There are ample data with which to parameterize and evaluate the methods. However, because there are very few experimental data relating to the equilibrium conformations of molecules and energy differences among different conformations, molecular mechanics calculations for these quantities need to be viewed with a very critical eye. In time, high-quality data from quantum mechanics will provide the needed data and allow more careful parameterization (and assessment) than now possible.

The most important limitation of molecular mechanics is its inability to provide thermochemical data. The reason for this is that the mechanics strain energy is specific to a given molecule (it provides a measure of how much this molecule deviates from an ideal arrangement), and different molecules have different ideal arrangements. For example, acetone and methyl vinyl ether have different bonds and would be referenced to different standards. The only exception occurs for conformational energy differences or, more generally, for energy comparisons among molecules with exactly the same bonding, for example, *cis*- and *trans*-2-butene.

Because a molecular mechanics calculation reveals nothing about the distribution of electrons or distribution of charge in molecules, and because mechanics

[398]Clark, M.; Cramer III, R.D.; van Opdenbosch, N. *J. Computational Chem.* ***1989***, *10*, 982.

[399]Allinger, N.L.; Li, F.; Yan, L. *J. Computational Chem.* ***1990***, *11*, 855, and later papers in this series.

[400]Allinger, N.L.; Chen, K.; Lii, J.-H. *J. Computational Chem.* ***1996***, *17*, 642, and later papers in this series.

[401]Halgren, T.A. *J. Computational Chem* ***1996***, *17*, 490, and later papers in this series.

methods have not (yet) been parameterized to reproduce transition state geometries, they are of limited value in describing either chemical reactivity or product selectivity. There are, however, situations where steric considerations associated with either the product or reactants are responsible for trends in reactivity and selectivity, and here molecular mechanics would be expected to be of some value.

Because of the different strengths and limitations of molecular mechanics and quantum chemical calculations, it is now common practice to combine the two, for example, to use molecular mechanics to establish conformation (or at least a set of reasonable conformations) and then to quantum calculations to evaluate energy differences.

In practical terms, molecular mechanics calculations may easily be performed on molecules comprising several thousand atoms. Additionally, molecular mechanics calculations are sufficiently rapid to permit extensive conformational searching on molecules containing upwards of a hundred atoms. Modern graphical based programs for desktop computers make the methods available to all chemists.

STRAIN

Steric strain[402] exists in a molecule when bonds are forced to make abnormal angles. This results in a higher energy than would be the case in the absence of angle distortions. It has been shown that there is a good correlation between the ^{13}C—H coupling constants in NMR and the bond angles and bond force angles in strained organic molecules.[403] There are, in general, two kinds of structural features that result in sterically caused abnormal bond angles. One of these is found in small-ring compounds, where the angles must be less than those resulting from normal orbital overlap.[404] Such strain is called *small-angle strain*. The other arises when nonbonded atoms are forced into close proximity by the geometry of the molecule. These are called *nonbonded interactions*.

Strained molecules possess *strain energy*. That is, their potential energies are higher than they would be if strain were absent.[405] The strain energy for a particular molecule can be estimated from heat of atomization or heat of combustion data. A strained molecule has a lower heat of atomization than it would have if it were strain-free (Fig. 4.6). As in the similar case of resonance energies (p. 36), strain energies can not be known exactly, because the energy of a real molecule can be measured, but not the energy of a hypothetical unstrained model. It is also possible

[402]For a monograph, see Greenberg, A.; Liebman, J.F. *Strained Organic Molecules*, Academic Press, NY, ***1978***. For reviews, see Wiberg, K.B. *Angew. Chem. Int. Ed.* ***1986***, *25*, 312; Greenberg, A.; Stevenson, T.A. *Mol. Struct. Energ.*, ***1986***, *3*, 193; Liebman, J.F.; Greenberg, A. *Chem. Rev.* ***1976***, *76*, 311. For a review of the concept of strain, see Cremer, D.; Kraka, E. *Mol. Struct. Energ.* ***1988***, *7*, 65.

[403]Zhao, C.-Y.; Duan, W.-S.; Zhang, Y.; You, X.-Z. *J. Chem. Res. (S)* ***1998***, 156.

[404]Wiberg, K.B. *Accts. Chem. Res.* ***1996***, *29*, 229.

[405]For discussions, see Wiberg, K.B.; Bader, R.F.W.; Lau, C.D.H. *J. Am. Chem. Soc.* ***1987***, *109*, 985, 1001.

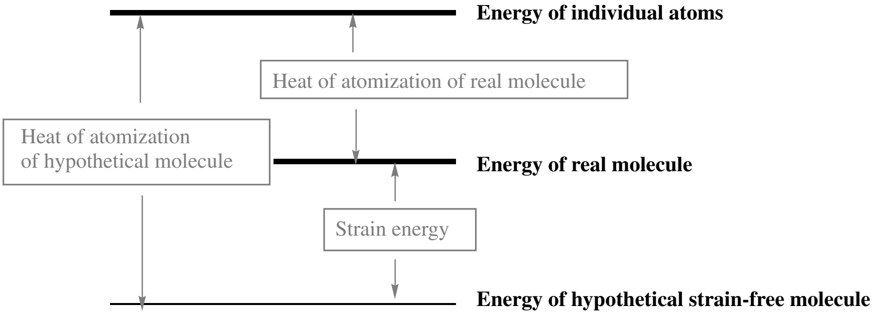


Fig. 4.6. Strain energy calculation.

to calculate strain energies by molecular mechanics, not only for real molecules, but also for those that cannot be made.[406]

Strain in Small Rings

Three-membered rings have a great deal of angle strain, since 60° angles represent a large departure from the tetrahedral angles. In sharp contrast to other ethers, ethylene oxide is quite reactive, the ring being opened by many reagents (see p. 496). Ring opening, of course, relieves the strain.[407] Cyclopropane,[408] which is even more strained[409] than ethylene oxide, is also cleaved more easily than would be expected for an alkane.[410] Thus, pyrolysis at 450–500°C converts it to propene, bromination gives 1,3-dibromopropane,[411] and it can be hydrogenated to propane (though at high pressure).[412] Other three-membered rings are similarly reactive.[413] Alkyl substituents influence the strain energy of small ring compounds.[414] *gem*-Dimethyl substitution, for example, "lowers the strain energy of cyclopropanes,

[406]For a review, see Rüchardt, C.; Beckhaus, K. *Angew. Chem. Int. Ed.* ***1985***, *24*, 529. See also Burkert, U.; Allinger, N.L. *Molecular Mechanisms*, American Chemical Society, Washington, ***1982***, pp. 169–194; Allinger, N.L. *Adv. Phys. Org. Chem.* ***1976***, *13*, 1, pp. 45–47.

[407]For reviews of reactions of cyclopropanes and cyclobutanes, see Trost, B.M. *Top. Curr. Chem.* ***1986***, *133*, 3; Wong, H.N.C.; Lau, C.D.H.; Tam, K. *Top. Curr. Chem.* ***1986***, *133*, 83.

[408]For a treatise, see Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, 2 pts., Wiley, NY, ***1987***.

[409]For reviews of strain in cyclopropanes, see, in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, 2 pts, Wiley, NY, ***1987***, the papers by Wiberg, K.B. pt. 1., pp. 1–26; Liebman, J.F.; Greenberg, A. pt. 2, pp. 1083–1119; Liebman, J.F.; Greenberg, A. *Chem. Rev.* ***1989***, *89*, 1225.

[410]For reviews of ring-opening reactions of cyclopropanes, see Wong, H.N.C.; Hon, M.; Ts, C.e; Yip, Y.; Tanko, J.; Hudlicky, T. *Chem. Rev.* ***1989***, *89*, 165; Reissig, H., in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 1, Wiley, NY, ***1987***, pp. 375–443.

[411]Ogg Jr., R.A.; Priest, W.J. *J. Am. Chem. Soc.* ***1938***, *60*, 217.

[412]Shortridge, R.W.; Craig, R.A.; Greenlee, K.W.; Derfer, J.M.; Boord, C.E. *J. Am. Chem. Soc.* ***1948***, *70*, 946.

[413]For a review of the pyrolysis of three- and four-membered rings, see Frey, H.M. *Adv. Phys. Org. Chem.* ***1966***, *4*, 147.

[414]Bach, R. D.; Dmitrenko, O. *J. Org. Chem.* ***2002***, *67*, 2588.

cyclobutanes, epoxides, and dimethyldioxirane by 6–10 kcal mol^{-1} (25.42 kJ mol^{-1}) relative to an unbranched acyclic reference molecule."[414] The C—H bond dissociation energy also tends to increase ring strain in small-ring alkenes.[415]

There is much evidence, chiefly derived from NMR coupling constants, that the bonding in cyclopropanes is not the same as in compounds that lack small-angle strain.[416] For a normal carbon atom, one *s* and three *p* orbitals are hybridized to give four approximately equivalent sp^3 orbitals, each containing ~25% *s* character. But for a cyclopropane carbon atom, the four hybrid orbitals are far from equivalent. The two orbitals directed to the outside bonds have more *s* character than a normal sp^3 orbital, while the two orbitals involved in ring bonding have less, because the more *p*-like they are the more they resemble ordinary *p* orbitals, whose preferred bond angle is 90° rather than 109.5°. Since the small-angle strain in cyclopropanes is the difference between the preferred angle and the real angle of 60°, this additional *p* character relieves some of the strain. The external orbitals have ~33% *s* character, so that they are ~sp^2 orbitals, while the internal orbitals have ~17% *s* character, so that they may be called ~sp^5 orbitals.[417] Each of the three carbon–carbon bonds of cyclopropane is therefore formed by overlap of two sp^5 orbitals. Molecular-orbital calculations show that such bonds are not completely *s* in character. In normal C—C bonds, sp^3 orbitals overlap in such a way that the straight line connecting the nuclei becomes an axis about which the electron density is symmetrical. But in cyclopropane, the electron density is directed *away from* the ring.[418] Fig. 4.7 shows the direction of orbital overlap.[419] For cyclopropane, the angle (marked θ) is 21°. Cyclobutane exhibits the same phenomenon but to a lesser extent, θ being 7°.[419,418] Molecular-orbital calculations also show that the

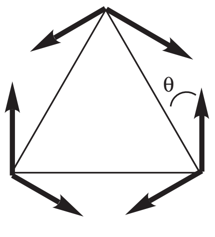


Fig. 4.7. Orbital overlap in cyclopropane. The arrows point toward the center of electron density.

[415]Bach, R.D.; Dmitrenko, O. *J. Am. Chem. Soc.* ***2004***, *126*, 4444.

[416]For discussions of bonding in cyclopropanes, see Bernett, W.A. *J. Chem. Educ.* ***1967***, *44*, 17; de Meijere, A. *Angew. Chem. Int. Ed.* ***1979***, *18*, 809; Honegger, E.; Heilbronner, E.; Schmelzer, A. *Nouv. J. Chem.* ***1982***, *6*, 519; Cremer, D.; Kraka, E. *J. Am. Chem. Soc.* ***1985***, *107*, 3800, 3811; Slee, T.S. *Mol. Struct. Energ.* ***1988***, *5*, 63; Casaarini, D.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem.* ***1997***, *62*, 7592.

[417]Randić, M.; Maksić, Z. *Theor. Chim. Acta* ***1965***, *3*, 59; Foote, C.S. *Tetrahedron Lett.* ***1963***, 579; Weigert, F.J.; Roberts, J.D. *J. Am. Chem. Soc.* ***1967***, *89*, 5962.

[418]Wiberg, K.B. *Acc. Chem. Res.* ***1996***, *29*, 229.

[419]Coulson, C.A.; Goodwin, T.H. *J. Chem. Soc.* ***1962***, 2851; ***1963***, 3161; Peters, D. *Tetrahedron* ***1963***, *19*, 1539; Hoffmann, R.; Davidson, R.B. *J. Am. Chem. Soc.* ***1971***, *93*, 5699.

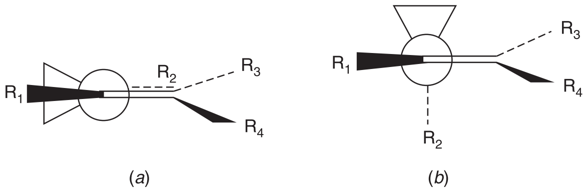


Fig. 4.8. Conformations of α-cyclopropylalkenes. Conformation (*a*) leads to maximum conjugation and conformation (*b*) to minimum conjugation.

maximum electron densities of the C—C σ orbitals are bent away from the ring, with $\theta = 9.4°$ for cyclopropane and 3.4° for cyclobutane.[420] The bonds in cyclopropane are called *bent bonds*, and are intermediate in character between σ and π, so that cyclopropanes behave in some respects like double-bond compounds.[421] For one thing, there is much evidence, chiefly from UV spectra,[422] that a cyclopropane ring is conjugated with an adjacent double bond and that this conjugation is greatest for the conformation shown in *a* in Fig. 4.8 and least or absent for the conformation shown in *b*, since overlap of the double-bond π-orbital with two of the *p*-like orbitals of the cyclopropane ring is greatest in conformation *a*. However, the conjugation between a cyclopropane ring and a double bond is less than that between two double bonds.[423] For other examples of the similarities in behavior of a cyclopropane ring and a double bond (see p. 212).

Four-membered rings also exhibit angle strain, but much less, and are less easily opened. Cyclobutane is more resistant than cyclopropane to bromination, and although it can be hydrogenated to butane, more strenuous conditions are required. Nevertheless, pyrolysis at 420°C gives two molecules of ethylene. As mentioned earlier (p. 212), cyclobutane is not planar.

Many highly strained compounds containing small rings in fused systems have been prepared,[424] showing that organic molecules can exhibit much more

[420]Wiberg, K.B.; Bader, R.F.W.; Lau, C.D.H. *J. Am. Chem. Soc.* ***1987***, *109*, 985, 1001; Cremer, D.; Kraka, E. *J. Am. Chem. Soc.* ***1985***, *107*, 3800, 1811.

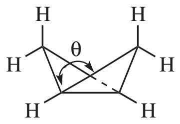
[421]For reviews, see Tidwell, T.T., in Rappoport, Z. *The Chemistry of the Cyclopropyl Groups*, pt. 1, Wiley, NY, ***1987***, pp. 565–632; Charton, M. in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, pp. 511–610, Wiley, NY, ***1970***.

[422]See, for example, Cromwell, N.H.; Hudson, G.V. *J. Am. Chem. Soc.* ***1953***, *75*, 872; Kosower, E.M.; Ito, M. *Proc. Chem. Soc.* ***1962***, 25; Dauben, W.G.; Berezin, G.H. *J. Am. Chem. Soc.* ***1967***, *89*, 3449; Jorgenson, M.J.; Leung, T. *J. Am. Chem. Soc.* ***1968***, *90*, 3769; Heathcock, C.H.; Poulter, S.R. *J. Am. Chem. Soc.* ***1968***, *90*, 3766; Tsuji, T.; Shibata, T.; Hienuki, Y.; Nishida, S. *J. Am. Chem. Soc.* ***1978***, *100*, 1806; Drumright, R.E.; Mas, R.H.; Merola, J.S.; Tanko, J.M. *J. Org. Chem.* ***1990***, *55*, 4098.

[423]Staley, S.W. *J. Am. Chem. Soc.* ***1967***, *89*, 1532; Pews, R.G.; Ojha, N.D. *J. Am. Chem. Soc.* ***1969***, *91*, 5769. See, however, Noe, E.A.; Young, R.M. *J. Am. Chem. Soc.* ***1982***, *104*, 6218.

[424]For reviews discussing the properties of some of these as well as related compounds, see the reviews in *Chem. Rev.* ***1989***, *89*, 975, and the following: Jefford, C.W. *J. Chem. Educ.* ***1976***, *53*, 477; Seebach, D. *Angew. Chem. Int. Ed.* ***1965***, *4*, 121; Greenberg, A.; Liebman, J.F. *Strained Organic Molecules*, Academic Press, NY, ***1978***, pp. 210–220. For a review of bicyclo[*n.m.0*]alkanes, see Wiberg, K.B. *Adv. Alicyclic Chem.* ***1968***, *2*, 185. Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***, pp. 771–811.

strain than simple cyclopropanes or cyclobutanes.[425] Table 4.5 shows a few of these compounds.[426] Perhaps the most interesting are cubane, prismane, and the substituted



tetrahedrane, since preparation of these ring systems had been the object of much endeavor. Prismane is tetracyclo[2.2.0.0^{2,6}.0^{3,5}]hexane and many derivatives are known,[427] including bis(homohexaprismane) derivatives.[428] The bicyclobutane molecule is bent, with the angle θ between the planes equal to $126 \pm 3°$.[429] The rehybridization effect, described above for cyclopropane, is even more extreme in this molecule. Calculations have shown that the central bond is essentially formed by overlap of two *p* orbitals with little or no *s* character.[430] *Propellanes* are compounds in which two carbons, directly connected, are also connected by three other bridges. [1.1.1]Propellane is in the table and it is the smallest possible propellane,[431] and is in fact more stable than the larger [2.1.1]propellane and [2.2.1]propellane, which have been isolated only in solid matrixes at low temperature.[432] The bicyclo[1.1.1]pentanes are obviously related to the propellanes except that the central connecting bond is missing, and several derivatives are known.[433] Even more complex systems are known.[434]

[425]For a useful classification of strained polycyclic systems, see Gund, P.; Gund, T.M. *J. Am. Chem. Soc.* ***1981***, *103*, 4458.

[426]For a computer program that generates IUPAC names for complex bridged systems, see Rücker, G.; Rücker, C. *Chimia*, ***1990***, *44*, 116.

[427]Gleiter, R.; Treptow, B.; Irngartinger, H.; Oeser, T. *J. Org. Chem.* ***1994***, *59*, 2787; Gleiter, R.; Treptow, B. *J. Org. Chem.* ***1993***, *58*, 7740.

[428]Golobish, T.D.; Dailey, W.P. *Tetrahedron Lett.* ***1996***, *37*, 3239.

[429]Haller, I.; Srinivasan, R. *J. Chem. Phys.* ***1964***, *41*, 2745.

[430]Schulman, J.M.; Fisanick, G.J. *J. Am. Chem. Soc.* ***1970***, *92*, 6653; Newton, M.D.; Schulman, J.M. *J. Am. Chem. Soc.* ***1972***, *94*, 767.

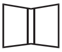
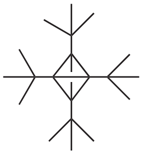
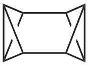
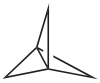
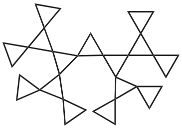
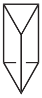
[431]Wiberg, K.B.; Waddell, S.T. *J. Am. Chem. Soc.* ***1990***, *112*, 2194; Seiler, S.T. *Helv. Chim. Acta* ***1990***, *73*, 1574; Bothe, H.; Schlüter, A. *Chem. Ber.* ***1991***, *124*, 587; Lynch, K.M.; Dailey, W.P. *J. Org. Chem.* ***1995***, *60*, 4666. For reviews of small-ring propellanes, see Wiberg, K.B. *Chem. Rev.* ***1989***, *89*, 975; Ginsburg, D., in Rappoport, Z *The Chemistry of the Cyclopropyl Group*, pt. 2, Wiley, NY, ***1987***, pp. 1193–1221. For a discussion of the formation of propellanes, see Ginsburg, D. *Top. Curr. Chem.* ***1987***, *137*, 1.

[432]Wiberg, K.B.; Walker, F.H.; Pratt, W.E.; Michl, J. *J. Am. Chem. Soc.* ***1983***, *105*, 3638.

[433]Della, E.W.; Taylor, D.K. *J. Org. Chem.* ***1994***, *59*, 2986.

[434]See Kuck, D.; Krause, R.A.; Gestmann, D.; Posteher, F.; Schuster, A. *Tetrahedron* ***1998***, *54*, 5247 for an example of a [5.5.5.5.5.5]centrohexacycline.

TABLE 4.5. Some Strained Small-Ring Compounds

Structural Formula of Compound Prepared	Systematic Name of Ring System	Common Name If Any	Reference
	Bicyclo[1.1.0]butane	Bicyclobutane	435
	$\Delta^{1,4}$-Bicyclo[2.2.0]hexene		436
	Tricyclo[1.1.0.$0^{2,4}$]butane	Tetrahedrane	437
	Pentacyclo[5.1.0.$0^{2,4}$.$0^{3,5}$.$0^{6,8}$]-octane	Octabisvalene	438
	Tricyclo[1.1.1.$0^{1,3}$]-pentane	a [1.1.1]propellane	364
	Tetradecaspiro[2.0.2.0.0.0.0.0.-2.0.2.0.0.0.2.0.2.0.0.1.0.0.2.0.2.-0.0.0]untriacontane	[15]-triangulane	439
	Tetracyclo[2.2.0.$0^{2,6}$.$0^{3,5}$]-hexane	Prismane	440

[435]Lemal, D.M.; Menger, F.M.; Clark, G.W. *J. Am. Chem. Soc.* ***1963***, *85*, 2529; Wiberg, K.B.; Lampman, G.M. *Tetrahedron Lett.* ***1963***, 2173. For reviews of preparations and reactions of this system, see Hoz, S., in Rappoport, Z *The Chemistry of the Cyclopropyl Group*, pt. 2, Wiley, NY, ***1987***, pp. 1121–1192; Wiberg, K.B.; Lampman, G.M.; Ciula, R.P.; Connor, D.S.; Schertler, P.; Lavanish, J.M. *Tetrahedron* ***1965***, *21*, 2749; Wiberg, K.B. *Rec. Chem. Prog.*, ***1965***, *26*, 143; Wiberg, K.B. *Adv. Alicyclic Chem.* ***1968***, *2*, 185. For a review of [*n*.1.1] systems, see Meinwald, J.; Meinwald, Y.C. *Adv. Alicyclic Chem.* ***1966***, *1*, 1.

[436]Casanova, J.; Bragin, J.; Cottrell, F.D. *J. Am. Chem. Soc.* ***1978***, *100*, 2264.

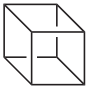
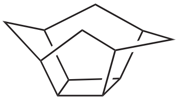
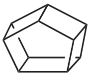
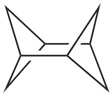
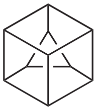
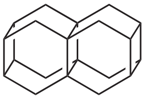
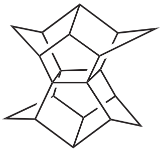
[437]Maier, G.; Pfriem, S.; Schäfer, U.; Malsch, K.; Matusch, R. *Chem. Ber.* ***1981***, *114*, 3965; Maier, G.; Pfriem, S.; Malsch, K.; Kalinowski, H.; Dehnicke, K. *Chem. Ber.* ***1981***, *114*, 3988; Irngartinger, H.; Goldmann, A.; Jahn, R.; Nixdorf, M.; Rodewald, H.; Maier, G.; Malsch, K.; Emrich, R. *Angew. Chem. Int. Ed.* ***1984***, *23*, 993; Maier, G.; Fleischer, F. *Tetrahedron Lett.* ***1991***, *32*, 57. For reviews of attempts to synthesize tetrahedrane, see Maier, G. *Angew. Chem. Int. Ed.* ***1988***, *27*, 309; Zefirov, N.S.; Koz'min, A.S.; Abramenkov, A.V. *Russ. Chem. Rev.* ***1978***, *47*, 163. For a review of tetrahedranes and other cage molecules stabilized by steric hindrance, see Maier, G.; Rang, H.; Born, D., in Olah, G.A. *Cage Hydrocarbons*, Wiley, NY, ***1990***, pp. 219–259. See also, Maier, G.; Born, D. *Angew. Chem. Int. Ed.* ***1989***, *28*, 1050.

[438]Rücker, C.; Trupp, B. *J. Am. Chem. Soc.* ***1988***, *110*, 4828.

[439]Von Seebach, M.; Kozhushkov, S.I.; Boese, R.; Benet-Buchholz, J.; Yufit, D.S.; Howard, J.A.K.; de Meijere, A. *Angew. Chem. Int. Ed.* ***2000***, *39*, 2495.

[440]Katz, T.J.; Acton, N. *J. Am. Chem. Soc.* ***1973***, *95*, 2738. See also Viehe, H.G.; Merényi, R.; Oth, J.F.M.; Senders, J.R.; Valange, P. *Angew. Chem. Int. Ed.* ***1964***, *3*, 755; Wilzbach, K.E.; Kaplan, L. *J. Am. Chem. Soc.* ***1965***, *87*, 4004.

TABLE 4.5 (*Continued*)

Structural Formula of Compound Prepared	Systematic Name of Ring System	Common Name If Any	Reference
	Pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}] octane	Cubane	441
	Pentacyclo[5.4.1.0^{3,1}.0^{5,9}.0^{8,11}] dodecane	4[Peristylane]	442
	Hexacyclo[5.3.0.0^{2,6}-.0^{3,10}.0^{4,9}.0^{5,8}]decane	Pentaprismane	443
	Tricyclo[3.1.1.1^{2,4}]octane	Diasterane	444
	Hexacyclo[4.4.0.0^{2,4}.0^{3,9}-.0^{5,8}.0^{7,10}]decane		445
	Nonacyclo[10.8.0^{2,11}.0^{4,9}-.0^{4,19}.0^{6,17}.0^{7,16}.0^{9,14}.0^{14,19}] eicosane	A double tetraesterane	446
	Undecacyclo[9.9.0.0^{1,5}-.0^{2,12}.0^{2,18}.0^{3,7}.0^{6,10}.0^{8,12}-.0^{11,15}.0^{13,17}.0^{16,20}]eicosane	Pagodane	447

[441]Barborak, J.C.; Watts, L.; Pettit, R. *J. Am. Chem. Soc.* ***1966***, *88*, 1328; Hedberg, L.; Hedberg, K.; Eaton, P.E.; Nodari, N.; Robiette, A.G. *J. Am. Chem. Soc.* ***1991***, *113*, 1514. For a review of cubanes, see Griffin, G.W.; Marchand, A.P. *Chem. Rev.* ***1989***, *89*, 997.

[442]Paquette, L.A.; Fischer, J.W.; Browne, A.R.; Doecke, C.W. *J. Am. Chem. Soc.* ***1985***, *105*, 686.

[443]Eaton, P.E.; Or, Y.S.; Branca, S.J.; Shankar, B.K.R. *Tetrahedron* ***1986***, *42*, 1621. See also Dauben, W.G.; Cunningham Jr., A.F. *J. Org. Chem.* ***1983***, *48*, 2842.

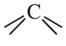
[444]Otterbach, A.; Musso, H. *Angew. Chem. Int. Ed.* ***1987***, *26*, 554.

[445]Allred, E.L.; Beck, B.R. *J. Am. Chem. Soc.* ***1973***, *95*, 2393.

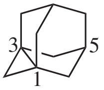
[446]Hoffmann, V.T.; Musso, H. *Angew. Chem. Int. Ed.* ***1987***, *26*, 1006.

[447]Rihs, G. *Tetrahedron Lett.* ***1983***, *24*, 5857. See Mathew, T.; Keller, M.; Hunkler, D.; Prinzbach, H. *Tetrahedron Lett.* ***1996***, *37*, 4491 for the synthesis of azapagodanes (also called azadodecahedranes).

In certain small-ring systems, including small propellanes, the geometry of one or more carbon atoms is so constrained that all four of their valences are directed to the same side of a plane (inverted tetrahedron), as in **124**.[448] An example is 1,3-dehydroadamantane, **125** (which is also a propellane).[449] X-ray crystallography of the 5-cyano derivative of ***125*** shows that the four carbon valences at C-1 and C-3 are all directed "into" the molecule and none point outside.[450] Compound ***125*** is quite reactive; it is unstable in air, readily adds hydrogen, water, bromine, or acetic acid to the $C_1—C_3$ bond, and is easily polymerized. When two such atoms are connected by a bond (as in **125**), the bond is very long (the $C_1—C_3$ bond length in the 5-cyano derivative of **125** is 1.64 Å), as the atoms try to compensate in this way for their enforced angles. The high reactivity of the $C_1—C_3$ bond of **125** is not only caused by strain, but also by the fact that reagents find it easy to approach these atoms since there are no bonds (e.g., C—H bonds on C-1 or C-3) to get in the way.



124



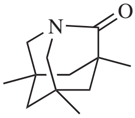
125

Strain in Other Rings[451]

In rings larger than four-membered, there is no small-angle strain, but there are three other kinds of strain. In the chair form of cyclohexane, which does not exhibit any of the three kinds of strain, all six carbon–carbon bonds have the two attached carbons in the gauche conformation. However, in five-membered rings and in rings containing from 7 to 13 carbons any conformation in which all the ring bonds are gauche contains transannular interactions, that is, interactions between the substituents on C-1 and C-3 or C-1 and C-4, and so on. These interactions occur because the internal space is not large enough for all the quasiaxial hydrogen atoms to fit without coming into conflict. The molecule can adopt other conformations in which this *transannular strain* is reduced, but then some of the carbon–carbon bonds must adopt eclipsed or partially eclipsed conformations. The strain resulting from eclipsed conformations is called *Pitzer strain*. For saturated rings from 3- to 13-membered (except for the chair form of cyclohexane) there is no escape from at least one of these two types of strain. In practice, each ring adopts conformations that minimize both sorts of strain as much as possible. For cyclopentane, as we have seen (p. 212), this means that the molecule is not planar. In rings larger than

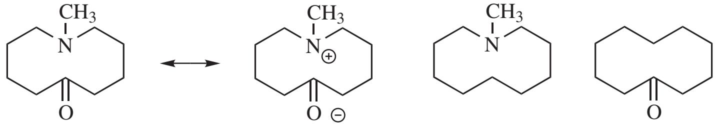
[448]For a review, see Wiberg, K.B. *Acc. Chem. Res.* ***1984***, *17*, 379.
[449]Scott, W.B.; Pincock, R.E. *J. Am. Chem. Soc.* ***1973***, *95*, 2040.
[450]Gibbons, C.S.; Trotter, J. *Can. J. Chem.* ***1973***, *51*, 87.
[451]For reviews, see Gol'dfarb, Ya.L.; Belen'kii, L.I. *Russ. Chem. Rev.* ***1960***, *29*, 214; Raphael, R.A. *Proc. Chem. Soc.* ***1962***, 97; Sicher, J. *Prog. Stereochem.* ***1962***, *3*, 202.

9-membered, Pitzer strain seems to disappear, but transannular strain is still present.[452] For 9- and 10-membered rings, some of the transannular and Pitzer strain may be relieved by the adoption of a third type of strain, *large-angle strain*. Thus, C—C—C angles of 115–120° have been found in X-ray diffraction of cyclononylamine hydrobromide and 1,6-diaminocyclodecane dihydrochloride.[453]



126

Strain can exert other influences on molecules. 1-Aza-2-adamantanone (**126**) is an extreme case of a twisted amide.[454] The overlap of the lone pair electrons on nitrogen with the π-system of the carbonyl is prevented.[454] In chemical reactions, **126** reacts more or less like a ketone, giving a Wittig reaction (**16-44**) and it can form a ketal (**16-7**). A twisted biadamantylidene compound has been reported.[455]



127a **127b** **128** **129**

The amount of strain in cycloalkanes is shown in Table 4.6,[456] which lists heats of combustion per CH_2 group. As can be seen, cycloalkanes larger than 13-membered are as strain-free as cyclohexane.

Transannular interactions can exist across rings from 8- to 11-membered and even larger.[457] Such interactions can be detected by dipole and spectral measurements. For example, that the carbonyl group in **127a** is affected by the nitrogen (**127b** is probably another canonical form) has been demonstrated by photoelectron spectroscopy, which shows that the ionization potentials of the nitrogen *n* and C=O π orbitals in **127** differ from those of the two comparison molecules **128** and **129**,[458] It is significant that when **127** accepts a proton, it goes to the

[452]Huber-Buser, E.; Dunitz, J.D. *Helv. Chim. Acta* ***1960***, *43*, 760.

[453]Dunitz, J.D.; Venkatesan, K. *Helv. Chim. Acta* ***1961***, *44*, 2033.

[454]Kirby, A.J.; Komarov, I.V.; Wothers, P.D.; Feeder, N. *Angew. Chem. Int. Ed.*, ***1998***, *37*, 785. For other examples of twisted amides, see Duspara, P.A.; Matta, C.F.; Jenkins, S.I.; Harrison, P.H.M. *Org. Lett.* ***2001***, *3*, 495; Madder, R.D.; Kim, C.-Y.; Chandra, P.P.; Doyon, J.B.; Barid Jr., T.A.; Fierke, C.A.; Christianson, D.W.; Voet, J.G.; Jain, A. *J. Org. Chem.* ***2002***, *67*, 582.

[455]Okazaki, T.; Ogawa, K.; Kitagawa, T.; Takeuchi, K. *J. Org. Chem.* ***2002***, *67*, 5981.

[456]Gol'dfarb, Ya.L.; Belen'kii, L.I. *Russ. Chem. Rev.* ***1960***, *29*, 214, p. 218.

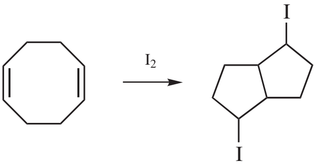
[457]For a review, see Cope, A.C.; Martin, M.M.; McKervey, M.A. *Q. Rev. Chem. Soc.* ***1966***, *20*, 119.

[458]Spanka, G.; Rademacher, P. *J. Org. Chem.* ***1986***, *51*, 592. See also, Spanka, G.; Rademacher, P.; Duddeck, H. *J. Chem. Soc. Perkin Trans. 2 1988*, 2119; Leonard, N.J.; Fox, R.C.; Ō ki, M. *J. Am. Chem. Soc.* ***1954***, *76*, 5708.

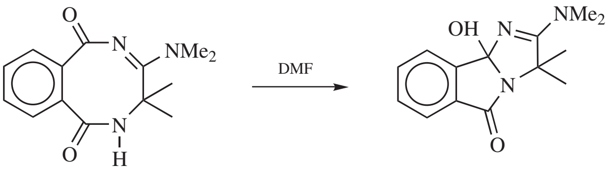
TABLE 4.6. Heats of Combustion in the Gas Phase for Cycloalkanes, per CH_2 Group[456]

	$-\Delta H_c$, (g)			$-\Delta H_c$, (g)	
Size of Ring	kcal mol^{-1}	kJ mol^{-1}	Size of Ring	kcal mol^{-1}	kJ mol^{-1}
3	166.3	695.8	10	158.6	663.6
4	163.9	685.8	11	158.4	662.7
5	158.7	664.0	12	157.8	660.2
6	157.4	658.6	13	157.7	659.8
7	158.3	662.3	14	157.4	658.6
8	158.6	663.6	15	157.5	659.0
9	158.8	664.4	16	157.5	659.0

oxygen rather than to the nitrogen. Many examples of transannular reactions are known, including:



Ref. 459



Ref. 460

In summary, we can divide saturated rings into four groups, of which the first and third are more strained than the other two.[461]

1. *Small rings* (3- and 4-membered). Small-angle strain predominates.
2. *Common rings* (5-, 6-, and 7-membered). Largely unstrained. The strain that is present is mostly Pitzer strain.
3. *Medium rings* (8- to 11-membered). Considerable strain; Pitzer, transannular, and large-angle strain.
4. *Large rings* (12-membered and larger). Little or no strain.[462]

[459]Uemura, S.; Fukuzawa, S.; Toshimitsu, A.; Okano, M.; Tezuka, H.; Sawada, S. *J. Org. Chem.* ***1983***, *48*, 270.

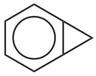
[460]Schläpfer-Dähler, M.; Prewo, R.; Bieri, J.H.; Germain, G.; Heimgartner, H. *Chimia* ***1988***, *42*, 25.

[461]For a review on the influence of ring size on the properties of cyclic systems, see Granik, V.G. *Russ. Chem. Rev.* ***1982***, *51*, 119.

[462]An example is the calculated strain of 1.4–3.2 kcal mol^{-1} in cyclotetradecane. See Chickos, J.S.; Hesse, D.G.; Panshin, S.Y.; Rogers, D.W.; Saunders, M.; Uffer, P.M.; Liebman, J.F. *J. Org. Chem.* ***1992***, *57*, 1897.

Unsaturated Rings[463]

Double bonds can exist in rings of any size. As expected, the most highly strained are the three-membered rings. Small-angle strain, which is so important in cyclopropane, is even greater in cyclopropene[464] because the ideal angle is greater. In cyclopropane, the bond angle is forced to be 60°, ~50° smaller than the tetrahedral angle; but in cyclopropene, the angle, also ~60°, is now ~60° smaller than the ideal angle of 120°. Thus, the angle is cyclopropene is ~10° more strained than in cyclopropane. However, this additional strain is offset by a decrease in strain arising from another factor. Cyclopropene, lacking two hydrogens, has none of the eclipsing



Benzocyclopropene

strain present in cyclopropane. Cyclopropene has been prepared[465] and is stable at liquid-nitrogen temperatures, although on warming even to −80°C it rapidly polymerizes. Many other cyclopropenes are stable at room temperature and above.[464] The highly strained benzocyclopropene,[466] in which the cyclopropene ring is fused to a benzene ring, has been prepared[467] and is stable for weeks at room temperature, although it decomposes on distillation at atmospheric pressure.

As previously mentioned, double bonds in relatively small rings must be cis. A stable trans double bond[468] first appears in an eight-membered ring (*trans*-cyclooctene, p. 150), although the transient existence of *trans*-cyclohexene and cycloheptene has been demonstrated.[469] Above ~11 members, the trans isomer

[463]For a review of strained double bonds, see Zefirov, N.S.; Sokolov, V.I. *Russ. Chem. Rev.* ***1967***, *36*, 87. For a review of double and triple bonds in rings, see Johnson, R.P. *Mol. Struct. Energ.* ***1986***, *3*, 85.

[464]For reviews of cyclopropenes, see Baird, M.S. *Top. Curr. Chem.* ***1988***, *144*, 137; Halton, B.; Banwell, M.G. in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 2, pp. Wiley, NY, ***1987***, pp. 1223–1339; Closs, G.L. *Adv. Alicyclic Chem.* ***1966***, *1*, 53; For a discussion of the bonding and hybridization, see Allen, F.H. *Tetrahedron* ***1982***, *38*, 645.

[465]Dem'yanov, N.Ya.; Doyarenko, M.N. *Bull. Acad. Sci. Russ.* ***1922***, *16*, 297, *Ber.* ***1923***, *56*, 2200; Schlatter, M.J. *J. Am. Chem. Soc.* ***1941***, *63*, 1733; Wiberg, K.B.; Bartley, W.J. *J. Am. Chem. Soc.* ***1960***, *82*, 6375; Stigliani, W.M.; Laurie, V.W.; Li, J.C. *J. Chem. Phys.* ***1975***, *62*, 1890.

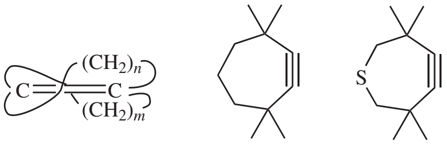
[466]For reviews of cycloproparenes, see Halton, B. *Chem. Rev.* ***1989***, *89*, 1161; ***1973***, *73*, 113; Billups, W.E.; Rodin, W.A.; Haley, M.M. *Tetrahedron* ***1988***, *44*, 1305; Halton, B.; Stang, P.J. *Acc. Chem. Res.* ***1987***, *20*, 443; Billups, W.E. *Acc. Chem. Res.* ***1978***, *11*, 245.

[467]Vogel, E.; Grimme, W.; Korte, S. *Tetrahedron Lett.* ***1965***, 3625. Also see Anet, R.; Anet, F.A.L. *J. Am. Chem. Soc.* ***1964***, *86*, 526; Müller, P.; Bernardinelli, G.; Thi, H.C.G. *Chimia* ***1988***, *42*, 261; Neidlein, R.; Christen, D.; Poignée, V.; Boese, R.; Bläser, D.; Gieren, A.; Ruiz-Pérez, C.; Hübner, T. *Angew. Chem. Int. Ed.* ***1988***, *27*, 294.

[468]For reviews of trans cycloalkenes, see Nakazaki, M.; Yamamoto, K.; Naemura, K. *Top. Curr. Chem.* ***1984***, *125*, 1; Marshall, J.A. *Acc. Chem. Res.* ***1980***, *13*, 213.

[469]Bonneau, R.; Joussot-Dubien, J.; Salem, L.; Yarwood, A.J. *J. Am. Chem. Soc.* ***1979***, *98*, 4329; Wallraff, G.M.; Michl, J. *J. Org. Chem.* ***1986***, *51*, 1794; Squillacote, M.; Bergman, A.; De Felippis, J. *Tetrahedron Lett.* ***1989***, *30*, 6805.

is more stable than the cis.[223] It has proved possible to prepare compounds in which a trans double bond is shared by two cycloalkene rings (e.g., **130**). Such compounds have been called *[m.n]betweenanenes*, and several have been prepared with *m* and *n* values from 8 to 26.[470] The double bonds of the smaller betweenanenes, as might be expected from the fact that they are deeply buried within the bridges, are much less reactive than those of the corresponding *cis-cis* isomers.



130 **131** **132**

The smallest unstrained cyclic triple bond is found in cyclononyne.[471] Cyclooctyne has been isolated,[472] but its heat of hydrogenation shows that it is considerably strained. There have been a few compounds isolated with triple bonds in seven-membered rings. 3,3,7,7-Tetramethylcycloheptyne (**131**) dimerizes within 1 h at room temperature,[473] but the thia derivative **132**, in which the C—S bonds are longer than the corresponding C—C bonds in **131**, is indefinitely stable even at 140°C.[474] Cycloheptyne itself has not been isolated, although its transient existence has been shown.[475] Cyclohexyne[476] and its 3,3,6,6-tetramethyl derivative[477] have been trapped at 77 K, and in an argon matrix at 12 K, respectively, and IR spectra

[470]Nakazaki, M.; Yamamoto, K.; Yanagi, J. *J. Am. Chem. Soc.* ***1979***, *101*, 147; Ceré, V.; Paolucci, C.; Pollicino, S.; Sandri, E.; Fava, A. *J. Chem. Soc. Chem. Commun.* ***1980***, 755; Marshall, J.A.; Flynn, K.E. *J. Am. Chem. Soc.* ***1983***, *105*, 3360. For reviews, see Nakazaki, M.; Yamamoto, K.; Naemura, K. *Top. Curr. Chem.* ***1984***, *125*, 1; Marshall, J.A. *Acc. Chem. Res.* ***1980***, *13*, 213. For a review of these and similar compounds, see Borden, W.T. *Chem. Rev.* ***1989***, *89*, 1095.

[471]For reviews of triple bonds in rings, see Meier, H. *Adv. Strain Org. Chem.* ***1991***, *1*, 215; Krebs, A.; Wilke, J. *Top. Curr. Chem.* ***1983***, *109*, 189; Nakagawa, M., in Patai, S. *The Chemistry of the C≡C Triple Bond*, pt. 2; Wiley, NY, ***1978***, pp. 635–712; Krebs, A. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 987–1062. For a list of strained cycloalkynes that also have double bonds, see Meier, H.; Hanold, N.; Molz, T.; Bissinger, H.J.; Kolshorn, H.; Zountsas, J. *Tetrahedron* ***1986***, *42*, 1711.

[472]Blomquist, A.T.; Liu, L.H. *J. Am. Chem. Soc.* ***1953***, *75*, 2153. See also, Bühl, H.; Gugel, H.; Kolshorn, H.; Meier, H. *Synthesis* ***1978***, 536.

[473]Krebs, A.; Kimling, H. *Angew. Chem. Int. Ed.* ***1971***, *10*, 509; Schmidt, H.; Schweig, A.; Krebs, A. *Tetrahedron Lett.* ***1974***, 1471.

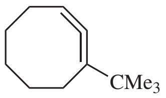
[474]Krebs, A.; Kimling, H. *Tetrahedron Lett. 1970*, 761.

[475]Wittig, G.; Meske-Schüller, J. *Liebigs Ann. Chem.* ***1968***, *711*, 65; Krebs, A.; Kimling, H. *Angew. Chem. Int. Ed.* ***1971***, *10*, 509; Bottini, A.T.; Frost II, K.A.; Anderson, B.R.; Dev, V. *Tetrahedron* ***1973***, *29*, 1975.

[476]Wentrup, C.; Blanch, R.; Briehl, H.; Gross, G. *J. Am. Chem. Soc.* ***1988***, *110*, 1874.

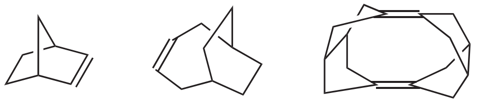
[477]See Sander, W.; Chapman, O.L. *Angew. Chem. Int. Ed.* ***1988***, *27*, 398; Krebs, A.; Colcha, W.; Müller, M.; Eicher, T.; Pielartzik, H.; Schnöckel, H. *Tetrahedron Lett.* ***1984***, *25*, 5027.

have been obtained. Transient six-and even five-membered rings containing triple bonds have also been demonstrated.[478]



133

A derivative of cyclopentyne has been trapped in a matrix.[479] Although cycloheptyne and cyclohexyne have not been isolated at room temperatures, Pt(0) complexes of these compounds have been prepared and are stable.[480] The smallest cyclic allene[481] so far isolated is 1-*tert*-butyl-1,2-cyclooctadiene **133**.[482] The parent 1,2-cyclooctadiene has not been isolated. It has been shown to exist transiently, but rapidly dimerizes.[483] The presence of the *tert*-butyl group apparently prevents this. The transient existence of 1,2-cycloheptadiene has also been shown,[484] and both 1,2-cyclooctadiene and 1,2-cycloheptadiene have been isolated in platinum complexes.[485] 1,2-Cyclohexadiene has been trapped at low temperatures, and its structure has been proved by spectral studies.[486] Cyclic allenes in general are less strained than their acetylenic isomers.[487] The cyclic cumulene 1,2,3-cyclononatriene has also been synthesized and is reasonably stable in solution at room temperature in the absence of air.[488]



134 **135** **136**

There are many examples of polycyclic molecules and bridged molecules that have one or more double bonds. There is flattening of the ring containing the C=C unit, and this can have a significant effect on the molecule. Norbornene (bicyclo[2.2.1]hept-2-ene; **134**) is a simple example and it has been calculated that it contains a distorted

[478]See, for example, Wittig, G. Mayer, U. *Chem. Ber.* ***1963***, *96*, 329, 342; Wittig, G.; Weinlich, J. *Chem. Ber.* ***1965***, *98*, 471; Bolster, J.M.; Kellogg, R.M. *J. Am. Chem. Soc.* ***1981***, *103*, 2868; Gilbert, J.C.; Baze, M.E. *J. Am. Chem. Soc.* ***1983***, *105*, 664.

[479]Chapman, O.L.; Gano, J.; West, P.R.; Regitz, M.; Maas, G. *J. Am. Chem. Soc.* ***1981***, *103*, 7033.

[480]Bennett, M.A.; Robertson, G.B.; Whimp, P.O.; Yoshida, T. *J. Am. Chem. Soc.* ***1971***, *93*, 3797.

[481]For reviews of cyclic allenes, see Johnson, R.P. *Adv. Theor. Interesting Mol.* ***1989***, *1*, 401; *Chem. Rev.* ***1989***, *89*, 1111; Thies, R.W. *Isr. J. Chem.* ***1985***, *26*, 191; Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis*; Wiley, NY, ***1984***, pp. 38–56.

[482]Price, J.D.; Johnson, R.P. *Tetrahedron Lett.* ***1986***, *27*, 4679.

[483]See Marquis, E.T.; Gardner, P.D. *Tetrahedron Lett.* ***1966***, 2793.

[484]Wittig, G.; Dorsch, H.; Meske-Schüller, J. *Liebigs Ann. Chem.* ***1968***, *711*, 55.

[485]Visser, J.P.; Ramakers, J.E. *J. Chem. Soc. Chem. Commun.* ***1972***, 178.

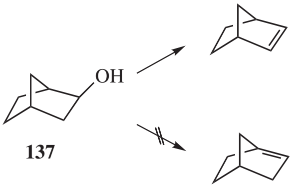
[486]Wentrup, C.; Gross, G.; Maquestiau, A.; Flammang, R. *Angew. Chem. Int. Ed.* ***1983***, *22*, 542. 1,2,3-Cyclohexatriene has also been trapped: Shakespeare, W.C.; Johnson, R.P. *J. Am. Chem. Soc.* ***1990***, *112*, 8578.

[487]Moore, W.R.; Ward, H.R. *J. Am. Chem. Soc.* ***1963***, *85*, 86.

[488]Angus Jr., R.O.; Johnson, R.P. *J. Org. Chem.* ***1984***, *49*, 2880.

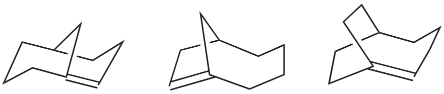
π-face.[489] The double bond can appear away from the bridgehead carbon atoms, as in bicyclo[4.2.2]dec-3-ene (**135**) and that part of the molecule is flattened. In pentacyclo[8.2.1.$1^{2,5}$.$1^{4,7}$.$1^{8,11}$]hexadeca-1,7-diene (**136**), the C=C units are held in a position where there is significant π–π interactions across the molecule.[490]

Double bonds at the bridgehead of bridged bicyclic compounds are impossible in small systems. This is the basis of *Bredt's rule*,[491] which states that elimination to give a double bond in a bridged bicyclic system (e.g., **137**) always leads away from the bridgehead. This rule no longer applies when the rings are large enough. In



137

determining whether a bicyclic system is large enough to accommodate a bridgehead double bond, the most reliable criterion is the size of the ring in which the double bond is located.[492] Bicyclo[3.3.1]non-1-ene[493] (**138**) and bicyclo-[4.2.1]non-1(8)ene[494] (**139**) are stable compounds. Both can be looked upon as derivatives of *trans*-cyclooctene, which is of course a known compound. Compound **138** has been shown to have a strain energy of the same order of magnitude



138 **139** **140**

as that of *trans*-cyclooctene.[495] On the other hand, in bicyclo[3.2.2]non-1-ene (**140**), the largest ring that contains the double bond is *trans*-cycloheptene, which is as yet unknown. Compound **140** has been prepared, but dimerized before it could be isolated.[496] Even smaller systems ([3.2.1] and [2.2.2]), but with imine double

[489]Ohwada, T. *Tetrahedron* ***1993***, *49*, 7649.

[490]Lange, H.; Schäfer, W.; Gleiter, R.; Camps, P.; Vázquez, S. *J. Org. Chem.* ***1998***, *63*, 3478.

[491]For reviews, see Shea, K.J. *Tetrahedron* ***1980***, *36*, 1683; Buchanan, G.L. *Chem. Soc. Rev.* ***1974***, *3*, 41; Köbrich, G. *Angew. Chem. Int. Ed.* ***1973***, *12*, 464. For reviews of bridgehead olefins, see Billups, W.E.; Haley, M.M.; Lee, G. *Chem. Rev.* ***1989***, *89*, 1147; Warner, P.M. *Chem. Rev.* ***1989***, *89*, 1067; Szeimies, G. *React. Intermed. (Plenum)* ***1983***, *3*, 299; Keese, R. *Angew. Chem. Int. Ed.* ***1975***, *14*, 528. Also see, Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY, ***2001***, pp. 502–504.

[492]For a discussion and predictions of stability in such compounds, see Maier, W.F.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1981***, *103*, 1891.

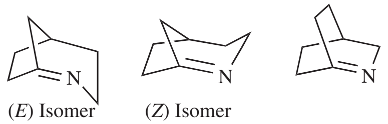
[493]Marshall, J.A.; Faubl, H. *J. Am. Chem. Soc.* ***1967***, *89*, 5965, ***1970***, *92*, 948; Wiseman, J.R.; Pletcher, W.A. *J. Am. Chem. Soc.* ***1970***, *92*, 956; Kim, M.; White, J.D. *J. Am. Chem. Soc.* ***1975***, *97*, 451; Becker, K.B. *Helv. Chim. Acta* ***1977***, *60*, 81. For the preparation of optically active **125**, see Nakazaki, M.; Naemura, K.; Nakahara, S. *J. Org. Chem.* ***1979***, *44*, 2438.

[494]Wiseman, J.R.; Chan, H.; Ahola, C.J. *J. Am. Chem. Soc.* ***1969***, *91*, 2812; Carruthers, W.; Qureshi, M.I. *Chem. Commun.* ***1969***, 832; Becker, K.B. *Tetrahedron Lett.* ***1975***, 2207.

[495]Lesko, P.M.; Turner, R.B. *J. Am. Chem. Soc.* ***1968***, *90*, 6888; Burkert, U. *Chem. Ber.* ***1977***, *110*, 773.

[496]Wiseman, J.R.; Chong, J.A. *J. Am. Chem. Soc.* ***1969***, *91*, 7775.

bonds (**141–143**), have been obtained in matrixes at low temperatures.[497] These compounds are destroyed on warming. Compounds **141** and **142** are the first reported example of (*E–Z*) isomerism at a strained bridgehead double bond.[498]

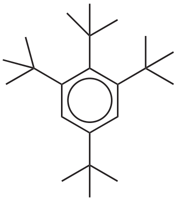


(*E*) Isomer (*Z*) Isomer

141 **142** **143**

Strain Due to Unavoidable Crowding[499]

In some molecules, large groups are so close to each other that they cannot fit into the available space in such a way that normal bond angles are maintained. It has proved possible to prepare compounds with a high degree of this type of strain. For example, success has been achieved in synthesizing benzene rings containing *ortho*-*tert*-butyl groups. Two examples that have been prepared, of several, are 1,2,3-tri-*tert*-butyl compound **144**[500] and the 1,2,3,4-tetra-*tert*-butyl compound **145**.[501] That these molecules are strained is demonstrated by UV and IR spectra,



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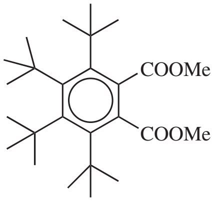

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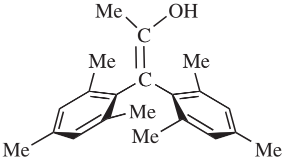

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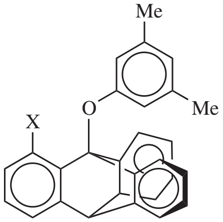


147

[497]Sheridan, R.S.; Ganzer, G.A. *J. Am. Chem. Soc.* ***1983***, *105*, 6158; Radziszewski, J.G.; Downing, J.W.; Wentrup, C.; Kaszynski, P.; Jawdosiuk, M.; Kovacic, P.; Michl, J. *J. Am. Chem. Soc.* ***1985***, *107*, 2799.

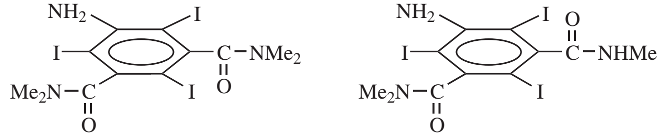
[498]Radziszewski, J.G.; Downing, J.W.; Wentrup, C.; Kaszynski, P.; Jawdosiuk, M.; Kovacic, P.; Michl, J. *J. Am. Chem. Soc.* ***1985***, *107*, 2799.

[499]For reviews, see Tidwell, T.T. *Tetrahedron* ***1978***, *34*, 1855; Voronenkov, V.V.; Osokin, Yu.G. *Russ. Chem. Rev.* ***1972***, *41*, 616. For a review of early studies, see Mosher, H.S.; Tidwell, T.T. *J. Chem. Educ.* ***1990***, *67*, 9. For a review of van der Waals radii, see Zefirov, Yu.V.; Zorkii, P.M. *Russ. Chem. Rev.* ***1989***, *58*, 421.

[500]Arnett, E.M.; Bollinger, J.M. *Tetrahedron Lett.* ***1964***, 3803.

[501]Maier, G.; Schneider, K. *Angew. Chem. Int. Ed.* ***1980***, *19*, 1022. For another example, see Krebs, A.; Franken, E.; Müller, S. *Tetrahedron Lett.* ***1981***, *22*, 1675.

which show that the ring is not planar in 1,2,4-tri-*tert*-butylbenzene, and by a comparison of the heats of reaction of this compound and its 1,3,5 isomer, which show that the 1,2,4 compound possesses ~22 kcal mol^{-1} (92 kJ mol^{-1}) more strain energy than its isomer[502] (see also, p. 1642). Since $SiMe_3$ groups are larger than CMe_3 groups, and it has proven possible to prepare $C_6(SiMe_3)_6$. This compound has a chair-shaped ring in the solid state, and a mixture of chair and boat forms in solution.[503] Even smaller groups can sterically interfere in ortho positions. In hexaisopropylbenzene, the six isopropyl groups are so crowded that they cannot rotate but are lined up around the benzene ring, all pointed in the same direction.[504] This compound is an example of a *geared molecule*.[505] The isopropyl groups fit into each other in the same manner as interlocked gears. Another example



cis trans

is **146** (which is a stable enol).[506] In this case each ring can rotate about its C—aryl bond only by forcing the other to rotate as well. In the case of triptycene derivatives, such as **147**, a complete 360° rotation of the aryl group around the O—aryl bond requires the aryl group to pass over three rotational barriers; one of which is the C—X bond and other two the "top" C–H bonds of the other two rings. As expected, the C—X barrier is the highest, ranging from 10.3 kcal mol^{-1} (43.1 kJ mol^{-1}) for X = F to 17.6 kcal mol^{-1} (73.6 kJ mol^{-1}) for X = *tert*-butyl.[507] In another instance, it has proved possible to prepare cis and trans isomers of 5-amino-2,4,6-triiodo-*N,N,N′,N′*-tetramethylisophthalamide because there is no room for the $CONMe_2$ groups to rotate, caught as they are between two bulky iodine atoms.[508] The trans isomer is chiral and has been resolved, while the cis isomer is a meso form. Another

[502] Arnett, E.M.; Sanda, J.C.; Bollinger, J.M.; Barber, M. *J. Am. Chem. Soc.* ***1967***, *89*, 5389; Krüerke, U.; Hoogzand, C.; Hübel, W. *Chem. Ber.* ***1961***, *94*, 2817; Dale, J. *Chem. Ber.* ***1961***, *94*, 2821. See also Barclay, L.R.C.; Brownstein, S.; Gabe, E.J.; Lee, F.L. *Can. J. Chem.* ***1984***, *62*, 1358.

[503] Sakurai, H.; Ebata, K.; Kabuto, C.; Sekiguchi, A. *J. Am. Chem. Soc.* ***1990***, *112*, 1799.

[504] Arnett, E.M.; Bollinger, J.M. *J. Am. Chem. Soc.* ***1964***, *86*, 4730; Hopff, H.; Gati, A. *Helv. Chim. Acta* ***1965***, *48*, 509; Siegel, J.; Gutiérrez, A.; Schweizer, W.B.; Ermer, O.; Mislow, K. *J. Am. Chem. Soc.* ***1986***, *108*, 1569. For the similar structure of hexakis(dichloromethyl)benzene, see Kahr, B.; Biali, S.E.; Schaefer, W.; Buda, A.B.; Mislow, K. *J. Org. Chem.* ***1987***, *52*, 3713.

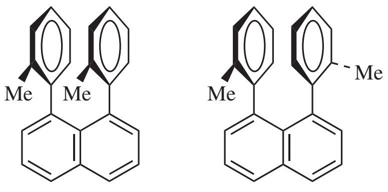
[505] For reviews, see Iwamura, H.; Mislow, K. *Acc. Chem. Res.* ***1988***, *21*, 175; Mislow, K. *Chemtracts: Org. Chem.* ***1989***, *2*, 151; *Chimia*, ***1986***, *40*, 395; Berg, U.; Liljefors, T.; Roussel, C.; Sandström, J. *Acc. Chem. Res.* ***1985***, *18*, 80.

[506] Nugiel, D.A.; Biali, S.E.; Rappoport, Z. *J. Am. Chem. Soc.* ***1984***, *106*, 3357.

[507] Yamamoto, G.; Ō ki, M. *Bull. Chem. Soc. Jpn.* ***1986***, *59*, 3597. For reviews of similar cases, see Yamamoto, G. *Pure Appl. Chem.* ***1990***, *62*, 569; Ō ki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, ***1985***, pp. 269–284.

[508] Ackerman, J.H.; Laidlaw, G.M.; Snyder, G.A. *Tetrahedron Lett.* ***1969***, 3879; Ackerman, J.H.; Laidlaw, G.M. *Tetrahedron Lett.* ***1969***, 4487. See also Cuyegkeng, M.A.; Mannschreck, A. *Chem. Ber.* ***1987***, *120*, 803.

example of cis–trans isomerism resulting from restricted rotation about single bonds[509] is found in 1,8-di-*o*-tolylnapthalene[510] (see also, p. 182).



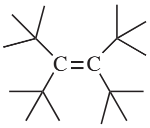
cis trans

There are many other cases of intramolecular crowding that result in the distortion of bond angles. We have already mentioned hexahelicene (p. 150) and bent benzene rings (p. 48). The compounds tri-*tert*-butylamine and tetra-*tert*-butylmethane are as yet unknown. In the latter, there is no way for the strain to be relieved and it is questionable whether this compound can ever be made. In tri-*tert*-butylamine the crowding can be eased somewhat if the three bulky groups assume a planar instead of the normal pyramidal configuration. In tri-*tert*-butylcarbinol, coplanarity of the three *tert*-butyl groups is prevented by the presence of the OH group, and yet this compound has been prepared.[511] Tri-*tert*-butylamine should have less steric strain than tri-*tert*-butylcarbinol and it should be possible to prepare it.[512] The tetra-*tert*-butylphosphonium cation $(t\text{-Bu})_4P^+$ has been prepared.[513] Although steric effects are nonadditive in crowded molecules, a quantitative measure has been proposed by D. F. DeTar, based on molecular mechanics calculations. This is called *formal steric enthalpy* (FSE), and values have been calculated for alkanes, alkenes, alcohols, ethers, and methyl esters.[514] For example, some FSE values for alkanes are butane 0.00; 2,2,3,3-tetramethylbutane 7.27; 2,2,4,4,5-pentamethylhexane 11.30; and tri-*tert*-butylmethane 38.53.

The two carbon atoms of a C=C double bond and the four groups attached to them are normally in a plane, but if the groups are large enough, significant

[509]For a monograph on restricted rotation about single bonds, see Ōki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, ***1985***. For reviews, see Förster, H.; Vögtle, F. *Angew. Chem. Int. Ed.* ***1977***, *16*, 429; Ōki, M. *Angew. Chem. Int. Ed.* ***1976***, *15*, 87.
[510]Clough, R.L.; Roberts, J.D. *J. Am. Chem. Soc.* ***1976***, *98*, 1018. For a study of rotational barriers in this system, see Cosmo, R.; Sternhell, S. *Aust. J. Chem.* ***1987***, *40*, 1107.
[511]Bartlett, P.D.; Tidwell, T.T. *J. Am. Chem. Soc.* ***1968***, *90*, 4421.
[512]For attempts to prepare tri-*tert*-butylamine, see Back, T.G.; Barton, D.H.R. *J. Chem. Soc. Perkin Trans 1*, ***1977***, 924. For the preparation of di-*tert*-butylmethylamine and other sterically hindered amines, see Kopka, I.E.; Fataftah, Z.A.; Rathke, M.W. *J. Org. Chem.* ***1980***, *45*, 4616; Audeh, C.A.; Fuller, S.E.; Hutchinson, R.J.; Lindsay Smith, J.R. *J. Chem. Res. (S)*, ***1979***, 270.
[513]Schmidbaur, H.; Blaschke, G.; Zimmer-Gasser, B.; Schubert, U. *Chem. Ber.* ***1980***, *113*, 1612.
[514]DeTar, D.F.; Binzet, S.; Darba, P. *J. Org. Chem.* ***1985***, *50*, 2826, 5298, 5304.

deviation from planarity can result.[515] The compound tetra-*tert*-butylethene (**148**) has not been prepared,[516] but the tetraaldehyde **149**, which should have about the same amount of strain, has been made. X-ray crystallography shows that **149** is twisted out of a planar shape by an angle of 28.6°.[517] Also, the C=C double-bond distance is 1.357 Å, significantly longer than a normal C=C bond of 1.32 Å (Table 1.5). (*Z*)-1,2-Bis(*tert*-butyldimethylsilyl)-1,2-bis(trimethylsilyl)ethene (**150**) has an even greater twist, but could not be made to undergo conversion to the (*E*) isomer, probably because the groups are too large to slide past each other.[518] A different kind of double bond strain is found in tricyclo[4.2.2.2^{2,5}]dodeca-1,5-diene (**151**),[519] cubene (**152**),[520] and homocub-4(5)-ene (**153**).[521] In these molecules, the four groups on the double bond are all forced to be on one side



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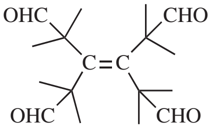

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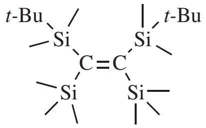
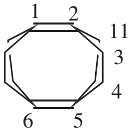


150

of the double-bond plane.[522] In **151**, the angle between the line C_1—C_2 (extended) and the plane defined by C_2, C_3, and C_{11} is 27°. An additional source of strain in this molecule is the fact that the two double bonds are pushed



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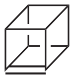

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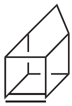


153

into close proximity by the four bridges. In an effort to alleviate this sort of strain, the bridge bond distances (C_3—C_4) are 1.595 Å, which is considerably longer than the 1.53 Å expected for a normal sp^3–sp^3 C—C bond (Table 1.5). Compounds **152** and **153** have ***not*** been isolated, but have been generated as intermediates that were trapped by reaction with other compounds.[520,521]

[515]For reviews, see Luef, W.; Keese, R. *Top. Stereochem.* ***1991***, *20*, 231; Sandström, J. *Top. Stereochem.* ***1983***, *14*, 83, pp. 160–169.

[516]For a list of crowded alkenes that have been made, see Drake, C.A.; Rabjohn, N.; Tempesta, M.S.; Taylor, R.B. *J. Org. Chem.* ***1988***, *53*, 4555. See also, Garratt, P.J.; Payne, D.; Tocher, D.A. *J. Org. Chem.* ***1990***, *55*, 1909.

[517]Krebs, A.; Nickel, W.; Tikwe, L.; Kopf, J. *Tetrahedron Lett.* ***1985***, *26*, 1639.

[518]Sakurai, H.; Ebata, K.; Kabuto, C.; Nakadaira, Y. *Chem. Lett.* ***1987***, 301.

[519]Wiberg, K.B.; Matturo, M.G.; Okarma, P.J.; Jason, M.E. *J. Am. Chem. Soc.* ***1984***, *106*, 2194; Wiberg, K.B.; Adams, R.D.; Okarma, P.J.; Matturo, M.G.; Segmuller, B. *J. Am. Chem. Soc.* ***1984***, *106*, 2200.

[520]Eaton, P.E.; Maggini, M. *J. Am. Chem. Soc.* ***1988***, *110*, 7230.

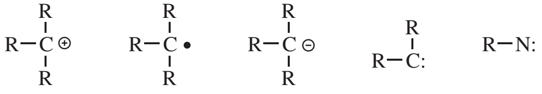
[521]Hrovat, D.A.; Borden, W.T. *J. Am. Chem. Soc.* ***1988***, *110*, 7229.

[522]For a review of such molecules, see Borden, W.T. *Chem. Rev.* ***1989***, *89*, 1095. See also, Hrovat, D.A.; Borden, W.T. *J. Am. Chem. Soc.* ***1988***, *110*, 4710.

CHAPTER 5

Carbocations, Carbanions, Free Radicals, Carbenes, and Nitrenes

There are four types of organic species in which a carbon atom has a valence of only 2 or 3.[1] They are usually very short-lived, and most exist only as intermediates that are quickly converted to more stable molecules. However, some are more stable than others and fairly stable examples have been prepared of three of the four



types. The four types of species are *carbocations* (**A**), *free radicals* (**B**), *carbanions* (**C**), and *carbenes* (**D**). Of the four, only carbanions have a complete octet around the carbon. There are many other organic ions and radicals with charges and unpaired electrons on atoms other than carbon, but we will discuss only *nitrenes* (**E**), the nitrogen analogs of carbenes. Each of the five types is discussed in a separate section, which in each case includes brief summaries of the ways in which the species form and react. These summaries are short and schematic. The generation and fate of the five types are more fully treated in appropriate places in Part 2 of this book.

[1]For general references, see Isaacs, N.S. *Reactive Intermediates in Organic Chemistry*, Wiley, NY, ***1974***; McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, ***1973***. Two serial publications devoted to review articles on this subject are *Reactive Intermediates (Wiley)* and *Reactive Intermediates (Plenum)*.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Sixth Edition, by Michael B. Smith and Jerry March
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CARBOCATIONS[2]

Nomenclature

First, we must say a word about the naming of **A**. For many years these species were called "carbonium ions," although it was suggested[3] as long ago as 1902 that this was inappropriate because "-onium" usually refers to a covalency higher than that of the neutral atom. Nevertheless, the name "carbonium ion" was well established and created few problems[4] until some years ago, when George Olah and his co-workers found evidence for another type of intermediate in which there is a positive charge at a carbon atom, but in which the formal covalency of the carbon atom is five rather than three. The simplest example is the methanonium ion CH_5^+ (see p. 766). Olah proposed[5] that the name "carbonium ion" be reserved for pentacoordinated positive ions, and that **A** be called "carbenium ions." He also proposed the term "carbocation" to encompass both types. The International Union of Pure and Applied Chemistry (IUPAC) has accepted these definitions.[6] Although some authors still refer to **A** as carbonium ions and others call them carbenium ions, the general tendency is to refer to them simply as *carbocations*, and we will follow this practice. The pentavalent species are much rarer than **A**, and the use of the term "carbocation" for **A** causes little or no confusion.

Stability and Structure

Carbocations are intermediates in several kinds of reactions.[7] The more stable ones have been prepared in solution and in some cases even as solid salts, and X-ray crystallographic structures have been obtained in some cases.[8] The X-ray of the

[2]For a treatise, see Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, 5 vols., Wiley, NY, ***1968–1976***. For monographs, see Vogel, P. *Carbocation Chemistry*, Elsevier, NY, ***1985***; Bethell, D.; Gold, V. *Carbonium Ions*, Academic Press, NY, ***1967***. For reviews, see Saunders, M.; Jiménez-Vázquez, H.A. *Chem. Rev.* ***1991***, *91*, 375; Arnett, E.M.; Hofelich, T.C.; Schriver, G.W. *React. Intermed. (Wiley)* ***1987***, *3*, 189; Bethell, D.; Whittaker, D. *React. Intermed. (Wiley)* ***1981***, *2*, 211; Bethell, D. *React. Intermed. (Wiley)* ***1978***, *1*, 117; Olah, G.A. *Chem. Scr.* ***1981***, *18*, 97, *Top. Curr. Chem.* ***1979***, *80*, 19, *Angew. Chem. Int. Ed.* ***1973***, *12*, 173 (this review has been reprinted as Olah, G.A. *Carbocations and Electrophilic Reactions*, Wiley, NY, ***1974***); Isaacs, N.S. *Reactive Intermediates in Organic Chemistry*, Wiley, NY, ***1974***, pp. 92–199; McManus, S.P.; Pittman, Jr., C.U., in McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, ***1973***, pp. 193–335; Buss, V.; Schleyer, P.v.R.; Allen, L.C. *Top. Stereochem.* ***1973***, *7*, 253; Olah, G.A.; Pittman Jr., C.U. *Adv. Phys. Org. Chem.* ***1966***, *4*, 305. For reviews of dicarbocations, see Lammertsma, K.; Schleyer, P.v.R.; Schwarz, H. *Angew. Chem. Int. Ed.* ***1989***, *28*, 1321; Pagni, R.M. *Tetrahedron* ***1984***, *40*, 4161; Prakash, G.K.S.; Rawdah, T.N.; Olah, G.A. *Angew. Chem. Int. Ed.* ***1983***, *22*, 390. See also, the series *Advances in Carbocation Chemistry.*

[3]Gomberg, M. *Berchte* ***1902***, *35*, 2397.

[4]For a history of the term "carbonium ion," see Traynham, J.G. *J. Chem. Educ.* ***1986***, *63*, 930.

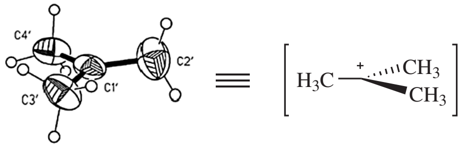
[5]Olah, G.A. *CHEMTECH* ***1971***, *1*, 566; *J. Am. Chem. Soc.* ***1972***, *94*, 808.

[6]Gold, V.; Loening, K.L.; McNaught, A.D.; Sehmi, P. *Compendium of Chemical Terminology: IUPAC Recommendations*, Blackwell Scientific Publications, Oxford, ***1987***.

[7]Olah, G.A. *J. Org. Chem.* ***2001***, *66*, 5943.

[8]See Laube, T. *J. Am. Chem.* ***2004***, 126, 10904 and references cited therein. For the X-ray of a vinyl carbocation, see Müller, T.; Juhasz, M.; Reed, C.A. *Angew. Chem. Int. Ed.* ***2004***, *43*, 1543.

tert-butyl cation complexed with dichloromethane was reported,[9] for example, and is presented as **1** with the solvent molecules removed for clarity. An isolable dioxa-stabilized pentadienylium ion was isolated and its structure was determined by ^{1}H-, ^{13}C-NMR, mass spectrometry (MS), and IR.[10] A β-fluoro substituted 4-methoxyphenethyl cation has been observed directly by laser flash photolysis.[11] In solution, the carbocation may be free (this is more likely in polar solvents, in which it is solvated) or it may exist as an ion pair,[12] which means that it is closely associated with a negative ion, called a *counterion* or *gegenion*. Ion pairs are more likely in nonpolar solvents.



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Among simple alkyl carbocations[13] the order of stability is tertiary > secondary > primary. There are many known examples of rearrangements of primary or secondary carbocations to tertiary, both in solution and in the gas phase. Since simple alkyl cations are not stable in ordinary strong-acid solutions (e.g., H_2SO_4), the study of these species was greatly facilitated by the discovery that many of them could be kept indefinitely in stable solutions in mixtures of fluorosulfuric acid and antimony pentafluoride. Such mixtures, usually dissolved in SO_2 or SO_2ClF, are among the strongest acidic solutions known and are often called *super acids*.[14] The original experiments involved the addition of alkyl fluorides to SbF_5.[15]

$$RF + SbF_5 \longrightarrow R^+ \; SbF_6^-$$

Subsequently, it was found that the same cations could also be generated from alcohols in super acid-SO_2 at −60°C[16] and from alkenes by the addition of a proton from super acid or HF—SbF_5 in SO_2 or SO_2ClF at low temperatures.[17] Even alkanes give carbocations in super acid by loss of H^-. For example,[18]

[9]Kato, T.; Reed, C.A. *Angew. Chem. Int. Ed.* ***2004***, *43*, 2908.

[10]Lüning, U.; Baumstark, R. *Tetrahedron Lett.* ***1993***, *34*, 5059.

[11]McClelland, R.A.; Cozens, F.L.; Steenken, S.; Amyes, T.L.; Richard, J.P. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 1717.

[12]For a treatise, see Szwarc, M. *Ions and Ion Pairs in Organic Reactions*, 2 vols., Wiley, NY, ***1972–1974***.

[13]For a review, see Olah, G.A.; Olah, J.A., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, WIley, NY, ***1969***, pp. 715–782. Also see Fărcaşiu, D.; Norton, S.H. *J. Org. Chem.* ***1997***, *62*, 5374.

[14]For a review of carbocations in super acid solutions, see Olah, G.A.; Prakash, G.K.S.; Sommer, J., in *Superacids*, Wiley, NY, ***1985***, pp. 65–175.

[15]Olah, G.A.; Baker, E.B.; Evans, J.C.; Tolgyesi, W.S.; McIntyre, J.S.; Bastien, I.J. *J. Am. Chem. Soc.* ***1964***, *86*, 1360; Brouwer, D.M.; Mackor, E.L. *Proc. Chem. Soc.* ***1964***, 147; Kramer, G.M. *J. Am. Chem. Soc.* ***1969***, *91*, 4819.

[16]Olah, G.A.; Sommer, J.; Namanworth, E. *J. Am. Chem. Soc.* ***1967***, *89*, 3576.

[17]Olah, G.A.; Halpern, Y. *J. Org. Chem.* ***1971***, *36*, 2354. See also, Herlem, M. *Pure Appl. Chem.* ***1977***, *49*, 107.

[18]Olah, G.A.; Lukas, J. *J. Am. Chem. Soc.* ***1967***, *89*, 4739.

isobutane gives the *tert*-butyl cation

$$\mathrm{Me_3CH} \xrightarrow{\mathrm{FSO_3H{-}SbF_6}} \mathrm{Me_3\overset{\oplus}{C}}\ \ \mathrm{SbF_5FS\overset{\ominus}{O}_3} \quad + \quad \mathrm{H_2}$$

No matter how they are generated, study of the simple alkyl cations has provided dramatic evidence for the stability order.[19] Both propyl fluorides gave the isopropyl cation; all four butyl fluorides[20] gave the *tert*-butyl cation, and all seven of the pentyl fluorides tried gave the *tert*-pentyl cation. *n*-Butane, in super acid, gave only the *tert*-butyl cation. To date, no primary cation has survived long enough for detection. Neither methyl nor ethyl fluoride gave the corresponding cations when treated with SbF_5. At low temperatures, methyl fluoride gave chiefly the methylated sulfur dioxide salt $(CH_3OSO)^+$ SbF_6^-,[21] while ethyl fluoride rapidly formed the *tert*-butyl and *tert*-hexyl cations by addition of the initially formed ethyl cation to ethylene molecules also formed.[22] At room temperature, methyl fluoride also gave the *tert*-butyl cation.[23] In accord with the stability order, hydride ion is abstracted from alkanes by super acid most readily from tertiary and least readily from primary positions.

The stability order can be explained by the polar effect and by hyperconjugation. In the polar effect, nonconjugated substituents exert an influence on stability through bonds (inductive effect) or through space (field effect). Since a tertiary carbocation has more carbon substituents on the positively charged carbon, relative to a primary, there is a greater polar effect that leads to great stability. In the hyperconjugation explanation,[24] we compare a primary carbocation with a tertiary. It should be made clear that "*the hyperconjugation concept arises solely from our model-building procedures*. When we ask whether hyperconjugation is important in a given situation, we are asking only whether the localized model is adequate for that situation at the particular level of precision we wish to use, or whether the model must be corrected by including some delocalization in order to get a good enough description."[25] Using the hyperconjugation model, is seen that the

[19]See Amyes, T.L.; Stevens, I.W.; Richard, J.P. *J. Org. Chem.* ***1993***, *58*, 6057 for a recent study.

[20]The *sec*-butyl cation has been prepared by slow addition of *sec*-butyl chloride to SbF_5—SO_2ClF solution at −110°C [Saunders, M.; Hagen, E.L.; Rosenfeld, J. *J. Am. Chem. Soc.* ***1968***, *90*, 6882] and by allowing molecular beams of the reagents to impinge on a very cold surface [Saunders, M.; Cox, D.; Lloyd, J.R. *J. Am. Chem. Soc.* ***1979***, *101*, 6656; Myhre, P.C.; Yannoni, C.S. *J. Am. Chem. Soc.* ***1981***, *103*, 230].

[21]Peterson, P.E.; Brockington, R.; Vidrine, D.W. *J. Am. Chem. Soc.* ***1976***, *98*, 2660; Calves, J.; Gillespie, R.J. *J. Chem. Soc. Chem. Commun.* ***1976***, 506; Olah, G.A.; Donovan, D.J. *J. Am. Chem. Soc.* ***1978***, *100*, 5163.

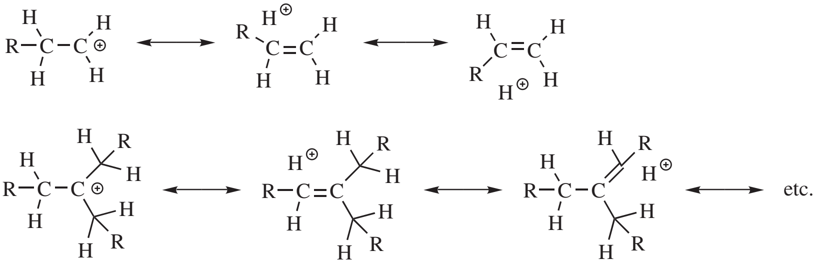
[22]Olah, G.A.; Olah, J.A., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1969***, p. 722.

[23]Olah, G.A.; DeMember, J.R.; Schlosberg, R.H. *J. Am. Chem. Soc.* ***1969***, *91*, 2112; Bacon, J.; Gillespie, R.J. *J. Am. Chem. Soc.* ***1971***, *91*, 6914.

[24]For a review of molecular-orbital theory as applied to carbocations, see Radom, L.; Poppinger, D.; Haddon, R.C., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 5, Wiley, NY, ***1976***, pp. 2303–2426.

[25]Lowry, T.H.; Richardson, K.S. *Mechanism and Theory in Organic Chemistry, 3rd ed.*, HarperCollins, NY, ***1987***, p. 68.

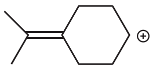
primary ion has only two hyperconjugative forms while the tertiary has six:



According to rule 6 for resonance contributors (p. 47), the greater the number of equivalent forms, the greater the resonance stability. Evidence used to support the hyperconjugation explanation is that the equilibrium constant for this reaction:

$$\underset{\mathbf{2}}{(CD_3)_3C^{\oplus}} + (CH_3)_3CH \rightleftharpoons \underset{\mathbf{3}}{(CH_3)_3C^{\oplus}} + (CD_3)_3CH \qquad K_{298} = 1.97 \pm 0.20$$

is 1.97, showing that **3** is more stable than **2**.[26] Due to a β secondary isotope effect, there is less hyperconjugation in **2** than in **3** (see p. 324 for isotope effects).[27]



4

There are several structural types of delocalization, summarized in Table 5.1.[28] The stabilization of dimethylalkylidine cation **4** is an example of double hyperconjugation.[28,29]

The field effect explanation is that the electron-donating effect of alkyl groups increases the electron density at the charge-bearing carbon, reducing the net charge on the carbon, and in effect spreading the charge over the α carbons. It is a general rule that the more concentrated any charge is, the less stable the species bearing it will be.

The most stable of the simple alkyl cations is the *tert*-butyl cation. Even the relatively stable *tert*-pentyl and *tert*-hexyl cations fragment at higher temperatures to

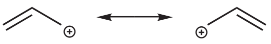
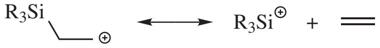
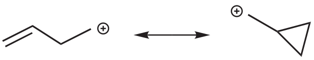
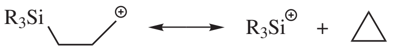
[26]Meot-Ner, M. *J. Am. Chem. Soc.* ***1987***, *109*, 7947.

[27]If only the field effect were operating, **2** would be more stable than **3**, since deuterium is electron-donating with respect to hydrogen (p. 23), assuming that the field effect of deuterium could be felt two bonds away.

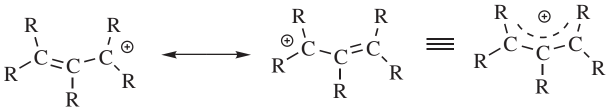
[28]Lambert, J.B.; Ciro, S.M. *J. Org. Chem.* ***1996***, *61*, 1940.

[29]Alabugin, I.V.; Manoharan, M. *J. Org. Chem.* ***2004***, *69*, 9011.

TABLE 5.1. Structural Types of Delocalization[25]

Valence Structures	Abbreviation	Name
	ππ	Simple conjugation
	σπ	Hyperconjugation
	πσ	Homoconjugation
	σσ	Homohyperconjugation
	σπ/ππ	Hyperconjugation/ conjugation
	σπ/σπ	Double hyperconjugation

produce the *tert*-butyl cation, as do all other alkyl cations with four or more carbons so far studied.[30] Methane,[31] ethane, and propane, treated with super acid, also yield *tert*-butyl cations as the main product (see reaction **12-20**). Even paraffin wax and polyethylene give *tert*-butyl cation. Solid salts of *tert*-butyl and *tert*-pentyl cations (e.g., Me_3C^+ SbF_6^-) have been prepared from super acid solutions and are stable below −20°C.[32]



5

In carbocations where the positive carbon is in conjugation with a double bond, as in allylic cations (the allyl cation is **5**, R = H), the stability is greater because of increased delocalization due to resonance,[33] where the positive charge is spread over several atoms instead of being concentrated on one (see the molecular-orbital picture of this species on p. 41). Each of the terminal atoms has a charge of $\sim\frac{1}{2}$ (the charge is exactly $\frac{1}{2}$ if all of the R groups are the same). Stable cyclic and

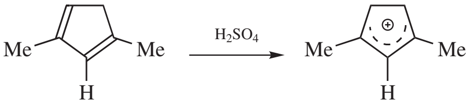
[30]Olah, G.A.; Lukas, J. *J. Am. Chem. Soc.* ***1967***, *89*, 4739; Olah, G.A.; Olah, J.A., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1969***, pp. 750–764.

[31]Olah, G.A.; Klopman, G.; Schlosberg, R.H. *J. Am. Chem. Soc.* ***1969***, *91*, 3261. See also, Hogeveen, H.; Gaasbeek, C.J. *Recl. Trav. Chim. Pays-Bas* ***1968***, *87*, 319.

[32]Olah, G.A.; Svoboda, J.J.; Ku, A.T. *Synthesis* ***1973***, 492; Olah, G.A.; Lukas, J. *J. Am. Chem. Soc.* ***1967***, *89*, 4739.

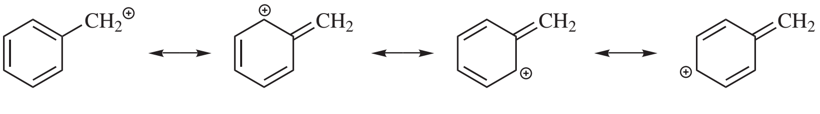
[33]See Barbour, J.B.; Karty, J.M. *J. Org. Chem.* ***2004***, *69*, 648; Mo, Y. *J. Org. Chem.* ***2004***, *69*, 5563 and references cited therein.

acyclic allylic-type cations[34] have been prepared by the solution of conjugated dienes in concentrated sulfuric acid, for example,[35]



Stable allylic cations have also been obtained by the reaction between alkyl halides, alcohols, or alkenes (by hydride extraction) and SbF_5 in SO_2 or SO_2ClF.[36] Bis(allylic) cations[37] are more stable than the simple allylic type, and some of these have been prepared in concentrated sulfuric acid.[38] Arenium ions (p. 658) are familiar examples of this type. Propargyl cations ($RC{\equiv}CCR_2^+$) have also been prepared.[39]

Canonical forms can be drawn for benzylic cations,[40] similar to those shown above for allylic cations, for example,



A number of benzylic cations have been obtained in solution as SbF_6^- salts.[41] Diarylmethyl and triarylmethyl cations are still more stable. Triphenylchloromethane ionizes in polar solvents that do not, like water, react with the ion. In SO_2, the equilibrium

$$Ph_3CCl \rightleftharpoons Ph_3C^{\oplus} + Cl^{\ominus}$$

has been known for many years. Both triphenylmethyl and diphenylmethyl cations have been isolated as solid salts[42] and, in fact, Ph_3C^+ BF_4^- and related salts are available commercially. Arylmethyl cations are further stabilized if they have

[34]For reviews, see Deno, N.C., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, pp. 783–806; Richey Jr., H.G., in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, ***1970***, pp. 39–114.

[35]Deno, N.C.; Richey, Jr., H.G.; Friedman, N.; Hodge, J.D.; Houser, J.J.; Pittman, Jr., C.U. *J. Am. Chem. Soc.* ***1963***, *85*, 2991.

[36]Olah, G.A.; Spear, R.J. *J. Am. Chem. Soc.* ***1975***, *97*, 1539 and references cited therein.

[37]For a review of divinylmethyl and trivinylmethyl cations, see Sorensen, T.S., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, pp. 807–835.

[38]Deno, N.C.; Pittman, Jr., C.U. *J. Am. Chem. Soc.* ***1964***, *86*, 1871.

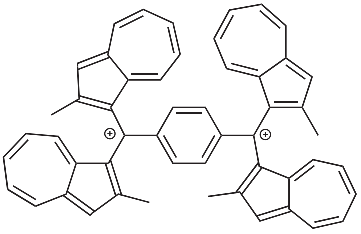
[39]Pittman, Jr., C.U.; Olah, G.A. *J. Am. Chem. Soc.* ***1965***, *87*, 5632; Olah, G.A.; Spear, R.J.; Westerman, P.W.; Denis, J. *J. Am. Chem. Soc.* ***1974***, *96*, 5855.

[40]For a review of benzylic, diarylmethyl, and triarymethyl cations, see Freedman, H.H., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 4, Wiley, NY, ***1971***, pp. 1501–1578.

[41]Olah, G.A.; Porter, R.D.; Jeuell, C.L.; White, A.M. *J. Am. Chem. Soc.* ***1972***, *94*, 2044.

[42]Volz, H.; Schnell, H.W. *Angew. Chem. Int. Ed.* ***1965***, *4*, 873.

electron-donating substituents in ortho or para positions.[43] Dications[44] and trications are also possible, including the particularly stable dication (**6**), where each positively charged benzylic carbon is stabilized by two azulene rings.[45] A related trication is known where each benzylic cationic center is also stabilized by two azulene rings.[46]



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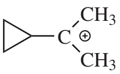
Cyclopropylmethyl cations[47] are even more stable than the benzyl type. Ion **9** has been prepared by solution of the corresponding alcohol in 96% sulfuric acid,[48] and **7**, **8**, and similar ions by solution of the alcohols in FSO_3H–SO_2–SbF_5.[49] This special stability, which increases with each additional cyclopropyl group, is a



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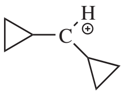

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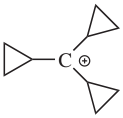
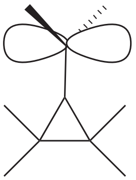


9



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result of conjugation between the bent orbitals of the cyclopropyl rings (p. $$$) and the vacant *p* orbital of the cationic carbon (see **10**). Nuclear magnetic resonance and other studies have shown that the vacant *p* orbital lies parallel to the C-2,C-3 bond of the cyclopropane ring and not perpendicular to it.[50] In this respect, the

[43]Goldacre, R.J.; Phillips, J.N. *J. Chem. Soc.* ***1949***, 1724; Deno, N.C.; Schriesheim, A. *J. Am. Chem. Soc.* ***1955***, *77*, 3051.

[44]Prakash, G.K.S. *Pure Appl. Chem.* ***1998***, *70*, 2001.

[45]Ito, S.; Morita, N.; Asao, T. *Tetrahedron Lett.* ***1992***, *33*, 3773.

[46]Ito, S.; Morita, N.; Asao, T. *Tetrahedron Lett.* ***1994***, *35*, 751.

[47]For reviews, see, in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, ***1972***: Richey, Jr., H.G. pp. 1201–294; Wiberg, K.B.; Hess Jr., B.A.; Ashe III, A.H. pp. 1295–1345.

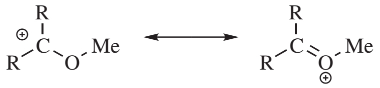
[48]Deno, N.C.; Richey, Jr., H.G.; Liu, J.S.; Hodge, J.D.; Houser, H.J.; Wisotsky, M.J. *J. Am. Chem. Soc.* ***1962***, *84*, 2016.

[49]Pittman Jr., C.U.; Olah, G.A. *J. Am. Chem. Soc.* ***1965***, *87*, 2998; Deno, N.C.; Liu, J.S.; Turner, J.O.; Lincoln, D.N.; Fruit, Jr., R.E. *J. Am. Chem. Soc.* ***1965***, *87*, 3000.

[50]For example, see Ree, B.; Martin, J.C. *J. Am. Chem. Soc.* ***1970***, *92*, 1660; Kabakoff, D.S.; Namanworth, E. *J. Am. Chem. Soc.* ***1970***, *92*, 3234; Buss, V.; Gleiter, R.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1971***, *93*, 3927; Poulter, C.D.; Spillner, C.J. *J. Am. Chem. Soc.* ***1974***, *96*, 7591; Childs, R.F.; Kostyk, M.D.; Lock, C.J.L.; Mahendran, M. *J. Am. Chem. Soc.* ***1990***, *112*, 8912; Deno, N.C.; Richey Jr., H.G.; Friedman, N.; Hodge, J.D.; Houser, J.J.; Pittman Jr., C.U. *J. Am. Chem. Soc.* ***1963***, *85*, 2991.

geometry is similar to that of a cyclopropane ring conjugated with a double bond (p. 218). Cyclopropylmethyl cations are further discussed on pp. 459–463. The stabilizing effect just discussed is unique to cyclopropyl groups. Cyclobutyl and larger cyclic groups are about as effective at stabilizing a carbocation as ordinary alkyl groups.[51]

Another structural feature that increases carbocation stability is the presence, adjacent to the cationic center, of a heteroatom bearing an unshared pair,[52] for example, oxygen,[53] nitrogen,[54] or halogen.[55] Such ions are stabilized by resonance:



The methoxymethyl cation can be obtained as a stable solid, $MeOCH_2^+$ SbF_6^-.[56] Carbocations containing either α, β, or γ silicon atom are also stabilized,[57] relative to similar ions without the silicon atom. In super acid solution, ions such as CX_3^+ (X = Cl, Br, I) have been prepared.[58] Vinyl-stabilized halonium ions are also known.[59]

Simple acyl cations RCO^+ have been prepared[60] in solution and the solid state.[61] The acetyl cation CH_3CO^+ is about as stable as the *tert*-butyl cation (see, e.g., Table 5.1). The 2,4,6-trimethylbenzoyl and 2,3,4,5,6-pentamethylbenzoyl cations are especially stable (for steric reasons) and are easily formed in 96% H_2SO_4.[62] These

[51]Sorensen, T.S.; Miller, I.J.; Ranganayakulu, K. *Aust. J. Chem.* ***1973***, *26*, 311.

[52]For a review, see Hevesi, L. *Bull. Soc. Chim. Fr.* ***1990***, 697. For examples of stable solutions of such ions, see Kabus, S.S. *Angew. Chem. Int. Ed.* ***1966***, *5*, 675; Dimroth, K.; Heinrich, P. *Angew. Chem. Int. Ed.* ***1966***, *5*, 676; Tomalia, D.A.; Hart, H. *Tetrahedron Lett.* ***1966***, 3389; Ramsey, B.; Taft, R.W. *J. Am. Chem. Soc.* ***1966***, *88*, 3058; Olah, G.A.; Liang, G.; Mo, Y.M. *J. Org. Chem.* ***1974***, *39*, 2394; Borch, R.F. *J. Am. Chem. Soc.* ***1968***, *90*, 5303; Rabinovitz, M.; Bruck, D. *Tetrahedron Lett.* ***1971***, 245.

[53]For a review of ions of the form $R_2C^+{-}OR'$, see Rakhmankulov, D.L.; Akhmatdinov, R.T.; Kantor, E.A. *Russ. Chem. Rev.* ***1984***, *53*, 888. For a review of ions of the form $R'C^+(OR)_2$ and $C^+(OR)_3$, see Pindur, U.; Müller, J.; Flo, C.; Witzel, H. *Chem. Soc. Rev.* ***1987***, *16*, 75.

[54]For a review of such ions where nitrogen is the heteroatom, see Scott, F.L.; Butler, R.N., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 4, Wiley, NY, ***1974***, pp. 1643–1696.

[55]See Allen, A.D.; Tidwell, T.T. *Adv. Carbocation Chem.* ***1989***, *1*, 1. See also, Teberekidis, V.I.; Sigalas, M.P. *Tetrahedron* ***2003***, *59*, 4749.

[56]Olah, G.A.; Svoboda, J.J. *Synthesis* ***1973***, 52.

[57]For a review and discussion of the causes, see Lambert, J.B. *Tetrahedron* ***1990***, *46*, 2677. See also, Lambert, J.B.; Chelius, E.C. *J. Am. Chem. Soc.* ***1990***, *112*, 8120.

[58]Olah, G.A.; Heiliger, L.; Prakash, G.K.S. *J. Am. Chem. Soc.* ***1989***, *111*, 8020.

[59]Haubenstock, H.; Sauers, R.R. *Tetrahedron* ***2004***, *60*, 1191.

[60]For reviews of acyl cations, see Al-Talib, M.; Tashtoush, H. *Org. Prep. Proced. Int.* ***1990***, *22*, 1; Olah, G.A.; Germain, A.; White, A.M., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 5, Wiley, NY, ***1976***, pp. 2049–2133. For a review of the preparation of acyl cations from acyl halides and Lewis acids, see Lindner, E. *Angew. Chem. Int. Ed.* ***1970***, *9*, 114.

[61]See, for example, Deno, N.C.; Pittman, Jr., C.U.; Wisotsky, M.J. *J. Am. Chem. Soc.* ***1964***, *86*, 4370; Olah, G.A.; Dunne, K.; Mo, Y.K.; Szilagyi, P. *J. Am. Chem. Soc.* ***1972***, *94*, 4200; Olah, G.A.; Svoboda, J.J. *Synthesis* ***1972***, 306.

[62]Hammett, L.P.; Deyrup, A.J. *J. Am. Chem. Soc.* ***1933***, *55*, 1900; Newman, M.S.; Deno, N.C. *J. Am. Chem. Soc.* ***1951***, *73*, 3651.

ions are stabilized by a canonical form containing a triple bond (**12**), although the positive charge is principally located on the carbon,[63] so that **11** contributes more than **12**.

11 **12**

The stabilities of most other stable carbocations can also be attributed to resonance. Among these are the tropylium, cyclopropenium,[64] and other aromatic cations discussed in Chapter 2. Where resonance stability is completely lacking, as in the phenyl ($C_6H_5^+$) or vinyl cations,[65] the ion, if formed at all, is usually very short lived.[66] Neither vinyl[67] nor phenyl cation has as yet been prepared as a stable species in solution.[68] However, stable alkenyl carbocations have been generated on Zeolite Y.[69]

Various quantitative methods have been developed to express the relative stabilities of carbocations.[70] One of the most common of these, although useful only for relatively stable cations that are formed by ionization of alcohols in acidic solutions, is based on the equation[71]

$$H_R = pK_{R^+} - \log\frac{C_{R^+}}{C_{ROH}}$$

[63]Boer, F.P. *J. Am. Chem. Soc.* ***1968***, *90*, 6706; Le Carpentier, J.; Weiss, R. *Acta Crystallogr. Sect. B*, ***1972***, 1430. See also, Olah, G.A.; Westerman, P.W. *J. Am. Chem. Soc.* ***1973***, *95*, 3706.

[64]See Komatsu, K.; Kitagawa, T. *Chem. Rev.* ***2003***, *103*, 1371. Also see, Gilbertson, R.D.; Weakley, T.J.R.; Haley, M.M. *J. Org. Chem.* ***2000***, *65*, 1422.

[65]For the preparation and reactivity of a primary vinyl carbocation see Gronheid, R.; Lodder, G.; Okuyama, T. *J. Org. Chem.* ***2002***, *67*, 693.

[66]For a review of destabilized carbocations, see Tidwell, T.T. *Angew. Chem. Int. Ed.* ***1984***, *23*, 20.

[67]Solutions of aryl-substituted vinyl cations have been reported to be stable for at least a short time at low temperatures. The NMR spectra was obtained: Abram, T.S.; Watts, W.E. *J. Chem. Soc. Chem. Commun.* ***1974***, 857; Siehl, H.; Carnahan, Jr., J.C.; Eckes, L.; Hanack, M. *Angew. Chem. Int. Ed.* ***1974***, *13*, 675. The l-cyclobutenyl cation has been reported to be stable in the gas phase: Franke, W.; Schwarz, H.; Stahl, D. *J. Org. Chem.* ***1980***, *45*, 3493. See also, Siehl, H.; Koch, E. *J. Org. Chem.* ***1984***, *49*, 575.

[68]For a monograph, see Stang, P.J.; Rappoport, Z.; Hanack, M.; Subramanian, L.R. *Vinyl Cations*, Academic Press, NY, 1979. For reviews of aryl and/or vinyl cations, see Hanack, M. *Pure Appl. Chem.* ***1984***, *56*, 1819, *Angew. Chem. Int. Ed.* ***1978***, *17*, 333; *Acc. Chem. Res.* ***1976***, *9*, 364; Rappoport, Z. *Reactiv. Intermed. (Plenum)* ***1983***, *3*, 427; Ambroz, H.B.; Kemp, T.J. *Chem. Soc. Rev.* ***1979***, *8*, 353; Richey Jr., H.G.; Richey, J.M., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, pp. 899–957; Richey Jr., H.G., in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, ***1970***, pp. 42–49; Modena, G.; Tonellato, U. *Adv. Phys. Org. Chem.* ***1971***, *9*, 185; Stang, P.J. *Prog. Phys. Org. Chem.* ***1973***, *10*, 205. See also, Charton, M. *Mol. Struct. Energ.* ***1987***, *4*, 271. For a computational study, see Glaser, R.; Horan, C. J.; Lewis, M.; Zollinger, H. *J. Org. Chem.* ***1999***, *64*, 902.

[69]Yang, S.; Kondo, J.N.; Domen, K. *Chem. Commun.* ***2001***, 2008.

[70]For reviews, see Bagno, A.; Scorrano, G.; More O'Ferrall, R.A. *Rev. Chem. Intermed.* ***1987***, *7*, 313; Bethell, D.; Gold, V. *Carbonium Ions*, Academic Press, NY, ***1967***, pp. 59–87.

[71]Deno, N.C.; Berkheimer, H.E.; Evans, W.L.; Peterson, H.J. *J. Am. Chem. Soc.* ***1959***, *81*, 2344.

pK_{R^+} is the pK value for the reaction $R^+ + 2\ H_2O \rightleftharpoons ROH + H_3O^+$ and is a measure of the stability of the carbocation. The H_R parameter is an early obtainable measurement of the stability of a solvent (see p. 371) and approaches pH at low concentrations of acid. In order to obtain pK_{R^+}, for a cation R^+, one dissolves the alcohol ROH in an acidic solution of known H_R. Then the concentration of R^+ and ROH are obtained, generally from spectra, and pK_{R^+} is easily calculated.[72] A measure of carbocation stability that applies to less-stable ions is the dissociation energy $D(R^+–H^-)$ for the cleavage reaction $R - H \rightarrow R^+ + H^-$, which can be obtained from photoelectron spectroscopy and other measurements. Some values of $D(R^+—H^-)$ are shown in Table 5.2.[75] Within a given class of ion (primary, secondary, allylic, aryl, etc.), $D(R^+—H^-)$ has been shown to be a linear function of the logarithm of the number of atoms in R^+, with larger ions being more stable.[74]

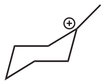


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TABLE 5.2. R–H → $R^+ + H^-$ Dissociation Energies in the Gas Phase

	$D(R^+–H^-)$		
Ion	kcal mol^{-1}	kJ mol^{-1}	Reference
CH_3^+	314.6	1316	73
$C_2H_5^+$	276.7	1158	73
$(CH_3)_2CH^+$	249.2	1043	73
$(CH_3)_3C^+$	231.9	970.3	73
$C_6H_5^+$	294	1230	74
$H_2C{=}CH^+$	287	1200	74
$H_2C{=}CH{-}CH_2^+$	256	1070	74
Cyclopentyl	246	1030	74
$C_6H_5CH_2^+$	238	996	74
CH_3CHO	230	962	74

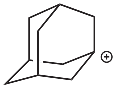
[72]For a list of stabilities of 39 typical carbocations, see Arnett, E.M.; Hofelich, T.C. *J. Am. Chem. Soc.* ***1983***, *105*, 2889. See also, Schade, C.; Mayr, H.; Arnett, E.M. *J. Am. Chem. Soc.* ***1988***, *110*, 567; Schade, C.; Mayr, H. *Tetrahedron* ***1988***, *44*, 5761.

[73]Schultz, J.C.; Houle, F.A.; Beauchamp, J.L. *J. Am. Chem. Soc.* ***1984***, *106*, 3917.

[74]Lossing, F.P.; Holmes, J.L. *J. Am. Chem. Soc.* ***1984***, *106*, 6917.

[75]Hammett, L.P.; Deyrup, A.J. *J. Am. Chem. Soc.* ***1933***, *55*, 1900; Newman, M.S.; Deno, N.C. *J. Am. Chem. Soc.* ***1951***, *73*, 3651; Boer, F.P. *J. Am. Chem. Soc.* ***1968***, *90*, 6706; Le Carpentier, J.; Weiss, R. *Acta Crystallogr. Sect. B*, ***1972***, 1430. See also, Olah, G.A.; Westerman, P.W. *J. Am. Chem. Soc.* ***1973***, *95*, 3706. See also, Staley, R.H.; Wieting, R.D.; Beauchamp, J.L. *J. Am. Chem. Soc.* ***1977***, *99*, 5964; Arnett, E.M.; Petro, C. *J. Am. Chem. Soc.* ***1978***, *100*, 5408; Arnett, E.M.; Pienta, N.J. *J. Am. Chem. Soc.* ***1980***, *102*, 3329.

Since the central carbon of tricoordinated carbocations has only three bonds and no other valence electrons, the bonds are sp^2 and should be planar.[76] Raman, IR, and NMR spectroscopic data on simple alkyl cations show this to be so.[77] In methylcycohexyl cations, there are two chair conformations where the carbon bearing the positive charge is planar (**13** and **14**), and there is evidence that **14** is more stable due to a difference in hyperconjugation.[78] Other evidence is that carbocations are difficult to form at bridgehead atoms in [2.2.1] systems,[79] where they cannot be planar (see p. 435).[80] Bridgehead carbocations are known, however, as in [2.1.1]hexanes[81] and cubyl carbocations.[82] However, larger bridgehead ions can exist. For example, the adamantyl cation (**15**) has been synthesized, as the SF_6^- salt.[83] The relative stability of 1-adamantyl cations is influenced by the number and nature of substituents. For example, the stability of the 1-adamantyl cation increases with the number of isopropyl substituents at C-3, C-5 and C-7.[84] Among other bridgehead cations that have been prepared in super acid solution at −78°C are the dodecahydryl cation (**16**)[85] and the 1-trishomobarrelyl cation (**17**).[86] In the latter



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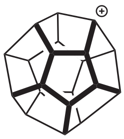

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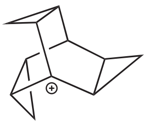

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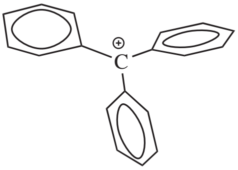

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[76]For discussions of the stereochemistry of carbocations, see Henderson, J.W. *Chem. Soc. Rev.* ***1973***, *2*, 397; Buss, V.; Schleyer, P.v.R.; Allen, L.C. *Top. Stereochem.* ***1973***, *7*, 253; Schleyer, P.v.R., in Chiurdoglu, G. *Conformational Analysis*; Academic Press, NY, ***1971***, p. 241; Hehre, W.J. *Acc. Chem. Res.* ***1975***, *8*, 369; Freedman, H.H., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 4, Wiley, NY, ***1974***, pp. 1561–574.

[77]Olah, G.A.; DeMember, J.R.; Commeyras, A.; Bribes, J.L. *J. Am. Chem. Soc.* ***1971***, *93*, 459; Yannoni, C.S.; Kendrick, R.D.; Myhre, P.C.; Bebout, D.C.; Petersen, B.L. *J. Am. Chem. Soc.* ***1989***, *111*, 6440.

[78]Rauk, A.; Sorensen, T.S.; Maerker, C.; de M. Carneiro, J.W.; Sieber, S.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1996***, *118*, 3761.

[79]For a review of bridgehead carbocations, see Fort, Jr., R.C., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 4, Wiley, NY, ***1974***, pp. 1783–1835.

[80]Della, E.W.; Schiesser, C.H. *J. Chem. Soc. Chem. Commun.* ***1994***, 417.

[81]Åhman, J.; Somfai, P.; Tanner, D. *J. Chem. Soc. Chem. Commun.* ***1994***, 2785.

[82]Della, E.W.; Head, N.J.; Janowski, W.K.; Schiesser, C.H. *J. Org. Chem.* ***1993***, *58*, 7876.

[83]Schleyer, P.v.R.; Fort, Jr., R.C.; Watts, W.E.; Comisarow, M.B.; Olah, G.A. *J. Am. Chem. Soc.* ***1964***, *86*, 4195; Olah, G.A.; Prakash, G.K.S.; Shih, J.G.; Krishnamurthy, V.V.; Mateescu, G.D.; Liang, G.; Sipos, G.; Buss, V.; Gund, T.M.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1985***, *107*, 2764. See also, Kruppa, G.H.; Beauchamp, J.L. *J. Am. Chem. Soc.* ***1986***, *108*, 2162; Laube, T. *Angew. Chem. Int. Ed.* ***1986***, *25*, 349.

[84]Takeuchi, K.; Okazaki, T.; Kitagawa, T.; Ushino, T.; Ueda, K.; Endo, T.; Notario, R. *J. Org. Chem.* ***2001***, *66*, 2034.

[85]Olah, G.A.; Prakash, G.K.S.; Fessner, W.; Kobayashi, T.; Paquette, L.A. *J. Am. Chem. Soc.* ***1988***, *110*, 8599.

[86]de Meijere, A.; Schallner, O. *Angew. Chem. Int. Ed.* ***1973***, *12*, 399.

TABLE 5.3. The ^{13}C Chemical Shift Values, in Parts Per Million from $^{13}CS_2$ for the Charged Carbon Atom of Some Carbocations in SO_2ClF–SbF_5, SO_2–FSO_3H–SbF_6, or SO_2–SbF_5[90]

Ion	Chemical Shift	Temperature, °C	Ion	Chemical Shift	Temperature, °C
Et_2MeC^+	−139.4	−20	$C(OH)_3^+$	+28.0	−50
Me_2EtC^+	−139.2	−60	$PhMe_2C^+$	−61.1	−60
Me_3C^+	−135.4	−20	$PhMeCH^+$	−40[91]	
Me_2CH^+	−125.0	−20	Ph_2CH^+	−5.6	−60
Me_2COH^+	−55.7	−50	Ph_3C^+	−18.1	−60
$MeC(OH)_2^+$	−1.6	−30	Me_2(cyclopropyl)C^+	−86.8	−60
$HC(OH)_2^+$	+17.0	−30			

case, the instability of the bridgehead position is balanced by the extra stability gained from the conjugation with the three cyclopropyl groups.

Triarylmethyl cations (**18**)[87] are propeller shaped, although the central carbon and the three ring carbons connected to it are in a plane:[88] The three benzene rings cannot be all in the same plane because of steric hindrance, although increased resonance energy would be gained if they could.

An important tool for the investigation of carbocation structure is measurement of the ^{13}C NMR chemical shift of the carbon atom bearing the positive charge.[89] This shift approximately correlates with electron density on the carbon. The ^{13}C chemical shifts for a number of ions are given in Table 5.3.[90] As shown in this table, the substitution of an ethyl for a methyl or a methyl for a hydrogen causes a downfield shift, indicating that the central carbon becomes somewhat more positive. On the other hand, the presence of hydroxy or phenyl groups decreases the positive character of the central carbon. The ^{13}C chemical shifts are not always in exact order of carbocation stabilities as determined in other ways. Thus the chemical shift shows that the triphenylmethyl cation has a more positive central carbon than diphenylmethyl cation, although the former is more stable. Also, the 2-cyclopropylpropyl and 2-phenylpropyl cations have shifts of −86.8 and −61.1, respectively, although we have seen that according to other criteria a cyclopropyl group is better

[87]For a review of crystal-structure determinations of triarylmethyl cations and other carbocations that can be isolated in stable solids, see Sundaralingam, M.; Chwang, A.K., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 5, Wiley, NY, ***1976***, pp. 2427–2476.

[88]Sharp, D.W.A.; Sheppard, N. *J. Chem. Soc.* ***1957***, 674; Gomes de Mesquita, A.H.; MacGillavry, C.H.; Eriks, K. *Acta Crystallogr.* ***1965***, *18*, 437; Schuster, I.I.; Colter, A.K.; Kurland, R.J. *J. Am. Chem. Soc.* ***1968***, *90*, 4679.

[89]For reviews of the nmr spectra of carbocations, see Young, R.N. *Prog. Nucl. Magn. Reson. Spectrosc.* ***1979***, *12*, 261; Farnum, D.G. *Adv. Phys. Org. Chem.* ***1975***, *11*, 123.

[90]Olah, G.A.; White, A.M. *J. Am. Chem. Soc.* ***1968***, *90*, 1884; ***1969***, *91*, 5801. For ^{13}C NMR data for additional ions, see Olah, G.A.; Donovan, D.J. *J. Am. Chem. Soc.* ***1977***, *99*, 5026; Olah, G.A.; Prakash, G.K.S.; Liang, G. *J. Org. Chem.* ***1977***, *42*, 2666.

than a phenyl group at stabilizing a carbocation.[91] The reasons for this discrepancy are not fully understood.[88,92]

Nonclassical Carbocations

These carbocations are discussed at pp. 450–455.

The Generation and Fate of Carbocations

A number of methods are available to generate carbocations, stable or unstable.

1. A direct ionization, in which a leaving group attached to a carbon atom leaves with its pair of electrons, as in solvolysis reactions of alkyl halides (see p. 480) or sulfonate esters (see p. 522):

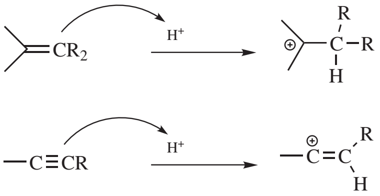
$$\text{R–X} \longrightarrow \text{R}^{\oplus} + \text{X}^{\ominus} \quad \text{(may be reversible)}$$

2. Ionization after an initial reaction that converts one functional group into a leaving group, as in protonation of an alcohol to give an oxonium ion or conversion of a primary amine to a diazonium salt, both of which ionize to the corresponding carbocation:

$$\text{R–OH} \xrightarrow{\text{H}^+} \text{R–OH}_2 \longrightarrow \text{R}^{\oplus} + \text{H}_2\text{O} \quad \text{(may be reversible)}$$

$$\text{R–NH}_2 \xrightarrow{\text{HONO}} \text{R–N}_2 \longrightarrow \text{R}^{\oplus} + \text{N}_2$$

3. A proton or other positive species adds to one atom of an alkene or alkyne, leaving the adjacent carbon atom with a positive charge (see Chapters 11, 15).

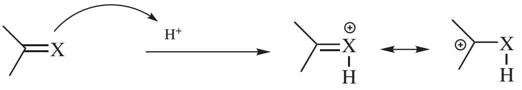


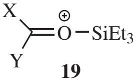
4. A proton or other positive species adds to one atom of an C=X bond, where X = O, S, N in most cases, leaving the adjacent carbon atom with a positive charge (see Chapter 16). When X = O, S this ion is resonance stabilized, as shown. When X = NR, protonation leads to an iminium ion, with the charge localized on the

[91]Olah, G.A.; Porter, R.D.; Kelly, D.P. *J. Am. Chem. Soc.* ***1971***, *93*, 464.

[92]For discussions, see Brown, H.C.; Peters, E.N. *J. Am. Chem. Soc.* ***1973***, *95*, 2400; ***1977***, *99*, 1712; Olah, G.A.; Westerman, P.W.; Nishimura, J. *J. Am. Chem. Soc.* ***1974***, *96*, 3548; Wolf, J.F.; Harch, P.G.; Taft, R.W.; Hehre, W.J. *J. Am. Chem. Soc.* ***1975***, *97*, 2902; Fliszár, S. *Can. J. Chem.* ***1976***, *54*, 2839; Kitching, W.; Adcock, W.; Aldous, G. *J. Org. Chem.* ***1979***, *44*, 2652. See also, Larsen, J.W.; Bouis, P.A. *J. Am. Chem. Soc.* ***1975***, *97*, 4418; Volz, H.; Shin, J.; Streicher, H. *Tetrahedron Lett.* ***1975***, 1297; Larsen, J.W. *J. Am. Chem. Soc.* ***1978***, *100*, 330.

nitrogen. A silylated carboxonium ion, such as **19**, has been reported.[93]





19

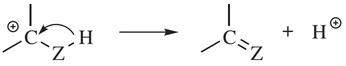
Formed by either process, carbocations are most often short-lived transient species and react further without being isolated. The intrinsic barriers to formation and reaction of carbocations has been studied.[94] Carbocations have been generated in zeolites.[95]

The two chief pathways by which carbocations react to give stable products are the reverse of the two pathways just described.

1. *The Carbocation May Combine with a Species Possessing an Electron Pair* (a Lewis acid–base reaction, see Chapter 8):

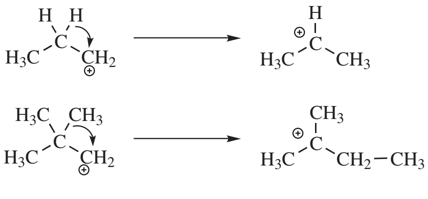
This species may be $^{-}$OH, halide ion, or any other negative ion, or it may be a neutral species with a pair to donate, in which case, of course, the immediate product must bear a positive charge (see Chapters 10, 13, 15, 16). These reactions are very fast. A recent study measured k_s (the rate constant for reaction of a simple tertiary carbocation) to be 3.5×10^{12} s^{-1}.[96]

2. *The Carbocation May Lose a Proton* (or much less often, another positive ion) from the adjacent atom (see Chapters 11, 17):



Carbocations can also adopt two other pathways that lead not to stable products, but to other carbocations:

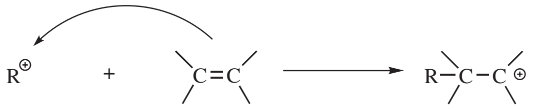
3. *Rearrangement.* An alkyl or aryl group or a hydrogen (sometimes another group) migrates with its electron pair to the positive center, leaving another positive charge behind (see Chapter 18):



[93]Prakash, G.K.S.; Bae, C.; Rasul, G.; Olah, G.A. *J. Org. Chem.* ***2002***, *67*, 1297.
[94]Richard, J.P.; Amyes, T.L.; Williams, K.B. *Pure. Appl. Chem.* ***1998***, *70*, 2007.
[95]Song, W.; Nicholas, J. B.; Haw, J. F. *J. Am. Chem. Soc.* ***2001***, *123*, 121.
[96]Toteva, M.M.; Richard, J.P. *J. Am. Chem. Soc.* ***1996***, *118*, 11434.

A novel rearrangement has been observed. The 2-methyl-2-butyl-1-^{13}C cation (^{13}C-labeled *tert*-amyl cation) shows an interchange of the inside and outside carbons with a barrier of 19.5 (±2.0 kcal mol^{-1}).[97] Another unusual migratory process has been observed for the nonamethylcyclopentyl cation. It has been shown that "four methyl groups undergo rapid circumambulatory migration with a barrier <2 kcal mol^{-1} while five methyl groups are fixed to ring carbons, and the process that equalizes the two sets of methyls has a barrier of 7.0 kcal mol^{-1}."[98]

4. *Addition*. A carbocation may add to a double bond, generating a positive charge at a new position (see Chapters 11, 15):



20

Whether formed by pathway 3 or 4, the new carbocation normally reacts further in an effort to stabilize itself, usually by pathway 1 or 2. However, **20** can add to another alkene molecule, and this product can add to still another, and so on. This is one of the mechanisms for vinyl polymerization.

CARBANIONS

Stability and Structure[99]

An *organometallic compound* is a compound that contains a bond between a carbon atom and a metal atom. Many such compounds are known, and organometallic chemistry is a very large area, occupying a borderline region between organic and inorganic chemistry. Many carbon–metal bonds (e.g., carbon–mercury bonds)

[97]Vrcek, V.; Saunders, M.; Kronja, O. *J. Am. Chem. Soc.* ***2004***, *126*, 13703.

[98]Kronja, O.; Kohli, T.-P.; Mayr, H.; Saunders, M. *J. Am. Chem. Soc.* ***2000***, *122*, 8067.

[99]For monographs, see Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, pts. A, B, and C; Elsevier, NY, ***1980***, ***1984***, ***1987***; Bates, R.B.; Ogle, C.A. *Carbanion Chemistry*, Springer, NY, ***1983***; Stowell, J.C. *Carbanions in Organic Synthesis*, Wiley, NY, ***1979***; Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, ***1965***. For reviews, see Staley, S.W. *React. Intermed. (Wiley)* ***1985***, *3*, 19; Staley, S.W.; Dustman, C.K. *React. Intermed. (Wiley)* ***1981***, *2*, 15; le Noble, W.J. *React. Intermed. (Wiley)* ***1978***, *1*, 27; Solov'yanov, A.A.; Beletskaya, I.P. *Russ. Chem. Rev.* ***1978***, *47*, 425; Isaacs, N.S. *Reactive Intermediates in Organic Chemistry*, Wiley, NY, ***1974***, pp. 234–293; Kaiser, E.M.; Slocum, D.W., in McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, ***1973***, pp. 337–422; Ebel, H.F. *Fortchr. Chem. Forsch.* ***1969***, *12*, 387; Cram, D.J. *Surv. Prog. Chem.* ***1968***, *4*, 45; Reutov, O.A.; Beletskaya, I.P. *Reaction Mechanisms of Organometallic Compounds*, North Holland Publishing Co, Amsterdam, The Netherlands, ***1968***, pp. 1–64; Streitwieser Jr., A.; Hammons, J.H. *Prog. Phys. Org. Chem.* ***1965***, *3*, 41. For reviews of nmr spectra of carbanions, see Young, R.N. *Prog. Nucl. Magn. Reson. Spectrosc.* ***1979***, *12*, 261. For a review of dicarbanions, see Thompson, C.M.; Green, D.L.C. *Tetrahedron* ***1991***, *47*, 4223.

are undoubtedly covalent, but in bonds between carbon and the more active metals the electrons are closer to the carbon. Whether the position of the electrons in a given bond is close enough to the carbon to justify calling the bond ionic and the carbon moiety a carbanion depends on the metal, on the structure of the carbon moiety, and on the solvent and in some cases is a matter of speculation. In this section, we discuss carbanions with little reference to the metal. In the next section, we will deal with the structures of organometallic compounds.

By definition, every carbanion possesses an unshared pair of electrons and is therefore a base. When a carbanion accepts a proton, it is converted to its conjugate acid (see Chapter 8). The stability of the carbanion is directly related to the strength of the conjugate acid. The weaker the acid, the greater the base strength and the lower the stability of the carbanion.[100] By stability here we mean stability toward a proton donor; the lower the stability, the more willing the carbanion is to accept a proton from any available source, and hence to end its existence as a carbanion. Thus the determination of the order of stability of a series of carbanions is equivalent to a determination of the order of strengths of the conjugate acids, and one can obtain information about relative carbanion stability from a table of acid strengths like Table 8.1.

Unfortunately, it is not easy to measure acid strengths of very weak acids like the conjugate acids of simple unsubstituted carbanions. There is little doubt that these carbanions are very unstable in solution, and in contrast to the situation with carbocations, efforts to prepare solutions in which carbanions, such as ethyl or isopropyl, exist in a relatively free state have not yet been successful. Nor has it been possible to form these carbanions in the gas phase. Indeed, there is evidence that simple carbanions, such as ethyl and isopropyl, are unstable toward loss of an electron, which converts them to radicals.[101] Nevertheless, there have been several approaches to the problem. Applequist and O'Brien[102] studied the position of equilibrium for the reaction

$$\mathrm{RLi} + \mathrm{R'I} \rightleftharpoons \mathrm{RI} + \mathrm{R'Li}$$

in ether and ether–pentane. The reasoning in these experiments was that the R group that forms the more stable carbanion would be more likely to be bonded to lithium than to iodine. Carbanion stability was found to be in this order: vinyl > phenyl > cyclopropyl > ethyl > *n*-propyl > isobutyl > neopentyl > cyclobutyl > cyclopentyl. In a somewhat similar approach, Dessy and co-workers[103] treated a

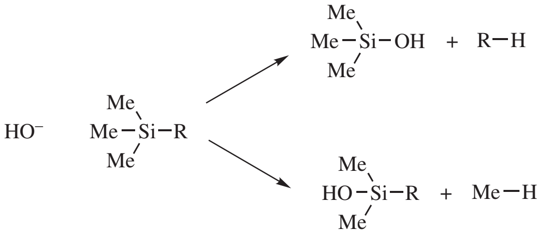
[100]For a monograph on hydrocarbon acidity, see Reutov, O.A.; Beletskaya, I.P.; Butin, K.P. *CH-Acids*; Pergamon: Elmsford, NY, ***1978***. For a review, see Fischer, H.; Rewicki, D. *Prog. Org. Chem.* ***1968***, *7*, 116.
[101]See Graul, S.T.; Squires, R.R. *J. Am. Chem. Soc.* ***1988***, *110*, 607; Schleyer, P.v.R.; Spitznagel, G.W.; Chandrasekhar, J. *Tetrahedron Lett.* ***1986***, *27*, 4411.
[102]Applequist, D.E.; O'Brien, D.F. *J. Am. Chem. Soc.* ***1963***, *85*, 743.
[103]Dessy, R.E.; Kitching, W.; Psarras, T.; Salinger, R.; Chen, A.; Chivers, T. *J. Am. Chem. Soc.* ***1966***, *88*, 460.

number of alkylmagnesium compounds with a number of alkylmercury compounds in tetrahydrofuran (THF), setting up the equilibrium

$$R_2Mg + R'_2Hg \rightleftharpoons R_2Hg + R'_2Mg$$

where the group of greater carbanion stability is linked to magnesium. The carbanion stability determined this way was in the order phenyl > vinyl > cyclopropyl > methyl > ethyl > isopropyl. The two stability orders are in fairly good agreement, and they show that stability of simple carbanions decreases in the order methyl > primary > secondary. It was not possible by the experiments of Dessy and co-workers to determine the position of *tert*-butyl, but there seems little doubt that it is still less stable. We can interpret this stability order solely as a consequence of the field effect since resonance is absent. The electron-donating alkyl groups of isopropyl result in a greater negative charge density at the central carbon atom (compared with methyl), thus decreasing its stability. The results of Applequist and O'Brien show that β branching also decreases carbanion stability. Cyclopropyl occupies an apparently anomalous position, but this is probably due to the large amount of *s* character in the carbanionic carbon (see p. 254).

A different approach to the problem of hydrocarbon acidity, and hence carbanion stability is that of Shatenshtein and co-workers, who treated hydrocarbons with deuterated potassium amide and measured the rates of hydrogen exchange.[104] The experiments did not measure *thermodynamic* acidity, since rates were measured, not positions of equilibria. They measured *kinetic* acidity, that is, which compounds gave up protons most rapidly (see p. 307 for the distinction between thermodynamic and kinetic control of product). Measurements of rates of hydrogen exchange enable one to compare acidities of a series of acids against a given base even where the positions of the equilibria cannot be measured because they lie too far to the side of the starting materials, that is, where the acids are too weak to be converted to their conjugate bases in measurable amounts. Although the correlation between thermodynamic and kinetic acidity is far from perfect,[105] the results of the rate measurements, too, indicated that the order of carbanion stability is methyl > primary > secondary > tertiary.[104]

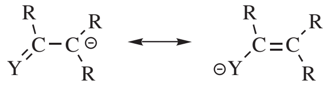


[104]For reviews, see Jones, J.R. *Surv. Prog. Chem.* ***1973***, *6*, 83; Shatenshtein, A.I.; Shapiro, I.O. *Russ. Chem. Rev.* ***1968***, *37*, 845.
[105]For example, see Bordwell, F.G.; Matthews, W.S.; Vanier, N.R. *J. Am. Chem. Soc.* ***1975***, *97*, 442.

However, experiments in the gas phase gave different results. In reactions of ^{-}OH with alkyltrimethylsilanes, it is possible for either R or Me to cleave. Since the R or Me comes off as a carbanion or incipient carbanion, the product ratio RH/MeH can be used to establish the relative stabilities of various R groups. From these experiments a stability order of neopentyl > cyclopropyl > *tert*-butyl > *n*-propyl > methyl > isopropyl > ethyl was found.[106] On the other hand, in a different kind of gas-phase experiment, Graul and Squires were able to observe CH_3^- ions, but not the ethyl, isopropyl, or *tert*-butyl ions.[107]

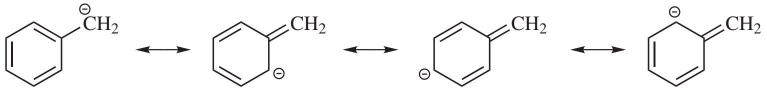
Many carbanions are far more stable than the simple kind mentioned above. The increased stability is due to certain structural features:

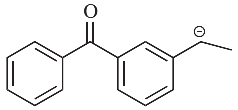
1. *Conjugation of the Unshared Pair with an Unsaturated Bond*:



In cases where a double or triple bond is located a to the carbanionic carbon, the ion is stabilized by resonance in which the unshared pair overlaps with the π electrons of the double bond. This factor is responsible for the stability of the allylic[108] and benzylic[109] types of carbanions:

$$R{-}CH{=}CH{-}\overset{\ominus}{C}H_2 \longleftrightarrow R{-}\overset{\ominus}{C}H{-}CH{=}CH_2$$





21

Diphenylmethyl and triphenylmethyl anions are still more stable and can be kept in solution indefinitely if water is rigidly excluded.[110]

[106]DePuy, C.H.; Gronert, S.; Barlow, S.E.; Bierbaum, V.M.; Damrauer, R. *J. Am. Chem. Soc.* ***1989***, *111*, 1968. The same order (for *t*-Bu, Me, *i*Pr, and Et) was found in gas-phase cleavages of alkoxides (**12-41**): Tumas, W.; Foster, R.F.; Brauman, J.I. *J. Am. Chem. Soc.* ***1984***, *106*, 4053.

[107]Graul, S.T.; Squires, R.R. *J. Am. Chem. Soc.* ***1988***, *110*, 607.

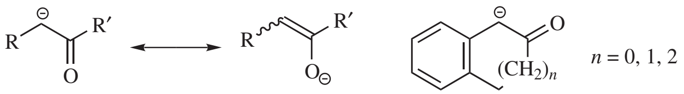
[108]For a review of allylic anions, see Richey, Jr., H.G., in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, ***1970***, pp. 67–77.

[109]Although benzylic carbanions are more stable than the simple alkyl type, they have not proved stable enough for isolation so far. The benzyl carbanion has been formed and studied in submicrosecond times; Bockrath, B.; Dorfman, L.M. *J. Am. Chem. Soc.* ***1974***, *96*, 5708.

[110]For a review of spectrophotometric investigations of this type of carbanion, see Buncel, E.; Menon, B., in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, pts. A, B, and C, Elsevier, NY, ***1980***, ***1984***, ***1987***, pp. 97–124.

Condensed aromatic rings fused to a cyclopentadienyl anion are known to stabilize the carbanion.[111] X-ray crystallographic structures have been obtained for Ph_2CH^- and Ph_3C^- enclosed in crown ethers.[112] Carbanion **21** has a lifetime of several minutes (hours in a freezer at −20 °C) in dry THF.[113]

Where the carbanionic carbon is conjugated with a carbon–oxygen or carbon–nitrogen multiple bond (Y = O or N), the stability of the ion is greater than that of the triarylmethyl anions, since these electronegative atoms are better capable of bearing a negative charge than carbon. However, it is questionable whether ions of this type should be called carbanions at all, since



22 **23** **24**

in the case of enolate ions, for example, **23** contributes more to the hybrid than **22** although such ions react more often at the carbon than at the oxygen. In benzylic enolate anions such as **24**, the conformation of the enolate can be coplanar with the aromatic ring or bent out of plane if the strain is too great.[114] Enolate ions can also be kept in stable solutions. In the case of carbanions at a carbon α- to a nitrile, the "enolate" resonance form would be a ketene imine nitranion, but the existence of this species has been called into question.[115] A nitro group is particularly effective in stabilizing a negative charge on an adjacent carbon, and the anions of simple nitro alkanes can exist in water. Thus pK_a for nitromethane is 10.2. Dinitromethane is even more acidic ($pK_a = 3.6$).

In contrast to the stability of cyclopropylmethyl cations (p. 241), the cyclopropyl group exerts only a weak stabilizing effect on an adjacent carbanionic carbon.[116]

By combining a very stable carbanion with a very stable carbocation, Okamoto and co-workers[117] were able to isolate the salt **25**, as well as several

[111]Kinoshita, T.; Fujita, M.; Kaneko, H.; Takeuchi, K-i.; Yoshizawa, K.; Yamabe, T. *Bull. Chem. Soc. Jpn.* ***1998***, *71*, 1145.

[112]Olmstead, M.M.; Power, P.P. *J. Am. Chem. Soc.* ***1985***, *107*, 2174.

[113]Laferriere, M.; Sanrame, C.N.; Scaiano, J.C. *Org. Lett.* ***2004***, *6*, 873.

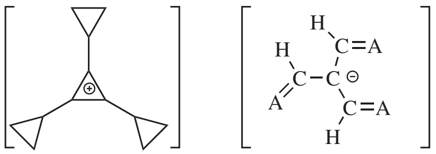
[114]Eldin, S.; Whalen, D.L.; Pollack, R.M. *J. Org. Chem.* ***1993***, *58*, 3490.

[115]Abbotto, A.; Bradamanti, S.; Pagani, G.A. *J. Org. Chem.* ***1993***, *58*, 449.

[116]Perkins, M.J.; Peynircioglu, N.B. *Tetrahedron* ***1985***, *41*, 225.

[117]Okamoto, K.; Kitagawa, T.; Takeuchi, K.; Komatsu, K.; Kinoshita, T.; Aonuma, S.; Nagai, M.; Miyabo, A. *J. Org. Chem.* ***1990***, *55*, 996. See also, Okamoto, K.; Kitagawa, T.; Takeuchi, K.; Komatsu, K.; Miyabo, A. *J. Chem. Soc. Chem. Commun.* ***1988***, 923.

similar salts, as stable solids. These are salts that consist entirely of carbon and hydrogen.



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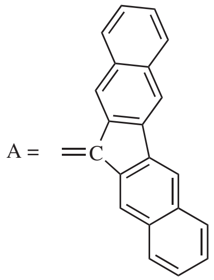
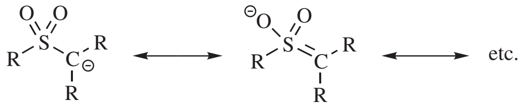


2. *Carbanions Increase in Stability with an Increase in the Amount of s Character at the Carbanionic Carbon.* Thus the order of stability is

$$RC{\equiv}C^- > R_2C{=}CH^- \sim Ar^- > R_3C{-}CH_2^-$$

Acetylene, where the carbon is *sp* hybridized with 50% *s* character, is much more acidic than ethylene[118] (sp^2, 33% *s*), which in turn is more acidic than ethane, with 25% *s* character. Increased *s* character means that the electrons are closer to the nucleus and hence of lower energy. As previously mentioned, cyclopropyl carbanions are more stable than methyl, owing to the larger amount of *s* character as a result of strain (see p. 218).

3. *Stabilization by Sulfur*[119] *or Phosphorus.* Attachment to the carbanionic carbon of a sulfur or phosphorus atom causes an increase in carbanion stability, although the reasons for this are in dispute. One theory is that there is overlap of the unshared pair with an empty *d* orbital[120] (*p*π–*d*π bonding, see p. 52). For example, a carbanion containing the SO_2R group would be written



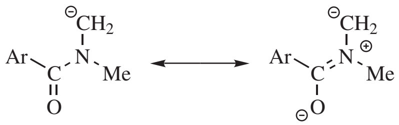
[118]For a review of vinylic anions, see Richey, Jr., H.G., in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, ***1970***, pp. 49–56.

[119]For reviews of sulfur-containing carbanions, see Oae, S.; Uchida, Y., in Patai, S.; Rappoport, Z.; Stirling, C. *The Chemistry of Sulphones and Sulphoxides*, Wiley, NY, ***1988***, pp. 583–664; Wolfe, S., in Bernardi, F.; Csizmadia, I.G.; Mangini, A. *Organic Sulfur Chemistry*, Elsevier, NY, ***1985***, pp. 133–190; Block, E. *Reactions of Organosulfur Compounds*; Academic Press, NY, ***1978***, pp. 42–56; Durst, T.; Viau, R. *Intra-Sci. Chem. Rep.* ***1973***, *7* (3), 63. For a review of selenium-stabilized carbanions, see Reich, H.J., in Liotta, D.C. *Organoselenium Chemistry*, Wiley, NY, ***1987***, pp. 243–276.

[120]For support for this theory, see Wolfe, S.; LaJohn, L.A.; Bernardi, F.; Mangini, A.; Tonachini, G. *Tetrahedron Lett.* ***1983***, *24*, 3789; Wolfe, S.; Stolow, A.; LaJohn, L.A. *Tetrahedron Lett.* ***1983***, *24*, 4071.

However, there is evidence against *d*-orbital overlap; and the stabilizing effects have been attributed to other causes.[121] In the case of a PhS substituent, carbanion stabilization is thought to be due to a combination of the inductive and polarizability effects of the group, and *d*–*p*π resonance and negative hyperconjugation play a minor role, if any.[122] An α silicon atom also stabilizes carbanions.[123]

4. *Field Effects*. Most of the groups that stabilize carbanions by resonance effects (either the kind discussed in 1 above or the kind discussed in paragraph 3) have electron-withdrawing field effects and thereby stabilize the carbanion further by spreading the negative charge, although it is difficult to separate the field effect from the resonance effect. However, in a nitrogen ylid $R_3N^+{-}^-CR_2$ (see p. 54), where a positive nitrogen is adjacent to the negatively charged carbon, only the field effect operates. Ylids are more stable than the corresponding simple carbanions. Carbanions are stabilized by a field effect if there is any heteroatom (O, N, or S) connected to the carbanionic carbon, provided that the heteroatom bears a positive charge in at least one important canonical form,[124] for example,



5. *Certain Carbanions are Stable because they are Aromatic* (see the cyclopentadienyl anion p. 63, and other aromatic anions in Chapter 2).

6. *Stabilization by a Nonadjacent* π *Bond*.[125] In contrast to the situation with carbocations (see pp. 450–455), there have been fewer reports of carbanions stabilized by interaction with a nonadjacent π bond. One that may be mentioned is **17**, formed when optically active camphenilone (**15**) was treated with a strong base (potassium *tert*-butoxide).[126] That **17** was truly formed was

[121]Bernardi, F.; Csizmadia, I.G.; Mangini, A.; Schlegel, H.B.; Whangbo, M.; Wolfe, S. *J. Am. Chem. Soc.* ***1975***, *97*, 2209; Lehn, J.M.; Wipff, G. *J. Am. Chem. Soc.* ***1976***, *98*, 7498; Borden, W.T.; Davidson, E.R.; Andersen, N.H.; Denniston, A.D.; Epiotis, N.D. *J. Am. Chem. Soc.* ***1978***, *100*, 1604; Bernardi, F.; Bottoni, A.; Venturini, A.; Mangini, A. *J. Am. Chem. Soc.* ***1986***, *108*, 8171.

[122]Bernasconi, C.F.; Kittredge, K.W. *J. Org. Chem.* ***1998***, *63*, 1944.

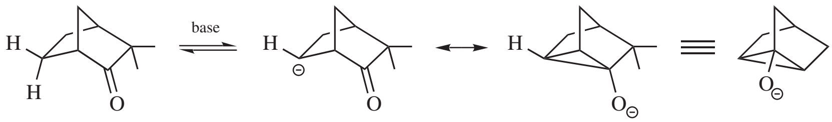
[123]Wetzel, D.M.; Brauman, J.I. *J. Am. Chem. Soc.* ***1988***, *110*, 8333.

[124]For a review of such carbanions, see Beak, P.; Reitz, D.B. *Chem. Rev.* ***1978***, *78*, 275. See also, Rondan, N.G.; Houk, K.N.; Beak, P.; Zajdel, W.J.; Chandrasekhar, J.; Schleyer, P.v.R. *J. Org. Chem.* ***1981***, *46*, 4108.

[125]For reviews, see Werstiuk, N.H. *Tetrahedron* ***1983***, *39*, 205; Hunter, D.H.; Stothers, J.B.; Warnhoff, E.W., in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 1, Academic Press, NY, ***1980***, pp. 410–437.

[126]Nickon, A.; Lambert, J.L. *J. Am. Chem. Soc.* ***1966***, *88*, 1905. Also see, Brown, J.M.; Occolowitz, J.L. *Chem. Commun.* ***1965***, 376; Grutzner, J.B.; Winstein, S. *J. Am. Chem. Soc.* ***1968***, *90*, 6562; Staley, S.W.; Reichard, D.W. *J. Am. Chem. Soc.* ***1969***, *91*, 3998; Miller, B. *J. Am. Chem. Soc.* ***1969***, *91*, 751; Werstiuk, N.H.; Yeroushalmi, S.; Timmins, G. *Can. J. Chem.* ***1983***, *61*, 1945; Lee, R.E.; Squires, R.R. *J. Am. Chem. Soc.* ***1986***, *108*, 5078; Peiris, S.; Ragauskas, A.J.; Stothers, J.B. *Can. J. Chem.* ***1987***, *65*, 789; Shiner, C.S.; Berks, A.H.; Fisher, A.M. *J. Am. Chem. Soc.* ***1988***, *110*, 957.

shown by the following facts: (*1*) A proton was abstracted: ordinary



26 **27** **28**

CH_2 groups are not acidic enough for this base; (*2*) recovered **26** was racemized: **28** is symmetrical and can be attacked equally well from either side; (*3*) when the experiment was performed in deuterated solvent, the rate of deuterium uptake was equal to the rate of racemization; and (*4*) recovered **26** contained up to three atoms of deuterium per molecule, although if **27** were the only ion, no more than two could be taken up. Ions of this type, in which a negatively charged carbon is stabilized by a carbonyl group two carbons away, are called *homoenolate ions*.

Overall, functional groups in the a position stabilize carbanions in the following order: $NO_2 > RCO > COOR > SO_2 > CN \sim CONH_2 > Hal > H > R$.

It is unlikely that free carbanions exist in solution. Like carbocations, they usually exist as either ion pairs or they are solvated.[127] Among experiments that demonstrated this was the treatment of $PhCOCHMe^-\ M^+$ with ethyl iodide, where M^+ was Li^+, Na^+, or K^+. The half-lives of the reaction were[128] for Li, 31×10^{-6}; Na, 0.39×10^{-6}; and K, 0.0045×10^{-6}, demonstrating that the species involved were not identical. Similar results[129] were obtained with Li, Na, and Cs triphenylmethides $Ph_3C^-\ M^+$.[130] Where ion pairs are unimportant, carbanions are solvated. Cram[99] has demonstrated solvation of carbanions in many solvents. There may be a difference in the structure of a carbanion depending on whether it is free (e.g., in the gas phase) or in solution. The negative charge may be more

[127]For reviews of carbanion pairs, see Hogen-Esch, T.E. *Adv. Phys. Org. Chem.* ***1977***, *15*, 153; Jackman, L.M.; Lange, B.C. *Tetrahedron* ***1977***, *33*, 2737. See also, Laube, T. *Acc. Chem. Res.* ***1995***, *28*, 399.

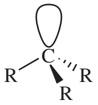
[128]Zook, H.D.; Gumby, W.L. *J. Am. Chem. Soc.* ***1960***, *82*, 1386.

[129]Solov'yanov, A.A.; Karpyuk, A.D.; Beletskaya, I.P.; Reutov, O.A. *J. Org. Chem. USSR* ***1981***, *17*, 381. See also, Solov'yanov, A.A.; Beletskaya, I.P.; Reutov, O.A. *J. Org. Chem. USSR* ***1983***, *19*, 1964.

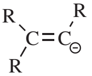
[130]For other evidence for the existence of carbanionic pairs, see Hogen-Esch, T.E.; Smid, J. *J. Am. Chem. Soc.* ***1966***, *88*, 307, 318; ***1969***, *91*, 4580; Abatjoglou, A.G.; Eliel, E.L.; Kuyper, L.F. *J. Am. Chem. Soc.* ***1977***, *99*, 8262; Solov'yanov, A.A.; Karpyuk, A.D.; Beletskaya, I.P.; Reutov, V.M. *Doklad. Chem.* ***1977***, *237*, 668; DePalma, V.M.; Arnett, E.M. *J. Am. Chem. Soc.* ***1978***, *100*, 3514; Buncel, E.; Menon, B. *J. Org. Chem.* ***1979***, *44*, 317; O'Brien, D.H.; Russell, C.R.; Hart, A.J. *J. Am. Chem. Soc.* ***1979***, *101*, 633; Streitwieser, Jr., A.; Shen, C.C.C. *Tetrahedron Lett.* ***1979***, 327; Streitwieser, Jr., A. *Acc. Chem. Res.* ***1984***, *17*, 353.

localized in solution in order to maximize the electrostatic attraction to the counterion.[131]

The structure of simple unsubstituted carbanions is not known with certainty since they have not been isolated, but it seems likely that the central carbon is sp^3 hybridized, with the unshared pair occupying one apex of the tetrahedron. Carbanions would thus have pyramidal structures similar to those of amines.



The methyl anion CH_3^- has been observed in the gas phase and reported to have a pyramidal structure.[132] If this is a general structure for carbanions, then any carbanion in which the three R groups are different should be chiral and reactions in which it is an intermediate should give retention of configuration. Attempts have been made to demonstrate this, but without success.[133] A possible explanation is that pyramidal inversion takes place here, as in amines, so that the unshared pair and the central carbon rapidly oscillate from one side of the plane to the other. There is, however, other evidence for the sp^3 nature of the central carbon and for its tetrahedral structure. Carbons at bridgeheads, although extremely reluctant to undergo reactions in which they must be converted to carbocations, undergo with ease reactions in which they must be carbanions and stable bridgehead carbanions are known.[134] Also, reactions at vinylic carbons proceed with retention,[135] indicating that the intermediate **29** has sp^2 hybridization and not the *sp* hybridization that would be expected in the analogous carbocation. A cyclopropyl anion can also hold its configuration.[136]



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[131]See Schade, C.; Schleyer, P.v.R.; Geissler, M.; Weiss, E. *Angew. Chem. Int. Ed.* ***1986***, *21*, 902.

[132]Ellison, G.B.; Engelking, P.C.; Lineberger, W.C. *J. Am. Chem. Soc.* ***1978***, *100*, 2556.

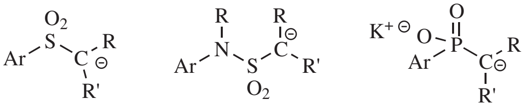
[133]Retention of configuration has never been observed with simple carbanions. Cram has obtained retention with carbanions stabilized by resonance. However, these carbanions are known to be planar or nearly planar, and retention was caused by asymmetric solvation of the planar carbanions (see p. $$$).

[134]For other evidence that carbanions are pyramidal, see Streitwieser, Jr., A.; Young, W.R. *J. Am. Chem. Soc.* ***1969***, *91*, 529; Peoples, P.R.; Grutzner, J.B. *J. Am. Chem. Soc.* ***1980***, *102*, 4709.

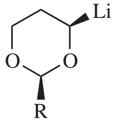
[135]Curtin, D.Y.; Harris, E.E. *J. Am. Chem. Soc.* ***1951***, *73*, 2716, 4519; Braude, E.A.; Coles, J.A. *J. Chem. Soc.* ***1951***, 2078; Nesmeyanov, A.N.; Borisov, A.E. *Tetrahedron* ***1957***, *1*, 158. Also see, Miller, S.I.; Lee, W.G. *J. Am. Chem. Soc.* ***1959***, *81*, 6313; Hunter, D.H.; Cram, D.J. *J. Am. Chem. Soc.* ***1964***, *86*, 5478; Walborsky, H.M.; Turner, L.M. *J. Am. Chem. Soc.* ***1972***, *94*, 2273; Arnett, J.F.; Walborsky, H.M. *J. Org. Chem.* ***1972***, *37*, 3678; Feit, B.; Melamed, U.; Speer, H.; Schmidt, R.R. *J. Chem. Soc. Perkin Trans. 1* ***1984***, 775; Chou, P.K.; Kass, S.R. *J. Am. Chem. Soc.* ***1991***, *113*, 4357.

[136]Walborsky, H.M.; Motes, J.M. *J. Am. Chem. Soc.* ***1970***, *92*, 2445; Motes, J.M.; Walborsky, H.M. *J. Am. Chem. Soc.* ***1970***, *92*, 3697; Boche, G.; Harms, K.; Marsch, M. *J. Am. Chem. Soc.* ***1988***, *110*, 6925. For a monograph on cyclopropyl anions, cations, and radicals, see Boche, G.; Walborsky, H.M. *Cyclopropane Derived Reactive Intermediates*, Wiley, NY, ***1990***. For a review, see Boche, G.; Walborsky, H.M., in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 1, Wiley, NY, ***1987***, pp. 701–808 (the monograph includes and updates the review).

Carbanions in which the negative charge is stabilized by resonance involving overlap of the unshared-pair orbital with the π electrons of a multiple bond are essentially planar, as would be expected by the necessity for planarity in resonance, although unsymmetrical solvation or ion-pairing effects may cause the structure to deviate somewhat from true planarity.[137] Cram and co-workers showed that where chiral carbanions possessing this type of resonance are generated, retention, inversion, or racemization can result, depending on the solvent (see p. 759). This result is explained by unsymmetrical solvation of planar or near-planar carbanions. However, some carbanions that are stabilized by adjacent sulfur or phosphorus, for example,



are inherently chiral, since retention of configuration is observed where they are generated, even in solvents that cause racemization or inversion with other carbanions.[138] It is known that in THF, PhCH(Li)Me behaves as a prochiral entity,[139] and **30** has been prepared as an optically pure α-alkoxylithium reagent.[140] Cyclohexyllithium **31** shows some configurationally stability, and it is known that isomerization is slowed by an increase in the strength of lithium coordination and by an increase in solvent polarity.[141] It is known that a vinyl anion is configurationally stable whereas a vinyl radical is not. This is due to the instability of the radical anion that must be an intermediate for conversion of one isomer of vinyllithium to the other.[142] The configuration about the carbanionic carbon, at least for some of the α-sulfonyl carbanions, seems to be planar,[143] and the inherent chirality is caused by lack of rotation about the C—S bond.[144]



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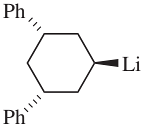

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[137]See the discussion, in Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, ***1965***, pp. 85–105.

[138]Cram, D.J.; Wingrove, A.S. *J. Am. Chem. Soc.* ***1962***, *84*, 1496; Goering, H.L.; Towns, D.L.; Dittmer, B. *J. Org. Chem.* ***1962***, *27*, 736; Corey, E.J.; Lowry, T.H. *Tetrahedron Lett.* ***1965***, 803; Bordwell, F.G.; Phillips, D.D.; Williams, Jr., J.M. *J. Am. Chem. Soc.* ***1968***, *90*, 426; Annunziata, R.; Cinquini, M.; Colonna, S.; Cozzi, F. *J. Chem. Soc. Chem. Commun.* ***1981***, 1005; Chassaing, G.; Marquet, A.; Corset, J.; Froment, F. *J. Organomet. Chem.* ***1982***, *232*, 293. For a discussion, see Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, ***1965***, pp. 105–113. Also see Hirsch, R.; Hoffmann, R.W. *Chem. Ber.* ***1992***, *125*, 975.

[139]Hoffmann, R.W.; Rühl, T.; Chemla, F.; Zahneisen, T. *Liebigs Ann. Chem.* ***1992***, 719.

[140]Rychnovsky, S.D.; Plzak, K.; Pickering, D. *Tetrahedron Lett.* ***1994***, *35*, 6799.

[141]Reich, H.J.; Medina, M.A.; Bowe, M.D. *J. Am. Chem. Soc.* ***1992***, *114*, 11003.

[142]Jenkins, P.R.; Symons, M.C.R.; Booth, S.E.; Swain, C.J. *Tetrahedron Lett.* ***1992***, *33*, 3543.

[143]Boche, G.; Marsch, M.; Harms, K.; Sheldrick, G.M. *Angew. Chem. Int. Ed.* ***1985***, *24*, 573; Gais, H.; Müller, J.; Vollhardt, J.; Lindner, H.J. *J. Am. Chem. Soc.* ***1991***, *113*, 4002. For a contrary view, see Trost, B.M.; Schmuff, N.R. *J. Am. Chem. Soc.* ***1985***, *107*, 396.

[144]Grossert, J.S.; Hoyle, J.; Cameron, T.S.; Roe, S.P.; Vincent, B.R. *Can. J. Chem.* ***1987***, *65*, 1407.

The Structure of Organometallic Compounds[145]

Whether a carbon–metal bond is ionic or polar-covalent is determined chiefly by the electronegativity of the metal and the structure of the organic part of the molecule. Ionic bonds become more likely as the negative charge on the metal-bearing carbon is decreased by resonance or field effects. Thus the sodium salt of acetoacetic ester has a more ionic carbon–sodium bond than methylsodium.

Most organometallic bonds are polar-covalent. Only the alkali metals have electronegativities low enough to form ionic bonds with carbon, and even here the behavior of lithium alkyls shows considerable covalent character. The simple alkyls and aryls of sodium, potassium, rubidium, and cesium[146] are nonvolatile solids[147] insoluble in benzene or other organic solvents, while alkyllithium reagents are soluble, although they too are generally nonvolatile solids. Alkyllithium reagents do not exist as monomeric species in hydrocarbon solvents or ether.[148] In benzene and cyclohexane, freezing-point-depression studies have shown that alkyllithium reagents are normally hexameric unless steric interactions favor tetrameric aggregates.[149] The NMR studies, especially measurements of ^{13}C–^{6}Li coupling, have also shown aggregation in hydrocarbon solvents.[150] Boiling-point-elevation studies have been performed in ether solutions, where alkyllithium reagents exist in two- to fivefold aggregates.[151] Even in the gas phase[152] and in

[145]For a monograph, see Elschenbroich, C.; Salzer, A. *Organometallics*, VCH, NY, ***1989***. For reviews, see Oliver, J.P., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 2, Wiley, NY, ***1985***, pp. 789–826; Coates, G.E.; Green, M.L.H.; Wade, K. *Organometallic Compounds*, 3rd ed., Vol. 1; Methuen: London, ***1967***. For a review of the structures of organodialkali compounds, see Grovenstein, Jr., E., in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, pt. C, Elsevier, NY, ***1987***, pp. 175–221.

[146]For a review of X-ray crystallographic studies of organic compounds of the alkali metals, see Schade, C.; Schleyer, P.v.R. *Adv. Organomet. Chem.* ***1987***, *27*, 169.

[147]X-ray crystallography of potassium, rubidium, and cesium methyls shows completely ionic crystal lattices: Weiss, E.; Sauermann, G. *Chem. Ber.* ***1970***, *103*, 265; Weiss, E.; Köster, H. *Chem. Ber.* ***1977***, *110*, 717.

[148]For reviews of the structure of alkyllithium compounds, see Setzer, W.N.; Schleyer, P.v.R. *Adv. Organomet. Chem.* ***1985***, *24*, 353; Schleyer, P.v.R. *Pure Appl. Chem.* ***1984***, *56*, 151; Brown, T.L. *Pure Appl. Chem.* ***1970***, *23*, 447, *Adv. Organomet. Chem.* ***1965***, *3*, 365; Kovrizhnykh, E.A.; Shatenshtein, A.I. *Russ. Chem. Rev.* ***1969***, *38*, 840. For reviews of the structures of lithium enolates and related compounds, see Boche, G. *Angew. Chem. Int. Ed.* ***1989***, *28*, 277; Seebach, D. *Angew. Chem. Int. Ed.* ***1988***, *27*, 1624. For a review of the use of nmr to study these structures, see Günther, H.; Moskau, D.; Bast, P.; Schmalz, D. *Angew. Chem. Int. Ed.* ***1987***, *26*, 1212. For monographs on organolithium compounds, see Wakefield, B.J. *Organolithium Methods*, Academic Press, NY, ***1988***, *The Chemistry of Organolithium Compounds*, Pergamon, Elmsford, NY, ***1974***.

[149]Lewis, H.L.; Brown, T.L. *J. Am. Chem. Soc.* ***1970***, *92*, 4664; Brown, T.L.; Rogers, M.T. *J. Am. Chem. Soc.* ***1957***, *79*, 1859; Weiner, M.A.; Vogel, G.; West, R. *Inorg. Chem.* ***1962***, *1*, 654.

[150]Fraenkel, G.; Henrichs, M.; Hewitt, M.; Su, B.M. *J. Am. Chem. Soc.* ***1984***, *106*, 255; Thomas, R.D.; Jensen, R.M.; Young, T.C. *Organometallics* ***1987***, *6*, 565. See also, Kaufman, M.J.; Gronert, S.; Streitwieser, Jr., A. *J. Am. Chem. Soc.* ***1988***, *110*, 2829.

[151]Wittig, G.; Meyer, F.J.; Lange, G. *Liebigs Ann. Chem.* ***1951***, *571*, 167. See also, McGarrity, J.F.; Ogle, C.A. *J. Am. Chem. Soc.* ***1985***, *107*, 1805; Bates, T.F.; Clarke, M.T.; Thomas, R.D. *J. Am. Chem. Soc.* ***1988***, *110*, 5109.

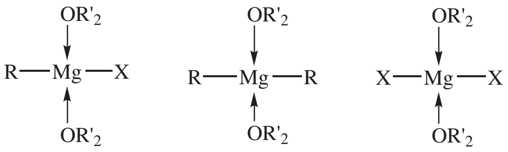
[152]Brown, T.L.; Dickerhoof, D.W.; Bafus, D.A. *J. Am. Chem. Soc.* ***1962***, *84*, 1371; Chinn, Jr., J.W.; Lagow, R.L. *Organometallics* ***1984***, *3*, 75; Plavšić, D.; Srzić, D.; Klasinc, L. *J. Phys. Chem.* ***1986***, *90*, 2075.

the solid state,[153] alkyllithium reagents exist as aggregates. X-ray crystallography has shown that methyllithium has the same tetrahedral structure in the solid state as in ether solution.[153] However, *tert*-butyllithium is monomeric in THF, although dimeric in ether and tetrameric in hydrocarbon solvents.[154] Neopentyllithium exists as a mixture of monomers and dimers in THF.[155]

The C—Mg bond in Grignard reagents is covalent and not ionic. The actual structure of Grignard reagents in solution has been a matter of much controversy over the years.[156] In 1929, it was discovered[157] that the addition of dioxane to an ethereal Grignard solution precipitates all the magnesium halide and leaves a solution of R_2Mg in ether; that is, there can be no RMgX in the solution since there is no halide. The following equilibrium, now called the *Schlenk equilibrium*, was proposed as the composition of the Grignard solution:

$$2\,RMgX \rightleftharpoons R_2Mg + MgX_2 \rightleftharpoons \underset{\mathbf{32}}{R_2Mg{\bullet}MgX_2}$$

in which **32** is a complex of some type. Much work has demonstrated that the Schlenk equilibrium actually exists and that the position of the equilibrium is dependent on the identity of R, X, the solvent, the concentration, and the temperature.[158] It has been known for many years that the magnesium in a Grignard solution, no matter whether it is RMgX, R_2Mg, or MgX_2, can coordinate with two molecules of ether in addition to the two covalent bonds:



Rundle and co-workers[159] performed X-ray diffraction studies on solid phenylmagnesium bromide dietherate and on ethylmagnesium bromide dietherate, which they obtained by cooling ordinary ethereal Grignard solutions until the

[153] Dietrich, H. *Acta Crystallogr.* ***1963***, *16*, 681; Weiss, E.; Lucken, E.A.C. *J. Organomet. Chem.* ***1964***, *2*, 197; Weiss, E.; Sauermann, G.; Thirase, G. *Chem. Ber.* ***1983***, *116*, 74.

[154] Bauer, W.; Winchester, W.R.; Schleyer, P.v.R. *Organometallics* ***1987***, *6*, 2371.

[155] Fraenkel, G.; Chow, A.; Winchester, W.R. *J. Am. Chem. Soc.* ***1990***, *112*, 6190.

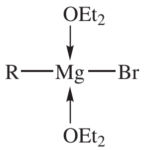
[156] For reviews, see Ashby, E.C. *Bull. Soc. Chim. Fr.* ***1972***, 2133; *Q. Rev. Chem. Soc.* ***1967***, *21*, 259; Wakefield, B.J. *Organomet. Chem. Rev.* ***1966***, *1*, 131; Bell, N.A. *Educ. Chem.* ***1973***, 143.

[157] Schlenk, W.; Schlenk Jr., W. *Ber.* ***1929***, *62B*, 920.

[158] See Parris, G.; Ashby, E.C. *J. Am. Chem. Soc.* ***1971***, *93*, 1206; Salinger, R.M.; Mosher, H.S. *J. Am. Chem. Soc.* ***1964***, *86*, 1782; Kirrmann, A.; Hamelin, R.; Hayes, S. *Bull. Soc. Chim. Fr.* ***1963***, 1395.

[159] Guggenberger, L.J.; Rundle, R.E. *J. Am. Chem. Soc.* ***1968***, *90*, 5375; Stucky, G.; Rundle, R.E. *J. Am. Chem. Soc.* ***1964***, *86*, 4825.

solids crystallized. They found that the structures were monomeric:



R = ethyl, phenyl

These solids still contained ether. When ordinary ethereal Grignard solutions[160] prepared from bromomethane, chloromethane, bromoethane, and chloroethane were evaporated at ~100°C under vacuum so that the solid remaining contained no ether, X-ray diffraction showed *no* RMgX, but a mixture of R_2Mg and MgX_2.[161] These results indicate that in the presence of ether $RMgX{\bullet}2Et_2O$ is the preferred structure, while the loss of ether drives the Schlenk equilibrium to $R_2Mg + MgX_2$. However, conclusions drawn from a study of the solid materials do not necessarily apply to the structures in solution.

Boiling-point-elevation and freezing-point-depression measurements have demonstrated that in THF at all concentrations and in ether at low concentrations (up to ~0.1 *M*) Grignard reagents prepared from alkyl bromides and iodides are monomeric, that is, there are few or no molecules with two magnesium atoms.[162] Thus, part of the Schlenk equilibrium is operating but not the other

$$2\,RMgX \rightleftharpoons R_2Mg + MgX_2$$

part; that is, **32** is not present in measurable amounts. This was substantiated by ^{25}Mg NMR spectra of the ethyl Grignard reagent in THF, which showed the presence of three peaks, corresponding to EtMgBr, Et_2Mg, and $MgBr_2$.[163] That the equilibrium between RMgX and R_2Mg lies far to the left for "ethylmagnesium bromide" in ether was shown by Smith and Becker, who mixed 0.1 *M* ethereal solutions of Et_2Mg and $MgBr_2$ and found that a reaction occurred with a heat evolution of 3.6 kcal mol^{-1} (15 kJ mol^{-1}) of Et_2Mg, and that the product was *monomeric* (by boiling-point-elevation measurements).[164] When either solution was added little by little to the other, there was a linear output of heat until almost a 1:1 molar ratio was reached. Addition of an excess of either reagent gave no further heat output. These results show that at least under some conditions the Grignard reagent is largely RMgX (coordinated with solvent) but that the equilibrium can be driven to R_2Mg by evaporation of all the ether or by addition of dioxane.

[160]The constitution of alkylmagnesium chloride reagents in THF has been determined. See Sakamoto, S.; Imamoto, T.; Yamaguchi, K. *Org. Lett.* ***2001***, *3*, 1793.

[161]Weiss, E. *Chem. Ber.* ***1965***, *98*, 2805.

[162]Ashby, E.C.; Smith, M.B. *J. Am. Chem. Soc.* ***1964***, *86*, 4363; Vreugdenhil, A.D.; Blomberg, C. *Recl. Trav. Chim. Pays-Bas* ***1963***, *82*, 453, 461.

[163]Benn, R.; Lehmkuhl, H.; Mehler, K.; Rufińska, A. *Angew. Chem. Int. Ed.* ***1984***, *23*, 534.

[164]Smith, M.B.; Becker, W.E. *Tetrahedron* ***1966***, *22*, 3027.

For some aryl Grignard reagents it has proved possible to distinguish separate NMR chemical shifts for ArMgX and Ar_2Mg.[165] From the area under the peaks it is possible to calculate the concentrations of the two species, and from them, equilibrium constants for the Schlenk equilibrium. These data show[165] that the position of the equilibrium depends very markedly on the aryl group and the solvent but that conventional aryl Grignard reagents in ether are largely ArMgX, while in THF the predominance of ArMgX is less, and with some aryl groups there is actually more Ar_2Mg present. Separate nmr chemical shifts have also been found for alkyl RMgBr and R_2Mg in HMPA[166] and in ether at low temperatures.[167] When Grignard reagents from alkyl bromides or chlorides are prepared in triethylamine the predominant species is RMgX.[168] Thus the most important factor determining the position of the Schlenk equilibrium is the solvent. For primary alkyl groups the equilibrium constant for the reaction as written above is lowest in Et_3N, higher in ether, and still higher in THF.[169]

However, Grignard reagents prepared from alkyl bromides or iodides in ether at higher concentrations (0.5–1 *M*) contain dimers, trimers, and higher polymers, and those prepared from alkyl chlorides in ether at all concentrations are dimeric,[170] so that **32** is in solution, probably in equilibrium with RMgX and R_2Mg; that is, the complete Schlenk equilibrium seems to be present.

The Grignard reagent prepared from 1-chloro-3,3-dimethylpentane in ether undergoes rapid inversion of configuration at the magnesium-containing carbon (demonstrated by NMR; this compound is not chiral).[171] The mechanism of this inversion is not completely known. Therefore, in almost all cases, it is not possible to retain the configuration of a stereogenic carbon while forming a Grignard reagent.

Organolithium reagents (RLi) are tremendously important reagents in organic chemistry. In recent years, a great deal has been learned about their structure[172] in both the solid state and in solution. X-ray analysis of complexes of *n*-butyllithium with *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), THF, and 1,2-dimethoxyethane (DME) shows them to be dimers and tetramers [e.g., $(BuLi•DME)_4$].[173] X-ray analysis of isopropyllithium shows it to be a hexamer,

[165]Evans, D.F.; Fazakerley, V. *Chem. Commun.* ***1968***, 974.

[166]Ducom, J. *Bull. Chem. Soc. Fr.* ***1971***, 3518, 3523, 3529.

[167]Ashby, E.C.; Parris, G.; Walker, F. *Chem. Commun.* ***1969***, 1464; Parris, G.; Ashby, E.C. *J. Am. Chem. Soc.* ***1971***, *93*, 1206.

[168]Ashby, E.C.; Walker, F. *J. Org. Chem.* ***1968***, *33*, 3821.

[169]Parris, G.; Ashby, E.C. *J. Am. Chem. Soc.* ***1971***, *93*, 1206.

[170]Ashby, E.C.; Smith, M.B. *J. Am. Chem. Soc.* ***1964***, *86*, 4363.

[171]Whitesides, G.M.; Witanowski, M.; Roberts, J.D. *J. Am. Chem. Soc.* ***1965***, *87*, 2854; Whitesides, G.M.; Roberts, J.D. *J. Am. Chem. Soc.* ***1965***, *87*, 4878. Also see, Witanowski, M.; Roberts, J.D. *J. Am. Chem. Soc.* ***1966***, *88*, 737; Fraenkel, G.; Cottrell, C.E.; Dix, D.T. *J. Am. Chem. Soc.* ***1971***, *93*, 1704; Pechhold, E.; Adams, D.G.; Fraenkel, G. *J. Org. Chem.* ***1971***, *36*, 1368; Maercker, A.; Geuss, R. *Angew. Chem. Int. Ed.* ***1971***, *10*, 270.

[172]For a computational study of acidities, electron affinities, and bond dissociation energies of selected organolithium reagents, see Pratt, L.M.; Kass, S.R. *J. Org. Chem.* ***2004***, *69*, 2123.

[173]Nichols, M.A.; Williard, P.G. *J. Am. Chem. Soc.* ***1993***, *115*, 1568.

(iPrLi)$_6$],[174] and unsolvated lithium aryls are tetramers.[175] α-Ethoxyvinyllithium [$CH_2=C(OEt)Li$] shows a polymeric structure with tetrameric subunits.[176] Aminomethyl aryllithium reagents have been shown to be chelated and dimeric in solvents such as THF.[177]

The dimeric, tetrameric, and hexameric structures of organolithium reagents[178] in the solid state is often retained in solution, but this is dependent on the solvent and complexing additives, if any. A tetrahedral organolithium compound is known,[179] and the X-ray of an α,α-dilithio hydrocarbon has been reported.[180] Phenyllithium is a mixture of tetramers and dimers in diethyl ether, but stoichiometric addition of THF, dimethoxyethane, or TMEDA leads to the dimer.[181] The solution structures of mixed aggregates of butyllithium and amino-alkaloids has been determined,[182] and also the solution structure of sulfur-stabilized allyllithium compounds.[183] Vinyllithium is an 8:1 mixture of tetramer:dimer in THF at −90°C, but addition of TMEDA changes the ratio of tetramer:dimer to 1:13 at −80°C.[184] Internally solvated allylic lithium compounds have been studied, showing the coordinated lithium to be closer to one of the terminal allyl carbons.[185] A relative scale of organolithium stability has been established,[186] and the issue of configurational stability of enantio-enriched organolithium reagents has been examined.[187]

Enolate anions are an important class of carbanions that appear in a variety of important reactions, including alkylation α- to a carbonyl group and the aldol (reaction **16-34**) and Claisen condensation (reaction **16-85**) reactions. Metal enolate anions of aldehydes, ketones, esters, and other acid derivatives exist as aggregates in ether solvents,[188] and there is evidence that the lithium enolate of

[174]Siemeling, U.; Redecker, T.; Neumann, B.; Stammler, H.-G. *J. Am. Chem. Soc.* ***1994***, *116*, 5507.

[175]Ruhlandt-Senge, K.; Ellison, J.J.; Wehmschulte, R.J.; Pauer, F.; Power, P.P. *J. Am. Chem. Soc.* ***1993***, *115*, 11353. For the X-ray structure of 1-methoxy-8-naphthyllithium see Betz, J.; Hampel, F.; Bauer, W. *Org. Lett.* ***2000***, *2*, 3805.

[176]Sorger, K.; Bauer, W.; Schleyer, P.v.R.; Stalke, D. *Angew. Chem. Int. Ed.* ***1995***, *34*, 1594.

[177]Reich, H.J.; Gudmundsson, B.O.; Goldenberg, W.S.; Sanders, A.W.; Kulicke, K.J.; Simon, K.; Guzei, I.A. *J. Am. Chem. Soc.* ***2001***, *123*, 8067.

[178]For an *ab initio* correlation of structure with NMR, see Parisel, O.; Fressigne, C.; Maddaluno, J.; Giessner-Prettre, C. *J. Org. Chem.* ***2003***, *68*, 1290.

[179]Sekiguchi, A.; Tanaka, M. *J. Am. Chem. Soc.* ***2003***, *125*, 12684.

[180]Linti, G.; Rodig, A.; Pritzkow, H. *Angew. Chem. Int. Ed.* ***2002***, *41*, 4503.

[181]Reich, H.J.; Green, D.P.; Medina, M.A.; Goldenberg, W.S.; Gudmundsson, B.Ö.; Dykstra, R.R.; Phillips. N.H. *J. Am. Chem. Soc.* ***1998***, *120*, 7201.

[182]Sun, X.; Winemiller, M.D.; Xiang, B.; Collum, D.B. *J. Am. Chem. Soc.* ***2001***, *123*, 8039. See also, Rutherford, J.L.; Hoffmann, D.; Collum, D.B. *J. Am. Chem. Soc.* ***2002***, *124*, 264.

[183]Piffl, M.; Weston, J.; Günther, W.; Anders, E. *J. Org. Chem.* ***2000***, *65*, 5942.

[184]Bauer, W.; Griesinger, C. *J. Am. Chem. Soc.* ***1993***, *115*, 10871.

[185]Fraenkel, G.; Chow, A.; Fleischer, R.; Liu, H. *J. Am. Chem. Soc.* ***2004***, *126*, 3983.

[186]Graña, P.; Paleo, M.R.; Sardina, F.J. *J. Am. Chem. Soc.* ***2002***, *124*, 12511.

[187]Basu, A.; Thayumanavan, S. *Angew. Chem. Int. Ed.* ***2002***, *41*, 717. See also, Fraenkel, G.; Duncan, J.H.; Martin, K.; Wang, J. *J. Am. Chem. Soc.* ***1999***, *121*, 10538.

[188]Stork, G.; Hudrlik, P.F. *J. Am. Chem. Soc.* ***1968***, *90*, 4464; Bernstein, M.P.; Collum, D.B. *J. Am. Chem. Soc.* ***1993***, *115*, 789; Bernstein, M.P.; Romesberg, F.E.; Fuller, D.J.; Harrison, A.T.; Collum, D.B.; Liu, Q.Y.; Williard, P.G. *J. Am. Chem. Soc.* ***1992***, *114*, 5100; Collum, D.B. *Acc. Chem. Res.* ***1992***, *25*, 448.

isobutyrophenone is a tetramer in THF,[189] but a dimer in DME.[190] X-ray crystallography of ketone enolate anions have shown that they can exist as tetramers and hexamers.[191] There is also evidence that the aggregate structure is preserved in solution and is probably the actual reactive species. Lithium enolates derived from esters are as dimers in the solid state[192] that contain four tetrahydrofuran molecules. It has also been established that the reactivity of enolate anions in alkylation and condensation reactions is influenced by the aggregate state of the enolate. It is also true that the relative proportions of (*E*) and (*Z*) enolate anions are influenced by the extent of solvation and the aggregation state. Addition of LiBr to a lithium enolate anion in THF suppresses the concentration of monomeric enolate.[193] *Ab initio* studies confirm the aggregate state of acetaldehyde.[194] It is also known that α-Li benzonitrile [PhCH(Li)CN] exists as a dimer in ether and with TMEDA.[195] Mixed aggregates of *tert*-butyllithium and lithium *tert*-butoxide are known to be hexameric.[196]

It might be mentioned that matters are much simpler for organometallic compounds with less-polar bonds. Thus Et_2Hg and EtHgCl are both definite compounds, the former a liquid and the latter a solid. Organocalcium reagents are also know, and they are formed from alkyl halides via a single electron-transfer (SET) mechanism with free-radical intermediates.[197]

The Generation and Fate of Carbanions

The two principal ways in which carbanions are generated are parallel with the ways of generating carbocations.

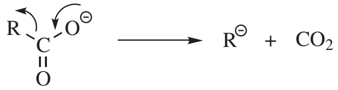
1. A group attached to a carbon leaves without its electron pair:

$$R{-}H \longrightarrow R^{\ominus} + H^{\oplus}$$

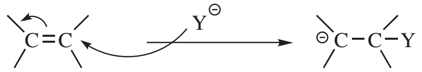
The leaving group is most often a proton. This is a simple acid–base reaction, and a base is required to remove the proton.[198] However, other

[189]Jackman, L.M.; Szeverenyi, N.M. *J. Am. Chem. Soc.* ***1977***, *99*, 4954; Jackman, L.M.; Lange, B.C. *J. Am. Chem. Soc.* ***1981***, *103*, 4494.
[190]Jackman, L.M.; Lange, B.C. *Tetrahedron* ***1977***, *33*, 2737.
[191]Williard, P.G.; Carpenter, G.B. *J. Am. Chem. Soc.* ***1986***, *108*, 462; Williard, P.G.; Carpenter, G.B. *J. Am. Chem. Soc.* ***1985***, *107*, 3345; Amstutz, R.; Schweizer, W.B.; Seebach, D.; Dunitz, J.D. *Helv. Chim. Acta* ***1981***, *64*, 2617; Seebach, D.; Amstutz, D.; Dunitz, J.D. *Helv. Chim. Acta* ***1981***, *64*, 2622.
[192]Seebach, D.; Amstutz, R.; Laube, T.; Schweizer, W.B.; Dunitz, J.D. *J. Am. Chem. Soc.* ***1985***, *107*, 5403.
[193]Abu-Hasanayn, F.; Streitwieser, A. *J. Am. Chem. Soc.* ***1996***, *118*, 8136.
[194]Abbotto, A.; Streitwieser, A.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1997***, *119*, 11255.
[195]Carlier, P.R.; Lucht, B.L.; Collum, D.B. *J. Am. Chem. Soc.* ***1994***, *116*, 11602.
[196]DeLong, G.T.; Pannell, D.K.; Clarke, M.T.; Thomas, R.D. *J. Am. Chem. Soc.* ***1993***, *115*, 7013.
[197]Walborsky, H.M.; Hamdouchi, C. *J. Org. Chem.* ***1993***, *58*, 1187.
[198]For a review of such reactions, see Durst, T., in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, pt. B, Elsevier, NY, ***1984***, pp. 239–291.

leaving groups are known (see Chapter 12):



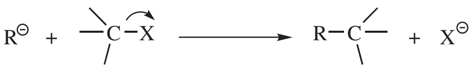
2. A negative ion adds to a carbon–carbon double or triple bond (see Chapter 15):



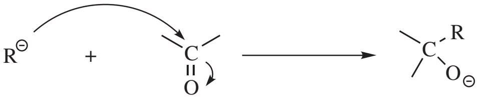
The addition of a negative ion to a carbon–oxygen double bond does not give a carbanion, since the negative charge resides on the oxygen.

The most common reaction of carbanions is combination with a positive species, usually a proton, or with another species that has an empty orbital in its outer shell (a Lewis acid–base reaction):

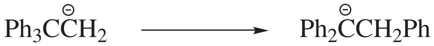
Carbanions may also form a bond with a carbon that already has four bonds, by displacing one of the four groups (S_N2 reaction, see Chapter 10):



Like carbocations, carbanions can also react in ways in which they are converted to species that are still not neutral molecules. They can add to double bonds (usually C=O double bonds; see Chapters 10 and 16),



or rearrange, although this is rare (see Chapter 18),



or be oxidized to free radicals.[199] A system in which a carbocation [Ph(p-$Me_2NC_6H_4)_2C^+$] oxidizes a carbanion [(p-$NO_2C_6H_4)_3C^-$] to give two free radicals, reversibly, so that all four species are present in equilibrium, has been demonstrated.[200,201]

[199]For a review, see Guthrie, R.D., in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, pt. A, Elsevier, NY, ***1980***, pp. 197–269.

[200]Arnett, E.M.; Molter, K.E.; Marchot, E.C.; Donovan, W.H.; Smith, P. *J. Am. Chem. Soc.* ***1987***, *109*, 3788.

[201]Okamoto, K.; Kitagawa, T.; Takeuchi, K.; Komatsu, K.; Kinoshita, T.; Aonuma, S.; Nagai, M.; Miyabo, A. *J. Org. Chem.* ***1990***, *55*, 996. See also, Okamoto, K.; Kitagawa, T.; Takeuchi, K.; Komatsu, K.; Miyabo, A. *J. Chem. Soc. Chem. Commun.* ***1988***, 923.

Organometallic compounds that are not ionic, but polar-covalent behave very much as if they were ionic and give similar reactions.

FREE RADICALS

Stability and Structure[202]

A *free radical* (often simply called a *radical*) may be defined as a species that contains one or more unpaired electrons. Note that this definition includes certain stable inorganic molecules (e.g., NO and NO_2), as well as many individual atoms (e.g., Na and Cl). As with carbocations and carbanions, simple alkyl radicals are very reactive. Their lifetimes are extremely short in solution, but they can be kept for relatively long periods frozen within the crystal lattices of other molecules.[203] Many spectral[204] measurements have been made on radicals trapped in this manner. Even under these conditions the methyl radical decomposes with a half-life of 10–15 min in a methanol lattice at 77 K.[205] Since the lifetime of a radical depends not only on its inherent stability, but also on the conditions under which it is generated, the terms *persistent* and *stable* are usually used for the different senses. A stable radical is inherently stable; a persistent radical has a relatively long lifetime under the conditions at which it is generated, although it may not be very stable.

Radicals can be characterized by several techniques, such as mass spectrometry[206] or the characterization of alkoxycarbonyl radicals by Step-Scan Time-Resolved Infrared Spectroscopy.[207] Another technique makes use of the magnetic moment that is associated with the spin of an electron, which can be expressed by a quantum number of $\frac{1}{+2}$ or $\frac{1}{-2}$. According to the Pauli principle, any two electrons occupying the same orbital must have opposite spins, so the total magnetic

[202]For monographs, see Alfassi, Z.B. *N-Centered Radicals*, Wiley, Chichester, ***1998***; Alfassi, Z.B. *Peroxyl Radicals*, Wiley, Chichester, ***1997***; Alfassi, Z.B. *Chemical Kinetics of Small Organic Radicals*, 4 vols., CRC Press: Boca Raton, FL, ***1988***; Nonhebel, D.C.; Tedder, J.M.; Walton, J.C. *Radicals*, Cambridge University Press, Cambridge, ***1979***; Nonhebel, D.C.; Walton, J.C. *Free-Radical Chemistry*, Cambridge University Press, Cambridge, ***1974***; Kochi, J.K. *Free Radicals*, 2 vols., Wiley, NY, ***1973***; Hay, J.M. *Reactive Free Radicals*, Academic Press, NY, ***1974***; Pryor, W.A. *Free Radicals*, McGraw-Hill, NY, ***1966***. For reviews, see Kaplan, L. *React. Intermed. (Wiley)* ***1985***, *3*, 227; ***1981***, *2*, 251–314; ***1978***, *1*, 163; Griller, D.; Ingold, K.U. *Acc. Chem. Res.* ***1976***, *9*, 13; Huyser, E.S., in McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, ***1973***, pp. 1–59; Isaacs, N.S. *Reactive Intermediates in Organic Chemistry*, Wiley, NY, ***1974***, pp. 294–374.

[203]For a review of the use of matrices to study radicals and other unstable species, see Dunkin, I.R. *Chem. Soc. Rev.* ***1980***, *9*, 1; Jacox, M.E. *Rev. Chem. Intermed.* ***1978***, *2*, 1. For a review of the study of radicals at low temperatures, see Mile, B. *Angew. Chem. Int. Ed.* ***1968***, *7*, 507.

[204]For a review of infrared spectra of radicals trapped in matrices, see Andrews, L. *Annu. Rev. Phys. Chem.* ***1971***, *22*, 109.

[205]Sullivan, P.J.; Koski, W.S. *J. Am. Chem. Soc.* ***1963***, *85*, 384.

[206]Sablier, M.; Fujii, T. *Chem. Rev.* ***2002***, *102*, 2855.

[207]Bucher, G.; Halupka, M.; Kolano, C.; Schade, O.; Sander, W. *Eur. J. Org. Chem.* ***2001***, 545.

moment is zero for any species in which all the electrons are paired. In radicals, however, one or more electrons are unpaired, so there is a net magnetic moment and the species is paramagnetic. Radicals can therefore be detected by magnetic-susceptibility measurements, but for this technique a relatively high concentration of radicals is required.

A much more important technique is *electron spin resonance* (esr), also called *electron paramagnetic resonance* (epr).[208] The principle of esr is similar to that of nmr, except that electron spin is involved rather than nuclear spin. The two electron spin states ($m_s = \frac{1}{2}$ and $m_s = \frac{1}{-2}$) are ordinarily of equal energy, but in a magnetic field the energies are different. As in NMR, a strong external field is applied and electrons are caused to flip from the lower state to the higher by the application of an appropriate radio-frequency (rf) signal. Inasmuch as two electrons paired in one orbital must have opposite spins which cancel, an esr spectrum arises only from species that have one or more unpaired electrons (i.e., free radicals).

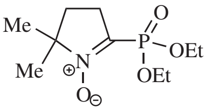
Since only free radicals give an esr spectrum, the method can be used to detect the presence of radicals and to determine their concentration.[209] Furthermore, information concerning the electron distribution (and hence the structure) of free radicals can be obtained from the splitting pattern of the esr spectrum (esr peaks are split by nearby protons).[210] Fortunately (for the existence of most free radicals is very short), it is not necessary for a radical to be persistent for an esr spectrum to be obtained. Electron spin resonance spectra have been observed for radicals with lifetimes considerably <1 s. Failure to observe an esr spectrum does not prove that radicals are not involved, since the concentration may be too low for direct observation. In such cases, the *spin trapping* technique can

[208]For monographs, see Wertz, J.E.; Bolton, J.R. *Electron Spin Resonance*; McGraw-Hill, NY, ***1972*** [reprinted by Chapman and Hall, NY, and Methuen, London, ***1986***]; Assenheim, H.M. *Introduction to Electron Spin Resonance*, Plenum, NY, ***1967***; Bersohn, R.; Baird, J.C. *An Introduction to Electron Paramagnetic Resonance*, W.A. Benjamin, NY, ***1966***. For reviews, see Bunce, N.J. *J. Chem. Educ.* ***1987***, *64*, 907; Hirota, N.; Ohya-Nishiguchi, H., in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed., pt. 2, Wiley, NY, ***1986***, pp. 605–655; Griller, D.; Ingold, K.U. *Acc. Chem. Res.* ***1980***, *13*, 193; Norman, R.O.C. *Chem. Soc. Rev.* ***1980***, *8*, 1; Fischer, H., in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 435–491; Russell, G.A., in Nachod, F.C.; Zuckerman, J.J. *Determination of Organic Structures by Physical Methods*, Vol. 3; Academic Press, NY, ***1971***, pp. 293–341; Rassat, A. *Pure Appl. Chem.* ***1971***, *25*, 623; Kevan, L. *Methods Free-Radical Chem.* ***1969***, *1*, 1; Geske, D.H. *Prog. Phys. Org. Chem.* ***1967***, *4*, 125; Norman, R.O.C.; Gilbert, B.C. *Adv. Phys. Org. Chem.* ***1967***, *5*, 53; Schneider, F.; Möbius, K.; Plato, M. *Angew. Chem. Int. Ed.* ***1965***, *4*, 856. For a review on the application of epr to photochemistry, see Turro, N.J.; Kleinman, M.H.; Karatekin, E. *Angew. Chem. Int. Ed.* ***2000***, *39*, 4437. For a review of the related ENDOR method, see Kurreck, H.; Kirste, B.; Lubitz, W. *Angew. Chem. Int. Ed.* ***1984***, *23*, 173. See also, Poole, Jr., C.P. *Electron Spin Resonance. A Comprehensive Treatise on Experimental Techniques*, 2nd ed., Wiley, NY, ***1983***.

[209]Davies, A.G. *Chem. Soc. Rev.* ***1993***, *22*, 299.

[210]For reviews of the use of esr spectra to determine structures, see Walton, J.C. *Rev. Chem. Intermed.* ***1984***, *5*, 249; Kochi, J.K. *Adv. Free-Radical Chem.* ***1975***, *5*, 189. For esr spectra of a large number of free radicals, see Bielski, B.H.J.; Gebicki, J.M. *Atlas of Electron Spin Resonance Spectra*; Academic Press, NY, ***1967***.

be used.[211] In this technique, a compound is added that is able to combine with very reactive radicals to produce more persistent radicals; the new radicals can be observed by esr. Azulenyl nitrones have been developed as chromotropic spin trapping agents.[212] The most important spin-trapping compounds are nitroso compounds, which react with radicals to give fairly stable nitroxide radicals:[213] $RN{=}O + R'^{\bullet} \rightarrow RR'N{-}O^{\bullet}$. An *N*-oxide spin trap has been developed [**33**; 2(diethylphosphino)-5,5-dimethyl-1-pyrroline-*N*-oxide], and upon trapping a reactive free radical, ^{31}P NMR can be used to identify it.[214] This is an effective technique, and short-lived species such as the oxiranylmethyl radical has been detected by spin trapping.[215] Other molecules have been used to probe the intermediacy of radicals via SET processes. They are called SET probes.[216]



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Because there is an equal probability that a given unpaired electron will have a quantum number of $\frac{1}{+2}$ or $\frac{1}{-2}$, radicals are observed as a single line in an esr spectrum unless they interact with other electronic or nuclear spins or possess magnetic anisotropy, in which case two or more lines may appear in the spectrum.[217]

Another magnetic technique for the detection of free radicals uses an ordinary NMR instrument. It was discovered[218] that if an nmr spectrum is taken during the course of a reaction, certain signals may be enhanced, either in a positive or negative direction; others may be reduced. When this type of behavior, called *chemically*

[211]For reviews, see Janzen, E.G.; Haire, D.L. *Adv. Free Radical Chem. (Greenwich, Conn.)* ***1990***, *1*, 253; Gasanov, R.G.; Freidlina, R.Kh. *Russ. Chem. Rev.* ***1987***, *56*, 264; Perkins, M.J. *Adv. Phys. Org. Chem.* ***1980***, *17*, 1; Zubarev, V.E.; Belevskii, V.N.; Bugaenko, L.T. *Russ. Chem. Rev.* ***1979***, *48*, 729; Evans, C.A. *Aldrichimica Acta* ***1979***, *12*, 23; Janzen, E.G. *Acc. Chem. Res.* ***1971***, *4*, 31. See also, the collection of papers on this subject in *Can. J. Chem.* ***1982***, *60*, 1379.

[212]Becker, D.A. *J. Am. Chem. Soc.* ***1996***, *118*, 905; Becker, D.A.; Natero, R.; Echegoyen, L.; Lawson, R.C. *J. Chem. Soc. Perkin Trans. 2* ***1998***, 1289. Also see, Klivenyi, P.; Matthews, R.T.; Wermer, M.; Yang, L.; MacGarvey, U.; Becker, D.A.; Natero, R.; Beal, M.F. *Experimental Neurobiology* ***1998***, *152*, 163.

[213]For a series of papers on nitroxide radicals, see *Pure Appl. Chem.* ***1990***, *62*, 177.

[214]Janzen, E.G.; Zhang, Y.-K. *J. Org. Chem.* ***1995***, *60*, 5441. For the preparation of a new but structurally related spin trap see Karoui, H.; Nsanzumuhire, C.; Le Moigne, F.; Tordo, P. *J. Org. Chem.* ***1999***, *64*, 1471.

[215]Grossi, L.; Strazzari, S. *Chem. Commun.* ***1997***, 917.

[216]Timberlake, J.W.; Chen, T. *Tetrahedron Lett.* ***1994***, *35*, 6043; Tanko, J.M.; Brammer Jr., L.E.; Hervas', M.; Campos, K. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 1407.

[217]Harry Frank, University of Connecticut, Storrs, CT., Personal Communication.

[218]Ward, H.R.; Lawler, R.G.; Cooper, R.A. *J. Am. Chem. Soc.* ***1969***, *91*, 746; Bargon, J.; Fischer, H.; Johnsen, U. *Z. Naturforsch., Teil A* ***1967***, *22*, 1551; Bargon, J.; Fischer, H. *Z. Naturforsch., Teil A* ***1967***, *22*, 1556; Lepley, A.R. *J. Am. Chem. Soc.* ***1969***, *91*, 749; Lepley, A.R.; Landau, R.L. *J. Am. Chem. Soc.* ***1969***, *91*, 748.

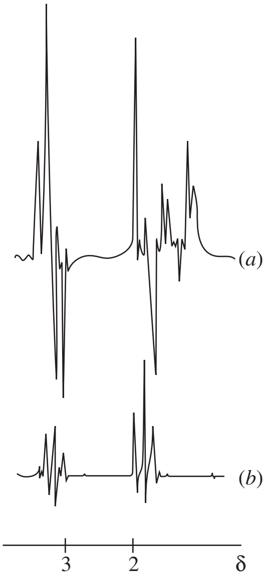


Fig. 5.1 (*a*) The NMR spectrum taken during reaction between EtI and EtLi in benzene (the region between 0.5 and 3.5 δ was scanned with an amplitude twice that of the remainder of the spectrum). The signals at 1.0–1.6 δ are due to butane, some of which is also formed in the reaction. (*b*) Reference spectrum of EtI.[221]

induced dynamic nuclear polarization[219] (CIDNP), is found in the nmr spectrum of the product of a reaction, it means that *at least a portion of that product was formed via the intermediacy of a free radical.*[220] For example, the question was raised whether radicals were intermediates in the exchange reaction between ethyl iodide and ethyllithium (reaction **12-39**):

$$\text{EtI} + \text{EtLi} \rightleftharpoons \text{EtLi} + \text{EtI}$$

Curve *a* in Fig. 5.1[221] shows an NMR spectrum taken during the course of the reaction. Curve *b* is a reference spectrum of ethyl iodide (CH_3 protons at $\delta = 1.85$; CH_2 protons at $\delta = 3.2$). Note that in curve *a* some of the ethyl iodide signals are

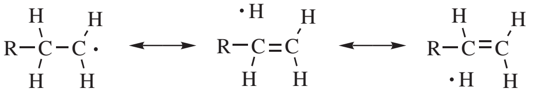
[219]For a monograph on CIDNP, see Lepley, R.L.; Closs, G.L. *Chemically Induced Magnetic Polarization*, Wiley, NY, ***1973***. For reviews, see Adrian, F.J. *Rev. Chem. Intermed.* ***1986***, *7*, 173; Closs, G.L.; Miller, R.J.; Redwine, O.D. *Acc. Chem. Res.* ***1985***, *18*, 196; Lawler, R.G.; Ward, H.R., in Nachod, F.C.; Zuckerman, J.J. *Determination of Rates and Mechanisms of Reactions*, Vol. 5, Academic Press, NY, ***1973***, pp. 99–150; Ward, H.R., in Kochi, J.K. *Free Radicals*, Vol. 1, Wiley, NY, ***1973***, pp. 239–273; *Acc. Chem. Res.* ***1972***, *5*, 18; Closs, G.L. *Adv. Magn. Reson.* ***1974***, *7*, 157; Lawler, R.G. *Acc. Chem. Res.* ***1972***, *5*, 25; Kaptein, R. *Adv. Free-Radical Chem.* ***1975***, *5*, 319; Bethell, D.; Brinkman, M.R. *Adv. Phys. Org. Chem.* ***1973***, *10*, 53.

[220]A related technique is called chemically induced dynamic electron polarization (CIDEP). For a review, see Hore, P.J.; Joslin, C.G.; McLauchlan, K.A. *Chem. Soc. Rev.* ***1979***, *8*, 29.

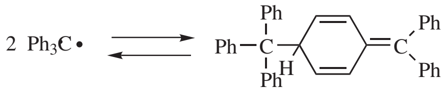
[221]Ward, H.R.; Lawler, R.G.; Cooper, R.A. *J. Am. Chem. Soc.* ***1969***, *91*, 746.

enhanced; others go below the base line (*negative enhancement*; also called *emission*). Thus the ethyl iodide formed in the exchange shows CIDNP, and hence was formed via a free-radical intermediate. Chemically induced dynamic nuclear polarization results when protons in a reacting molecule become dynamically coupled to an unpaired electron while traversing the path from reactants to products. Although the presence of CIDNP almost always means that a free radical is involved,[222] its absence does not prove that a free-radical intermediate is necessarily absent, since reactions involving free-radical intermediates can also take place without observable CIDNP. Also, the presence of CIDNP does not prove that *all* of a product was formed via a free-radical intermediate, only that some of it was. It is noted that dynamic nuclear polarization (DNP) enhance signal intensities in NMR spectra of solids and liquids. In a contemporary DNP experiment, a diamagnetic sample is doped with a paramagnet and the large polarization of the electron spins is transferred to the nuclei via microwave irradiation of the epr spectrum.[223] Dynamic nuclear polarization has been used to examine biradicals.[224]

As with carbocations, the stability order of free radicals is tertiary > secondary > primary, explainable by field effects and hyperconjugation, analogous to that in carbocations (p. 235):



With resonance possibilities, the stability of free radicals increases;[225] some can be kept indefinitely.[226] Benzylic and allylic[227] radicals for which canonical forms can be drawn similar to those shown for the corresponding cations



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(pp. 239, 240) and anions (pp. 252) are more stable than simple alkyl radicals, but still have only a transient existence under ordinary conditions. However, the triphenylmethyl and similar radicals[228] are stable enough to exist in solution

[222]It has been shown that CIDNP can also arise in cases where para hydrogen (H_2 in which the nuclear spins are opposite) is present: Eisenschmid, T.C.; Kirss, R.U.; Deutsch, P.P.; Hommeltoft, S.I.; Eisenberg, R.; Bargon, J.; Lawler, R.G.; Balch, A.L. *J. Am. Chem. Soc.* ***1987***, *109*, 8089.

[223]Wind, R.A.; Duijvestijn, M.J.; van der Lugt, C.; Manenschijn, A; Vriend, J. *Prog. Nucl. Magn. Reson. Spectrosc.* ***1985***, *17*, 33.

[224]Hu, K.-N.; Yu, H.-h.; Swager, T.M.; Griffin, R.G. *J. Am. Chem. Soc.* ***2004***, *126*, 10844.

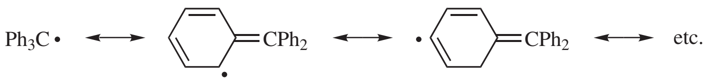
[225]For a discussion, see Robaugh, D.A.; Stein, S.E. *J. Am. Chem. Soc.* ***1986***, *108*, 3224.

[226]For a monograph on stable radicals, including those in which the unpaired electron is not on a carbon atom, see Forrester, A.R.; Hay, J.M.; Thomson, R.H. *Organic Chemistry of Stable Free Radicals*, Academic Press, NY, ***1968***.

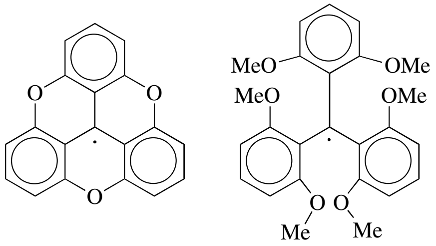
[227]For an electron diffraction study of the allyl radical, see Vajda, E.; Tremmel, J.; Rozsondai, B.; Hargittai, I.; Maltsev, A.K.; Kagramanov, N.D.; Nefedov, O.M. *J. Am. Chem. Soc.* ***1986***, *108*, 4352.

[228]For a review, see Sholle, V.D.; Rozantsev, E.G. *Russ. Chem. Rev.* ***1973***, *42*, 1011.

at room temperature, although in equilibrium with a dimeric form. The concentration of triphenylmethyl radical in benzene solution is ~2% at room temperature. For many years it was assumed that Ph_3C•, the first stable free radical known,[229] dimerized to hexaphenylethane (Ph_3C—CPh_3),[230] but UV and NMR investigations have shown that the true structure is **34**.[231] Although triphenylmethyl-type radicals are stabilized by resonance:



it is steric hindrance to dimerization and not resonance that is the major cause of their stability.[232] This was demonstrated by the preparation of the radicals **35** and **36**.[233] These radicals are electronically very similar, but **35**, being planar, has much less steric hindrance to dimerization than Ph_3C•, while **36**, with six groups in ortho positions, has much more. On the other hand, the planarity of **35** means that



35 **36**

it has a maximum amount of resonance stabilization, while **36** must have much less, since its degree of planarity should be even less than Ph_3C•, which itself is propeller shaped and not planar. Thus if resonance is the chief cause of the stability of Ph_3C•, **36** should dimerize and **35** should not, but if steric hindrance is

[229]Gomberg, M. *J. Am. Chem. Soc.* ***1900***, *22*, 757, *Ber.* ***1900***, *33*, 3150.

[230]Hexaphenylethane has still not been prepared, but substituted compounds [hexakis(3,5-di-*tert*-butyl-4-biphenylyl)ethane and hexakis(3,5-di-*tert*-butylphenyl)ethane] have been shown by X-ray crystallography to be nonbridged hexaarylethanes in the solid state: Stein, M.; Winter, W.; Rieker, A. *Angew. Chem. Int. Ed.* ***1978***, *17*, 692; Yannoni, N.; Kahr, B.; Mislow, K. *J. Am. Chem. Soc.* ***1988***, *110*, 6670. In solution, both dissociate into free radicals.

[231]Lankamp, H.; Nauta, W.T.; MacLean, C. *Tetrahedron Lett.* ***1968***, 249; Staab, H.A.; Brettschneider, H.; Brunner, H. *Chem. Ber.* ***1970***, *103*, 1101; Volz, H.; Lotsch, W.; Schnell, H. *Tetrahedron* ***1970***, *26*, 5343; McBride, J. *Tetrahedron* ***1974***, *30*, 2009. See also, Guthrie, R.D.; Weisman, G.R. *Chem. Commun.* ***1969***, 1316; Takeuchi, H.; Nagai, T.; Tokura, N. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 753. For an example where a secondary benzilic radical undergoes this type of dimerization, see Peyman, A.; Peters, K.; von Schnering, H.G.; Rüchardt, C. *Chem. Ber.* ***1990***, *123*, 1899.

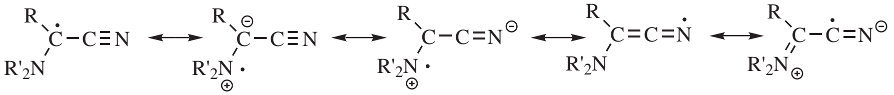
[232]For a review of steric effects in free-radical chemistry, see Rüchardt, C. *Top. Curr. Chem.* ***1980***, *88*, 1.

[233]Sabacky, M.J.; Johnson Jr., C.S.; Smith, R.G.; Gutowsky, H.S.; Martin, J.C. *J. Am. Chem. Soc.* ***1967***, *89*, 2054.

the major cause, the reverse should happen. It was found[233] that **36** gave no evidence of dimerization, even in the solid state, while **35** existed primarily in the dimeric form, which is dissociated to only a small extent in solution,[234] indicating that steric hindrance to dimerization is the major cause for the stability of triarylmethyl radicals. A similar conclusion was reached in the case of $(NC)_3C•$, which dimerizes readily although considerably stabilized by resonance.[235] Nevertheless, that resonance is still an important contributing factor to the stability of radicals is shown by the facts that (*1*) the radical *t*-Bu$(Ph)_2C•$ dimerizes more than $Ph_3C•$, while *p*-$PhCOC_6H_4(Ph_2)C•$ dimerizes less.[236] The latter has more canonical forms than $Ph_3C•$, but steric hindrance should be about the same (for attack at one of the two rings). (*2*) A number of radicals (*p*-$XC_6H_4)_3C•$, with X = F, Cl, O_2N, CN, and so on do not dimerize, but are kinetically stable.[237] Completely chlorinated triarylmethyl radicals are more stable than the unsubstituted kind, probably for steric reasons, and many are quite inert in solution and in the solid state.[238]

Allylic radical are relatively stable, and the pentadienyl radical is particularly stable. In such molecules, (*E,E*)-(*E,Z*)-, and (*Z,Z*)-stereoisomers can form. It has been calculated that (*Z,Z*)-pentadienyl radical is 5.6 kcal mol^{-1}(23.4 kJ mol^{-1}) less stable than (*E,E*)-pentadienyl radical.[239] 2-Phenylethyl radicals have been shown to exhibit bridging of the phenyl group.[240] It is noted that vinyl radical have (*E*)- and (*Z*)-forms and the inversion barrier from one to the other increases as the electronegativity of substituents increase.[241] Enolate radicals are also known.[242]

It has been postulated that the stability of free radicals is enhanced by the presence at the radical center of *both* an electron-donating and an electron-withdrawing group.[243] This is called the *push–pull* or *captodative effect* (see also, pp. 185). The effect arises from increased resonance, for example:



[234]Müller, E.; Moosmayer, A.; Rieker, A.; Scheffler, K. *Tetrahedron Lett.* ***1967***, 3877. See also, Neugebauer, F.A.; Hellwinkel, D.; Aulmich, G. *Tetrahedron Lett.* ***1978***, 4871.

[235]Kaba, R.A.; Ingold, K.U. *J. Am. Chem. Soc.* ***1976***, *98*, 523.

[236]Zarkadis, A.K.; Neumann, W.P.; Marx, R.; Uzick, W. *Chem. Ber.* ***1985***, *118*, 450; Zarkadis, A.K.; Neumann, W.P.; Uzick, W. *Chem. Ber.* ***1985***, *118*, 1183.

[237]Dünnebacke, D.; Neumann, W.P.; Penenory, A.; Stewen, U. *Chem. Ber.* ***1989***, *122*, 533.

[238]For reviews, see Ballester, M. *Adv. Phys. Org. Chem.* ***1989***, *25*, 267, pp. 354–405, *Acc. Chem. Res.* ***1985***, *18*, 380. See also, Hegarty, A.F.; O'Neill, P. *Tetrahedron Lett.* ***1987***, *28*, 901.

[239]Fort Jr., R.C.; Hrovat, D.A.; Borden, W.T. *J. Org. Chem.* ***1993***, *58*, 211.

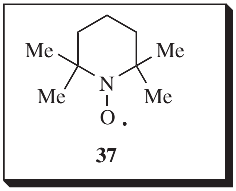
[240]Asensio, A.; Dannenberg, J.J. *J. Org. Chem.* ***2001***, *66*, 5996.

[241]Galli, C.; Guarnieri, A.; Koch, H.; Mencarelli, P.; Rappoport, Z. *J. Org. Chem.* ***1997***, *62*, 4072.

[242]Giese, B.; Damm, W.; Wetterich, F.; Zeltz, H.-G.; Rancourt, J.; Guindon, Y. *Tetrahedron Lett.* ***1993***, *34*, 5885.

[243]For reviews, see Sustmann, R.; Korth, H. *Adv. Phys. Org. Chem.* ***1990***, *26*, 131; Viehe, H.G.; Janousek, Z.; Merényi, R.; Stella, L. *Acc. Chem. Res.* ***1985***, *18*, 148.

There is some evidence in favor[244] of the captodative effect, some of it from esr studies.[245] However, there is also experimental[246] and theoretical[247] evidence against it. There is evidence that while $FCH_2^{\bullet}$ and $F_2CH^{\bullet}$ are more stable than $CH_3^{\bullet}$, the radical $CF_3^{\bullet}$ is less stable; that is, the presence of the third F destabilizes the radical.[248]



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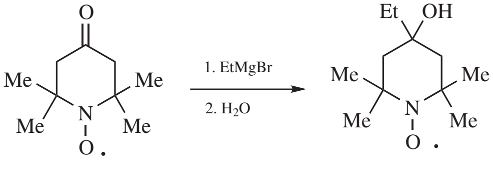

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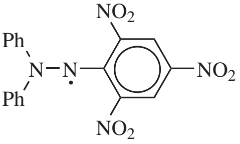
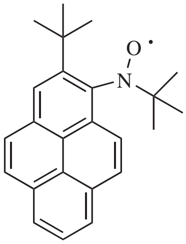


Diphenylpicrylhydrazyl



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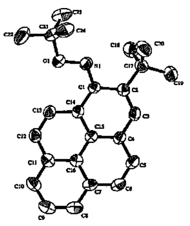

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Certain radicals with the unpaired electron not on a carbon are also very stable.[249] Radicals can be stabilized by intramolecular hydrogen bonding.[250]

[244]For a summary of the evidence, see Pasto, D.J. *J. Am. Chem. Soc.* ***1988***, *110*, 8164. See also, Ashby, E.C. *Bull. Soc. Chim. Fr.* ***1972***, 2133; *Q. Rev. Chem. Soc.* ***1967***, *21*, 259; Wakefield, B.J. *Organomet. Chem. Rev.* ***1966***, *1*, 131; Bell, N.A. *Educ. Chem.* ***1973***, 143.

[245]See, for example, Korth, H.; Lommes, P.; Sustmann, R.; Sylvander, L.; Stella, L. *New J. Chem.* ***1987***, *11*, 365; Sakurai, H.; Kyushin, S.; Nakadaira, Y.; Kira, M. *J. Phys. Org. Chem.* ***1988***, *1*, 197; Rhodes, C.J.; Roduner, E. *Tetrahedron Lett.* ***1988***, *29*, 1437; Viehe, H.G.; Merényi, R.; Janousek, Z. *Pure Appl. Chem.* ***1988***, *60*, 1635; Creary, X.; Sky, A.F.; Mehrsheikh-Mohammadi, M.E. *Tetrahedron Lett.* ***1988***, *29*, 6839; Bordwell, F.G.; Lynch, T. *J. Am. Chem. Soc.* ***1989***, *111*, 7558.

[246]See, for example, Beckhaus, H.; Rüchardt, C. *Angew. Chem. Int. Ed.* ***1987***, *26*, 770; Neumann, W.P.; Penenory, A.; Stewen, U.; Lehnig, M. *J. Am. Chem. Soc.* ***1989***, *111*, 5845; Bordwell, F.G.; Bausch, M.J.; Cheng, J.P.; Cripe, T.H.; Lynch, T.-Y.; Mueller, M.E. *J. Org. Chem.* ***1990***, *55*, 58; Bordwell, F.G.; Harrelson Jr., J.A. *Can. J. Chem.* ***1990***, *68*, 1714.

[247]See Pasto, D.J. *J. Am. Chem. Soc.* ***1988***, *110*, 8164.

[248]Jiang, X.; Li, X.; Wang, K. *J. Org. Chem.* ***1989***, *54*, 5648.

[249]For reviews of radicals with the unpaired electron on atoms other than carbon, see, in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, the reviews by Nelson, S.F. pp. 527–593 (*N*-centered); Bentrude, W.G. pp. 595–663 (*P*-centered); Kochi, J.K. pp. 665–710 (*O*-centered); Kice, J.L. pp. 711–740 (*S*-centered); Sakurai, H. pp. 741–807 (Si, Ge, Sn, and Pb centered).

[250]Maki, T.; Araki, Y.; Ishida, Y.; Onomura, O.; Matsumura, Y. *J. Am. Chem. Soc.* ***2001***, *123*, 3371.

Diphenylpicrylhydrazyl is a solid that can be kept for years, and stable neutral azine radicals have been prepared.[251] Nitroxide radicals were mentioned previously (p. 273),[252] and the commercially available TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl free radical, **37**) is a stable nitroxyl radical used in chemical reactions such as oxidations.[253] or as a spin trap.[254] Nitroxyl radical **38** is a nitroxide radical so stable that reactions can be performed on it without affecting the unpaired electron[255] (the same is true for some of the chlorinated triarylmethyl radicals mentioned above[256]). Several nitrogen-containing groups are known to stabilize radicals, and the most effective radical stabilization is via spin delocalization.[257] A number of persistent *N-tert*-butoxy-1-aminopyrenyl radicals, such as **39**, have been isolated as monomeric radical crystals (see **40**, the X-ray crystal structure of **39**),[258] and monomeric *N*-alkoxyarylaminyls have been isolated.[259] α-Trichloromethylbenzyl(*tert*-butyl)aminoxyl (**41**) is extremely stable.[260] In aqueous media it is stable for >30 days, and in solution in an aromatic hydrocarbon solvent it has survived for more than 90 days.[260] Although the stable nitroxide radicals have the α-carbon blocked to prevent radical formation there, stable nitroxide radicals are also known with hydrogen at the α-carbon,[261] and long-lived vinyl nitroxide radicals are known.[262] A stable organic radical lacking resonance stabilization has been prepared (**42**) and its X-ray crystal structure was

[251]Jeromin, G.E. *Tetrahedron Lett.* ***2001***, *42*, 1863.

[252]For a study of the electronic structure of persistent nitroxide radicals see Novak, I.; Harrison, L.J.; Kovač, B.; Pratt, L.M. *J. Org. Chem.* ***2004***, *69*, 7628.

[253]See Anelli, P.L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* ***1987***, *52*, 2559; Anelli, P.L.; Banfi, S.; Montanari, F.; Quici, S. *J. Org. Chem.* ***1989***, *54*, 2970; Anelli, P.L.; Montanari, F.; Quici, S. *Org. Synth.* ***1990***, *69*, 212; Fritz-Langhals, E. *Org. Process Res. Dev.* ***2005***, *9*, 577. See also, Rychnovsky, S.D.; Vaidyanathan, R.; Beauchamp, T.; Lin, R.; Farmer, P.J. *J. Org. Chem.* ***1999***, *64*, 6745.

[254]Volodarsky, L.B.; Reznikov, V.A.; Ovcharenko, V.I. *Synthetic Chemistry of Stable Nitroxides*, CRC Press: Boca Raton, FL, ***1994***; Keana, J.F.W. *Chem. Rev.* ***1978***, *78*, 37; Aurich, H.G. *Nitroxides. In Nitrones, Nitronates, Nitroxides*, Patai, S., Rappoport, Z., (Eds.), Wiley, NY, ***1989***; Chapt. 4.

[255]Neiman, M.B.; Rozantsev, E.G.; Mamedova, Yu.G. *Nature* ***1963***, *200*, 256. For reviews of such radicals, see Aurich, H.G., in Patai, S. *The Chemistry of Functional Groups*, *Supplement F*, pt. 1, Wiley, NY, ***1982***, pp. 565–622 [This review has been reprinted, and new material added, in Breuer, E.; Aurich, H.G.; Nielsen, A. *Nitrones*, *Nitronates*, *and Nitroxides*, Wiley, NY, ***1989***, pp. 313–399]; Rozantsev, E.G.; Sholle, V.D. *Synthesis* ***1971***, 190, 401.

[256]See Ballester, M.; Veciana, J.; Riera, J.; Castañer, J.; Armet, O.; Rovira, C. *J. Chem. Soc. Chem. Commun.* ***1983***, 982.

[257]Adam, W.; Ortega Schulte, C.M. *J. Org. Chem.* ***2002***, *67*, 4569.

[258]Miura, Y.; Matsuba, N.; Tanaka, R.; Teki, Y.; Takui, T. *J. Org. Chem.* ***2002***, *67*, 8764. For another stable nitroxide radical, see Huang, W.-l.; Chiarelli, R.; Rassat, A. *Tetrahedron Lett.* ***2000***, *41*, 8787.

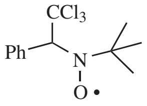
[259]Miura, Y.; Tomimura, T.; Matsuba, N.; Tanaka, R.; Nakatsuji, M.; Teki, Y. *J. Org. Chem.* ***2001***, *66*, 7456.

[260]Janzen, E.G.; Chen, G.; Bray, T.M.; Reinke, L.A.; Poyer, J.L.; McCay, P.B. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 1983.

[261]Reznikov, V.A.; Volodarsky, L.B. *Tetrahedron Lett.* ***1994***, *35*, 2239.

[262]Reznikov, V.A.; Pervukhina, N.V.; Ikorskii, V.N.; Ovcharenko, V.I; Grand, A. *Chem. Commun.* ***1999***, 539.

obtained.[263]



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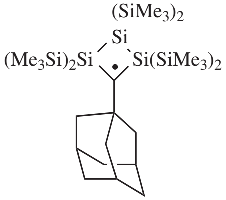


42

Dissociation energies (*D* values) of R—H bonds provide a measure of the relative inherent stability of free radicals R.[264] Table 5.4 lists such values.[265] The higher the *D* value, the less stable the radical. Bond dissociation energies have also been reported for the C—H bond of alkenes and dienes[266] and for the C—H bond in radical precursors XYC—H, where X,Y can be H, alkyl, COOR, COR, SR, CN, NO_2, and so on.[267] Bond dissociation energies for the C—O bond in hydroperoxide radicals (ROO•) have also been reported.[268]

TABLE 5.4. The D_{298} Values for Some R—H Bonds.[265] Free-radical Stability is in the Reverse Order

R	*D* (kcal mol^{-1})	*D* (kJ mol^{-1})
Ph•[269]	111	464
CF_3•	107	446
CH_2=CH•	106	444
Cyclopropyl[270]	106	444
Me•	105	438
Et•	100	419

[263]Apeloig, Y.; Bravo-Zhivotovskii, D.; Bendikov, M.; Danovich, D.; Botoshansky, M.; Vakulrskaya, T.; Voronkov, M.; Samoilova, R.; Zdravkova, M.; Igonin, V.; Shklover, V.; Struchkov, Y. *J. Am. Chem. Soc.* ***1999***, *121*, 8118.

[264]It has been claimed that relative *D* values do not provide such a measure: Nicholas, A.M. de P.; Arnold, D.R. *Can. J. Chem.* ***1984***, *62*, 1850, 1860.

[265]Except where noted, these values are from Kerr, J.A., in Weast, R.C. *Handbook of Chemistry and Physics*, 69th ed.; CRC Press: Boca Raton, FL, ***1988***, p. F-183. For another list of *D* values, see McMillen, D.F.; Golden, D.M. *Annu. Rev. Phys. Chem.* ***1982***, *33*, 493. See also, Tsang, W. *J. Am. Chem. Soc.* ***1985***, *107*, 2872; Holmes, J.L.; Lossing, F.P.; Maccoll, A. *J. Am. Chem. Soc.* ***1988***, *110*, 7339; Holmes, J.L.; Lossing, F.P. *J. Am. Chem. Soc.* ***1988***, *110*, 7343; Roginskii, V.A. *J. Org. Chem. USSR* ***1989***, *25*, 403.

[266]Zhang, X.-M. *J. Org. Chem.* ***1998***, *63*, 1872.

[267]Brocks, J.J.; Beckhaus, H.-D.; Beckwith, A.L.J.; Rüchardt, C. *J. Org. Chem.* ***1998***, *63*, 1935.

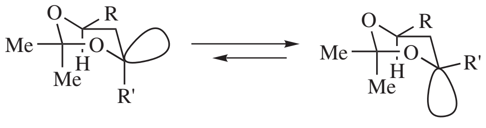
[268]Pratt, D.A.; Porter, N.A. *Org. Lett.* ***2003***, *5*, 387.

[269]For the infra-red of a matrix-isolated phenyl radical see Friderichsen, A.V.; Radziszewski, J.G.; Nimlos, M.R.; Winter, P.R.; Dayton, D.C.; David, D.E.; Ellison, G.B. *J. Am. Chem. Soc.* ***2001***, *123*, 1977.

[270]For a review of cyclopropyl radicals, see Walborsky, H.M. *Tetrahedron* ***1981***, *37*, 1625. See also, Boche, G.; Walborsky, H.M. *Cyclopropane Derived Reactive Intermediates*, Wiley, NY, ***1990***.

Me_3CCH_2•	100	418
Pr•	100	417
Cl_3C•	96	401
Me_2CH•	96	401
Me_3C•[271]	95.8	401
Cyclohexyl	95.5	400
$PhCH_2$•	88	368
HCO•	87	364
CH_2=CH–CH_2•	86	361

There are two possible structures for simple alkyl radicals.[272] They might have sp^2 bonding, in which case the structure would be planar, with the odd electron in a p orbital, or the bonding might be sp^3, which would make the structure pyramidal and place the odd electron in an sp^3 orbital. The esr spectra of •CH_3 and other simple alkyl radicals, as well as other evidence indicate that these radicals have planar structures.[273] This is in accord with the known loss of optical activity when a free radical is generated at a chiral carbon.[274] In addition, electronic spectra of the CH_3 and CD_3 radicals (generated by flash photolysis) in the gas phase have definitely established that under these conditions the radicals are planar or near planar.[275] IR spectra of •CH_3 trapped in solid argon led to a similar conclusion.[276]



43a **43b**

Despite the usual loss of optical activity noted above, asymmetric radicals can be prepared in some cases. For example, asymmetric nitroxide radicals are known.[277] An anomeric effect was observed in alkoxy radical **43**, where the ratio of **43a/43b** was 1:1.78.[278]

[271]This value is from Gutman, D. *Acc. Chem. Res.* ***1990***, *23*, 375.

[272]For a review, see Kaplan, L., in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 361–434.

[273]See, for example, Cole, T.; Pritchard, D.E.; Davidson, N.; McConnell, H.M. *Mol. Phys.* ***1958***, *1*, 406; Fessenden, R.W.; Schuler, R.H. *J. Chem. Phys.* ***1963***, *39*, 2147; Symons, M.C.R. *Nature* ***1969***, *222*, 1123, *Tetrahedron Lett.* ***1973***, 207; Bonazzola, L.; Leray, E.; Roncin, J. *J. Am. Chem. Soc.* ***1977***, *99*, 8348; Giese, B.; Beckhaus, H. *Angew. Chem. Int. Ed.* ***1978***, *17*, 594; Ellison, G.B.; Engelking, P.C.; Lineberger, W.C. *J. Am. Chem. Soc.* ***1978***, *100*, 2556. See, however, Paddon-Row, M.N.; Houk, K.N. *J. Am. Chem. Soc.* ***1981***, *103*, 5047.

[274]There are a few exceptions. See p. $$$.

[275]Herzberg, G.; Shoosmith, J. *Can. J. Phys.* ***1956***, *34*, 523; Herzberg, G. *Proc. R. Soc. London, Ser. A* ***1961***, *262*, 291. See also, Tan, L.Y.; Winer, A.M.; Pimentel, G.C. *J. Chem. Phys.* ***1972***, *57*, 4028; Yamada, C.; Hirota, E.; Kawaguchi, K. *J. Chem. Phys.* ***1981***, *75*, 5256.

[276]Andrews, L.; Pimentel, G.C. *J. Chem. Phys.* ***1967***, *47*, 3637; Milligan, D.E.; Jacox, M.E. *J. Chem. Phys.* ***1967***, *47*, 5146.

[277]Tamura, R.; Susuki, S.; Azuma, N.; Matsumoto, A.; Todda, F.; Ishii, Y. *J. Org. Chem.* ***1995***, *60*, 6820.

[278]Rychnovsky, S.D.; Powers, J.P.; LePage, T.J. *J. Am. Chem. Soc.* ***1992***, *114*, 8375.

Evidence from studies on bridgehead compounds shows that although a planar configuration is more stable, pyramidal structures are not impossible. In contrast to the situation with carbocations, free radicals have often been generated at bridgeheads, although studies have shown that bridgehead free radicals are less rapidly formed than the corresponding open-chain radicals.[279] In sum, the available evidence indicates that although simple alkyl free radicals prefer a planar, or near-planar shape, the energy difference between a planar and a pyramidal free radical is not great. However, free radicals in which the carbon is connected to atoms of high electronegativity, for example, $\bullet CF_3$, prefer a pyramidal shape;[280] increasing the electronegativity increases the deviation from planarity.[281] Cyclopropyl radicals are also pyramidal.[282] Free radicals with resonance are definitely planar, although triphenylmethyl-type radicals are propeller-shaped,[283] like the analogous carbocations (p. 245). Radicals possessing simple alkyl substituents attached to the radical carbon (C•) that have C^{sp^3}—C^{sp^3} bonds, and rotation about those bonds is possible. The internal rotation barrier for the *t*-butyl radical ($Me_3C\bullet$), for example, was estimated to be $\sim$1.4 kcal mol^{-1} (6 kJ mol^{-1}).[284]

A number of diradicals (also called biradicals) are known,[285] and the thermodynamic stability of diradicals has been examined.[286] Orbital phase theory has been applied to the development of a theoretical model of localized 1,3-diradicals, and used to predict the substitution effects on the spin preference and S–T gaps, and to design stable localized carbon-centered 1,3-diradicals.[287] When the unpaired electrons of a diradical are widely separated, for example, as in $\bullet CH_2CH_2CH_2CH_2\bullet$,

[279]Lorand, J.P.; Chodroff, S.D.; Wallace, R.W. *J. Am. Chem. Soc.* ***1968***, *90*, 5266; Humphrey, L.B.; Hodgson, B.; Pincock, R.E. *Can. J. Chem.* ***1968***, *46*, 3099; Oberlinner, A.; Rüchardt, C. *Tetrahedron Lett.* ***1969***, 4685; Danen, W.C.; Tipton, T.J.; Saunders, D.G. *J. Am. Chem. Soc.* ***1971***, *93*, 5186; Fort, Jr., R.C.; Hiti, J. *J. Org. Chem.* ***1977***, *42*, 3968; Lomas, J.S. *J. Org. Chem.* ***1987***, *52*, 2627.

[280]Fessenden, R.W.; Schuler, R.H. *J. Chem. Phys.* ***1965***, *43*, 2704; Rogers, M.T.; Kispert, L.D. *J. Chem. Phys.* ***1967***, *46*, 3193; Pauling, L. *J. Chem. Phys.* ***1969***, *51*, 2767.

[281]For example, 1,1-dichloroalkyl radicals are closer to planarity than the corresponding 1,1-difluoro radicals, though still not planar: Chen, K.S.; Tang, D.Y.H.; Montgomery, L.K.; Kochi, J.K. *J. Am. Chem. Soc.* ***1974***, *96*, 2201. For a discussion, see Krusic, P.J.; Bingham, R.C. *J. Am. Chem. Soc.* ***1976***, *98*, 230.

[282]See Deycard, S.; Hughes, L.; Lusztyk, J.; Ingold, K.U. *J. Am. Chem. Soc.* ***1987***, *109*, 4954.

[283]Adrian, F.J. *J. Chem. Phys.* ***1958***, *28*, 608; Andersen, P. *Acta Chem. Scand.* ***1965***, *19*, 629.

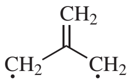
[284]Kubota, S.; Matsushita, M.; Shida, T.; Abu-Raqabah, A.; Symons, M.C.R.; Wyatt, J.L. *Bull. Chem. Soc. Jpn.* ***1995***, *68*, 140.

[285]For a monograph, see Borden, W.T. *Diradicals*, Wiley, NY, ***1982***. For reviews, see Johnston, L.J.; Scaiano, J.C. *Chem. Rev.* ***1989***, *89*, 521; Doubleday, Jr., C.; Turro, N.J.; Wang, J. *Acc. Chem. Res.* ***1989***, *22*, 199; Scheffer, J.R.; Trotter, J. *Rev. Chem. Intermed.* ***1988***, *9*, 271; Wilson, R.M. *Org. Photochem.* ***1985***, *7*, 339; Borden, W.T. *React. Intermed. (Wiley)* ***1985***, *3*, 151; ***1981***, *2*, 175; Borden, W.T.; Davidson, E.R. *Acc. Chem. Res.* ***1981***, *14*, 69; Salem, L.; Rowland, C. *Angew. Chem. Int. Ed.* ***1972***, *11*, 92; Salem, L. *Pure Appl. Chem.* ***1973***, *33*, 317; Jones II, G. *J. Chem. Educ.* ***1974***, *51*, 175; Morozova, I.D.; Dyatkina, M.E. *Russ. Chem. Rev.* ***1968***, *37*, 376. See also, Döhnert, D.; Koutecky, J. *J. Am. Chem. Soc.* ***1980***, *102*, 1789. For a series of papers on diradicals, see *Tetrahedron* ***1982***, *38*, 735.

[286]Zhang, D.Y.; Borden, W.T. *J. Org. Chem.* ***2002***, *67*, 3989.

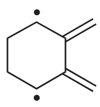
[287]Ma, J.; Ding, Y.; Hattori, K.; Inagaki, S. *J. Org. Chem.* ***2004***, *69*, 4245.

the species behaves spectrally like two doublets. When they are close enough for interaction or can interact through an unsaturated system as in trimethylenemethane,[288] they can have total spin numbers of +1, 0, or −1, since each

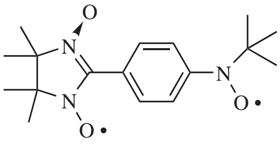


Trimethylenemethane

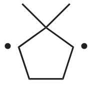
electron could be either $\frac{1}{+2}$ or $\frac{1}{-2}$. Spectroscopically they are called *triplets*,[289] since each of the three possibilities is represented among the molecules and gives rise to its own spectral peak. In triplet molecules the two unpaired electrons have the same spin. Not all diradicals have a triplet ground state. In 2,3-dimethylelecycohexane-1,4-diyl (**44**), the singlet and triplet states were found to be almost degenerate.[290] Some diradicals, such as **45**, are very stable with a triplet ground state.[291] Diradicals are generally short-lived species. The lifetime of **46** was measured to be <0.1 ns and other diradicals were found to have lifetimes in the 4–316-ns range.[292] Diradical **47** [3,5-di-*tert*-butyl-3′-(*N*-*tert*-butyl-*N*-aminoxy)-4-oxybiphenyl] was found to have a lifetime of weeks even in the presence of oxygen, and survived brief heating in toluene up to ~60°C.[293] Radicals with both unpaired electrons on the same carbon are discussed under carbenes.



44



45



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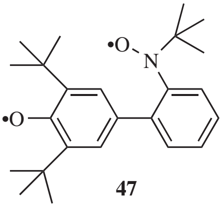


47

[288]For reviews of trimethylenemethane, see Borden, W.T.; Davidson, E.R. *Ann. Rev. Phys. Chem.* ***1979***, *30*, 125; Bergman, R.G., in Kochi, J.K. *Free Radicals*, Vol. 1, Wiley, NY, ***1973***, pp. 141–149.

[289]For discussions of the triplet state, see Wagner, P.J.; Hammond, G.S. *Adv. Photochem.* ***1968***, *5*, 21; Turro, N.J. *J. Chem. Educ.* ***1969***, *46*, 2. For a discussion of esr spectra of triplet states, see Wasserman, E.; Hutton, R.S. *Acc. Chem. Res.* ***1977***, *10*, 27. For the generation and observation of triplet 1,3-biradicals see Ichinose, N.; Mizuno, K.; Otsuji, Y.; Caldwell, R.A.; Helms, A.M. *J. Org. Chem.* ***1998***, *63*, 3176.

[290]Matsuda, K.; Iwamura, H. *J. Chem. Soc. Perkin Trans. 2* ***1998***, 1023. Also see, Roth, W.R.; Wollweber, D.; Offerhaus, R.; Rekowski, V.; Lenmartz, H.-W.; Sustmann, R.; Müller, W. *Chem. Ber.* ***1993***, *126*, 2701.

[291]Inoue, K.; Iwamura, H. *Angew. Chem. Int. Ed.* ***1995***, *34*, 927. Also see, Ulrich, G.; Ziessel, R.; Luneau, D.; Rey, P. *Tetrahedron Lett.* ***1994***, *35*, 1211.

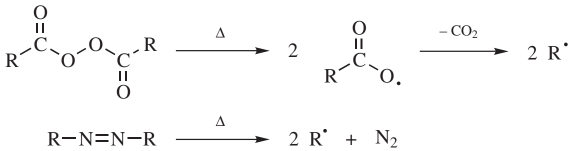
[292]Engel, P.S.; Lowe, K.L. *Tetrahedron Lett.* ***1994***, *35*, 2267.

[293]Liao, Y.; Xie, C.; Lahti, P.M.; Weber, R.T.; Jiang, J.; Barr, D.P. *J. Org. Chem.* ***1999***, *64*, 5176.

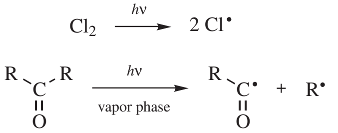
The Generation and Fate of Free Radicals[294]

Free radicals are formed from molecules by breaking a bond so that each fragment keeps one electron.[295,296] The energy necessary to break the bond is supplied in one of two ways.

1. *Thermal Cleavage*. Subjection of any organic molecule to a high enough temperature in the gas phase results in the formation of free radicals. When the molecule contains bonds with *D* values or 20–40 kcal mol^{-1} (80–170 kJ mol^{-1}), cleavage can be caused in the liquid phase. Two common examples are cleavage of diacyl peroxides to acyl radicals that decompose to alkyl radicals[297] and cleavage of azo compounds to alkyl radicals[298]



2. *Photochemical Cleavage* (see p. 335). The energy of light of 600–300 nm is 48–96 kcal mol^{-1} (200–400 kJ mol^{-1}), which is of the order of magnitude of covalent-bond energies. Typical examples are photochemical cleavage of alkyl halides in the presence of triethylamine,[299] alcohols in the presence of mercuric oxide and iodine,[300] alkyl 4-nitrobenzenesulfenates,[301] chlorine, and of ketones:



The photochemistry of radicals and biradicals has been reviewed.[302]

[294]For a summary of methods of radical formation, see Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: Elmsford, NY, ***1986***, pp. 267–281. For a review on formation of free radicals by thermal cleavage, see Brown, R.F.C. *Pyrolytic Methods in Organic Chemistry*; Academic Press, NY, ***1980***, pp. 44–61.

[295]It is also possible for free radicals to be formed by the collision of two nonradical species. For a review, see Harmony, J.A.K. *Methods Free-Radical Chem.* ***1974***, *5*, 101.

[296]For a review of homolytic cleavage of carbon–metal bonds, see Barker, P.J.; Winter, J.N., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 2, Wiley, NY, ***1985***, pp. 151–218.

[297]Chateauneuf, J.; Lusztyk, J.; Ingold, K.U. *J. Am. Chem. Soc.* ***1988***, *110*, 2877, 2886; Matsuyama, K.; Sugiura, T.; Minoshima, Y. *J. Org. Chem.* ***1995***, *60*, 5520; Ryzhkov, L.R. *J. Org. Chem.* ***1996***, *61*, 2801. For a review of free radical mechanisms involving peroxides in solution, see Howard, J.A., in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, ***1983***, pp. 235–258. For a review of pyrolysis of peroxides in the gas phase, see Batt, L.; Liu, M.T.H. in the same volume, pp. 685–710.

[298]For a review of the cleavage of azoalkanes, see Engel, P.S. *Chem. Rev.* ***1980***, *80*, 99. For summaries of later work, see Adams, J.S.; Burton, K.A.; Andrews, B.K.; Weisman, R.B.; Engel, P.S. *J. Am. Chem. Soc.* ***1986***, *108*, 7935; Schmittel, M.; Rüchardt, C. *J. Am. Chem. Soc.* ***1987***, *109*, 2750.

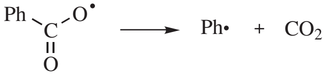
[299]Cossy, J.; Ranaivosata, J.-L.; Bellosta, V. *Tetrahedron Lett.* ***1994***, *35*, 8161.

[300]Courtneidge, J.L. *Tetrahedron Lett.* ***1992***, *33*, 3053.

[301]Pasto, D.J.; Cottard, F. *Tetrahedron Lett.* ***1994***, *35*, 4303.

[302]Johnston, L.J. *Chem. Rev.* ***1993***, *93*, 251.

Radicals are also formed from other radicals, either by the reaction between a radical and a molecule (which *must* give another radical, since the total number of electrons is odd) or by cleavage of a radical[303] to give another radical, for example,



Radicals can also be formed by oxidation or reduction, including electrolytic methods.

Reactions of free radicals either give stable products (termination reactions) or lead to other radicals, which themselves must usually react further (propagation reactions). The most common termination reactions are simple combinations of similar or different radicals:

$$R\cdot \ + \ R'\cdot \longrightarrow R{-}R'$$

Another termination process is disproportionation:[304]

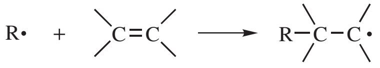
There are four principal propagation reactions, of which the first two are most common:

$$2CH_3{-}CH_2^{\bullet} \longrightarrow CH_3{-}CH_3 + CH_2{=}CH_2$$

1. *Abstraction of Another Atom or Group, Usually a Hydrogen Atom* (see Chapter 14):

$$R\cdot \ + \ R'{-}H \longrightarrow R{-}H \ + \ R'\cdot$$

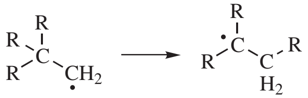
2. *Addition to a Multiple Bond* (see Chapter 15):



The radical formed here may add to another double bond and so on. This is one of the chief mechanisms for vinyl polymerization.

3. *Decomposition*. This can be illustrated by the decomposition of the benzoxy radical (above).

4. *Rearrangement*:



[303]For a deterimination of activation barriers in the homolytic cleavage of radicals and ion radicals see Costentin, C.; Robert, M.; Saveant, J.-M. *J. Am. Chem. Soc.* ***2003***, *125*, 105.

[304]For reviews of termination reactions, see Pilling, M.J. *Int. J. Chem. Kinet.* ***1989***, *21*, 267; Khudyakov, I.V.; Levin, P.P.; Kuz'min, V.A. *Russ. Chem. Rev.* ***1980***, *49*, 982; Gibian, M.J.; Corley, R.C. *Chem. Rev.* ***1973***, *73*, 441.

This is less common than rearrangement of carbocations, but it does occur (though not when R = alkyl or hydrogen; see Chapter 18). Perhaps the best-known rearrangement is that of cyclopropylcarbinyl radicals to a butenyl radical.[305] The rate constant for this rapid ring opening has been measured in certain functionalized cyclopropylcarbinyl radicals by picosecond radical kinetics.[306] Substituent effects on the kinetics of ring opening in substituted cyclopropylcarbinyl radicals has been studied.[307] "The cyclopropylcarbinyl radical has found an important application as a radical clock.[308] Various radical processes can be clocked by the competition of direct reaction with the cyclopropylcarbinyl radical (k_t) and opening of that radical to the 1-buten-4-yl radical (k_r) followed by trapping. Relative rates (k_t/k_r) can be determined from yields of 4-X-1-butene and cyclopropylcarbinyl products as a function of the radical trap[309] (X—Y) concentration. Absolute rate constants have been determined for a number of radicals with various radical traps by laser flash photolysis methods.[310] From these absolute rate constants, reasonably accurate values of k_t can be estimated, and with the relative rate (k_t/k_r), a value for k_r can be calculated. From the calibrated radical-clock reaction rate (k_r), rates (k_t) of other competing reactions can be determined from relative rate data (k_t/k_r)."[306] Other radical clocks are known.[311]

Free radicals can also be oxidized to carbocations or reduced to carbanions.[312]

[305]For a discussion of radical vs. radical anion character see Stevenson, J. P.; Jackson, W. F.; Tanko, J. M. *J. Am. Chem. Soc.* ***2002***, *124*, 4271.

[306]LeTadic-Biadatti, M.-H.; Newcomb, M. *J. Chem. Soc. Perkin Trans. 2* ***1996***, 1467. See also, Choi, S.-Y.; Horner, J.H.; Newcomb, M. *J. Org. Chem.* ***2000***, *65*, 4447. For determination of k for rearrangement and for and competing reactions, see Cooksy, A. L.; King, H.F.; Richardson, W.H. *J. Org. Chem.* ***2003***, *68*, 9441. For the ring opening of fluorinated cyclopropylcarbinyl systems see Tian, F.; Dolbier Jr., W.R. *Org. Lett.* ***2000***, *2*, 835.

[307]Halgren, T.A.; Roberts, J.D.; Horner, J.H.; Martinez, F.N.; Tronche, C.; Newcomb, M. *J. Am. Chem. Soc.* ***2000***, *122*, 2988.

[308]Griller, D.; Ingold, K.U. *Acc. Chem. Res.* ***1980***, *13*, 317; Newcomb, M.; Choi, S.-Y.; Toy, P.H. *Can. J. Chem.* ***1999***, *77*, 1123; Le Tadic-Biadatti, M.-H.; Newcomb, M. *J. Chem. Soc., Perkin Trans. 2* ***1996***, 1467; Choi, S.Y.; Newcomb, M. *Tetrahedron* ***1995***, *51*, 657; Newcomb, M. *Tetrahedron* ***1993***, *49*, 1151; Newcomb, M.; Johnson, C.; Manek, M.B.; Varick, T.R. *J. Am. Chem. Soc.* ***1992***, *114*, 10915; Nevill, S.M.; Pincock, J.A. *Can. J. Chem.* ***1997***, *75*, 232.

[309]For an alkyl radical trap in aqueous medium see Barton, D.H.R.; Jacob, M.; Peralez, E. *Tetrahedron Lett.* ***1999***, *40*, 9201.

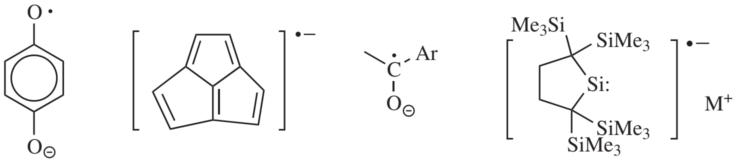
[310]Choi, S.-Y.; Horner, J.H.; Newcomb, M. *J. Org. Chem.* ***2000***, *65*, 4447; Engel, P.S.; He, S.-L.; Banks, J.T.; Ingold, K.U.; Lusztyk, J. *J. Org. Chem.* ***1997***, *62*, 1210; Johnston, L.J.; Lusztyk, J.; Wayner, D.D.M.; Abeywickreyma, A.N.; Beckwith, A.L.J.; Scaiano, J.J.; Ingold, K.U. *J. Am. Chem. Soc.* ***1985***, *107*, 4594; Chatgilialoglu, C.; Ingold, K.U.; Scaiano, J.J. *J. Am. Chem. Soc.* ***1981***, *103*, 7739.

[311]For example, see Leardini, R.; Lucarini, M.; Pedulli, G.F.; Valgimigli, L. *J. Org. Chem.* ***1999***, *64*, 3726.

[312]For a review of the oxidation and reduction of free radicals, see Khudyakov, I.V.; Kuz'min, V.A. *Russ. Chem. Rev.* ***1978***, *47*, 22.

Radical Ions[313]

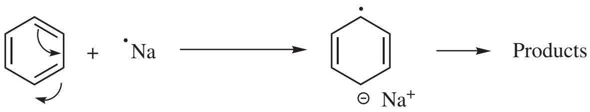
Several types of radical anions are known with the unpaired electron or the charge or both on atoms other than carbon. Examples include semiquinones[314] (**48**),



48 **49** **50** **51**

M = Cs, Rb, Na, Li

acepentalenes (**49**),[315] ketyls[316] (**50**) and the radical anion of the isolable dialkylsilylene **51**.[317] Reactions in which alkali metals are reducing agents often involve radical anion intermediates, for example, reaction **15-13**:



Several types of radical cation are also known.[318] Typical examples include alkyl azulene cation radicals (**52**),[319] trialkyl amine radical cations,[320]

[313]For a monograph, see Kaiser, E.T.; Kevan, L. *Radical Ions*, Wiley, NY, ***1968***. For reviews, see Gerson, F.; Huber, W. *Acc. Chem. Res.* ***1987***, *20*, 85; Todres, Z.V. *Tetrahedron* ***1985***, *41*, 2771; Russell, G.A.; Norris, R.K., in McManus, S.P. *Organic Reactive Intermediates*; Academic Press, NY, ***1973***, pp. 423–448; Holy, N.L.; Marcum, J.D. *Angew. Chem. Int. Ed.* ***1971***, *10*, 115; Bilevitch, K.A.; Okhlobystin, O.Yu. *Russ. Chem. Rev.* ***1968***, *37*, 954; Szwarc, M. *Prog. Phys. Org. Chem.* ***1968***, *6*, 322. For a related review, see Chanon, M.; Rajzmann, M.; Chanon, F. *Tetrahedron* ***1990***, *46*, 6193. For a series of papers on this subject, see *Tetrahedron* ***1986***, *42*, 6097.

[314]For a review of semiquinones, see Depew, M.C.; Wan, J.K.S., in Patai, S.; Rappoport, Z. *The Chemistry of the Quinonoid Compounds*, Vol. 2, pt. 2, Wiley, NY, ***1988***, pp. 963–1018. For a discussion of the thermodynamic stability of aromatic radical anions see Huh, C.; Kang, C.H.; Lee, H.W.; Nakamura, H.; Mishima, M.; Tsuno, Y.; Yamataka, H. *Bull. Chem. Soc. Jpn.* ***1999***, *72*, 1083.

[315]de Meijere, A.; Gerson, F.; Schreiner, P.R.; Merstetter, P.; Schüngel, F.-M. *Chem. Commun.* ***1999***, 2189.

[316]For a review of ketyls, see Russell, G.A., in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 1, Wiley, NY, ***1989***, pp. 471–512. See Davies, A.G.; Neville, A.G. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 163, 171 for ketyl and thioketyl cation radicals.

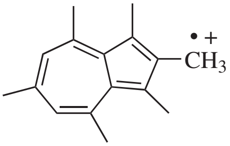
[317]Ishida, S.; Iwamoto, T.; Kira, M. *J. Am. Chem. Soc.* ***2003***, *125*, 3212. For bis(tri-*tert*-butylsilyl)silylene: triplet ground state silylene see Sekiguchi, A.; Tanaka, T.; Ichinohe, M.; Akiyama, K.; Tero-Kubota, S. *J. Am. Chem. Soc.* ***2003***, *125*, 4962.

[318]For reviews, see Roth, H.D. *Acc. Chem. Res.* ***1987***, *20*, 343; Courtneidge, J.L.; Davies, A.G. *Acc. Chem. Res.* ***1987***, *20*, 90; Hammerich, O.; Parker, V.D. *Adv. Phys. Org. Chem.* ***1984***, *20*, 55; Symons, M.C.R. *Chem. Soc. Rev.* ***1984***, *13*, 393; Bard, A.J.; Ledwith, A.; Shine, H.J. *Adv. Phys. Org. Chem.* ***1976***, *13*, 155.

[319]Gerson, F.; Scholz, M.; Hansen, H.-J.; Uebelhart, P. *J. Chem. Soc. Perkin Trans. 2* ***1995***, 215.

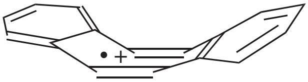
[320]de Meijere, A.; Chaplinski, V.; Gerson, F.; Merstetter, P.; Haselbach, E. *J. Org. Chem.* ***1999***, *64*, 6951.

1,2-bis(dialkylamino)benzenes radical cations, such as **53**,[321] dimethylsulfonium cation radicals ($Me_2S^{+\bullet}$),[322] *N*-alkyl substituted imine cation radicals ($Ph_2C{=}NEt^{\bullet +}$),[323] dibenzo[*a,e*]cyclooctene (**54**, a nonplanar cation radical),[324] and [*n.n*]paracyclophane cation radicals.[325] A twisted radical cation derived from bicyclo[2.2.2]oct-2-ene has been reported.[326]



52

53



54

CARBENES

Stability and Structure[327]

Carbenes are highly reactive species, practically all having lifetimes considerably under 1 s. With exceptions noted below (p. 289), carbenes have been isolated only by entrapment in matrices at low temperatures (77 K or less).[328] The parent species CH_2 is usually called *methylene*, although derivatives are more often named by the carbene nomenclature. Thus CCl_2 is generally known as dichlorocarbene, although it can also be called dichloromethylene.

[321]Neugebauer, F.A.; Funk, B.; Staab, H.A. *Tetrahedron Lett.* ***1994***, *35*, 4755. See Stickley, K.R.; Blackstock, S.C. *Tetrahedron Lett.* ***1995***, *36*, 1585 for a *tris*-diarylaminobenzene cation radical.

[322]Dauben, W.G.; Cogen, J.M.; Behar, V.; Schultz, A.G.; Geiss, W.; Taveras, A.G. *Tetrahedron Lett.* ***1992***, *33*, 1713.

[323]Rhodes, C.J.; AgirBas H. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 397.

[324]Gerson, F.; Felder, P.; Schmidlin, R.; Wong, H.N.C. *J. Chem. Soc. Chem. Commun.* ***1994***, 1659.

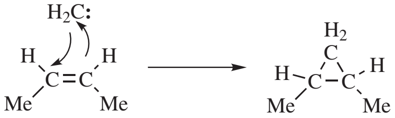
[325]Wartini, A.R.; Valenzuela, J.; Staab, H.A.; Neugebauer, F.A. *Eur. J. Org. Chem.* ***1998***, 139.

[326]Nelson, S.F.; Reinhardt, L.A.; Tran, H.Q.; Clark, T.; Chen, G.-F.; Pappas, R.S.; Williams, F. *Chem. Eur. J.* ***2002***, *8*, 1074.

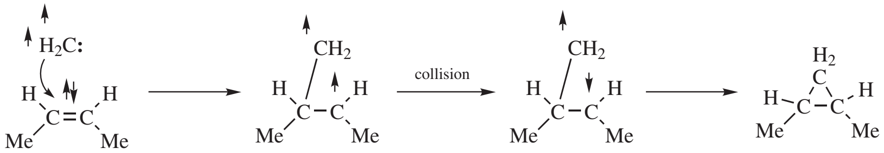
[327]For monographs, see Jones, Jr., M.; Moss, R.A. *Carbenes*, 2 vols., Wiley, NY, ***1973–1975***; Kirmse, W. *Carbene Chemistry*, 2nd ed.; Academic Press, NY, ***1971***; Rees, C.W.; Gilchrist, T.L. *Carbenes, Nitrenes, and Arynes*, Nelson, London, ***1969***. For reviews, see Minkin, V.I.; Simkin, B.Ya.; Glukhovtsev, M.N. *Russ. Chem. Rev.* ***1989***, *58*, 622; Moss, R.A.; Jones, Jr., M. *React. Intermed. (Wiley)* ***1985***, *3*, 45; ***1981***, *2*, 59; ***1978***, *1*, 69; Isaacs, N.S. *Reactive Intermediates in Organic Chemistry*, Wiley, NY, ***1974***, pp. 375–407; Bethell, D. *Adv. Phys. Org. Chem.* ***1969***, *7*, 153; Bethell, D., in McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, ***1973***, pp. 61–126; Closs, G.L. *Top. Stereochem.* ***1968***, *3*, 193; Herold, B.J.; Gaspar, P.P. *Fortschr. Chem. Forsch.*, ***1966***, *5*, 89; Rozantsev, G.G.; Fainzil'berg, A.A.; Novikov, S.S. *Russ. Chem. Rev.* ***1965***, *34*, 69. For a theoretical study, see Liebman, J.F.; Simons, J. *Mol. Struct. Energ.* ***1986***, *1*, 51.

[328]For example, see Murray, R.W.; Trozzolo, A.M.; Wasserman, E.; Yager, W.A. *J. Am. Chem. Soc.* ***1962***, *84*, 3213; Brandon, R.W.; Closs, G.L.; Hutchison, C.A. *J. Chem. Phys.* ***1962***, *37*, 1878; Milligan, D.E.; Mann, D.E.; Jacox, M.E.; Mitsch, R.A. *J. Chem. Phys.* ***1964***, *41*, 1199; Nefedov, O.M.; Maltsev, A.K.; Mikaelyan, R.G. *Tetrahedron Lett.* ***1971***, 4125; Wright, B.B. *Tetrahedron* ***1985***, *41*, 1517. For reviews, see Zuev, P.S.; Nefedov, O.M. *Russ. Chem. Rev.* ***1989***, *58*, 636; Sheridan, R.S. *Org. Photochem.* ***1987***, *8*, 159, pp. 196–216; Trozzolo, A.M. *Acc. Chem. Res.* ***1968***, *1*, 329.

The two nonbonded electrons of a carbene can be either paired or unpaired. If they are paired, the species is spectrally a *singlet*, while, as we have seen (p. 278), two unpaired electrons appear as a *triplet*. An ingenious method of distinguishing



between the two possibilities was developed by Skell,[329] based on the common reaction of addition of carbenes to double bonds to form cyclopropane derivatives (**15-51**). If the singlet species adds to *cis*-2-butene, the resulting cyclopropane should be the cis isomer since the movements of the two pairs of electrons should



occur either simultaneously or with one rapidly succeeding another. However, if the attack is by a triplet species, the two unpaired electrons cannot both go into a new covalent bond, since by Hund's rule they have parallel spins. So one of the unpaired electrons will form a bond with the electron from the double bond that has the opposite spin, leaving two unpaired electrons that have the same spin and therefore cannot form a bond at once but must wait until, by some collision process, one of the electrons can reverse its spin. During this time, there is free rotation about the C—C bond and a mixture of *cis*- and *trans*-1,2-dimethylcyclopropanes should result.[330]

The results of this type of experiment show that CH_2 itself is usually formed as a singlet species, which can decay to the triplet state, which consequently has a lower energy (molecular-orbital calculations[331] and experimental determinations show that the difference in energy between singlet and triplet CH_2 is ~8–10 kcal mol^{-1} or 33–42 kJ mol^{-1}[332]). However, it is possible to prepare triplet CH_2 directly by a

[329]Skell, P.S.; Woodworth, R.C. *J. Am. Chem. Soc.* ***1956***, *78*, 4496; Skell, P.S. *Tetrahedron* ***1985***, *41*, 1427.

[330]These conclusions are generally accepted though the reasoning given here may be oversimplified. For discussions, see Closs, G.L. *Top. Stereochem.* ***1968***, *3*, 193, pp. 203–210; Bethell, D. *Adv. Phys. Org. Chem.* ***1969***, *7*, 153, pp. 194; Hoffmann, R. *J. Am. Chem. Soc.* ***1968***, *90*, 1475.

[331]Richards, Jr., C.A.; Kim, S.-J.; Yamaguchi, Y.; Schaefer III, H.F. *J. Am. Chem. Soc.* ***1995***, *117*, 10104.

[332]See, for example, Hay, P.J.; Hunt, W.J.; Goddard III, W.A. *Chem. Phys. Lett.* ***1972***, *13*, 30; Dewar, M.J.S.; Haddon, R.C.; Weiner, P.K. *J. Am. Chem. Soc.* ***1974***, *96*, 253; Frey, H.M.; Kennedy, G.J. *J. Chem. Soc. Chem. Commun.* ***1975***, 233; Lucchese, R.R.; Schaefer III, H.F. *J. Am. Chem. Soc.* ***1977***, *99*, 6765; Roos, B.O.; Siegbahn, P.M. *J. Am. Chem. Soc.* ***1977***, *99*, 7716; Lengel, R.K.; Zare, R.N. *J. Am. Chem. Soc.* ***1978***, *100*, 7495; Borden, W.T.; Davidson, E.R. *Ann. Rev. Phys. Chem.* ***1979***, *30*, 125, see pp. 128–134; Leopold, D.G.; Murray, K.K.; Lineberger, W.C. *J. Chem. Phys.* ***1984***, *81*, 1048.

photosensitized decomposition of diazomethane.[333] The CH_2 group is so reactive[334] that it generally reacts as the singlet before it has a chance to decay to the triplet state.[335] As to other carbenes, some react as triplets, some as singlets, and others as singlets or triplets, depending on how they are generated. There are, however, molecules that generate persistent triplet carbenes.[336] Indeed, remarkably stable diaryl triplet carbenes have been prepared.[337]

There is a limitation to the use of stereospecificity of addition as a diagnostic test for singlet or triplet carbenes.[338] When carbenes are generated by photolytic methods, they are often in a highly excited singlet state. When they add to the double bond, the addition is stereospecific; but the cyclopropane formed carries excess energy; that is, it is in an excited state. It has been shown that under certain conditions (low pressures in the gas phase) the excited cyclopropane may undergo cis-trans isomerization *after* it is formed, so that triplet carbene may seem to be involved although in reality the singlet was present.[339]

Studies of the IR spectrum of CCl_2 trapped at low temperatures in solid argon indicate that the ground state for this species is the singlet.[340] The geometrical structure of triplet methylene can be investigated by esr measurements,[341] since triplet species are diradicals. Such measurements made on triplet CH_2 trapped in matrices at very low temperatures (4 K) show that triplet CH_2 is a bent molecule, with an angle of ~136°.[342] Epr measurements cannot be made on singlet species, but from electronic spectra of CH_2 formed in flash photolysis of diazomethane it was concluded that singlet CH_2 is also bent, with an angle of ~103°.[343] Singlet CCl_2[286] and CBr_2[344] are also bent, with angles of 100 and 114°, respectively. It

[333]Kopecky, K.R.; Hammond, G.S.; Leermakers, P.A. *J. Am. Chem. Soc.* ***1961***, *83*, 2397; ***1962***, *84*, 1015; Duncan, F.J.; Cvetanović, R.J. *J. Am. Chem. Soc.* ***1962***, *84*, 3593.

[334]For a review of the kinetics of CH_2 reactions, see Laufer, A.H. *Rev. Chem. Intermed.* ***1981***, *4*, 225.

[335]Decay of singlet and triplet CH_2 has been detected in solution, as well as in the gas phase: Turro, N.J.; Cha, Y.; Gould, I.R. *J. Am. Chem. Soc.* ***1987***, *109*, 2101.

[336]Tomioka, H. *Acc. Chem. Res.* ***1997***, *30*, 315; Kirmse, W. *Angew. Chem. Int. Ed.* ***2003***, *42*, 2117.

[337]Hirai, K.; Tomioka, H. *J. Am. Chem. Soc.* ***1999***, *121*, 10213; Woodcock, H.L.; Moran, D.; Schleyer, P.v.R.; Schaefer III, H.F. *J. Am. Chem. Soc.* ***2001***, *123*, 4331.

[338]For other methods of distinguishing singlet from triplet carbenes, see Hendrick, M.E.; Jones Jr., M. *Tetrahedron Lett.* ***1978***, 4249; Creary, X. *J. Am. Chem. Soc.* ***1980***, *102*, 1611.

[339]Rabinovitch, B.S.; Tschuikow-Roux, E.; Schlag, E.W. *J. Am. Chem. Soc.* ***1959***, *81*, 1081; Frey, H.M. *Proc. R. Soc. London, Ser. A* ***1959***, *251*, 575. It has been reported that a singlet carbene (CBr_2) can add nonstereospecifically: Lambert, J.B.; Larson, E.G.; Bosch, R.J. *Tetrahedron Lett.* ***1983***, *24*, 3799.

[340]Andrews, L. *J. Chem. Phys.* ***1968***, *48*, 979.

[341]The technique of spin trapping (p. 268) has been applied to the detection of transient triplet carbenes: Forrester, A.R.; Sadd, J.S. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 1273.

[342]Wasserman, E.; Kuck, V.J.; Hutton, R.S.; Anderson, E.D.; Yager, W.A. *J. Chem. Phys.* ***1971***, *54*, 4120; Bernheim, R.A.; Bernard, H.W.; Wang, P.S.; Wood, L.S.; Skell, P.S. *J. Chem. Phys.* ***1970***, *53*, 1280; ***1971***, *54*, 3223.

[343]Herzberg, G.; Johns, J.W.C. *Proc. R. Soc. London, Ser. A* ***1967***, *295*, 107, *J. Chem. Phys.* ***1971***, *54*, 2276 and cited references.

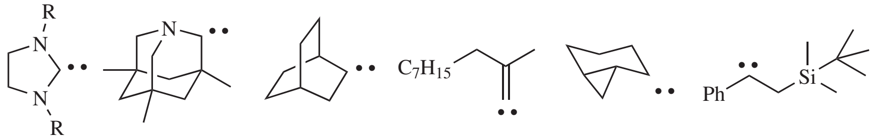
[344]Ivey, R.C.; Schulze, P.D.; Leggett, T.L.; Kohl, D.A. *J. Chem. Phys.* ***1974***, *60*, 3174.

has long been known that triplet aryl carbenes are bent.[345]

136° 103°

Triplet methylene   Singlet methylene

The most common carbenes are $:CH_2$ and: CCl_2,[346] but many others have been reported, [347] including heterocyclic carbenes, such as **55** (stabilized by the steric constraints of the ring geometry),[348] **56** (an aminocarbene without π conjugation),[349] bicyclo[2.2.2]octylidene, **57**,[350] alkylidene carbenes, such as **58**,[351] conformationally restricted cyclopropylcarbenes, such as **59**,[352] β-Silylcarbenes, such as **60**,[353] α-keto carbenes,[354] vinyl carbenes,[355] and chiral carbenoids.[356] In the case of **55** (R = Ph),[357] the precursor is a tetraaminoethylene, and when potassium hydride is present to preclude electrophilic catalysis, starting tetraaminoethylenes are recovered unchanged.



55 **56** **57** **58** **59** **60**

[345]Trozzolo, A.M.; Wasserman, E.; Yager, W.A. *J. Am. Chem. Soc.* ***1965***, *87*, 129; Senthilnathan, V.P.; Platz, M.S. *J. Am. Chem. Soc.* ***1981***, *103*, 5503; Gilbert, B.C.; Griller, D.; Nazran, A.S. *J. Org. Chem.* ***1985***, *50*, 4738.

[346]For reviews of halocarbenes, see Burton, D.J.; Hahnfeld, J.L. *Fluorine Chem. Rev.* ***1977***, *8*, 119; Margrave, J.L.; Sharp, K.G.; Wilson, P.W. *Fort. Chem. Forsch.* ***1972***, *26*, 1, pp. 3–13.

[347]For reviews of unsaturated carbenes, see Stang, P.J. *Acc. Chem. Res.* ***1982***, *15*, 348; *Chem. Rev.* ***1978***, *78*, 383. For a review of carbalkoxycarbenes, see Marchand, A.P.; Brockway, N.M. *Chem. Rev.* ***1974***, *74*, 431. For a review of arylcarbenes, see Schuster, G.B. *Adv. Phys. Org. Chem.* ***1986***, *22*, 311. For a review of carbenes with neighboring hetero atoms, see Taylor, K.G. *Tetrahedron* ***1982***, *38*, 2751.

[348]Denk, M.K.; Thadani, A.; Hatano, K.; Lough, A.J. *Angew. Chem. Int. Ed.* ***1997***, *36*, 2607; Herrmann, W.A. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1290.

[349]Ye, Q.; Komarov, I.V.; Kirby, A.J.; Jones, Jr., M. *J. Org. Chem.* ***2002***, *67*, 9288.

[350]Ye, Q.; Jones, Jr., M.; Chen, T.; Shevlin, P.B. *Tetrahedron Lett.* ***2001***, *42*, 6979.

[351]Ohira, S.; Okai, K.; Moritani, T. *J. Chem. Soc. Chem. Commun.* ***1992***, 721; Walsh, R.; Wolf, C.; Untiedt, S.; de Meijere, A. *J. Chem. Soc. Chem. Commun.* ***1992***, 421, 422; Ohira, S.; Yamasaki, K.; Nozaki, H.; Yamato, M.; Nakayama, M. *Tetrahedron Lett.* ***1995***, *36*, 8843. For dimethylvinylidene carbene, see Reed, S.C.; Capitosti, G.J.; Zhu, Z.; Modarelli, D.A. *J. Org. Chem.* ***2001***, *66*, 287. For a review of akylidenecarbenes, see Knorr, R. *Chem. Rev.* ***2004***, *104*, 3795.

[352]Fernamberg, K.; Snoonian, J.R.; Platz, M.S. *Tetrahedron Lett.* ***2001***, *42*, 8761.

[353]Creary, X.; Butchko, M.A. *J. Org. Chem.* ***2002***, *67*, 112.

[354]Bonnichon, F.; Richard, C.; Grabner, G. *Chem. Commun.* ***2001***, 73.

[355]Zuev, P.S.; Sheridan, R.S. *J. Am. Chem. Soc.* ***2004***, *126*, 12220.

[356]Topolski, M.; Duraisamy, M.; Rachoń, J.; Gawronski, J.; Gawronska, K.; Goedken, V.; Walborsky, H.M. *J. Org. Chem.* ***1993***, *58*, 546.

[357]See Wanzlick, H.-W.; Schikora, E. *Angew. Chem.* ***1960***, *72*, 494.

Flash photolysis of $CHBr_3$ produced the intermediate CBr.[358]

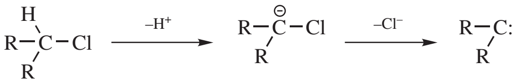
$$\mathrm{CHBr_3} \xrightarrow[\text{photolysis}]{\text{flash}} \cdot\bar{\mathrm{C}}\mathrm{-Br}$$

This is a *carbyne*. The intermediates CF and CCl were generated similarly from $CHFBr_2$ and $CHClBr_2$, respectively.

The Generation and Fate of Carbenes[359]

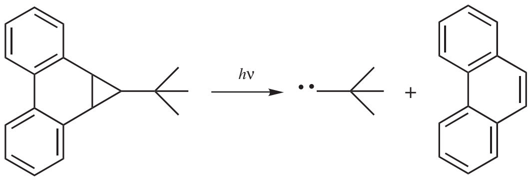
Carbenes are chiefly formed in two ways, although other pathways are also known.

1. In α elimination, a carbon loses a group without its electron pair, usually a proton, and then a group with its pair, usually a halide ion:[360]



The most common example is formation of dichlorocarbene by treatment of chloroform with a base (see reaction **10-3**) and geminal alkyl dihalides with Me_3Sn^-,[361] but many other examples are known, such as

$$\mathrm{CCl_3{-}COO^{\ominus}} \xrightarrow{\Delta} \mathrm{CCl_2} + \mathrm{CO_2} + \mathrm{Cl^{\ominus}}$$ Ref. 362



Ref. 363

2. Disintegration of compounds containing certain types of double bonds:

$$\mathrm{R_2C{=}Z} \longrightarrow \mathrm{R_3C:} + \mathrm{Z}$$

[358]Ruzsicska, B.P.; Jodhan, A.; Choi, H.K.J.; Strausz, O.P. *J. Am. Chem. Soc.* ***1983***, *105*, 2489.

[359]For reviews, see Jones Jr., M. *Acc. Chem. Res.* ***1974***, *7*, 415; Kirmse, W., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9; Elsevier, NY, ***1973***, pp. 373–415; Ref. 327. For a review of electrochemical methods of carbene generation, see Petrosyan, V.E.; Niyazymbetov, M.E. *Russ. Chem. Rev.* ***1989***, *58*, 644.

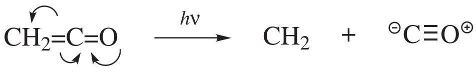
[360]For a review of formation of carbenes in this manner, see Kirmse, W. *Angew. Chem. Int. Ed.* ***1965***, *4*, 1.

[361]Ashby, E.C.; Deshpande, A.K.; Doctorovich, F. *J. Org. Chem.* ***1993***, *58*, 4205.

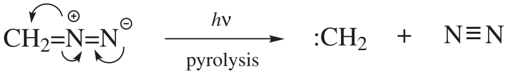
[362]Wagner, W.M. *Proc. Chem. Soc.* ***1959***, 229.

[363]Glick, H.C.; Likhotvovik, I.R.; Jones Jr., M. *Tetrahedron Lett.* ***1995***, *36*, 5715; Stang, P.J. *Acc. Chem. Res.* ***1982***, *15*, 348; *Chem. Rev.* ***1978***, *78*, 383.

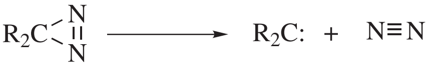
The two most important ways of forming $:CH_2$ are examples: the photolysis of ketene



and the isoelectronic decomposition of diazomethane.[364]



Diazirines[365] (isomeric with diazoalkanes) give carbenes,[366] but arylmethyl radicals have also been generated from diazirines.[367] In a different study, thermolysis of diaryloxydiazirines gave the anticipated carbene products, but photolysis gave both carbenes and aryloxy radicals by α-scission.[368]



Because most carbenes are so reactive, it is often difficult to prove that they are actually present in a given reaction. The lifetime of formylcarbene was measured by transient absorption and transient grating spectroscopy to be 0.15–0.73 ns in dichloromethane.[369] In many instances where a carbene is *apparently* produced by an α elimination or by disintegration of a double-bond compound there is evidence that no free carbene is actually involved. The neutral term *carbenoid* is used where it is known that a free carbene is not present or in cases where there is doubt. α-Halo organometallic compounds, R_2CXM, are often called carbenoids because they readily give a elimination reactions[370] (e.g., see **12-39**).

The reactions of carbenes are more varied than those of the species previously discussed in this chapter. Solvent effects have been observed in carbene reactions. The selectivity of certain carbenes is influenced by the nature of the solvent.[371] the distribution of rearrangement products (see below) from *tert*-butylcarbene[372] are

[364]For a review, see Regitz, M.; Maas, G. *Diazo Compounds*, Academic Press, NY, ***1986***, pp. 170–184.

[365]For syntheses, see Martinu, T.; Dailey, W.P. *J. Org. Chem.* ***2004***, *69*, 7359; Likhotvorik, I.R.; Tae, E.L.; Ventre, C.; Platz, M.S. *Tetahedron Lett.* ***2000***, *41*, 795.

[366]For a treatise, see Liu, M.T.H. *Chemistry of Diazirines*, 2 vols., CRC Press, Boca Raton, FL, ***1987***. For reviews, see Liu, M.T.H. *Chem. Soc. Rev.* ***1982***, *11*, 127; Frey, H.M. *Adv. Photochem.* ***1966***, *4*, 225.

[367]Moss, R.A.; Fu, X. *Org. Lett.* ***2004***, *6*, 3353.

[368]Fede, J.-M.; Jockusch, S.; Lin, N.; Moss, R.A.; Turro, N.J. *Org. Lett.* ***2003***, *5*, 5027.

[369]Toscano, J.P.; Platz, M.S.; Nikolaev, V.; Cao, Y.; Zimmt, M.B. *J. Am. Chem. Soc.* ***1996***, *118*, 3527.

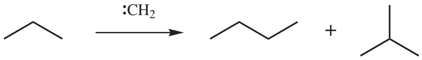
[370]For a review, see Nefedov, O.M.; D'yachenko, A.I.; Prokof'ev, A.K. *Russ. Chem. Rev.* ***1977***, *46*, 941.

[371]Tomioka, H.; Ozaki, Y.; Izawa, Y. *Tetrahedron* ***1985***, *41*, 4987.

[372]Moss, R.A.; Yan, S.; Krogh-Jesperson, K. *J. Am. Chem. Soc.* ***1998***, *120*, 1088.; Krogh-Jesperson, K.; Yan, S.; Moss, R.A. *J. Am. Chem. Soc.* ***1999***, *121*, 6269.

influenced by changes in solvent.[373] It is known that singlet methylene forms a charge-transfer complex with benzene.[374] Solvent interactions for chlorophenylcarbene and fluorophenylcarbene, however, are weak.[375]

1. Additions to carbon–carbon double bonds have already been mentioned. Carbenes also add to aromatic systems, but the immediate products rearrange, usually with ring enlargement (see **15-65**). Additions of carbenes to other double bonds, such as C=N (**16-46** and **16-48**), and to triple bonds have also been reported.
2. An unusual reaction of carbenes is that of insertion into C—H bonds (**12-21**). Thus, :CH_2 reacts with methane to give ethane and with propane to give



n-butane and isobutane, as shown. Elimination to give an alkene is a competing side reaction in polar solvents, but this is suppressed in nonpolar solvents.[376] Simple alkyl carbenes, such as this, are not very useful for synthetic purposes, but do illustrate the extreme reactivity of carbene. However, carbenoids generated by rhodium catalyzed decomposition of diazoalkanes are very useful (p. 803) and have been used in a variety of syntheses. Treatment in the liquid phase of an alkane, such as pentane with carbene formed from the photolysis of diazomethane, gives the three possible products in statistical ratios[377] demonstrating that carbene is displaying no selectivity. For many years, it was a generally accepted principle that the lower the selectivity the greater the reactivity; however, this principle is no longer regarded as general because many exceptions have been found.[378] Singlet CH_2 generated by photolysis of diazomethane is probably the most reactive organic species known, but triplet CH_2 is somewhat less reactive, and other carbenes are still less reactive. The following series of carbenes of decreasing reactivity has

[373]Ruck, R.T.; Jones Jr., M. *Tetrahedron Lett.* ***1998***, *39*, 2277.

[374]Khan, M.I.; Goodman, J.L. *J. Am. Chem. Soc.* ***1995***, *117*, 6635.

[375]Sun, Y.; Tippmann, E.M.; Platz, M.S. *Org. Lett.* ***2003***, *5*, 1305.

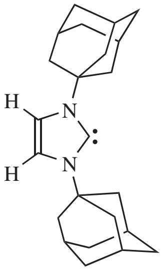
[376]Ruck, R.T.; Jones Jr., M. *Tetrahedron Lett.* ***1998***, *39*, 2277.

[377]Doering, W. von E.; Buttery, R.G.; Laughlin, R.G.; Chaudhuri, N. *J. Am. Chem. Soc.* ***1956***, *78*, 3224; Richardson, D.B.; Simmons, M.C.; Dvoretzky, I. *J. Am. Chem. Soc.* ***1961***, *83*, 1934; Halberstadt, M.L.; McNesby, J.R. *J. Am. Chem. Soc.* ***1967***, *89*, 3417.

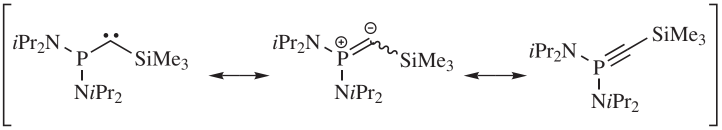
[378]For reviews of this question, see Buncel, E.; Wilson, H. *J. Chem. Educ.* ***1987***, *64*, 475; Johnson, C.D. *Tetrahedron* ***1980***, *36*, 3461; *Chem. Rev.* ***1975***, *75*, 755; Giese, B. *Angew. Chem. Int. Ed.* ***1977***, *16*, 125; Pross, A. *Adv. Phys. Org. Chem.* ***1977***, *14*, 69. See also, Ritchie, C.D.; Sawada, M. *J. Am. Chem. Soc.* ***1977***, *99*, 3754; Argile, A.; Ruasse, M. *Tetrahedron Lett.* ***1980***, *21*, 1327; Godfrey, M. *J. Chem. Soc. Perkin Trans. 2* ***1981***, 645; Kurz, J.L.; El-Nasr, M.M.S. *J. Am. Chem. Soc.* ***1982***, *104*, 5823; Srinivasan, C.; Shunmugasundaram, A.; Arumugam, N. *J. Chem. Soc. Perkin Trans. 2* ***1985***, 17; Bordwell, F.G.; Branca, J.C.; Cripe, T.A. *Isr. J. Chem.* ***1985***, *26*, 357; Formosinho, S.J. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 839; Johnson, C.D.; Stratton, B. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 1903. For a group of papers on this subject, see *Isr. J. Chem.* ***1985***, *26*, 303.

been proposed on the basis of discrimination between insertion and addition reactions: $CH_2 > HCCOOR > PhCH > BrCH \sim ClCH$.[379] Dihalocarbenes generally do not give insertion reactions at all. Insertion of carbenes into other bonds has also been demonstrated, although not insertion into C—C bonds.[380]

Two carbenes that are stable at room temperature have been reported.[381] These are **61** and **62**. In the absence of oxygen and moisture, **61** exists as stable crystals with a melting point of 240–241°C.[382] Its structure was proved by X-ray crystallography.



61



62

3. It would seem that dimerization should be an important reaction of carbenes

$$R_2C: \; + \; R_2C: \longrightarrow R_2C{=}CR_2$$

but it is not, because the reactivity is so great that the carbene species do not have time to find each other and because the dimer generally has so much energy that it dissociates again. Apparent dimerizations have been observed, but it is likely that the products in many reported instances of "dimerization" do not arise from an actual dimerization of two carbenes but from attack by a carbene on a molecule of carbene precursor, for example,

$$R_2C: \; + \; R_2CN_2 \longrightarrow R_2C{=}CR_2 \; + \; N_2$$

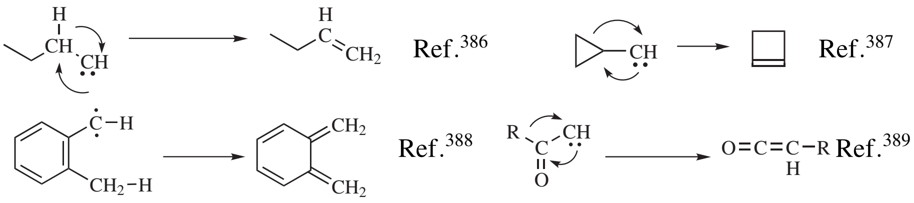
[379]Closs, G.L.; Coyle, J.J. *J. Am. Chem. Soc.* ***1965***, *87*, 4270.

[380]See, for example, Doering, W. von E.; Knox, L.H.; Jones, Jr., M. *J. Org. Chem.* ***1959***, *24*, 136; Franzen, V. *Liebigs Ann. Chem.* ***1959***, *627*, 22; Bradley, J.; Ledwith, A. *J. Chem. Soc.* ***1961***, 1495; Frey, H.M.; Voisey, M.A. *Chem. Commun.* ***1966***, 454; Seyferth, D.; Damrauer, R.; Mui, J.Y.; Jula, T.F. *J. Am. Chem. Soc.* ***1968***, *90*, 2944; Tomioka, H.; Ozaki, Y.; Izawa, Y. *Tetrahedron* ***1985***, *41*, 4987; Frey, H.M.; Walsh, R.; Watts, I.M. *J. Chem. Soc. Chem. Commun.* ***1989***, 284.

[381]For a discussion, see Regitz, M. *Angew. Chem. Int. Ed.* ***1991***, *30*, 674.

[382]Arduengo III, A.J.; Harlow, R.L.; Kline, M. *J. Am. Chem. Soc.* ***1991***, *113*, 361.

4. Alkylcarbenes can undergo rearrangement, with migration of alkyl or hydrogen.[383] Indeed these rearrangements are generally so rapid[384] that additions to multiple bonds and insertion reactions, which are so common for CH_2, are seldom encountered with alkyl or dialkyl carbenes. Unlike rearrangement of the species previously encountered in this chapter, most rearrangements of carbenes directly give stable molecules. A carbene intermediate has been suggested for the isomerization of cyclopropane.[385] Some examples of carbene rearrangement are



The rearrangement of acylcarbenes to ketenes is called the Wolff rearrangement (reaction **18-8**). A few rearrangements in which carbenes rearrange to other carbenes are also known.[390] Of course, the new carbene must stabilize itself in one of the ways we have mentioned.

[383]For a probe of migratory aptitudes of hydrogen to carbenes see Locatelli, F.; Candy, J.-P.; Didillon, B.; Niccolai, G.P.; Uzio, D.; Basset, J.-M. *J. Am. Chem. Soc.* ***2001***, *123*, 1658. For reviews of carbene and nitrene rearrangements, see Brown, R.F.C. *Pyrolytic Methods in Organic Chemistry*, Academic Press, NY, ***1980***, pp. 115–163; Wentrup, C. *Adv. Heterocycl. Chem.* ***1981***, *28*, 231; *React. Intermed. (Plenum)* ***1980***, *1*, 263; *Top. Curr. Chem.* ***1976***, *62*, 173; Jones, W.M., in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 1, Academic Press, NY, ***1980***, pp. 95–160; Schaefer III, H.F. *Acc. Chem. Res.* ***1979***, *12*, 288; Kirmse, W. *Carbene Chemistry*, 2nd ed., Academic Press, NY, ***1971***, pp. 457–496.

[384]The activation energy for the 1,2-hydrogen shift has been estimated at 1.1 kcal mol^{-1} (4.5 kJ mol^{-1}), an exceedingly low value: Stevens, I.D.R.; Liu, M.T.H.; Soundararajan, N.; Paike, N. *Tetrahedron Lett.* ***1989***, *30*, 481. Also see, Pezacki, J.P.; Couture, P.; Dunn, J.A.; Warkentin, J.; Wood, P.D.; Lusztyk, J.; Ford, F.; Platz, M.S. *J. Org. Chem.* ***1999***, *64*, 4456.

[385]Bettinger, H.F.; Rienstra-Kiracofe, J.C.; Hoffman, B.C.; Schaefer III, H.F.; Baldwin, J.E.; Schleyer, P.v.R. *Chem. Commun.* ***1999***, 1515.

[386]Kirmse, W.; Doering, W. von E. *Tetrahedron* ***1960***, *11*, 266. For kinetic studies of the rearrangement: Cl–$\bar{C}$–$CHR_2 \rightarrow ClCH{=}CR_2$, see Liu, M.T.H.; Bonneau, R. *J. Am. Chem. Soc.* ***1989***, *111*, 6873; Jackson, J.E.; Soundararajan, N.; White, W.; Liu, M.T.H.; Bonneau, R.; Platz, M.S. *J. Am. Chem. Soc.* ***1989***, *111*, 6874; Ho, G.; Krogh-Jespersen, K.; Moss, R.A.; Shen, S.; Sheridan, R.S.; Subramanian, R. *J. Am. Chem. Soc.* ***1989***, *111*, 6875; LaVilla, J.A.; Goodman, J.L. *J. Am. Chem. Soc.* ***1989***, *111*, 6877.

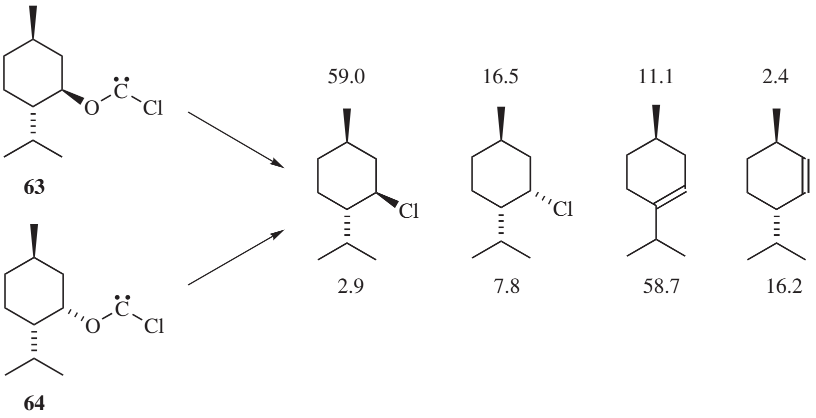
[387]Friedman, L.; Shechter, H. *J. Am. Chem. Soc.* ***1960***, *82*, 1002.

[388]McMahon, R.J.; Chapman, O.L. *J. Am. Chem. Soc.* ***1987***, *109*, 683.

[389]Friedman, L.; Berger, J.G. *J. Am. Chem. Soc.* ***1961***, *83*, 492, 500.

[390]For a review, see Jones, W.M. *Acc. Chem. Res.* ***1977***, *10*, 353.

5. The fragmentation reactions of alicyclic oxychlorocarbenes such as **63** and **64**[391] give substitution and elimination products. Menthyloxychlorocarbene, **63**, gave primarily the substitution product, whereas neomenthyloxychlorocarbene, **64**, gave primarily the elimination product, as shown. In this case, the substitution product is likely due to rearrangement of the chlorocarbene.[392] It is known that fragmentation of nortricyclyloxychlorocarbene in pentane occurs by an S_Ni-like process to give nortricyclyl chloride.[393] In more polar solvents, fragmentation leads to nortricyclyl cation–chloride anion pair that gives nortricyclyl chloride and a small amount of *exo*-2-norbornenyl chloride. Fragmentation can also lead to radicals.[394]



6. Triplet carbenes can abstract hydrogen or other atoms to give free radicals, for example,

$$\cdot\dot{C}H_2 \;+\; CH_3CH_3 \longrightarrow \;\cdot CH_3 \;+\; \cdot CH_2CH_3$$

This is not surprising, since triplet carbenes are free radicals. But singlet carbenes can also give this reaction, although in this case only halogen atoms are abstracted, not hydrogen.[395]

[391]Moss, R.A.; Johnson, L.A.; Kacprzynski, M.; Sauers, R.R. *J. Org. Chem.* ***2003***, *68*, 5114.
[392]A rearrangement product was noted for adamantylchlorocarbenes, possibly due to rearrangement of the chlorine atom from a chlorocarbene. See Yao, G.; Rempala, P.; Bashore, C.; Sheridan, R.S. *Tetrahedron Lett.* ***1999***, *40*, 17.
[393]Moss, R.A.; Ma, Y.; Sauers, R.R.; Madni, M. *J. Org. Chem.* ***2004***, *69*, 3628.
[394]Mekley, N.; El-Saidi, M.; Warkentin, J. *Can. J. Chem.* ***2000***, *78*, 356.
[395]Roth, H.D. *J. Am. Chem. Soc.* ***1971***, *93*, 1527, 4935, *Acc. Chem. Res.* ***1977***, *10*, 85.

NITRENES

Nitrenes,[396] R—N, are the nitrogen analogs of carbenes, and most of what we have said about carbenes also applies to them. Nitrenes are too reactive for isolation under ordinary conditions,[397] although *ab initio* calculations show that nitrenes are more stable than carbenes with an enthalpy difference of 25–26 kcal mol^{-1} (104.7–108.8 kJ mol^{-1}).[398]

Singlet Triplet

Alkyl nitrenes have been isolated by trapping in matrices at 4 K,[399] while aryl nitrenes, which are less reactive, can be trapped at 77 K.[400] The ground state of NH, and probably of most nitrenes,[401] is a triplet, although nitrenes can be generated in both triplet[402] and singlet states. In additions of EtOOC—N to C=C double bonds two species are involved, one of which adds in a stereospecific manner and the other not. By analogy with Skell's proposal involving carbenes (p. 284) these are taken to be the singlet and triplet species, respectively.[403]

The two principal means of generating nitrenes are analogous to those used to form carbenes.

1. *Elimination.* An example is

[396]For monographs, see Scriven, E.F.V. *Azides and Nitrenes*, Academic Press, NY, **1984**; Lwowski, W. *Nitrenes*, Wiley, NY, ***1970***. For reviews, see Scriven, E.F.V. *React. Intermed. (Plenum)* ***1982***, *2*, 1; Lwowski, W. *React. Intermed. (Wiley)* ***1985***, *3*, 305; ***1981***, *2*, 315; ***1978***, *1*, 197; *Angew. Chem. Int. Ed.* ***1967***, *6*, 897; Abramovitch, R.A., in McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, ***1973***, pp. 127–192; Hünig, S. *Helv. Chim. Acta* ***1971***, *54*, 1721; Belloli, R. *J. Chem. Educ.* ***1971***, *48*, 422; Kuznetsov, M.A.; Ioffe, B.V. *Russ. Chem. Rev.* ***1989***, *58*, 732 (*N*- and *O*-nitrenes); Meth-Cohn, O. *Acc. Chem. Res.* ***1987***, *20*, 18 (oxycarbonylnitrenes); Abramovitch, R.A.; Sutherland, R.G. *Fortsch. Chem. Forsch.*, ***1970***, *16*, 1 (sulfonyl nitrenes); Ioffe, B.V.; Kuznetsov, M.A. *Russ. Chem. Rev.* ***1972***, *41*, 131 (*N*-nitrenes).

[397]McClelland, R.A. *Tetrahedron* ***1996***, *52*, 6823.

[398]Kemnitz, C.R.; Karney, W.L.; Borden, W.T. *J. Am. Chem. Soc.* ***1998***, *120*, 3499.

[399]Wasserman, E.; Smolinsky, G.; Yager, W.A. *J. Am. Chem. Soc.* ***1964***, *86*, 3166. For the structure of CH_3–N:, as determined in the gas phase, see Carrick, P.G.; Brazier, C.R.; Bernath, P.F.; Engelking, P.C. *J. Am. Chem. Soc.* ***1987***, *109*, 5100.

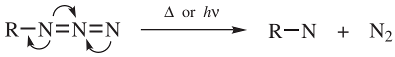
[400]Smolinsky, G.; Wasserman, E.; Yager, W.A. *J. Am. Chem. Soc.* ***1962***, *84*, 3220. For a review, see Sheridan, R.S. *Org. Photochem.* ***1987***, *8*, 159, pp. 159–248.

[401]A few nitrenes have been shown to have singlet ground states. See Sigman, M.E.; Autrey, T.; Schuster, G.B. *J. Am. Chem. Soc.* ***1988***, *110*, 4297.

[402]For the direct detection of triplet alkyl nitrenes in solution via photolysis of α-azidoacetophenones see Singh, P.N.D.; Mandel, S.M.; Robinson, R.M.; Zhu, Z.; Franz, R.; Ault, B.S.; Gudmundsdottir, A.D. *J. Org. Chem.* ***2003***, *68*, 7951.

[403]McConaghy, Jr., J.S.; Lwowski, W. *J. Am. Chem. Soc.* ***1967***, *89*, 2357, 4450; Mishra, A.; Rice, S.N.; Lwowski, W. *J. Org. Chem.* ***1968***, *33*, 481.

2. *Breakdown of Certain Double-Bond Compounds*. The most common method of forming nitrenes is photolytic or thermal decomposition of azides,[404]

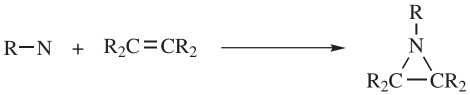


The unsubstituted nitrene NH has been generated by photolysis of or electric discharge through NH_3, N_2H_4, or HN_3.

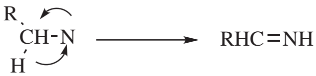
The reactions of nitrenes are also similar to those of carbenes.[405] As in that case, many reactions in which nitrene intermediates are suspected probably do not involve free nitrenes. It is often very difficult to obtain proof in any given case that a free nitrene is or is not an intermediate.

1. *Insertion* (see reaction **12-13**). Nitrenes, especially acyl nitrenes and sulfonyl nitrenes, can insert into C—H and certain other bonds, for example,

2. *Addition to C=C Bonds* (see reaction **15-54**):



3. *Rearrangements*.[383] Alkyl nitrenes do not generally give either of the two preceding reactions because rearrangement is more rapid, for example,



Such rearrangements are so rapid that it is usually difficult to exclude the possibility that a free nitrene was never present at all, that is, that migration takes place at the same time that the nitrene is formed[406] (see p. 1606). However, the rearrangement of naphthylnitrenes to novel bond-shift isomers has been reported.[407]

[404]For reviews, see Dyall, L.K., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement D*, pt. 1, Wiley, NY, ***1983***, pp. 287–320; Dürr, H.; Kober, H. *Top. Curr. Chem.* ***1976***, *66*, 89; L'Abbé, G. *Chem. Rev.* ***1969***, *69*, 345.

[405]For a discussion of nitrene reactivity, see Subbaraj, A.; Subba Rao, O.; Lwowski, W. *J. Org. Chem.* ***1989***, *54*, 3945.

[406]For example, see Moriarty, R.M.; Reardon, R.C. *Tetrahedron* ***1970***, *26*, 1379; Abramovitch, R.A.; Kyba, E.P. *J. Am. Chem. Soc.* ***1971***, *93*, 1537.

[407]Maltsev, A.; Bally, T.; Tsao, M.-L.; Platz, M.S.; Kuhn, A.; Vosswinkel, M.; Wentrup, C. *J. Am. Chem. Soc.* ***2004***, *126*, 237.

4. *Abstraction*, for example,

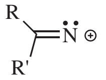
$$R{-}N \;+\; R{-}H \longrightarrow R{-}\dot{\ddot{N}}{-}H \;+\; R\cdot$$

5. *Dimerization*. One of the principal reactions of NH is dimerization to diimide N_2H_2. Azobenzenes are often obtained in reactions where aryl nitrenes are implicated:[408]

$$2\ Ar{-}N \longrightarrow Ar{-}N{=}N{-}Ar$$

It would thus seem that dimerization is more important for nitrenes than it is for carbenes, but again it has not been proved that free nitrenes are actually involved.

65



66

At least two types of *nitrenium ions*,[409] the nitrogen analogs of carbocations, can exist as intermediates, although much less work has been done in this area than on carbocations. In one type (**65**), the nitrogen is bonded to two atoms (R or R′ can be H)[410] and in the other (**66**) to only one atom.[411] When R = H in **65** the species is a protonated nitrene. Like carbenes and nitrenes, nitrenium ions can exist in singlet or triplet states.[412]

[408]See, for example, Leyva, E.; Platz, M.S.; Persy, G.; Wirz, J. *J. Am. Chem. Soc.* ***1986***, *108*, 3783.

[409]Falvey, D.E. *J. Phys. Org. Chem.* ***1999***, *12*, 589; Falvey, D.E., in Ramamurthy, V., Schanze, K. *Organic, Physical, and Materials Photochemistry*, Marcel Dekker, NY, ***2000***; pp. 249–284; Novak, M.; Rajagopal, S. *Adv. Phys. Org. Chem.* ***2001***, *36*, 167; Falvey, D.E., in Moss, R.A., Platz, M.S., Jones, Jr., M. *Reactve Intermediate Chemistry*, Wiley-Interscience: Hoboken, NJ, ***2004***; Vol. 1, pp. 593–650.

[410]Winter, A.H.; Falvey, D.E.; Cramer, C.J. *J. Am. Chem. Soc.*, ***2004***, *126*, 9661.

[411]For reviews of **65**, see Abramovitch, R.A.; Jeyaraman, R., in Scriven, E.F.V. *Azides and Nitrenes*, Academic Press, NY, ***1984***, pp. 297–357; Gassman, P.G. *Acc. Chem. Res.* ***1970***, *3*, 26. For a review of **66**, see Lansbury, P.T., in Lwowski, W. *Nitrenes*, Wiley, NY, ***1970***, pp. 405–419.

[412]Gassman, P.G.; Cryberg, R.L. *J. Am. Chem. Soc.* ***1969***, *91*, 5176.

CHAPTER 6

Mechanisms and Methods of Determining Them

A mechanism is the actual process by which a reaction takes place: which bonds are broken, in what order, how many steps are involved, the relative rate of each step, and so on. In order to state a mechanism completely, we should have to specify the positions of all atoms, including those in solvent molecules, and the energy of the system, at every point in the process. A proposed mechanism must fit all the facts available. It is always subject to change as new facts are discovered. The usual course is that the gross features of a mechanism are the first to be known and then increasing attention is paid to finer details. The tendency is always to probe more deeply, to get more detailed descriptions.

Although for most reactions gross mechanisms can be written today with a good degree of assurance, no mechanism is known completely. There is much about the fine details that is still puzzling, and for some reactions even the gross mechanism is not yet clear. The problems involved are difficult because there are so many variables. Many examples are known where reactions proceed by different mechanisms under different conditions. In some cases, there are several proposed mechanisms, each of which completely explains all the data.

TYPES OF MECHANISM

In most reactions of organic compounds, one or more covalent bonds are broken. We can divide organic mechanisms into three basic types, depending on how the bonds break.

1. If a bond breaks in such a way that both electrons remain with one fragment, the mechanism is called *heterolytic*. Such reactions do not necessarily involve ionic intermediates, although they usually do. The important thing is that the electrons are never unpaired. For most reactions, it is convenient to call one reactant the *attacking reagent* and the other the *substrate*. In this book,

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we will always designate as the substrate that molecule that supplies carbon to the new bond. When carbon–carbon bonds are formed, it is necessary to be arbitrary about which is the substrate and which is the attacking reagent. In heterolytic reactions, the reagent generally brings a pair of electrons to the substrate or takes a pair of electrons from it. A reagent that brings an electron pair is called a *nucleophile* and the reaction is *nucleophilic*. A reagent that takes an electron pair is called an *electrophile* and the reaction is *electrophilic*. In a reaction in which the substrate molecule becomes cleaved, part of it (the part not containing the carbon) is usually called the *leaving group*. A leaving group that carries away an electron pair is called a *nucleofuge*. If it comes away without the electron pair, it is called an *electrofuge*.

2. If a bond breaks in such a way that each fragment gets one electron, free radicals are formed and such reactions are said to take place by *homolytic* or *free-radical mechanisms*.
3. It would seem that all bonds must break in one of the two ways previously noted. But there is a third type of mechanism in which electrons (usually six, but sometimes some other number) move in a closed ring. There are no intermediates, ions or free radicals, and it is impossible to say whether the electrons are paired or unpaired. Reactions with this type of mechanism are called *pericyclic*.[1]

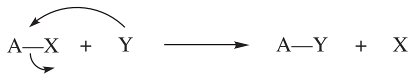
Examples of all three types of mechanisms are given in the next section.

TYPES OF REACTION

The number and range of organic reactions is so great as to seem bewildering, but actually almost all of them can be fitted into just six categories. In the description of the six types that follows, the immediate products are shown, although in many cases they then react with something else. All the species are shown without charges, since differently charged reactants can undergo analogous changes. The descriptions given here are purely formal and are for the purpose of classification and comparison. All are discussed in detail in Part 2 of this book.

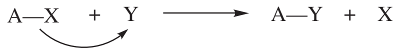
1. *Substitutions*. If heterolytic, these can be classified as nucleophilic or electrophilic depending on which reactant is designated as the substrate and which as the attacking reagent (very often Y must first be formed by a previous bond cleavage).

   a. Nucleophilic substitution (Chapters 10, 13).



[1] For a classification of pericyclic reactions, see Hendrickson, J.B. *Angew. Chem. Int. Ed.* ***1974***, *13*, 47. Also see, Fleming, I. *Pericyclic Reactions*, Oxford University Press, Oxford, ***1999***.

b. Electrophilic substitution (Chapters 11, 12).



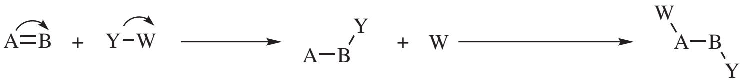
c. Free-radical substitution (Chapter 14).

$$\text{A—X} + \text{Y}\bullet \longrightarrow \text{A—Y} + \text{X}\bullet$$

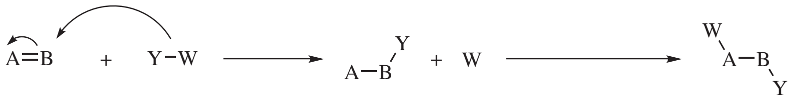
In free-radical substitution, Y• is usually produced by a previous free-radical cleavage, and X• goes on to react further.

2. *Additions to Double or Triple Bonds* (Chapters 15, 16). These reactions can take place by all three of the mechanistic possibilities.

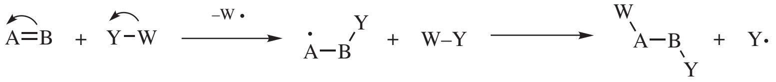
a. Electrophilic addition (heterolytic).



b. Nucleophilic addition (heterolytic).



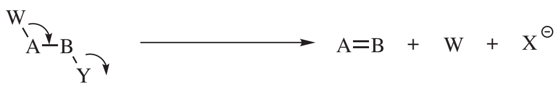
c. Free-radical addition (homolytic).



d. Simultaneous addition (pericyclic).

The examples show Y and W coming from the same molecule, but very often (except in simultaneous addition) they come from different molecules. Also, the examples show the Y—W bond cleaving at the same time that Y is bonding to B, but often (again except for simultaneous addition) this cleavage takes place earlier.

3. β *Elimination* (Chapter 17).



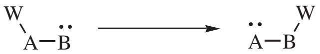
These reactions can take place by either heterolytic or pericyclic mechanisms. Examples of the latter are shown on p. $$$. Free-radical β eliminations are extremely rare. In heterolytic eliminations W and X may or may not leave simultaneously and may or may not combine.

4. *Rearrangement* (Chapter 18). Many rearrangements involve migration of an atom or group from one atom to another. There are three types, depending on how many electrons the migrating atom or group carries with it.

a. Migration with electron pair (nucleophilic).

b. Migration with one electron (free-radical).

c. Migration without electrons (electrophilic; rare).



The illustrations show 1,2 rearrangements, in which the migrating group moves to the adjacent atom. These are the most common, although longer rearrangements are also possible. There are also some rearrangements that do not involve simple migration at all (see Chapter 18). Some of the latter involve pericyclic mechanisms.

5. *Oxidation and Reduction* (Chapter 19). Many oxidation and reduction reactions fall naturally into one of the four types mentioned above, but many others do not. For a description of oxidation–reduction mechanistic types, see p. 1704.

6. *Combinations of the above.* Note that arrows are used to show movement of *electrons.* An arrow always follows the motion of electrons and never of a nucleus or anything else (it is understood that the rest of the molecule follows the electrons). Ordinary arrows (double-headed) follow electron pairs, while single-headed arrows follow unpaired electrons. Double-headed arrows are also used in pericyclic reactions for convenience, although in these reactions we do not really know how or in which direction the electrons are moving.

THERMODYNAMIC REQUIREMENTS FOR REACTION

In order for a reaction to take place spontaneously, the free energy of the products must be lower than the free energy of the reactants; that is, ΔG must be negative. Reactions can go the other way, of course, but only if free energy is added. Like water on the surface of the earth, which only flows downhill and never uphill

(though it can be carried or pumped uphill), molecules seek the lowest possible potential energy. Free energy is made up of two components, enthalpy H and entropy S. These quantities are related by the equation

$$\Delta G = \Delta H - T\Delta S$$

The enthalpy change in a reaction is essentially the difference in bond energies (including resonance, strain, and solvation energies) between the reactants and the products. The enthalpy change can be calculated by totaling the bond energies of all the bonds broken, subtracting from this the total of the bond energies of all the bonds formed, and adding any changes in resonance, strain, or solvation energies. Entropy changes are quite different, and refer to the disorder or randomness of the system. The less order in a system, the greater the entropy. The preferred conditions in Nature are *low* enthalpy and *high* entropy, and in reacting systems, enthalpy spontaneously decreases while entropy spontaneously increases.

For many reactions entropy effects are small and it is the enthalpy that mainly determines whether the reaction can take place spontaneously. However, in certain types of reaction entropy is important and can dominate enthalpy. We will discuss several examples.

1. In general, liquids have lower entropies than gases, since the molecules of gas have much more freedom and randomness. Solids, of course, have still lower entropies. Any reaction in which the reactants are all liquids and one or more of the products is a gas is therefore thermodynamically favored by the increased entropy; the equilibrium constant for that reaction will be higher than it would otherwise be. Similarly, the entropy of a gaseous substance is higher than that of the same substance dissolved in a solvent.
2. In a reaction in which the number of product molecules is equal to the number of reactant molecules, for example, $A + B \rightarrow C + D$, entropy effects are usually small, but if the number of molecules is increased, for example, $A \rightarrow B + C$, there is a large gain in entropy because more arrangements in space are possible when more molecules are present. Reactions in which a molecule is cleaved into two or more parts are therefore thermodynamically favored by the entropy factor. Conversely, reactions in which the number of product molecules is less than the number of reactant molecules show entropy decreases, and in such cases there must be a sizable decrease in enthalpy to overcome the unfavorable entropy change.
3. Although reactions in which molecules are cleaved into two or more pieces have favorable entropy effects, many potential cleavages do not take place because of large increases in enthalpy. An example is cleavage of ethane into two methyl radicals. In this case, a bond of $\sim$79 kcal mol^{-1} (330 kJ mol^{-1}) is broken, and no new bond is formed to compensate for this enthalpy increase. However, ethane can be cleaved at very high temperatures, which illustrates the principle that *entropy becomes more important as the temperature increases*, as is obvious from the equation $\Delta G = \Delta H - T\Delta S$. The

enthalpy term is independent of temperature, while the entropy term is directly proportional to the absolute temperature.

4. An acyclic molecule has more entropy than a similar cyclic molecule because there are more conformations (cf. hexane and cyclohexane). Ring opening therefore means a gain in entropy and ring closing a loss.

KINETIC REQUIREMENTS FOR REACTION

Just because a reaction has a negative ΔG does not necessarily mean that it will take place in a reasonable period of time. A negative ΔG is a *necessary*, but not a *sufficient*, condition for a reaction to occur spontaneously. For example, the reaction between H_2 and O_2 to give H_2O has a large negative ΔG, but mixtures of H_2 and O_2 can be kept at room temperature for many centuries without reacting to any significant extent. In order for a reaction to take place, *free energy of activation* $\Delta G^{\ddagger}$ must be added.[2] This situation is illustrated in Fig. 6.1,[3] which is an energy

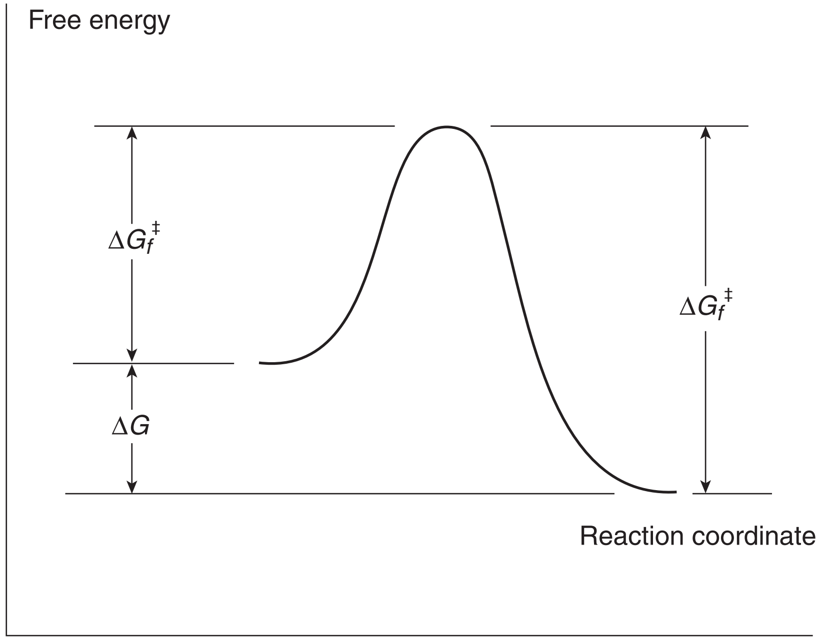


Fig. 6.1. Free-energy profile of a reaction without an intermediate where the products have a lower free energy than the reactants.

[2]For mixtures of H_2 and O_2 this can be done by striking a match.

[3]Strictly speaking, this is an energy profile for a reaction of the type $XY + Z \rightarrow X + YZ$. However, it may be applied, in an approximate way, to other reactions.

profile for a one-step reaction without an intermediate. In this type of diagram, the horizontal axis (called the *reaction coordinate*)[4] signifies the progression of the reaction. The parameter $\Delta G_f^{\ddagger}$ is the free energy of activation for the forward reaction. If the reaction shown in Fig. 6.1 is reversible, must be $>\Delta G_f^{\ddagger}$, since it is the sum of ΔG and $\Delta G_f^{\ddagger}$.

When a reaction between two or more molecules has progressed to the point corresponding to the top of the curve, the term *transition state* is applied to the positions of the nuclei and electrons. The transition state possesses a definite geometry and charge distribution but has no finite existence; the system passes through it. The system at this point is called an *activated complex.*[5]

In the *transition-state theory*[6] the starting materials and the activated complex are taken to be in equilibrium, the equilibrium constant being designated $K^{\ddagger}$. According to the theory, all activated complexes go on to product at the same rate (which, although at first sight surprising, is not unreasonable, when we consider that they are all "falling downhill") so that the rate constant (see p. 315) of the reaction depends only on the position of the equilibrium between the starting materials and the activated complex, that is, on the value of $K^{\ddagger}$. The parameter $\Delta G^{\ddagger}$ is related to $K^{\ddagger}$ by

$$\Delta G^{\ddagger} = -2.3\ RT\ \log\ K^{\ddagger}$$

so that a higher value of $\Delta G^{\ddagger}$ is associated with a smaller rate constant. The rates of nearly all reactions increase with increasing temperature because the additional energy thus supplied helps the molecules to overcome the activation energy barrier.[7] Some reactions have no free energy of activation at all, meaning that $K^{\ddagger}$ is essentially infinite and that virtually all collisions lead to reaction. Such processes are said to be *diffusion-controlled.*[8]

Like ΔG, $\Delta G^{\ddagger}$ is made up of enthalpy and entropy components

$$\boldsymbol{\Delta G^{\ddagger} = \Delta H^{\ddagger} - \mathrm{T}\Delta S^{\ddagger}}$$

$\Delta H^{\ddagger}$, the *enthalpy of activation*, is the difference in bond energies, including strain, resonance, and solvation energies, between the starting compounds and the *transition state*. In many reactions, bonds have been broken or partially broken by the time the transition state is reached; the energy necessary for this is $\Delta H^{\ddagger}$. It is

[4]For a review of reaction coordinates and structure–energy relationships, see Grunwald, E. *Prog. Phys. Org. Chem.* ***1990***, *17*, 55.

[5]For a discussion of transition states, see Laidler, K.J. *J. Chem. Educ.* ***1988***, *65*, 540.

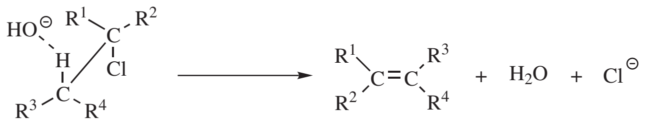
[6]For fuller discussions, see Kreevoy, M.M.; Truhlar, D.G. in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, ***1986***, pp. 13–95; Moore, J.W.; Pearson, R.G. *Kinetics and Mechanism*, 3rd ed, Wiley, NY, ***1981***, pp. 137–181; Klumpp, G.W. *Reactivity in Organic Chemistry*, Wiley, NY, ***1982***; pp. 227–378.

[7]For a review concerning the origin and evolution of reaction barriers see Donahue, N.M. *Chem. Rev.* ***2003***, *103*, 4593.

[8]For a monograph on diffusion-controlled reactions, see Rice, S.A. *Comprehensive Chemical Kinetics*, Vol. 25 (edited by Bamford, C.H.; Tipper, C.F.H.; Compton, R.G.); Elsevier: NY, ***1985***.

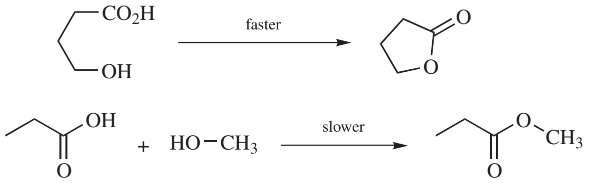
true that additional energy will be supplied by the formation of new bonds, but if this occurs after the transition state, it can affect only ΔH and not $\Delta H^{\ddagger}$.

Entropy of activation, $\Delta S^{\ddagger}$, which is the difference in entropy between the starting compounds and the transition state, becomes important when two reacting molecules must approach each other in a specific orientation in order for the reaction to take place. For example, the reaction between a simple noncyclic alkyl chloride and hydroxide ion to give an alkene (reaction **17-13**) takes place only if, in the transition state, the reactants are oriented as shown.



Not only must the ^{-}OH be near the hydrogen, but the hydrogen must be oriented anti to the chlorine atom.[9] When the two reacting molecules collide, if the ^{-}OH should be near the chlorine atom or near R^1 or R^2, no reaction can take place. In order for a reaction to occur, the molecules must surrender the freedom they normally have to assume many possible arrangements in space and adopt only that one that leads to reaction. Thus, a considerable loss in entropy is involved, that is, $\Delta S^{\ddagger}$ is negative.

Entropy of activation is also responsible for the difficulty in closing rings[10] larger then six membered. Consider a ring-closing reaction in which the two groups that must interact are situated on the ends of a 10-carbon



chain. In order for reaction to take place, the groups must encounter each other. But a 10-carbon chain has many conformations, and in only a few of these are the ends of the chain near each other. Thus, forming the transition state requires a great loss of entropy.[11] This factor is also present, although less so, in closing rings of six members or less (except three-membered rings), but with rings of this size the

[9]As we will see in Chapter 17, with some molecules elimination is also possible if the hydrogen is oriented syn, instead of anti, to the chlorine atom. Of course, this orientation also requires a considerable loss of entropy.

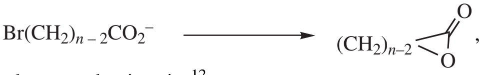
[10]For discussions of the entropy and enthalpy of ring-closing reactions, see De Tar, D.F.; Luthra, N.P. *J. Am. Chem. Soc.* ***1980***, *102*, 4505; Mandolini, L. *Bull. Soc. Chim. Fr.* ***1988***, 173. For a related discussion, see Menger, F.M. *Acc. Chem. Res.* ***1985***, *18*, 128.

[11]For reviews of the cyclization of acyclic molecules, see Nakagaki. R.; Sakuragi, H.; Mutai, K. *J. Phys. Org. Chem.* ***1989***, *2*, 187; Mandolini, L. *Adv. Phys. Org. Chem.* ***1986***, *22*, 1. For a review of the cyclization and conformation of hydrocarbon chains, see Winnik, M.A. *Chem. Rev.* ***1981***, *81*, 491. For a review of steric and electronic effects in heterolytic ring closures, see Valters, R. *Russ. Chem. Rev.* ***1982***, *51*, 788.

TABLE 6.1. Relative Rate Constants at 50°C.[a] The rate for an eight-membered ring = 1 for the reaction.

Ring Size	Relative Rate
3	21.7
4	5.4×10^3
5	1.5×10^6
6	1.7×10^4
7	97.3
8	1.00
9	1.12
10	3.35
11	8.51
12	10.6
13	32.2
14	41.9
15	45.1
16	52.0
18	51.2
23	60.4

[a](Eight-membered ring = 1) for the reaction



where n = the ring size[12].

entropy loss is less than that of bringing two individual molecules together. For example, a reaction between an OH group and a COOH group in the same molecule to form a lactone with a five- or six-membered ring takes place much faster than the same reaction between a molecule containing an OH group and another containing a COOH group. although $\Delta H^\ddagger$ is about the same, $\Delta S^\ddagger$ is much less for the cyclic case. However, if the ring to be closed has three or four members, small-angle strain is introduced and the favorable $\Delta S^\ddagger$ may not be sufficient to overcome the unfavorable $\Delta H^\ddagger$ change. Table 6.1 shows the relative rate constants for the closing of rings of 3–23 members all by the same reaction.[12] Reactions in which the transition state has more disorder than the starring compounds, for example, the pyrolytic conversion of cyclopropane to propene, have positive $\Delta S^\ddagger$ values and are thus favored by the entropy effect.

Reactions with intermediates are two-step (or more) processes. In these reactions there is an energy "well." There are two transition states, each with an energy higher than the intermediate (Fig. 6.2). The deeper the well, the more stable the intermediate. In Fig. 6.2*a*, the second peak is higher than the first. The opposite situation

[12]The values for ring sizes 4, 5, and 6 are from Mandolini, L. *J. Am. Chem. Soc.* ***1978***, *100*, 550; the others are from Galli, C.; Illuminati, G.; Mandolini, L.; Tamborra, P. *J. Am. Chem. Soc.* ***1977***, *99*, 2591. See also, Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* ***1981***, *14*, 95. See, however, van der Kerk, S.M.; Verhoeven, J.W.; Stirling, C.J.M. *J. Chem. Soc. Perkin Trans. 2* ***1985***, 1355; Benedetti, F.; Stirling, C.J.M. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 605.

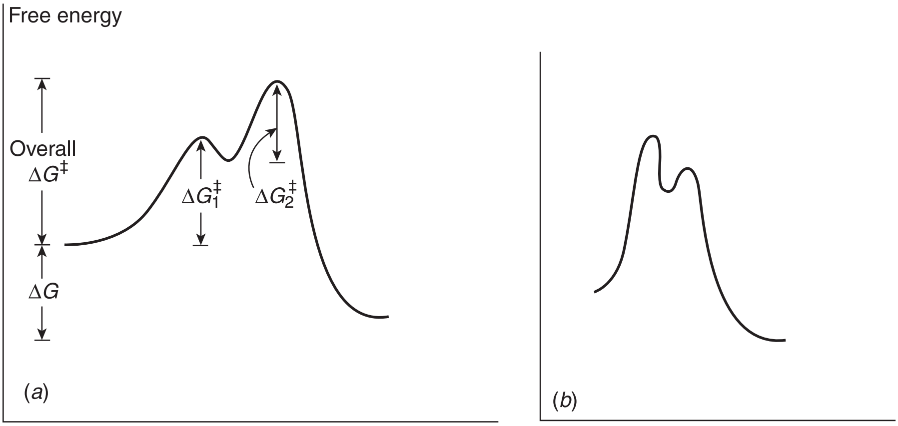


Fig. 6.2. (*a*) Free-energy profile for a reaction with an intermediate $\Delta G_1^{\ddagger}$ and $\Delta G_2^{\ddagger}$ are the free energy of activation for the first and second stages, respectively. (*b*) Free-energy profile for a reaction with an intermediate in which the first peak is higher than the second.

is shown in Fig. 6.2*b*. Note that in reactions in which the second peak is higher than the first, the overall $\Delta G^{\ddagger}$ is less than the sum of the $\Delta G^{\ddagger}$ values for the two steps. Minima in free-energy-profile diagrams (*intermediates*) correspond to real species, which have a finite although usually short existence. These may be the carbocations, carbanions, free radicals, etc., discussed in Chapter 5 or molecules in which all the atoms have their normal valences. In either case, under the reaction conditions they do not live long (because $\Delta G_2^{\ddagger}$ is small), but rapidly go on to products. Maxima in these curves, however, do not correspond to actual species but only to transition states in which bond breaking and/or bond making have partially taken place. Transition states have only a transient existence with an essentially zero lifetime.[13]

THE BALDWIN RULES FOR RING CLOSURE[14]

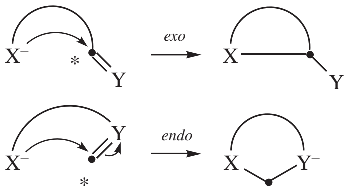
In previous sections, we discussed, in a general way, the kinetic and thermodynamic aspects of ring-closure reactions. J. E. Baldwin has supplied a more specific set of rules for certain closings of three- to seven-membered rings.[15] These rules

[13]Despite their transient existences, it is possible to study transition states of certain reactions in the gas phase with a technique called laser femtochemistry: Zewall, A.H.; Bernstein, R.B. *Chem. Eng. News* ***1988***, *66*, No. 45 (Nov. 7), 24–43. For another method, see Collings, B.A.; Polanyi, J.C.; Smith, M.A.; Stolow, A.; Tarr, A.W. *Phys. Rev. Lett.* ***1987***, *59*, 2551.

[14]See Smith, M.B. *Organic Synthesis,* 2nd ed., McGraw-Hill, NY, ***2001***, pp. 517–523.

[15]Baldwin, J.E. *J. Chem. Soc. Chem. Commun.* ***1976***, 734; Baldwin, J.E., in *Further Perspectives in Organic Chemistry* (*Ciba Foundation Symposium 53*), Elsevier North Holland, Amsterdam, The Netherlands, ***1979***, pp. 85–99. See also, Baldwin, J.E.; Thomas, R.C.; Kruse, L.I.; Silberman, L. *J. Org. Chem.* ***1977***, *42*, 3846; Baldwin, J.E.; Lusch, M.J. *Tetrahedron* ***1982***, *38*, 2939; Anselme, J. *Tetrahedron Lett.* ***1977***, 3615; Fountain, K.R.; Gerhardt, G. *Tetrahedron Lett.* ***1978***, 3985.

distinguish two types of ring closure, called Exo and Endo, and three kinds of atoms at the starred positions: *Tet* for sp^3, *Trig* for sp^2, and *Dig* for *sp*. The following are Baldwin's rules for closing rings of three to seven members.



Rule 1. Tetrahedral systems
- (a) 3–7-*Exo–Tet* are all favored processes
- (b) 5–6-*Endo–Tet* are disfavored

Rule 2. Trigonal systems
- (a) 3–7-*Exo–Trig* are favored
- (b) 3–5-*Endo–Trig* are disfavored[16]
- (c) 6–7-*Endo–Trig* are favored

Rule 3. Digonal systems
- (a) 3–4-*Exo–Dig* are disfavored
- (b) 5–7-*Exo–Dig* are favored
- (c) 3–7-*Endo–Dig* are favored

"Disfavored" does not mean it cannot be done: only that it is more difficult than the favored cases. These rules are empirical and have a stereochemical basis. The favored pathways are those in which the length and nature of the linking chain enables the terminal atoms to achieve the proper geometries for reaction. The disfavored cases require severe distortion of bond angles and distances. Many cases in the literature are in substantial accord with these rules, and they important in the formation of five- and six-membered rings.[17]

Although Baldwin's rules can be applied to ketone enolates,[18] additional rules were added to make the terminology more specific.[19] The orientation of the orbital as it approaches the reactive center must be considered for determining

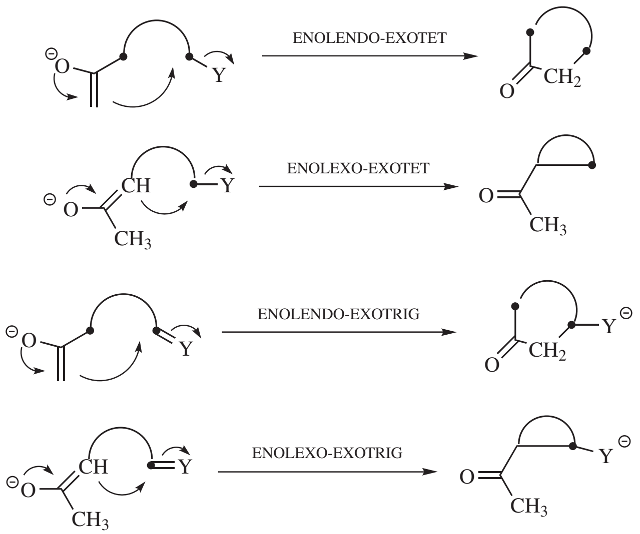
[16]For some exceptions to the rule in this case, see Trost, B.M.; Bonk, P.J. *J. Am. Chem. Soc.* ***1985***, *107*, 1778; Auvray, P.; Knochel, P.; Normant, J.F. *Tetrahedron Lett.* ***1985***, *26*, 4455; Torres, L.E.; Larson, G.L. *Tetrahedron Lett.* ***1986***, *27*, 2223.

[17]Johnson, C.D. *Acc. Chem. Res.* ***1997***, *26*, 476.

[18]Baldwin, J.E.; Kruse, L.I. *J. Chem. Soc. Chem. Commun.* ***1977***, 233.

[19]Baldwin, J.E.; Lusch, M.J. *Tetrahedron* ***1982***, *38*, 2939.

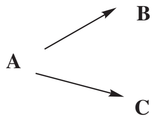
the correct angle of approach. Diagrams that illustrate the enolate rules are



The rules are

(a) 6–7 enolendo–exo–tet reactions are favored.
(b) 3–5 enolendo–exo–tet reactions are disfavored.
(c) 3–7 enolexo–exo–tet reactions are favored.
(d) 3–7 enolexo–exo–trig reactions are favored.
(e) 6–7 enolendo–exo–trig reactions are favored.
(f) 3–5 enolendo–exo–trig reactions are disfavored.

KINETIC AND THERMODYNAMIC CONTROL



There are many cases in which a compound under a given set of reaction conditions can undergo competing reactions to give different products:

Figure 6.3 shows a free-energy profile for a reaction in which **B** is thermodynamically more stable than **C** (ΔG_B is $>$ ΔG_C), but **C** is formed faster (lower $\Delta G^{\ddagger}$). If neither reaction is reversible, **C** will be formed in larger amount because it is formed faster. The product is said to be *kinetically controlled*. However, if the reactions are reversible, this will not necessarily be the case. If such a process is stopped well before the equilibrium has been established, the reaction will be kinetically controlled since more of the faster-formed product will be present.

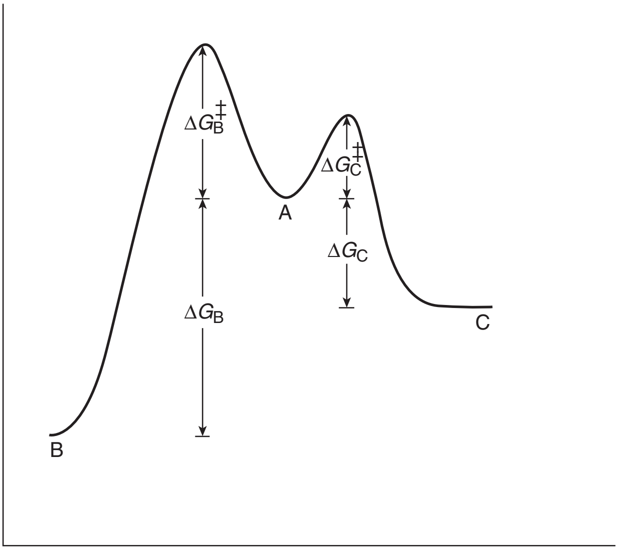


Fig. 6.3. Free-energy profile illustrating kinetic versus thermodynamic control of products. The starting compounds (**A**) can react to give either **B** or **C**.

However, if the reaction is permitted to approach equilibrium, the predominant or even exclusive product will be **B.** Under these conditions the **C** that is first formed reverts to **A**, while the more stable **B** does so much less. We say the product is *thermodynamically controlled.*[20] Of course, Fig. 6.3 does not describe all reactions in which a compound **A** can give two different products. In many cases the more stable product is also the one that is formed faster. In such cases, the product of kinetic control is also the product of thermodynamic control.

THE HAMMOND POSTULATE

Since transition states have zero lifetimes, it is impossible to observe them directly and information about their geometries must be obtained from inference. In some cases our inferences can be very strong. For example, in the S_N2 reaction (p. 426) between CH_3I and I^- (a reaction in which the product is identical to the starting compound), the transition state should be perfectly symmetrical. In most cases, however, we cannot reach such easy conclusions, and we are greatly aided by the *Hammond postulate*,[21] which states that for any single reaction step, *the geometry of the transition state for that step resembles the side to which it is closer*

[20]For a discussion of thermodynamic versus kinetic control, see Klumpp, G.W. *Reactivity in Organic Chemistry*, Wiley, NY, ***1982***, pp. 36–89.
[21]Hammond, G.S. *J. Am. Chem. Soc.* ***1955***, *77*, 334. For a discussion, see Fărcaşiu, D. *J. Chem. Educ.* ***1975***, *52*, 76.

in free energy. Thus, for an exothermic reaction like that shown in Fig. 6.1, the transition state resembles the reactants more than the products, although not much more because there is a substantial $\Delta G^{\ddagger}$ on both sides. The postulate is most useful in dealing with reactions with intermediates. In the reaction illustrated in Fig. 6.2*a*, the first transition state lies much closer in energy to the intermediate than to the reactants, and we can predict that the geometry of the transition state resembles that of the intermediate more than it does that of the reactants. Likewise, the second transition state also has a free energy much closer to that of the intermediate than to the products, so that both transition states resemble the intermediate more than they do the products or reactants. This is generally the case in reactions that involve very reactive intermediates. Since we usually know more about the structure of intermediates than of transition states, we often use our knowledge of intermediates to draw conclusions about the transition states (e.g., see pp. 479, 1019).

MICROSCOPIC REVERSIBILITY

In the course of a reaction, the nuclei and electrons assume positions that at each point correspond to the lowest free energies possible. If the reaction is reversible, these positions must be the same in the reverse process, too. This means that the forward and reverse reactions (run under the same conditions) must proceed by the same mechanism. This is called the *principle of microscopic reversibility*. For example, if in a reaction **A** → **B** there is an intermediate **C**, then **C** must also be an intermediate in the reaction **B** → **A**. This is a useful principle since it enables us to know the mechanism of reactions in which the equilibrium lies far over to one side. Reversible photochemical reactions are an exception, since a molecule that has been excited photochemically does not have to lose its energy in the same way (Chapter 7).

MARCUS THEORY

It is often useful to compare the reactivity of one compound with that of similar compounds. What we would like to do is to find out how a reaction coordinate (and in particular the transition state) changes when one reactant molecule is replaced by a similar molecule. Marcus theory is a method for doing this.[22]

In this theory, the activation energy $\Delta G^{\ddagger}$ is thought of as consisting of two parts.

1. An *intrinsic* free energy of activation, which would exist if the reactants and products had the same ΔG°.[23] This is a kinetic part, called the *intrinsic barrier* $\Delta G^{\ddagger}_{\text{int}}$
2. A thermodynamic part, which arises from the ΔG° for the reaction.

[22]For reviews, see Albery, W.J. *Annu. Rev. Phys. Chem.* ***1980***, *31*, 227; Kreevoy, M.M.; Truhlar, D.G., in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, ***1986***, pp. 13–95.

[23]The parameter ΔG° is the standard free energy; that is, ΔG at atmospheric pressure.

The Marcus equation says that the overall $\Delta G^{\ddagger}$ for a one-step reaction is[24]

$$\Delta G^{\ddagger} = \Delta G^{\ddagger}_{\text{int}} + \frac{1}{2}\Delta G^{\Delta} + \frac{(\Delta G^{\Delta})^2}{16(\Delta G^{\ddagger}_{\text{int}} - w^{\text{R}})}$$

where the term ΔG^{Δ} stands for

$$\Delta G^{\Delta} = \Delta G^{\circ} - w^{\text{R}} + w^{\text{P}}$$

w^{R}, a work term, is the free energy required to bring the reactants together and w^{P} is the work required to form the successor configuration from the products.

For a reaction of the type $\text{AX} + \text{B} \rightarrow \text{BX}$, the intrinsic barrier[25] $\Delta G^{\ddagger}_{\text{int}}$ is taken to be the average $\Delta G^{\ddagger}$ for the two symmetrical reactions

$$\text{AX} + \text{A} \longrightarrow \text{AX} + \text{A} \qquad \Delta G^{\ddagger}_{\text{A,A}}$$

$$\text{BX} + \text{B} \longrightarrow \text{BX} + \text{B} \qquad \Delta G^{\ddagger}_{\text{B,B}}$$

so that

$$\Delta G^{\ddagger}_{\text{int}} + \frac{1}{2}(\Delta G^{\ddagger}_{\text{A,A}} + \Delta G^{\ddagger}_{\text{B,B}})$$

One type of process that can successfully be treated by the Marcus equation is the S_N2 mechanism (p. 426)

$$\text{R—X} + \text{Y} \longrightarrow \text{R—Y} + \text{X}$$

When R is CH_3 the process is called *methyl transfer.*[26] For such reactions, the work terms w^{R} and w^{P} are assumed to be very small compared to ΔG°, and can be neglected, so that the Marcus equation simplifies to

$$\Delta G^{\ddagger} = \Delta G^{\ddagger}_{\text{int}} + \frac{1}{2}\Delta G^{\circ} + \frac{(\Delta G)^2}{16\Delta G^{\ddagger}_{\text{int}}}$$

The Marcus equation allows $\Delta G^{\ddagger}$ for $\text{RX} + \text{Y} \rightarrow \text{RY} + \text{X}$ to be calculated from the barriers of the two symmetrical reactions $\text{RX} + \text{X} \rightarrow \text{RX} + \text{X}$ and

[24]Albery, W.J.; Kreevoy, M.M. *Adv. Phys. Org. Chem.* ***1978**, 16*, 87, pp. 98–99.

[25]For discussions of intrinsic barriers, see Lee, I. *J. Chem. Soc. Perkin Trans. 2* ***1989***, 943, *Chem. Soc. Rev.* ***1990***, *19*, 133.

[26]For a review of Marcus theory applied to methyl transfer, see Albery, W.J.; Kreevoy, M.M. *Adv. Phys. Org. Chem.* ***1978***, *16*, 87. See also, Lee, I. *J. Chem. Soc., Perkin Trans. 2* ***1989***, 943; Lewis, E.S.; Kukes, S.; Slater, C.D. *J. Am. Chem. Soc.* ***1980***, *102*, 1619; Lewis, E.S.; Hu, D.D. *J. Am. Chem. Soc.* ***1984***, *106*, 3292; Lewis, E.S.; McLaughlin, M.L.; Douglas, T.A. *J. Am. Chem. Soc.* ***1985***, *107*, 6668; Lewis, E.S. *Bull. Soc. Chim. Fr.* ***1988***, 259.

RY + Y → RY + Y. The results of such calculations are generally in agreement with the Hammond postulate.

Marcus theory can be applied to any single-step process where something is transferred from one particle to another. It was originally derived for electron transfers,[27] and then extended to transfers of H^+ (see p. 372),

H^-,[28] and H•,[29] as well as methyl transfers.

METHODS OF DETERMINING MECHANISMS

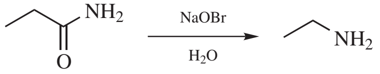
There are a number of commonly used methods for determining mechanisms.[30] In most cases, one method is not sufficient, and the problem is generally approached from several directions.

Identification of Products

Obviously, any mechanism proposed for a reaction must account for all the products obtained and for their relative proportions, including products formed by side reactions. Incorrect mechanisms for the von Richter reaction (reaction **13-30**) were accepted for many years because it was not realized that nitrogen was a major product. A proposed mechanism cannot be correct if it fails to predict the products in approximately the observed proportions. For example, any mechanism for the reaction

$$CH_4 + Cl_2 \xrightarrow{h\nu} CH_3Cl$$

that fails to account for the formation of a small amount of ethane cannot be correct (see **14-1**), and any mechanism proposed for the Hofmann rearrangement (**18-13**):



must account for the fact that the missing carbon appears as CO_2.

Determination of the Presence of an Intermediate

Intermediates are postulated in many mechanisms. There are several ways, none of them foolproof,[31] for attempting to learn whether or not an intermediate is present and, if so, its structure.

[27]Marcus, R.A. *J. Phys. Chem.* ***1963***, *67*, 853, *Annu. Rev. Phys. Chem.* ***1964***, *15*, 155; Eberson, L. *Electron Transfer Reactions in Organic Chemistry*; Springer: NY, ***1987***.

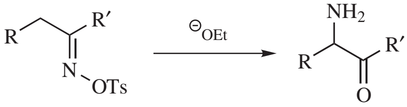
[28]Kim, D.; Lee, I.H.; Kreevoy, M.M. *J. Am. Chem. Soc.* ***1990***, *112*, 1889, and references cited therein.

[29]See, for example, Dneprovskii, A.S.; Eliseenkov, E.V. *J. Org. Chem. USSR* ***1988***, *24*, 243.

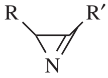
[30]For a treatise on this subject, see Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), 2 pts., Wiley, NY, ***1986***. For a monograph, see Carpenter, B.K. *Determination of Organic Reaction Mechanisms*, Wiley, NY, ***1984***.

[31]For a discussion, see Martin, R.B. *J. Chem. Educ.* ***1985***, *62*, 789.

1. *Isolation of an Intermediate*. It is sometimes possible to isolate an intermediate from a reaction mixture by stopping the reaction after a short time or by the use of very mild conditions. For example, in the Neber rearrangement (reaction **18-12**)

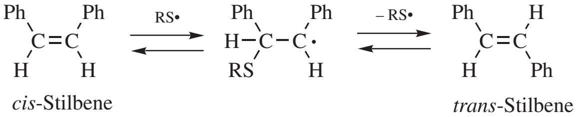


the intermediate **1** (an azirene)[32] has been isolated. If it can be shown that the isolated compound gives the same product when subjected to the reaction conditions and at a rate no slower than the starting compound, this constitutes strong evidence that the reaction involves that intermediate, although it is not conclusive, since the compound may arise by an alternate path and by coincidence give the same product.



1

2. *Detection of an intermediate*. In many cases, an intermediate cannot be isolated, but can be detected by IR, NMR, or other spectra.[33] The detection by Raman spectra of NO_2^+ was regarded as strong evidence that this is an intermediate in the nitration of benzene (see **11-2**). Free radical and triplet intermediates can often be detected by esr and by CIDNP (see Chapter 5). Free radicals (as well as radical ions and EDA complexes) can also be detected by a method that does not rely on spectra. In this method, a double-bond compound is added to the reaction mixture, and its fate traced.[34] One possible result is cis–trans conversion. For example, *cis*-stilbene is isomerized to the trans isomer in the presence of RS• radicals, by this mechanism:



Since the trans isomer is more stable than the cis, the reaction does not go the other way, and the detection of the isomerized product is evidence for the presence of the RS• radicals.

[32]See Gentilucci, L.; Grijzen, Y.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* ***1995***, *36*, 4665 for the synthesis of an azirene derivative.

[33]For a review on the use of electrochemical methods to detect intermediates, see Parker, V.D. *Adv. Phys. Org. Chem.* ***1983***, *19*, 131. For a review of the study of intermediates trapped in matrixes, see Sheridan, R.S. *Org. Photochem.* ***1987***, *8*, 159.

[34]For a review, see Todres, Z.V. *Tetrahedron* ***1987***, *43*, 3839.

3. *Trapping of an Intermediate.* In some cases, the suspected intermediate is known to be one that reacts in a given way with a certain compound. The intermediate can then be trapped by running the reaction in the presence of that compound. For example, benzynes (p. 859) react with dienes in the Diels–Alder reaction (reaction **15-60**). In any reaction where a benzyne is a suspected intermediate, the addition of a diene and the detection of the Diels–Alder adduct indicate that the benzyne was probably present.
4. *Addition of a Suspected Intermediate.* If a certain intermediate is suspected, and if it can be obtained by other means, then under the same reaction conditions it should give the same products. This kind of experiment can provide conclusive negative evidence: if the correct products are not obtained, the suspected compound is not an intermediate. However, if the correct products are obtained, this is not conclusive since they may arise by coincidence. The von Richter reaction (reaction **13-30**) provides us with a good example here too. For many years, it had been assumed that an aryl cyanide was an intermediate, since cyanides are easily hydrolyzed to carboxylic acids (**16-4**). In fact, in 1954, *p*-chlorobenzonitrile was shown to give *p*-chlorobenzoic acid under normal von Richter conditions.[35] However, when the experiment was repeated with 1-cyanonaphthalene, no 1-naphthoic acid was obtained, although 2-nitronaphthalene gave 13% 1-naphthoic acid under the same conditions.[36] This proved that 2-nitronaphthalene must have been converted to 1-naphthoic acid by a route that does not involve 1-cyanonaphthalene. It also showed that even the conclusion that *p*-chlorobenzonitrile was an intermediate in the conversion of *m*-nitrochlorobenzene to *p*-chlorobenzoic acid must now be suspect, since it is not likely that the mechanism would substantially change in going from the naphthalene to the benzene system.

The Study of Catalysis[37]

Much information about the mechanism of a reaction can be obtained from a knowledge of which substances catalyze the reaction, which inhibit it, and which do neither. Of course, just as a mechanism must be compatible with the products, so must it be compatible with its catalysts. In general, catalysts perform their actions by providing an alternate pathway for the reaction in which $\Delta G^{\ddagger}$ is less than it would be without the catalyst. Catalysts do not change ΔG.

[35]Bunnett, J.F.; Rauhut, M.M.; Knutson, D.; Bussell, G.E. *J. Am. Chem. Soc.* ***1954***, *76*, 5755.

[36]Bunnett, J.F.; Rauhut, M.M. *J. Org. Chem.* ***1956***, *21*, 944.

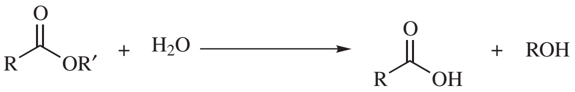
[37]For treatises, see Jencks, W.P. *Catalysis in Chemistry and Enzymology*, McGraw-Hill, NY, ***1969***; Bender, M.L. *Mechanisms of Homogeneous Catalysis from Protons to Proteins*, Wiley, NY, ***1971***. For reviews, see Coenen, J.W.E. *Recl. Trav. Chim. Pays-Bas* ***1983***, *102*, 57; and in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, ***1986***, the articles by Keeffe, J.R.; Kresge, A.J. pp. 747–790; Haller, G.L.; Delgass, W.N. pp. 951–979.

Isotopic Labeling[38]

Much useful information has been obtained by using molecules that have been isotopically labeled and tracing the path of the reaction in that way. For example, in the reaction

$$R\overset{*}{C}OO \ + \ BrCN \longrightarrow R\overset{*}{C}N$$

does the CN group in the product come from the CN in the BrCN? The use of ^{14}C supplied the answer, since $R^{14}CO_2^-$ gave *radioactive* RCN.[39] This surprising result saved a lot of labor, since it ruled out a mechanism involving the replacement of CO_2 by CN (see reaction **16-94**). Other radioactive isotopes are also frequently used as tracers, but even stable isotopes can be used. An example is the hydrolysis of esters



Which bond of the ester is broken, the acyl–O or the alkyl–O bond? The answer is found by the use of $H_2^{18}O$. If the acyl–O bond breaks, the labeled oxygen will appear in the acid; otherwise it will be in the alcohol (see **16-59**). Although neither compound is radioactive, the one that contains ^{18}O can be determined by submitting both to mass spectrometry. In a similar way, deuterium can be used as a label for hydrogen. In this case, it is not necessary to use mass spectrometry, since ir and nmr spectra can be used to determine when deuterium has been substituted for hydrogen. Carbon-13 NMR is also nonradioactive: It can be detected by ^{13}C NMR.[40]

In the labeling technique, it is not generally necessary to use completely labeled compounds. Partially labeled material is usually sufficient.

Stereochemical Evidence[41]

If the products of a reaction are capable of existing in more than one stereoisomeric form, the form that is obtained may give information about the mechanism. For example, (+)-malic acid was discovered by Walden[42] to give (−)-chlorosuccinic acid when treated with PCl_5 and the (+) enantiomer when treated with $SOCl_2$,

[38]For reviews see Wentrup, C., in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, ***1986***, pp. 613–661; Collins, C.J. *Adv. Phys. Org. Chem.* ***1964***, *2*, 3. See also, the series *Isotopes in Organic Chemistry.*

[39]Douglas, D.E.; Burditt, A.M. *Can. J. Chem.* ***1958***, *36*, 1256.

[40]For a review, see Hinton, J.; Oka, M.; Fry, A. *Isot. Org. Chem.* ***1977***, *3*, 41.

[41]For lengthy treatments of the relationship between stereochemistry and mechanism, see Billups, W.E.; Houk, K.N.; Stevens, R.V., in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, ***1986***, pp. 663–746; Eliel, E.L. *Stereochemistry of Carbon Compounds*; McGraw-Hill: NY, ***1962***; Newman, M.S. *Steric Effects in Organic Chemistry*, Wiley, NY, ***1956***.

[42]Walden, P. *Ber.* ***1896***, *29*, 136; ***1897***, *30*, 3149; ***1899***, *32*, 1833.

showing that the mechanisms of these apparently similar conversions could not be the same (see pp. 427, 469). Much useful information has been obtained about nucleophilic substitution, elimination, rearrangement, and addition reactions from this type of experiment. The isomers involved need not be enantiomers. Thus, the fact that *cis*-2-butene treated with $KMnO_4$ gives *meso*-2,3-butanediol and not the racemic mixture is evidence that the two OH groups attack the double bond from the same side (see reaction **15-48**).

Kinetic Evidence[43]

The rate of a homogeneous reaction[44] is the rate of disappearance of a reactant or appearance of a product. The rate nearly always changes with time, since it is usually proportional to concentration and the concentration of reactants decreases with time. However, the rate is not always proportional to the concentration of all reactants. In some cases, a change in the concentration of a reactant produces no change at all in the rate, while in other cases the rate may be proportional to the concentration of a substance (a catalyst) that does not even appear in the stoichiometric equation. A study of which reactants affect the rate often tells a good deal about the mechanism.

If the rate is proportional to the change in concentration of only one reactant (**A**), the *rate law* (the rate of change of concentration of **A** with time *t*) is

$$\text{Rate} = \frac{-d[\mathbf{A}]}{dt} = k[\mathbf{A}]$$

where *k* is the *rate constant* for the reaction.[45] There is a minus sign because the concentration of **A** decreases with time. A reaction that follows such a rate law is called a *first-order reaction*. The units of *k* for a first-order reaction are s^{-1}. The rate of a *second-order reaction* is proportional to the concentration of two reactants, or to the square of the concentration of one:

$$\text{Rate} = \frac{-d[\mathbf{A}]}{dt} = k[\mathbf{A}][\mathbf{B}] \qquad \text{or} \qquad \text{Rate} = \frac{-d[\mathbf{A}]}{dt} = k[\mathbf{A}]^2$$

For a second-order reaction the units are $L\ mol^{-1}\ s^{-1}$ or some other units expressing the reciprocal of concentration or pressure per unit time interval.

[43]For the use of kinetics in determining mechanisms, see Connors, K.A. *Chemical Kinetics*, VCH, NY, ***1990***; Zuman, P.; Patel, R.C. *Techniques in Organic Reaction Kinetics*, Wiley, NY, ***1984***; Drenth, W.; Kwart, H. *Kinetics Applied to Organic Reactions*, Marcel Dekker, NY, ***1980***; Hammett, L.P. *Physical Organic Chemistry*, 2nd ed.; McGraw-Hill: NY, ***1970***, pp. 53–100; Gardiner, Jr., W.C. *Rates and Mechanisms of Chemical Reactions*, W.A. Benjamin, NY, ***1969***; Leffler, J.E.; Grunwald, E. *Rates and Equilibria of Organic Reactions*, Wiley, NY, ***1963***; Jencks, W.P. *Catalysis in Chemistry and Enzymology*, McGraw-Hill, NY, ***1969***, pp. 555–614; Refs. 6 and 26

[44]A homogeneous reaction occurs in one phase. Heterogeneous kinetics have been studied much less.

[45]Colins, C.C.; Cronin, M.F.; Moynihan, H.A.; McCarthy, D.G. *J. Chem. Soc. Perkin Trans. 1* ***1997***, 1267 for the use of Marcus theory to predict rate constants in organic reactions.

Similar expressions can be written for third-order reactions. A reaction whose rate is proportional to [**A**] and to [**B**] is said to be first order in **A** and in **B**, second order overall. A reaction rate can be measured in terms of any reactant or product, but the rates so determined are not necessarily the same. For example, if the stoichiometry of a reaction is $2\mathbf{A} + \mathbf{B} \rightarrow \mathbf{C} + \mathbf{D}$ then, on a molar basis, **A** must disappear twice as fast as **B**, so that $-d[\mathbf{A}]/dt$ and $-d[\mathbf{B}]/dt$ are not equal, but the former is twice as large as the latter.

The rate law of a reaction is an experimentally determined fact. From this fact, we attempt to learn the *molecularity*, which may be defined as the number of molecules that come together to form the activated complex. It is obvious that if we know how many (and which) molecules take part in the activated complex, we know a good deal about the mechanism. The experimentally determined rate order is not necessarily the same as the molecularity. Any reaction, no matter how many steps are involved, has only one rate law, but each step of the mechanism has its own molecularity. For reactions that take place in one step (reactions without an intermediate) the order is the same as the molecularity. A first-order, one-step reaction is always unimolecular; a one-step reaction that is second order in **A** always involves two molecules of **A**; if it is first order in **A** and in **B**, then a molecule of **A** reacts with one of **B**, and so on. For reactions that take place in more than one step, the order *for each step* is the same as the molecularity *for that step*. This fact enables us to predict the rate law for any proposed mechanism, although the calculations may get lengthy at times.[46] If any one step of a mechanism is considerably slower than all the others (this is usually the case), the rate of the overall reaction is essentially the same as that of the slow step, which is consequently called the *rate-determining* step.[47]

For reactions that take place in two or more steps, two broad cases can be distinguished:

1. The first step is slower than any subsequent step and is consequently rate determining. In such cases, the rate law simply includes the reactants that participate in the slow step. For example, if the reaction $\mathbf{A} + 2\mathbf{B} \rightarrow \mathbf{C}$ has the mechanism

$$\mathbf{A} + \mathbf{B} \xrightarrow{\text{slow}} \mathbf{I}$$

$$\mathbf{I} + \mathbf{B} \xrightarrow{\text{fast}} \mathbf{C}$$

where I is an intermediate, the reaction is second order, with the rate law

$$\text{Rate} = \frac{-d[\mathbf{A}]}{dt} = k[\mathbf{A}][\mathbf{B}]$$

[46]For a discussion of how order is related to molecularity in many complex situations, see Szabó, Z.G. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 2; Elsevier: NY, ***1969***, pp. 1–80.

[47]Many chemists prefer to use the term *rate-limiting step or rate-controlling step* for the slow step, rather than *rate-determining step*. See the definitions, in Gold, V.; Loening, K.L.; McNaught, A.D.; Sehmi, P. *IUPAC Compedium of Chemical Terminology;* Blackwell Scientific Publications: Oxford, ***1987***, p. 337. For a discussion of rate-determining steps, see Laidler, K.J. *J. Chem. Educ.* ***1988***, *65*, 250.

2. When the first step is not rate determining, determination of the rate law is usually much more complicated. For example, consider the mechanism

$$\mathbf{A} + \mathbf{B} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{I}$$

$$\mathbf{I} + \mathbf{B} \xrightarrow{k_2} \mathbf{C}$$

where the first step is a rapid attainment of equilibrium, followed by a slow reaction to give **C**. The rate of disappearance of **A** is

$$\text{Rate} = \frac{-d[\mathbf{A}]}{dt} = k_1[\mathbf{A}][\mathbf{B}] - k_{-1}[\mathbf{I}]$$

Both terms must be included because **A** is being formed by the reverse reaction as well as being used up by the forward reaction. This equation is of very little help as it stands since we cannot measure the concentration of the intermediate. However, the combined rate law for the formation and disappearance of **I** is

$$\text{Rate} = \frac{-d[\mathbf{A}]}{dt} = k_1[\mathbf{A}][\mathbf{B}] - k_{-1}[\mathbf{I}] - k_2[\mathbf{I}][\mathbf{B}]$$

At first glance, we seem no better off with this equation, but we can make the assumption that *the concentration of **I** does not change with time*, since it is an intermediate that is used up (going either to **A** + **B** or to **C**) as fast as it is formed. This assumption, called the assumption of the *steady state*,[48] enables us to set $d[\mathbf{I}]/dt$ equal to zero and hence to solve for [**I**] in terms of the measurable quantities [**A**] and [**B**]:

$$[\mathbf{I}] = \frac{k_1[\mathbf{A}][\mathbf{B}]}{k_2[\mathbf{B}] + k_{-1}}$$

We now insert this value for [**I**] into the original rate expression to obtain

$$\frac{-d[\mathbf{A}]}{dt} = \frac{k_1 k_2[\mathbf{A}][\mathbf{B}]^2}{k_2[\mathbf{B}] + k_{-1}}$$

Note that this rate law is valid whatever the values of k_1, k_{-1}, and k_2. However, our original hypothesis was that the first step was faster than the second, or that

$$k_1[\mathbf{A}][\mathbf{B}] \gg k_2[\mathbf{I}][\mathbf{B}]$$

[48]For a discussion, see Raines, R.T.; Hansen, D.E. *J. Chem. Educ.* ***1988***, *65*, 757.

Since the first step is an equilibrium

$$k_1[\mathbf{A}][\mathbf{B}] = k_{-1}[\mathbf{I}]$$

we have

$$k_{-1}[\mathbf{I}] \gg k_2[\mathbf{I}][\mathbf{B}]$$

Canceling [**I**], we get

$$k_{-1} \gg k_2[\mathbf{B}]$$

We may thus neglect k_2[**B**] in comparison with k_{-1} and obtain

$$\frac{-d[\mathbf{A}]}{dt} = \frac{k_1 k_2}{k_{-1}}[\mathbf{A}][\mathbf{B}]^2$$

The overall rate is thus third order: first order in **A** and second order in **B**. Incidentally, if the first step is rate determining (as was the case in the preceding paragraph), then

$$k_2[\mathbf{B}] \gg k_{-1} \qquad \text{and} \qquad \frac{-d[\mathbf{A}]}{dt} = k_1[\mathbf{A}][\mathbf{B}]$$

which is the same rate law we deduced from the rule that where the first step is rate determining, the rate law includes the reactants that participate in that step.

It is possible for a reaction to involve **A** and **B** in the rate-determining step, although only [**A**] appears in the rate law. This occurs when a large excess of **B** is present, say 100 times the molar quantity of **A**. In this case, the complete reaction of **A** uses up only 1 equivalent of **B**, leaving 99 equivalents. It is not easy to measure the change in concentration of **B** with time in such a case, and it is seldom attempted, especially when **B** is also the solvent. Since [**B**], for practical purposes, does not change with time, the reaction appears to be first order in **A** although actually both **A** and **B** are involved in the rate-determining step. This is often referred to as a *pseudo-first-order* reaction. Pseudo-order reactions can also come about when one reactant is a catalyst whose concentration does not change with time because it is replenished as fast as it is used up and when a reaction is conducted in a medium that keeps the concentration of a reactant constant, for example, in a buffer solution where H^+ or ^-OH is a reactant. Pseudo-first-order conditions are frequently used in kinetic investigations for convenience in experimentation and calculations.

What is actually being measured is the change in concentration of a product or a reactant with time. Many methods have been used to make such measurements.[49]

[49]For a monograph on methods of interpreting kinetic data, see Zuman, P.; Patel, R.C. *Techniques in Organic Reaction Kinetics*, Wiley, NY, ***1984***. For a review of methods of obtaining kinetic data, see Batt, L. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics,* Vol. 1, Elsevier, NY, ***1969***, pp. 1–111.

The choice of a method depends on its convenience and its applicability to the reaction being studied. Among the most common methods are

1. *Periodic or Continuous Spectral Readings.* In many cases, the reaction can be carried out in the cell while it is in the instrument. Then all that is necessary is that the instrument be read, periodically or continuously. Among the methods used are ir and uv spectroscopy, polarimetry, nmr, and esr.[50]
2. *Quenching and Analyzing.* A series of reactions can be set up and each stopped in some way (perhaps by suddenly lowering the temperature or adding an inhibitor) after a different amount of time has elapsed. The materials are then analyzed by spectral readings, titrations, chromatography, polarimetry, or any other method.
3. *Removal of Aliquots at Intervals.* Each aliquot is then analyzed as in method 2.
4. *Measurement of Changes in Total Pressure, for Gas-Phase Reactions.*[51]
5. *Calorimetric Methods.* The output or absorption of heat can be measured at time intervals.

Special methods exist for kinetic measurements of very fast reactions.[52]

In any case, what is usually obtained is a graph showing how a concentration varies with time. This must be interpreted[53] to obtain a rate law and a value of k. If a reaction obeys simple first- or second-order kinetics, the interpretation is generally not difficult. For example, if the concentration at the start is $\mathbf{A}_0$, the first-order rate law

$$\frac{-d[\mathbf{A}]}{dt} = k[\mathbf{A}] \qquad \text{or} \qquad \frac{-d[\mathbf{A}]}{[\mathbf{A}]} = kdt$$

[50]For a review of esr to measure kinetics, see Norman, R.O.C. *Chem. Soc. Rev.* ***1979***, *8*, 1.

[51]For a review of the kinetics of reactions in solution at high pressures, see le Noble, W.J. *Prog. Phys. Org. Chem.* ***1967***, *5*, 207. For reviews of synthetic reactions under high pressure, see Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* ***1985***, 1; Matsumoto, K.; Sera, A. *Synthesis* ***1985***, 999.

[52]For reviews, see Connors, K.A. *Chemical Kinetics*, VCH, NY, ***1990***, pp. 133–186; Zuman, P.; Patel, R.C. *Techniques in Organic Reaction Kinetics*, Wiley, NY, ***1984***, pp. 247–327; Krüger, H. *Chem. Soc. Rev.* ***1982***, *11*, 227; Hague, D.N. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 1, Elsevier, NY, ***1969***, pp. 112–179, Elsevier, NY, ***1969***; Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 2, Wiley, NY, ***1986***,. See also, Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 24, Elsevier, NY, ***1983***.

[53]For discussions, much fuller than that given here, of methods for interpreting kinetic data, see Connors, K.A. *Chemical Kinetics*, VCH, NY, ***1990***, pp. 17–131; Ritchie, C.D. *Physical Organic Chemistry*, 2nd ed., Marcel Dekker, NY, ***1990***, pp. 1–35; Zuman, P.; Patel, R.C. *Techniques in Organic Reaction Kinetics,* Wiley, NY, ***1984***; Margerison, D., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 1, Elsevier, NY, ***1969***, pp. 343–421; Moore, J.W.; Pearson, R.G. *Kinetics and Mechanism*, 3rd ed., Wiley, NY, ***1981***, pp. 12–82; in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, ***1986***, the articles by Bunnett, J.F. pp. 251–372, Noyes Pub., pp. 373–423, Bernasconi, C.F. pp. 425–485, Wiberg, K.B. pp. 981–1019.

can be integrated between the limits $t = 0$ and $t = t$ to give

$$-\ln\frac{[\mathbf{A}]}{\mathbf{A}_0} = kt \qquad \text{or} \qquad \ln[\mathbf{A}] = -kt + \ln \mathbf{A}_0$$

Therefore, if a plot of ln [**A**] against t is linear, the reaction is first order and k can be obtained from the slope. For first-order reactions, it is customary to express the rate not only by the rate constant k, but also by the *half-life*, which is the time required for one-half of any given quantity of a reactant to be used up. Since the half-life $t_{1/2}$ is the time required for [**A**] to reach $\mathbf{A}_0/2$, we may say that

$$\ln\frac{\mathbf{A}_0}{2} = kt_{1/2} + \ln \mathbf{A}_0$$

so that

$$t_{1/2} = \frac{\ln\left[\frac{\mathbf{A}_0}{\mathbf{A}_0/2}\right]}{k} = \frac{\ln 2}{k} = \frac{0.693}{k}$$

For the general case of a reaction first order in **A** and first order in **B**, second order overall, integration is complicated, but it can be simplified if equimolar amounts of **A** and **B** are used, so that $\mathbf{A}_0 = \mathbf{B}_0$. In this case,

$$\frac{-d[\mathbf{A}]}{dt} = k[\mathbf{A}][\mathbf{B}]$$

is equivalent to

$$\frac{-d[\mathbf{A}]}{dt} = k[\mathbf{A}]^2 \qquad \text{or} \qquad \frac{-d[\mathbf{A}]}{[\mathbf{A}]^2} = k\,dt$$

Integrating as before gives

$$\frac{1}{[\mathbf{A}]} - \frac{1}{\mathbf{A}_0} = kt$$

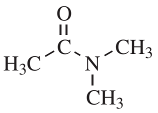
Thus, under equimolar conditions, if a plot of 1/[**A**] against t is linear, the reaction is second order with a slope of k. It is obvious that the same will hold true for a reaction second order in **A**.[54]

Although many reaction-rate studies do give linear plots, which can therefore be easily interpreted, the results in many other studies are not so simple. In some cases, a reaction may be first order at low concentrations but second order at higher concentrations. In other cases, fractional orders are obtained, and even negative orders. The interpretation of complex kinetics often requires much skill and effort. Even where the kinetics are relatively simple, there is often a problem in interpreting the data because of the difficulty of obtaining precise enough measurements.[55]

[54]We have given the integrated equations for simple first- and second-order kinetics. For integrated equations for a large number of kinetic types, see Margerison, D., in Bamford, C.H.; Tipper C.F.H. *Comprehensive Chemical Kinetics,* Vol. 1, Elsevier, NY, ***1969***, p. 361.

[55]See, Hammett, L.P. *Physical Organic Chemistry,* 2nd ed., McGraw-Hill, NY, ***1970***, pp. 62–70.

Nuclear magnetic resonance spectra can be used to obtain kinetic information in a completely different manner from that mentioned on p. 319. This method, which involves the study of NMR line shapes,[56] depends on the fact that NMR spectra have an inherent time factor: If a proton changes its environment less rapidly than $\sim 10^3$ times/s, an NMR spectrum shows a separate peak for each position the proton assumes. For example, if the rate of rotation around



the C—N bond of *N,N*-dimethylacetamide is slower than 10^3 rotations per second, the two *N*-methyl groups each have separate chemical shifts since they are not equivalent, one being cis to the oxygen and the other trans. However, if the environmental change takes place more rapidly than $\sim 10^3$ times per second, only one line is found, at a chemical shift that is the weighted average of the two individual positions. In many cases, two or more lines are found at low temperatures, but as the temperature is increased, the lines coalesce because the interconversion rate increases with temperature and passes the 10^3 per second mark. From studies of the way line shapes change with temperature it is often possible to calculate rates of reactions and of conformational changes. This method is not limited to changes in proton line shapes but can also be used for other atoms that give nmr spectra and for esr spectra.

Several types of mechanistic information can be obtained from kinetic studies.

1. From the order of a reaction, information can be obtained about which molecules and how many take part in the rate-determining step. Such knowledge is very useful and often essential in elucidating a mechanism. For any mechanism that can be proposed for a given reaction, a corresponding rate law can be calculated by the methods discussed on pp. 316–320. If the experimentally obtained rate law fails to agree with this, the proposed mechanism is wrong. However, it is often difficult to relate the order of a reaction to the mechanism, especially when the order is fractional or negative. In addition, it is frequently the case that two or more proposed mechanisms for a reaction are kinetically indistinguishable, that is, they predict the same rate law.
2. Probably the most useful data obtained kinetically are the rate constants themselves. They are important since they can tell us the effect on the rate of

[56]For a monograph, see Ōki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, ***1985***. For reviews, see Fraenkel, G., in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 2, Wiley, NY, ***1986***, pp. 547–604; Aganov, A.V.; Klochkov, V.V.; Samitov, Yu.Yu. *Russ. Chem. Rev.* ***1985***, *54*, 931; Roberts, J.D. *Pure Appl. Chem.* ***1979***, *51*, 1037; Binsch, G. *Top. Stereochem.* ***1968***, *3*, 97; Johnson Jr., C.S. *Adv. Magn. Reson.* ***1965***, *1*, 33.

a reaction of changes in the structure of the reactants (see Chapter 9), the solvent, the ionic strength, the addition of catalysts, and so on.

3. If the rate is measured at several temperatures, in most cases a plot of ln k against $1/T$ (T stands for absolute temperature) is nearly linear[57] with a negative slope, and fits the equation

$$\ln k = \frac{-E_a}{RT} + \ln A$$

where R is the gas constant and A is a constant called the *frequency factor.* This permits the calculation of E_a, which is the Arrhenius activation energy of the reaction. The parameter $\Delta H^{\ddagger}$ can then be obtained by

$$E_a = \Delta H^{\ddagger} + RT$$

It is also possible to use these data to calculate $\Delta S^{\ddagger}$ by the formula[58]

$$\frac{\Delta S^{\ddagger}}{4.576} = \log k - 10.753 - \log T + \frac{E_a}{4.576T}$$

for energies in calorie units. For joule units the formula is

$$\frac{\Delta S^{\ddagger}}{19.15} = \log k - 10.753 - \log T + \frac{E_a}{19.15T}$$

One then obtains $\Delta G^{\ddagger}$ from $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$.

Isotope Effects

When a hydrogen in a reactant molecule is replaced by deuterium, there is often a change in the rate. Such changes are known as *deuterium isotope effects*[59] and are

[57]For a review of cases where such a plot is nonlinear, see Blandamer, M.J.; Burgess, J.; Robertson, R.E.; Scott, J.M.W. *Chem. Rev.* ***1982***, *82*, 259.

[58]For a derivation of this equation, see Bunnett, J.F., in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, ***1986***, p. 287.

[59]For a monograph, see Melander, L.; Saunders, Jr., W.H. *Reaction Rates of Isotopic Molecules*, Wiley, NY, ***1980***. For reviews, see Isaacs, N.S. *Physical Organic Chemistry*, Longman Scientific and Technical, Essex, ***1987***, pp. 255–281; Lewis, E.S. *Top. Curr. Chem.* ***1978***, *74*, 31; Saunders, Jr., W.H. in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, ***1986***, pp. 565–611; Bell, R.P. *The Proton in Chemistry*, 2nd ed.; Cornell University Press: Ithaca, NY, ***1973***, pp. 226–296, *Chem. Soc. Rev.* ***1974***, *3*, 513; Bigeleisen, J.; Lee, M.W.; Mandel, F. *Annu. Rev. Phys. Chem.* ***1973***, *24*, 407; Wolfsberg, M. *Annu. Rev. Phys. Chem.* ***1969***, *20*, 449; Saunders, Jr., W.H. *Surv. Prog. Chem.* ***1966***, *3*, 109; Simon, H.; Palm, D. *Angew. Chem. Int. Ed.* ***1966***, *5*, 920; Jencks, W.P. *Catalysis in Chemistry and Enzymology*, McGraw-Hill, NY, ***1969***, pp. 243–281. For a review of temperature dependence of primary isotope effects as a mechanistic criterion, see Kwart, H. *Acc. Chem. Res.* ***1982***, *15*, 401. For a review of the effect of pressure on isotope effects, see Isaacs, E.S. *Isot. Org. Chem.* ***1984***, *6*, 67. For a review of isotope effects in the study of reactions in which there is branching from a common intermediate, see Thibblin, A.; Ahlberg, P. *Chem. Soc. Rev.* ***1989***, *18*, 209. See also, the series *Isotopes in Organic Chemistry.*

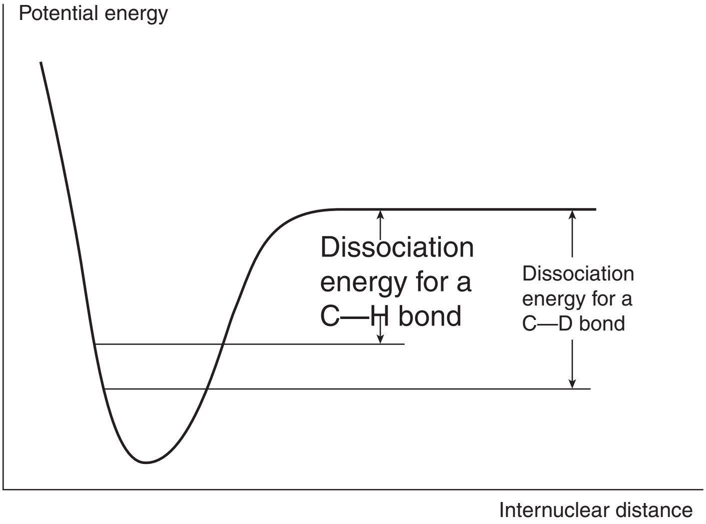


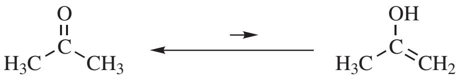
Fig. 6.4. A C—D bond has a lower zero point than does a corresponding C—H bond; thus the dissociation energy is higher.

expressed by the ratio k_H/k_D. The ground-state vibrational energy (called the zero-point vibrational energy) of a bond depends on the mass of the atoms and is lower when the reduced mass is higher.[60] Therefore, D—C, D—O, D—N bonds, and so on, have lower energies in the ground state than the corresponding H—C, H—O, H—N bonds, and so on. Complete dissociation of a deuterium bond consequently requires more energy than that for a corresponding hydrogen bond in the same environment (Fig. 6.4). If an H—C, H—O, or H—N bond is not broken at all in a reaction or is broken in a nonrate-determining step, substitution of deuterium for hydrogen causes no change in the rate (see below for an exception to this statement), but if the bond is broken in the rate-determining step, the rate must be lowered by the substitution.

This provides a valuable diagnostic tool for determination of mechanism. For example, in the bromination of acetone (reaction **12-4**)

$$CH_3COCH_3 + Br_2 \longrightarrow CH_3COCH_2Br$$

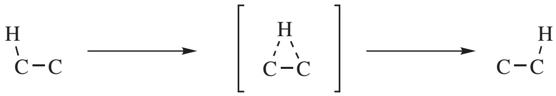
the fact that the rate is independent of the bromine concentration led to the postulate that the rate-determining step was prior tautomerization of the acetone:



In turn, the rate-determining step of the tautomerization involves cleavage of a C—H bond (see **12-3**). Thus there should be a substantial isotope effect if deuterated

[60]The reduced mass μ of two atoms connected by a covalent bond is $\mu = m_1m_2/(m_1 + m_2)$.

acetone is brominated. In fact, k_H/k_D was found to be $\sim$7.[61] Deuterium isotope effects usually range from 1 (no isotope effect at all) to $\sim$7 or 8, although in a few cases, larger[62] or smaller values have been reported.[63] Values of $k_H/k_D < 1$ are called *inverse isotope effects*. Isotope effects are greatest when, in the transition state, the hydrogen is symmetrically bonded to the atoms between which it is being transferred.[64] Also, calculations show that isotope effects are at a maximum when the hydrogen in the transition state is on the straight line connecting the two atoms between which the hydrogen is being transferred and that for sufficiently nonlinear configurations they decrease to $k_H/k_D = 1$–2.[65] Of course, in open systems there is no reason for the transition state to be nonlinear, but this is not the case in many intramolecular mechanisms, for example, in a 1,2 migration of a hydrogen



Transition state

To measure isotope effects it is not always necessary to prepare deuterium-enriched starting compounds. It can also be done by measuring the change in deuterium concentration at specific sites between a compound containing deuterium in natural abundance and the reaction product, using a high-field NMR instrument.[66]

The substitution of tritium for hydrogen gives isotope effects that are numerically larger. Isotope effects have also been observed with other elements, but they are much smaller, $\sim$1.02–1.10. For example, $k_{^{12}C}/k_{^{13}C}$ for

$$\text{Ph*CH}_2\text{Br} + \text{CH}_3\text{O}^{\ominus} \xrightarrow{\text{CH}_3\text{OH}} \text{Ph*CH}_2\text{OCH}_3$$

[61]Reitz, O.; Kopp, J. *Z. Phys. Chem. Abt. A* ***1939***, *184*, 429.

[62]For an example of a reaction with a deuterium isotope effect of 24.2, see Lewis, E.S.; Funderburk, L.H. *J. Am. Chem. Soc.* ***1967***, *89*, 2322. The high isotope effect in this case has been ascribed to *tunneling* of the proton: because it is so small a hydrogen atom can sometimes get through a thin potential barrier without going over the top, that is, without obtaining the usually necessary activation energy. A deuterium, with a larger mass, is less able to do this. The phenomenon of tunneling is a consequence of the uncertainty principle. k_H/k_D for the same reaction is 79: Lewis, E.S.; Robinson, J.K. *J. Am. Chem. Soc.* ***1968***, *90*, 4337. An even larger deuterium isotope effect ($\sim$50) has been reported for the oxidation of benzyl alcohol. This has also been ascribed to tunneling: Roecker, L.; Meyer, T.J. *J. Am. Chem. Soc.* ***1987***, *109*, 746. For discussions of high isotope effects, see Kresge, A.J.; Powell, M.F. *J. Am. Chem. Soc.* ***1981***, *103*, 201; Caldin, E.F.; Mateo, S.; Warrick, P. *J. Am. Chem. Soc.* ***1981***, *103*, 202. For arguments that high isotope effects can be caused by factors other than tunneling, see McLennan, D.J. *Aust. J. Chem.* ***1979***, *32*, 1883; Thibblin, A. *J. Phys. Org. Chem.* ***1988***, *1*, 161; Kresge, A.J.; Powell, M.F. *J. Phys. Org. Chem.* ***1990***, *3*, 55.

[63]For a review of a method for calculating the magnitude of isotope effects, see Sims, L.B.; Lewis, D.E. *Isot. Org. Chem.* ***1984***, *6*, 161.

[64]Kwart, H.; Latimore, M.C. *J. Am. Chem. Soc.* ***1971***, *93*, 3770; Pryor, W.A.; Kneipp, K.G. *J. Am. Chem. Soc.* ***1971***, *93*, 5584; Bell, R.P.; Cox, B.G. *J. Chem. Soc. B* ***1971***, 783; Bethell, D.; Hare, G.J.; Kearney, P.A. *J. Chem. Soc. Perkin Trans. 2* ***1981***, 684, and references cited therein. See, however, Motell, E.L.; Boone, A.W.; Fink, W.H. *Tetrahedron* ***1978***, *34*, 1619.

[65]More O'Ferrall, R.A. *J. Chem. Soc. B* ***1970***, 785, and references cited therein.

[66]Pascal, R.A.; Baum, M.W.; Wagner, C.K.; Rodgers, L.R.; Huang, D. *J. Am. Chem. Soc.* ***1986***, *108*, 6477.

is 1.053.[67] Although they are small, heavy-atom isotope effects can be measured quite accurately and are often very useful.[68]

Deuterium isotope effects have been found even where it is certain that the C—H bond does not break at all in the reaction. Such effects are called *secondary isotope effects*,[69] the term *primary isotope effect* being reserved for the type discussed previously. Secondary isotope effects can be divided into α and β effects. In a β secondary isotope effect, substitution of deuterium for hydrogen β to the position of bond breaking slows the reaction. An example is solvolysis of isopropyl bromide:

$$(CH_3)_2CHBr + H_2O \xrightarrow{k_H} (CH_3)_2CHOH$$

$$(CD_3)_2CHBr + H_2O \xrightarrow{k_D} (CD_3)_2CHOH$$

where k_H/k_D was found to be 1.34.[70] The cause of β isotope effects has been a matter of much controversy, but they are most likely due to hyperconjugation effects in the transition state. The effects are greatest when the transition state has considerable carbocation character.[71] Although the C—H bond in question is not broken in the transition state, the carbocation is stabilized by hyperconjugation involving this bond. Because of hyperconjugation, the difference in vibrational energy between the C—H bond and the C—D bond in the transition state is less than it is in the ground state, so the reaction is slowed by substitution of deuterium for hydrogen.

Support for hyperconjugation as the major cause of β isotope effects is the fact that the effect is greatest when D is anti to the leaving group[72] (because of the requirement that all atoms in a resonance system be coplanar, planarity of the D—C—C—X system would most greatly increase the hyperconjugation), and the fact that secondary isotope effects can be transmitted through unsaturated systems.[73] There is evidence that at least some β isotope effects are steric in

[67]Stothers, J.B.; Bourns, A.N. *Can. J. Chem.* ***1962***, *40*, 2007. See also, Ando, T.; Yamataka, H.; Tamura, S.; Hanafusa, T. *J. Am. Chem. Soc.* ***1982***, *104*, 5493.

[68]For a review of carbon isotope effects, see Willi, A.V. *Isot. Org. Chem.* ***1977***, *3*, 237.

[69]For reviews, see Westaway, K.C. *Isot. Org. Chem.* ***1987***, *7*, 275; Sunko, D.E.; Hehre, W.J. *Prog. Phys. Org. Chem.* ***1983***, *14*, 205; Shiner, Jr., V.J., in Collins, C.J.; Bowman, N.S. *Isotope Effects in Chemical Reactions*, Van Nostrand-Reinhold, Princeton, NJ, ***1970***, pp. 90–159; Laszlo, P.; Welvart, Z. *Bull. Soc. Chim. Fr.* ***1966***, 2412; Halevi, E.A. *Prog. Phys. Org. Chem.* ***1963***, *1*, 109. For a review of model calculations of secondary isotope effects, see McLennan, D.J. *Isot. Org. Chem.* ***1987***, *7*, 393. See also, Sims, L.B.; Lewis, D.E. *Isot. Org. Chem.* ***1984***, *6*, 161.

[70]Leffek, K.T.; Llewellyn, J.A.; Robertson, R.E. *Can. J. Chem.* ***1960***, *38*, 2171.

[71]Bender, M.L.; Feng, M.S. *J. Am. Chem. Soc.* ***1960***, *82*, 6318; Jones, J.M.; Bender, M.L. *J. Am. Chem. Soc.* ***1960***, *82*, 6322.

[72]Shiner, Jr., V.J.; Jewett, J.G. *J. Am. Chem. Soc.* ***1964***, *86*, 945; DeFrees, D.J.; Hehre, W.J.; Sunko, D.E. *J. Am. Chem. Soc.* ***1979***, *101*, 2323. See also, Siehl, H.; Walter, H. *J. Chem. Soc. Chem. Commun.* ***1985***, 76.

[73]Shiner, Jr., V.J.; Kriz, Jr., G.S. *J. Am. Chem. Soc.* ***1964***, *86*, 2643.

origin[74] (e.g., a CD_3 group has a smaller steric requirement than a CH_3 group) and a field-effect explanation has also been suggested (CD_3 is apparently a better electron donor than CH_3[75]), but hyperconjugation is the most probable cause in most instances.[76] Part of the difficulty in attempting to explain these effects is their small size, ranging only as high as ~1.5.[77] Another complicating factor is that they can change with temperature. In one case,[78] k_H/k_D was 1.00 ± 0.01 at 0°C, 0.90 ± 0.01 at 25°C, and 1.15 ± 0.09 at 65°C. Whatever the cause, there seems to be a good correlation between β secondary isotope effects and carbocation character in the transition state, and they are thus a useful tool for probing mechanisms.

The other type of secondary isotope effect results from a replacement of hydrogen by deuterium at the carbon containing the leaving group. These (called *secondary isotope effects*) are varied, with values so far reported[79] ranging from 0.87 to 1.26.[80] These effects are also correlated with carbocation character. Nucleophilic substitutions that do not proceed through carbocation intermediates (S_N2 reactions) have a isotope effects near unity.[81] Those that do involve carbocations (S_N1 reactions) have higher a isotope effects, which depend on the nature of the leaving group.[82] The accepted explanation for a isotope effects is that one of the bending C—H vibrations is affected by the substitution of D for H more or less strongly in the transition state than in the ground state.[83] Depending on the nature of the transition state, this may increase or decrease the rate of the reaction. The α isotope effects on S_N2 reactions can vary with concentration,[84] an

[74]Bartell, L.S. *J. Am. Chem. Soc.* ***1961***, *83*, 3567; Brown, H.C.; Azzaro, M.E.; Koelling, J.G.; McDonald, G.J. *J. Am. Chem. Soc.* ***1966***, *88*, 2520; Kaplan, E.D.; Thornton, E.R. *J. Am. Chem. Soc.* ***1967***, *89*, 6644; Carter, R.E.; Dahlgren, L. *Acta Chem. Scand.* ***1970***, *24*, 633; Leffek, K.T.; Matheson, A.F. *Can. J. Chem.* ***1971***, *49*, 439; Sherrod, S.A.; Boekelheide, V. *J. Am. Chem. Soc.* ***1972***, *94*, 5513.

[75]Halevi, E.A.; Nussim, M.; Ron, M. *J. Chem. Soc.* ***1963***, 866; Halevi, E.A.; Nussim, M. *J. Chem. Soc.* ***1963***, 876.

[76]Karabatsos, G.J.; Sonnichsen, G.; Papaioannou, C.G.; Scheppele, S.E.; Shone, R.L. *J. Am. Chem. Soc.* ***1967***, *89*, 463; Kresge, A.J.; Preto, R.J. *J. Am. Chem. Soc.* ***1967***, *89*, 5510; Jewett, J.G.; Dunlap, R.P. *J. Am. Chem. Soc.* ***1968***, *90*, 809; Sunko, D.E.; Szele, I.; Hehre, W.J. *J. Am. Chem. Soc.* ***1977***, *99*, 5000; Kluger, R.; Brandl, M. *J. Org. Chem.* ***1986***, *51*, 3964.

[77]Halevi, E.A.; Margolin, Z. *Proc. Chem. Soc.* ***1964***, 174. A value for k_{CH_3}/k_{CD_3} of 2.13 was reported for one case: Liu, K.; Wu, Y.W. *Tetrahedron Lett.* ***1986***, *27*, 3623.

[78]Halevi, E.A.; Margolin, Z. *Proc. Chem. Soc.* ***1964***, 174.

[79]A value of 2.0 has been reported in one case, for a cis–trans isomerization, rather than a nucleophilic substitution: Caldwell, R.A.; Misawa, H.; Healy, E.F.; Dewar, M.J.S. *J. Am. Chem. Soc.* ***1987***, *109*, 6869.

[80]Shiner, Jr., V.J.; Buddenbaum, W.E.; Murr, B.L.; Lamaty, G. *J. Am. Chem. Soc.* ***1968***, *90*, 418; Harris, J.M.; Hall, R.E.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1971***, *93*, 2551.

[81]For reported exceptions, see Tanaka, N.; Kaji, A.; Hayami, J. *Chem. Lett.* ***1972***, 1223; Westaway, K.C. *Tetrahedron Lett.* ***1975***, 4229.

[82]Willi, A.V.; Ho, C.; Ghanbarpour, A. *J. Org. Chem.* ***1972***, *37*, 1185; Shiner Jr., V.J.; Neumann, A.; Fisher, R.D. *J. Am. Chem. Soc.* ***1982***, *104*, 354; and references cited therein.

[83]Streitwieser, Jr., A.; Jagow, R.H.; Fahey, R.C.; Suzuki, S. *J. Am. Chem. Soc.* ***1958***, *80*, 2326.

[84]Westaway, K.C.; Waszczylo, Z.; Smith, P.J.; Rangappa, K.S. *Tetrahedron Lett.* ***1985***, *26*, 25.

effect attributed to a change from a free nucleophile to one that is part of an ion pair[85] (see p. 492). This illustrates the use of secondary isotope effects as a means of studying transition state structure. The γ secondary isotope effects have also been reported.[86]

Another kind of isotope effect is the *solvent isotope effect*.[87] Reaction rates often change when the solvent is changed from H_2O to D_2O or from ROH to ROD. These changes may be due to any of three factors or a combination of all of them.

1. The solvent may be a reactant. If an O—H bond of the solvent is broken in the rate-determining step, there will be a primary isotope effect. If the molecules involved are D_2O or D_3O^+ there may also be a secondary effect caused by the O—D bonds that are not breaking.
2. The substrate molecules may become labeled with deuterium by rapid hydrogen exchange, and then the newly labeled molecule may become cleaved in the rate-determining step.
3. The extent or nature of solvent–solute interactions may be different in the deuterated and nondeuterated solvents; this may change the energies of the transition state, and hence the activation energy of the reaction. These are secondary isotope effects. Two physical models for this third factor have been constructed.[88]

It is obvious that in many cases the first and third factors at least, and often the second, are working simultaneously. Attempts have been made to separate them.[89]

The methods described in this chapter are not the only means of determining mechanisms. In an attempt to elucidate a mechanism, the investigator is limited only by their ingenuity.

[85]Westaway, K.C.; Lai, Z. *Can. J. Chem.* ***1988***, *66*, 1263.

[86]Leffek, K.T.; Llewellyn, J.A.; Robertson, R.E. *J. Am. Chem. Soc.* ***1960***, *82*, 6315; *Chem. Ind. (London)* ***1960***, 588; Werstiuk, N.H.; Timmins, G.; Cappelli, F.P. *Can. J. Chem.* ***1980***, *58*, 1738.

[87]For reviews, see Alvarez, F.J.; Schowen, R.L. *Isot. Org. Chem.* ***1987***, *7*, 1; Kresge, A.J.; More O'Ferrall, R.A.; Powell, M.F. *Isot. Org. Chem.* ***1987***, *7*, 177; Schowen, R.L. *Prog. Phys. Org. Chem.* ***1972***, *9*, 275; Gold, V. *Adv. Phys. Org. Chem.* ***1969***, *7*, 259; Laughton, P.M.; Robertson, R.E., in Coetzee; Ritchie *Solute–Solvent Interactions*, Marcel Dekker, NY, ***1969***, pp. 399–538. For a review of the effect of isotopic changes in the solvent on the properties of nonreacting solutes, see Arnett, E.M.; McKelvey, D.R., in Coetzee, J.F.; Ritchie, C.D. cited above, pp. 343–398.

[88]Bunton, C.A.; Shiner, Jr., V.J. *J. Am. Chem. Soc.* ***1961***, *83*, 42, 3207, 3214; Swain, C.G.; Thornton, E.R. *J. Am. Chem. Soc.* ***1961***, *83*, 3884, 3890. See also, Mitton, C.G.; Gresser, M.; Schowen, R.L. *J. Am. Chem. Soc.* ***1969***, *91*, 2045.

[89]More O'Ferrall, R.A.; Koeppl, G.W.; Kresge, A.J. *J. Am. Chem. Soc.* ***1971***, *93*, 9.

CHAPTER 7

Irradiation Processes in Organic Chemistry

Most reactions carried out in organic chemistry laboratories take place between molecules all of which are in their ground electronic states. In a *photochemical reaction*,[1] however, a reacting molecule has been previously promoted by absorption of light to an electronically excited state. A molecule in an excited state must lose its extra energy in some manner; it cannot remain in the excited condition for long. The subject of electronic spectra is closely related to photochemistry. A chemical reaction is not the only possible means of relinquishing the extra energy in a photochemical process. In this chapter, first we discuss electronically excited states and the processes of promotion to these states. Two other methods are available to facilitate chemical reactions: sonochemistry and microwave chemistry. Although the physical processes involved are not necessarily the same excitation processes observed in photochemistry, irradiation with ultrasound or with microwaves have a significant influence on chemical reactivity. For that reason, they are included in this chapter.

[1]There are many books on photochemistry. Some recent ones are Michl, J.; Bonačić-Koutecký, V. *Electronic Aspects of Organic Photochemistry*, Wiley, NY, ***1990***; Scaiano, J.C. *Handbook of Organic Photochemistry*, 2 vols., CRC Press, Boca Raton, FL, ***1989***; Coxon, J.M.; Halton, B. *Organic Photochemistry*, 2nd ed.; Cambridge University Press: Cambridge, ***1987***; Coyle, J.D. *Photochemistry in Organic Synthesis*, Royal Society of Chemistry, London, ***1986***, *Introduction to Organic Photochemistry*, Wiley, NY, ***1986***; Horspool, W.M. *Synthetic Organic Photochemistry*, Plenum, NY, ***1984***; Margaretha, P. *Preparative Organic Photochemistry*, *Top. Curr. Chem.* ***1982***, *103*; Turro, N.J. *Modern Molecular Photochemistry*, W.A. Benjamin, NY, ***1978***; Rohatgi-Mukherjee. K.K. *Fundamentals of Photochemistry*, Wiley, NY, ***1978***; Barltrop, J.A.; Coyle, J.D. *Principles of Photochemistry*, Wiley, NY, ***1978***. For a comprehensive older treatise, see Calvert, J.G.; Pitts, Jr., J.N. *Photochemistry*, Wiley, NY, ***1966***. For a review of the photochemistry of radicals and carbenes, see Scaiano, J.; Johnston, L.J. *Org. Photochem.* ***1989***, *10*, 309. For a history of photochemistry, see Roth, H.D. *Angew. Chem. Int. Ed.* ***1989***, *28*, 1193. For a glossary of terms used in photochemistry, see Braslavsky, S.E.; Houk, K.N. *Pure Appl. Chem.* ***1988***, *60*, 1055. See also, the series, *Advances in Photochemistry*, *Organic Photochemistry*, and *Excited States*.

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PHOTOCHEMISTRY

Excited States and the Ground State

Electrons can move from the ground-state energy level of a molecule to a higher level (i.e., an unoccupied orbital of higher energy) if outside energy is supplied. In a photochemical process, this energy is in the form of light. Light of any wavelength has associated with it an energy value given by $E = h\nu$, where n is the frequency of the light ($n =$ velocity of light c divided by the wavelength λ) and h is Planck's constant. Since the energy levels of a molecule are quantized, the amount of energy required to raise an electron in a given molecule from one level to a higher one is a fixed quantity. Only light with exactly the frequency corresponding to this amount of energy will cause the electron to move to the higher level. If light of another frequency (too high or too low) is sent through a sample, it will pass out without a loss in intensity, since the molecules will not absorb it. However, if light of the correct frequency is passed in, the energy will be used by the molecules for electron promotion, and hence the light that leaves the sample will be diminished in intensity or altogether gone. A *spectrophotometer* is an instrument that allows light of a given frequency to pass through a sample and that detects (by means of a phototube) the amount of light that has been transmitted, that is, not absorbed. A spectrophotometer compares the intensity of the transmitted light with that of the incident light. Automatic instruments gradually and continuously change the frequency, and an automatic recorder plots a graph of absorption versus frequency or wavelength.

The energy of electronic transitions corresponds to light in the visible, UV, and far-UV regions of the spectrum (Fig. 7.1). Absorption positions are normally expressed in wavelength units, usually nanometers (nm).[2] If a compound absorbs in the visible, it is colored, possessing a color complementary to that which is absorbed.[3] Thus a compound absorbing in the violet is yellow. The far-uv region is studied by organic chemists less often than the visible or ordinary uv regions because special vacuum instruments are required owing to the fact that oxygen and nitrogen absorb in these regions.

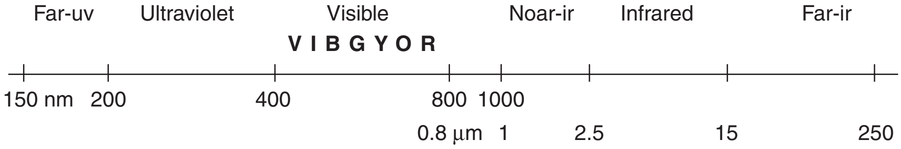


Fig. 7.1. The uv, visible, and ir portions of the electromagnetic spectrum.

[2]Formerly, millimicrons (mμ) were frequently used; numerically they are the same as nanometers.

[3]For monographs, see Zollinger, H. *Color Chemistry*, VCH, NY, ***1987***; Gordon, P.F.; Gregory, P. *Organic Chemistry in Colour*, Springer, NY, ***1983***; Griffiths, J. *Colour and Constitution of Organic Molecules*, Academic Press, NY, ***1976***. See also, Fabian, J.; Zahradník, R. *Angew. Chem. Int. Ed.* ***1989***, *28*, 677.

From these considerations it would seem that an electronic spectrum should consist of one or more sharp peaks, each corresponding to the transfer of an electron from one electronic level to another. Under ordinary conditions the peaks are seldom sharp. In order to understand why, it is necessary to realize that molecules are constantly vibrating and rotating and that these motions are also quantized. A molecule at any time is not only in a given electronic state but also in a given vibrational and rotational state. The difference between two adjacent vibrational levels is much smaller than the difference between adjacent electronic levels, and the difference between adjacent rotational levels is smaller still. A typical situation is shown in Fig. 7.2. When an electron moves from one electronic level to another, it moves from a given vibrational and rotational level within that electronic level to some vibrational and rotational level at the next electronic level. A given sample contains a large number of molecules, and even if all of them are in the ground electronic state, they are still distributed among the vibrational and rotational states (though the ground vibrational state V_0 is most heavily populated). This means that not just one wavelength of light will be absorbed, but a number of them close together, with the most probable transition causing the most intense peak. But in molecules containing more than a few atoms there are so many possible transitions and these are so close together that what is observed is a relatively broad band. The height of the peak depends on the number of molecules making the transition and is proportional to log ε, where ε is the *extinction coefficient*. The extinction coefficient can be expressed by $\varepsilon = E/cl$, where c is the concentration in moles per liter, l is the

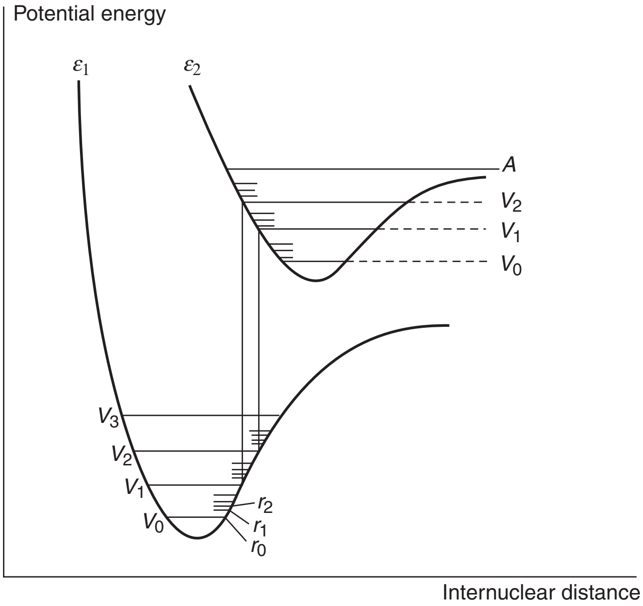


Fig. 7.2. Energy curves for a diatomic molecule. Two possible transitions are shown. When an electron has been excited to the point marked A, the molecule may cleave (p. 335).

cell length in centimeters, and $E = \log I_0/I$, where I_0 is the intensity of the incident light and I of the transmitted light. The wavelength is usually reported as λ_{max}, meaning that this is the top of the peak. Purely vibrational transitions, such as between V_0 and V_1 of E_1, which require much less energy, are found in the ir region and are the basis of ir spectra. Purely rotational transitions are found in the far-ir and microwave (beyond the far-ir) regions.

A UV or visible absorption peak is caused by the promotion of an electron in one orbital (usually a ground-state orbital) to a higher orbital. Normally, the amount of energy necessary to make this transition depends mostly on the nature of the two orbitals involved and much less on the rest of the molecule. Therefore, a simple functional group such as the C=C double bond always causes absorption in the same general area. A group that causes absorption is called a *chromophore*.

Singlet and Triplet States: "Forbidden" Transitions

In most organic molecules, all electrons in the ground state are paired, with each member of a pair possessing opposite spin as demanded by the Pauli principle. When one of a pair of electrons is promoted to an orbital of higher energy, the two electrons no longer share an orbital, and the promoted electron may, in principle, have the same spin as its former partner or the opposite spin. As we saw in Chapter 5, a molecule in which two unpaired electrons have the same spin is called a *triplet*,[4] while one in which all spins are paired is a *singlet*. Thus, at least in principle, for every excited singlet state there is a corresponding triplet state. In most cases, the triplet state has a lower energy than the corresponding singlet, which is in accord with Hund's rule. Therefore, a different amount of energy, and hence a different wavelength is required to promote an electron from the ground state (which is almost always a singlet) to an excited singlet than to the corresponding triplet state.

It would thus seem that promotion of a given electron in a molecule could result either in a singlet or a triplet excited state depending on the amount of energy added. However, this is often not the case because transitions between energy levels are governed by selection rules, which state that certain transitions are "forbidden." There are several types of "forbidden" transitions, two of which are more important than the others.

1. *Spin-Forbidden Transitions*. Transitions in which the spin of an electron changes are not allowed, because a change from one spin to the opposite involves a change in angular momentum and such a change would violate the law of conservation of angular momentum. Therefore, singlet–triplet and triplet–singlet transitions are forbidden, whereas singlet–singlet and triplet–triplet transitions are allowed.
2. *Symmetry-Forbidden Transitions*. Among the transitions in this class are those in which a molecule has a center of symmetry. In such cases, a $g \rightarrow g$ or

[4]See Kurreck, H. *Angew. Chem. Int. Ed.* ***1993***, *32*, 1409 for a brief discussion of the triplet state in organic chemistry.

$u \rightarrow u$ transition (see p. 5) is "forbidden," while a $g \rightarrow u$ or $u \rightarrow g$ transition is allowed.

We have put the word "forbidden" into quotation marks because these transitions are not actually forbidden but only highly improbable. In most cases, promotions from a singlet ground state to a triplet excited state are so improbable that they cannot be observed, and it is safe to state that in most molecules only singlet–singlet promotions take place. However, this rule does break down in certain cases, most often when a heavy atom (e.g., iodine) is present in the molecule, in which cases it can be shown from spectra that singlet–triplet promotions are occurring.[5] Symmetry-forbidden transitions can frequently be observed, though usually with low intensity.

Types of Excitation

When an electron in a molecule is promoted (normally only one electron in any molecule), it usually goes into the lowest available vacant orbital, though promotion to higher orbitals is also possible. For most organic molecules, there are consequently four types of electronic excitation:

1. $\sigma \rightarrow \sigma^*$. Alkanes, which have no n or π electrons, can be excited only in this way.[6]
2. $n \rightarrow \sigma^*$. Alcohols, amines,[7] ethers, and so on, can also be excited in this manner.
3. $\pi \rightarrow \pi^*$. This pathway is open to alkenes as well as to aldehydes, carboxylic esters, and so on.
4. $n \rightarrow \pi^*$. Aldehydes, ketones, carboxylic esters, and so on, can undergo this promotion as well as the other three.

The four excitation types above are listed in what is normally the order of decreasing energy. Thus light of the highest energy (in the far uv) is necessary for $\sigma \rightarrow \sigma^*$ excitation, while $n \rightarrow \pi^*$ promotions are caused by ordinary uv light. However, the order may sometimes be altered in some solvents.

In 1,3-butadiene (and other compounds with two conjugated double bonds) there are two π and two π^* orbitals (p. 39). The energy difference between the higher $\pi(\chi_2)$ and the lower $\pi^*(\chi_3)$ orbital is less than the difference between the π and π^* orbitals of ethylene. Therefore 1,3-butadiene requires less energy than ethylene, and thus light of a higher wavelength, to promote an electron. This is a general phenomenon, and it may be stated that, in general, *the more conjugation in a molecule, the more the absorption is displaced toward higher wavelengths* (see Table 7.1).[8]

[5]For a review of photochemical heavy-atom effects, see Koziar, J.C.; Cowan, D.O. *Acc. Chem. Res.* ***1978***, *11*, 334.

[6]An n electron is one in an unshared pair.

[7]For a review of the photochemistry of amines, see Malkin, Yu.N.; Kuz'min, V.A. *Russ. Chem. Rev.* ***1985***, *54*, 1041.

[8]Bohlmann, F.; Mannhardt, H. *Chem. Ber.* ***1956***, *89*, 1307.

TABLE 7.1. Ultraviolet Absorption[8] of CH_3–(CH=CH)$_n$–CH_3 for Some Values of *n*

n	nm
2	227
3	263
6	352
9	413

When a chromophore absorbs at a certain wavelength and the substitution of one group for another causes absorption at a longer wavelength, a *bathochromic shift* is said to have occurred. The opposite kind of shift is called *hypsochromic*.

Of the four excitation types listed above, the $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ are far more important in organic photochemistry than the other two. Compounds containing C=O groups can be excited in both ways, giving rise to at least two peaks in the UV.

As we have seen, a chromophore is a group that causes a molecule to absorb light. Examples of chromophores in the visible or UV are C=O, N=N,[9] Ph, and NO_2. Some chromophores in the far UV (beyond 200 nm) are C=C, C≡C, Cl, and OH. An *auxochrome* is a group that displaces (through resonance) and usually intensifies the absorption of a chromophore present in the same molecule. Groups, such as Cl, OH, and NH_2, are generally regarded as auxochromes since they shift (usually bathochromically) the uv and visible bands of chromophores, such as Ph or C=O (see Table 7.2).[10] Since auxochromes are themselves chromophores

TABLE 7.2. Some UV Peaks of Substituted Benzenes in Water, or Water With a Trace of Methanol (for Solubility)[a]

	Primary Band		Secondary Band	
	λ_{max}, nm	ε_{max}	λ_{max}, nm	ε_{max}
PhH	203.5	7,400	254	204
PhCl	209.5	7,400	263.5	190
PhOH	210.5	6,200	270	1,450
PhOMe	217	6,400	269	1,480
PhCN	224	13,000	271	1,000
PhCOOH	230	11,600	273	970
$PhNH_2$	230	8,600	280	1,430
PhO^-	235	9,400	287	2,600
PhAc	245.5	9,800		
PhCHO	249.5	11,400		
$PhNO_2$	268.5	7,800		

[a]Note how auxochromes shift and usually intensify the peaks.

[9]For a review of the azo group as a chromophore, see Rau, H. *Angew. Chem. Int. Ed.* 1973, *12*, 224.

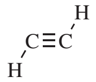
[10]These values are from Jaffé, H.H.; Orchin, M. *Theory and Applications of Ultraviolet Spectroscopy*, Wiley, NY, ***1962***, p. 257.

(to be sure, generally in the far-UV), it is sometimes difficult to decide which group in a molecule is an auxochrome and which a chromophore. For example, in acetophenone (PhCOMe) is the chromophore Ph or C=O? In such cases, the distinction becomes practically meaningless.

Nomenclature and Properties of Excited States

An excited state of a molecule can be regarded as a distinct chemical species, different from the ground state of the same molecule and from other excited states. It is obvious that we need some method of naming excited states. Unfortunately, there are several methods in use, depending on whether one is primarily interested in photochemistry, spectroscopy, or molecular-orbital theory.[11] One of the most common methods simply designates the original and newly occupied orbitals, with or without a superscript to indicate singlet or triplet. Thus the singlet state arising from promotion of a π to a π^* orbital in ethylene would be the $^1(\pi,\pi^*)$ state or the π,π^* singlet state. Another very common method can be used even in cases where one is not certain which orbitals are involved. The lowest energy excited state is called S_1, the next S_2, and so on, and triplet states are similarly labeled T_1, T_2, T_3, and so on. In this notation, the ground state is S_o. Other notational systems exist, but in this book we will confine ourselves to the two types just mentioned.

The properties of excited states are not easy to measure because of their generally short lifetimes and low concentrations, but enough work has been done for us to know that they often differ from the ground state in geometry, dipole moment and acid or base strength.[12] For example, acetylene, which is linear in the ground state, has a trans geometry in the excited state



with $\sim sp^2$ carbons in the $^1(\pi,\pi^*)$ state.[13] Similarly, the $^1(\pi,\pi^*)$ and the $^3(\pi,\pi^*)$ states of ethylene have a perpendicular and not a planar geometry,[14] and the $^1(n,\pi^*)$ and $^3(n,\pi^*)$ states of formaldehyde are both pyramidal.[15] Triplet species tend to stabilize themselves by distortion, which relieves interaction between the

[11] For discussions of excited-state notation and other terms in photochemistry, see Pitts, Jr., J.N.; Wilkinson, F.; Hammond, G.S. *Adv. Photochem.* ***1963***, *1*, 1; Porter, G.B.; Balzani, V.; Moggi, L. *Adv. Photochem.* ***1974***, *9*, 147. See also, Braslavsky, S.E.; Houk, K.N. *Pure Appl. Chem.* ***1988***, *60*, 1055.

[12] For reviews of the structures of excited states, see Zink, J.I.; Shin, K.K. *Adv. Photochem.* ***1991***, *16*, 119; Innes, K.K. *Excited States* ***1975***, *2*, 1; Hirakawa, A.Y.; Masamichi, T. *Vib. Spectra Struct.* ***1983***, *12*, 145.

[13] Ingold, C.K.; King, G.W. *J. Chem. Soc.* ***1953***, 2702, 2704, 2708, 2725, 2745. For a review of acetylene photochemistry, see Coyle, J.D. *Org. Photochem.* ***1985***, *7*, 1.

[14] Merer, A.J.; Mulliken, R.S. *Chem. Rev.* ***1969***, *69*, 639.

[15] Robinson, G.W.; Di Giorgio, V.E. *Can. J. Chem.* ***1958***, *36*, 31; Buenker, R.J.; Peyerimhoff, S.D. *J. Chem. Phys.* ***1970***, *53*, 1368; Garrison, B.J.; Schaefer III, H.F.; Lester, Jr., W.A. *J. Chem. Phys.* ***1974***, *61*, 3039; Streitwieser, Jr., A.; Kohler, B. *J. Am. Chem. Soc.* ***1988***, *110*, 3769. For reviews of excited states of formaldehyde, see Buck, H.M. *Recl. Trav. Chim. Pays-Bas* ***1982***, *101*, 193, 225; Moule, D.C.; Walsh, A.D. *Chem. Rev.* ***1975***, *75*, 67.

TABLE 7.3. Typical Energies for Some Covalent Single Bonds (see Table 1.7) and the Corresponding Approximate Wavelengths

	E		
Bond	kcal mol^{-1}	kJ mol^{-1}	nm
C—H	95	397	300
C—O	88	368	325
C—C	83	347	345
Cl—Cl	58	243	495
C—O	35	146	820

unpaired electrons. Obviously, if the geometry is different, the dipole moment will probably differ also and the change in geometry and electron distribution often results in a change in acid or base strength.[16] For example, the S_1 state of 2-naphthol is a much stronger acid (pK 3.1) than the ground state (S_0) of the same molecule (pK 9.5).[17]

Photolytic Cleavage

We have said that when a molecule absorbs a quantum of light, it is promoted to an excited state. Actually, that is not the only possible outcome. Because the energy of visible and UV light is of the same order of magnitude as that of covalent bonds (Table 7.3), another possibility is that the molecule may cleave into two parts, a process known as *photolysis*. There are three situations that can lead to cleavage:

1. The promotion may bring the molecule to a vibrational level so high that it lies above the right-hand portion of the E_2 curve (line A in Fig. 7.2). In such a case, the excited molecule cleaves at its first vibration.
2. Even where the promotion is to a lower vibrational level, one which lies wholly within the E_2 curve (e.g., V_1 or V_2), the molecule may still cleave. As Fig. 7.2 shows, equilibrium distances are greater in excited states than in the ground state. The *Franck–Condon principle* states that promotion of an electron takes place much faster than a single vibration (the promotion takes $\sim 10^{-15}$ s; a vibration $\sim 10^{-12}$ s). Therefore, when an electron is suddenly promoted, even to a low vibrational level, the distance between the atoms is essentially unchanged and the bond finds itself in a compressed condition like a pressed-in spring; this condition may be relieved by an outward surge that is sufficient to break the bond.

[16]For a review of acid–base properties of excited states, see Ireland, J.F.; Wyatt, P.A.H. *Adv. Phys. Org. Chem.* ***1976***, *12*, 131.
[17]Weller, A. *Z. Phys. Chem. (Frankfurt am Main)* ***1955***, *3*, 238, *Discuss. Faraday Soc.* ***1959***, *27*, 28.

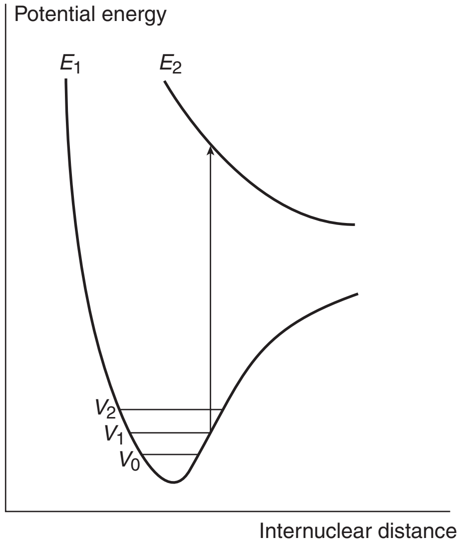


Fig. 7.3. Promotion to a dissociative state results in bond cleavage.

3. In some cases, the excited state is entirely dissociative (Fig. 7.3), that is, there is no distance where attraction outweighs repulsion, and the bond must cleave. An example is the hydrogen molecule, where a $\sigma \rightarrow \sigma*$ promotion always results in cleavage.

A photolytic cleavage can break the molecule into two smaller molecules or into two free radicals (see p. 343). Cleavage into two ions, though known, is much rarer. Once free radicals are produced by a photolysis, they behave like free radicals produced in any other way (Chapter 5) except that they may be in excited states, and this can cause differences in behavior.[18]

The Fate of the Excited Molecule: Physical Processes

When a molecule has been photochemically promoted to an excited state, it does not remain there for long. Most promotions are from the S_o to the S_1 state. As we have seen, promotions from S_o to triplet states are "forbidden." Promotions to S_2 and higher singlet states take place, but in liquids and solids these higher states usually drop very rapidly to the S_1 state ($\sim 10^{-13}$–10^{-11} s). The energy lost when an S_2 or S_3 molecule drops to S_1 is given up in small increments to the environment by collisions with neighboring molecules. Such a process is called an *energy cascade*. In a similar manner, the initial excitation and the decay from higher singlet states initially populate many of the vibrational levels of S_1, but these also cascade, down to the lowest vibrational level of S_1. Therefore, in most cases, the lowest

[18]Lubitz, W.; Lendzian, F.; Bittl, R. *Acc. Chem. Res.* ***2002***, *35*, 313.

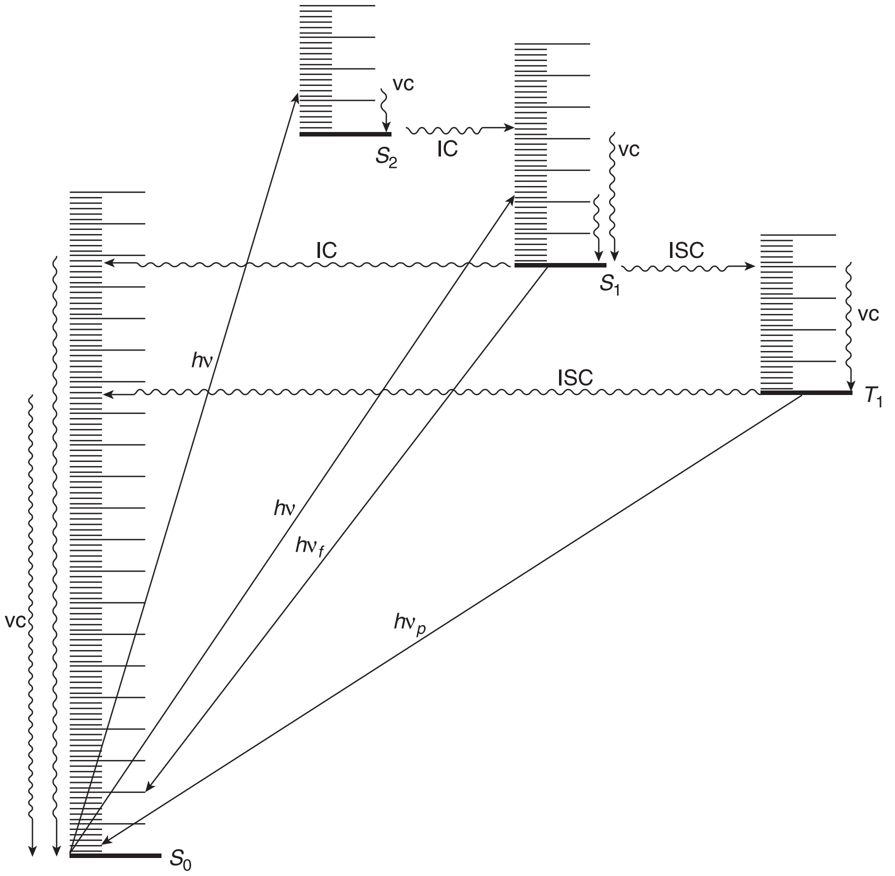


Fig. 7.4. Modified Jablonski diagram showing transitions between excited states and the ground state. Radiative processes are shown by straight lines, radiationless processes by wavy lines. vc = vibrational cascade; $h\nu_f$ = fluorescence; $h\nu_p$ = phosphorescence.

vibrational level of the S_1 state is the only important excited singlet state.[19] This state can undergo various physical and chemical processes. In the following list, we describe the physical pathways open to molecules in the S_1 and excited triplet states. These pathways are also shown in a modified Jablonski diagram (Fig. 7.4) and in Table 7.4.

1. A molecule in the S_1 state can cascade down through the vibrational levels of the S_0 state and thus return to the ground state by giving up its energy in small increments to the environment, but this is generally quite slow because the

[19]For a review of physical and chemical processes undergone by higher states, see Turro, N.J.; Ramamurthy, V.; Cherry, W.; Farneth, W. *Chem. Rev.* ***1978***, *78*, 125.

TABLE 7.4. Physical Processes Undergone by Excited Molecules[a]

$S_0 + h\nu \rightarrow S_1^v$	Excitation
S_1^v	$\rightsquigarrow \rightarrow S_1 + \Delta$ Vibrational relaxation
$S_1 \rightarrow S_1 + h\nu$	Fluorescence
S_1	$\rightsquigarrow \rightarrow S_0 + \Delta$ Internal conversion
$S_1 \rightsquigarrow T_1^v$	Intersystem crossing
$T_1^v \rightsquigarrow T_1 + \Delta$	Vibrational relaxation
$T_1 \rightarrow S_0 + h\nu$	Phosphorescence
$T_1 \rightsquigarrow S_0 + \Delta$	Intersystem crossing
$S_1 + A_{(S_0)} \rightarrow S_0 + A_{(S_1)}$	Singlet–singlet transfer (photosensitization)
$T_1 + A_{(S_0)} \rightarrow S_0 + A_{(T_1)}$	Triplet–triplet transfer (photosensitization)

[a]The superscript ν indicates vibrationally excited state: excited states higher than S_1 or T_1 are omitted.

amount of energy is large. The process is called *internal conversion* (IC, see Fig. 7.4). Because it is slow, most molecules in the S_1 state adopt other pathways.[20]

2. A molecule in the S_1 state can drop to some low vibrational level of the S_o state all at once by giving off the energy in the form of light. This process, which generally happens within 10^{-9} s, is called *fluorescence*. This pathway is not very common either (because it is relatively slow), except for small molecules, for example, diatomic, and rigid molecules, for example, aromatic. For most other compounds, fluorescence is very weak or undetectable. For compounds that do fluoresce, the fluorescence emission spectra are usually the approximate mirror images of the absorption spectra. This comes about because the fluorescing molecules all drop from the lowest vibrational level of the S_1 state to various vibrational levels of S_o, while excitation is from the lowest vibrational level of S_o to various levels of S_1 (Fig. 7.5). The only peak in common is the one (called the 0–0 peak) that results from transitions between the lowest vibrational levels of the two states. In solution, even the 0–0 peak may be noncoincidental because the two states are solvated differently. Fluorescence nearly always arises from a $S_1 \rightarrow S_0$ transition, though azulene (p. $$$) and its simple derivatives are exceptions,[21] emitting fluorescence from $S_2 \rightarrow S_0$ transitions.

Because of the possibility of fluorescence, any chemical reactions of the S_1 state must take place very fast, or fluorescence will occur before they can happen.

[20]For a monograph on radiationless transitions, see Lin, S.H. *Radiationless Transitions*; Academic Press, NY, ***1980***. For reviews, see Kommandeur, J. *Recl. Trav. Chim. Pays-Bas* ***1983***, *102*, 421; Freed, K.F. *Acc. Chem. Res.* ***1978***, *11*, 74.

[21]For other exceptions, see Gregory, T.A.; Hirayama, F.; Lipsky, S. *J. Chem. Phys.* ***1973***, *58*, 4697; Sugihara, Y.; Wakabayashi, S.; Murata, I.; Jinguji, M.; Nakazawa, T.; Persy, G.; Wirz, J. *J. Am. Chem. Soc.* ***1985***, *107*, 5894, and references cited therein. See also Turro, N.J.; Ramamurthy, V.; Cherry, W.; Farneth, W. *Chem. Rev.* ***1978***, *78*, 125, see pp. 126–129.

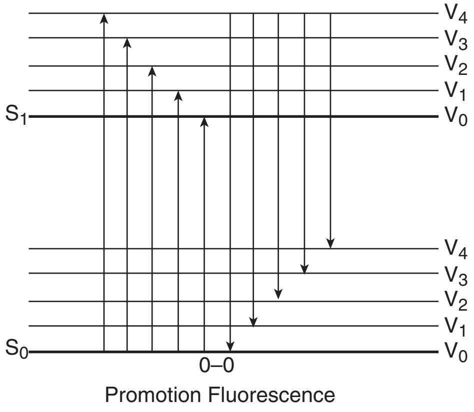


Fig. 7.5. Promotion and fluorescence between S_1 and S_0 states.

3. Most molecules (though by no means all) in the S_1 state can undergo an intersystem crossing (ISC, see Fig. 7.4) to the lowest triplet state T_1.[22] An important example is benzophenone, of which ~100% of the molecules that are excited to the S_1 state cross over to the T_1.[23] Intersystem crossing from singlet to triplet is of course a "forbidden" pathway, since the angular-momentum problem (p. 331) must be taken care of, but this often takes place by compensations elsewhere in the system. Intersystem crossings take place without loss of energy. Since a singlet state usually has a higher energy than the corresponding triplet, this means that energy must be given up. One way for this to happen is for the S_1 molecule to cross to a T_1 state at a high vibrational level and then for the T_1 to cascade down to its lowest vibrational level (see Fig. 7.4). This cascade is very rapid (10^{-12} s). When T_2 or higher states are populated, they too rapidly cascade to the lowest vibrational level of the T_1 state.
4. A molecule in the T_1 state may return to the S_o state by giving up heat (intersystem crossing) or light (this is called *phosphorescence*).[24] Of course, the angular-momentum difficulty exists here, so that both intersystem crossing and phosphorescence are very slow (~10^{-3}–10^1 s). This means that T_1 states generally have much longer lifetimes than S_1 states. When they occur in the same molecule, phosphorescence is found at lower frequencies than fluorescence

[22]Intersystem crossing from S_1 to T_2 and higher triplet states has also been reported in some aromatic molecules: Li, R.; Lim, E.C. *Chem. Phys.* ***1972***, *57*, 605; Sharf, B.; Silbey, R. *Chem. Phys. Lett.* ***1970***, *5*, 314. See also, Schlag, E.W.; Schneider, S.; Fischer, S.F. *Annu. Rev. Phys. Chem.* ***1971***, *22*, 465, pp. 490. There is evidence that ISC can also occur from the S_2 state of some molecules: Samanta, A. *J. Am. Chem. Soc.* ***1991***, *113*, 7427. Also see, Tanaka, R.; Kuriyama, Y.; Itoh, H.; Sakuragi, H.; Tokumaru, K. *Chem. Lett.* ***1993***, 1447; Ohsaku, M.; Koga, N.; Morokuma, K. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 71.

[23]Moore, W.M.; Hammond, G.S.; Foss, R.P. *J. Am. Chem. Soc.* ***1961***, *83*, 2789.

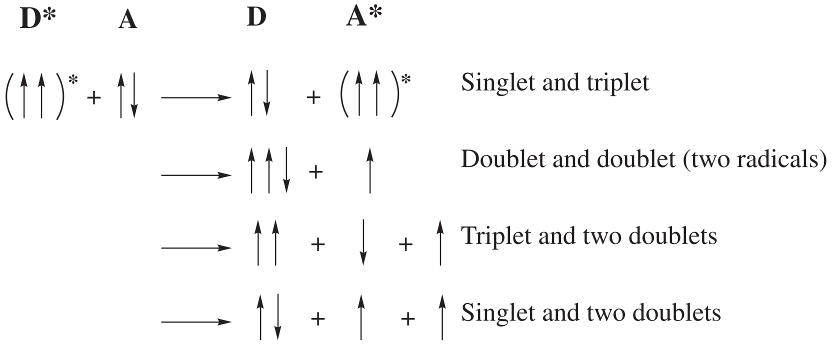
[24]For a review of physical processes of triplet states, see Lower, S.K.; El-Sayed, M.A. *Chem. Rev.* ***1966***, *66*, 199. For a review of physical and chemical processes of triplet states see Wagner, P.J.; Hammond, G.S. *Adv. Photochem.* ***1968***, *5*, 21.

(because of the higher difference in energy between S_1 and S_0 than between T_1 and S_0) and is longer-lived (because of the longer lifetime of the T_1 state).

5. If nothing else happens to it first, a molecule in an excited state (S_1 or T_1) may transfer its excess energy all at once to another molecule in the environment, in a process called *photosensitization*.[25] The excited molecule (which we will call D for donor) thus drops to S_0 while the other molecule (A for acceptor) becomes excited:

$$D^* + A \longrightarrow A^* + D$$

Thus there are *two* ways for a molecule to reach an excited state: by absorption of a quantum of light or by transfer from a previously excited molecule.[26] The donor D is also called a *photosensitizer*. This energy transfer is subject to the *Wigner spin-conservation rule*, which is actually a special case of the law of conservation of momentum we encountered previously. According to the Wigner rule, the total electron spin does not change after the energy transfer. For example, when a triplet species interacts with a singlet these are some allowed possibilities:[27]



In all these cases, the products have three electrons spinning "up" and the fourth "down" (as do the starting molecules). However, formation of, say, two triplets (↑↓ + ↓↓) or two singlets (↑↓ + ↑↓), whether ground states or excited, would violate the rule.

In the two most important types of photosensitization, both of which are in accord with the Wigner rule, a triplet excited state generates another triplet and a singlet generates a singlet:

$$D_{T_1} + A_{S_0} \longrightarrow A_{T_1} + D_{S_0} \qquad \text{triplet–triplet transfer}$$

$$D_{S_1} + A_{S_0} \longrightarrow A_{S_1} + D_{S_0} \qquad \text{singlet–triplet transfer}$$

[25]For reviews, see Albini, A. *Synthesis*, ***1981***, 249; Turro, N.J.; Dalton, J.C.; Weiss, D.S. *Org. Photochem.* ***1969***, *2*, 1.

[26]There is also a third way: in certain cases excited states can be produced directly in ordinary reactions. For a review, see White, E.H.; Miano, J.D.; Watkins, C.J.; Breaux, E.J. *Angew. Chem. Int. Ed.* ***1974***, *13*, 229.

[27]For another table of this kind, see Calvert, J.G.; Pitts, Jr., J.N. *Photochemistry*, Wiley, NY, ***1966***, p. 89.

Singlet–singlet transfer can take place over relatively long distances (e.g., 40 Å), but triplet transfer normally requires a collision between the molecules.[28] Both types of photosensitization can be useful for creating excited states when they are difficult to achieve by direct irradiation. Photosensitization is therefore an important method for carrying out photochemical reactions when a molecule cannot be brought to the desired excited state by direct absorption of light. Triplet–triplet transfer is especially important because triplet states are usually much more difficult to prepare by direct irradiation than singlet states (often impossible) and because triplet states, having longer lifetimes, are much more likely than singlets to transfer energy by photosensitization. Photosensitization can also be accomplished by electron transfer.[29]

In choosing a photosensitizer, one should avoid a compound that absorbs in the same region as the acceptor because the latter will then compete for the light.[30] For examples of the use of photosensitization to accomplish reactions, see **15-62** and **15-63**.

6. An excited species can be quenched. Qunching is the deactivation of an excited molecular entity intermolecularly by an external environmental influence (e.g., a quencher) or intramolecularly by a substituent through a nonradiative process.[31] When the external environmental influence (quencher) interferes with the behavior of the excited state after its formation, the process is referred to as dynamic quenching. Common mechanisms include energy transfer, charge transfer, and so on. When the environmental influence inhibits the excited state formation the process is referred to as static quenching. A quencher is defined as a molecular entity that deactivates (quenches) an excited state of another molecular entity, either by energy tranfer, electron transfer, or by a chemical mechanism.[31]

An example is the rapid triplet quenching of aromatic ketone triplets by amines, which is well known.[32] Alkyl and aryl thiols and thioethers also serve as quenchers in this system[33] In this latter case, the mechanism involves electron

[28]Long-range triplet-triplet transfer has been observed in a few cases: Bennett, R.G.; Schwenker, R.P.; Kellogg, R.E. *J. Chem. Phys.* ***1964***, *41*, 3040; Ermolaev, V.L.; Sveshnikova, E.B. *Izv. Akad. Nauk SSSR, Ser. Fiz.* ***1962***, *26*, 29 [*C. A.* ***1962***, *57*, 1688], *Opt. Spectrosc. (USSR)* ***1964***, *16*, 320.

[29]For a review, see Kavarno, G.J.; Turro, N.J. *Chem. Rev.* ***1986***, *86*, 401. See also, Mariano, P.S. *Org. Photochem.* ***1987***, *9*, 1.

[30]For a review of other complications that can take place in photosensitized reactions, see Engel, P.S.; Monroe, B.M. *Adv. Photochem.* ***1971***, *8*, 245.

[31]Verhoeven, J.W. *Pure Appl. Chem.* ***1996***, *68*, 2223 (see p 2268).

[32]See Aspari, P.; Ghoneim, N.; Haselbach, E.; von Raumer, M.; Suppan, P.; Vauthey, E. *J. Chem. Soc., Faraday Trans.* ***1996***, *92*, 1689; Cohen, S.G.; Parola, A.; Parsons, Jr., G.H. *Chem. Rev.* ***1973***, *73*, 141; Inbar, S.; Linschitz, H.; Cohen, S.G. *J. Am. Chem. Soc.* ***1981***, *103*, 1048; Peters, K.S.; Lee, J. *J. Phys. Chem.* ***1993***, *97*, 3761; von Raumer, M.; Suppan, P.; Haselbach, E. *Helv. Chim. Acta* ***1997***, *80*, 719.

[33]Guttenplan, J.B.; Cohen, S.G. *J. Org. Chem.* ***1973***, *38*, 2001; Inbar, S.; Linschitz, H.; Cohen, S.G. *J. Am. Chem. Soc.* ***1982***, *104*, 1679; Bobrowski, K.; Marciniak, B.; Hug, G.L. *J. Photochem. Photobiol. A: Chem.* ***1994***, *81*, 159; Wakasa, M.; Hayashi, H. *J. Phys. Chem.* ***1996***, *100*, 15640.

transfer from the sulfur atom to the triplet ketone, and this is supported by theoretical calculations.[34] Aromatic ketone triplets are quenched by phenols and the photochemical reaction between aromatic ketones and phenols is efficient only in the presence of an acid catalyst.[35] Indirect evidence has been provided for involvement of the hydrogen-bonded triplet exciplex and for the role of electron transfer in this reaction.[36]

The Fate of the Excited Molecule: Chemical Processes

Although both excited singlet and triplet species can undergo chemical reactions, they are much more common for triplets, simply because these generally have much longer lifetimes. Excited singlet species, in most cases, have a lifetime of $<10^{-10}$ s and undergo one of the physical processes already discussed before they have a chance to react chemically. Therefore, photochemistry is largely the chemistry of triplet states.[37] Table 7.5[38] lists many of the possible chemical pathways that can be taken by an excited molecule.[39] The first four of these are unimolecular reactions; the others are bimolecular. In the case of bimolecular reactions, it is rare for two excited molecules to react with each other (because the concentration of excited molecules at any one time is generally low); reactions are between an excited molecule and an unexcited molecule of either the same or another species. The reactions listed in Table 7.5 are primary processes. Secondary reactions often follow, since the primary products are frequently radicals or carbenes; even if they are ordinary molecules, they are often in upper vibrational levels and so have excess energy. In almost all cases, the primary products of photochemical reactions are in their ground states, though exceptions are known.[40] Of the reactions listed in Table 7.5, the most common are cleavage into radicals (1), decomposition into molecules (2), and (in the presence of a suitable acceptor molecule) photosensitization (7), which we have already discussed. The following are some specific examples of reaction categories (1)–(6). Other examples are discussed in Part 2 of this book.[41]

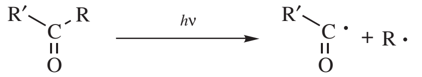
[34]Marciniak, B.; Bobrowski, K.; Hug, G.L. *J. Phys. Chem.* ***1993***, *97*, 11937.
[35]Becker, H.-D. *J. Org. Chem.* ***1967***, *32*, 2115; J. *Org. Chem.* ***1967***, *32*, 2124; *J. Org. Chem.* ***1967***, *32*, 2140.
[36]Lathioor, E.C.; Leigh, W.J.; St. Pierre, M.J. *J. Am. Chem. Soc.* ***1999***, *121*, 11984.
[37]For a review of the chemical reactions of triplet states, see Wagner, P.J.; Hammond, G.S. Wagner, P.J.; Hammond, G.S. *Adv. Photochem.* ***1968***, *5*, 21. For other reviews of triplet states, see *Top. Curr. Chem.* ***1975***, Vols. 54 and 55.
[38]Adapted from Calvert, J.G.; Pitts, Jr., J.N. *Photochemistry*, Wiley, NY, ***1966***, p. 367.
[39]For a different kind of classification of photochemical reactions, see Dauben, W.G.; Salem, L.; Turro, N.J. *Acc. Chem. Res.* ***1975***, *8*, 41. For reviews of photochemical reactions where the molecules are geometrically constrained, see Ramamurthy, V. *Tetrahedron* ***1986***, *42*, 5753; Ramamurthy, V.; Eaton, D.F. *Acc. Chem. Res.* ***1988***, *21*, 300; Turro, N.J.; Cox, G.S.; Paczkowski, M.A. *Top. Curr. Chem.* ***1985***, *129*, 57.
[40]Turro, N.J.; Lechtken, P.; Lyons, A.; Hautala, R.T.; Carnahan, E.; Katz, T.J. *J. Am. Chem. Soc.* ***1973***, ***95***, 2035.
[41]For monographs on the use of photochemistry for synthesis, see Ninomiya, I.; Naito, T. *Photochemical Synthesis*, Academic Press, NY, ***1989***; Coyle, J.D. *Photochemistry in Organic Synthesis*, Royal Society of Chemistry, London, ***1986***; Schönberg, A. *Preparative Organic Photochemistry*, Springer, Berlin, ***1968***.

TABLE 7.5. Primary photochemical reactions[a] of an excited molecule A—B—C[38]

Reaction	Reaction Type	Example Number
(A—B—C) ⟶ A—B• + C•	Simple cleavage into radicals[42]	(1)
(A—B—C) ⟶ E + F	Decomposition into molecules	(2)
(A—B—C) ⟶ A—C—B	Intramolecular rearrangement	(3)
(A—B—C) ⟶ A—B—C′	Photoisomerization	(4)
(A—B—C) $\xrightarrow{RH}$ A—B—C—H + R•	Hydrogen-atom abstraction	(5)
(A—B—C) ⟶ $(ABD)_2$	Photodimerization	(6)
(A—B—C) $\xrightarrow{A}$ ABC + A*	Photosensitization	(7)

[a]Examples are given in the text; the most common are (1), (2), and, in the presence of a suitable acceptor molecule, (7).

Category 1. *Simple Cleavage into Radicals.*[43] Aldehydes and ketones absorb in the 230–330-nm region. This is assumed to result from an $n \rightarrow \pi^*$ singlet–singlet transition. The excited aldehyde or ketone can then cleave.[44]



When applied to ketones, this is called *Norrish Type I cleavage* or often just *Type I cleavage*. In a secondary process, the acyl radical R′—CO• can then lose CO to give R′• radicals. Another example of a category 1 process is cleavage of Cl_2 to give two Cl atoms. Other bonds that are easily cleaved by photolysis are the O—O bonds of peroxy compounds and the C—N bonds of aliphatic azo

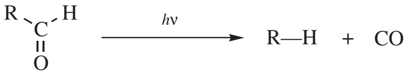
[42]For a polymer-supported reagent used for the photochemical generation of radicals in solution see DeLuca, L.; Giacomelli, G.; Porcu, G.; Taddei, M. *Org. Lett.* ***2001***, *3*, 855.

[43]For reviews, see Jackson, W.M.; Okabe, H. *Adv. Photochem.* ***1986***, *13*, 1; Kresin, V.Z.; Lester Jr., W.A. *Adv. Photochem.* ***1986***, *13*, 95.

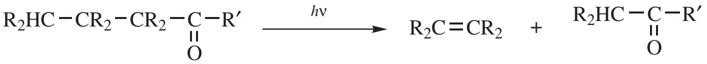
[44]For full discussions of aldehyde and ketone photochemistry, see Formosinho, S.J.; Arnaut, L.G. *Adv. Photochem.* ***1991***, *16*, 67; Newton, R.F., in Coyle, J.D. *Photochemistry in Organic Synthesis*, Royal Society of Chemistry, London, ***1986***, pp. 39–60; Lee, E.K.C.; Lewis, R.S. *Adv. Photochem.* ***1980***, *12*, 1; Calvert, J.G.; Pitts, Jr., J.N. *Photochemistry*, Wiley, NY, ***1966***, pp. 368–427; Coyle, J.D.; Carless, H.A. J. *Chem. Soc. Rev.* ***1972***, *1*, 465; Pitts, Jr., J.N.; Wan, J.K.S., in Patai, S. *The Chemistry of the Carbonyl Group*, Wiley, NY, ***1966***, pp. 823–916; Dalton, J.C.; Turro, N.J. *Annu. Rev. Phys. Chem.* ***1970***, *21*, 499; Bérces, T. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 5; Elsevier, NY, ***1972***, pp. 277–380; Turro, N.J.; Dalton, J.C.; Dawes, K.; Farrington, G.; Hautala, R.; Morton, D.; Niemczyk, M.; Shore, N. *Acc. Chem. Res.* ***1972***, *5*, 92; Wagner, P.J. *Top. Curr. Chem.* ***1976***, *66*, 1; Wagner, P.J.; Hammond, G.S. *Adv. Photochem.* ***1968***, *5*, 21, 87–129. For reviews of the photochemistry of cyclic ketones, see Weiss, D.S. *Org. Photochem.* ***1981***, *5*, 347; Chapman, O.L.; Weiss, D.S. *Org. Photochem.* ***1973***, *3*, 197; Morton, B.M.; Turro, N.J. *Adv. Photochem.* ***1974***, *9*, 197. For reviews of the photochemistry of α-diketones, see Rubin, M.B. *Top. Curr. Chem.* ***1985***, *129*, 1; ***1969***, *13*, 251; Monroe, B.M. *Adv. Photochem.* ***1971***, *8*, 77. For a review of the photochemistry of protonated unsaturated carbonyl compounds, see Childs, R.F. *Rev. Chem. Intermed.* ***1980***, *3*, 285. For reviews of the photochemistry of C=S compounds, see Coyle, J.D. *Tetrahedron* ***1985***, *41*, 5393; Ramamurthy, V. *Org. Photochem.* ***1985***, *7*, 231. For a review of the chemistry of C=N compounds, see Mariano, P.S. *Org. Photochem.* ***1987***, *9*, 1.

compounds R—N=N—R.[45] The latter is an important source of radicals R•, since the other product is the very stable N_2.

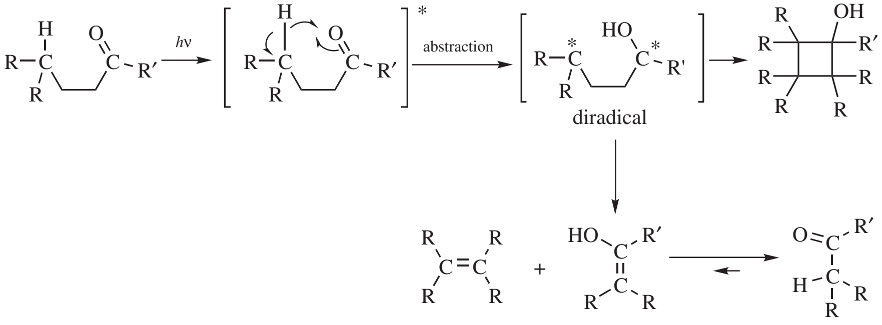
Category 2. *Decomposition into Molecules*. Aldehydes (though not generally ketones) can also cleave in this manner:



This is an extrusion reaction (see Chapter 17). In another example of a process in category 2, aldehydes and ketones with a γ hydrogen can cleave in still another way (a β elimination, see Chapter 17):



This reaction, called *Norrish Type II cleavage*,[46] involves intramolecular abstraction of the γ hydrogen followed by cleavage of the resulting diradical[47] (a secondary reaction) to give an enol that tautomerizes to the aldehyde or ketone product.[48]



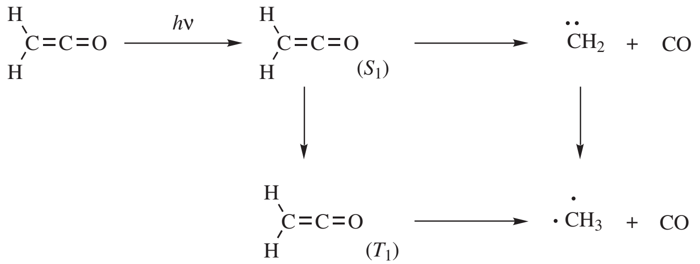
[45]For reviews of the photochemistry of azo compounds, see Adam, W.; Oppenländer, T. *Angew. Chem. Int. Ed.* ***1986***, *25*, 661; Dürr, H.; Ruge, B. *Top. Curr. Chem.* ***1976***, *66*, 53; Drewer, R.J., in Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 2, Wiley, NY, ***1975***, pp. 935–1015.

[46]For thorough discussions of the mechanism, see Wagner, P.J., in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, ***1980***, pp. 381–444; *Acc. Chem. Res.* ***1971***, *4*, 168; Dalton, J.C.; Turro, N.J. *Annu. Rev. Phys. Chem.* ***1970***, *21*, 499, 526–538. See Niu, Y.; Christophy, E.; Hossenlopp, J.M. *J. Am. Chem. Soc.* ***1996***, *118*, 4188 for a new view of Norrish Type II elimination.

[47]For reviews of the diradicals produced in this reaction, see Wilson, R.M. *Org. Photochem.* ***1985***, *7*, 339, 349–373; Scaiano, J.C.; Lissi, E.A.; Encina, M.V. *Rev. Chem. Intermed.* ***1978***, *2*, 139. For a review of a similar process, where δ hydrogens are abstracted, see Wagner, P.J. *Acc. Chem. Res.* ***1989***, *22*, 83.

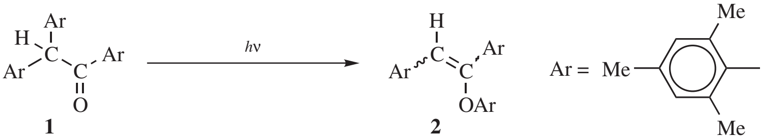
[48]This mechanism was proposed by Yang, N.C.; Yang, D.H. *J. Am. Chem. Soc.* ***1958***, *80*, 2913. Among the evidence for this mechanism is the fact that the diradical intermediate has been trapped: Wagner, P.J.; Zepp, R.G. *J. Am. Chem. Soc.* ***1972***, *94*, 287; Wagner, P.J.; Kelso, P.A.; Zepp, R.G. *J. Am. Chem. Soc.* ***1972***, *94*, 7480; Adam, W.; Grabowski, S.; Wilson, R.M. *Chem. Ber.* ***1989***, *122*, 561. See also Caldwell, R.A.; Dhawan, S.N.; Moore, D.E. *J. Am. Chem. Soc.* ***1985***, *107*, 5163.

Both singlet and triplet n,π^* states undergo the reaction.[49] The intermediate diradical can also cyclize to a cyclobutanol, which is often a side product. Carboxylic esters, anhydrides, and other carbonyl compounds can also give this reaction.[50] The photolysis of ketene to CH_2 (p. 288) is still another example of a reaction in category 2. Both singlet and triplet CH_2 are generated, the latter in two ways:

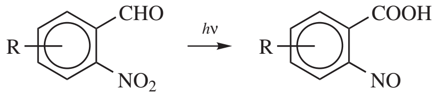


Reactions are known where *both* Norrish Type I and Norrish Type II reactions compete, and the substituents on and nature of the substrate will determine which leads to the major product.[51]

Category 3. *Intramolecular Rearrangement*. Two examples are the rearrangement of the trimesityl compound (**1**) to the enol ether (**2**),[52] and irradiation of *o*-nitrobenzaldehydes (**3**) to give *o*-nitrosobenzoic acids (**4**).[53]



1 **2**



3 **4**

[49]Wagner, P.J.; Hammond, G.S. *J. Am. Chem. Soc.* ***1965***, *87*, 4009; Dougherty, T.J. *J. Am. Chem. Soc.* ***1965***, *87*, 4011; Ausloos, P.; Rebbert, R.E. *J. Am. Chem. Soc.* ***1964***, *86*, 4512; Casey, C.P.; Boggs, R.A. *J. Am. Chem. Soc.* ***1972***, *94*, 6457.

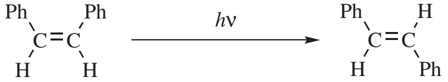
[50]For a review of the photochemistry of carboxylic acids and acid derivatives, see Givens, R.S.; Levi, N., in Patai, S. *The Chemistry of Acid Derivatives*, pt. 1, Wiley, NY, ***1979***, pp. 641–753.

[51]See Hwu, J.R.; Chen, B.-L.; Huang, L.W.; Yang, T.-H. *J. Chem. Soc. Chem. Commun.* ***1995***, 299 for an example.

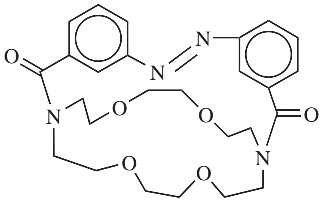
[52]Hart, H.; Lin, L.W. *Tetrahedron Lett.* ***1985***, *26*, 575; Wagner, P.J.; Zhou, B. *J. Am. Chem. Soc.* ***1988***, *110*, 611.

[53]For a review of this and closely related reactions, see Morrison, H.A., in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, pt. 1; Wiley, NY, ***1969***, pp. 165–213, 185–191. For a review of photochemical rearrangements of benzene derivatives, see Kaupp, G. *Angew. Chem. Int. Ed.* ***1980***, *19*, 243. See also, Yip, R.W.; Sharma, D.K. *Res. Chem. Intermed.* ***1989***, *11*, 109.

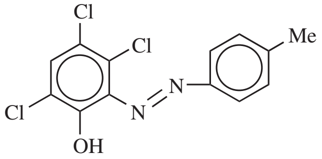
Category 4. *Photoisomerization*. The most common reaction in this category is photochemical cis–trans isomerization.[54] For example, *cis*-stilbene can be converted to the trans isomer,[55] and the photoisomerization of *O*-methyl oximes is known.[56]



The isomerization takes place because the excited states, both S_1 and T_1, of many alkenes have a perpendicular instead of a planar geometry (p. 334), so cis–trans isomerism disappears upon excitation. When the excited molecule drops back to the S_0 state, either isomer can be formed. A useful example is the photochemical conversion of *cis*-cyclooctene to the much less stable trans isomer.[57] Another interesting example of this isomerization involves azo crown ethers. The crown ether **5**, in which the N=N bond is anti, preferentially binds NH_4^+, Li^+, and Na^+, but the syn isomer preferentially binds K^+ and Rb^+ (see p. 119). Thus, ions can be selectively put in or taken out of solution merely by turning a light source on or off.[58]



5



6

In another example, the trans azo compound **6** is converted to its cis isomer when exposed to light. In this case[59] the cis isomer is a stronger acid than the

[54]For reviews of cis–trans isomerizations, see Sonnet, P.E. *Tetrahedron* ***1980***, *36*, 557; Schulte-Frohlinde, D.; Görner, H. *Pure Appl. Chem.* ***1979***, *51*, 279; Saltiel, J.; Charlton, J.L., in de Mayo, P. *Rearrangements in Grund and Excited States*, Vol. 3, Academic Press, NY, ***1980***, pp. 25–89; Saltiel, J.; Chang, D.W.L.; Megarity, E.D.; Rousseau, A.D.; Shannon, P.T.; Thomas, B.; Uriarte, A.K. *Pure Appl. Chem.* ***1975***, *41*, 559; Saltiel, J.; D'Agostino, J.; Megarity, E.D.; Metts, L.; Neuberger, K.R.; Wrighton, M.; Zafiriou, O.C. *Org. Photochem.* ***1979***, *3*, 1. For reviews of the photochemistry of alkenes, see Leigh, W.J.; Srinivasan, R. *Acc. Chem. Res.* ***1987***, *20*, 107; Steinmetz, M.G. *Org. Photochem.* ***1987***, *8*, 67; Adam, W.; Oppenländer, T. *Angew. Chem. Int. Ed.* ***1986***, *25*, 661; Mattes, S.L.; Farid, S. *Org. Photochem.* ***1984***, *6*, 233; Kropp, P.J. *Org. Photochem.* ***1979***, *4*, 1; Morrison, H. *Org. Photochem.* ***1979***, *4*, 143; Kaupp, G. *Angew. Chem. Int. Ed.* ***1978***, *17*, 150. For a review of the photochemistry of allenes and cumulenes, see Johnson, R.P. *Org. Photochem.* ***1985***, *7*, 75.

[55]For a review of the photoisomerization of stilbenes, see Waldeck, D.H. *Chem. Rev.* ***1991***, *91*, 415.

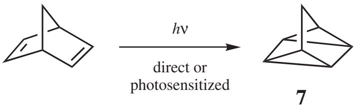
[56]Kawamura, Y.; Takayama, R.; Nishiuchi, M.; Tsukayama, M. *Tetrahedron Lett.* ***2000***, *41*, 8101.

[57]Deyrup, J.A.; Betkouski, M. *J. Org. Chem.* ***1972***, *37*, 3561.

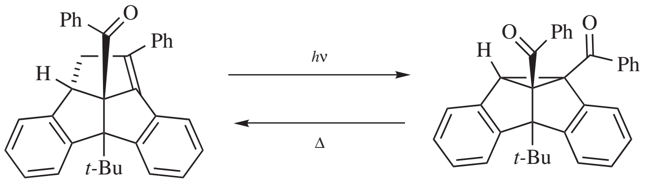
[58]Shinkai, S.; Nakaji, T.; Nishida, Y.; Ogawa, T.; Manabe, O. *J. Am. Chem. Soc.* ***1980***, *102*, 5860. See also, Irie, M.; Kato, M. *J. Am. Chem. Soc.* ***1985***, *107*, 1024; Akabori, S.; Kumagai, T.; Habata, Y.; Sato, S. *J. Chem. Soc. Perkin Trans. 1* ***1989***, 1497; Shinkai, S.; Yoshioka, A.; Nakayama, H.; Manabe, O. *J. Chem. Soc. Perkin Trans. 2* ***1990***, 1905. For a review, see Shinkai, S.; Manabe, O. *Top. Curr. Chem.* ***1984***, *121*, 67.

[59]Haberfield, P. *J. Am. Chem. Soc.* ***1987***, *109*, 6177.

trans. The trans isomer is dissolved in a system containing a base, wherein a liquid membrane separates two sides, one of which is illuminated, the other kept dark. On the illuminated side, the light converts the trans isomer to the cis. The cis isomer, being a stronger acid, donates its proton to the base, converting *cis*-ArOH to *cis*-ArO^-. This ion migrates to the dark side, where it rapidly reverts to the *trans* ion, which reacquires a proton. Because each cycle forms one H_3O^+ ion in the illuminated compartment and one ^-OH ion in the dark compartment, the process reverses the normal reaction whereby these ions neutralize each other.[60] Thus the energy of light is used to do chemical work.[61] Another example of a category 4 reaction is the conversion of bicyclo[2.2.1]hept-2,5-diene to **7**.[54] The thermal isomerization of dibenzosemibullvalene **9** to the corresponding dibenzodihydropentalenofuran **8** in quantitative yield was known,[62] but in another example of a category 4 reaction the photochemical isomerization of **8** to **9** has now been reported.[63]



7



8 **9**

These examples illustrate that the use of photochemical reactions can make it very easy to obtain compounds that would be difficult to get in other ways. Reactions similar to these are discussed at **15-63**.

Category 5. *Hydrogen-Atom Abstraction*. When benzophenone is irradiated in isopropyl alcohol, the initially formed S_1 state crosses to the T_1 state, which abstracts hydrogen from the solvent to give the radical **10**. Radical **10** then

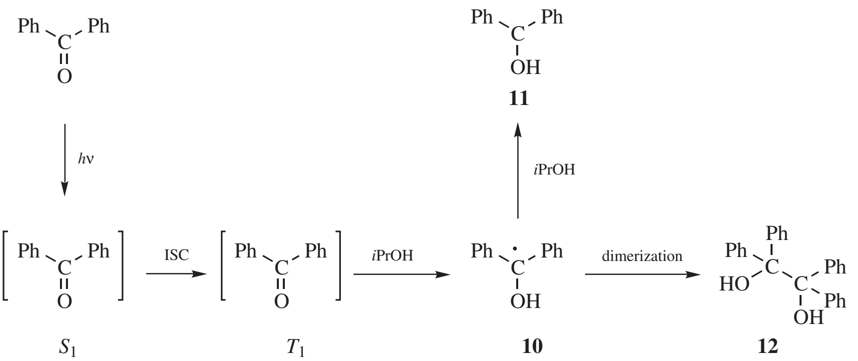
[60]Haberfield, P. *J. Am. Chem. Soc.* ***1987***, *109*, 6178.

[61]For a review of instances where macrocycles change in response to changes in light, pH, temperature, and so on, see Beer, P.D. *Chem. Soc. Rev.* ***1989***, *18*, 409. For an example not involving a macrocycle, see Feringa, B.L.; Jager, W.F.; de Lange, B.; Meijer, E.W. *J. Am. Chem. Soc.* ***1991***, *113*, 5468.

[62]Sajimon, M.C.; Ramaiah, D.; Muneer, M.; Ajithkumar, E.S.; Rath, N.P.; George, M.V. *J. Org. Chem.* ***1999***, *64*, 6347; Sajimon, M.C.; Ramaiah, D.; Muneer, M.; Rath, N.P.; George, M.V. *J. Photochem. Photobiol. A Chem.* ***2000***, *136*, 209.

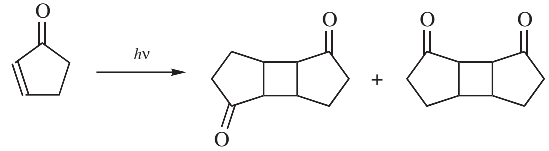
[63]Sajimon, M.C.; Ramaiah, D.; Thomas, K.G.; George, M.V. *J. Org. Chem.* ***2001***, *66*, 3182.

abstracts another hydrogen to give benzhydrol (**11**) or dimerizes to benzpinacol (**12**):



An example of intramolecular abstraction has already been given (p. $$$).

Category 6. *Photodimerization.* An example is dimerization of cyclopentenone:[64]



See reaction **15-63** for a discussion of this and similar reactions.

The Determination of Photochemical Mechanisms[65]

The methods used for the determination of photochemical mechanisms are largely the same as those used for organic mechanisms in general (Chapter 6): product identification, isotopic tracing, the detection and trapping of intermediates, and kinetics. There are, however, a few new factors: (*1*) there are generally many products in a photochemical reaction, as many as 10 or 15; (*2*) in measuring kinetics, there are more variables, since we can study the effect on the rate of the intensity or the wavelength of light; (*3*) in the detection of intermediates by spectra we can use the technique of *flash photolysis*, which can detect extremely short-lived intermediates.

In addition to these methods, there are two additional techniques.

1. The use of emission (fluorescence and phosphorescence) as well as absorption spectroscopy. From these spectra the presence of as well as the energy and lifetime of singlet and triplet excited states can often be calculated.

[64]Eaton, P.E. *J. Am. Chem. Soc.* ***1962***, *84*, 2344, 2454, *Acc. Chem. Res.* ***1968***, *1*, 50. For a review of the photochemistry of α,β-unsaturated ketones, see Schuster, D.I., in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 2, Wiley, NY, ***1989***, pp. 623–756.

[65]For a review, see Calvert, J.G.; Pitts, Jr., J.N. *Photochemistry*, Wiley, NY, ***1966***, pp. 580–670.

2. The study of quantum yields. The *quantum yield* is the fraction of absorbed light that goes to produce a particular result. There are several types. A *primary quantum yield* for a particular process is the fraction of molecules absorbing light that undergo that particular process. Thus, if 10% of all the molecules that are excited to the S_1 state cross over to the T_1 state, the primary quantum yield for that process is 0.10. However, primary quantum yields are often difficult to measure. A *product quantum yield* (usually designated Φ) for a product P that is formed from a photoreaction of an initially excited molecule A can be expressed as

$$\Phi = \frac{\text{number of molecules of P formed}}{\text{number of quanta absorbed by A}}$$

Product quantum yields are much easier to measure. The number of quanta absorbed can be determined by an instrument called an *actinometer*, which is actually a standard photochemical system whose quantum yield is known. An example of the information that can be learned from quantum yields is the following. If the quantum yield of a product is finite and invariant with changes in experimental conditions, it is likely that the product is formed in a primary rate-determining process. Another example: in some reactions, the product quantum yields are found to be well over 1 (perhaps as high as 1000). Such a finding indicates a chain reaction (see p. $$$ for a discussion of chain reactions).

SONOCHEMISTRY

Sonochemistry (chemical events induced by exposure to ultrasound) occupies an important place in organic chemistry.[66] The chemical effects of high-intensity ultrasound were extensively studied in aqueous solutions for many years,[67] but is now applied to a variety of organic solvents. The origin of sonochemistry is acoustic cavitation: the creation, growth, and implosive collapse of gas vacuoles in solution by the sound field. Acoustic cavitation is the phenomenon by which intense ultrasonic waves induce the formation, oscillation, and implosion of gas

[66]Mason, T.J., Ed. *Advances in Sonochemistry*; JAI Press, NY, ***1990-1994***; Vols. 1–3; Price, G.J., Ed. *Current Trends in Sonochemistry*, Royal Society of Chemistry, Cambridge, UK, ***1992***; Suslick, K.S. *Science* ***1990***, *247*, 1439; Suslick, K.S. *Ultrasound: Its Chemical, Physical, and Biological Effects*, VCH, NY, ***1988***; Knapp, R.T.; Daily, J.W.; Hammitt, F.G. *Cavitation*, McGraw-Hill, NY, ***1970***; Young, F.R. *Cavitation*, McGraw-Hill, NY, ***1989***; Brennen, C.E. *Cavitation and Bubble Dynamics*, Oxford University Press, Oxford, UK, ***1995***; Anbar, M. *Science* ***1968***, *161*, 1343.

[67]Apfel, R.E., in Edmonds, P. *Methods in Experimental Physics*, Academic Press: New York, ***1981***; Vol. 19; Margulis, M.A. *Russ. J. Phys. Chem.* ***1976***, *50*, 1; Chendke, P.K.; Fogler, H.S. *Chem. Eng. J.* ***1974***, *8*, 165; Makino, K.; Mossoba, M.M.; Riesz, P. *J. Am. Chem. Soc.* ***1982***, *104*, 3537.

bubbles in liquids.[68] Liquids irradiated with high-power ultrasound undergo chemical decomposition and emit light.[69] These phenomena occur near the end of the collapse of bubbles expanded many times their equilibrium sizes. Chemistry (sonochemistry), light emission (sonoluminescence), and cavitation noise often accompany the process of acoustic cavitation.[70]

The collapse of gas vaculoes generates transient hot spots with local temperatures and pressures of several thousand degree K and hundreds of atmosphere. A sonochemical hot spot forms where the gas- and liquid-phase reaction zones have effective temperatures of 5200 and 1900 K, respectively.[71] The high temperatures and pressures that are achieved in the bubbles during the quasiadiabatic collapse[72] lead to the generation of chemistry and to the emission of light, most probably coming from molecular excited states and molecular recombination results. Note that work has been done that shows the commonly held view that bubbles are filled with saturated gas is inconsistent with a realistic estimate of condensation rates.[73] The alternative view of extensive solvent vapor supersaturation in bubbles uniformly heated to a few thousand K, depending on the conditions, is in accord with sonochemical rates and products.[74]

There is a correlation between sonochemical and sonoluminescence measurements, which is usually not observed. Sonoluminescence is the consequence that both the sonochemical production (under air) of oxidizing species and the emission of light reflect the variations of the primary sonochemical acts, which are themselves due to variations of the number of "active" bubbles.[75] Pulsed ultrasound in the high-frequency range (>1 MHz) is extensively used in medical diagnosis, and the effects of pulsed ultrasound in the 20-kHz range using an immersed titanium horn has been reported.[76]

The chemical effects of ultrasound have been studied for >50 years,[77] and applied to colloid chemistry in the 1940s.[78] Modern interest in the chemical uses

[68]Stottlemeyer, T.R.; Apfel, R.E. *J. Acoust. Soc. Am.* ***1997***, *102*, 1413.

[69]Suslick, K.S.; Crum, L.A., in *Sonochemistry and Sonoluminescence, Handbook of Acoustics*; Crocker, M.J., Ed., Wiley, NY, ***1998***, Chapt. 23; Leighton, T.G. *The Acoustic Bubble*, Academic Press, London, ***1994***, Chapter 4, Brennen, C.E. *Cavitation and Bubble Dynamics*, Oxford University Press, ***1995***; Chapts. 1–4. (4) Hua, I.; Hoffmann, M.R. *Environ. Sci. Technol.* ***1997***, *31*, 2237.

[70]Suslick, K.S.; Didenko, Y.T.; Fang, M.M.; Hyeon, T.; Kolbeck, K.J.; McNamara, III, W.B.; Mdleleni, M.M.; Wong, M. *Philos. Trans. R. Soc. London A* ***1999***, *357*, 335. For problems of sonochemistry and cavitation, see Margulis, M.A. *Ultrasonics Sonochemistry*, ***1994***, *1*, S87.

[71]Suslick, K.S.; Hammerton, D.A.; Cline Jr., R.E. *J. Am. Chem. Soc.* ***1986***, *108*, 5641.

[72]Didenko, Y.T.; McNamara III, W.B.; Suslick, K.S. *J. Am. Chem. Soc.* ***1999***, *121*, 5817.

[73]Colussi, A. J.; Hoffmann, M.R. *J. Phys. Chem. A.* ***1999***, *103*, 11336.

[74]Colussi, A.J.; Weavers, L.K.; Hoffmann, M.R. *J. Phys. Chem. A* ***1998***, *102*, 6927; Hart, E.J.; Henglein, A. *J. Phys. Chem.* ***1985***, *89*, 4342.

[75]Segebarth, N.; Eulaerts, O.; Reisse, J.; Crum, L. A.; Matula, T. J. *J. Phys. Chem. B.* ***2002***, *106*, 9181.

[76]Dekerckheer, C.; Bartik, K.; Lecomte, J.-P.; Reisse, J. *J. Phys. Chem. A.* ***1998***, *102*, 9177.

[77]Elpiner, I. E. *Ultrasound: Physical, Chemical, and Biological Effects*, Consultants Bureau, NY, ***1964***.

[78]Sollner, K. *Chem. Rev.* ***1944***, *34*, 371.

of ultrasound involve chemistry in both homogeneous[79] and heterogeneous[80] systems. Organic solvents, such as alkanes, support acoustic cavitation and the associated sonochemistry, and this leads to carbon–carbon bond cleavage and radical rearrangements, with the peak temperatures reached in such cavities controlled by the vapor pressure of the solvent.[81]

It is often difficult to compare the sonochemical results reported from different laboratories (the reproducibility problem in sonochemistry).[82] The sonochemical power irradiated into the reaction system can be different for different instruments. Several methods are available to estimate the amount of ultrasonic power entered into a sonochemical reaction,[82] the most common being calorimetry. This experiment involves measurement of the initial rate of a temperature rise produced when a system is irradiated by power ultrasound. It has been shown that calorimetric methods combined with the Weissler reaction can be used to standardize the ultrasonic power of individual ultrasonic devices.[83]

Sonochemistry has been used to facilitate or assist many organic reactions,[84] as well as other applications.[85] The scope of reactions studied is beyond this work, but some representative examples will be listed. Ultrasound has been used to promote lithiation of organic compounds,[86] for the generation of carbenes,[87] and

[79]Suslick, K.S.; Schubert, P.F.; Goodale, J.W. *J. Am. Chem. Soc.* ***1981***, *103*, 7342; Lorimer, J.P.; Mason, T.J. *J. Chem. Soc., Chem. Commun.* ***1980***,1135; Margulis, M.A. *Khim. Zh.* ***1981***, 57; Nishikawa, S.; Obi, U.; Mashima, M. *Bull. Chem. Soc. Jpn.* ***1977***, *50*, 1716; Yu, T.J.; Sutherland, R.G.; Verrall, R.E. *Can. J. Chem.* ***1980***, *58*, 1909; Sehgal, C.; Sutherland, R.G.; Verrall, R.E. *J. Phys. Chem.* ***1980***, *84*, 2920; Sehgal, C.; Yu, T.J.; Sutherland, R.G.; Verrall, R.E. *J. Phys. Chem.* ***1982***, *86*,2982; Sehgal, C.M.; Wang, S.Y. *J. Am. Chem. Soc.* ***1981***, *103*, 6606; Staas, W.H.; Spurlock, L.A. *J. Chem. Soc., Perkin Trans. I* ***1975***, 1675.

[80]Han, B.-H.; Boudjouk, P. *J. Org. Chem.* ***1982***, *47*, 5030; Boudjouk, P.; Han, B.-H. *Tetrahedron Lett.* ***1981***, *22*, 3813; Han, B.-H.; Boudjouk, P. *J. Org. Chem.* ***1982***, *47*, 751; Boudjouk, P.; Han, B.-H.; Anderson, K.R. *J. Am. Chem. Soc.* ***1982***, *104*, 4992; Boudjouk, P.; Han, B.-H. *J. Catal.* ***1983***, *79*, 489; Fry, A.J.; Ginsburg, G.S. *J. Am. Chem. Soc.* ***1979***, *101*, 3927; Kitazume, T.; Ishikawa, N. *Chem. Lett.* ***1981***, 1679; Kristol, D.S.; Klotz, H.; Parker, R.C. *Tetrahedron Lett.* ***1981***, *22*, 907; Lintner, W.; Hanesian, D. *Ultrasonics* ***1977***, *15*, 21; Luche, J.-L.; Damiano, J. *J. Am. Chem. Soc.* ***1980***, *102*, 7926; Moon, S.; Duchin, L.; Cooney, J.V. *Tetrahedron Lett.* ***1979***, 3917; Racher, S.; Klein, P. *J. Org. Chem.* ***1981***, *46*, 3558; Regen, S.L.; Singh, A. *J. Org. Chem.* ***1982***, *47*, 1587; Kegelaers, Y.; Eulaerts, O.; Reisse, J.; Segebarth, N. *Eur. J. Org. Chem.* ***2001***, 3683.

[81]Suslick, K.S. Gawienowski, J.J.; Schubert, P.F.; Wang, H.H. *J. Phys. Chem.* ***1983***, *87*, 2299.

[82]Mason, T.J. *Practical Sonochemistry: User's Guide to Applications in Chemistry and Chemical Engineering*, Ellis Horwood, West Sussex, ***1991***, pp. 43–46; Broeckaert, L.; Caulier, T.; Fabre, O.; Maerschalk, C.; Reisse, J.; Vandercammen, J.; Yang, D.H.; Lepoint, T.; Mullie, F. *Current Trends in Sonochemistry*, Price, G.J., Ed., Royal Society of Chemistry, Cambridge, ***1992***, p. 8; Mason, T.J.; Lorimer, J.P.; Bates, D.M.; Zhao, Y. *Ultrasonics Sonochemistry* ***1994***, *1*, S91; Mason, T.J.; Lorimer, J.P.; Bates, D.M. *Ultrasonics* ***1992***, *30*, 40.

[83]Kimura, T.; Sakamoto, T.; Leveque, J.-M.; Sohmiya, H.; Fujita, M.; Ikeda, S.; Ando, T. *Ultrasonics Sonochemistry* ***1996***, *3*, S157.

[84]*Synthetic Organic Sonochemistry*, Luche, J.-L. (Universite de Savoie, France), Plenum Press, NY. ***1998***; Luche, J.-L. *Ultrasonics Sonochemistry* ***1996***, *3*, S215; Bremner, D.H. *Ultrasonics Sonochemistry* ***1994***, *1*, S119.

[85]Thompson, L.H.; Doraiswamy, L.K. *Ind. Eng. Chem. Res.* ***1999***, *38*, 1215; Adewuyi, Y.G. *Ind. Eng. Chem. Res.* ***2001***, *40*, 4681.

[86]Boudjouk, P.; Sooriyakumaran, R.; Han, B.H. *J. Org. Chem.* ***1986***, *51*, 2818, and Ref. 1 therein.

[87]Regen, S.L.; Singh, A. *J. Org. Chem.* ***1982***, *47*, 1587.

reactions of metal carbonyls where sonochemical ligand dissociation has been observed, which often produces multiple CO substitution.[88] The influence of ultrasound on phase-transfer catalyzed thioether synthesis has been studied.[89]

Sonochemistry has been applied to acceleration of the Reformatsky reaction,[90] Diels–Alder reactions,[91] the arylation of active methylene compounds[92] nucleophilic aromatic substitution of haloarenes,[93] and to hydrostannation and tin hydride reduction.[94] Other sonochemical applications involve the reaction of benzyl chloride and nitrobenzene,[95] a $S_{RN}1$ reaction in liquid ammonia at room temperature,[96] and Knoevenagel condensation of aromatic aldehydes.[97] Iodination of aliphatic hydrocarbons can be accelerated,[98] and oxyallyl cations have been prepared from α,α'-diiodoketones using sonochemistry.[99] Sonochemistry has been applied to the preparation of carbohydrate compounds.[100] When sonochemistry is an important feature of a chemical reaction, this fact will be noted in the reactions presented in Chapters 10–19.

MICROWAVE CHEMISTRY

In 1986, independent work by Gedye and co-workers[101] as well as Giguere and Majetich[102] reported the advantages of microwave irradiation for organic synthesis. Gedye described four different types of reactions were studied, including the hydrolysis of benzamide to benzoic acid under acidic conditions, and all reactions showed significant rate enhancements when compared to the same reactions done at reflux conditions.[103] Giguere and Majetich reported rate enhancements for microwave-promoted Diels–Alder, Claisen, and ene reactions. At this point,

[88]Suslick, K.S.; Goodale, J.W.; Schubert, P.F.; Wang, H.H. *J. Am. Chem. Soc.* ***1983***, *105*, 5781.
[89]Wang, M.-L.; Rajendran, V. *J. Mol. Catalysis A: Chemical* ***2005***, *244*, 237.
[90]Han, B.H.; Boudjouk, P. *J. Org. Chem.*, ***1982***, *47*, 5030.
[91]Nebois, P.; Bouaziz, Z.; Fillion, H.; Moeini, L.; Piquer, Ma.J.A.; Luche, J.-L.; Riera, A.; Moyano, A.; Pericàs, M.A. *Ultrasonics Sonochemistry* ***1996***, *3*, 7.
[92]Mečiarová, M.; Kiripolský, M.; Toma, Š *Ultrasonics Sonochemistry* ***2005***, *12*, 401.
[93]Mečiarová, M.; Toma, S.; Magdolen, P. *Ultrasonics Sonochemistry* ***2003***, *10*, 265.
[94]Nakamura, E.; Machii, D.; Inubushi, T. *J. Am. Chem. Soc.* ***1989***, *111*, 6849.
[95]Vinatoru, M.; Stavrescua, R.; Milcoveanu, A.B.; Toma, M.; T.J. Mason, T.J. *Ultrasonics Sonochemistry* ***2002***, *9*, 245.
[96]Manzo, P.G.; Palacios, S.M.; Alonso, R.A. *Tetrahedron Lett.* ***1994***, *35*, 677.
[97]McNulty, J.; Steere, J.A.; Wolf, S. *Tetrahedron Lett.* ***1998***, *39*, 8013.
[98]Kimura, T.; Fujita, M.; Sohmiya, H. Ando, T. *Ultrasonics Sonochemistry* ***2002***, *9*, 205.
[99]Montaña, A.M.; Grima, P.M. *Tetrahedron Lett.* ***2001***, *42*, 7809.
[100]Kardos, N.; Luche, J.-L. *Carbohydrate Res.* ***2001***, *332*, 115.
[101]Gedye R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L. *Tetrahedron Lett.* ***1986***, *27*, 279; Gedye, R. N.; Smith, F. E.; Westaway, K. C. *Can. J. Chem.* ***1987***, *66*, 17.
[102]Giguere, R.J.; Bray, T.; Duncan, S.M.; Majetich, G. *Tetrahedron Lett.* ***1986***, *27*, 4945.
[103]Taken from Horeis, G.; Pichler, S.; Stadler, A.; Gössler, W.; Kappe, C.O. *Microwave-Assisted Organic Synthesis - Back to the Roots*, Fifth International Electronic Conference on Synthetic Organic Chemistry (ECSOC-5), ***2001*** (http://www.mdpi.org/ecsoc-5.htm).

>2000 publications[104] have appeared describing chemical synthesis promoted by microwave irradiation, including many review articles[105] and books.[106]

Microwaves are electromagnetic waves (see p. 329) and there are electric and magnetic field components. Charged particles start to migrate or rotate as the electric field is applied,[107] which leads to further polarization of polar particles. Because the concerted forces applied by the electric and magnetic components of microwaves are rapidly changing in direction (2.4×10^9/s), warming occurs.[107] In general, the most common frequencies used for microwave dielectric heating[108] are 918 MHz and 2.45 GHz[109] (wavelengths of 33.3 and 12.2 cm, respectively), which are in the region between the IR and radiowave wavelengths in the electromagnetic spectrum. For chemical reactions done with microwave irradiation, rapid heating is usually observed, and if a solvent is used superheating of that solvent was always observed.[108] In the early days of microwave chemistry, reactions were often done in open vessels, but also in sealed Teflon or glass vessels using unmodified domestic household ovens.[110] Dielectric heating is direct so if the reaction matrix has a sufficiently large dielectric loss tangent, and contains molecules possessing a dipole moment, a solvent is not required. The use of dry-reaction microwave chemistry is increasingly popular.[111]

Microwave dielectric heating was initially categorized by thermal effects and nonthermal effects.[112] "Thermal effects are those which are caused by the different temperature regime which can be created due to microwave dielectric heating. Nonthermal effects are effects,[113] which are caused by effects specifically inherent to

[104]Kappe, C. O. *Angew. Chem. Int. Ed.* ***2004***, *43*, 6250.

[105]Majetich, G.; Karen, W. in Kingston, H.M.; Haswell, S.J. *Microwave-Enhanced Chemistry: Fundamentals, Sample Preparation, and Applications*. American Chemical Society, Washington, DC, ***1997***, p 772; Giguere, R.J. *Org. Synth.: Theory Appl.* ***1989***, *1*, 103; Mingos, D.M.P.; Baghurst, D.R. *Chem. Soc. Rev.* ***1991***, *20*, 1; Abramovitch, R.A. *Org. Prep. Proced. Int.* ***1991***, *23*, 683; Bose, A.K.; Manhas, M.S.; Banik, B.K.; Robb, E.W. *Res. Chem. Intermed.* ***1994***, *20*, 1; Majetich, G.; Hicks, R. *Res. Chem. Intermed.* ***1994***, *20*, 61; Strauss, C.R.; Trainor, R.W. *Aust. J. Chem.* ***1995***, *48*, 1665; Caddick, S. *Tetrahedron* ***1995***, *51*, 10403; Mingos, D M.P. *Res. Chem. Intermed.* ***1994***, *20*, 85; Berlan, J. *Rad. Phys. Chem.* ***1995***, *45*, 581; Fini, A.; Breccia, A. *Pure Appl. Chem.* ***1999***, *71*, 573.

[106]Kingston, H. M.; Haswell, S.J. *Microwave-Enhanced Chemistry. Fundamentals, Sample Preparation, and Applications*, American Chemical Society, ***1997***; Loupy, A. *Microwaves in Organic Synthesis*, Wiley-VCH, Weinheim, ***2002***; Hayes, B.L. *Microwave Synthesis: Chemistry at the Speed of Light*, CEM Publishing, Matthews, NC, ***2002***; Lidström, P., Tierney, J.P. *Microwave-Assisted Organic Synthesis*, Blackwell Scientific, ***2005*** ; Kappe, C.O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*, Wiley-VCH, Weinheim, ***2005***.

[107]Galema, S.A. *Chem. Soc. Rev.* ***1997***, *26*, 233.

[108]Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S. J.; Mingos, D. M. P. *Chem. Soc. Rev.* ***1998***, *27*, 213.

[109]This frequencey is usually applied in domestic microwave ovens.

[110]Caddick, S. *Tetrahedron* ***1995***, *51*, 10403.

[111]Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathé, D. *Synthesis* ***1998***, 1213; Varma, R. S. *Green Chem.* ***1999***, 43; Kidawi, M. *Pure Appl. Chem.* ***2001***, *73*, 147; Varma, R. S. *Pure Appl. Chem.* ***2001***, *73*, 193.

[112]Langa, F.; de la Cruz, P.; de la Hoz, A.; Díaz-Ortiz, A.; Díez-Barra, E. *Contemp. Org. Synth.* ***1997***, *4*, 373.

[113]See Kuhnert, N. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1863.

the microwaves and are not caused by different temperature regimes."[107] Some claimed special effects[114] in microwave chemistry, such as lowering of Gibbs energy of activation, but later study under careful temperature control indicated no special rate effects.[115] When conventional microwave ovens were used, temperature control was difficult particularly when reactions are carried out in closed reaction vessels. The main contributing factor to any rate acceleration caused by microwave dielectric heating seems to be due to a thermal effect. The thermal effect may be due to a faster initial heating rate or to the occurrence of local regions with higher temperatures.[107]

Conventional microwave ovens are used less often for microwave chemistry today. Microwave reactors for chemical synthesis are commercially available and widely used in academia and in industry. These instruments have built-in magnetic stirring, direct temperature control of the reaction mixture, shielded thermocouples or IR sensors, and the ability to control temperature and pressure by regulating microwave output power.

The applications of microwave chemistry to organic chemistry are too numerous to mention. A few representative examples will be given to illustrate the scope and utility. Microwave chemistry is widely used in synthesis.[116] Examples include the Heck reaction (reaction **13-10**),[117] the Suzuki reaction (reaction **13-12**),[118] the Sonogashira reaction (reaction **13-13**),[119] Ullman type couplings (reaction

[114]Laurent, R.; Laporterie, A.; Dubac, J.; Berlan, J.; Lefeuvre, S.; Audhuy, M. *J. Org. Chem.* ***1992***, *57*, 7099, and references cited therein.

[115]Raner, K.D.; Strauss, C.R.; Vyskoc, F.; Mokbel, L. J. *Org. Chem.* ***1993***, *58*, 950, and references cited therein.

[116]Abramovitch, R. A. *Org. Prep. Proced. Int.* ***1991***, *23*, 685; Caddick, S. *Tetrahedron* ***1995***, *51*, 10403; Strauss, C. R.; Trainor, R. W. *Aust. J. Chem.* ***1995***, *48*, 1665; Bose, A. K.; Banik, B. K.; Lavlinskaia, N.; Jayaraman, M.; Manhas, M. S. *Chemtech* ***1997***, *27*, 18; Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* ***2001***, *57*, 9225; Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* ***2002***, *35*, 717; Nüchter, M.; Ondruschka, B.; Bonrath, W.; Gum, A. *Green Chem.* ***2004***, *6*, 128; Hayes, B.L. *Aldrichim. Acta* ***2004***, *37*, 66.

[117]Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* ***2002***, *35*, 717; Olofsson, K.; Larhed, M. in Lidström, P.; Tierney, J.P. *Microwave-Assisted Organic Synthesis*, Blackwell, Oxford, ***2004***, Chapt. 2.; Andappan, M.M.S.; Nilsson, P.; Larhed, M. *Mol. Diversity* ***2003***, *7*, 97.

[118]Nuteberg, D.; Schaal, W.; Hamelink, E.; Vrang, L.; Larhed, M. *J. Comb. Chem.* ***2003***, *5*, 456; Miller, S.P.; Morgan, J.B.; Nepveux, F.J.; Morken, J.P. *Org. Lett.* ***2004***, *6*, 131; Kaval, N.; Bisztray, K.; Dehaen, W.; Kappe, C.O.; Van der Eycken, E. *Mol. Diversity* ***2003***, *7*, 125; Gong, Y.; He, W. *Heterocycles* ***2004***, *62*, 851; Organ, M.G.; Mayer, S.; Lepifre, F.; N'Zemba, B.; Khatri, J. *Mol. Diversity* ***2003***, *7*, 211; Luo, G.; Chen, L.; Pointdexter, G.S. *Tetrahedron Lett.* ***2002***, *43*, 5739; Wu, T.Y.H.; Schultz, P.G.; Ding, S. *Org. Lett.* ***2003***, *5*, 3587; Han, J.W.; Castro, J.C.; Burgess, K. *Tetrahedron Lett.* ***2003***, *44*, 9359; Leadbeater, N.E.; Marco, M. *J. Org. Chem.* ***2003***, *68*, 888; Bai, L.; Wang, J.-X.; Zhang, Y. *Green Chem.* ***2003***, *5*, 615 ; Leadbeater, N.E.; Marco, M. *J. Org. Chem.* ***2003***, *68*, 5660.

[119]Kaval, N.; Bisztray, K.; Dehaen, W.; Kappe, C.O.; Van der Eycken, E. *Mol. Diversity* ***2003***, *7*, 125; Gong, Y.; He, W. *Heterocycles* ***2004***, *62*, 851; Miljani, O.Š; Vollhardt, K.P.C.; Whitener, G.D. *Synlett* ***2003***, 29; Petricci, E.; Radi, M.; Corelli, F.; Botta, M. *Tetrahedron Lett.* ***2003***, *44*, 9181; Leadbeater, N.E.; Marco, M.; Tominack, B.J. *Org. Lett.* ***2003***, *5*, 3919 ; Appukkuttan, P.; Dehaen, W.; Van der Eycken, E. *Eur. J. Org. Chem.* ***2003***, 4713.

13-3),[120] cycloaddition reactions (reactions **15-58–15-66**),[121] dihydroxylation (reaction **15-48**),[122] and the Mitsunobu reaction (reaction **10-23**).[123] There are a multitude of other reactions types from earlier literature that can be found in the cited review articles. When microwave chemistry is an important feature of a chemical reaction, this fact will be noted in the reactions presented in Chapters 10–19.

[120]Wu, Y.-J.; He, H.; L'Heureux, A. *Tetrahedron Lett.* ***2003***, *44*, 4217; Lange, J.H.M.; Hofmeyer, L.J.F.; Hout, F.A.S.; Osnabrug, S.J.M.; Verveer, P.C.; Kruse, C.G.; Feenstra, R.W. *Tetrahedron Lett.* ***2002***, *43*, 1101.

[121]For example, see de la Hoz, A.; D'az-Ortis, A.; Moreno, A.; Langa, F. *Eur. J. Org. Chem.* ***2000***, 3659; Van der Eycken, E.; Appukkuttan, P.; De Borggraeve, W.; Dehaen, W.; Dallinger, D.; Kappe, C.O. *J. Org. Chem.* ***2002***, *67*, 7904 ; Pinto, D.C.G.A.; Silva, A.M.S.; Almeida, L.M.P.M.; Carrillo, J.R.; D'az-Ortiz, A.; de la Hoz, A.; Cavaleiro, J.A.S. *Synlett* ***2003***, 1415.

[122]Dupau, P.; Epple, R.; Thomas, A.A.; Fokin, V.V.; Sharpless, K.B. *Adv. Synth. Catal.* ***2002***, *344*, 421.

[123]Lampariello, L.R.; Piras, D.; Rodriquez, M.; Taddei, M. *J. Org. Chem.* ***2003***, *68*, 7893; Raheem, I.T.; Goodman, S.N.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2004***, *126*, 706.

CHAPTER 8

Acids and Bases

Two acid–base theories are used in organic chemistry today: the Brønsted theory and the Lewis theory.[1] These theories are quite compatible and are used for different purposes.[2]

BRØNSTED THEORY

According to this theory, an acid is defined as a *proton donor*[3] and a base as a *proton acceptor* (a base must have a pair of electrons available to share with the proton; this is usually present as an unshared pair, but sometimes is in a π orbital). An acid–base reaction is simply the transfer of a proton from an acid to a base. (Protons do not exist free in solution but must be attached to an electron pair.) When the acid gives up a proton, the species remaining still retains the electron pair to which the proton was formerly attached. Thus the new species, in theory at least, can reacquire a proton and is therefore a base. It is referred to as the *conjugate base* of the acid. All acids have a conjugate base, and all bases have a *conjugate acid*. All acid–base reactions fit the equation

$$\underset{\text{Acid}_1}{\text{A—H}} \quad + \quad \underset{\text{Base}_2}{\text{B}} \quad \rightleftharpoons \quad \underset{\text{Base}_1}{\text{A}} \quad + \quad \underset{\text{Acid}_2}{\text{B—H}}$$

[1]For monographs on acids and bases, see Stewart, R. *The Proton: Applications to Organic Chemistry*, Academic Press, NY, ***1985***; Bell, R.P. *The Proton in Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, ***1973***; Finston, H.L.; Rychtman, A.C. *A New View of Current Acid–Base Theories*, Wiley, NY, ***1982***.
[2]For discussion of the historical development of acid–base theory, see Bell, R.P. *Q. Rev. Chem. Soc.* ***1947***, *1*, 113; Bell, R.P. *The Proton in Chemistry*, 1st ed., Cornell University Press, Ithaca, NY, ***1959***, pp. 7–17.
[3]According to IUPAC terminology (Bunnett, J.F.; Jones, R.A.Y. *Pure Appl. Chem.* ***1988***, *60*, 1115), an acid is a *hydron* donor. IUPAC recommends that the term *proton* be restricted to the nucleus of the hydrogen isotope of mass 1, while the nucleus of the naturally occurring element (which contains ~0.015% deuterium) be called the *hydron* (the nucleus of mass 2 has always been known as the *deuteron*). This accords with the naturally occurring negative ion, which has long been called the *hydride* ion. In this book, however, we will continue to use *proton* for the naturally occurring form, because most of the literature uses this term.

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No charges are shown in this equation, but an acid always has a charge one positive unit higher than that of its conjugate base.

Acid strength may be defined as the tendency to give up a proton and *base strength* as the tendency to accept a proton. Acid–base reactions occur because acids are not equally strong. If an acid, say HCl, is placed in contact with the conjugate base of a weaker acid, say acetate ion, the proton will be transferred because the HCl has a greater tendency to lose its proton than acetic acid. That is, the equilibrium

$$HCl + CH_3COO^- \rightleftharpoons CH_3COOH + Cl^-$$

lies well to the right. On the other hand, treatment of acetic acid with chloride ion gives essentially no reaction, since the weaker acid already has the proton.

This is always the case for any two acids, and by measuring the positions of the equilibrium the relative strengths of acids and bases can be determined.[4] Of course, if the two acids involved are close to each other in strength, a measurable reaction will occur from both sides, though the position of equilibrium will still be over to the side of the weaker acid (unless the acidities are equal within experimental limits). In this manner, it is possible to construct a table in which acids are listed in order of acid strength (Table 8.1).[5] Next to each acid in Table 8.1 is shown its conjugate base. It is obvious that if the acids in such a table are listed in *decreasing* order of acid strength, the bases must be listed in *increasing* order of base strength, since the stronger the acid, the weaker must be its conjugate base. The pK_a values in Table 8.1 are most accurate in the middle of the table. They are much harder to measure[6] for very strong and very weak acids, and these values must be regarded as approximate. Qualitatively, it can be determined that $HClO_4$ is a stronger acid than H_2SO_4, since a mixture of $HClO_4$ and H_2SO_4 in 4-methyl-2-pentanone can be titrated to an $HClO_4$ end point without interference by H_2SO_4.[7] Similarly, $HClO_4$ can be shown to be stronger than HNO_3 or HCl. However, this is not quantitative, and the value of -10 in the table is not much more than an educated guess. The values for RNO_2H^+, $ArNO_2H^+$, HI, $RCNH^+$ and RSH_2^+ must also be regarded as highly speculative.[8] A wide variety of pK_a values has been reported for the conjugate acids of even such simple bases

[4]Although equilibrium is reached in most acid–base reactions extremely rapidly (see p. $$$), some are slow (especially those in which the proton is given up by a carbon) and in these cases time must be allowed for the system to come to equilibrium.

[5]Table 8.1 is a thermodynamic acidity scale and applies only to positions of equilibria. For the distinction between thermodynamic and kinetic acidity (see p. 367).

[6]For a review of methods of determining pK_a values, see Cookson, R.F. *Chem. Rev.* ***1974***, *74*, 5.

[7]Kolthoff, I.M.; Bruckenstein, S., in Kolthoff, I.M.; Elving, P.J. *Treatise on Analytical Chemistry*, Vol. 1, pt. 1; Wiley, NY, ***1959***, pp. 475–542, p. 479.

[8]For reviews of organic compounds protonated at O, N, or S, see Olah, G.A.; White, A.M.; O'Brien, D.H. *Chem. Rev.* ***1970***, *70*, 561; Olah, G.A.; White, A.M.; O'Brien, D.H., in Olah, G.A.; Schleyer, P.V.R. *Carbonium Ions*, Vol. 4; Wiley, NY, ***1973***, pp. 1697–1781.

as acetone[9] (−0.24 to −7.2), diethyl ether (−0.30 to −6.2), ethanol (−0.33 to −4.8), methanol (−0.34 to −4.9), and 2-propanol (−0.35 to −5.2), depending on the method used to measure them.[10] Very accurate values can be obtained only for acids weaker than hydronium ion and stronger than water.

A crystallographic scale of acidity has been developed, including the acidity of C—H compounds. Measuring the mean C—H•••O distances in crystal structures correlated well with conventional $pK_{a(DMSO)}$ values, where dimethyl sulfoxide = DMSO.[11] An *ab initio* study was able to correlate ring strain in strained hydrocarbons with hydrogen-bond acidity.[12]

The bottom portion of Table 8.1 consists of very weak acids (pK_a above ~17).[13] In most of these acids, the proton is lost from a carbon atom, and such acids are known as *carbon acids*. The pK_a values for such weak acids are often difficult to measure and are known only approximately. The methods used to determine the relative positions of these acids are discussed in Chapter 5.[14] The acidity of carbon acids is proportional to the stability of the carbanions that are their conjugate bases (see p. 249).

The extremely strong acids at the top of the table are known as *super acids* (see p. 236).[15] The actual species present in the FSO_3H—SbF_5 mixture are probably $H[SbF_5(SO_3F)]$ and $H[SbF_2(SO_3F)_4$.[16] The addition of SO_3 causes formation of the still stronger $H[SbF_4(SO_3F)_2]$, $H[SbF_3(SO_3F)_3]$, and $H[(SbF_5)_2(SO_3F)]$.[16]

By the use of tables, such as Table 8.1, it is possible to determine whether a given acid will react with a given base. For tables in which acids are listed in order of decreasing strength, the rule is that *any acid will react with any base in the table that is below it but not with any above it*.[17] It must be emphasized that the order of

[9]For discussions of pK_a determinations for the conjugate acids of ketones, see Bagno, A.; Lucchini, V.; Scorrano, G. *Bull. Soc. Chim. Fr.* ***1987***, 563; Toullec, J. *Tetrahedron Lett.* ***1988***, *29*, 5541.

[10]Rochester, C.H. *Acidity Functions*; Academic Press, NY, ***1970***. For discussion of the basicity of such compounds, see Liler, M. *Reaction Mechanisms in Sulfuric Acid*, Academic Press, NY, ***1971***, pp. 118–139.

[11]Pedireddi, V.R.; Desiraju, G.R. *J. Chem. Soc. Chem. Commun.* ***1992***, 988.

[12]Alkorta, I.; Campillo, N.; Rozas, I.; Elguero, J. *J. Org. Chem.* ***1998***, *63*, 7759.

[13]For a monograph on very weak acids, see Reutov, O.A.; Beletskaya, I.P.; Butin, K.P. *CH-Acids*, Pergamon, NY, ***1978***. For other discussions, see Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, ***1965***, pp. 1–45; Streitwieser, Jr., A.; Hammons, J.H. *Prog. Phys. Org. Chem.* ***1965***, *3*, 41. For a study of substituent effects of weak acids see Wiberg, K.B. *J. Org. Chem.* ***2002***, *67*, 1613.

[14]For reviews of methods used to measure the acidity of carbon acids, see Jones, J.R. *Q. Rev. Chem. Soc.* ***1971***, *25*, 365; Fischer, H.; Rewicki, D. *Prog. Org. Chem.* ***1968***, *7*, 116; Reutov, O.A.; Beletskaya, I.P.; Butin, K.P. *CH-Acids*, Chapt. 1, Pergamon, NY, ***1978*** [an earlier version of this chapter appeared in *Russ. Chem. Rev.* ***1974***, *43*, 17]; Ref. 6. For reviews on acidities of carbon acids, see Gau, G.; Assadourian, L.; Veracini, S. *Prog. Phys. Org. Chem.* ***1987***, *16*, 237; in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, pt. A, Elsevier, NY, ***1980***, the reviews by Pellerite, M.J.; Brauman, J.I. pp. 55–96 (gas-phase acidities); and Streitwieser, Jr., A.; Juaristi, E.; Nebenzahl, L. pp. 323–381.

[15]For a monograph, see Olah, G.A.; Prakash, G.K.S.; Sommer, J. *Superacids*; Wiley, NY, ***1985***. For a review, see Gillespie, R.J.; Peel, T.E. *Adv. Phys. Org. Chem.* ***1971***, *9*, 1. For a review of solid super acids, see Arata, K. *Adv. Catal.* ***1990***, *37*, 165. For a review of methods of measuring superacidity, see Jost, R.; Sommer, J. *Rev. Chem. Intermed.* ***1988***, *9*, 171.

[16]Gillespie, R.J. *Acc. Chem. Res.* ***1968***, *1*, 202.

[17]These reactions are equilibria. What the rule actually says is that the position of equilibrium will be such that the weaker acid predominates. However, this needs to be taken into account only when the acid and base are close to each other in the table (within ~2 p*K* units).

TABLE 8.1. Thep K_a Values for Many Types of Acids. The values in boldface are exact values; the others are approximate, especially above 18 and below −2.[18]

Acid	Base	Approximate pK_a (relative to water)	References
Super Acids			
HF—SbF_5	SbF_6^-		19
FSO_3H—SbF_5—SO_3			16
FSO_3H—SbF_5			16,19
FSO_3H	FSO_3^-		16
RNO_2H^+	RNO_2	−12	20
$ArNO_2H^+$	$ArNO_2$	−11	20
$HClO_4$	ClO_4^-	−10	21
HI	I^-	−10	21
$RCNH^+$	RCN	−10	22
R—C(=$^+$OH)—H	R—C(=O)—H	−10	23
H_2SO_4	HSO_4^-		
HBr	Br^-	−9	21

(*continued*)

[18]In this table we do not give pK_a values for individual compounds (with a few exceptions), only average values for functional groups. Extensive tables of pK values for many carboxylic and other acids and amines are given in Brown, H.C.; McDaniel, D.H.; Häflinger, O., in Braude, E.A.; Nachod, F.C. *Determination of Organic Structures by Physical Methods*, Vol. 1, Academic Press, NY, ***1955***. Values for >5500 organic acids are given, in Serjeant, E.P.; Dempsey, B. *Ionisation Constants of Organic Acids in Aqueous Solution*, Pergamon, Elmsford NY, ***1979***; Kortüm, G.; Vogel, W.; Andrussow, K. *Dissociation Constants of Organic Acids in Aqueous Solution*, Butterworth, London, ***1961***. The index in the 1979 volume covers both volumes. Kortüm, G.; Vogel, W.; Andrussow, K. *Pure Appl. Chem.* ***1960***, *1*, 190 give values for 631 carboxylic acids and 110 phenols. Arnett, E.M. *Prog. Phys. Org. Chem.* ***1963***, *1*, 223 gives hundreds of values for very strong acids (very weak bases). Perrin, D.D. *Dissociation Constants of Organic Bases in Aqueous Solution*, Butterworth, London, ***1965***, and Supplement, 1972 list pK values for >7000 amines and other bases. Collumeau, A. *Bull. Soc. Chim. Fr.* ***1968***, 5087 gives pK values for ~800 acids and bases. Bordwell, F.G. *Acc. Chem. Res.* ***1988***, *21*, 456 gives values for >300 acids in dimethyl sulfoxide. For inorganic acids and bases, see Perrin, D.D. *Ionisation Constants of Inorganic Acids and Bases in Aqueous Solution*, 2nd ed., Pergamon, Elmsford NY, ***1982***; *Pure Appl. Chem.* ***1969***, *20*, 133.

[19]Brouwer, D.M.; van Doorn, J.A. *Recl. Trav. Chim. Pays-Bas* ***1972***, *91*, 895; Gold,V.; Laali, K.; Morris, K.P.; Zdunek, L.Z. *J. Chem. Soc. Chem. Commun.* ***1981***, 769; Sommer, J.; Canivet, P.; Schwartz, S.; Rimmelin, P. *Nouv. J. Chim.* ***1981***, *5*, 45.

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TABLE 8.1. (*Continued*)

Acid	Base	Approximate pK_a (relative to water)	References
Ar–C(=$^{+}$OH)–OR [24]	Ar–C(=O)–OR	−7.4	20
HCl	Cl^-	−7	21
RSH_2+	RSH	−7	20
Ar–C(=$^{+}$OH)–OH [24]	Ar–C(=O)–OH	−7	25
Ar–C(=$^{+}$OH)–H	Ar–C(=O)–H	−7	26
R–C(=$^{+}$OH)–R	R–C(=O)–R	−7	9,22,27
$ArSO_3H$	$ArSO_3^-$	−6.5	28
R–C(=$^{+}$OH)–OR [24]	R–C(=O)–OR	−6.5	20
$ArOH_2^+$	ArOH	−6.4	29
R–C(=$^{+}$OH)–OH [24]	R–C(=O)–OH	−6	20
Ar–C(=$^{+}$OH)–R	Ar–C(=O)–R	−6	26,30
Ar–$\overset{+}{O}$(H)–R	Ar–O–R	−6	29,31
$CH(CN)_3$	$^{-}C(CN)_3$	−5	32

[24]Carboxylic acids, esters, and amides are shown in this table to be protonated on the carbonyl oxygen. There has been some controversy on this point, but the weight of evidence is in that direction. See, for example, Katritzky, A.R.; Jones, R.A.Y. *Chem. Ind. (London)* ***1961***, 722; Ottenheym, J.H.; van Raayen, W.; Smidt, J.; Groenewege, M.P.; Veerkamp, T.A. *Recl. Trav. Chim. Pays-Bas* ***1961***, *80*, 1211; Stewart, R.; Muenster, L.J. *Can. J. Chem.* ***1961***, *39*, 401; Smith, C.R.; Yates, K. *Can. J. Chem.* ***1972***, *50*, 771; Benedetti, E.; Di Blasio, B.; Baine, P. *J. Chem. Soc. Perkin Trans. 2* ***1980***, 500; Ref. 8; Homer, R.B.; Johnson, C.D., in Zabicky, J. *The Chemistry of Amides*; Wiley, NY, ***1970***, pp. 188–197. It has been shown that some amides protonate at nitrogen: see Perrin, C.L. *Acc. Chem. Res.* ***1989***, *22*, 268. For a review of alternative proton sites, see Liler, M. *Adv. Phys. Org. Chem.* ***1975***, *11*, 267.

[25]Stewart, R.; Granger, M.R. *Can. J. Chem.* ***1961***, *39*, 2508.

[26]Yates, K.; Stewart, R. *Can. J. Chem.* ***1959***, *37*, 664; Stewart, R.; Yates, K. *J. Am. Chem. Soc.* ***1958***, *80*, 6355.

[27]Lee, D.G. *Can. J. Chem.* ***1970***, *48*, 1919.

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[30]Fischer, A.; Grigor, B.A.; Packer, J.; Vaughan, J. *J. Am. Chem. Soc.* ***1961***, *83*, 4208.

[31]Arnett, E.M.; Wu, C.Y. *J. Am. Chem. Soc.* ***1960***, *82*, 4999.

[32]Boyd, R.H. *J. Phys. Chem.* ***1963***, *67*, 737.

TABLE 8.1. (*Continued*)

Acid	Base	Approximate pK_a (relative to water)	References
Ar_3NH^+	Ar_3N	−5	33
$H{-}C(={}^{+}OH){-}H$	$H{-}C(=O){-}H$	−4	34
$R{-}\overset{+}{O}(H){-}R$	$R{-}O{-}R$	−3.5	22,31,35
$R_3COH_2^+$	R_3COH	−2	35
$R_2CHOH_2^+$	R_2CHOH	−2	35,36
$RCH_2OH_2^+$	RCH_2OH	−2	22,35,36
H_3O^+	H_2O	**−1.74**	37
$Ar{-}C(={}^{+}OH){-}NH_2$ [24]	$Ar{-}C(=O){-}NH_2$	−1.5	38
HNO_3	NO_3^-	−1.4	21
$R{-}C(={}^{+}OH){-}NH_2$ [24]	$R{-}C(=O){-}NH_2$	−0.5	38
$Ar_2NH_2^+$	Ar_2NH	1	33
HSO_4^-	SO_4^{2-}	**1.99**	39
HF	F^-	**3.17**	39
HONO	NO_2^-	**3.29**	39
$ArNH_3^+$	$ArNH_2$	3-5	40
$ArNR_2H^+$	$ArNR_2$	3-5	40
RCOOH	$RCOO^-$	4-5	40
$HCOCH_2CHO$	HCOC–HCHO	5	41
H_2CO_3 [42]	HCO_3^-	**6.35**	39
H_2S	HS^-	**7.00**	39
ArSH	ArS^-	6–8	43

(*continued*)

[33]Arnett, E.M.; Quirk, R.P.; Burke, J.J. *J. Am. Chem. Soc.* ***1970***, *92*, 1260.

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[41]Pearson, R.G.; Dillon, R.L. *J. Am. Chem. Soc.* ***1953***, *75*, 2439.

[42]This value includes the CO_2 usually present. The value for H_2CO_3 alone is 3.9, in Bell, R.P. *The Proton in Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, ***1973***.

[43]Crampton, M.R., in Patai, S. *The Chemistry of the Thiol Group*, pt. 1, Wiley, NY, ***1974***, pp. 396–410.

TABLE 8.1. (*Continued*)

Acid	Base	Approximate pK_a (relative to water)	References
$CH_3COCH_2COCH_3$[44]	$CH_3COC{-}HCOCH_3$	9	41
HCN	CN^-	9.2	45
NH_4^+	NH_3	**9.24**	39
ArOH	ArO^-	8–11	46
RCH_2NO_2	$RC{-}HNO_2$	10	47
R_3NH^+	R_3N	10–11	40
RNH_3^+	RNH_2	10–11	40
HCO_3^-	CO_3^{2-}	**10.33**	39
RSH	RS^-	10–11	43
$R_2NH_2^+$	R_2NH	11	40
$N{\equiv}CCH_2C{\equiv}N$	$N{\equiv}CC{-}HC{\equiv}N$	11	41,48
CH_3COCH_2COOR	$CH_3COC{-}HCOOR$	11	41
$CH_3SO_2CH_2SO_2CH_3$	$CH_3SO_2C{-}HSO_2CH_3$	12.5	49
$EtOOCCH_2COOEt$	$EtOOCC{-}HCOOEt$	13	41
CH_3OH	CH_3O^-	15.2	50,51
H_2O	OH^-	**15.74**	52
		16	53
RCH_2OH	RCH_2O^-	16	50
RCH_2CHO	$RC{-}HCHO$	16	54
R_2CHOH	R_2CHO^-	16.5	50
R_3COH	R_3CO^-	17	50
$RCONH_2$	$RCONH^-$	17	55
$RCOCH_2R$	$RCOC{-}HR$	19-20[56]	57

[44]See Bunting, J.W.; Kanter, J.P. *J. Am. Chem. Soc.* ***1993***, *115*, 11705 for pK_a values of several β-ketone esters and amides.

[45]Perrin, D.D. *Ionisation Constants of Inorganic Acids and Bases in Aqueous Solution*, 2nd ed., Pergamon, Elmsford, NY, ***1982***.

[46]Rochester, C.H., in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, ***1971***, p. 374.

[47]Cram, D.J. *Chem. Eng. News* ***1963***, *41* (No. 33, Aug. 19), 94.

[48]Bowden, K.; Stewart, R. *Tetrahedron* ***1965***, *21*, 261.

[49]Hine, J.; Philips, J.C.; Maxwel, J.I. *J. Org. Chem.* ***1970***, *35*, 3943. See also, Ang, K.P.; Lee, T.W.S. *Aust. J. Chem.* ***1977***, *30*, 521.

[50]Reeve, W.; Erikson, C.M.; Aluotto, P.F. *Can. J. Chem.* ***1979***, *57*, 2747.

[51]See also Mackay, G.I.; Bohme, D.K. *J. Am. Chem. Soc.* ***1978***, *100*, 327; Olmstead, W.N.; Margolin, Z.; Bordwell, F.G. *J. Org. Chem.* ***1980***, *45*, 3295.

[52]Harned, H.S.; Robinson, R.A. *Trans. Faraday Soc.* ***1940***, *36*, 973.

[53]Streitwieser Jr., A.; Nebenzahl, L. *J. Am. Chem. Soc.* ***1976***, *98*, 2188.

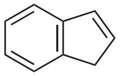
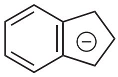
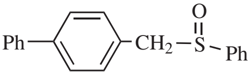
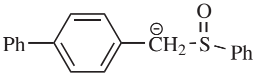
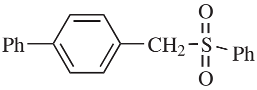
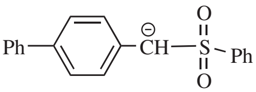
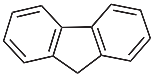
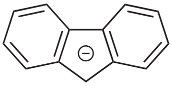
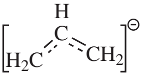
[54]Guthrie, J.P.; Cossar, J. *Can. J. Chem.* ***1986***, *64*, 2470.

[55]Homer, R.B.; Johnson, C.D., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 238–240.

[56]The pK_a of acetone in DMSO is reported to be 26.5. See Bordwell, F.G.; Zhang, X.-M. *Accts. Chem. Res.* ***1997***, *26*, 510.

[57]Tapuhi, E.; Jencks, W.P. *J. Am. Chem. Soc.* ***1982***, *104*, 5758; Guthrie, J.P.; Cossar, J.; Klym, A. *J. Am. Chem. Soc.* ***1984***, *106*, 1351; Chiang, Y.; Kresge, A.J.; Tang, Y.S.; Wirz, J. *J. Am. Chem. Soc.* ***1984***, *106*, 460.

TABLE 8.1. (*Continued*)

Acid	Base	Approximate pK_a (relative to water)	References
		20	58,59
		20.08[a]	60
		18.91[a]	60
		23	58,59
$ROOCCH_2R$	ROOCC–HR	24.5	41
$RCH_2C{\equiv}N$	RC–HC=N	25	41,61
$HC{\equiv}CH$	$HC{\equiv}CC^-$	25	62
Ph_2NH	PH_2N^-	24.95[b]	56
$EtOCOCH_3$	$EtOCOCH_2^-$	25.6	63
$PhNH_2$	$PhNH^-$	30.6[b]	56
Ar_3CH	Ar_3C^-	31.5	58,64
Ar_2CH_2	Ar_2CH^-	33.5	58,64
H_2	H^-	35	65
NH_3	NH_2^-	38	66
$PhCH_3$	$PhCH_2^-$	40	67
$CH_2{=}CHCH_3$		43	68
PhH	Ph^-	43	69

[58]Streitwieser, Jr., A.; Ciuffarin, E.; Hammons, J.H. *J. Am. Chem. Soc.* ***1967***, *89*, 63.

[59]Streitwieser, Jr., A.; Hollyhead, W.B.; Pudjaatmaka, H.; Owens, P.H.; Kruger, T.L.; Rubenstein, P.A.; MacQuarrie, R.A.; Brokaw, M.L.; Chu, W.K.C.; Niemeyer, H.M. *J. Am. Chem. Soc.* ***1971***, *93*, 5088.

[60]Streitwieser, A.; Wang, G.P.; Bors, D.A. *Tetrahedron* ***1997***, *53*, 10103.

[61]For a review of the acidity of cyano compounds, see Hibbert, F., in Patai, S.; Rappoport, Z. *The Chemistry of Triple-bonded Functional Groups*, pt. 1; Wiley, NY, ***1983***, pp. 699–736.

[62]Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, ***1965***, p. 19. See also, Dessy, R.E.; Kitching, W.; Psarras, T.; Salinger, R.; Chen, A.; Chivers, T. *J. Am. Chem. Soc.* ***1966***, *88*, 460.

[63]Amyes, T.L.; Richard J.P. *J. Am. Chem. Soc.* ***1996***, *118*, 3129.

[64]Streitwieser, Jr., A.; Hollyhead W.B.; Sonnichsen, G.; Pudjaatmaka, H.; Chang, C.J.; Kruger. T.L. *J. Am. Chem. Soc.* ***1971***, *93*, 5096.

[65]Buncel, E.; Menon, B. *J. Am. Chem. Soc.* ***1977***, *99*, 4457.

[66]Buncel, E.; Menon, B. *J. Organomet. Chem.* ***1977***, *141*, 1.

[67]Streitwieser, Jr., A.; Ni, J.X. *Tetrahedron Lett.* ***1985***, *26*, 6317; Albrech, H.; Schneider, G. *Tetrahedron* ***1986***, *42*, 4729.

[68]Boerth, D.W.; Streitwieser, Jr., A. *J. Am. Chem. Soc.* ***1981***, *103*, 6443.

[69]Streitwieser, Jr., A.; Scannon, P.J.; Niemeyer, H.M. *J. Am. Chem. Soc.* ***1972***, *94*, 7936.

TABLE 8.1. (*Continued*)

Acid	Base	Approximate pK_a (relative to water)	References
$CH_2{=}CH_2$	$CH_2{=}CH^-$	44	70
cyclo-C_3H_6	*c*-$C_3H_5^-$	46	71
CH_4[72]	CH_3^-	48	73
C_2H_6	$C_2H_5^-$	50	74
$(CH_3)_2CH_2$[72]	$(CH_3)_2CH^-$	51	74
$(CH_3)_3CH$[72]	$(CH_3)_3C^-$		75

[a]pK_a in THF.
[b]pK_a in DMSO.

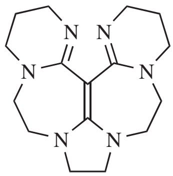
acid strength in Table 8.1 applies when a given acid and base react without a solvent or, when possible, in water. In other solvents the order may be greatly different (see p. 392). In the gas phase, where solvation effects are completely or almost completely absent, acidity orders may also differ greatly.[76] For example, in the gas phase, toluene is a stronger acid than water and *tert*-butoxide ion is a weaker base than methoxide ion[77] (see also, pp. 390–394). It is also possible for the acidity order to change with temperature. For example, >50°C the order of base strength is BuOH > H_2O > Bu_2O; from 1 to 50°C the order is BuOH > Bu_2O > H_2O; while <1°C the order becomes Bu_2O > BuOH > H_2O.[78]

A hydrogen-bond basicity scale has been developed that can be used to determine the relative basicity of molecules. Table 8.2 gives the pK_{HB} values for several common heteroatom containing molecules. This is obtained from the protonated form (conjugated acid) of the base in question. The larger the number, the more basic is that compound. The basicity of aliphatic amines has been calculated,[79] the ion-pair

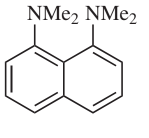
[70]Streitwieser, Jr., A.; Boerth, D.W. *J. Am. Chem. Soc.* ***1978***, *100*, 755.
[71]This value is calculated from results given in Streitwieser, Jr., A.; Caldwell, R.A.; Young, W.R. *J. Am. Chem. Soc.* ***1969***, *91*, 529. For a review of acidity and basicity of cyclopropanes, see Battiste, M.A.; Coxon, J.M., in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 1; Wiley, NY, ***1987***, pp. 255–305.
[72]See Daasbjerg, K. *Acta Chem. Scand. B* ***1995***, *49*, 878 for pK_a values of various hydrocarbons in DMF.
[73]This value is calculated from results given in Streitwieser, Jr., A.; Taylor, D.R. *J. Chem. Soc. D* ***1970***, 1248.
[74]These values are based on those given in Cram, D.J. *Chem. Eng. News* ***1963***, *41* (No. 33, Aug. 19), 94, but are corrected to the newer scale of Streitwieser, A.; Streitwieser, Jr., A.; Scannon, P.J.; Niemeyer, H.M. *J. Am. Chem. Soc.* ***1972***, *94*, 7936; Streitwieser, Jr., A.; Boerth, D.W. *J. Am. Chem. Soc.* ***1978***, *100*, 755.
[75]Breslow, R. and co-workers report a value of 71 [Breslow, R.; Grant, J.L. *J. Am. Chem. Soc.* ***1977***, *99*, 7745], but this was obtained by a different method, and is not comparable to the other values in Table 8.1. A more comparable value is ~53. See also Juan, B.; Schwarz, J.; Breslow, R. *J. Am. Chem. Soc.* ***1980***, *102*, 5741.
[76]For a review of acidity and basicity scales in the gas phase and in solution, see Gal, J.; Maria, P. *Prog. Phys. Org. Chem.* ***1990***, *17*, 159.
[77]Brauman, J.I.; Blair, L.K. *J. Am. Chem. Soc.* ***1970***, *92*, 5986; Bohme, D.K.; Lee-Ruff, E.; Young, L.B. *J. Am. Chem. Soc.* ***1972***, *94*, 4608, 5153.
[78]Gerrard, W.; Macklen, E.D. *Chem. Rev.* ***1959***, *59*, 1105. For other examples, see Calder, G.V.; Barton, T.J. *J. Chem. Educ.* ***1971***, *48*, 338; Hambly, A.N. *Rev. Pure Appl. Chem.* ***1965***, *15*, 87, 88.
[79]Caskey, D.C.; Damrauer, R.; McGoff, D. *J. Org. Chem.* ***2002***, *67,* 5098.

basicity of amines in THF[80] and in water[81] has been determined, and the basicity of pyridine was examined.[82] Weaker bases have also been examined, and the basicity of carbonyl compound in carbon tetrachloride has been determined.[83]

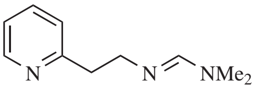
A class or organic compounds termed *super bases* has been developed. Vinamidine type or Schwesinger proton sponges (see p. 386), **1**,[84] are dubbed super bases and are probably the most powerful organic neutral bases known. The pK_a (p$K_{BH}{}^+$) in MeCN was measure as 31.94. It has been shown that the pK_a values of strong neutral organic (super)bases in acetonitrile are well described by the density functional theory.[85] The fundamental type of proton sponge is 1,8-bis(dimethylamino)-naphthalene, **2** (see p. 386), with a p$K_{BH}{}^+$ of 18.18.[86] Other super base type compounds include amidinazines such as N^1,N^1-dimethyl-N^2-β-(2-pyridylethyl)-formamidine (**3**), p$K_{BH}{}^+$ in DMSO = 25.1,[87] 1,8-bis(tetramethylguanidino) naphthalene, **4**,[88] and quinolino[7,8-*h*]quinolines, such as **5** with a pK_{BH^+} = 12.8.[89]



1



2



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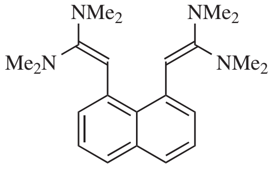

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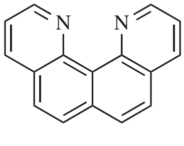

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TABLE 8.2. pK_{HB} Values for Many Types of Bases

Base	Approximate pK_{HB}	Reference
N-Methyl-2-piperidone	2.60	90
$Et_2NCONEt_2$	2.43	90
N-Methyl-2-pyrrolidinone	2.38	90
$PhCONMe_2$	2.23	90
$HCONMe_2$	2.10	90
PhCONHMe	2.03	90
18-crown-6	1.98	91
HCONHMe	1.96	90
15-crown-5	1.82	91
12-crown-4	1.73	91
$PhOCONMe_2$	1.70	90
$Et_2N{-}CN$	1.63	92
$Me_2N{-}CN$	1.56	92
δ-Valerolactone	1.43	93
Oxetane	1.36	91
γ-Butyrolactone	1.32	93
Tetrahydrofuran (THF)	1.28	91
Cyclopentanone	1.27	94
t-BuOMe	1.19	91
Acetone	1.18	94
MeCOOEt	1.07	93
1,4-Dioxane	1.03	91
Et_2O	1.01	91
1,3-Dioxane	0.93	91
1-Methyloxirane	0.97	91
PhCOOMe	0.89	93
MeOCOOMe	0.82	93
PhCHO	0.78	94
Bu_2O	0.75	91
HCOOEt	0.66	93
Me_3CHO	0.65	94
Me_2NO_2	0.41	95
$MeNO_2$	0.27	95
$PhNO_2$	0.30	95
Furan	−0.40	91

[90]Le Questel, J.-Y.; Laurence, C.; Lachkar, A.; Helbert, M.; Berthelot, M. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 2091.

[91]Berthelot, M.; Besseau, F.; Laurence, C. *Eur. J. Org. Chem.* ***1998***, 925.

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[93]Besseau, F.; Laurence, C.; Berthelot, M. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 485.

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[95]Laurence, C.; Berthelot, M.; Luçon, M.; Morris, D.G. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 491.

THE MECHANISM OF PROTON-TRANSFER REACTIONS

Proton transfers between oxygen and nitrogen acids and bases are usually extremely fast.[96] In the thermodynamically favored direction they are generally diffusion controlled.[97] In fact, a *normal acid* is defined[98] as one whose proton-transfer reactions are completely diffusion controlled, except when the conjugate acid of the base to which the proton is transferred has a p*K* value very close (differs by $<\sim 2$ p*K* units) to that of the acid. The normal acid–base reaction mechanism consists of three steps:

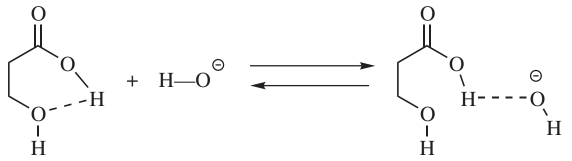
1. HA + |B ⇌ AH•••|•B

2. AH••••|•B ⇌ A•|••••HB

3. A|••••HB ⇌ A| + HB

The actual proton transfer takes place in the second step the first step is formation of a hydrogen-bonded complex. The product of the second step is another hydrogen-bonded complex, which dissociates in the third step.

However, not all such proton transfers are diffusion controlled. For example, if an internal hydrogen bond exists in a molecule, reaction with an external acid or base is often much slower.[99] In a case such as 3-hydroxypropanoic acid,



3-Hydroxypropanoic acid

the $^{-}$OH ion can form a hydrogen bond with the acidic hydrogen only if the internal hydrogen bond breaks. Therefore only some of the collisions between $^{-}$OH ions and 3-hydroxypropanoic acid molecules result in proton transfer. In many collisions, the $^{-}$OH ions will come away empty handed, resulting in a lower reaction rate. Note that this affects only the rate, not the equilibrium. Other systems are capable of hydrogen bonding, such as 1,2-diols. In the case of cyclohexane-1,2-diols, hydrogen bonding, ion–dipole interactions, polarizability, and stereochemistry all

[96]For reviews of such proton transfers, see Hibbert, F. *Adv. Phys. Org. Chem.* ***1986***, *22*, 113; Crooks, J.E., in Bamford, C.H.; Tipper, C.F.H. *Chemical Kinetics*, Vol. 8; Elsevier, NY, ***1977***, pp. 197–250.
[97]Kinetic studies of these very fast reactions were first carried out by Eigen. See Eigen, M. *Angew. Chem. Int. Ed.* ***1964***, *3*, 1.
[98]See, for example, Hojatti, M.; Kresge, A.J.; Wang, W. *J. Am. Chem. Soc.* ***1987***, *109*, 4023.
[99]For an example of a slow proton transfer from F_3CCOOH to $(PhCH_2)_3N$, see Ritchie, C.D.; Lu, S. *J. Am. Chem. Soc.* ***1989***, *111*, 8542.

play a role in determining the acidity.[100] The presence of halogen atoms such as chlorine can lead to hydrogen-bonding effects.[101] Another factor that can create lower rates is a molecular structure in which the acidic proton is protected within a molecular cavity (e.g., the in–in and out–in isomers shown on p. 190). See also, the proton sponges mentioned on p. 386. Proton transfers between an acidic and a basic group within the same molecule can also be slow, if the two groups are too far apart for hydrogen bonding. In such cases, participation of solvent molecules may be necessary.

Proton transfers to or from a carbon atom[102] in most cases are much slower than those strictly between oxygen or nitrogen atoms. At least three factors can be responsible for this,[103] not all of them applying in every case:

1. Hydrogen bonding is very weak or altogether absent for carbon (Chapter 3).
2. Many carbon acids, upon losing the proton, form carbanions that are stabilized by resonance. Structural reorganization (movement of atoms to different positions within the molecule) may accompany this. Chloroform, HCN, and 1-alkynes do not form resonance-stabilized carbanions, and these[104] behave kinetically as normal acids.[105] It has been reported that carborane acids, such as $H(CHB_{11}H_5Cl_6)$, are the strongest isolable (Lewis-free) Brønsted acids known.[106]
3. There may be considerable reorganization of solvent molecules around the ion as compared to the neutral molecule.[107]

In connection with factors 2 and 3, it has been proposed[103] that any factor that stabilizes the product (e.g., by resonance or solvation) lowers the rate constant if it develops late on the reaction coordinate, but increases the rate constant if it develops early. This is called the *Principle of Imperfect Synchronization*.

Mechanisms of proton transfer have been studied for many compounds, including the reactions of acids with lactams,[108] amides with various bases,[109] and amines with alkoxide bases.[110]

[100]Chen, X.; Walthall, D.A.; Brauman, J.I. *J. Am. Chem. Soc.* ***2004***, *126*, 12614.
[101]Abraham, M. H.; Enomoto, K.; Clarke, E. D.; Sexton, G. *J. Org. Chem.* ***2002***, *67*, 4782.
[102]For reviews of proton transfers to and from carbon, see Hibbert, F., in Bamford, C.H.; Tipper, C.F.H. *Chemical Kinetics*, Vol. 8, Elsevier, NY, ***1977***, pp. 97–196; Kreevoy, M.M. *Isot. Org. Chem.* ***1976***, *2*, 1; Leffek, K.T. *Isot. Org. Chem.* ***1976***, *2*, 89.
[103]See Bernasconi, C.F. *Tetrahedron* ***1985***, *41*, 3219.
[104]Bednar, R.A.; Jencks, W.P. *J. Am. Chem. Soc.* ***1985***, *107*, 7117, 7126, 7135; Kresge, A.J.; Powell, M.F. *J. Org. Chem.* ***1986***, *51*, 822; Formosinho, S.J.; Gal, V.M.S. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 1655.
[105]Not all 1-alkynes behave as normal acids; see Aroella, T.; Arrowsmith, C.H.; Hojatti, M.; Kresge, A.J.; Powell, M.F.; Tang, Y.S.; Wang, W. *J. Am. Chem. Soc.* ***1987***, *109*, 7198.
[106]Juhasz, M.; Hoffmann, S.; Stoyanov, E.; Kim, K.-C.; Reed, C.A. *Angew. Chem. Int. Ed.* ***2004***, *43*, 5352.
[107]See Bernasconi, C.F.; Terrier, F. *J. Am. Chem. Soc.* ***1987***, *109*, 7115; Kurz, J.L. *J. Am. Chem. Soc.* ***1989***, *111*, 8631.
[108]Wang, W.; Cheng, P.; Huang, C.; Jong, Y. *Bull. Chem. Soc. Jpn.* ***1992***, *65*, 562.
[109]Wang, W.-h.; Cheng, C.-c. *Bull. Chem. Soc. Jpn.* ***1994***, *67*, 1054.
[110]Lambert, C.; Hampel, F.; Schleyer, P.v.R. *Angew. Chem. Int. Ed.* ***1992***, *31*, 1209.

MEASUREMENTS OF SOLVENT ACIDITY[111]

When a solute is added to an acidic solvent it may become protonated by the solvent. This effect can lead to an enhancement of acidity, as in the effect of using formic acid rather than methanol.[112] An acidity scale has been reported for ionic liquids[113] (see p 415 for a discussion of ionic liquids), and the Lewis acidity of ionic liquids has been established using ir.[114] If the solvent is water and the concentration of solute is not very great, then the pH of the solution is a good measure of the proton-donating ability of the solvent. Unfortunately, this is no longer true in concentrated solutions because activity coefficients are no longer unity. A measurement of solvent acidity is needed which works in concentrated solutions and applies to mixed solvents as well. The Hammett acidity function[115] is a measurement that is used for acidic solvents of high dielectric constant.[116] For any solvent, including mixtures of solvents (but the proportions of the mixture must be specified), a value H_0 is defined as

$$H_o = pK_{BH_w^+} - \log \frac{[BH^+]}{[B]}$$

H_0 is measured by using "indicators" that are weak bases (B) and so are partly converted, in these acidic solvents, to the conjugate acids BH^+. Typical indicators are *o*-nitroanilinium ion, with a pK in water of −0.29, and 2,4-dinitroanilinium ion, with a pK in water of −4.53. For a given solvent, $[BH^+]/[B]$ is measured for one indicator, usually by spectrophotometric means. Then, using the known pK in water ($pK_{BH_w^+}$) for that indicator, H_0 can be calculated for that solvent system. In practice, several indicators are used, so that an average H_0 is taken. Once H_0 is known for a given solvent system, pK_a values in it can be calculated for any other acid-base pair.

The symbol H_0 is defined as

$$h_o = \frac{a_{H^+} f I}{f_{HI^+}}$$

[111]For fuller treatments, see Hammett, L.P. *Physical Organic Chemistry*, 2nd ed., McGraw-Hill, NY, ***1970***, pp. 263–313; Jones, R.A.Y. *Physical and Mechanistic Organic Chemistry*, 2nd ed., Cambridge University Press, Cambridge, ***1984***, pp. 83–93; Arnett, E.M.; Scorrano, G. *Adv. Phys. Org. Chem.* ***1976***, *13*, 83.

[112]Holt, J.; Karty, J.M. *J. Am. Chem. Soc.* ***2003***, *125*, 2797.

[113]Thomazeau, C.; Olivier-Bourbigou, H.; Magna, L.; Luts, S.; Gilbert, B. J. *Am. Chem. Soc.* ***2003***, *125*, 5264.

[114]Yang, Y.-l.; Kou, Y. *Chem. Commun.* ***2004***, 226.

[115]Hammett, L.P.; Deyrup, A.J. *J. Am. Chem. Soc.* ***1932***, *54*, 2721.

[116]For a monograph on acidity functions, see Rochester, C.H. *Acidity Functions*, Academic Press, NY, ***1970***. For reviews, see Ref. 111; Cox, R.A.; Yates, K. *Can. J. Chem.* ***1983***, *61*, 2225; Boyd R.H., in Coetzee, J.F.; Ritchie, C.D. *Solute–Solvent Interactions*, Marcel Dekker, NY, ***1969***, pp. 97–218; Vinnik, M.I. *Russ. Chem. Rev.* ***1966***, *35*, 802; Liler, M. *Reaction Mechanisms in Sulfuric Acid*, Academic Press, NY, ***1971***, pp. 26–58.

where a_{H^+} is the activity of the proton and f_I and f_{HI^+} are the activity coefficients of the indicator and conjugate acid of the indicator,[117] respectively. The parameter H_0 is related to H_0 by

$$H_o = -\log h_o$$

so that H_0 is analogous to pH and H_0 to $[H^+]$, and indeed in dilute aqueous solution $H_o = \text{pH}$.

The parameter H_0 reflects the ability of the solvent system to donate protons, but it can be applied only to acidic solutions of high dielectric constant, mostly mixtures of water with acids, such as nitric, sulfuric, perchloric, and so on. It is apparent that the H_0 treatment is valid only when f_I/f_{HI^+} is independent of the nature of the base (the indicator). Since this is so only when the bases are structurally similar, the treatment is limited. Even when similar bases are compared, many deviations are found.[118] Other acidity scales[119] have been set up, including a scale for C—H acids,[120] among them H_- for bases with a charge of -1, H_R for aryl carbinols,[121] H_C for bases that protonate on carbon,[122] and H_A for unsubstituted amides.[123] It is now clear that there is no single acidity scale that can be applied to a series of solvent mixtures, irrespective of the bases employed.[124]

Although most acidity functions have been applied only to acidic solutions, some work has also been done with strongly basic solutions.[125] The H_- function, which is used for highly acidic solutions when the base has a charge of -1, can also be used for strongly basic solvents, in which case it measures the ability of these

[117]For a review of activity coefficient behavior of indicators in acid solutions, see Yates, K.; McClelland, R.A. *Prog. Phys. Org. Chem.* ***1974***, *11*, 323.

[118]For example, see Kresge, A.J.; Barry, G.W.; Charles, K.R.; Chiang, Y. *J. Am. Chem. Soc.* ***1962***, *84*, 4343; Katritzky, A.R.; Waring, A.J.; Yates, K. *Tetrahedron* ***1963***, *19*, 465; Arnett, E.M.; Mach, G.W. *J. Am. Chem. Soc.* ***1964***, *86*, 2671; Jorgenson, M.J.; Hartter, D.R. *J. Am. Chem. Soc.* ***1963***, *85*, 878; Kreevoy, M.M.; Baughman, E.H. *J. Am. Chem. Soc.* ***1973***, *95*, 8178; García, B.; Leal, J.M.; Herrero, L.A.; Palacios, J.C. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 1759; Arnett, E.M.; Quirk, R.P.; Burke, J.J. *J. Am. Chem. Soc.* ***1970***, *92*, 1260.

[119]For lengthy tables of many acidity scales, with references, see Cox, R.A.; Yates, K. *Can. J. Chem.* ***1983***, *61*, 2225. For an equation that is said to combine the vast majority of acidity functions, see Zalewski, R.I.; Sarkice, A.Y.; Geltz, Z. *J. Chem. Soc. Perkin Trans. 2* ***1983***, 1059.

[120]See Vianello, R.; Maksić, Z.B. *Eur. J. Org. Chem.* ***2004***, 5003.

[121]Deno, N.C.; Berkheimer, H.E.; Evans, W.L.; Peterson, H.J. *J. Am. Chem. Soc.* ***1959***, *81*, 2344.

[122]Reagan, M.T. *J. Am. Chem. Soc.* ***1969***, *91*, 5506.

[123]Yates, K.; Stevens, J.B.; Katritzky, A.R. *Can. J. Chem.* ***1964***, *42*, 1957; Yates, K.; Riordan, J.D. *Can. J. Chem.* ***1965***, *43*, 2328; Edward, J.T.; Wong, S.C. *Can. J. Chem.* ***1977***, *55*, 2492; Liler, M.; Marković, D. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 551.

[124]Hammett, L.P. *Physical Organic Chemistry*, 2nd ed., McGraw-Hill, NY, ***1970***, p. 278; Rochester, C.H. *Acidity Functions*, Academic Press, NY, ***1970***, p. 21.

[125]For another approach to solvent basicity scales, see Catalán, J.; Gómez, J.; Couto, A.; Laynez, J. *J. Am. Chem. Soc.* ***1990***, *112*, 1678.

solvents to abstract a proton from a neutral acid BH.[126] When a solvent becomes protonated, its conjugate acid is known as a *lyonium ion*.

Another approach to the acidity function problem was proposed by Bunnett and Olsen,[127] who derived the equation

$$\log \frac{[\mathrm{SH}^+]}{[\mathrm{S}]} + H_o = \phi(H_o + \log[\mathrm{H}^+]) + \mathrm{p}K_{\mathrm{SH}^+}$$

where S is a base that is protonated by an acidic solvent. Thus the slope of a plot of log $([\mathrm{SH}^+]/[\mathrm{S}]) + H_0$ against $H_0 + \log[\mathrm{H}^+]$ is the parameter ϕ, while the intercept is the pK_a of the lyonium ion SH^+ (referred to infinite dilution in water). The value of ϕ expresses the response of the equilibrium $\mathrm{S} + \mathrm{H}^+ \rightleftharpoons \mathrm{SH}^+$ to changing acid concentration. A negative ϕ indicates that the log of the ionization ratio $[\mathrm{SH}^+]/[\mathrm{S}]$ increases, as the acid concentration increases, more rapidly than $-H_0$. A positive ϕ value indicates the reverse. The Bunnett–Olsen equation given above is a linear free-energy relationship (see p. 405) that pertains to acid-base equilibria. A corresponding equation that applies to kinetic data is

$$\log k_\psi + H_0 = \phi(H_o + \log[\mathrm{H}^+]) + \log k_2^0$$

where k_ψ is the pseudo-first-order rate constant for a reaction of a weakly basic substrate taking place in an acidic solution and k_2^0 is the second-order rate constant at infinite dilution in water. In this case, ϕ characterizes the response of the reaction rate to changing acid concentration of the solvent. The Bunnett–Olsen treatment has also been applied to basic media, where, in a group of nine reactions in concentrated NaOMe solutions, no correlation was found between reaction rates and either H_- or stoichiometric base concentration but where the rates were successfully correlated by a linear free-energy equation similar to those given above.[128]

A treatment partially based on the Bunnett–Olsen one is that of Bagno Scorrano, and More O'Ferrall,[129] which formulates medium effects (changes in acidity of solvent) on acid–base equilibria. An appropriate equilibrium is chosen as reference, and the acidity dependence of other reactions compared with it, by use of the linear free-energy equation

$$\log \frac{K'}{K'_0} = m^* \log \frac{K}{K_o}$$

[126]For reviews, see Rochester, C.H. *Q. Rev. Chem. Soc.* ***1966***, *20*, 511; Rochester, C.H. *Acidity Functions*, Academic Press, NY, ***1970***, pp. 234–264; Bowden, K. *Chem. Rev.* ***1966***, *66*, 119 (the last review is reprinted in (Coetzee, J.F.; Ritchie, C.D. *Solute–Solvent Interactions*, Marcel Dekker, NY, ***1969***, pp. 186–215).

[127]Bunnett, J.F.; McDonald, R.L.; Olsen, F.P. *J. Am. Chem. Soc.* ***1974***, *96*, 2855.

[128]More O'Ferrall, R.A. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 976.

[129]Bagno, A.; Scorrano, G.; More O'Ferrall, R.A. *Rev. Chem. Intermed.* ***1987***, *7*, 313. See also, Sampoli, M.; De Santis, A.; Marziano, N.C. *J. Chem. Soc. Chem. Commun.* ***1985***, 110; Cox, R.A. *Acc. Chem. Res.* ***1987***, *20*, 27.

where the K values are the equilibrium constants for the following: K for the reaction under study in any particular medium; K' for the reference reaction in the same medium; K_0 for the reaction under study in a reference solvent; K_0' for the reference reaction in the same reference solvent; and m^* is the slope of the relationship [corresponding to $(1-\phi)$ of the Bunnett–Olsen treatment]. This equation has been shown to apply to many acid–base reactions.

Another type of classification system was devised by Bunnett[130] for reactions occurring in moderately concentrated acid solutions. Log $k_\psi + H_0$ is plotted against log a_{H_2O}, where K_ψ is the pseudo-first-order rate constant for the protonated species and a_{H_2O} is the activity of water. Most such plots are linear or nearly so. According to Bunnett, the slope of this plot w tells something about the mechanism. Where w is between -2.5 and 0, water is not involved in the rate-determining step; where w is between 1.2 and 3.3, water is a nucleophile in the rate-determining step; where w is between 3.3 and 7, water is a proton-transfer agent. These rules hold for acids in which the proton is attached to oxygen or nitrogen.

A new acidity scale has been developed based on calorimetric measurement of *N*-methylimidazole and *N*-methylpyrrole in bulk solvents.[131] A revised version of this method was shown to give better results in some cases.[132] Another scale of solvent acidities was developed based on the hydrogen-bond donor acidities in aqueous DMSO.[133] It is noted that bond energies, acidities, and electron affinities are related in a thermodynamic cycle, and Kass and Fattahi have shown that by measuring two of these quantities the third can be found.[134]

ACID AND BASE CATALYSIS[135]

Many reactions are catalyzed by acids, bases, or both. In such cases, the catalyst is involved in a fundamental way in the mechanism. Nearly always the first step of such a reaction is a proton transfer between the catalyst and the substrate.

Reactions can be catalyzed by acid or base in two different ways, called *general* and *specific catalysis*. If the rate of an acid-catalyzed reaction run in a solvent S is

[130]Bunnett, J.F. *J. Am. Chem. Soc.* ***1961***, *83*, 4956, 4968, 4973, 4978.

[131]Catalán, J.; Couto, A.; Gomez, J.; Saiz, J.L.; Laynez, J. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 1181.

[132]Abraham, M.H.; Taft, R.W. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 305.

[133]Liu, P.C.; Hoz, S.; Buncel, E. *Gazz. Chim. Ital.* ***1996***, *126*, 31. See also Abraham, M.H.; Zhao, Y.J. *J. Org. Chem.* ***2004***, *69*, 4677.

[134]Fattahi, A.; Kass, S.R. *J. Org. Chem.* ***2004***, *69*, 9176.

[135]For reviews, see Stewart, R. *The Proton: Applications to Organic Chemistry*, Academic Press, NY, ***1985***, pp. 251–305; Hammett, L.P. *Physical Organic Chemistry*, 2nd ed., McGraw-Hill, NY, ***1970***, pp. 315–345; Willi, A.V., in Bamford, C.H.; Tipper, C.F.H. *Chemical Kinetics*, Vol. 8, Elsevier, NY, ***1977***, pp. 1–95; Jones, R.A.Y. *Physical and Mechanistic Organic Chemistry*, 2nd ed., Cambridge University Press, Cambridge, ***1984***, pp. 72–82; Bell, R.P. *The Proton in Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, ***1973***, pp. 159–193; Jencks, W.P. *Catalysis in Chemistry and Enzymology*, McGraw-Hill, NY, ***1969***, pp. 163–242; Bender, M.L. *Mechanisms of Homogeneous Catalysis from Protons to Proteins*; Wiley, NY, ***1971***, pp. 19–144.

proportional to $[SH^+]$, the reaction is said to be subject to *specific acid catalysis*, the acid being the lyonium ion SH^+. The acid that is put into the solvent may be stronger or weaker than SH^+, but the rate is proportional only to the $[SH^+]$ that is actually present in the solution (derived from $S + HA \rightleftharpoons SH^+ + A^-$). The identity of HA makes no difference except insofar as it determines the position of equilibrium and hence the $[SH^+]$. Most measurements have been made in water, where SH^+ is H_3O^+.

In *general acid catalysis*, the rate is increased not only by an increase in $[SH^+]$, but also by an increase in the concentration of other acids (e.g., in water by phenols or carboxylic acids). These other acids increase the rate even when $[SH^+]$ is held constant. In this type of catalysis the strongest acids catalyze best, so that, in the example given, an increase in the phenol concentration catalyzes the reaction much less than a similar increase in $[H_3O^+]$. This relationship between acid strength of the catalyst and its catalytic ability can be expressed by the *Brønsted catalysis equation*[136]

$$\log k = \alpha \log K_\alpha + C$$

where k is the rate constant for a reaction catalyzed by an acid of ionization constant K_α. According to this equation, when log k is plotted against log K_α for catalysis of a given reaction by a series of acids, a straight line should be obtained with slope and intercept C. Although straight lines are obtained in many cases, this is not always the case. The relationship usually fails when acids of different types are compared. For example, it is much more likely to hold for a group of substituted phenols than for a collection of acids that contains both phenols and carboxylic acids. The Brønsted equation is another linear free-energy relationship (see p. 405).

Analogously, there are *general* and *specific* (S^- from an acidic solvent SH) *base-catalyzed reactions*. The Brønsted law for bases is

$$\log k = \beta \log K_b + C$$

The Brønsted equations relate a rate constant k to an equilibrium constant K_a. In Chapter 6, we saw that the Marcus equation also relates a rate term (in that case $\Delta G^\ddagger$) to an equilibrium term ΔG°. When the Marcus treatment is applied to proton transfers[137] between a carbon and an oxygen (or a nitrogen), the simplified[138] equation (p. 309)

$$\Delta G^\ddagger = \Delta G^\ddagger_{\text{int}} + \frac{1}{2}\Delta G^\circ + \frac{(\Delta G^\circ)^2}{16\Delta G^\ddagger_{\text{int}}}$$

[136]For reviews, see Klumpp, G.W. *Reactivity in Organic Chemistry*; Wiley, NY, ***1982***, pp. 167–179; Bell, R.P., in Chapman, N.B.; Shorter, J. *Correlation Analysis in Chemistry: Recent Advances*; Plenum Press, NY, ***1978***, pp. 55–84; Kresge, A.J. *Chem. Soc. Rev.* ***1973***, *2*, 475.

[137]For applications of Marcus theory to proton transfers, see Marcus, R.A. *J. Phys. Chem.* ***1968***, *72*, 891; Kreevoy, M.M.; Konasewich, D.E. *Adv. Chem. Phys.* ***1971***, *21*, 243; Kresge, A.J. *Chem. Soc. Rev.* ***1973***, *2*, 475.

[138]Omitting the work terms.

where

$$\Delta G^{\ddagger}_{\text{int}} = \frac{1}{2}\left(\Delta G_{(0^{\ddagger},0)} + \Delta G_{(C^{\ddagger},C)}\right)$$

can be further simplified: Because proton transfers between oxygen and oxygen (or nitrogen and nitrogen) are much faster than those between carbon and carbon, $\Delta G(_0,^{\ddagger}{}_0)$ is much smaller than $\Delta G(_C,^{\ddagger}{}_C)$ and we can write[139]

$$\Delta G\ddagger = \frac{1}{2}\Delta G(_C,^{\ddagger}{}_C) + \frac{1}{2}\Delta G^{\circ} + \frac{(\Delta G^{\circ})^2}{8\Delta G_{(C,^{\ddagger}C)}}$$

Thus, if the carbon part of the reaction is kept constant and only the A of HA is changed (where A is an oxygen or nitrogen moiety), then $\Delta G^{\ddagger}$ is dependent only on ΔG°. Differentiation of this equation yields the Brønsted α:

$$\frac{d\Delta G\ddagger}{d\Delta G^{\circ}} = \alpha = \frac{1}{2}\left(1 + \frac{\Delta G^{\circ}}{2\Delta G_{(C\ddagger,C)}}\right)$$

The Brønsted law is therefore a special case of the Marcus equation.

A knowledge of whether a reaction is subject to general or specific acid catalysis supplies information about the mechanism. For any acid-catalyzed reaction we can write

Step 1 $A \overset{SH^+}{\rightleftharpoons} AH^+$

Step 2 $AH^+ \rightarrow$ products

If the reaction is catalyzed only by the specific acid SH^+, it means that step 1 is rapid and step 2 is rate-controlling, since an equilibrium has been rapidly established between A and the strongest acid present in the solution, namely, SH^+ (since this is the strongest acid that can be present in S). On the other hand, if step 2 is faster, there is no time to establish equilibrium and the rate-determining step must be step 1. This step is affected by all the acids present, and the rate reflects the sum of the effects of each acid (general acid catalysis). General acid catalysis is also observed if the slow step is the reaction of a hydrogen-bond complex A•••HB, since each complex reacts with a base at a different rate. A comparable discussion can be used for general and specific base catalysis.[140] Further information can be obtained from the values α and β in the Brønsted catalysis equations, since these are

[139]Albery, W.J. *Annu. Rev. Phys. Chem.* ***1980***, *31*, 227, p. 244.

[140]For discussions of when to expect general or specific acid or base catalysis, see Jencks, W.P. *Acc. Chem. Res.* ***1976***, *9*, 425; Stewart, R.; Srinivasan, R. *Acc. Chem. Res.* ***1978***, *11*, 271; Guthrie, J.P. *J. Am. Chem. Soc.* ***1980***, *102*, 5286.

approximate measures of the extent of proton transfer in the transition state. In most cases values of α and β are between 1 and 0. A value of α or β near 0 is generally taken to mean that the transition state resembles the reactants; that is, the proton has been transferred very little when the transition state has been reached. A value of α or β near 1 is taken to mean the opposite; that is, in the transition state the proton has been almost completely transferred. However, cases are known in which these generalizations are not followed,[141] and their theoretical basis has been challenged.[142] In general, the proton in the transition state lies closer to the weaker base.

LEWIS ACIDS AND BASES: HARD AND SOFT ACIDS AND BASES

At about the same time that Brønsted proposed his acid–base theory, Lewis put forth a broader theory. A base in the Lewis theory is the same as in the Brønsted one, namely, a compound with an available pair of electrons, either unshared or in a π orbital. A *Lewis acid*, however, is any species with a vacant orbital.[143] In a Lewis acid–base reaction the unshared pair of the base forms a covalent bond with the vacant orbital of the acid, as represented by the general equation

$$\text{A} + \text{:B} \longrightarrow \text{A–B}$$

in which charges are not shown, since they may differ. A specific example is

$$BF_3 + :NH_3 \longrightarrow F_3\overset{\ominus}{B}\rightarrow\overset{\oplus}{N}H_3$$

In the Brønsted picture, the acid is a proton donor, but in the Lewis picture the proton itself is the acid since it has a vacant orbital. A Brønsted acid becomes, in the Lewis picture, the compound that gives up the actual acid. The advantage of the Lewis theory is that it correlates the behavior of many more processes. For example, $AlCl_3$ and BF_3 are Lewis acids because they have only six electrons in the outer shell and have room for eight. Lewis acids $SnCl_4$ and SO_3 have eight, but their central elements, not being in the first row of the Periodic table, have room for 10 or 12. Other Lewis acids are simple cations, like Ag^+. The simple reaction

[141]See, for example, Bordwell, F.G.; Boyle, Jr., W.J. *J. Am. Chem. Soc.* ***1972***, *94*, 3907; Davies, M.H. *J. Chem. Soc. Perkin Trans. 2* ***1974***, 1018; Agmon, N. *J. Am. Chem. Soc.* ***1980***, *102*, 2164; Murray, C.J.; Jencks, W.P. *J. Am. Chem. Soc.* ***1988***, *110*, 7561.

[142]Pross, A.; Shaik, S.S. *New J. Chem.* ***1989***, *13*, 427; Lewis, E.S. *J. Phys. Org. Chem.* ***1990***, *3*, 1.

[143]For a monograph on Lewis acid–base theory, see Jensen, W.B. *The Lewis Acid–Base Concept*, Wiley, NY, ***1980***. For a discussion of the definitions of Lewis acid and base, see Jensen, W.B. *Chem. Rev.* ***1978***, *78*, 1.

$A + \bar{B} \rightarrow A{-}B$ is not very common in organic chemistry, but the scope of the Lewis picture is much larger because reactions of the types

$$A^1 + A^2{—}B \longrightarrow A^1{—}B + A^2$$
$$B^1 + A{—}B^2 \longrightarrow A{—}B^1 + B^2$$
$$A^1{—}B^1 + A^2{—}B^2 \longrightarrow A^1{—}B^2 + A^2{—}B^1$$

which are very common in organic chemistry, are also Lewis acid-base reactions. In fact, all reactions in which a covalent bond is formed through one species contributing a filled and the other a vacant orbital may be regarded as Lewis acid–base reactions. An *ab initio* analysis of the factors that determine Lewis versus Lowry–Brønsted acidity–basicity is available.[144]

When a Lewis acid combines with a base to give a negative ion in which the central atom has a higher than normal valence, the resulting salt is called an *ate complex*.[145] Examples are

$$Me_3B + LiMe \longrightarrow Me_4B^- \; Li^+$$
An ate complex

$$Ph_5Sb + LiPh \longrightarrow Ph_6Sb^- \; Li^+$$
An ate complex

The ate complexes are analogous to the onium salts formed when a Lewis base expands its valence, for example,

$$Me_3N + MeI \longrightarrow Me_4N^+ \; I^-$$
Onium salt

Far fewer quantitative measurements have been made of Lewis acid strength compared to that of Brønsted acids.[146] A simple table of Lewis acidities based on some quantitative measurement (e.g., that given for Brønsted acids in Table 8.1) is not feasible because Lewis acidity depends on the nature of the base and any solvent that can function as a base. For example, lithium perchlorate functions as a weak Lewis acid in ether.[147] Qualitatively, the following approximate sequence

[144]Rauk, A.; Hunt, I.R.; Keay, B.A. *J. Org. Chem.* ***1994***, *59*, 6808.

[145]For a review of ate complexes, see Wittig, G. *Q. Rev. Chem. Soc.* ***1966***, *20*, 191.

[146]For reviews of the quantitative aspects of Lewis acidity, see Satchell, D.P.N.; Satchell, R.S. *Q. Rev. Chem. Soc.* ***1971***, *25*, 171; *Chem. Rev.* ***1969***, *69*, 251. See also Maria, P.; Gal, J. *J. Phys. Chem.* ***1985***, *89*, 1296; Larson, J.W.; Szulejko, J.E.; McMahon, T.B. *J. Am. Chem. Soc.* ***1988***, *110*, 7604; Sandström, M.; Persson, I.; Persson, P. *Acta Chem. Scand.* ***1990***, *44*, 653; Laszlo, P.; Teston-Henry, M. *Tetrahedron Lett.* ***1991***, *32*, 3837.

[147]Springer, G.; Elam, C.; Edwards, A.; Bowe, C.; Boyles, D.; Bartmess, J.; Chandler, M.; West, K.; Williams, J.; Green, J.; Pagni, R.M.; Kabalka, G.W. *J. Org. Chem.* ***1999***, *64*, 2202.

of acidity of Lewis acids of the type MX_n has been suggested, where X is a halogen atom or an inorganic radical: $BX_3 > AlX_3 > FeX_3 > GaX_3 > SbX_5 > SnX_4 > AsX_5 > ZnX_2 > HgX_2$.

The facility with which an acid–base reaction takes place depends of course on the strengths of the acid and the base. But it also depends on quite another quality, called the *hardness*[148] or *softness* of the acid or base.[149] Hard and soft acids and bases have these characteristics:

Soft Bases. The donor atoms are of low electronegativity and high polarizability and are easy to oxidize. They hold their valence electrons loosely.

Hard Bases. The donor atoms are of high electronegativity and low polarizability and are hard to oxidize. They hold their valence electrons tightly.

Soft Acids. The acceptor atoms are large, have low positive charge, and contain unshared pairs of electrons (*p* or *d*) in their valence shells. They have high polarizability and low electronegativity.

Hard Acids. The acceptor atoms are small, have high positive charge, and do not contain unshared pairs in their valence shells. They have low polarizability and high electronegativity.

A qualitative listing of the hardness of some acids and bases is given in Table 8.3.[150] The treatment has also been made quantitative,[151] with the following operational definition:

$$\eta = \frac{I - A}{2}$$

In this equation, η, the *absolute hardness*, is half the difference between I, the ionization potential, and A, the electron affinity.[152] The softness, σ, is the reciprocal of

[148]See Ayers, P.W.; Parr, R.G. *J. Am. Chem. Soc.* ***2000***, *122*, 2010.

[149]Pearson, R.G. *J. Am. Chem. Soc.* ***1963***, *85*, 3533; *Science*, ***1966***, *151*, 172; Pearson, R.G.; Songstad, J. *J. Am. Chem. Soc.* ***1967***, *89*, 1827. For a monograph on the concept, see Ho, T. *Hard and Soft Acids and Bases Principle in Organic Chemistry*; Academic Press, NY, ***1977***. For reviews, see Pearson, R.G. *J. Chem. Educ.* ***1987***, *64*, 561; Ho, T. *Tetrahedron* ***1985***, *41*, 1, *J. Chem. Educ.* ***1978***, *55*, 355; *Chem. Rev.* ***1975***, *75*, 1; Pearson, R.G. in Chapman, N.B.; Shorter, J. *Advances in Linear Free-Energy Relationships*, Plenum Press, NY, ***1972***, pp. 281–319; Pearson, R.G. *Surv. Prog. Chem.* ***1969***, *5*, 1 [portions of this article slightly modified also appear in Pearson, R.G. *J. Chem. Educ.* ***1968***, *45*, 581, 643]; Garnovskii, A.D.; Osipov, O.A.; Bulgarevich, S.B. *Russ. Chem. Rev.* ***1972***, *41*, 341; Seyden-Penne, J. *Bull. Soc. Chim. Fr.* ***1968***, 3871. For a collection of papers, see Pearson, R.G. *Hard and Soft Acids and Bases*, Dowden, Hutchinson, and Ross, Stroudsberg, PA, ***1973***.

[150]Taken from larger listings, in Pearson, R.G. Ref. 149.

[151]Pearson, R.G. *Inorg. Chem.* ***1988***, *27*, 734; *J. Org. Chem.* ***1989***, *54*, 1423. See also, Orsky, A.R.; Whitehead M.A. *Can. J. Chem.* ***1987***, *65*, 1970.

[152]For a computational study of proton and electron affinities see Sauers, R.R. *Tetrahedron* ***1999***, *55*, 10013.

TABLE 8.3. Hard and Soft Acids and Bases[150]

Hard Bases	Soft Bases	Borderline Cases
H_2O	OH^- F^-	R_sS RSH RS^- $ArNH_2C_5H_5N$
AcO^-	$SO_4{}^{2-}$	Cl^- I^- R_3P $(RO)_3P$
	$N_3{}^-$	Br
$CO_3{}^{2-}$	$NO_3{}^-$	ROH CN^- RCN CO $NO_2{}^-$
RO^-	R_2O	NH_3 C_2H_4 C_6H_6
RNH_2	H^-	R^-
Hard Acids	**Soft Acids**	**Borderline Cases**
H^+	Li^+	Na^+ Cu^+ Ag^+ Pd^{2+} Fe^{2+}
	Co^{2+}	Cu^{2+}
K^+	Mg^{2+}	Ca^{2+} Pt^{2+} Hg^{2+} BH_3 Zn^{2+}
	Sn^{2+}	Sb^{3+}
Al^{3+}	Cr^{2+}	Fe^{3+} $GaCl_3$ I_2 Br_2 Bi^{3+}
	BMe_3	SO_2
BF_3	$B(OR)_3$	$AlMe_3$ CH_2 Carbenes
	R_3C^+	NO^+ GaH_3
$AlCl_3$	AlH_3	SO_3 $C_6H_5{}^+$
RCO^+	CO_2	
HX (hydrogen-bonding molecules)		

η. Values of η for some molecules and ions are given in Table 8.4.[153] Note that the proton, which is involved in all Brønsted acid–base reactions, is the hardest acid listed, with $\eta = \infty$ (it has no ionization potential). The above equation cannot be applied to anions, because electron affinities cannot be measured for them. Instead, the assumption is made that η for an anion X^- is the same as that for the radical $X^\bullet$.[154] Other methods are also needed to apply the treatment to polyatomic cations.[154]

Once acids and bases have been classified as hard or soft, a simple rule can be given: *hard acids prefer to bond to hard bases, and soft acids prefer to bond to soft bases (the HSAB principle).*[155] The rule has nothing to do with acid or base *strength* but merely says that the product A—B will have extra stability if both A and B are hard or if both are soft. Another rule is that a soft Lewis acid and a soft Lewis base tend to form a covalent bond, while a hard acid and a hard base tend to form ionic bonds.

One application of the first rule given above is found in complexes between alkenes or aromatic compounds and metal ions (p. 376). Alkenes and aromatic rings

[153]Note that there is not always a strict correlation between the values in Table 8.3 and the categories of Table 8.2.

[154]Pearson, R.G. *J. Am. Chem. Soc.* ***1988***, *110*, 7684.

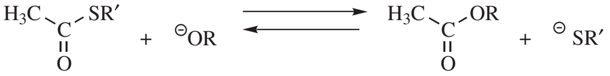
[155]For proofs of this principle, see Chattaraj, P.K.; Lee, H.; Parr, R.G. *J. Am. Chem. Soc.* ***1991***, *113*, 1855.

TABLE 8.4. Some Absolute Hardness Values in Electron Volts[151]

Cations		Molecules		Anions[b]	
Ion	η	Compound	η	Ion	η
H^+	∞	HF	11.0	F^-	7.0
Al^{3+}	45.8	CH_4	10.3	H^-	6.4
Li^+	35.1	BF_3	9.7	OH^-	5.7
Mg^{2+}	32.6	H_2O	9.5	NH_2^-	5.3
Na^+	21.1	NH_3	8.2	CN^-	5.1
Ca^{2+}	19.5	HCN	8.0	CH_3^-	4.9
K^+	13.6	$(CH_3)_2O$	8.0	Cl^-	4.7
Zn^{2+}	10.9	CO	7.9	$CH_3CH_2^-$	4.4
Cr^{3+}	9.1	C_2H_2	7.0	Br^-	4.2
Cu^{2+}	8.3	$(CH_3)_3N$	6.3	$C_6H_5^-$	4.1
Pt^{2+}	8.0	H_2S	6.2	SH^-	4.1
Sn^{2+}	7.9	C_2H_4	6.2	$(CH_3)_2CH^-$	4.0
Hg^{2+}	7.7	$(CH_3)_2S$	6.0	I^-	3.7
Fe^{2+}	7.2	$(CH_3)_3P$	5.9	$(CH_3)_3C^-$	3.6
Pd^{2+}	6.8	CH_3COCH_3	5.6		
Cu^+	6.3	C_6H_6	5.3		
		HI	5.3		
		C_5H_5N	5.0		
		C_6H_5OH	4.8		
		CH_2[a]	4.7		
		C_6H_5SH	4.6		
		Cl_2	4.6		
		$C_6H_5NH_2$	4.4		
		Br_2	4.0		
		I_2	3.4		

[a]For singlet state.
[b]The same as for the corresponding radical.

are soft bases and should prefer to complex with soft acids. Thus, Ag^+, Pt^{2+}, and Hg^{2+} complexes are common, but complexes of Na^+, Mg^{2+}, or Al^{3+} are rare. Chromium complexes are also common, but in such complexes the chromium is in a low or zero oxidation state (which softens it) or attached to other soft ligands. In another application, we may look at this reaction:



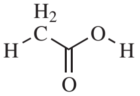
The HSAB principle predicts that the equilibrium should lie to the right, because the hard acid CH_3CO^+ should have a greater affinity for the hard base RO^- than for the soft base RS^-. Indeed, thiol esters are easily cleaved by RO^- or hydrolyzed

by dilute base ($^{-}$OH is also a hard base).[156] Another application of the rule is discussed on p. 493.[157] The HSAB principles have been applied to analyze the reactivity of ketone and ester enolates,[158] and in analyzing catalyst selectivity in synthesis.[159]

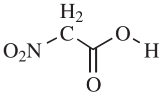
THE EFFECTS OF STRUCTURE ON THE STRENGTHS OF ACIDS AND BASES[160]

The structure of a molecule can affect its acidity or basicity in a number of ways. Unfortunately, in most molecules two or more of these effects (as well as solvent effects) are operating, and it is usually very difficult or impossible to say how much each effect contributes to the acid or base strength.[161] Small differences in acidity or basicity between similar molecules are particularly difficult to interpret. It is well to be cautious when attributing them to any particular effect.

1. *Field Effects*. These were discussed on p. 19. In general, changes in substituents can have an effect on acidity. As an example of the influence of field effects on acidity, we may compare the acidity of acetic acid and nitroacetic acid:



pK_a = 4.76



pK_a = 1.68

The only difference in the structure of these molecules is the substitution of NO_2 for H. Since NO_2 is a strongly electron-withdrawing group, it withdraws electron density from the negatively charged COO^- group in the anion of

[156]Wolman, Y., in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, ***1974***, p. 677; Maskill, H. *The Physical Basis of Organic Chemistry*, Oxford University Press, Oxford ***1985***, p. 159.
[157]See also Bochkov, A.F. *J. Org. Chem. USSR* ***1986***, *22*, 1830, 1837.
[158]Méndez, F.; Gázguez, J.L. *J. Am. Chem. Soc.* ***1994***, *116*, 9298.
[159]Woodward, S. *Tetrahedron* ***2002***, *58*, 1017.
[160]For a monograph, see Hine, J. *Structural Effects on Equilibria in Organic Chemistry*, Wiley, NY, ***1975***. For reviews, see Taft, R.W. *Prog. Phys. Org. Chem.* ***1983***, *14*, 247; Petrov, E.S. *Russ. Chem. Rev.* ***1983***, *52*, 1144 (NH acids); Bell, R.P. *The Proton in Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, ***1973***, pp. 86–110; Barlin, G.B.; Perrin, D.D., in Bentley, K.W.; Kirby, G.W. *Elucidation of Organic Structures by Physical and Chemical Methods*, 2nd ed. (Vol. 4 of Weissberger, A. *Techniques of Chemistry*), pt. 1; Wiley, NY, ***1972***, pp. 611–676. For discussions, see Bolton, P.D.; Hepler, L.G. *Q. Rev. Chem. Soc.* ***1971***, *25*, 521; Barlin, G.B.; Perrin, D.D. *Q. Rev. Chem. Soc.* ***1966***, *20*, 75; Thirot, G. *Bull. Soc. Chim. Fr.* ***1967***, 3559; Liler, M. *Reaction Mechanisms in Sulfuric acid*, Academic Press, NY, ***1971***, pp. 59–144. For a monograph on methods of estimating pK values by analogy, extrapolation, and so on, see Perrin, D.D.; Dempsey, B.; Serjeant, E.P. pK_a *Prediction for Organic Acids and Bases*, Chapman and Hall, NY, ***1981***.
[161]The varying degrees by which the different factors that affect gas-phase acidities of 25 acids has been calculated: Taft, R.W.; Koppel, I.A.; Topsom, R.D.; Anvia, F. *J. Am. Chem. Soc.* ***1990***, *112*, 2047.

nitroacetic acid (compared with the anion of acetic acid) and, as the pK_a values indicate, nitroacetic acid is ~1000 times stronger than acetic acid.[162] Any effect that results in electron withdrawal from a negatively charged center is a stabilizing effect because it spreads the charge. Thus, –*I* groups increase the acidity of uncharged acids, such as acetic because they spread the negative charge of the anion. However, –*I* groups also increase the acidity of any acid, no matter what the charge. For example, if the acid has a charge of +1 (and its conjugate base is therefore uncharged), a −*I* group destabilizes the positive center (by increasing and concentrating the positive charge) of the acid, a destabilization that will be relieved when the proton is lost. In general, we may say that *groups that withdraw electrons by the field effect increase acidity and decrease basicity, while electron-donating groups act in the opposite direction.* Another example is the molecule $(C_6F_5)_3CH$, which has three strongly electron-withdrawing C_6F_5 groups and a pK_a of 16,[163] compared with Ph_3CH, with a pK_a of 31.5 (Table 8.1), an acidity enhancement of $\sim 10^{15}$. Table 8.5 shows pK_a values for some acids. An approximate idea of field effects can be obtained from this table. In the case of the chlorobutyric acids note how the effect decreases with distance. It must be remembered, however, that field effects are not the sole cause of the acidity differences noted and that in fact solvation effects may be more important in many cases (see pp. 390–394).[164] The influence of various substituents on the acidity of acetic acid has been calculated,[165] Substituent effects for weak acids, such as phenols and benzyl alcohols, have been discussed.[166]

6

Field effects are important in benzoic acid derivatives, and the pK_a of the acid will vary with the nature and placement of the "X" group in **6**.[167] The pK_a of 3-OMe **6** is 5.55, but 4-OMe **6** is 6.02 in 50% aq. methanol,[168] compared with a pK_a of 5.67 when X = H. When X = 4-NO_2, the pK_a is 4.76 and 4-Br is 5.36.[157] The pK_a of 2,6-diphenylbenzoic acid is 6.39.[169]

[162]For a review of the enhancement of acidity by NO_2, see Lewis, E.S., in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 2, Wiley, NY, ***1982***, pp. 715–729.

[163]Filler, R.; Wang, C. *Chem. Commun.* ***1968***, 287.

[164]For discussions, see Edward, J.T. *J. Chem. Educ.* ***1982***, *59*, 354; Schwartz, L.M. *J. Chem. Educ.* ***1981***, *58*, 778.

[165]Headley, A.D.; McMurry, M.E.; Starnes, S.D. *J. Org. Chem.* ***1994***, *59*, 1863.

[166]Wiberg, K.B. *J. Org. Chem.* ***2003***, *68*, 875.

[167]For calculated gas-phase acidities of substituted benzoic acids, see Wiberg, K. B. *J. Org. Chem.* ***2002***, *67*, 4787.

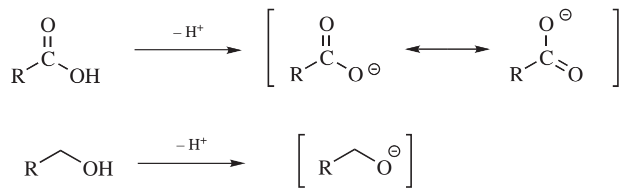
[168]DeMaria, P.; Fontana, A.; Spinelli, D.; Dell'Erba, C.; Novi, M.; Petrillo, G.; Sancassan, F. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 649.

[169]Chen, C.-T.; Siegel, J.S. *J. Am. Chem. Soc.* ***1994***, *116*, 5959. Several 2,6-diaryl derivatives are also reported. See also Sotomatsu, T.; Shigemura, M.; Murata, Y.; Fujita, T. *Bull. Chem. Soc. Jpn.* ***1992***, *65*, 3157.

TABLE 8.5. The p*K* Values for Some Acids[40]

Acid	p*K*	Acid	p*K*
HCOOH	3.77	$ClCH_2COOH$	2.86
CH_3COOH	4.76	$Cl_2CHCOOH$	1.29
CH_3CH_2COOH	4.88	Cl_3COOH	0.65
$CH_3(CH_2)_nCOOH$	4.82–4.95		
($n = 2$–7)		O_2NCH_2COOH	1.68
$(CH_3)_2CHCOOH$	4.86	$(CH_3)_3N^HCH_2COOH$	1.83
$(CH_3)_3CCOOH$	5.05	$HOOCCH_2COOH$	2.83
		$PhCH_2COOH$	4.31
FCH_2COOH	2.66		
$ClCH_2COOH$	2.86	$^-OOCCH_2COOH$	5.69
$BrCH_2COOH$	2.86		
ICH_2COOH	3.12	$^-O_3SCH_2COOH$	4.05
		$HOCH_2COOH$	3.83
$ClCH_2CH_2CH_2COOH$	4.52	$H_2C{=}CHCH_2COOH$	4.35
$CH_3CHClCH_2COOH$	4.06		
$CH_3CH_2CHClCOOH$	2.84		

2. *Resonance Effects*. Resonance that stabilizes a base but not its conjugate acid results in the acid having a higher acidity than otherwise expected and vice versa. An example is found in the higher acidity of carboxylic acids[170] compared with primary alcohols.

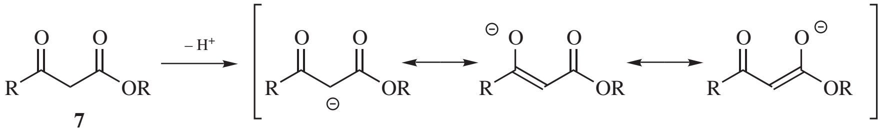


The $RCOO^-$ ion is stabilized by resonance not available to the RCH_2O^- ion (or to RCOOH).[171] Note that the $RCOO^-$ is stabilized not only by the fact that there are two equivalent canonical forms, but also by the fact that the negative charge is spread over both oxygen atoms and is therefore less

[170]See Exner, O.; Čársky, P. *J. Am. Chem. Soc.* ***2001***, *123*, 9564. See also, Liptak, M.D.; Shields, G.C. *J. Am. Chem. Soc.* ***2001***, *123*, 7314.

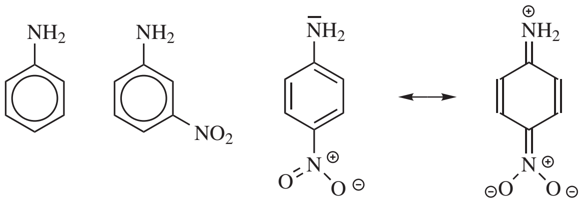
[171]It has been contended that resonance delocalization plays only a minor role in the increased strength of carboxylic acids compared to alcohols, and the "...higher acidity of acids arises principally because the electrostatic potential of the acidic hydrogens is more positive in the neutral acid molecule...": Siggel, M.R.; Streitwieser, Jr., A.; Thomas, T.D. *J. Am. Chem. Soc.* ***1988***, *110*, 8022; Thomas, T.D.; Carroll, T.X.; Siggel, M.R. *J. Org. Chem.* ***1988***, *53*, 1812. For contrary views, see Exner, O. *J. Org. Chem.* ***1988***, *53*, 1810; Dewar, M.J.S.; Krull, K.L. *J. Chem. Soc. Chem. Commun.* ***1990***, 333; Perrin, D.D. *J. Am. Chem. Soc.* ***1991***, *113*, 2865. See also, Godfrey, M. *Tetrahedron Lett.* ***1990***, *31*, 5181.

concentrated than in RCH_2O^-.The same effect is found in other compounds containing a C=O or CN group. Thus amides $RCONH_2$ are more acidic than amines RCH_2NH_2; esters RCH_2-COOR′ than ethers RCH_2CH_2OR'; and ketones RCH_2COR' than alkanes RCH_2CH_2R' (Table 8.1). The effect is enhanced when two carbonyl groups are attached to the same carbon (because of additional resonance and spreading of charge); for example, β-keto esters (see **7**) are more acidic than simple ketones or carboxylic esters (Table 8.1). The influence of substituents in the α-position of substituted ethyl acetate derivatives has been studied.[172] Extreme examples of this effect are found in the molecules tricyanomethane $(NC)_3CH$, with a pK_a of −5 (Table 8.1, p. 359), and 2-(dicyanomethylene)-1,1,3,3-tetracyanopropene$(NC)_2$ C=C[CH$(CN)_2]_2$, whose first pK_a is below −8.5 and whose second pK_a is −2.5.



7

Resonance effects are also important in aromatic amines. *m*-Nitroaniline is a weaker base than aniline, a fact that can be accounted for by the −*I* effect of the nitro group. But *p*-nitroaniline is weaker still, though the −*I* effect should be less because of the greater distance. It is noted that the pK_a values reported are those of the conjugate acid, the ammonium ion.[173] We can explain this result by taking into account the canonical form **A**. Because **A** contributes to the resonance hybrid,[174] the electron density of the unshared pair is lower in *p*-nitroaniline than in *m*-nitroaniline, where a canonical form such as **A** is impossible. The basicity is lower in the



4.60 2.47 1.11 **A**

para compound for two reasons, both caused by the same effect: (*1*) the unshared pair is less available for attack by a proton, and (*2*) when the conjugate acid is formed, the resonance stabilization afforded by **A** is no longer available because the previously unshared pair is now being shared by the proton. The acidity of phenols is affected by substituents in a similar manner.[175]

[172]Goumont, R.; Magnier, E.; Kizilian, E.; Terrier, F. *J. Org. Chem.* ***2003***, *68*,6566.

[173]Smith, J.W. in Patai, S. *The Chemistry of the Amino Group;* Wiley, NY, ***1968***, pp. 161–204.

[174]See, however, Lipkowitz, K.B. *J. Am. Chem. Soc.* ***1982***, *104*, 2647; Krygowski, T.M.; Maurin, J. *J. Chem. Soc. Perkin Trans. 2* ***1989***, 695.

[175]Liptak, M.D.; Gross, K.C.; Seybold, P.G.; Feldus, S.; Shields, G.C. *J. Am. Chem. Soc.* ***2002***, *124*, 6421.

In general, resonance effects lead to the same result as field effects. That is, here too, electron-withdrawing groups increase acidity and decrease basicity, and electron-donating groups act in the opposite manner. As a result of both resonance and field effects, charge dispersal leads to greater stability.

3. *Periodic Table Correlations.* When comparing Brønsted acids and bases that differ in the position of an element in the periodic table:

a. Acidity increases and basicity decreases in going from left to right across a row of the Periodic table. Thus acidity increases in the order $CH_4 < NH_3 < H_2O < HF$, and basicity decreases in the order $^-CH_3 > ^-NH_2 > ^-OH > ^-F$. This behavior can be explained by the increase in electronegativity upon going from left to right across the table. It is this effect that is responsible for the great differences in acidity between carboxylic acids, amides, and ketones: $RCOOH \gg RCONH_2 \gg RCOCH_3$.

b. Acidity increases and basicity decreases in going down a column of the periodic table, despite the decrease in electronegativity. Thus acidity increases in the order $HF < HCl < HBr < HI$ and $H_2O < H_2S$, and basicity decreases in the order $NH_3 > PH_3 > AsH_3$. This behavior is related to the size of the species involved. Thus, for example, F^-, which is much smaller than I^-, attracts a proton much more readily because its negative charge occupies a smaller volume and is therefore more concentrated (note that F^- is also much harder than I^- and is thus more attracted to the hard proton; see p. $$$). This rule does not always hold for positively charged acids. Thus, although the order of acidity for the group 16 hydrides is $H_2O < H_2S < H_2Se$, the acidity order for the positively charged ions is $H_3O^+ > H_3S^+ > H_3Se^+$.[176]

Lewis acidity is also affected by Periodic table considerations. In comparing acid strengths of Lewis acids of the form MX_n:[146]

c. Acids that require only one electron pair to complete an outer shell are stronger than those that require two. Thus $GaCl_3$ is stronger than $ZnCl_2$. This results from the relatively smaller energy gain in adding an electron pair that does not complete an outer shell and from the buildup of negative charge if two pairs come in.

d. Other things being equal, the acidity of MX_n decreases in going down the periodic table because as the size of the molecule increases, the attraction between the positive nucleus and the incoming electron pair is weaker. Thus BCl_3 is a stronger acid than $AlCl_3$.[177]

4. *Statistical Effects.* In a symmetrical diprotic acid, the first dissociation constant is twice as large as expected since there are two equivalent ionizable

[176]Taft, R.W. *Prog. Phys. Org. Chem.* ***1983***, *14*, 247, see pp. 250–254.

[177]Note that Lewis acidity *decreases*, whereas Brønsted acidity *increases*, going down the table. There is no contradiction here when we remember that in the Lewis picture the actual acid in all Brønsted acids is the same, namely, the proton. In comparing, say, HI and HF, we are not comparing different Lewis acids but only how easily F^- and I^- give up the proton.

TABLE 8.6. Bases Listed in Increasing Order of Base Strength when Compared with Certain Reference Acids

Increasing Order of Base Strength[a]	Reference Acid			
	H^+ or BMe_3	BMe_3	$B(CMe_3)_3$	
	NH_3	Et_3N	Me_3N	Et_3N
	Me_3N	NH_3	Me_2NH	Et_2NH
	$MeNH_2$	Et_2NH	NH_3	$EtNH_2$
	Me_2NH	$EtNH_2$	$MeNH_2$	NH_3

[a]The order of basicity (when the reference acids were boranes) was determined by the measurement of dissociation pressures

hydrogens, while the second constant is only half as large as expected because the conjugate base can accept a proton at two equivalent sites. So K_1/K_2 should be 4, and approximately this value is found for dicarboxylic acids where the two groups are sufficiently far apart in the molecule that they do not influence each other. A similar argument holds for molecules with two equivalent basic groups.[178]

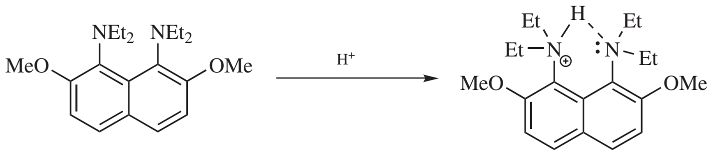
5. *Hydrogen Bonding*. Internal hydrogen bonding can greatly influence acid or base strength. For example, the pK for *o*-hydroxybenzoic acid is 2.98, while the value for the para isomer is 4.58. Internal hydrogen bonding between the OH and COO^- groups of the conjugate base of the ortho isomer stabilizes it and results in an increased acidity.

6. *Steric Effects*. The proton itself is so small that direct steric hindrance is seldom encountered in proton transfers. Steric effects are much more common in Lewis acid–base reactions in which larger acids are used. Spectacular changes in the order of base strength have been demonstrated when the size of the acid was changed. Table 8.6 shows the order of base strength of simple amines when compared against acids of various size.[179] It can be seen that the usual order of basicity of amines (when the proton is the reference acid) can be completely inverted by using a large enough acid. The strain caused by formation of a covalent bond when the two atoms involved each have three large groups is called *face strain* or *F strain*.

Steric effects can indirectly affect acidity or basicity by affecting the resonance (see p. 48). For example, *o-tert*-butylbenzoic acid is ~10 times as strong as the para isomer, because the carboxyl group is forced out of the plane by the *tert*-butyl group. Indeed, virtually all ortho benzoic acids are stronger than the corresponding para isomers, regardless of whether the group on the ring is electron-donating or electron-withdrawing.

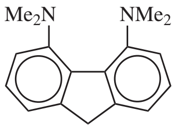
[178]The effect discussed here is an example of a symmetry factor. For an extended discussion, see Eberson, L., in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 211–293.

[179]Brown, H.C. *J. Am. Chem. Soc.* ***1945***, *67*, 378, 1452, *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, ***1972***, pp. 53–64. See also, Brown, H.C.; Krishnamurthy, S.; Hubbard, J.L. *J. Am. Chem. Soc.* ***1978***, *100*, 3343.



8 **9**

Steric effects can also be caused by other types of strain. 1,8-Bis(diethylamino)-2,7-dimethoxynaphthalene (**8**) is an extremely strong base for a tertiary amine (pK_a of the conjugate acid = 16.3; compare *N,N*-dimethylaniline, pK_a = 5.1), but proton transfers to and from the nitrogen are exceptionally slow; slow enough to be followed by a UV spectrophotometer.[180] Compound **8** is severely strained because the two nitrogen lone pairs are forced to be near each other.[181] Protonation relieves the strain: one lone pair is now connected to a hydrogen, which forms a hydrogen bond to the other lone pair (shown in **9**).



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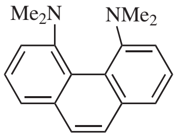


11

The same effects are found in 4,5-bis(dimethylamino)fluorene (**10**)[182] and 4,5-bis(dimethylamino)phenanthrene (**11**).[183] Compounds, such as **8**, **10**, and **11**, are known as *proton sponges*.[184] The basicity of proton sponge has been calculated as the sum of the proton affinity[152] of an appropriate reference monoamine, the strain released on protonation, and the energy of the intramolecular hydrogen bond formed on protonation.[185] Another type of proton sponge is quino[7,8-*h*]quinoline (**12**).[186] Protonation of this compound also gives a stable mono-protonated ion similar to **9**, but the steric hindrance found in **8**, **10**, and **11** is absent. Therefore, **12** is a much stronger base than quinoline (**13**) (pK_a values of the conjugate acids are 12.8 for **12** and 4.9 for **13**), but proton transfers are not abnormally slow. A cyclam-like macrocyclic

[180]Barnett, G.H.; Hibbert, F. *J. Am. Chem. Soc.* ***1984***, *106*, 2080; Hibbert, F.; Simpson, G.R. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 243, 613.

[181]For a review of the effect of strain on amine basicities, see Alder, R.W. *Chem. Rev.* ***1989***, *89*, 1215.

[182]Staab, H.A.; Saupe, T.; Krieger, C. *Angew. Chem. Int. Ed.* ***1983***, *22*, 731.

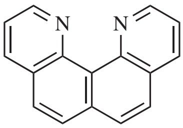
[183]Saupe, T.; Krieger, C.; Staab, H.A. *Angew. Chem. Int. Ed.* ***1986***, *25*, 451.

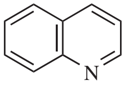
[184]For a review, see Staab, H.A.; Saupe, T. *Angew. Chem. Int. Ed.* ***1988***, *27*, 865.

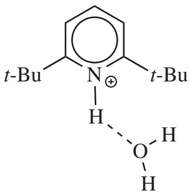
[185]Howard, S.T. *J. Am. Chem. Soc.* ***2000***, *122*, 8238.

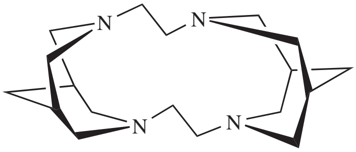
[186]Krieger, C.; Newsom, I.; Zirnstein, M.A.; Staab, H.A. *Angew. Chem. Int. Ed.* ***1989***, *28*, 84. See also, Schwesinger, R.; Missfeldt, M.; Peters, K.; Schnering, H.G. von *Angew. Chem. Int. Ed.* ***1987***, *26*, 1165; Alder, R.W.; Eastment, P.; Hext, N.M.; Moss, R.E.; Orpen, A.G.; White, J.M. *J. Chem. Soc. Chem. Commun.* ***1988***, 1528; Staab, H.A.; Zirnstein, M.A.; Krieger, C. *Angew. Chem. Int. Ed.* ***1989***, *28*, 86.

tetramine (**15**) was prepared by a coupling reaction of bispidine, and was shown to be a new class of proton sponge.[187]







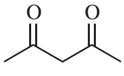


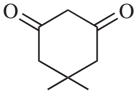
12 **13** **14** **15**

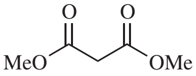
Chiral Lewis acids are known. Indeed, an air stable and storable chiral Lewis acid catalyst has been prepared, a chiral zirconium catalyst combined with molecular sieves powder.[188] Association of a bulky silicon group with the bis(trifluoromethanesulfonyl)imide anion leads to enhancement of the electrophilic character of R_3SiNTf_2. The presence of a chiral substituent derived from (−)-myrtenal on the silicon atom led to a chiral silicon Lewis acid.[189]

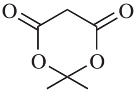
Another type of steric effect is the result of an entropy effect. The compound 2,6-di-*tert*-butylpyridine is a weaker base than either pyridine or 2,6-dimethylpyridine.[190] The reason is that the conjugate acid (**14**) is less stable than the conjugate acids of non-sterically hindered pyridines. In all cases, the conjugate acids are hydrogen bonded to a water molecule, but in the case of **14** the bulky *tert*-butyl groups restrict rotations in the water molecule, lowering the entropy.[191]

The conformation of a molecule can also affect its acidity. The following pK_a values were determined for these compounds:[192]









	16	**17**	**18**	**19**
pK_a	13.3	11.2	15.9	7.3

Since ketones are stronger acids than carboxylic esters (Table 8.1), we are not surprised that **16** is a stronger acid than **18**. But cyclization of **16** to **17** increases the acidity by only 2.1 pK units while cyclization of **18** to **19**

[187]Miyahara, Y.; Goto, K.; Inazu, T. *Tetrahedron Lett.* ***2001***, *42*, 3097.

[188]Ueno, M.; Ishitani, H.; Kobayashi, S. *Org. Lett.* ***2002***, *4*, 3395.

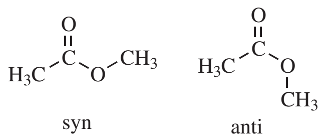
[189]Mathieu, B.; de Fays, L.; Ghosez, L. *Tetrahedron Lett* ***2000***, *41*, 9651

[190]Brown, H.C.; Kanner, B. *J. Am. Chem. Soc.* ***1953***, *75*, 3865; ***1966***, *88*, 986.

[191]Hopkins, Jr., H.P.; Janagirdar, D.V.; Moulik, P.S.; Aue, D.H.; Webb, H.M.; Davidson, W.R.; Pedley; M.D. *J. Am. Chem. Soc.* ***1984***, *106*, 4341; Meot-Ner, M.; Smith, S.C. *J. Am. Chem. Soc.* ***1991***, *113*, 862, and references cited therein. See also, Benoit, R.L.; Fréchette, M.; Lefebvre, D. *Can. J. Chem.* ***1988***, *66*, 1159.

[192]Arnett, E.M.; Harrelson Jr., J.A. *J. Am. Chem. Soc.* ***1987***, *109*, 809.

increases it by 8.6 units. Indeed, it has long been known that **19** (called *Meldrum's acid*) is an unusually strong



acid for a 1,3-diester. In order to account for this very large cyclization effect, molecular-orbital calculations were carried out two conformations of methyl acetate and of its enolate ion by two groups.[193] Both found that loss of a proton is easier by ~5 kcal mol^{-1} (21 kJ mol^{-1}) for the syn than for the anti conformer of the ester. In an acyclic molecule like **18**, the preferred conformations are anti, but in Meldrum's acid (**19**) the conformation on both sides is constrained to be syn.

Facial differences in proton reactivity can lead to enantioselective deprotonation. A more common way to achieve enantioselective deprotonation is to use a chiral base and/or a chiral complexing agent. Enantioselective deprotonation in cyclic ketones has been studied.[194] Enantioselective deprotonation with heterodimer bases has been studied.[195]

When a Lewis acid coordinates to a base, the resulting complex can have conformational properties that influence reactivity. Coordination of $SnCl_4$ with aldehydes and esters, for example, leads to a complex where the conformation is determined by interactions of the C=O•••$SnCl_4$ unit with substituents attached to the carbonyl.[196]

7. *Hybridization.* An *s* orbital has a lower energy than a *p* orbital. Therefore the energy of a hybrid orbital is lower the more *s* character it contains. It follows that a carbanion at an *sp* carbon is more stable than a corresponding carbanion at an sp^2 carbon. Thus $HC{\equiv}C^-$, which has more *s* character in its unshared pair than $CH_2{=}CH^-$ or $CH_3CH_2^-$ (*sp* vs. sp^2 vs. sp^3, respectively), is a much weaker base. This explains the relatively high acidity of acetylenes and HCN. Another example is that alcohol and ether oxygens, where the unshared pair is sp^3, are more strongly basic than carbonyl oxygens, where the unshared pair is sp^2 (Table 8.1).

A recent development in understanding the reactivity of bases has focused on their structures in solution and in the crystalline state. Due to the importance of dialkyl amide bases, there is a significant body of work, led by Williard and by Collum, that has attempted to understand the structures of

[193]Wang, X.; Houk, K.N. *J. Am. Chem. Soc.* ***1988***, *110*, 1870; Wiberg, K.B.; Laidig, K.E. *J. Am. Chem. Soc.* ***1988***, *110*, 1872.
[194]Majewski, M.; Wang, F. *Tetrahedron* **2002**, *58*, 4567.
[195]Amedjkouh, M. *Tetrahedron Asymm.* **2004**, *15*, 577.
[196]Gung, B.W.; Yanik, M.M. *J. Org. Chem.* ***1996***, *61*, 947.

these reactive molecules. It is clear that they are aggregates. Note that the simplest member of the amide base family, lithium amide ($LiNH_2$) was shown to be monomeric and unsolvated, as determined using a combination of gas-phase synthesis and millimeter–submillimeter wave spectroscopy.[197] Note that monomeric $LiNH_2$ and $LiNMe_2$ are planar.[198] Lithium diisopropylamide ($LiNiPr_2$, LDA) was isolated from a THF solution and X-ray crystallography revealed a dimeric structure (**20**; R = *i*Pr, S = THF) in the solid state.[199] Lithium diisopropylamide was also shown to be a dimer in solutions of THF[200] and/or HMPA (see **20**, R = *i*Pr and S = THF, HMPA).[201] In the presence of HMPA, many derivatives **20** tend to be mixed aggregates.[202] Extremely hindered $LiNR_2$ (R = 2-adamantyl) are monomeric under all conditions.[203] In hydrocarbon solvents, lithium tetramethylpiperidide [LTMP, RR'NLi where RR′ = $-CMe_2(CH_2)_3C(Me_2)-$] forms cyclic trimers and tetramers, with the tetrameric species predominating.[204] In THF, lithium hexamethyldisilazide [LHMDS, $(Me_3Si)_2NLi$] forms a five-coordinate tetrasolvate $[(Me_3Si)_2NLi(thf)_4]$,[205] but in ether there is an equilibrium mixture of monomer and dimer.[206] A review is available that discusses the solution structures of amide bases $LiNR_2$.[207] Chiral lithium amide bases are known and they show similar behavior in solution.[208] Chelation effects are common in enantio-enriched amide bases, which also form aggregates.[209] The aggregation state of lithium phenylacetonitrile has been studied.[210] Dianion aggregates can be generated, and in the case of the lithiation reaction of *N*-silyl allylamine, X-ray structure determination showed the presence of three

[197]Grotjahn, D.B.; Sheridan, P.M.; Al Jihad, I.; Ziurys, L.M. *J. Am. Chem. Soc.* ***2001***, *123*, 5489.

[198]Fressigné, C.; Maddaluno, J.; Giessner-Prettre, C.; Silvi, B. *J. Org. Chem.* ***2001***, *66*, 6476.

[199]Williard P.G.; Salvino, J.M. *J. Org. Chem.* ***1993***, *58*, 1. For a study of the oligomer structure of LDA at low ligand concentrations, see Rutherford, J.L.; Collum, D.B. *J. Am. Chem. Soc.* ***2001***, *123*, 199.

[200]Ito, H.; Nakamura, T.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* ***1992***, *33*, 3769.

[201]Aubrecht, K.B.; Collum, D.B. *J. Org. Chem.* ***1996***, *61*, 8674.

[202]Romesberg, F.E.; Collum, D.B. *J. Am.Chem. Soc.* ***1994***, *116*, 9198, 9187. For a study of other mixed aggregates see Thomas, R.D.; Huang, J. *J. Am. Chem. Soc.* ***1999***, *121*, 11239.

[203]Sakuma, K.; Gilchrist, J.H.; Romesberg, F.E.; Cajthami, C.E.; Collum, D.B. *Tetrahedron Lett.* ***1993***, *34*, 5213.

[204]Lucht, B.L.; Collum, D.B. *J. Am. Chem. Soc.* ***1994***, *116*, 7949.

[205]Lucht, B.L.; Collum, D.B. *J. Am. Chem. Soc.* ***1995***, *117*, 9863. See also, Lucht, B.L.; Collum, D.B. *J. Am. Chem. Soc.* ***1996***, *118*, 2217, 3529. See Romesberg, F.E.; Bernstein, M.P.; Gilchrist, J.H.; Harrison, A.T.; Fuller, D.J.; Collum, D.B. *J. Am. Chem. Soc.* ***1993***, *115*, 3475 for the structure in HMPA.

[206]Lucht, B.L.; Collum, D.B. *J. Am. Chem. Soc.* ***1994***, *116*, 6009.

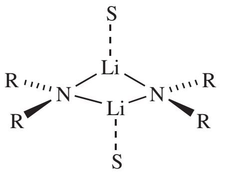
[207]Collum, D.B. *Acc. Chem. Res.* ***1993***, *26*, 227. For NMR studies of $LiNEt_2$ and ring laddering see Rutherford, J.L.; Collum, D.B. *J. Am. Chem. Soc.* ***1999***, *121*, 10198.

[208]Hilmersson, G.; Davidsson, Ö. *J. Org. Chem.* ***1995***, *60*, 7660. See also, O'Brien, P. *J. Chem. Soc. Perkin Trans. 1* ***1998***, 1439. See also, Sott, R.; Grandander, J.; Dinér, P.; Hilmersson, G. *Tetrahedron Asymm.* ***2004***, *15*, 267.

[209]Arvidsson, P.I.; Hilmersson, G.; Ahlberg, P. *J. Am. Chem. Soc.* ***1999***, *121*, 183.

[210]Carlier, P.R.; Madura, J.D. *J. Org. Chem.* ***2002***, *67*, 3832.

uniquely different aggregates.[211] A mixed aggregate is formed when the lithium enolate of a ketone is mixed with a lithium amide.[212]



S=solvent

20

Similar information is available for other bases. Lithium phenoxide (LiOPh) is a tetramer in THF.[213] Lithium 3,5-dimethylphenoxide is a tetramer in ether, but addition of HMPA leads to dissociation to a monomer.[214]

Enolate anions are nucleophiles in reactions with alkyl halides (reaction **10-68**), with aldehydes and ketones (reactions **16-34**, **16-36**) and with acid derivatives (reaction **16-85**). Enolate anions are also bases, reacting with water, alcohols and other protic solvents, and even the carbonyl precursor to the enolate anion. Enolate anions exist as aggregates, and the effect of solvent on aggregation and reactivity of lithium enolate anions has been studied.[215] The influence of alkyl substitution on the energetics of enolate anions has been studied.[216]

THE EFFECTS OF THE MEDIUM ON ACID AND BASE STRENGTH

Structural features are not the only factors that affect acidity or basicity. The same compound can have its acidity or basicity changed when the conditions are changed. The effect of temperature (p. 364) has already been mentioned. More important is the effect of the solvent, which can exert considerable influence on acid and base strengths by differential solvation.[217] If a base is more solvated than its conjugate acid, its stability is increased relative to the conjugate acid. For example,

[211]Williard, P. G.; Jacobson, M. A. *Org. Lett.* ***2000***, *2*, 2753. For the structure and bonding of dilithiodiamines see Pratt, L.M.; Mu, R. *J. Org. Chem.* ***2004***, *69*, 7519.

[212]Sun, C.; Williard, P.G. *J. Am. Chem. Soc.* ***2000***, *122* , 7829. See also, Pratt, L.M.; Streitwieser, A. *J. Org. Chem.* ***2003***, *68*, 2830.

[213]Jackman, L.M.; Çizmeciyan, D.; Williard, P.G.; Nichols, M.A. *J. Am. Chem. Soc.* ***1993***, *115*, 6262.

[214]Jackman, L.M.; Chen, X. *J. Am. Chem. Soc.* ***1992***, *114*, 403.

[215]Streitwieser, A.; Juaristi, E.; Kim, Y.-J.; Pugh, J.K. *Org. Lett.* ***2000***, *2*, 3839.

[216]Alconcel, L.S.; Deyerl, H.-J.; Continetti, R.E. *J. Am. Chem. Soc.* ***2001***, *123*, 12675.

[217]For reviews of the effects of solvent, see Epshtein, L.M.; Iogansen, A.V. *Russ. Chem. Rev.* ***1990***, *59*, 134; Dyumaev, K.M.; Korolev, B.A. *Russ. Chem. Rev.* ***1980***, *49*, 1021. For a review of the effects of the solvent DMSO, see Taft, R.W.; Bordwell, F.G. *Acc. Chem. Res.* ***1988***, *21*, 463. For determination of pK_a values of various compounds in acetonitrile see Heemstra, J.M.; Moore, J.S. *Tetrahedron* ***2004***, *60*, 7287.

Table 8.6 shows that toward the proton, where steric effects are absent, methylamine is a stronger base than ammonia and dimethylamine is stronger still.[218] These results are easily explainable if one assumes that methyl groups are electron donating. However, trimethylamine, which should be even stronger, is a weaker base than dimethylamine or methylamine. This apparently anomalous behavior can be explained by differential hydration.[219] Thus, NH_4^+ is much better hydrated (by hydrogen bonding to the water solvent) than NH_3 because of its positive charge.[220] It has been estimated that this effect contributes ~11 p*K* units to the base strength of ammonia.[221] When methyl groups replace hydrogen, this difference in hydration decreases[222] until, for trimethylamine, it contributes only ~6 p*K* units to the base strength.[179] Thus two effects act in opposite directions, the field effect increasing the basicity as the number of methyl groups increases and the hydration effect decreasing it. When the effects are added, the strongest base is dimethylamine and the weakest is ammonia. If alkyl groups are electron donating, one would expect that in the gas phase,[223] where the solvation effect does not exist, the basicity order of amines toward the proton should be $R_3N > R_2NH > RNH_2 > NH_3$, and this has indeed been confirmed, for R = Me as well as R = Et and Pr.[224] Aniline

[218]For a review of the basicity of amines, see Smith, J.W., in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, pp. 161–204.

[219]Trotman-Dickenson, A.F. *J. Chem. Soc.* ***1949***, 1293; Pearson, R.G.; Williams, F.V. *J. Am. Chem. Soc.* ***1954***, *76*, 258; Hall, Jr., H.K. *J. Am. Chem. Soc.* ***1957***, *79*, 5441; Arnett, E.M.; Jones III, F.M; Taagepera, M.; Henderson, W.G.; Beauchamp, J.L.; Holtz, D.; Taft, R.W. *J. Am. Chem. Soc.* ***1972***, *94*, 4724; Aue, D.H.; Webb, H.M.; Bowers, M.T. *J. Am. Chem. Soc.* ***1972***, *94*, 4726; ***1976***, *98*, 311, 318; Mucci, A.; Domain, R.; Benoit, R.L. *Can. J. Chem.* ***1980***, *58*, 953. See also Drago, R.S.; Cundari, T.R.; Ferris, D.C. *J. Org. Chem.* ***1989***, *54*, 1042.

[220]For discussions of the solvation of ammonia and amines, see Jones III, F.M.; Arnett, E.M. *Prog. Phys. Org. Chem.* ***1974***, *11*, 263; Grunwald, E.; Ralph, E.K. *Acc. Chem. Res.* ***1971***, *4*, 107.

[221]Condon, F.E. *J. Am. Chem. Soc.* ***1965***, *87*, 4481, 4485.

[222]For two reasons: (*1*) the alkyl groups are poorly solvated by the water molecules, and (*2*) the strength of the hydrogen bonds of the BH^+ ions decreases as the basicity of B increases: Lau, Y.K.; Kebarle, P. *Can. J. Chem.* ***1981***, *59*, 151.

[223]For reviews of acidities and basicities in the gas phase, see Liebman, J.F. *Mol. Struct. Energ.* ***1987***, *4*, 49; Dixon, D.A.; Lias, S.G. *Mol. Struct. Energ.* 1987, *2*, 269; Bohme, D.K., in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 2, Wiley, NY, ***1982***, pp. 731–762; Bartmess, J.E.; McIver, Jr., R.T., in Bowers, M.T. *Gas Phase Ion Chemistry*, Vol. 2, Academic Press, NY, ***1979***, pp. 88–121; Kabachnik, M.I. *Russ. Chem. Rev.* ***1979***, *48*, 814; Kebarle, P. *Annu. Rev. Phys. Chem.* ***1977***, *28*, 445; Arnett, E.M. *Acc. Chem. Res.* ***1973***, *6*, 404. For a comprehensive table of gas-phase basicities, see Lias, S.G.; Liebman, J.F.; Levin, R.D. *J. Phys. Chem. Ref. Data*, ***1984***, *13*, 695. See also the tables of gas-phase acidities and basicities in the following articles, and their cited references: Meot-Ner, M.; Kafafi, S.A. *J. Am. Chem. Soc.* ***1988***, *110*, 6297; Headley, A.D. *J. Am. Chem. Soc.* ***1987***, *109*, 2347; McMahon, T.B.; Kebarle, P. *J. Am. Chem. Soc.* ***1985***, *107*, 2612; ***1977***, *99*, 2222, 3399; Wolf, J.F.; Staley, R.H.; Koppel, I.; Bartmess, J.E.; Scott, J.A.; McIver, Jr., R.T. *J. Am. Chem. Soc.* ***1979***, *101*, 6046; Fujio, M.; McIver, Jr., R.T.; Taft, R.W. *J. Am. Chem. Soc.* ***1981***, *103*, 4017; Lau, Y.K.; Nishizawa, K.; Tse, A.; Brown, R.S.; Kebarle, P. *J. Am. Chem. Soc.* ***1981***, *103*, 6291.

[224]Munson, M.S.B. *J. Am. Chem. Soc.* ***1965***, *87*, 2332; Brauman, J.I.; Riveros, J.M.; Blair, L.K. *J. Am. Chem. Soc.* ***1971***, *93*, 3914; Briggs, J.P.; Yamdagni, R.; Kebarle, P. *J. Am. Chem. Soc.* ***1972***, *94*, 5128; Aue, D.H.; Webb H.M.; Bowers, M.T. *J. Am. Chem. Soc.* ***1972***, *94*, 4726; ***1976***, *98*, 311, 318.

too, in the gas phase, is a stronger base than NH_3,[225] so its much lower basicity in aqueous solution (pK_a of $PhNH_3^+$ 4.60 compared with 9.24 for aqueous NH_4^+) is caused by similar solvation effects and not by resonance and field electron-withdrawing effects of a phenyl group. Similarly, pyridine[226] and pyrrole[227] are both much less basic than NH_3 in aqueous solution (pyrrole[228] is neutral in aqueous solution), but *more* basic in the gas phase. These examples in particular show how careful one must be in attributing relative acidities or basicities to any particular effect. Solvent has a significant influence on the Hammett reaction constant (p. 679), which influences the acidity of substituted benzoic acids.[229]

In the case of Lewis acids, protic solvents such as water or alcohol can strongly influence their reactivity, cause it to react via an alternative path to the one desired, or even cause decomposition. Recently, rare earth metal triflates were used to develop water tolerant Lewis acids that can be used in many organic reactions.[230]

For simple alcohols, the order of gas-phase *acidity* is completely reversed from that in aqueous solution. In solution, the acidity is in the order $H_2O > MeCH_2OH > Me_2CHOH > Me_3COH$, but in the gas phase the order is precisely the opposite.[231] Once again solvation effects can be invoked to explain the differences. Comparing the two extremes, H_2O and Me_3COH, we see that the OH^- ion is very well solvated by water while the bulky Me_3CO^- is much more poorly solvated because the water molecules cannot get as close to the oxygen. Thus in solution H_2O gives up its proton more readily. When solvent effects are absent, however, the intrinsic acidity is revealed and Me_3COH is a stronger acid than H_2O. This result demonstrates that simple alkyl groups cannot be simply regarded as electron donating. If methyl is an electron-donating group, then Me_3COH should be an intrinsically weaker acid than H_2O, yet it is stronger. A similar pattern is found with carboxylic acids, where simple aliphatic acids, such as propanoic, are stronger than acetic acid in the gas phase,[232] though weaker in aqueous solution (Table 8.5).

[225]Briggs, J.P.; Yamdagni, R.; Kebarle, P. *J. Am. Chem. Soc.* ***1972***, *94*, 5128; Dzidic, I. *J. Am. Chem. Soc.* ***1972***, *94*, 8333; Ikuta, S.; Kebarle, P. *Can. J. Chem.* ***1983***, *61*, 97.

[226]Taft, R.W.; Taagepera, M.; Summerhays, K.D.; Mitsky, J. *J. Am. Chem. Soc.* ***1973***, *95*, 3811; Briggs, J.P.; Yamdagni, R.; Kebarle, P. *J. Am. Chem. Soc.* ***1972***, *94*, 5128.

[227]Yamdagni, R.; Kebarle, P. *J. Am. Chem. Soc.* ***1973***, *95*, 3504.

[228]For a review of the basicity and acidity of pyrroles, see Catalan, J.; Abboud, J.L.M.; Elguero, J. *Adv. Heterocycl. Chem.* ***1987***, *41*, 187.

[229]Bartnicka, H.; Bojanowska, I.; Kalinowski, M.K. *Aust. J. Chem.* ***1993***, *46*, 31.

[230]Kobayashi, S. *Synlett*, ***1994***, 689.

[231]Baird, N.C. *Can. J. Chem.* ***1969***, *47*, 2306; Arnett, E.M.; Small, L.E.; McIver, Jr., R.T.; Miller, J.S. *J. Am. Chem. Soc.* ***1974***, *96*, 5638; Blair, L.K.; Isolani, P.C.; Riveros, J.M. *J. Am. Chem. Soc.* ***1973***, *95*, 1057; McIver, Jr., R.T.; Scott, J.A.; Riveros, J.M. *J. Am. Chem. Soc.* ***1973***, *95*, 2706. The alkylthiols behave similarly; gas-phase acidity increases with increasing group size while solution (aqueous) acidity decreases: Bartmess, J.E.; McIver Jr., R.T. *J. Am. Chem. Soc.* ***1977***, *99*, 4163.

[232]For a table of gas-phase acidities of 47 simple carboxylic acids, see Caldwell, G.; Renneboog, R.; Kebarle, P. *Can. J. Chem.* ***1989***, *67*, 611.

The evidence in these and other cases[233] is that alkyl groups can be electron donating when connected to unsaturated systems, but in other systems may have either no effect or may actually be electron withdrawing. The explanation given for the intrinsic gas-phase acidity order of alcohols as well as the basicity order of amines is that alkyl groups, because of their polarizability, can spread both positive and negative charges.[234] It has been calculated that even in the case of alcohols the field effects of the alkyl groups are still operating normally, but are swamped by the greater polarizability effects.[235] Polarizability effects on anionic centers are a major factor in gas-phase acid–base reactions.[236]

It has been shown (by running reactions on ions that are solvated in the gas phase) that solvation by even one molecule of solvent can substantially affect the order of basicities.[237]

An important aspect of solvent effects is the effect on the orientation of solvent molecules when an acid or base is converted to its conjugate. For example, consider an acid RCOOH converted to $RCOO^-$ in aqueous solution. The solvent molecules, by hydrogen bonding, arrange themselves around the COO^- group in a much more orderly fashion than they had been arranged around the COOH group (because they are more strongly attracted to the negative charge). This represents a considerable loss of freedom and a decrease in entropy. Thermodynamic measurements show that for simple aliphatic and halogenated aliphatic acids in aqueous solution at room temperature, the entropy ($T\Delta S$) usually contributes much more to the total free-energy change ΔG than does the enthalpy ΔH.[238] Two examples are shown in Table 8.7.[239] Resonance and field effects of functional groups therefore affect the acidity of RCOOH in two distinct ways. They affect the enthalpy (electron withdrawing groups increase acidity by stabilizing $RCOO^-$by charge dispersal), but they also affect the entropy (by lowering the charge on the COO^- group and by changing the electron-density distribution in the COOH group, electron-withdrawing groups alter the solvent orientation patterns around both the acid and the ion, and consequently change ΔS).

[233]Brauman, J.I.; Blair, L.K. *J. Am. Chem. Soc.* ***1971***, *93*, 4315; Kwart, H.; Takeshita, T. *J. Am. Chem. Soc.* ***1964***, *86*, 1161; Fort, Jr., R.C.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1964***, *86*, 4194; Holtz, H.D.; Stock, L.M. *J. Am. Chem. Soc.* ***1965***, *87*, 2404; Laurie, V.W.; Muenter, J.S. *J. Am. Chem. Soc.* ***1966***, *88*, 2883.

[234]Brauman, J.I.; Blair, L.K. *J. Am. Chem. Soc.* ***1970***, *92*, 5986; Munson, M.S.B. *J. Am.Chem. Soc.* ***1965***, *87*, 2332; Brauman, J.I.; Riveros, J.M.; Blair, L.K. *J. Am. Chem. Soc.* ***1971***, *93*, 3914; Huheey, J.E. *J. Org. Chem.* ***1971***, *36*, 204; Radom, L. *Aust. J. Chem.* ***1975***, *28*, 1; Aitken, E.J.; Bahl, M.K.; Bomben, K.D.; Gimzewski, J.K.; Nolan, G.S.; Thomas, T.D. *J. Am. Chem. Soc.* ***1980***, *102*, 4873.

[235]Taft, R.W.; Taagepera, M.; Abboud J.M.; Wolf, J.F.; Defrees, D.J.; Hehre, W.J.; Bartmess, J.E.; McIver Jr., R.T. *J. Am. Chem. Soc.* ***1978***, *100*, 7765. For a scale of polarizability parameters, see Hehre, W.J.; Pau, C.; Headley, A.D.; Taft, R.W.; Topsom, R.D. *J. Am. Chem. Soc.* ***1986***, *108*, 1711.

[236]Bartmess, J.E.; Scott, J.A.; McIver Jr., R.T. *J. Am. Chem. Soc.* ***1979***, *101*, 6056.

[237]Bohme, D.K.; Rakshit, A.B.; Mackay, G.I. *J. Am. Chem. Soc.* ***1982***, *104*, 1100.

[238]Bolton, P.D.; Hepler, L.G. *Q. Rev. Chem. Soc.* ***1971***, *25*, 521; Gerrard, W.; Macklen, E.D. *Chem. Rev.* ***1959***, *59*, 1105. See also Wilson, B.; Georgiadis, R.; Bartmess, J.E. *J. Am. Chem. Soc.* ***1991***, *113*, 1762.

[239]Bolton, P.D.; Hepler, L.G. *Q. Rev. Chem. Soc.* ***1971***, *25*, 521; p. 529; Hambly, A.N.*Rev. Pure Appl. Chem.* ***1965***, *15*, 87, p. 92.

TABLE 8.7. Thermodynamic Values for the Ionizations of Acetic and Chloroacetic Acids in H_2O at 25°C[238]

		ΔG		ΔH		$T\Delta S$	
Acid	pK_a	kcal mol^{-1}	kJ mol^{-1}	kcal mol^{-1}	kJ mol^{-1}	kcal mol^{-1}	kJ mol^{-1}
CH_3COOH	4.76	+6.5	+27	−0.1	−0.4	−6.6	−28
$ClCH_2COOH$	2.86	+3.9	+16	−1.1	−4.6	−5.0	−21
Cl_3CCOOH	0.65	+0.9	+3.8	+1.5	+6.3	+0.6	+2.5

A change from a protic to an aprotic solvent can also affect the acidity or basicity, since there is a difference in solvation of anions by a protic solvent (which can form hydrogen bonds) and an aprotic one.[240] The effect can be extreme: in DMF, picric acid is stronger than HBr,[241] though in water HBr is far stronger. This particular result can be attributed to size. That is, the large ion $(O_2N)_3C_6H_2O^-$ is better solvated by DMF than the smaller ion Br^-.[242] The ionic strength of the solvent also influences acidity or basicity, since it has an influence on activity coefficients.

In summary, solvation can have powerful effects on acidity and basicity. In the gas, phase the effects discussed in the previous section, especially resonance and field effects, operate unhindered by solvent molecules. As we have seen, electron-withdrawing groups generally increase acidity (and decrease basicity); electron-donating groups act in the opposite way. In solution, especially aqueous solution, these effects still largely persist (which is why pK values in Table 8.5 do largely correlate with resonance and field effects), but in general are much weakened, and occasionally reversed.[164]

[240]For a review, see Parker, A.J. *Q. Rev. Chem. Soc.* ***1962***, *16*, 163.
[241]Sears, P.G.; Wolford, R.K.; Dawson, L.R. *J. Electrochem. Soc.* ***1956***, *103*, 633.
[242]Miller, J.; Parker, A.J. *J. Am. Chem. Soc.* ***1961***, *83*, 117.

CHAPTER 9

Effects of Structure and Medium on Reactivity

When the equation for a reaction of, say, carboxylic acids, is written, it is customary to use the formula RCOOH, which implies that all carboxylic acids undergo the reaction. Since most compounds with a given functional group do give more or less the same reactions, the custom is useful, and the practice is used in this book. It allows a large number of individual reactions to be classified together and serves as an aid both for memory and understanding. Organic chemistry would be a huge morass of unconnected facts without the symbol R. Nevertheless, it must be borne in mind that a given functional group does not always react the same way, regardless of what molecule it is a part of. The reaction at the functional group is influenced by the rest of the molecule. This influence may be great enough to stop the reaction completely or to make it take an entirely different course. Even when two compounds with the same functional group undergo the same reaction, the rates and/or the positions of equilibrium are usually different, sometimes slightly, sometimes greatly, depending on the structures of the compounds. The greatest variations may be expected when additional functional groups are present.

The effects of structure on reactivity can be divided into three major types: field, resonance (or mesomeric), and steric.[1] In most cases, two or all three of these are operating, and it is usually not easy to tell how much of the rate enhancement (or decrease) is caused by each of the three effects.

[1]For a monograph, see Klumpp, G.W. *Reactivity in Organic Chemistry*, Wiley, NY, ***1982***. For a general theoretical approach to organic reactivity, see Pross, A. *Adv. Phys. Org. Chem.* ***1985***, *21*, 99.

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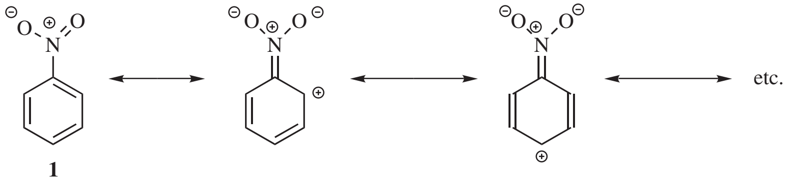
RESONANCE AND FIELD EFFECTS

It is often particularly difficult to separate resonance and field effects; they are frequently grouped together under the heading of *electrical effects*.[2] Field effects were discussed on pp. 19–22. Table 1.3 contains a list of some $+I$ and $-I$ groups. As for resonance effects, on p. 48 it was shown how the electron density distribution in aniline is not the same as it would be if there were no resonance interaction between the ring and the NH_2 group. Most groups that contain an unshared pair on an atom connected to an unsaturated system display a similar effect; that is, the electron density on the group is less than expected, and the density on the unsaturated system is greater. Such groups are said to be electron donating by the resonance effect ($+M$ groups). Alkyl groups, which do not have an unshared pair, are also $+M$ groups, presumably because of hyperconjugation.

On the other hand, groups that have a multiple-bonded electronegative atom directly connected to an unsaturated system are $-M$ groups. In such cases, we can draw canonical forms in which electrons have been taken from the unsaturated system into the group, as in nitrobenzene, **1**. Table 9.1 contains a list of some $+M$ and $-M$ groups.



1

TABLE 9.1. Some Groups with $+M$ and $-M$ Effects, Not Listed in Order of Strength of Effect[a]

$+M$		$-M$	
O^-	SR	NO_2	CHO
S^-	SH	CN	COR
NR_2	Br	COOH	SO_2R
NHR	I	COOR	SO_2OR
NH_2	Cl	$CONH_2$	NO
NHCOR	F	CONHR	Ar
OR	R	$CONR_2$	
OH	Ar		
OCOR			

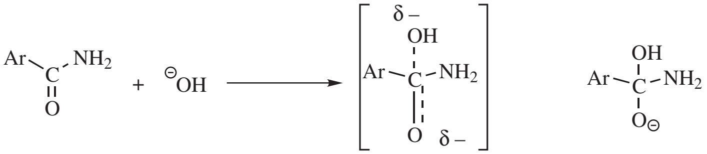
[a]Ar appears in both lists because it is capable of both kinds of effect.

[2]For reviews of the study of electrical effects by ab initio mo methods, see Topsom, R.D. *Prog. Phys. Org. Chem.* ***1987***, *16*, 125, *Mol. Struct. Energ.* ***1987***, *4*, 235.

The resonance effect of a group, whether $+M$ or $-M$, operates only when the group is directly connected to an unsaturated system, so that, for example, in explaining the effect of the CH_3O group on the reactivity of the COOH in $CH_3OCH_2CH_2COOH$, only the field effect of the CH_3O need be considered. This is one way of separating the two effects. In *p*-methoxybenzoic acid both effects must be considered. The field effect operates through space, solvent molecules, or the σ bonds of a system, while the resonance effect operates through π electrons.

It must be emphasized once again that neither by the resonance nor by the field effect are any electrons actually being donated or withdrawn, though these terms are convenient (and we will use them). As a result of both effects, the electron-density distribution is not the same as it would be without the effect (see pp. 21, 48). One thing that complicates the study of these effects on the reactivity of compounds is that a given group may have an effect in the transition state that is considerably more or less than it has in the molecule that does not react.

An example will show the nature of electrical effects (resonance and field) on reactivity. In the alkaline hydrolysis of aromatic amides (reaction **16-60**), the rate-determining step is the attack of hydroxide ion at the carbonyl carbon:



Transition state

Intermediate

2 **3**

In the transition state, which has a structure somewhere between that of the starting amide (**2**) and the intermediate (**3**), the electron density on the carbonyl carbon is increased. Therefore, electron-withdrawing groups ($-I$ or $-M$) on the aromatic ring will lower the free energy of the transition state (by spreading the negative charge). These groups have much less effect on the free energy of **2**. Since G is lowered for the transition state, but not substantially for **2**, $\Delta G^{\ddagger}$ is lowered and the reaction rate is increased (Chapter 6). Conversely, electron-donating groups ($+I$ or $+M$) should decrease the rate of this reaction. Of course, many groups are $-I$ and $+M$, and for these it is not always possible to predict which effect will predominate.

STERIC EFFECTS

It occasionally happens that a reaction proceeds much faster or much slower than expected on the basis of electrical effects alone. In these cases it can often be shown that steric effects are influencing the rate. For example, Table 9.2 lists relative rates for the S_N2 ethanolysis of certain alkyl halides (see p. 426).[3] All these compounds

[3]Hughes, E.D. *Q. Rev. Chem. Soc.* ***1948***, *2*, 107.

TABLE 9.2. Relative Rates of Reaction of RBr with Ethanol[3]

R	Relative Rate
CH_3	17.6
CH_3CH_2	1
$CH_3CH_2CH_2$	0.28
$(CH_3)_2CHCH_2$	0.030
$(CH_3)_3CCH_2$	4.2×10^{-6}

are primary bromides; the branching is on the second carbon, so that field-effect differences should be small. As Table 9.2 shows, the rate decreases with increasing β branching and reaches a very low value for neopentyl bromide. This reaction is known to involve an attack by the nucleophile from a position opposite to that of the bromine (see p. 426). The great decrease in rate can be attributed to *steric hindrance*, a sheer physical blockage to the attack of the nucleophile. Another example of steric hindrance is found in 2,6-disubstituted benzoic acids, which are difficult to esterify no matter what the resonance or field effects of the groups in the 2 or the 6 position. Similarly, once 2,6-disubstituted benzoic acids *are* esterified, the esters are difficult to hydrolyze.

Not all steric effects decrease reaction rates. In the hydrolysis of RCl by an S_N1 mechanism (see p. 433), the first step, which is rate determining, involves ionization of the alkyl chloride to a carbocation:

The central carbon in the alkyl chloride is sp^3 hybridized, with angles of $\sim$109.5°, but when it is converted to the carbocation, the hybridization becomes sp^2 and the preferred angle is 120°. If the halide is tertiary and the three alkyl groups are large enough, they will be pushed together by the enforced tetrahedral angle, resulting in strain (see p. 232). This type of strain is called *B strain*[4] (for back strain), and it can be relieved by ionization to the carbocation.[5]

The rate of ionization (and hence the solvolysis rate) of a molecule in which there is B strain is therefore expected to be larger than in cases where B strain is not present. Table 9.3 shows that this is so.[6] Substitution of ethyl groups for the

[4]For a discussion, see Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, ***1972***, pp. 114–121.

[5]For reviews of the effects of strain on reactivity, see Stirling, C.J.M. *Tetrahedron* ***1985***, *41*, 1613; *Pure Appl. Chem.* ***1984***, *56*, 1781.

[6]Brown, H.C.; Fletcher, R.S. *J. Am. Chem. Soc.* ***1949***, *71*, 1845.

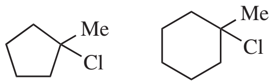
TABLE 9.3. Rates of Hydrolysis of Tertiary Alkyl Chlorides at 25°C in 80% Aqueous Ethanol[6]

Halide	Rate	Halide	Rate
Me_3Cl	0.033	Et_3CCl	0.099
Me_2EtCCl	0.055	$Me_2(i\text{Pr})CCl$	0.029
$MeEt_2CCl$	0.086	$Me(i\text{Pr})_2CCl$	0.45

methyl groups of *tert*-butyl chloride does not cause B strain; the increase in rate is relatively small, and the rate smoothly rises with the increasing number of ethyl groups. The rise is caused by normal field and resonance (hyperconjugation) effects. Substitution by one isopropyl group is not greatly different. But with the second isopropyl group the crowding is now great enough to cause B strain, and the rate is increased 10-fold. Substitution of a third isopropyl group increases the rate still more. Another example where B strain increases solvolysis rates is found with the highly crowded molecules tri-*tert*-butylcarbinol, di-*tert*-butylneopentylcarbinol, *tert*-butyldineopentylcarbinol, and trineopentylcarbinol, where rates of solvolysis of the *p*-nitrobenzoate esters are faster than that of *tert*-butyl nitrobenzoate by factors of 13,000, 19,000, 68,000, and 560, respectively.[7]

Another type of strain, that can affect rates of cyclic compounds, is called *I strain* (internal strain).[8] This type of strain results from changes in ring strain in going from a tetrahedral to a trigonal carbon or vice versa. For example, as mentioned above, S_N1 solvolysis of an alkyl halide involves a change in the bond angle of the central carbon from ~109.5 to ~120°. This change is highly favored in 1-chloro-1-methylcyclopentane because it relieves eclipsing strain (p. 223); thus this compound undergoes solvolysis in 80% ethanol at 25°C, 43.7 times faster

t-BuCl



Relative solvolysis rates 1.0 43.7 0.35

than the reference compound *tert*-butyl chloride.[9] In the corresponding cyclohexyl compound, this factor is absent because the substrate does not have eclipsing strain (p. 223), and this compound undergoes the reaction at about

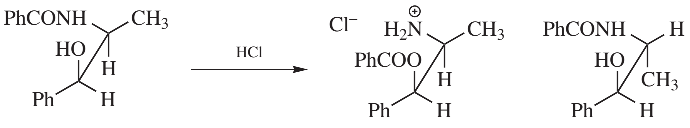
[7]Bartlett, P.D.; Tidwell, T.T. *J. Am. Chem. Soc.* ***1968***, *90*, 4421.

[8]For a discussion, see Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, ***1972***, pp. 105–107, 126–128.

[9]Brown, H.C.; Borkowski, M. *J. Am. Chem. Soc.* ***1952***, *74*, 1894. See also, Brown, H.C.; Ravindranathan, M.; Peters, E.N.; Rao, C.G.; Rho, M.M. *J. Am. Chem. Soc.* ***1977***, *99*, 5373.

one-third the rate of *tert*-butyl chloride. The reasons for this small decrease in rate are not clear. Corresponding behavior is found in the other direction, in changes from a trigonal to a tetrahedral carbon. Thus cyclohexanone undergoes addition reactions faster than cyclopentanone. Similar considerations apply to larger rings. Rings of 7–11 members exhibit eclipsing and transannular strain; and in these systems reactions in which a tetrahedral carbon becomes trigonal generally proceed faster than in open-chain systems.[10] I-Strain has been shown to be a factor in other reactions as well.[11]

Conformational effects on reactivity can be considered under the heading of steric effects,[12] though in these cases we are considering not the effect of a group X and that of another group X′ upon reactivity at a site Y but the effect of the conformation of the molecule. Many reactions fail entirely unless the molecules are able to assume the proper conformation. An example is the rearrangement of *N*-benzoylnorephedrine. The two diastereomers of this compound behave very



4 **5**

differently when treated with alcoholic HCl. In one of the isomers, nitrogen-to-oxygen migration takes place, while the other does not react at all.[13] In order for the migration to take place, the nitrogen must be near the oxygen (*gauche* to it). When **4** assumes this conformation, the methyl and phenyl groups are anti to each other, which is a favorable position, but when **5** has the nitrogen gauche to the oxygen, the methyl must be *gauche* to the phenyl, which is so unfavorable that the reaction does not occur. Other examples are electrophilic additions to C=C double bonds (see p. 999) and E2 elimination reactions (see p. 1478). Also, many examples are known where axial and equatorial groups behave differently.[14]

In steroids and other rigid systems, a functional group in one part of the molecule can strongly affect the rate of a reaction taking place at a remote part of the

[10]See, for example, Schneider, H.; Thomas, F. *J. Am. Chem. Soc.* ***1980***, *102*, 1424.

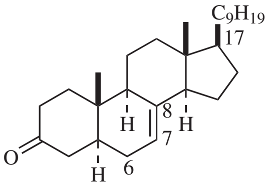
[11]Sands, R.D. *J. Org. Chem.* ***1994***, *59*, 468.

[12]For reviews of conformational effects, see Green, B.S.; Arad-Yellin, R.; Cohen, M.D. *Top. Stereochem.* ***1986***, *16*, 131; Ōki, M. *Acc. Chem. Res.* ***1984***, *17*, 154; Seeman, J.I. *Chem. Rev.* ***1983***, *83*, 83. See also Ōki, M.; Tsukahara, J.; Moriyama, K.; Nakamura, N. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 223, and other papers in this series.

[13]Fodor, G.; Bruckner, V.; Kiss, J.; Óhegyi, G. *J. Org. Chem.* ***1949***, *14*, 337.

[14]For a discussion, see Eliel, E.L. *Stereochemistry of Carbon Compounds*, McGraw-Hill, NY, ***1962***, pp. 219–234.

same molecule by altering the conformation of the whole skeleton.



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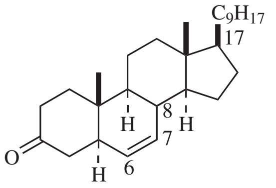


7

An example of this effect, called *conformational transmission*, is found in ergost-7-en-3-one (**6**) and cholest-6-en-3-one (**7**), where **7** condenses with benzaldehyde 15 times faster than **6**.[15] The reaction site in both cases is the carbonyl group, and the rate increases because moving the double bond from the 7 to the 6 position causes a change in conformation at the carbonyl group (the difference in the side chain at C-17 does not affect the rate).

QUANTITATIVE TREATMENTS OF THE EFFECT OF STRUCTURE ON REACTIVITY[16]

Suppose a reaction is performed on a substrate molecule that can be represented as XGY, where Y is the site of the reaction, X a variable substituent, and G a skeleton group to which X and Y are attached, and we find that changing X from H to CH_3 results in a rate increase by a factor, say, 10. We would like to know just what part of the increase is due to each of the effects previously mentioned. The obvious way to approach such a problem is to try to find compounds in which one or two of the factors are absent or at least negligible. This is not easy to do acceptably because factors that seem negligible to one investigator do not always appear so to another. The first attempt to give numerical values was that of Hammett.[17] For the cases of

[15]Barton, D.H.R.; McCapra, F.; May, P.J.; Thudium, F. *J. Chem. Soc.* ***1960***, 1297.

[16]For monographs, see Exner, O. *Correlation Analysis of Chemical Data*, Plenum, NY, ***1988***; Johnson, C.D. *The Hammett Equation*, Cambridge University Press, Cambridge, ***1973***; Shorter, J. *Correlation Analysis of Organic Reactivity*, Wiley, NY, ***1982***, *Correlation Analysis in Organic Chemistry*, Clarendon, N.B. Press, Oxford, ***1973***; Chapman, N.B.; Shorter, J. *Correlation Analysis in Chemistry: Recent Advances*, Plenum, NY, ***1978***, *Advances in Linear Free Energy Relationships*, Plenum, NY, ***1972***; Wells, P.R. *Linear Free Energy Relationships*, Academic Press, NY, ***1968***. For reviews, see Connors, K.A. *Chemical Kinetics*, VCH, NY, ***1990***, pp. 311–383; Lewis, E.S., in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions* (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), 4th ed., Wiley, NY, ***1986***, pp. 871–901; Jones, R.A.Y. *Physical and Mechanistic Organic Chemistry*, 2nd ed., Cambridge University Press: Cambridge, ***1984***, pp. 38–68; Charton, M. *CHEMTECH* ***1974***, 502, **1975**, 245; Hine, J. *Structural Effects in Organic Chemistry*, Wiley, NY, ***1975***, pp. 55–102; Afanas'ev, I.B. *Russ. Chem. Rev.* ***1971***, *40*, 216; Laurence, C.; Wojtkowiak, B. *Ann. Chim.* (*Paris*) ***1970***, [*14*] *5*, 163. For a historical perspective, see Grunwald, E. *CHEMTECH* ***1984***, 698.

[17]For a review, see Jaffé, H.H. *Chem. Rev.* ***1953***, *53*, 191.

m- and *p*-XC_6H_4Y, Hammett set up the equation

$$\log \frac{k}{k_0} = \sigma\rho$$

where k_0 is the rate constant or equilibrium constant for X = H, k is the constant for the group X, ρ is a constant for a given reaction under a given set of conditions, and σ is a constant characteristic of the group X. The equation is called the *Hammett equation*.

The value of ρ was set at 1.00 for ionization of XC_6H_4COOH in water at 25°C. The values of σ_m and σ_p were then calculated for each group (for a group X, σ is different for the meta and para positions). Once a set of σ values was obtained, ρ values could be obtained for other reactions from the rates of just two X-substituted compounds, if the σ values of the X groups were known (in practice, at least four well-spaced values are used to calculate ρ because of experimental error and because the treatment is not exact). With the ρ value thus calculated and the known σ values for other groups, rates can be predicted for reactions that have not yet been run.

The σ values are numbers that sum up the total electrical effects (resonance plus field) of a group X when attached to a benzene ring. The treatment usually fails for the ortho position. The Hammett treatment has been applied to many reactions and to many functional groups and correlates quite well an enormous amount of data. Jaffé's review article[17] lists ρ values for 204 reactions,[18] many of which have different ρ values for different conditions. Among them are reactions as disparate as the following:

Rate constants for

$$ArCOOMe + OH^- \longrightarrow ArCOO^-$$

$$ArCH_2Cl + I^- \longrightarrow ArCH_2I$$

$$ArNH_2 + PhCOCl \longrightarrow ArNHCOPh$$

$$ArH + NO_2^+ \longrightarrow ArNO_2$$

$$ArCO_2OCMe_3 \longrightarrow \text{Decomposition (a free-radical process)}$$

Equilibrium constants for

$$ArCOOH + H_2O \rightleftharpoons ArCOO^- + H_3O^+$$

$$ArCHO + HCN \rightleftharpoons ArCH(CN)OH$$

[18]Additional ρ values are given in Wells, P.R. *Chem. Rev.* ***1963***, *63*, 171 and van Bekkum, H.; Verkade, P.E.; Wepster, B.M. *Recl. Trav. Chim. Pays-Bas* ***1959***, *78*, 821.

The Hammett equation has also been shown to apply to many physical measurements, including ir frequencies and nmr chemical shifts.[19] The treatment is reasonably successful whether the substrates are attacked by electrophilic, nucleophilic, or free-radical reagents, the important thing being that the mechanism be the same *within* a given reaction series.

However, there are many reactions that do not fit the treatment. These are mostly reactions where the attack is directly on the ring and where the X group can enter into direct resonance interaction with the reaction site in the transition state (i.e., the substrate is XY rather than XGY). For these cases, two new sets of σ values have been devised: σ^+ values (proposed by H.C. Brown) for cases in which an electron-donating group interacts with a developing positive charge in the transition state (this includes the important case of electrophilic aromatic substitutions; see Chapter 11), and σ values, where electron-withdrawing groups interact with a developing negative charge. Table 9.4 gives σ, σ^+, and σ^- values for some common X groups.[20] As shown in the table, σ is not very different from σ^+ for most electron-withdrawing groups. The values of σ_m^- are not shown in Table 9.4, since they are essentially the same as the σ_m values.

A positive value of σ indicates an electron-withdrawing group and a negative value an electron-donating group.[21] The constant ρ measures the susceptibility of the reaction to electrical effects.[22] Reactions with a positive ρ are helped by electron-withdrawing groups and vice versa. The following ρ values for the ionization of some carboxylic acids illustrate this:[23]

XC_6H_4—COOH	1.00	XC_6H_4—CH=CH—COOH	0.47
XC_6H_4—CH_2—COOH	0.49	XC_6H_4—CH_2CH_2—COOH	0.21

[19]For a review of Hammett treatment of nmr chemical shifts, see Ewing, D.F., in Chapman, N.B.; Shorter, J. *Correlation Analysis in Chemistry: Recent Advances*, Plenum, NY, ***1978***, pp. 357–396.

[20]Unless otherwise noted, σ values are from Exner, O. in Chapman, N.B.; Shorter, J. *Correlation Analysis in Chemistry: Recent Advances*, Plenum, NY, ***1978***, pp. 439–540, and σ^+ values from Okamoto,Y.; Inukai, T.; Brown, H.C. *J. Am. Chem. Soc.* ***1958***, *80*, 4969 and Brown, H.C.; Okamoto,Y. *J. Am. Chem. Soc.* ***1958***, *80*, 4979. σ^- values, except as noted, are from Jaffé, H.H. *Chem. Rev.* ***1953***, *53*, 191. Exner, O. pp. 439–540, has extensive tables giving values for >500 groups, as well as σ^+, σ^-, σ_I, σ_R^o, and E_s values for many of these groups. Other large tables of the various sigma values are found in Hansch, C.; Leo, A.; Taft, R.W. *Chem. Rev.* ***1991***, *91*, 165. For tables of σ_p, σ_m, σ^+, σ_I, and σ_R^o values of many groups containing Si, Ge, Sn, and Pb atoms, see Egorochkin, A.N.; Razuvaev, G.A. *Russ. Chem. Rev.* ***1987***, *56*, 846. For values for heteroaromatic groups, see Mamaev, V.P.; Shkurko, O.P.; Baram, S.G. *Adv. Heterocycl. Chem.* ***1987***, *42*, 1.

[21]For discussions of the precise significance of σ, see Dubois, J.E.; Ruasse, M.; Argile, A. *J. Am. Chem. Soc.* ***1984***, *106*, 4840; Ruasse, M.; Argile, A.; Dubois, J.E. *J. Am. Chem. Soc.* ***1984***, *106*, 4846; Lee, I.; Shim, C.S.; Chung, S.Y.; Kim, H.Y.; Lee, H.W. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 1919.

[22]Hine, J. *J. Am. Chem. Soc.* ***1960***, *82*, 4877.

[23]Binev, I.G.; Kuzmanova, R.B.; Kaneti, J.; Juchnovski, I.N. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 1533.

TABLE 9.4. The σ, σ^+, and σ^- Values for Some Common Groups[20]

Group	σ_p	σ_m	σ_p^+	σ_m^+	σ_p^-
O^-	−0.81[24]	−0.47[24]	−4.27[25]	−1.15[25]	
NMe_2	−0.63	10.10	−1.7		
NH_2	−0.57	−0.09	−1.3	−0.16	
OH	−0.38[26]	0.13[26]	−0.92[27]		
OMe	−0.28[26]	0.10	−0.78	0.05	
CMe_3	−0.15	−0.09	−0.26	−0.06	
Me	−0.14	−0.06	−0.31	−0.10[28]	
H	0	0	0	0	0
Ph	0.05[29]	0.05	−0.18	0[29]	
COO^-	0.11[24]	0.02[24]	−0.41[25]	−0.10[25]	
F	0.15	0.34	−0.07	0.35	
Cl	0.24	0.37	0.11	0.40	
Br	0.26	0.37	0.15	0.41	
I	0.28[29]	0.34	0.14	0.36	
N=NPh[30]	0.34	0.28	0.17		
COOH[31]	0.44	0.35	0.42	0.32	0.73
COOR	0.44	0.35	0.48	0.37	0.68
COMe	0.47	0.36			0.87
CF_3	0.53	0.46		0.57[28]	
NH_3^+	0.60[25]	0.86[26]			
CN[32]	0.70	0.62	0.66	0.56	1.00
SO_2Me	0.73	0.64			
NO_2	0.81	0.71	0.79	0.73[28]	1.27
NMe_3^+	0.82[33]	0.88[33]	0.41	0.36	
N_2^+	1.93[34]	1.65[34]	1.88[34]		3[35]

[24]Hine, J. *J. Am. Chem. Soc.* ***1960***, *82*, 4877; Jones, R.A.Y. *Physical and Mechanistic Organic Chemistry*, 2nd ed., Cambridge University Press, Cambridge, ***1984***, p. 42.

[25]See Hine, J. *J. Am. Chem. Soc.* ***1960***, *82*, 4877.

[26]Matsui, T.; Ko, H.C.; Hepler, L.G. *Can. J. Chem.* ***1974***, *52*, 2906.

[27]de la Mare, P.B.D.; Newman, P.A. *Tetrahedron Lett.* ***1982***, *23*, 1305 give this value as −1.6.

[28]Amin, H.B.; Taylor, R. *Tetrahedron Lett.* ***1978***, 267.

[29]Sjöström, M.; Wold, S. *Chem. Scr.* ***1976***, *9*, 200.

[30]Byrne, C.J.; Happer, D.A.R.; Hartshorn, M.P.; Powell, H.K.J. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 1649.

[31]For a review of directing and activating effects of C=O, C=C, C=N, and C=S groups, see Charton, M., in Patai, S. *The Chemistry of Double-Bonded Functional Groups*, Vol. 2, pt. 1, Wiley, NY, ***1989***, pp. 239–298.

[32]For a review of directing and activating effects of C≡N and C≡C groups, see Charton, M., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups*, *Supplement C*, pt. 1, Wiley, NY, ***1983***, pp. 269–323.

[33]McDaniel, D.H.; Brown, H.C. *J. Org. Chem.* ***1958***, *23*, 420.

[34]Ustynyuk, Yu. A.; Subbotin, O.A.; Buchneva, L.M.; Gruzdneva, V.N.; Kazitsyna, L.A. *Doklad. Chem.* ***1976***, *227*, 175.

[35]Lewis, E.S.; Johnson, M.D. *J. Am. Chem. Soc.* ***1959***, *81*, 2070.

This example shows that the insertion of a CH_2 or a CH=CH group diminishes electrical effects to about the same extent, while a CH_2CH_2 group diminishes them much more. A $\rho > 1$ would mean that the reaction is more sensitive to electrical effects than is the ionization of XC_6H_4COOH ($\rho = 1.00$).

Similar calculations have been made for compounds with two groups X and X′ on one ring, where the σ values are sometimes additive and sometimes not,[36] for other ring systems, such as naphthalene[37] and heterocyclic rings,[38] and for ethylenic and acetylenic systems.[39]

The Hammett equation is a *linear free-energy relationship* (*LFER*). This can be demonstrated as follows for the case of equilibrium constants (for rate constants a similar demonstration can be made with $\Delta G^{\ddagger}$ instead of ΔG). For each reaction, where X is any group,

$$\Delta G = -RT \ln K$$

For the unsubstituted case,

$$\Delta G_0 = -RT \ln K_0$$

The Hammett equation can be rewritten

$$\log K - \log K_0 = \sigma\rho$$

so that

$$\frac{-\Delta G}{2.3RT} + \frac{\Delta G_0}{2.3RT} = \sigma\rho$$

and

$$-\Delta G = \sigma\rho 2.3RT - \Delta G_0$$

[36]Stone, R.M.; Pearson, D.E. *J. Org. Chem.* ***1961***, *26*, 257.

[37]Berliner, E.; Winikov, E.H. *J. Am. Chem. Soc.* ***1959***, *81*, 1630; see also, Well, P.R.; Ehrenson, S.; Taft, R.W. *Prog. Phys.Org. Chem.* ***1968***, *6*, 147.

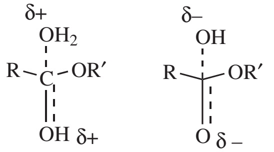
[38]For reviews, see Charton, M. in Chapman, N.B.; Shorter, J. *Correlation Analysis in Chemistry: Recent Advances*, Plenum, NY, ***1978***, pp. 175–268; Tomasik, P.; Johnson, C.D. *Adv. Heterocycl. Chem.* ***1976***, *20*, 1.

[39]For reviews of the application of the Hammett treatment to unsaturated systems, see Ford, G.P.; Katritzky, A.R.; Topsom, R.D., in *Correlation Analysis in Chemistry: Recent Advances*, Plenum, NY, ***1978***, pp. 269–311; Charton, M. *Prog. Phys. Org. Chem.* ***1973***, *10*, 81.

For a given reaction under a given set of conditions, σ, R, T, and ΔG_0 are all constant, so that σ is linear with ΔG.

The Hammett equation is not the only LFER.[40] Some, like the Hammett equation, correlate structural changes in reactants, but the Grunwald–Winstein relationship (see p. 505) correlates changes in solvent and the Brønsted relation (see p. 373) relates acidity to catalysis. The Taft equation is a structure-reactivity equation that correlates only field effects.[41]

Taft, following Ingold,[42] assumed that for the hydrolysis of carboxylic esters, steric and resonance effects will be the same whether the hydrolysis is catalyzed by acid or base (see the discussion of ester-hydrolysis mechanisms, reaction **16-59**). Rate differences would therefore be caused only by the field effects of R and R′ in RCOOR′. This is presumably a good system to use for this purpose because the transition state for acid-catalyzed hydrolysis (**8**) has a



8 **9**

greater positive charge (and is hence destabilized by $-I$ and stabilized by $+I$ substituents) than the starting ester, while the transition state for base-catalyzed hydrolysis (**9**) has a greater negative charge than the starting ester. Field effects of substituents X could therefore be determined by measuring the rates of acid- and base-catalyzed hydrolysis of a series XCH_2COOR',[43] where R′ is held constant.[38] From these rate constants, a value σ_I could be determined by the equation[44]

$$\sigma_I + 0.181\left[\log\left(\frac{k}{k_0}\right)_B - \log\left(\frac{k}{k_0}\right)_A\right]$$

[40]For a discussion of physicochemical preconditions for LFERs, see Exner, O. *Prog. Phys. Org. Chem.* ***1990***, *18*, 129.

[41]For reviews of the separation of resonance and field effects, see Charton, M. *Prog. Phys. Org. Chem.* ***1981***, *13*, 119; Shorter, J. *Q. Rev. Chem. Soc.* ***1970***, *24*, 433; *Chem. Ber.* ***1969***, *5*, 269. For a review of field and inductive effects, see Reynolds, W.F. *Prog. Phys. Org. Chem.* ***1983***, *14*, 165. For a review of field effects on reactivity, see Grob, C.A. *Angew. Chem. Int. Ed.* ***1976***, *15*, 569.

[42]Ingold, C.K. *J. Chem. Soc.* ***1930***, 1032.

[43]For another set of field-effect constants, based on a different premise, see Draffehn, J.; Ponsold, K. *J. Prakt. Chem.* ***1978***, *320*, 249.

[44]The symbol σ_F is also used in the literature; sometimes in place of σ_I, and sometimes to indicate only the field (not the inductive) portion of the total effect (p. 19).

In this equation $(k/k_0)_B$ is the rate constant for basic hydrolysis of XCH_2COOR' divided by the rate constant for basic hydrolysis of CH_3COOR', $(k/k_0)_A$ is the similar rate-constant ratio for acid catalysis, and 0.181 is an arbitrary constant. σ_I is a substituent constant for a group X, substituted at a saturated carbon, that reflects only field effects.[45] Once a set of σ_I values was obtained, it was found that the equation

$$\sigma_I + 0.181\left[\log\left(\frac{k}{k_0}\right)_B - \log\left(\frac{k}{k_0}\right)_A\right]$$

holds for a number of reactions, among them:[46]

$$RCH_2OH \longrightarrow RCH_2O^-$$

$$RCH_2Br + PhS^- \longrightarrow RCH_2SPh + Br^-$$

$$\text{Acetone} + I_2\text{, catalyzed by RCOOH} \longrightarrow$$

$$o\text{-Substituted-ArNH}_2 + \text{PhCOCl} \longrightarrow \text{ArNHCOPh}$$

As with the Hammett equation, σ_I is constant for a given reaction under a given set of conditions. For very large groups the relationship may fail because of the presence of steric effects, which are not constant. The equation also fails when X enters into resonance with the reaction center to different extents in the initial and transition states. A list of some σ_I values is given in Table 9.5.[47] The σ_I values are about what we would expect for pure field-effect values (see p. 21) and are additive, as field effects (but not resonance or steric effects) would be expected to be. Thus, in moving a group one carbon down the chain, there is a decrease by a factor of 2.8 ± 0.5 (cf. the values of R and RCH_2 in Table 9.5 for R = Ph and CH_3CO). An inspection of Table 9.5 shows that σ_I values for most groups are fairly close to the σ_m values (Table 9.4) for the same groups. This is not surprising, since σ_m values would be expected to arise almost entirely from field effects, with little contribution from resonance.

[45]There is another set of values (called σ* values) that are also used to correlate field effects. These are related to σ_I values by = $\sigma_I(X) = 0.45\sigma$. We discuss only σ_I, and not σ* values.

[46]Wells, P.R. *Chem. Rev.* ***1963***, *63*, 171, p. 196.

[47]These values are from Bromilow, J.; Brownlee, R.T.C.; Lopez, V.O.; Taft, R.W. *J. Org. Chem.* ***1979***, *44*, 4766, except that the values for NHAc, OH, and I are from Wells, P.R.; Ehrenson, S.; Taft, R.W. *Prog. Phys. Org. Chem.* ***1968***, *6*, 147, the values for Ph and NMe_3^+ are from Taft, R.W.; Ehrenson, S.; Lewis, I.C.; Glick, R. *J. Am.Chem. Soc.* ***1959***, *81*, 5352 and Taft, R.W.; Deno, N.C.; Skell, P.S. *Annu. Rev. Phys. Chem.* ***1958***, *8*, 287, and the value for CMe_3 is from Seth-Paul, W.A.; de Meyer-van Duyse, A.; Tollenaere, J.P. *J. Mol. Struct.* ***1973***, *19*, 811. The values for the CH_2Ph and CH_2COCH_3 groups were calculated from σ* values by the formula given in reference 45. For much larger tables of σ_I and σ_R values, see Charton, M. *Prog. Phys. Org. Chem.* ***1981***, *13*, 119. See also Ref. 20 and Taylor, P.J.; Wait, A.R. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 1765.

TABLE 9.5. The σ_I and σ_R^0 Values for Some Groups[47]

Group	σ_I	σ_R^0	Group	σ_I	σ_R^0
CMe_3	−0.07	−0.17	OMe	0.27	−0.42
Me	−0.05	−0.13	OH	0.27	−0.44
H	0	0	I	0.39	−0.12
$PhCH_2$	0.04		CF_3	0.42	0.08
NMe_2[48]	0.06	−0.55	Br	0.44	−0.16
Ph	0.10	−0.10	Cl	0.46	−0.18
CH_3COCH_2	0.10		F	0.50	−0.31
NH_2	0.12	−0.50	CN	0.56	0.08
CH_3CO	0.20	0.16	SO_2Me	0.60	0.12
COOEt	0.20	0.16	NO_2	0.65	0.15
NHAc	0.26	−0.22	NMe_3[49]	0.86	

Since σ_p values represent the sum of resonance and field effects, these values can be divided into resonance and field contributions if σ_I is taken to represent the field-effect portion.[50] The resonance contribution σ_R[51] is defined as

$$\sigma_R = \sigma_p - \sigma_I$$

As it stands, however, this equation is not very useful because the σ_R value for a given group, which should be constant if the equation is to have any meaning, is actually not constant but depends on the nature of the reaction.[52] In this respect, the σ_I values are much better. Although they vary with solvent in some cases, σ_I values are essentially invariant throughout a wide variety of reaction series. However, it is possible to overcome[53] the problem of varying σ_R values by using a special set of σ_R values, called

[48]For σ_R^0 values for some other NR_2 groups, see Korzhenevskaya, N.G.; Titov, E.V.; Chotii, K.Yu.; Chekhuta, V.G. *J. Org. Chem. USSR* ***1987***, *28*, 1109.

[49]Although we give a σ_I value for NMe_3^+, (and *F* values for three charged groups in Table 9.6), it has been shown that charged groups (called polar substituents) cannot be included with uncharged groups (dipolar substituents) in one general scale of electrical substituent effects: Marriott, S.; Reynolds, J.D.; Topsom, R.D. *J. Org. Chem.* ***1985***, *50*, 741.

[50]Roberts, J.D.; Moreland, Jr., W.T. *J. Am. Chem. Soc.* ***1953***, *75*, 2167; Taft, R.W. *J. Am. Chem. Soc.* ***1957***, *79*, 1045; *J. Phys. Chem.* ***1960***, *64*, 1805; Taft, R.W.; Lewis, I.C. *J. Am. Chem. Soc.* ***1958***, *80*, 2436; Taft, R.W.; Deno, N.C.; Skell, P.S. *Annu. Rev. Phys. Chem.* ***1958***, *9*, 287, see pp. 290–293.

[51]For reviews of the σ_I and σ_R concept as applied to benzenes and naphthalenes, respectively, see Ehrenson, S.; Brownlee, R.T.C.; Taft, R.W. *Prog. Phys. Org. Chem.* ***1973***, *10*, 1. See also, Taft, R.W.; Topsom, R.D. *Prog. Phys. Org. Chem.* ***1987***, *16*, 1; Charton, M. *Prog. Phys. Org. Chem.* ***1987***, *16*, 287.

[52]Taft, R.W.; Lewis, I.C. *J. Am. Chem. Soc.* ***1959***, *81*, 5343; Reynolds, W.F.; Dais, P.; MacIntyre, D.W.; Topsom, R.D.; Marriott, S.; von Nagy-Felsobuki, E.; Taft, R.W. *J. Am. Chem. Soc.* ***1983***, *105*, 378.

[53]For a different way of overcoming this problem, see Happer, D.A.R.; Wright, G.J. *J. Chem. Soc. Perkin Trans. 2* ***1979***, 694.

σ_R^o,[54] that measure the ability to delocalize π electrons into or out of an unperturbed or "neutral" benzene ring. Several σ_R^o scales have been reported; the most satisfactory values are obtained from ^{13}C chemical shifts of substituted benzenes.[55] Table 9.5 lists some values of σ_R^o, most of which were obtained in this way.[56]

An equation such as

$$\log\frac{k}{k_0} = \rho_I\sigma_I + \rho_R\sigma_R^o$$

which treats resonance and field effects separately, is known as a *dual substituent parameter equation*.[57]

The only groups in Table 9.5 with negative values of σ_I are the alkyl groups methyl and *t*-butyl. There has been some controversy on this point.[58] One opinion is that σ_I values decrease in the series methyl, ethyl, isopropyl, *tert*-butyl (respectively, −0.046, −0.057, −0.065, −0.074).[59] Other evidence, however, has led to the belief that all alkyl groups have approximately the same field effect and that the σ_I values are invalid as a measure of the intrinsic field effects of alkyl groups.[60]

Another attempt to divide σ values into resonance and field contributions[61] is that of Swain and Lupton, who have shown that the large number of sets of σ values (σ_m, σ_p, σ_p^-, σ_p^+, σ_I, σ_R^o, etc., as well as others we have not mentioned) are not entirely independent and that linear combinations of two sets of new values *F* (which expresses the field-effect contribution) and *R* (the resonance contribution) satisfactorily express 43 sets of values.[62] Each set is expressed as

$$\sigma = fF + rR$$

[54]Taft, R.W.; Ehrenson, S.; Lewis, I.C.; Glick, R.E. *J. Am. Chem. Soc.* ***1959***, *81*, 5352.

[55]Bromilow, J.; Brownlee, R.T.C.; Lopez, V.O.; Taft, R.W. *J. Org. Chem.* ***1979***, *44*, 4766. See also, Marriott, S.; Topsom, R.D. *J. Chem. Soc. Perkin Trans. 2* ***1985***, 1045.

[56]For a set of σ_R values for use in XY^+ systems, see Charton, M. *Mol. Struct. Energ.* ***1987***, *4*, 271.

[57]There are also three-parameter equations. See, for example, de Ligny, C.L.; van Houwelingen, H.C. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 559.

[58]For a discussion, see Shorter, J. in Chapman, N.B.; Shorter, J. *Advances in Linear Free Energy Relationships*, Plenum, NY, ***1972***, pp. 98–103.

[59]For support for this point of view, see Levitt, L.S.; Widing, H.F. *Prog. Phys. Org. Chem.* ***1976***, *12*, 119; Taft, R.W.; Levitt, L.S. *J. Org. Chem.* ***1977***, *42*, 916; MacPhee, J.A.; Dubois, J.E. *Tetrahedron Lett.* ***1978***, 2225; Screttas, C.G. *J. Org. Chem.* ***1979***, *44*, 3332; Hanson, P. *J. Chem. Soc. Perkin Trans. 2* ***1984***, 101.

[60]For support for this point of view, see, for example, Ritchie, C.D. *J. Phys. Chem.* ***1961***, *65*, 2091; Bordwell, F.G.; Drucker, G.E.; McCollum, G.J. *J. Org. Chem.* ***1976***, *41*, 2786; Bordwell, F.G.; Fried, H.E. *Tetrahedron Lett.* ***1977***, 1121; Charton, M. *J. Am. Chem. Soc.* ***1977***, *99*, 5687; *J. Org. Chem.* ***1979***, *44*, 903; Adcock, W.; Khor, T. *J. Org. Chem.* ***1978***, *43*, 1272; DeTar, D.F. *J. Org. Chem.* ***1980***, *45*, 5166; *J. Am. Chem. Soc.* ***1980***, *102*, 7988.

[61]Yukawa and Tsuno have still another approach, also involving dual parameters: Yukawa, Y.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* ***1959***, *32*, 971. For a review and critique of this method, see Shorter, J., in Chapman, N.B.; Shorter, J. *Correlation Analysis in Chemistry: Recent Advances*, Plenum, NY, ***1978***, pp. 119–173, 126–144. This article also discusses the Swain–Lupton and Taft σ_I, σ_R approaches. For yet other approaches, see Afanas'ev, I.B. *J. Org. Chem. USSR* ***1981***, *17*, 373; *J. Chem. Soc. Perkin Trans. 2* ***1984***, 1589; Ponec, R. *Coll. Czech. Chem. Commun.* ***1983***, *48*, 1564.

[62]Swain, C.G.; Unger, S.H.; Rosenquist, N.R.; Swain, M.S. *J. Am. Chem. Soc.* ***1983***, *105*, 492 and references cited therein.

TABLE 9.6. The *F* and *R* Values for Some Groups[63]

Group	*F*	*R*	Group	*F*	*R*
COO^-	−0.27	0.40	OMe	0.54	−1.68
Me_3C	−0.11	−0.29	CF_3	0.64	0.76
Et	−0.02	−0.44	I	0.65	−0.12
Me	−0.01	−0.41	Br	0.72	−0.18
H	0	0	Cl	0.72	−0.24
Ph	0.25	−0.37	F	0.74	−0.60
NH_2	0.38	−2.52	$NHCOCH_3$	0.77	−1.43
COOH	0.44	0.66	CN	0.90	0.71
OH	0.46	−1.89	NMe_3^+	1.54	
COOEt	0.47	0.67	N_2^+	2.36	2.81
$COCH_3$	0.50	0.90			

where f and r are weighting factors. Some F and R values for common groups are given in Table 9.6.[63] From the calculated values of f and r, Swain and Lupton calculated that the importance of resonance, % R, is 20% for σ_m, 38% for σ_p, and 62% for σ_p^+.[64] This is another dual substituent parameter approach.

Taft was also able to isolate steric effects.[65] For the acid-catalyzed hydrolysis of esters in aqueous acetone, long (k/k_0) was shown to be insensitive to polar effects.[66] In cases where resonance interaction was absent, this value was proportional only to steric effects (and any others[67] that are not field or resonance). The equation is

$$\log \frac{k}{k_0} = E_S$$

[63]Taken from a much longer list in Swain, C.G.; Unger, S.H.; Rosenquist, N.R.; Swain, M.S. *J. Am. Chem. Soc.* ***1983***, *105*, 492. Long tables of *R* and *F* values are also given in Hansch, C.; Leo, A.; Taft, R.W. *Chem. Rev.* ***1991***, *91*, 165.

[64]The Swain–Lupton treatment has been criticized by Reynolds, W.F.; Topsom, R.D. *J. Org. Chem.* ***1984***, *49*, 1989; Hoefnagel, A.J.; Oosterbeek, W.; Wepster, B.M. *J. Org. Chem.* ***1984***, *49*, 1993; and Charton, M. *J. Org. Chem.* ***1984***, *49*, 1997. For a reply to these criticisms, see Swain, C.G. *J. Org. Chem.* ***1984***, *49*, 2005. A study of the rates of dediazoniation reactions (**13-32**) was more in accord with the Taft and Charton (see Charton, M. *Prog. Phys. Org. Chem.* ***1981***, *13*, 119) σ_I and σ_R values than with the Swain–Lupton *F* and *R* values: Nakazumi, H.; Kitao, T.; Zollinger, H. *J. Org. Chem.* ***1987***, *52*, 2825.

[65]For reviews of quantitative treatments of steric effects, see Gallo, R.; Roussel, C.; Berg, U. *Adv. Heterocycl. Chem.* ***1988***, *43*, 173; Gallo, R. *Prog. Phys. Org. Chem.* ***1983***, *14*, 115; Unger, S.H.; Hansch, C. *Prog. Phys. Org. Chem.* ***1976***, *12*, 91.

[66]Another reaction used for the quantitative measurement of steric effects is the aminolysis of esters (**16-75**); De Tar, D.F.; Delahunty, C. *J. Am. Chem. Soc.* ***1983***, *105*, 2734.

[67]It has been shown that E_s values include solvation effects: McClelland, R.A.; Steenken, S. *J. Am. Chem. Soc.* ***1988***, *110*, 5860.

TABLE 9.7. The E_s, υ, and V^a Values for Some Groups[68]

Group	E_s	υ	$V^a \times 10^2$	Group	E_s	υ	$V^a \times 10^2$
H	0	0		Cyclohexyl	−2.03	0.87	6.25
F	−0.46	0.27	1.22	*i*-Bu	−2.17	0.98	5.26
CN	−0.51			*sec*-Bu	−2.37	1.02	6.21
OH	−0.55			CF_3	−2.4	0.91	3.54
OMe	−0.55		3.39	*t*-Bu	−2.78	1.24	7.16
NH_2	−0.61			NMe_3^+	−2.84		
Cl	−0.97	0.55	2.54	Neopentyl	−2.98	1.34	5.75
Me	−1.24	0.52	2.84	CCl_3	−3.3	1.38	6.43
Et	−1.31	0.56	4.31	CBr_3	−3.67	1.56	7.29
I	−1.4	0.78	4.08	$(Me_3CCH_2)_2CH$	−4.42	2.03	
Pr	−1.6	0.68	4.78	Et_3C	−5.04	2.38	
*i*Pr	−1.71	0.76	5.74	Ph_3C	−5.92	2.92	

Some E_s values are given in Table 9.7,[68] where hydrogen is taken as standard, with a value of 0.[69] This treatment is more restricted than those previously discussed, since it requires more assumptions, but the E_s values are approximately in order of the size of the groups. Charton has shown that E_s values for substituents of types CH_2X, CHX_2, and CX_3 are linear functions of the van der Waals radii for these groups.[70]

Two other steric parameters are independent of any kinetic data. Charton's υ values are derived from van der Waals radii,[71] and Meyer's V^a values from the volume of the portion of the substituent that is within 0.3 nm of the reaction center.[72] The V^a values are obtained by molecular mechanics calculations based on the structure of the molecule. Table 9.7 gives υ and V^a values for some groups.[73] As can be seen in the table, there is a fair, but not perfect, correlation among the E_s, υ, and V^a values. Other sets of steric values, for example, E_s',[74] E_s^*,[75] Ω_s,[76] and f,[77] have also been proposed.[73]

[68]The E_s, υ, and V^a values are taken from longer tables in, respectively, Gallo, R.; Roussel, C.; Berg, U. *Adv. Heterocycl. Chem.* ***1988***, *43*, 173; Gallo, R. *Prog. Phys. Org. Chem.* ***1983***, *14*, 115; Unger, S.H.; Hansch, C. *Prog. Phys. Org. Chem.* ***1976***, *12*, 91. Charton, M. *J. Am. Chem. Soc.* ***1975***, *97*, 1552; *J. Org. Chem.* ***1976***, *41*, 2217; and Meyer, A.Y. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 1567.

[69]In Taft's original work, Me was given the value 0. The E_s values in Table 9.7 can be converted to the orginal values by adding 1.24.

[70]Charton, M. *J. Am. Chem. Soc.* ***1969***, *91*, 615.

[71]Charton, M. *J. Am. Chem. Soc.* ***1975***, *97*, 1552; *J. Org. Chem.* ***1976***, *41*, 2217. See also, Charton, M. *J. Org. Chem.* ***1978***, *43*, 3995; Idoux, J.P.; Schreck, J.O. *J. Org. Chem.* ***1978***, *43*, 4002.

[72]Meyer, A.Y. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 1567.

[73]For a discussion of the various steric parameters, see DeTar, D.F. *J. Org. Chem.* ***1980***, *45*, 5166; *J. Am. Chem. Soc.* ***1980***, *102*, 7988.

[74]MacPhee, J.A.; Panaye, A.; Dubois, J.E. *J. Org. Chem.* ***1980***, *45*, 1164; Dubois, J.E.; MacPhee, J.A.; Panaye, A. *Tetrahedron* ***1980***, *36*, 919. See also, Datta, D.; Sharma, G.T. *J. Chem. Res. (S)* ***1987***, 422.

[75]Fellous, R.; Luft, R. *J. Am. Chem. Soc.* ***1973***, *95*, 5593.

[76]Komatsuzaki, T.; Sakakibara, K.; Hirota, M. *Tetrahedron Lett.* ***1989***, *30*, 3309; *Chem. Lett.* ***1990***, 1913.

[77]Beckhaus, H. *Angew. Chem. Int. Ed.* ***1978***, *17*, 593.

Since the Hammett equation has been so successful in the treatment of the effects of groups in the meta and para positions, it is not surprising that attempts have been made to apply it to ortho positions also.[78] The effect on a reaction rate or equilibrium constant of a group in the ortho position is called the *ortho effect*.[79] Despite the many attempts made to quantify ortho effects, no set of values has so far commanded general agreement. However, the Hammett treatment is successful for ortho compounds when the group Y in *o*-XC_6H_4Y is separated from the ring; for example, ionization constants of *o*-$XC_6H_4OCH_2COOH$ can be successfully correlated.[80]

Linear free-energy relationships can have mechanistic implications. If log (k/k_0) is linear with the appropriate σ, it is likely that the same mechanism operates throughout the series. If not, a smooth curve usually indicates a gradual change in mechanism, while a pair of intersecting straight lines indicates an abrupt change,[81] though nonlinear plots can also be due to other causes, such as complications arising from side reactions. If a reaction series follows σ^+ or σ^- better than σ it generally means that there is extensive resonance interaction in the transition state.[82]

Information can also be obtained from the magnitude and sign of ρ. For example, a strongly negative ρ value indicates a large electron demand at the reaction center, from which it may be concluded that a highly electron-deficient center, perhaps an incipient carbocation, is involved. Conversely, a positive ρ value is associated with a developing negative charge in the transition state.[83] The $\sigma\rho$ relationship even applies to free-radical reactions, because free radicals can have some polar character (p. 939), though ρ values here are usually small (less than ~1.5) whether positive or negative. Reactions involving cyclic transition states (p. 297) also exhibit very small ρ values.

EFFECT OF MEDIUM ON REACTIVITY AND RATE

There is no question that the solvent chosen for a given reaction has a profound influence on the course of that reaction. Protic versus aprotic solvents as well as polar versus nonpolar solvents can have effects ranging from solubility to solvent assisted ionization or stabilization of transition states. Reactions can

[78]For reviews, see Fujita, T.; Nishioka, T. *Prog. Phys. Org. Chem.* ***1976***, *12*, 49; Charton, M. *Prog. Phys. Org. Chem.* ***1971***, *8*, 235; Shorter, J., in Chapman, N.B.; Shorter, J. *Advances in Linear Free Energy Relaltionships*, Plenum, NY, ***1972***, pp. 103–110. See also, Segura, P. *J. Org. Chem.* ***1985***, *50*, 1045; Robinson, C.N.; Horton, J.L.; Fosheé, D.O.; Jones, J.W.; Hanissian, S.H.; Slater, C.D. *J. Org. Chem.* ***1986***, *51*, 3535.

[79]This is not the same as the ortho effect discussed on p. $$$.

[80]Charton, M. *Can. J. Chem.* ***1960***, *38*, 2493.

[81]For a discussion, see Schreck, J.O. *J. Chem. Educ.* ***1971***, *48*, 103.

[82]See, however, Gawley, R.E. *J. Org. Chem.* ***1981***, *46*, 4595.

[83]For another method of determining transition state charge, see Williams, A. *Acc. Chem. Res.* ***1984***, *17*, 425.

also be done neat in one of the reactants, in the gas phase, on solid support or in the solid phase. Environmental friendly chemistry (green chemistry) is becoming increasingly important, and chemical reactions in nonpolluting (often non-organic) solvents is of particular interest.[84] This section will describe alternative reaction media as well as other medium-related things that influence chemical reactions.

HIGH PRESSURE

Acceleration of some chemical reactions is possible when high-pressure techniques are employed.[85,86] The effects on a given reaction can be predicted to a certain extent because the thermodynamic properties of solutions are well known. The rate of a reaction can be expressed in terms of the activation volume, $\Delta V^{\ddagger}$

$$\frac{\delta \ln k}{\delta p} = \frac{\Delta V^{\ddagger}}{RT}$$

so rate constants vary with pressure.[86] "The activation volume[87] is the difference in partial molal volume between the transition state and the initial state. From a synthetic point of view this could be approximated by the molar volume."[86] If the volume of activation is negative, the rate of the reaction will be accelerated by increasing pressure. As the pressure increases, the value of $\Delta V^{\ddagger}$ decreases and the system does not strictly obey equation (11.4) > 10 kbar (1 bar $= 0.986924$ atm $= 1.1019716\,\text{kg cm}^{-2}$). If the transition state of a reaction involves bond formation, concentration of charge, or ionization, a negative volume of activation often results. Cleavage of a bond, dispersal of charge, or neutralization of the transition state and diffusion control lead to a positive volume of activation. Matsumoto summarized the reactions for which rate enhancement is expected at high pressure.[86]

1. Reactions in which the molecularity number (number of molecules) decreases when starting materials are converted to products: cycloadditions, condensations.
2. Reactions that proceed via cyclic transition states.
3. Reactions that take place through dipolar transition states.
4. Reactions with steric hindrance.

[84]For example, see Clark, J.H. *Green Chem.* ***1999***, *1*, 1; Cave, G.W.V.; Raston, C.L.; Scott, J.L. *Chem. Commun.* ***2001***, 2159.

[85]Jenner, G. *Tetrahedron* ***2002***, *58*, 5185; Matsumoto, K.; Morris, A.R. *Organic Synthesis at High Pressure*, Wiley, New York, ***1991***.

[86]Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* ***1985***, 1; Matsumoto, K.; Sera, A. *Synthesis* ***1985***, 999.

[87]See le Noble, W.J. *Progr. Phys. Org. Chem.* ***1967***, *5*, 207; Isaacs, N.S. *Liquid Phase High Pressure Chemistry*, Wiley, Chichester, ***1981***; Asano, T.; le Noble, W.J. *Chem. Rev.* ***1978***, *78*, 407.

Many high-pressure reactions are done neat, but if a solvent is used, the influence of pressure on that solvent is important. The melting point generally increases at elevated pressures, and this influences the viscosity of the medium (the viscosity of liquids increases approximately two times per kilobar increase in pressure). Controlling the rate of diffusion of reactants in the medium is also important, leading to another influence of high pressure on reactivity.[86,88] In most reactions, pressure is applied (5–20 kbar) at room temperature and then the temperature is increased until reaction takes place. The temperature is lowered and the pressure is reduced to isolate the products.

WATER AND OTHER NONORGANIC SOLVENTS

Chemical reactions of organic substrates usually employs an organic solvent, such as a hydrocarbon, ether, dichloromethane, and so on. With the exception of small molecular weight molecules with polar functional groups and polyfunctional molecules or salts, organic chemicals have poor solubility in water. The first indication that water accelerated a reaction was in a patent by Hopff and Rautenstrauch in 1939,[89] who reported that yields in the Diels–Alder reaction (**15-60**) were enhanced in aqueous detergent solutions. In an early study, Berson showed a clear relationship between the endo/exo product ratio and solvent polarity, in the Diels–Alder reaction of cyclopentadiene and acrylates.[90] Breslow showed there was a hydrophobic acceleration for an intermolecular Diels–Alder reaction in which cyclopentadiene reacted with methyl vinyl ketone.[91] Clearly, there is an accelerating effect on some chemical reactions when done in water that is useful in organic chemistry.[92]

When nonpolar compounds are suspended in water their relative insolubility causes them to associate, diminishing the water–hydrocarbon interfacial area (a hydrophobic effect). This association is greater in water than in methanol and brings the reactive partners into close proximity, increasing the rate of reaction. Any additive that increases the hydrophobic effect will increase the rate.[91]

Carbon dioxide can be used as a reaction solvent when pressurized (supercritical carbon dioxide, $scCO_2$). Carbon dioxide is nontoxic, inexpensive, abundant, and easily recycled. These properties have made it attractive as an extraction solvent.[93] The low critical temperature of CO_2 (T_c) 31.1 °C ensures that $scCO_2$ is a safe solvent for many applications.[94] There are solubility issues that suggest $scCO_2$ is a rather polar solvent.[95] For example, many systems with hydrocarbon chains are

[88]Firestone, R.A.; Vitale, M.A. *J. Org. Chem.* ***1981***, *46*, 2160.

[89]Hopff, H.; Rautenstrauch, C.W. *U.S. Patent* 2,262,002, ***1939*** [*Chem. Abstr. 36*: 10469, ***1942***].

[90]Berson, J.A.; Hamlet, Z.; Mueller, W.A. *J. Am. Chem. Soc.* ***1962***, *84*, 297.

[91]Rideout, D.; Breslow, R. *J. Am. Chem. Soc.* ***1980***, *102*, 7816.

[92]Engberts, J.B.F.N.; Blandamer, M.J. *Chem. Commun.* ***2001***, 1701; Lindström, U.M. *Chem. Rev.* ***2002***, *102*, 2751; Ribe, S.; Wipf, P. *Chem. Commun.* ***2001***, 299.

[93]See Raynie, D.E. *Anal. Chem.* ***2004***, *76*, 4659.

[94]Subramaniam, B.; Rajewski, R.A.; Snavely, K. *J. Pharm. Sci.* ***1997***, *86*, 885.

[95]Raveendran, P.; Ikushima, Y.; Wallen, S.L. *Acc. Chem. Res.* ***2005***, *38*, 478.

not very soluble in CO_2.[96] Water/carbon dioxide emulsions have also been employed.[97]

The use of supercritical carbon dioxide ($ScCO_2$) has been explored in many reactions,[98] including catalysis.[99] Some applications of this technique include the electrochemical synthesis of conducting polymers[100] and highly cross-linked polymers[101] in $scCO_2$, the synthesis of octyl palmitate,[102] of carbonated fatty methyl esters,[103] and of methyl carbamates.[104] A carbonylation reaction was done is $ScCO_2$ in the course of a synthesis of trisubstituted cyclopentanes and cyclohexanes as key components of substance P antagonists.[105] A continuous flow acid catalyzed dehydration of alcohols was accomplished in $ScCO_2$.[106] Supercritical fluids are playing an increasingly important role in synthetic organic chemistry.[107]

Other supercritical fluids can be used for chemical reactions, such as supercritical ammonia in the synthesis of labeled guanidines.[108]

IONIC SOLVENTS

Environmentally friendly solvents, such as ionic liquids, is of great interest. It was discovered that some molecules form ionic liquids that are suitable as a medium for chemical reactions.[109] An ionic liquid is a salt in which the ions are poorly coordinated, usually leading to their being liquid $<100°C$ and sometimes at room temperature. In such ionic species, there is usually at least one ion with a delocalized charge whereas the other component is usually organic. This combination inhibits the formation of a stable crystal lattice. Both methylimidazolium and pyridinium ions form the basis of common ionic liquids that have been used in organic chemistry. One of the most common ionic solvents is 1-butyl-3-methylimidazolium as the hexafluorophosopahte, **10**

[96]Consani, K.A.; Smith, R.D.J. *Supercrit. Fluids* ***1990***, *3*, 51.

[97]Jacobson, G.B.; Lee Jr., C.T.; da Rocha, S.R.P.; Johnston, K.P. *J. Org. Chem.* ***1999***, *64*, 1207; Jacobson, G.B.; Lee, Jr., C.T.; Johnston, K.P. *J. Org. Chem.* ***1999***, *64*, 1201.

[98]Gopalan, A.D.; Wai, C.M.; Jacobs, H.K. *Supercritical Carbon Dioxide: Separations and Processes*, American Chemical Society (distributed by Oxford University Press), Washington, DC, ***2003***; Beckman, E.J. *Ind. Eng. Chem. Res.* ***2003***, *42*, 1598; Wang, S.; Kienzle, F. *Ind. Eng. Chem. Res.* ***2000***, *39*, 4487.

[99]Leitner, W. *Acc. Chem. Res.* ***2002***, *35*, 746.

[100]Anderson, P.E.; Badlani, R.N.; Mayer, J.; Mabrouk, P.A. *J. Am. Chem. Soc.* ***2002***, *124*, 10284.

[101]Cooper, A.I.; Hems, W.P.; Holmes, A.B. *Macromolecules* ***1999***, *32*, 2156.

[102]Madras, G.; Kumar, R.; Modak, J. *Ind. Eng. Chem. Res.* ***2004***, *43*, 7697,1568.

[103]Doll, K.M.; Erhan, S.Z. *J. Agric. Food Chem.* ***2005***, *53*, 9608.

[104]Selva, M.; Tundo, P.; Perosa, A.; Dall'Acqua, F. *J. Org. Chem.* ***2005***, *70*, 2771.

[105]Kuethe, J.T.; Wong, A.; Wu, J.; Davies, I.W.; Dormer, P.G.; Welch, C.J.; Hillier, M.C.; Hughes, D.L.; Reider, P.J. *J. Org. Chem.* ***2002***, *67*, 5993.

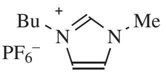
[106]Gray, W.K.; Smail, F.R.; Hitzler, M.G.; Ross, S.K.; Poliakoff, M. *J. Am. Chem. Soc.* ***1999***, *121*, 10711.

[107]Oakes, R.S.; Clifford, A.A.; Rayner, C.M. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 917; Prajapati, D.; Gohain, M. *Tetrahedron* ***2004***, *60*, 815.

[108]Jacobson, G.B.; Westerberg, G.; Markides, K.E.; Langstrom, B. *J. Am. Chem. Soc.* ***1996***, *118*, 6868.

[109]Wasserscheid, P.; Keim, W. *Angew. Chem. Int. Ed.* ***2000***, *39*, 3772; Earle, M.J.; Seddon, K.R. *Pure. Appl. Chem.* ***2000***, *72*, 1391; Wasserscheid, P.; Welton, T. *Ionic Liquids in Synthesis*, Wiley-VCH, NY, ***2002***; Adams, D.J.; Dyson, P.J.; Taverner, S.J. *Chemistry in Alternative Reaction Media*, Wiley, NY, ***2003***.

(Bmim PF_6).[110] Hydrogenbutylimidazolium tetrafluoroborate (HBuIm, **11**) and 1,3-dibutylimidazolium, tetrafluoroborate (DiBuIm, **12**), for example,[111] have been reported to facilitate Diels–Alder reactions (**15-60**).[112] Pyridinium based ionic liquids, such as ethylpyridinium tetrafluoroborate (**13**), have also been used.[113]



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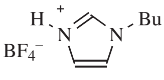

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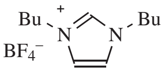
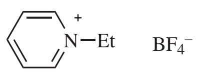


12



13

Ionic solvents have been used to facilitate the Heck reaction (**13-9**),[114] the oxidation of alcohols with hypervalent iodine reagents (**19-3**),[115] and the catalytic asymmetric dihydroxylation of olefins (**15-48**) using a recoverable and reusable osmium/ligand.[116] Reactions in ionic liquids is a rapidly growing area of organic chemistry, including microwave reactions (see p. 354) in ionic solvents.[117] The development and use of ionic solvents is a growth area of organic chemistry.[118]

SOLVENTLESS REACTIONS

In some cases, it should be possible to accomplish a chemical transformation without the use of a solvent. Dry media reaction under microwaves is an important area of study (see p. 352).[119] There are several advantages of solventless reactions: (*1*) the possibility of direct formation of high purity compounds, (*2*) the possibility of sequential reactions, (*3*) fast kinetics, (*4*) lower energy usage, (*5*) minimal need for preformed salts and metal–metalloid complexes, (*6*) simplicity and low equipment cost, and (*7*) the possibility of avoiding functional group protection–deprotection.[120] Potential difficulties include the possibility of hot spots and runaway reactions, and difficulties in handling solid or highly viscous materials.[121] An example of this approach is the aldol condensation, where a single aldol product was obtained in high yield.[122] 3-Carboxylcoumarins have been produced via a solventless aldol.[120]

[110]Dupont, J.; Consorti, C.S.; Suarez, P.A.Z.; de Souza, R.F. *Org. Synth. Coll. Vol. X*, 184.

[111]For discussion of HBuIM and DiBuIm, see Harlow, K.J.; Hill, A.F.; Welton, T. *Synthesis* ***1996***, 697; Holbrey, J.D.; Seddon, K.R. *J. Chem. Soc., Dalton Trans.* ***1999***, 2133; Larsen, A.S.; Holbrey, J.D.; Tham, F.S.; Reed, C.A. *J. Am. Chem. Soc.* ***2000***, *122*, 7264.

[112]Jaegar, D.A.; Tucker, C.E. *Tetrahedron Lett.* ***1989***, *30*, 1785.

[113]See Xiao, Y.; Malhotra, S.V. *Tetrahedron Lett.* ***2004***, *45*, 8339.

[114]Handy, S.T.; Okello, M.; Dickenson, G. *Org. Lett.* ***2003***, *5*, 2513.

[115]Yadav, J.S.; Reddy, B.V.S.; Basak, A.K.; Narsaiah, A.V. *Tetrahedron* ***2004***, *60*, 2131.

[116]Branco, L.C.; Afonso, C.A.M. *J. Org. Chem.* ***2004***, *69*, 4381.

[117]See Leadbeater, N.E.; Torenius, H.M. *J. Org. Chem.* ***2002***, *67*, 3145.

[118]For studies to expand the polarity range of ionic solvents see Dzyuba, S.V.; Bartsch, R.A. *Tetrahedron Lett.* ***2002***, *43*, 4657.

[119]Kidwai, M. *Pure Appl. Chem.* ***2001***, *73*, 147.

[120]Cave, G.W.V.; Raston, C.L.; Scott, J.L. *Chem. Commun.* ***2001***, 2159; Toda, F.; Tanaka, K. *Chem. Rev.* ***2000***, *100*, 1025.

[121]Raston, C.L. *Chemistry in Australia* ***2004***, 10.

[122]Toda, F.; Tanaka, K.; Hamai, K. *J. Chem. Soc., Perkin Trans. 1* ***1990***, 3207.

PART TWO

In Part 2 of this book, we will be directly concerned with organic reactions and their mechanisms. The reactions have been classified into 10 chapters, based primarily on reaction type: substitutions, additions to multiple bonds, eliminations, rearrangements, and oxidation–reduction reactions. Five chapters are devoted to substitutions; these are classified on the basis of mechanism as well as substrate. Chapters 10 and 13 include nucleophilic substitutions at aliphatic and aromatic substrates, respectively. Chapters 12 and 11 deal with electrophilic substitutions at aliphatic and aromatic substrates, respectively. All free-radical substitutions are discussed in Chapter 14. Additions to multiple bonds are classified not according to mechanism, but according to the type of multiple bond. Additions to carbon–carbon multiple bonds are dealt with in Chapter 15; additions to other multiple bonds in Chapter 16. One chapter is devoted to each of the three remaining reaction types: Chapter 17, eliminations; Chapter 18, rearrangements; Chapter 19, oxidation–reduction reactions. This last chapter covers only those oxidation–reduction reactions that could not be conveniently treated in any of the other categories (except for oxidative eliminations).

Each chapter in Part 2 consists of two main sections. The first section of each chapter (except Chapter 19) deals with mechanism and reactivity. For each reaction type the various mechanisms are discussed in turn, with particular attention given to the evidence for each mechanism and to the factors that cause one mechanism rather than another to prevail in a given reaction. Following this, each chapter contains a section on reactivity, including, where pertinent, a consideration of orientation and the factors affecting it.

The second main section of each chapter is a treatment of the reactions belonging to the category indicated by the title of the chapter. It is not possible to discuss in a book of this nature all or nearly all known reactions. However, an attempt has been made to include all the important reactions of standard organic chemistry that can be used to prepare relatively pure compounds in reasonable yields. In order to present a well-rounded picture and to include some reactions that are traditionally discussed in textbooks, a number of reactions that do not fit into the above category have been included. The scope of the coverage is apparent from the fact that more than 90% of the individual preparations given in *Organic Syntheses* are treated. However, certain special areas have been covered only lightly or not at all. Among these are electrochemical and polymerization reactions, and the preparation and reactions of heterocyclic compounds, carbohydrates, steroids, and compounds containing phosphorus, silicon, arsenic, boron, and mercury. The basic principles

involved in these areas are of course no different from those in the areas more fully treated. Even with these omissions, however, some 580 reactions are treated in this book.

Each reaction is discussed in its own numbered section.[1] These are numbered consecutively within a chapter, each section number preceded by the chapter number, so that reaction **16-1** is the first reaction of Chapter 16 and reaction **13-21** is the twenty-first reaction of Chapter 13. The order in which the reactions are presented is not arbitrary, but is based on an orderly outline that depends on the type of reaction. Within each section, the scope and utility of the reaction are discussed and references are given to review articles, if any. If there are features of the mechanism that especially pertain to that reaction, these are also discussed within the section rather than in the first part of the chapter where the discussion of mechanism is more general.

IUPAC NOMENCLATURE FOR TRANSFORMATIONS

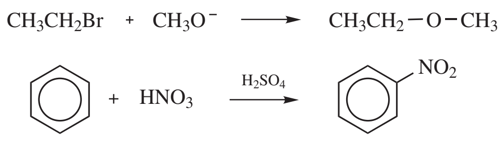
There has long been a need for a method of naming reactions. As most students know well, many reactions are given the names of their discoverers or those who popularized them (e.g., Claisen, Diels–Alder, Stille, Wittig, Cope, Dess–Martin). This is useful as far as it goes, but each name must be individually memorized, and there are many reactions that do not have such names. The IUPAC Commission on Physical Organic Chemistry has produced a *system* for naming not reactions, but transformations (a reaction includes all reactants; a transformation shows only the substrate and product, omitting the reagents). The advantages of a systematic method are obvious. Once the system is known, no memorization is required; the name can be generated directly from the equation. The system includes rules for naming eight types of transformation: substitutions, additions, eliminations, attachments and detachments, simple rearrangements, coupling and uncoupling, insertions and extrusions, and ring opening and closing. We give here only the most basic rules for the first three of these types, which, however, will suffice for naming many transformations.[2] The complete rules give somewhat different names for speech writing and indexing. In this book, we give only the speech-writing names.

[1]The classification of reactions into sections is, of course, to some degree arbitrary. Each individual reaction (e.g., $CH_3Cl + CN^- \rightarrow CH_3CN$ and $C_2H_5Cl + CN^- \rightarrow C_2H_5CN$) is different, and custom generally decides how we group them together. Individual preferences also play a part. Some chemists would say that $C_6H_5N_2^+ + CuCN \rightarrow C_6H_5CN$ and $C_6H_5N_2^+ + CuCl \rightarrow C_6H_5Cl$ are examples of the "same" reaction. Others would say that they are not, but that $C_6H_5N_2^+ + CuCl \rightarrow C_6H_5Cl$ and $C_6H_5N_2^+ + CuBr \rightarrow C_6H_5Br$ are examples of the "same" reaction. No claim is made that the classification system used in this book is more valid than any other. For another way of classifying reactions, see Fujita, S. *J. Chem. Soc., Perkin Trans. 2* ***1988***, 597.

[2]For the complete rules, as so far published, see Jones, R.A.Y.; Bunnett, J.F. *Pure Appl. Chem.* ***1989***, *61*, 725.

Substitutions

A name consists of the entering group, the syllable "de," and the leaving group. If the leaving group is hydrogen, it may be omitted (in all examples, the substrate is written on the left).



Metthoxy-de-hydrogenation

Nitro-de-hydrogenation
or Nitration

Multivalent substitutions are named by a modification of this system that includes suffixes, such as "bisubstitution" and "tersubstitution."

$CH_2Cl_2 + 2\ EtO^- \longrightarrow CH_2(OEt)_2$ Diethoxy-de-chloro-bisubstitution

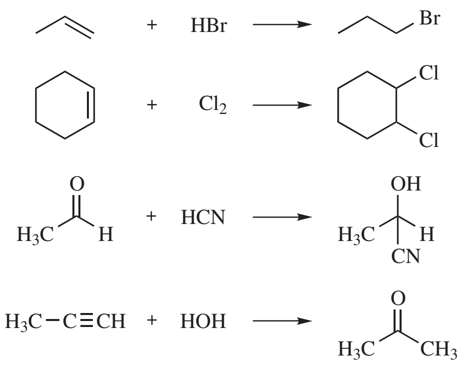
$CH_3CHO + Ph_3P{=}CH_2 \longrightarrow CH_3CH{=}CH_2$ Methylene-de-oxo-bisubstitution

$CH_3C{\equiv}N + H_2O \xrightarrow{H^+} H_3C{-}C({=}O){-}OH$ Hydroxy, oxo-de-nitrilo-tersubstitution

(Note: The nitrilo group is ≡N.)

Additions

For simple 1,2-additions, the names of both addends are given followed by the suffix "addition." The addends are named in order of priority in the Cahn–Ingold–Prelog system (p. 155), the lower ranking addend coming first. Multivalent addition is indicated by "biaddition," and so on.



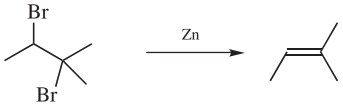
Hydro-bromo-addition

Dichloro-addition

O-Hydro-*C*-cyano-addition

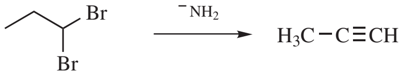
Dihydro-oxo-biaddition

Eliminations are named the same way as additions, except that "elimination" is used instead of "addition."



Dibromo-elimination

O-Hydro-*C*-sulfonato-elimination



Dihydro-dibromo-bielimination

In the reaction sections of this book, we will give IUPAC names for most transformations (these names will be printed in the same typeface used above), including examples of all eight types.[3] As will become apparent, some transformations require more rules than we have given here.[2] However, it is hoped that the simplicity of the system will also be apparent.

Two further notes: (*1*) Many transformations can be named using either of two reactants as the substrate. For example, the transformation methylene-de-oxo-bisubstitution above, can also be named ethylidene-de-triphenylphosphoranediyl-bisubstitution. In this book, unless otherwise noted, we will show only those names in which the substrate is considered to undergo the reactions indicated by the titles of the chapters. Thus the name we give to **11-11** (ArH + RCl → ArR) is alkyl-de-hydrogenation, not aryl-de-chlorination, though the latter name is also perfectly acceptable under the IUPAC system. (*2*) The IUPAC rules recognize that some transformations are too complex to be easily fitted into the system, so they also include a list of names for some complex transformations, which are IUPAC approved, but nonsystematic (for some examples, see reactions **12-44**, **18-34**).

IUPAC SYSTEM FOR SYMBOLIC REPRESENTATION OF MECHANISMS

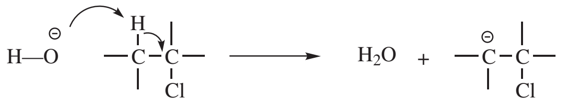
In addition to providing a system for naming transformations, the IUPAC Commission on Physical Organic Chemistry has also produced one for representing mechanisms.[4] As we will see in Part 2, many mechanisms (though by no means all) are commonly referred to by designations, such as S_N2, $A_{AC}2$, $E1_{cB}$, and $S_{RN}1$, many of them devised by C.K. Ingold and his co-workers. While these

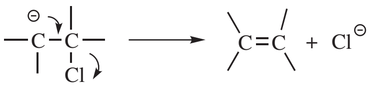
[3]For some examples, see: attachments (**18-27**, **19-29**), detachments (**19-72**), simple rearrangements (**18-7**, **18-29**), coupling (**10-56**, **19-34**), uncoupling (**19-9**, **19-75**), insertions (**12-21**, **18-9**), extrusions (**17-35**, **17-38**), ring opening (**10-14**, **10-35**), ring closing (**10-9**, **15-60**).

[4]Guthrie, R.D. *Pure Appl. Chem.* ***1989***, *61*, 23. For a briefer description, see Guthrie, R.D.; Jencks, W.P. *Acc. Chem. Res.* ***1989***, *22*, 343.

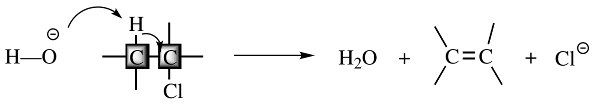
designations have been useful (and we will continue to use them in this book), the sheer number of them can be confusing, especially since the symbols do not give a direct clue to what is happening. For example, there is no way to tell directly from the symbols how S_N2' is related to S_N2 (see p. 426). The IUPAC system is based on a very simple description of bond changes.[5] The letter A represents formation of a bond (association); D the breaking of a bond (dissociation). These are *primitive changes*. The basic description of a mechanism consists of these letters, with subscripts to indicate where the electrons are going. In any mechanism, the *core atoms* are defined as (*1*) the two atoms in a multiple bond that undergoes addition, or (*2*) the two atoms that will be in a multiple bond after elimination, or (*3*) the single atom at which substitution takes place.

As an example of the system, this is how an $E1_{cB}$ mechanism (p. 1488) would be represented:

Step 1  A_nD_E (or A_{xh} D_H)

Step 2  D_N

Overall designation: $A_nD_E + D_N$ (or $A_{xh}D_H + D_N$)
In this case, the overall reaction is



and the core atoms are the two carbons in boldface.

Step 1, *First Symbol*. A bond is being formed between O and H. Bond formation is represented by A. For this particular case, the system gives two choices for subscript. In any process, the subscript is N if a core atom is forming a bond to a nucleophile (A_N) or breaking a bond to a nucleofuge (D_N). If a noncore atom is doing the same thing, lowercase n is used instead. Since H and O are noncore atoms, the lowercase n is used, and the formation of the O—H bond is designated by A_n. However, because involvement of H^+ is so common in organic mechanisms, the rules allow an alternative. The subscript H or h may

[5]There are actually two IUPAC systems. The one we use in this book (Ref. 4) is intended for general use. A more detailed system, which describes every conceivable change happening in a system, and which is designed mostly for computer handling and storage, is given by Littler, J.S. *Pure Appl. Chem.* ***1989***, *61*, 57. The two systems are compatible; the Littler system uses the same symbols as the Guthrie system, but has additional symbols.

replace N or n. The symbol xh denotes that the H^+ comes from or goes to an unspecified carrier atom X. Thus the term A_{xh} means that a bond is being formed between H (moving without electrons) and an outside atom, in this case O. The same subscript, xh, would be used if the outside atom were any other nucleophilic atom, say, N or S.

Step 1, *Second Symbol*. A bond is being broken between C and H. The symbol is D. In any process, the subscript is E if a core atom is forming a bond to an electrophile (A_E) or breaking a bond to an electrofuge (D_E). Since C is a core atom, the symbol here is D_E. Alternatively, the symbol could be D_H. The rules allow A_H or D_H to replace A_E or D_E if the electrophile or electrofuge is H^+. Because a core atom is involved in this primitive change the H in the subscript is capitalized.

Step 1, *Combined Symbols*. In step 1, two bond changes take place simultaneously. In such cases, they are written together with no space or punctuation:

$$A_nD_E \qquad \text{or} \qquad A_{xh}D_H$$

Step 2. Only one bond is broken in this step and no bonds are formed. (The movement of a pair of unshared electrons into the C—C bond, forming a double bond, is not designated by any symbol. In this system bond multiplicity changes are understood without being specified.) Thus the symbol is D. The broken bond is between a core atom (C) and a nucleofuge (Cl), so the designation is D_N.

Overall designation. This can be either $A_nD_N + D_N$ or $A_{xh}D_H + D_N$. The + symbol shows that there are two separate steps. If desired, rate-limiting steps can be shown by the symbol. In this case, if the first step is the slow step [old designation $(E1_{cB})_I$], the designation would be $A_nD_E + D_N$ or $A_{xh}D_H + D_N$.

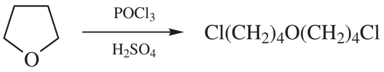
For most mechanisms (other than rearrangements), there will be only two A or D terms with uppercase subscripts, and the nature of the reaction can be immediately recognized by looking at them. If both are A, the reaction is an addition; if both are D (as in $A_nD_E + D_N$) it is an elimination. If one is A and the other D, the reaction is a substitution.

Here, we have given only a brief description of the system. Other IUPAC designations will be shown in Part Two, where appropriate. For more details, further examples, and additional symbols, see Ref. 4.

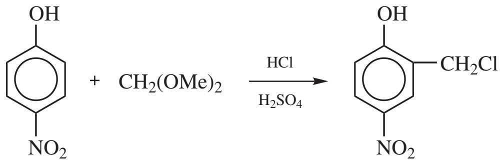
ORGANIC SYNTHESES REFERENCES

At the end of each numbered section there is a list of *Organic Syntheses* references (abbreviated OS). With the exception of a few very common reactions (**12-3**, **12-23**, **12-24**, and **12-38**) the list includes *all* OS references for each reaction. The volumes

of OS that have been covered are Collective Volumes **I–X** and individual volumes **80–81**. Where no OS references are listed at the end of a section, the reaction has not been reported in OS through volume **81**. These listings thus constitute a kind of index to OS.[6] Certain ground rules were followed in assembling these lists. A reaction in which two parts of a molecule independently undergo simultaneous reaction is listed under both reactions. Similarly, if two reactions happen (or might happen) rapidly in succession without the isolation of an intermediate, the reactions are listed in both places. For example, at OS **IV**, 266 is



This reaction is treated as **10-49** followed by **10-12** and is listed in both places. However, certain reactions are not listed because they are trivial examples. An instance of this is the reaction found at OS **III**, 468:



This is a chloromethylation reaction and is consequently listed at **11-14**. However, in the course of the reaction formaldehyde is generated from the acetal. This reaction is not listed at **10-6** (hydrolysis of acetals), because it is not really a preparation of formaldehyde.

[6]Two indexes to *Organic Syntheses* have been published as part of the series. One of these, Liotta, D.C.; Volmer, M. *Organic Syntheses Reaction Guide*, Wiley, NY, ***1991***, which covers the series through Vol. 68, is described on p. 1896. There are two others. One covers the series through Collective Vol. V, Shriner, R.L.; Shriner, R.H. *Organic Syntheses Collective Volumes I-V, Cumulative Indices*, Wiley, NY, ***1976***. An updated version covers through Collective Vol. VIII: Freeman, J.P. *Organic Syntheses Collective Volumes I–VIII, Cumulative Indices*, Wiley: NY, ***1995***. For an older index to *Organic Syntheses* (through Vol. 45), see Sugasawa, S.; Nakai, S. *Reaction Index of Organic Syntheses*, Wiley, NY, ***1967***.

CHAPTER 10

Aliphatic Substitution: Nucleophilic and Organometallic

In nucleophilic aliphatic substitution the attacking (electron donating) reagent (the nucleophile) brings an electron pair to the substrate, using this pair to form the new bond, and the leaving group (the nucleofuge) comes away with an electron pair:

$$R{-}X \quad + \quad Y{:} \longrightarrow R{-}Y \quad + \quad X{:}$$

This equation says nothing about charges. Nuclephile Y may be neutral or negatively charged; RX may be neutral or positively charged; so there are four charge types, examples of which are

Type I	$R{-}I$	+	OH^-	$\longrightarrow$	$R{-}OH$	+	I^-
Type II	$R{-}I$	+	NMe_3	$\longrightarrow$	$R{-}\overset{\oplus}{N}Me_3$	+	I^-
Type III	$R{-}\overset{\oplus}{N}Me_3$	+	OH^-	$\longrightarrow$	$R{-}OH$	+	NMe_3
Type IV	$R{-}\overset{\oplus}{N}Me_3$	+	H_2S	$\longrightarrow$	$R{-}\overset{\oplus}{S}H_2$	+	NMe_3

In all cases, Y must have an unshared pair of electrons, so that all nucleophiles are Lewis bases. When Y is the solvent, the reaction is called *solvolysis*. Nucleophilic substitution at an aromatic carbon is considered in Chapter 13.

Nucleophilic substitution at an alkyl carbon is said to *alkylate* the nucleophile. For example, the above reaction between RI and NMe_3 is an *alkylation* of trimethylamine. Similarly, nucleophilic substitution at an acyl carbon is an *acylation* of the nucleophile.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Sixth Edition, by Michael B. Smith and Jerry March
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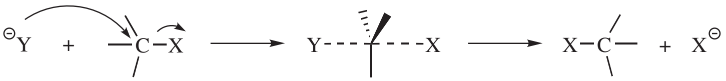
MECHANISMS

Several distinct mechanisms are possible for aliphatic nucleophilic substitution reactions, depending on the substrate, nucleophile, leaving group, and reaction conditions. In all of them, however, the attacking reagent carries the electron pair with it, so that the similarities are greater than the differences. Mechanisms that occur at a saturated carbon atom are considered first.[1] By far the most common are the S_N1 and S_N2 mechanisms.

The S_N2 Mechanism

The designation S_N2 stands for *substitution nucleophilic bimolecular*. The IUPAC designation (p. 420) is A_ND_N. In this mechanism, there is *backside attack*:[2] the nucleophile approaches the substrate from a position 180° away from the leaving group. The reaction is a one-step process with no intermediate (see, however, pp. 428–431 and 440). The C—Y bond is formed as the C—X bond is broken to generate transition state **1**.



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The energy necessary to break the C—X bond is supplied by simultaneous formation of the C—Y bond. The position of the atoms at the top of the curve of free energy of activation is represented as transition state **1**. Of course, the reaction does not stop here since this is the transition state. The group X must leave as the group Y comes in, because at no time can the carbon have more than eight electrons in its outer shell. When the transition state is reached, the central carbon atom has gone from its initial sp^3 hybridization to an sp^2 state with an approximately perpendicular p orbital. One lobe of this p orbital overlaps with the nucleophile and the other with the leaving group. This is why a frontside S_N2 mechanism has never been observed. In a hypothetical frontside transition state, both the nucleophile and the leaving group would have to overlap with the same lobe of the p orbital. The backside mechanism involves the maximum amount of overlap throughout the course of the reaction. During the transition state the three nonreacting substituents and the central carbon are approximately coplanar. They will be exactly coplanar if both the entering and the leaving group are the same.

[1]For a monograph on this subject, see Hartshorn, S.R. *Aliphatic Nucleophilic Substitution*, Cambridge University Press, Cambridge, ***1973***. For reviews, see Katritzky, A.R.; Brycki, B.E. *Chem. Soc. Rev.* ***1990***, *19*, 83; Richard, J.P. *Adv. Carbocation Chem.* ***1989***, *1*, 121; de la Mare, P.B.D.; Swedlund, B.E., in Patai, S. *The Chemistry of the Carbon–Halogen Bond*, pt. 1, Wiley, NY, ***1973***, pp. 409–490. Streitwieser, A. *Solvolytic Displacement Reactions*, McGraw-Hill, NY, ***1962***.

[2]See Sun, L.; Hase, W.L.; Song, K. *J. Am. Chem. Soc.* ***2001***, *123*, 5753.

There is a large amount of evidence for the S_N2 mechanism. First, there is the kinetic evidence. Since both the nucleophile and the substrate are involved in the rate-determining step (the only step, in this case), the reaction should be first order in each component, second order overall, and satisfy the rate expression, Eq. (10.1).

$$\text{Rate} = k[\text{RX}][\text{Y}] \tag{10.1}$$

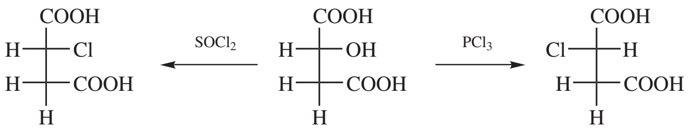
This rate law has been found to apply. Note that the 2 in S_N2 stands for bimolecular. It must be remembered that this is not always the same as second order (see p. 315). If a large excess of nucleophile is present (for example, if it is the solvent) the mechanism may still be bimolecular, although the experimentally determined kinetics will be first order, Eq. (10.2).

$$\text{Rate} = k[\text{RX}] \tag{10.2}$$

As previously mentioned (p. 318), such kinetics are called *pseudo-first order.*

The kinetic evidence is a necessary but not a sufficient condition; we will meet other mechanisms that are also consistent with these data. Much more convincing evidence is obtained from the fact that the mechanism predicts inversion of configuration when substitution occurs at a chiral carbon and this has been observed many times. This inversion of configuration (see p. 158) that proceeds through transition state **1** is called the *Walden inversion* and was observed long before the S_N2 mechanism was formulated by Hughes and Ingold.[3]

At this point it is desirable for us to see just how it was originally proved that a given substitution reaction proceeds with inversion of configuration, even before the mechanism was known. Walden presented a number of examples[4] in which inversion *must* have taken place. For example, (+)-malic acid (**2**) could be converted to (+)-chlorosuccinic acid by thionyl chloride and to (−)-chlorosuccinic acid by phosphorus pentachloride.



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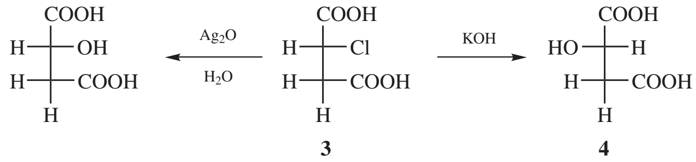
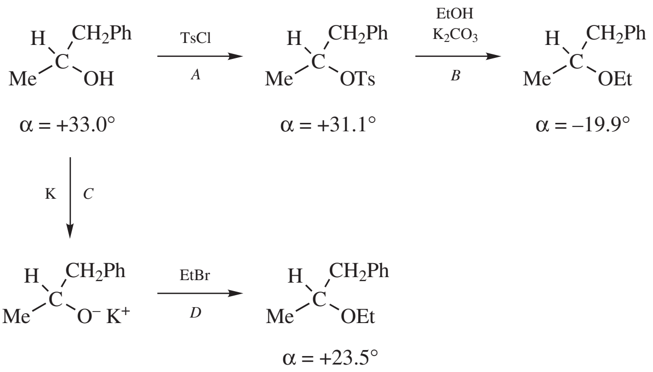
[3]Cowdrey, W.A.; Hughes, E.D.; Ingold, C.K.; Masterman, S.; Scott, A.D. *J. Chem. Soc.* ***1937***, 1252. The idea that the addition of one group and removal of the other are simultaneous was first suggested by Lewis, G.N., in *Valence and the Structure of Atoms and Molecules*, Chemical Catalog Company, NY, ***1923***, p. 113. The idea that a one-step substitution leads to inversion was proposed by Olsen, A.R. *J. Chem. Phys.* ***1933***, *1*, 418.

[4]Walden, P. *Berichte* ***1893***, *26*, 210; ***1896***, *29*, 133; ***1899***, *32*, 1855.

One of these must be an inversion and the other a retention of configuration, but the question is which is which? The signs of rotation are of no help in answering this question since, as we have seen (p. 154), rotation need not be related to configuration. Another example discovered by Walden is formation of **3** from **4**.[5]



A series of experiments designed to settle the matter of exactly where inversion takes place was performed by Phillips, Kenyon, and co-workers. In 1923, Phillips carried out the following cycle based on (+)-1-phenyl-2-propanol.[6]



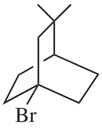
In this cycle, (+)-1-phenyl-2-propanol is converted to its ethyl ether by two routes, path *AB* giving the (−) ether, and path *CD* giving the (+) ether. Therefore, at least one of the four steps must be an inversion. It is extremely unlikely that there is inversion in step *A*, *C*, or *D*, since in all these steps the C—O bond is unbroken, and in none of them could the oxygen of the bond have come from the reagent. There is therefore a high probability that *A*, *C*, and *D* proceeded with retention, leaving *B* as the inversion. A number of other such cycles were carried out, always with nonconflicting results.[7] These experiments not only definitely showed that certain specific reactions proceed with inversion, but also established the configurations of many compounds.

Walden inversion has been found at a primary carbon atom by the use of a chiral substrate containing a deuterium and a hydrogen atom at the carbon bearing the

[5]For a discussion of these cycles, see Kryger, L.; Rasmussen, S.E. *Acta Chem. Scand.* ***1972***, *26*, 2349.
[6]Phillips, H. *J. Chem. Soc.* ***1923***, *123*, 44. For analyses of such cycles and general descriptions of more complex ones, see Garwood, D.C.; Cram, D.J. *J. Am. Chem. Soc.* ***1970***, *92*, 4575; Cram, D.J.; Cram, J.M. *Fortschr. Chem. Forsch.* ***1972***, *31*, 1.
[7]See Kenyon, J.; Phillips, H.; Shutt, G.R. *J. Chem. Soc.* ***1935***, 1663 and references cited therein.

leaving group.[8] Inversion of configuration has also been found for S_N2 reactions proceeding in the gas phase.[9] High-pressure mass spectrometry has been used to probe the energy surface for gas-phase S_N2 reactions, which have two transition states (a "loose" transitions state and a "tight" transition state).[10]

Another kind of evidence for the S_N2 mechanism comes from compounds with potential leaving groups at bridgehead carbons. If the S_N2 mechanism is correct, these compounds should not be able to react by this mechanism, since



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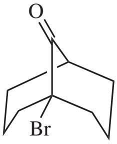

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the nucleophile cannot approach from the rear. Among the many known examples of unsuccessful reaction attempts at bridgeheads under S_N2 conditions[11] are treatment of the [2.2.2] system **5** with ethoxide ion[12] and treatment of the [3.3.1] system **6** with sodium iodide in acetone.[13] In these cases, open-chain analogs underwent the reactions readily. As a final example of evidence for the S_N2 mechanism, the reaction between optically active 2-octyl iodide and radioactive iodide ion may be mentioned:

$$C_6H_{13}CHMeI \quad + \quad {}^*I^- \longrightarrow C_6H_{13}CHMe{}^*I \quad + \quad I^-$$

We expect racemization in this reaction, since if we start with the pure *R* isomer, at first each exchange will produce an *S* isomer, but with increasing concentration of *S* isomer, *it* will begin to compete for I^- with the (*R*) isomer, until at the end a racemic mixture is left. The point investigated was a comparison of the rate of inversion with the rate of uptake of radioactive ${}^*I^-$. It was found[14] that the rates were identical within experimental error:

Rate of inversion	$2.88 \pm 0.03 \times 10^{-5}$
Rate of exchange	$3.00 \pm 0.25 \times 10^{-5}$

[8]Streitwieser, Jr., A. *J. Am. Chem. Soc.* ***1953***, *75*, 5014.

[9]Speranza, M.; Angelini, G. *J. Am. Chem. Soc.* ***1980***, *102*, 3115 and references cited therein; Sauers, R.R. *J. Org. Chem.* ***2002***, *67*, 1221; Kempf, B.; Hampel, N.; Ofial, A.R.; Mayr, H. *Chem. Eur. J.* ***2003***, *9*, 2209. For a review of nucleophilic displacements in the gas phase, see Riveros, J.M.; José, S.M.; Takashima, K. *Adv. Phys. Org. Chem.* ***1985***, *21*, 197.

[10]Li, C.; Ross, P.; Szulejko, J.E.; McMahon, T.B. *J. Am. Chem. Soc.* ***1996***, *118*, 9360.

[11]For a review of bridgehead reactivity in nucleophilic substitution reactions, see Müller, P.; Mareda, J., in Olah, G.A. *Cage Hydrocarbons*, Wiley, NY, ***1990***, pp. 189–217. For a review of reactions at bridgehead carbons, see Fort, Jr., R.C.; Schleyer, P.v.R. *Adv. Alicyclic Chem.* ***1966***, *1*, 283.

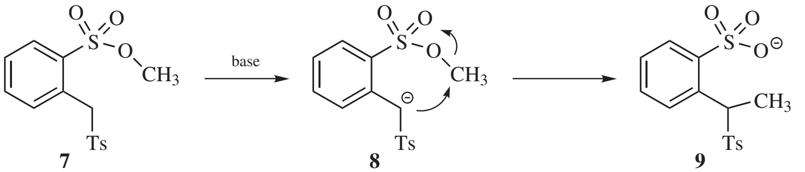
[12]Doering, W. von E.; Levitz, M.; Sayigh, A.; Sprecher, M.; Whelan, Jr., W.P. *J. Am. Chem. Soc.* ***1953***, *75*, 1008. Actually, a slow substitution was observed in this case, but not by an S_N2 mechanism.

[13]Cope, A.C.; Synerholm, M.E. *J. Am. Chem. Soc.* ***1950***, *72*, 5228.

[14]Hughes, E.D.; Juliusburger, F.; Masterman, S.; Topley, B.; Weiss, J. *J. Chem. Soc.* ***1935***, 1525.

What was actually measured was the rate of racemization, which is twice the rate of inversion, since each inversion creates, in effect, two racemic molecules. The significance of this result is that it shows that every act of exchange is an act of inversion.

Eschenmoser and co-workers have provided strong evidence that the transition state in an S_N2 reaction must be linear.[15] Base treatment of methyl α-tosyl-*o*-toluenesulfonate (**7**) gives the *o*-(l-tosylethyl)benzenesulfonate ion (**9**). The role of



7 **8** **9**

the base is to remove the a proton to give the ion **8**. It might be supposed that the negatively charged carbon of **8** attacks the methyl group in an internal S_N2 process, but this is not the case. Cross-over experiments[15] (p. 736) have shown that the negatively charged carbon attacks the methyl group of another molecule rather than the nearby one in the same molecule, that is, the reaction is intermolecular and not intramolecular, despite the more favorable entropy of the latter pathway (p. 302). The obvious conclusion is that intramolecular attack does not take place because complete linearity cannot be attained. This behavior is in sharp contrast to that in cases in which the leaving group is not constrained (p. 446), where intramolecular S_N2 mechanisms operate freely.

There is evidence, both experimental and theoretical, that there are intermediates in at least some S_N2 reactions in the gas phase, in charge type I reactions, where a negative ion nucleophile attacks a neutral substrate.[16] Two energy minima, one before and one after the transition state appear in the reaction coordinate (Fig. 10.1).[17] The energy surface for the S_N2 Menshutkin reaction (p. 555) has been examined and it was shown that charge separation was promoted by the solvent.[18] An *ab initio* study of the S_N2 reaction at primary and secondary carbon centers has looked at the energy barrier (at the transition state) to the reaction.[19] These minima correspond to unsymmetrical ion–dipole complexes.[20] Theoretical calculations also show such minima in certain solvents (e.g., DMF), but not in water.[21] The

[15]Tenud, L.; Farooq, S.; Seibl, J.; Eschenmoser, A. *Helv. Chim. Acta* ***1970***, *53*, 2059. See also, King, J.F.; McGarrity, M.J. *J. Chem. Soc., Chem. Commun.* ***1979***, 1140.

[16]See Angel, L.A; Ervin, K.M. *J. Am. Chem. Soc.* ***2003***, *125*, 1014.

[17]Taken from Chandrasekhar, J.; Smith, S.F.; Jorgensen, W.L. *J. Am. Chem. Soc.* ***1985***, *107*, 154.

[18]Gao, J.; Xia, X. *J. Am. Chem. Soc.* ***1993***, *115*, 9667.

[19]Lee, I.; Kim, C.K.; Chung, D.S.; Lee, B.-S. *J. Org. Chem.* ***1994***, *59*, 4490.

[20]Pellerite, M.J.; Brauman, J.I. *J. Am. Chem. Soc.* ***1980***, *102*, 5993; Wolfe, S.; Mitchell, D.J.; Schlegel, H.B. *J. Am. Chem. Soc.* ***1981***, *103*, 7692; Evanseck, J.D.; Blake, J.F.; Jorgensen, W.L. *J. Am. Chem. Soc.* ***1987***, *109*, 2349; Kozaki, T.; Morihashi, K.; Kikuchi, O. *J. Am. Chem. Soc.* ***1989***, *111*, 1547; Jorgensen, W.L. *Acc. Chem. Res.* ***1989***, *22*, 184.

[21]Chandrasekhar, J.; Jorgensen, W.L. *J. Am. Chem. Soc.* ***1985***, *107*, 2974.

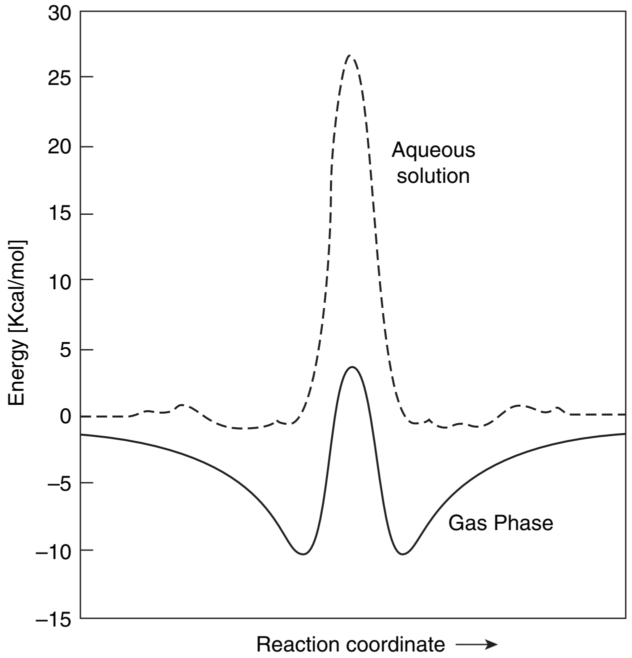


Fig. 10.1. Free-energy profile for the gas-phase (solid line) and aqueous solution (dashed line) S_N2 reaction between CH_3Cl and Cl^-, from molecular orbital calculations.[17]

S_N2 reactions can occur at atoms other than carbon, X (e.g., nitrogen or sulfur[22]), and analogous to the phenomenon observed for S_N2 reactions at carbon.[23] The valence of the element X, controls the intrinsic barrier for the reaction in accord with the properties seen in the Periodic table.[24]

For a list of some of the more important reactions that operate by the S_N2 mechanism, see Table 10.7.

Note that in some reactions, such as bromine transfer between carbanions via nucleophilic attack on bromine, anomalous kinetic behavior is observed. The largest rate constants are associated with bromine transfer between cyano-activated carbanions and the smallest relate to the removal of bromine from the nitromethane and nitroethane moieties.[25] The Brønsted plot ($\log k$ vs. ΔpK_a) for this reaction shows that unlike any normal Brønsted plot, which by definition displays a positive slope, the plot for $MeNO_2$ and $EtNO_2$ is negative. In deprotonation reactions of carbon compounds, the reactivity of nitroethane and nitromethane were shown to be anomalous.[26] In the series nitromethane, ethane, and isopropane, contrary

[22]See reactions **10-60–10-68** and Bachrach, S.M.; Gailbreath, B.D. *J. Org. Chem.* ***2001***, *66*, 2005.

[23]Hoz, S.; Basch, H.; Wolk, J.L.; Hoz, T.; Rozental, E. *J. Am. Chem. Soc.* ***1999***, *121*, 7724.

[24]Yi, R.; Basch, H.; Hoz, S. *J. Org. Chem.* ***2002***, *67*, 5891.

[25]Grinblat, J.; Ben-Zion, M.; Hoz, S. *J. Am. Chem. Soc.* ***2001***, *123*, 10738.

[26]Pearson, R.G.; Dillon, R.L. *J. Am. Chem. Soc.* ***1953***, *75*, 2439.

to expectations, compounds with higher acidity undergo slower deprotonation (i.e., the Brønsted plot displays a negative slope).[27]

The S_N1 Mechanism

The most ideal version of the S_N1 mechanism (*substitutional nucleophilic unimolecular*) consists of two steps[28] (once again, possible charges on the substrate and nucleophile are not shown):

$$\text{Step 1} \qquad \text{R–X} \underset{}{\overset{\text{slow}}{\rightleftharpoons}} \text{R}^+ + \text{X}$$

$$\text{Step 2} \qquad \text{R}^+ + \text{Y} \xrightarrow{\text{fast}} \text{R–Y}$$

The first step is a slow ionization of the substrate and is the rate-determining step. The second is a rapid reaction between the intermediate carbocation and the nucleophile. The reactive nature of the carbocation can be expressed by its electrophilic character, or electrophlicity. A theoretical discussion concerning the origin of the electrophilicity concept was proposed by Parr et al.[29] In general, a good electrophile was characterized by having a high value of electronegativity (or a high value of electronic chemical potential), and a low value of the chemical hardness. The effect of substitution has been studied[30] in the context of superelectrophilicity (where carbocations are generated in super acidic media). Solvent effects have also been studied.[31] Electrophlicity scales have been proposed using other carbocations.[32]

Returning to the S_N1 mechanism, ionization of a leaving group to form the carbocation is always assisted by the solvent,[33] since the energy necessary to break the bond is largely recovered by solvation of R^+ and of X. For example, the ionization of *t*-BuCl to *t*-Bu^+ and Cl^- in the gas phase without a solvent requires 150 kcal mol^{-1} (630 kJ mol^{-1}). In the absence of a solvent, such a process simply would not take place, except at very high temperatures. In water, this ionization requires only 20 kcal mol^{-1} (84 kJ mol^{-1}). The difference is solvation energy. In

[27]Kresge, A.J. *Can. J. Chem.* ***1974***, *52*, 1897; Yamataka, H.; Mustanir; Mishima, M. *J. Am. Chem. Soc.* ***1999***, *121*, 10223.

[28]For a direct observation of the two steps see Mayr, H.; Minegishi, S. *Angew. Chem. Int. Ed.* ***2002***, *41*, 4493.

[29]Parr, R. G.; Szentpály, L.V.; Liu, S. *J. Am. Chem. Soc.* ***1999***, *121*, 1922.

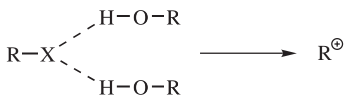
[30]See Pérez, P. *J. Org. Chem.* ***2004***, *69*, 5048.

[31]Pérez, P.; Toro-Labbé, A.; Contreras, R. *J. Am. Chem. Soc.* ***2001***, *123*, 5527.

[32]Pérez, P.; Toro-Labbé, A.; Aizman, A.; Contreras, R. *J. Org. Chem.* ***2002***, *67*, 4747; Parr, R.G.; Szentpály, L.-v.; Liu, S. *J. Am. Chem. Soc.* ***1999***, *121*, 1922.

[33]For reviews of solvolysis, see Okamoto, K. *Adv. Carbocation Chem.* ***1989***, *1*, 171; Blandamer, M.J.; Scott, J.M.W.; Robertson, R.E. *Prog. Phys. Org. Chem.* ***1985***, *15*, 149; Robertson, R.E. *Prog. Phys. Org. Chem.* ***1967***, *4*, 213. For a review of the solvolytic cleavage of *tert*-butyl substrates, see Dvorko, G.F.; Ponomareva, E.A.; Kulik, N.I. *Russ. Chem. Rev.* ***1984***, *53*, 547.

cases where the role of the solvent is solely to assist in departure of the leaving group from the frontside, that is, where there is a complete absence of backside (S_N2) participation by solvent molecules, the mechanism is called *limiting* S_N1. There is kinetic and other evidence[34] that in pulling the leaving group X away from RX, two molecules of a protic solvent form weak hydrogen bonds with X.



In the IUPAC system, the S_N1 mechanism is $D_N + A_N$ or $D_N^{\ddagger} + A_N$ (where ‡ denotes the rate-determining step). The IUPAC designations for the S_N1 and S_N2 mechanisms thus clearly show the essential differences between them: $A_N D_N$ indicates that bond breaking is concurrent with bond formation; $D_N + A_N$ shows that the former happens first.

In looking for evidence for the S_N1 mechanism, the first thought is that it should be a first-order reaction following the rate law:

$$\text{Rate} = k[\text{RX}] \tag{10.3}$$

Since the slow step involves only the substrate, the rate should be dependent only on the concentration of that. Although the solvent is necessary to assist in the process of ionization, it does not enter the rate expression, because it is present in large excess. However, the simple rate law given in Eq. (10.3) is not sufficient to account for all the data. Many cases are known where pure first-order kinetics are followed, but in many other cases more complicated kinetics are found. We can explain this by taking into account the reversibility of the first step. The X formed in this step competes with Y for the cation and the rate law must be modified as shown (see Chapter 6).

$$\begin{gathered}\mathbf{RX} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{R^+ + X} \\ \mathbf{R^+ + Y} \xrightarrow{k_2} \mathbf{RY} \\ \mathbf{Rate} = \frac{k_1 k_2\,[\mathbf{RX}][\mathbf{Y}]}{k_{-1}\,[\mathbf{X}] + k_2\,[\mathbf{Y}]}\end{gathered} \tag{10.4}$$

At the beginning of the reaction, when the concentration of X is very small, k_{-1}[X] is negligible compared with k_2[Y] and the rate law is reduced to Eq. (10.3). Indeed, S_N1 reactions generally do display simple first-order kinetics in their initial stages. Most kinetic studies of S_N1 reactions fall into this category. In the later stages of S_N1 solvolyses, [X] becomes large and Eq. (10.4) predicts that the rate should

[34]Blandamer, M.J.; Burgess, J.; Duce, P.P.; Symons, M.C.R.; Robertson, R.E.; Scott, J.M.W. *J. Chem. Res. (S)* ***1982***, 130.

decrease. This is found to be the case for diarylmethyl halides,[35] although not for *tert*-butylhalides, which follow Eq. (10.3) for the entire reaction.[36] An explanation for this difference is that *tert*-butylcations are less selective than the relatively stable diarylmethyl type (p. 240). Although halide ion is a much more powerful nucleophile than water, there is much more water available since it is the solvent.[37] The selective diphenylmethyl cation survives many collisions with solvent molecules before combining with a reactive halide, but the less selective *tert*-butylion cannot wait for a reactive but relatively rare halide ion and combines with the solvent.

If the X formed during the reaction can decrease the rate, at least in some cases, it should be possible to *add* X from the outside and further decrease the rate in that way. This retardation of rate by addition of X is called *common-ion effect* or the *mass-law effect*. Once again, addition of halide ions decreases the rate for diphenylmethyl but not for *tert*-butylhalides.

One factor that complicates the kinetic picture is the *salt effect*. An increase in ionic strength of the solution usually increases the rate of an S_N1 reaction (p. 501). But when the reaction is of charge type II, where both Y and RX are neutral, so that X is negatively charged (and most solvolyses are of this charge type), the ionic strength increases as the reaction proceeds and this increases the rate. This effect must be taken into account in studying the kinetics. Incidentally, the fact that the addition of outside ions *increases* the rate of most S_N1 reactions makes especially impressive the *decrease* in rate caused by the common ion.

Note that the pseudo-first-order rate law for an S_N2 reaction in the presence of a large excess of Y [Eq. (10.1)] is the same as that for an ordinary S_N1 reaction [Eq. (10.3)]. It is thus not possible to tell these cases apart by simple kinetic measurements. However, we can often distinguish between them by the common-ion effect mentioned above. Addition of a common ion will not markedly affect the rate of an S_N2 reaction beyond the effect caused by other ions. Unfortunately, as we have seen, not all S_N1 reactions show the common-ion effect, and this test fails for *tert*-butyl and similar cases.

Kinetic studies also provide other evidence for the S_N1 mechanism. One technique used ^{19}F NMR to follow the solvolysis of trifluoroacetyl esters.[38] If this mechanism operates essentially as shown on p. 432, the rate should be the same for a given substrate under a given set of conditions, *regardless of the identity of the nucleophile or its concentration*. In one experiment that demonstrates this, benzhydryl chloride (Ph_2CHCl) was treated in SO_2 with the nucleophiles fluoride ion, pyridine, and triethylamine at several concentrations of each nucleophile.[39] In each case the initial rate of the reaction was approximately the same when

[35]Benfey, O.T.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1952***, 2488.

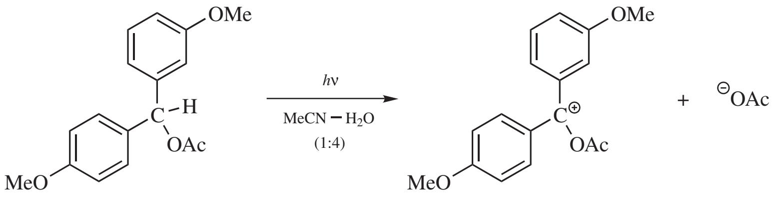
[36]Bateman, L.C.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1940***, 960.

[37]In the experiments mentioned, the solvent was actually "70%" or "80%" aqueous acetone. The "80%" aqueous acetone consists of 4 vol of dry acetone and 1 vol of water.

[38]Creary, X.; Wang, Y.-X. *J. Org. Chem.* ***1992***, *57*, 4761. Also see, Fărcaşiu, D.; Marino, G.; Harris, J.M.; Hovanes, B.A.; Hsu, C.S. *J. Org. Chem.* ***1994***, *59*, 154.

[39]Bateman, L.C.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1940***, 1011.

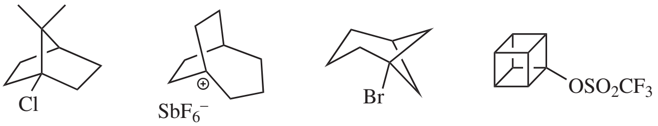
corrections were made for the salt effect. The same type of behavior has been shown in a number of other cases, even when the reagents are as different in their nucleophilicities (see p. 490) as H_2O and HO^-.



10

It is normally not possible to detect the carbocation intermediate of an S_N1 reaction directly, because its lifetime is very short. However, in the case of 3,4-dimethoxydiphenylmethyl acetate (**10**) and certain other substrates in polar solvents it was possible to initiate the reaction photolytically, and under these conditions the UV spectra of the intermediate carbocations could be obtained,[40] providing additional evidence for the S_N1 mechanism.

Further evidence for the S_N1 mechanism is that reactions run under S_N1 conditions fail or proceed very slowly at the bridgehead positions[10] of [2.2.1] (norbornyl) systems[41] (e.g., 1-chloroapocamphane, **8**). If S_N1 reactions require carbocations



11 **12** **13** **14**

and if carbocations must be planar or nearly planar, then it is no surprise that bridgehead 1-norbornyl carbon atoms, which cannot assume planarity, do not become the seat of carbocations. As an example, **11**, boiled 21 h with 30% KOH in 80% ethanol or 48 h with aqueous ethanolic silver nitrate, gave no reaction in either case,[42] although analogous open-chain systems reacted readily. According to this theory, S_N1 reactions should be possible with larger rings, since near-planar carbocations might be expected there. This turns out to be the case. For example, [2.2.2] bicyclic systems undergo S_N1 reactions much faster than smaller bicyclic systems, although the reaction is still slower than with open-chain systems.[43] Proceeding to a still larger system, the bridgehead [3.2.2] cation **12** is actually stable enough to be kept in solution in SbF_5–SO_2ClF at temperatures below −50°C[44] (see also, p. 486). Other small bridgehead systems that undergo S_N1 reactions are the

[40]McClelland, R.A.; Kanagasabapathy, V.M.; Steenken, S. *J. Am. Chem. Soc.* ***1988***, *110*, 6913.

[41]For a review, see Fort, Jr., R.C., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 4; Wiley, NY, ***1973***, pp. 1783–1835.

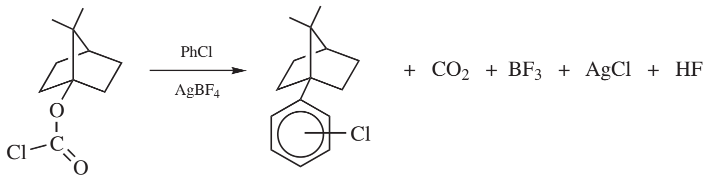
[42]Bartlett, P.D.; Knox, L.H. *J. Am. Chem. Soc.* ***1939***, *61*, 3184.

[43]For synthetic examples, see Kraus, G.A.; Hon, Y. *J. Org. Chem.* ***1985***, *50*, 4605.

[44]Olah, G.A.; Liang, G.; Wiseman, J.R.; Chong, J.A. *J. Am. Chem. Soc.* ***1972***, *74*, 4927.

[3.1.1] (e.g., **13**)[45] and the cubyl (e.g., **14**)[46] systems. *Ab initio* calculations show that the cubyl cation, although it cannot be planar, requires less energy to form than the 1-norbornyl cation.[47] There are reactions where the cationic carbon is not coplanar with conjugating substituents (such as phenyl), and formation of the carbocation is more difficult but the reaction proceeds.[48]

Certain nucleophilic substitution reactions that normally involve carbocations can take place at norbornyl bridgeheads[49] (though it is not certain that carbocations are actually involved in all cases) if the leaving group used is of the type that cannot function as a nucleophile (and thus come back) once it has gone, and in the displacement of $ClCO_2$ in **15**. In this example,[50] chlorobenzene is the nucleophile (see **11-10**).



15

Additional evidence for the S_N1 mechanism, in particular, for the intermediacy of carbocations, is that solvolysis rates of alkyl chlorides in ethanol parallel carbocation stabilities as determined by heats of ionization measured in superacid solutions (p. 236).[51] It is important to note that some solvolysis reactions proceed by an S_N2 mechanism.[52]

Ion Pairs in the S_N1 Mechanism[53]

Like the kinetic evidence, the stereochemical evidence for the S_N1 mechanism is less clear-cut than it is for the S_N2 mechanism.[54] If there is a free carbocation, it is planar (p. 245), and the nucleophile should attack with equal facility from either

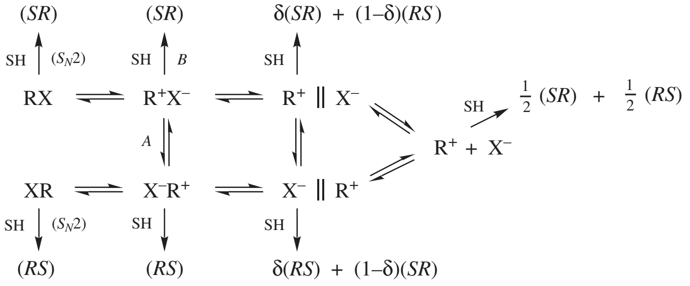
[45]Della, E.W.; Pigou, P.E.; Tsanaktsidis, J. *J. Chem. Soc., Chem. Commun.* ***1987***, 833.
[46]Eaton, P.E.; Yang, C.; Xiong, Y. *J. Am. Chem. Soc.* ***1990***, *112*, 3225; Moriarty, R.M.; Tuladhar, S.M.; Penmasta, R.; Awasthi, A.K. *J. Am. Chem. Soc.* ***1990***, *112*, 3228.
[47]Hrovat, D.A.; Borden, W.T. *J. Am. Chem. Soc.* ***1990***, *112*, 3227.
[48]Lee, I.; Kim, N.D.; Kim, C.K. *Tetrahedron Lett.* ***1992***, *33*, 7881.
[49]Bartlett, P.D.; Knox, L.H. *J. Am. Chem. Soc.* ***1939***, *61*, 3184; Clive, D.L.J.; Denyer, C.V. *Chem. Commun.* ***1971***, 1112; White, E.H.; McGirk, R.H.; Aufdermarsh, Jr., C.A.; Tiwari, H.P.; Todd, M.J. *J. Am. Chem. Soc.* ***1973***, *95*, 8107; Beak, P.; Harris, B.R. *J. Am. Chem. Soc.* ***1974***, *96*, 6363.
[50]For a review of reactions with the OCOCl leaving group, see Beak, P. *Acc. Chem. Res.* ***1976***, *9*, 230.
[51]Arnett, E.M.; Petro, C.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1979***, *101*, 522; Arnett, E.M.; Pienta, N.J. *J. Am. Chem. Soc.* ***1980***, *102*, 3329; Arnett, E.M.; Molter, K.E. *Acc. Chem. Res.* ***1985***, *18*, 339.
[52]Lee, I.; Lee, Y.S.; Lee, B.-S.; Lee, H.W. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 1441.
[53]For reviews of ion pairs in S_N reactions, see Beletskaya, I.P. *Russ. Chem. Rev.* ***1975***, *44*, 1067; Harris, J.M. *Prog. Phys. Org. Chem.* ***1974***, *11*, 89; Raber, D.J.; Harris, J.M.; Schleyer, P.v.R., in Szwarc, M. *Ions and Ion Pairs in Organic Reactions*, Vol. 2; Wiley, NY, ***1974***, pp. 247–374.
[54]For an alternative view of the S_N1/S_N2 mechanism see Uggerud, E. *J. Org. Chem.* ***2001***, *66*, 7084.

side of the plane, resulting in complete racemization. Although many first-order substitutions do give complete racemization, many others do not. Typically there is 5–20% inversion, although in a few cases, a small amount of retention of configuration has been found. These and other results have led to the conclusion that in many S_N1 reactions at least some of the products are not formed from free carbocations but rather from *ion pairs*. According to this concept,[55] S_N1 reactions proceed in this manner:

$$\underset{}{R{-}X} \rightleftharpoons \underset{\mathbf{16}}{R^+X^-} \rightleftharpoons \underset{\mathbf{17}}{R^+\|X^-} \rightleftharpoons \underset{\mathbf{18}}{R^+ + X^-}$$

where **16** is an *intimate*, *contact*, or *tight* ion pair, **17** a *loose*, or *solvent-separated* ion pair, and **18** the dissociated ions (each surrounded by molecules of solvent).[56] The reaction in which the intimate ion pair recombines to give the original substrate is referred to as *internal return*. The reaction products can result from attack by the nucleophile at any stage. In the intimate ion pair **16**, R^+ does not behave like the free cation of **18**. There is probably significant bonding between R^+ and X^- and asymmetry may well be maintained.[57] Here, X^- "solvates" the cation on the side from which it departed, while solvent molecules near **16** can only solvate it from the opposite side. Nucleophilic attack by a solvent molecule on **16** thus leads to inversion.

Ignoring the possibilities of elimination or rearrangement (see Chapters 17 and 18), a complete picture of the possibilities for solvolysis reactions[58] in a solvent SH is represented by following diagram,[59] although in any particular case it is unlikely that all these reactions occur:



[55]Proposed by Winstein, S.; Clippinger, E.; Fainberg, A.H.; Heck, R.; Robinson, G.C. *J. Am. Chem. Soc.* ***1956***, *78*, 328.

[56]For a review of the energy factors involved in the recombination of ion pairs, see Kessler, H.; Feigel, M. *Acc. Chem. Res.* ***1982***, *15*, 2.

[57]Fry, J.L.; Lancelot, C.J.; Lam, L.K.M.; Harris, J.M.; Bingham, R.C.; Raber, D.J.; Hall, R.E.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1970***, *92*, 2538.

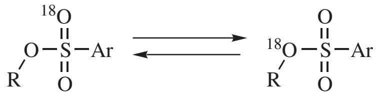
[58]For solvolysis of tertiary derivatives with a discussion of solvent participation versus solvation see Richard, J.P.; Toteva, M.M.; Amyes, T.L. *Org. Lett.* ***2001***, *3*, 2225.

[59]Shiner, Jr., V.J.; Fisher, R.D. *J. Am. Chem. Soc.* ***1971***, *93*, 2553.

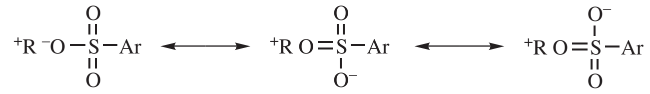
In this scheme RS and SR represent enantiomers, and so on, and δ represents some fraction. The following are the possibilities: (*1*) Direct attack by SH on RX gives SR (complete inversion) in a straight S_N2 process. (*2*) If the intimate ion pair $R^+ X^-$ is formed, the solvent can attack at this stage. This can lead to total inversion if reaction A does not take place or to a combination of inversion and racemization if there is competition between A and B. (*3*) If the solvent-separated ion pair is formed, SH can attack here. The stereochemistry is not maintained as tightly and more racemization (perhaps total) is expected. (*4*) Finally, if free R^+ is formed, it is planar, and attack by SH gives complete racemization.

The ion-pair concept thus predicts that S_N1 reactions can display either complete racemization or partial inversion. The fact that this behavior is generally found is evidence that ion pairs are involved in many S_N1 reactions. There is much other evidence for the intervention of ion pairs,[60] includng ion-molecule pairs.[61]

1. The compound 2-octyl brosylate was labeled at the sulfone oxygen with ^{18}O and solvolyzed. The unreacted brosylate recovered at various stages of solvolysis had the ^{18}O considerably, although not completely, scrambled:[62]



In an intimate ion pair, the three oxygens become equivalent:



Similar results were obtained with several other sulfonate esters.[63] The possibility must be considered that the scrambling resulted from ionization

[60]For further evidence beyond that given here, see Winstein, S.; Baker, R.; Smith, S. *J. Am. Chem. Soc.* ***1964***, *86*, 2072; Streitwieser, Jr., A.; Walsh, T.D. *J. Am. Chem. Soc.* ***1965***, *87*, 3686; Sommer, L.H.; Carey, F.A. *J. Org. Chem.* ***1967***, *32*, 800, 2473; Kwart, H.; Irvine, J.L. *J. Am. Chem. Soc.* ***1969***, *91*, 5541; Harris, J.M.; Becker, A.; Fagan, J.F.; Walden, F.A. *J. Am. Chem. Soc.* ***1974***, *96*, 4484; Bunton, C.A.; Huang, S.K.; Paik, C.H. *J. Am. Chem. Soc.* ***1975***, *97*, 6262; Humski, K.; Sendijarević, V.; Shiner, Jr., V.J. *J. Am. Chem. Soc.* ***1976***, *98*, 2865; Maskill, H.; Thompson, J.T.; Wilson, A.A. *J. Chem. Soc., Chem. Commun.* ***1981***, 1239; McManus, S.P.; Safavy, K.K.; Roberts, F.E. *J. Org. Chem.* ***1982***, *47*, 4388; McLennan, D.J.; Stein, A.R.; Dobson, B. *Can. J. Chem.* ***1986***, *64*, 1201; Kinoshita, T.; Komatsu, K.; Ikai, K.; Kashimura, K.; Tanikawa, S.; Hatanaka, A.; Okamoto, K. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 1875; Ronco, G.; Petit, J.; Guyon, R.; Villa, P. *Helv. Chim. Acta* ***1988***, *71*, 648; Kevill, D.N.; Kyong, J.B.; Weitl, F.L. *J. Org. Chem.* ***1990***, *55*, 4304.

[61]Jia, Z.S.; Ottosson, H.; Zeng, X.; Thibblin, A. *J. Org. Chem.* ***2002***, *67*, 182.

[62]Diaz, A.F.; Lazdins, I.; Winstein, S. *J. Am. Chem. Soc.* ***1968***, *90*, 1904.

[63]Goering, H.L.; Jones, B.E. *J. Am. Chem. Soc.* ***1980***, *102*, 1628; Yukawa, Y.; Morisaki, H.; Tsuji, K.; Kim, S.; Ando, T. *Tetrahedron Lett.* ***1981***, *22*, 5187; Chang, S.; le Noble, W.J. *J. Am. Chem. Soc.* ***1983***, *105*, 3708; Paradisi, C.; Bunnett, J.F. *J. Am. Chem. Soc.* ***1985***, *107*, 8223; Fujio, M.; Sanematsu, F.; Tsuno, Y.; Sawada, M.; Takai, Y. *Tetrahedron Lett.* ***1988***, *29*, 93.

of one molecule of $ROSO_2Ar$ to R^+ and $ArSO_2O^-$ followed by attack by the $ArSO_2O^-$ ion on *another* carbocation or perhaps on a molecule of $ROSO_2Ar$ in an S_N2 process. However, this was ruled out by solvolyzing unlabeled substrate in the presence of labeled $HOSO_2Ar$. These experiments showed that there was some intermolecular exchange (3–20%), but not nearly enough to account for the amount of scrambling found in the original experiments. Similar scrambling was found in solvolysis of labeled carboxylic esters R—^{18}O—COR′, where the leaving group is R′COO$^-$.[64] In this case also, the external addition of RCOO$^-$ did not result in significant exchange. However, it has been proposed that the scrambling could result from a concerted process, not involving ion-pair intermediates, and there is some evidence for this view.[65]

2. The *special salt effect*. The addition of $LiClO_4$ or LiBr in the acetolysis of certain tosylates produced an initial steep rate acceleration that then decreased to the normal linear acceleration (caused by the ordinary salt effect).[66] This is interpreted as follows: the ClO_4^- (or Br^-) traps the solvent-separated ion pair to give $R^+ \parallel ClO_4^-$ which, being unstable under these conditions, goes to product. Hence, the amount of solvent-separated ion pair that would have returned to the starting material is reduced, and the rate of the overall reaction is increased. The special salt effect has been directly observed by the use of picosecond absorption spectroscopy.[67]

3. We have previously discussed the possibilities of racemization or inversion of the *product* RS of a solvolysis reaction. However, the formation of an ion pair followed by internal return can also affect the stereochemistry of the *substrate* molecule RX. Cases have been found where internal return racemizes an original optically active RX, an example being solvolysis in aqueous acetone of α-*p*-anisylethyl *p*-nitrobenzoate,[68] while in other cases partial or complete retention is found, for example, solvolysis in aqueous acetone of *p*-chlorobenzhydryl *p*-nitrobenzoate.[69] Racemization of RX is presumably caused by the equilibrium pathway: $RX \rightleftharpoons R^+X^- \rightleftharpoons X^-R^+ \rightleftharpoons XR$. Evidence for ion pairs is that, in some cases where internal return involves racemization, it has been shown that such racemization is *faster* than solvolysis. For example, optically active *p*-chlorobenzhydryl chloride racemizes ~30 times faster than it solvolyzes in acetic acid.[70]

[64]Goering, H.L.; Hopf, H. *J. Am. Chem. Soc.* ***1971***, *93*, 1224, and references cited therein.

[65]Dietze, P.E.; Wojciechowski, M. *J. Am. Chem. Soc.* ***1990***, *112*, 5240.

[66]Winstein, S.; Clippinger, E.; Fainberg, A.H.; Heck, R.; Robinson, G.C. *J. Am. Chem. Soc.* ***1956***, *78*, 328; Winstein, S.; Klinedinst, Jr., P.E.; Clippinger, E. *J. Am. Chem. Soc.* ***1961***, *83*, 4986; Cristol, S.J.; Noreen, A.L.; Nachtigall, G.W. *J. Am. Chem. Soc.* ***1972***, *94*, 2187.

[67]Simon, J.D.; Peters, K.S. *J. Am. Chem. Soc.* ***1982***, *104*, 6142.

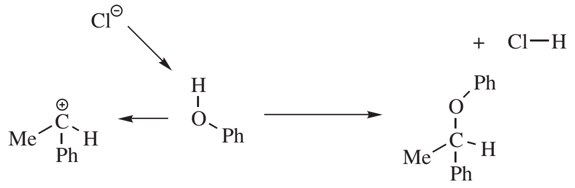
[68]Goering, H.L.; Briody, R.G.; Sandrock, G. *J. Am. Chem. Soc.* ***1970***, *92*, 7401.

[69]Goering, H.L.; Briody, R.G.; Levy, J.F. *J. Am. Chem. Soc.* ***1963***, *85*, 3059.

[70]Winstein, S.; Gall, J.S.; Hojo, M.; Smith, S. *J. Am. Chem. Soc.* ***1960***, *82*, 1010. See also, Shiner, Jr., V.J.; Hartshorn, S.R.; Vogel, P.C. *J. Org. Chem.* ***1973***, *38*, 3604.

Molecular orbital calculations[71] made on *t*-BuCl show that the C—Cl distance in the intimate ion pair is 2.9 Å and the onset of the solvent-separated ion pair takes place at about 5.5 Å (cf. the C—Cl bond length of 1.8 Å).

In a few cases, S_N1 reactions have been found to proceed with partial retention (20–50%) of configuration. Ion pairs have been invoked to explain some of these.[72] For example, it has been proposed that the phenolysis of optically active α-phenylethyl chloride, in which the ether of net retained configuration is obtained, involves a four-center mechanism:



This conclusion is strengthened by the fact that partial retention was obtained in this system only with chloride or other neutral leaving groups; with leaving groups bearing a positive charge, which are much less likely to form hydrogen bonds with the solvent, no retention was found.[73] Partial retention can also arise when the ion pair is shielded at the backside by an additive such as acetonitrile, acetone, or aniline.[74]

The difference between the S_N1 and S_N2 mechanisms is in the timing of the steps. In the S_N1 mechanism, first X leaves, then Y attacks. In the S_N2 case, the two things happen simultaneously. One could imagine a third possibility: first the attack of Y and then the removal of X. This is not possible at a saturated carbon, since it would mean more than eight electrons in the outer shell of carbon. However, this type of mechanism is possible and indeed occurs at other types of substrate (p. 473; Chapter 13).

Mixed S_N1 and S_N2 Mechanisms

Some reactions of a given substrate under a given set of conditions display all the characteristics of S_N2 mechanisms; other reactions seem to proceed by S_N1 mechanisms, but cases are found that cannot be characterized so easily. There seems to be something in between, a mechanistic "borderline" region.[75] At least two broad

[71]Jorgensen, W.L.; Buckner, J.K.; Huston, S.E.; Rossky, P.J. *J. Am. Chem. Soc.* ***1987***, *109*, 1891.
[72]Okamoto, K. *Pure Appl. Chem.* ***1984***, *56*, 1797. For a similar mechanism with amine nucleophiles, see Lee, I.; Kim, H.Y.; Kang, H.K.; Lee, H.W. *J. Org. Chem.* ***1988***, *53*, 2678; Lee, I.; Kim, H.Y.; Lee, H.W.; Kim, I.C. *J. Phys. Org. Chem.* ***1989***, *2*, 35.
[73]Okamoto, K.; Kinoshita, T.; Shingu, H. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 1545.
[74]Okamoto, K.; Nitta, I.; Dohi, M.; Shingu, H. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 3220; Kinoshita, T.; Ueno, T.; Ikai, K.; Fujiwara, M.; Okamoto, K. *Bull. Chem. Soc. Jpn.* ***1988***, *61*, 3273; Kinoshita, T.; Komatsu, K.; Ikai, K.; Kashimura, K.; Tanikawa, S.; Hatanaka, A.; Okamoto, K. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 1875.
[75]For an essay on borderline mechanisms in general, see Jencks, W.P. *Chem. Soc. Rev.* ***1982***, *10*, 345.

theories have been devised to explain these phenomena. One theory holds that intermediate behavior is caused by a mechanism that is neither "pure" S_N1 nor "pure" S_N2, but some "in-between" type. According to the second theory, there is no intermediate mechanism at all, and borderline behavior is caused by simultaneous operation, in the same flask, of both the S_N1 and S_N2 mechanisms; that is, some molecules react by the S_N1, while others react by the S_N2 mechanism.

One formulation of the intermediate-mechanism theory is that of Sneen.[76] The formulation is in fact very broad and applies not only to borderline behavior but to all nucleophilic substitutions at a saturated carbon.[77] According to Sneen, all S_N1 and S_N2 reactions can be accommodated by one basic mechanism (the *ion-pair mechanism*). The substrate first ionizes to an intermediate ion pair that is then converted to products:

$$\text{RX} \underset{}{\overset{k_1}{\rightleftharpoons}} \text{R}^+\ \text{X}^- \underset{}{\overset{k_2}{\rightleftharpoons}} \text{Products}$$

The difference between the S_N1 and S_N2 mechanisms is that in the former case the *formation* of the ion pair (k_1) is rate determining, while in the S_N2 mechanism its *destruction* (k_2) is rate determining. Borderline behavior is found where the rates of formation and destruction of the ion pair are of the same order of magnitude.[78] However, a number of investigators have asserted that these results could also be explained in other ways.[79]

There is evidence for the Sneen formulation where the leaving group has a positive charge. In this case, there is a cation–molecule pair ($RX^+ \rightarrow R^+X$)[80] instead of the ion pair that would be present if the leaving group were uncharged. Katritzky

[76]Sneen, R.A.; Felt, G.R.; Dickason, W.C. *J. Am. Chem. Soc.* ***1973***, *95*, 638 and references cited therein; Sneen, R.A. *Acc. Chem. Res.* ***1973***, *6*, 46.

[77]Including substitution at an allylic carbon; see Sneen, R.A.; Bradley, W.A. *J. Am. Chem. Soc.* ***1972***, *94*, 6975; Sneen, R.A.; Carter, J.V. *J. Am. Chem. Soc.* ***1972***, *94*, 6990; Bordwell, F.G.; Mecca, T.G. *J. Am. Chem. Soc.* ***1975***, *97*, 123, 127; Bordwell, F.G.; Wiley, P.F.; Mecca, T.G. *J. Am. Chem. Soc.* ***1975***, *97*, 132; Kevill, D.N.; Degenhardt, C.R. *J. Am. Chem. Soc.* ***1979***, *101*, 1465.

[78]For evidence for this point of view, see Sneen, R.A.; Felt, G.R.; Dickason, W.C. *J. Am. Chem. Soc.* ***1973***, *95*, 638 and references cited therein; Sneen, R.A. *Acc. Chem. Res.* ***1973***, *6*, 46; Robbins, H.M. *J. Am. Chem. Soc.* ***1972***, *94*, 7868; Graczyk, D.G.; Taylor, J.W. *J. Am. Chem. Soc.* ***1974***, *96*, 3255; Peeters, H.L.; Anteunis, M. *J. Org. Chem.* ***1975***, *40*, 312; Pross, A.; Aronovitch, H.; Koren, R. *J. Chem. Soc. Perkin Trans. 2* ***1978***, 197; Blandamer, M.J.; Robertson, R.E.; Scott, J.M.W.; Vrielink, A. *J. Am. Chem. Soc.* ***1980***, *102*, 2585; Stein, A.R. *Can. J. Chem.* ***1987***, *65*, 363.

[79]See, for example, Gregory, B.J.; Kohnstam, G.; Queen, A.; Reid, D.J. *Chem. Commun.* ***1971***, 797; Raber, D.J.; Harris, J.C.; Hall, R.E.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1971***, *93*, 4821; McLennan, D.J. *Acc. Chem. Res.* ***1976***, *9*, 281; McLennan, D.J.; Martin, P.L. *Tetrahedron Lett.* ***1973***, 4215; Raaen, V.F.; Juhlke, T.; Brown, F.J.; Collins, C.J. *J. Am. Chem. Soc.* ***1974***, *96*, 5928; Gregoriou, G.A. *Tetrahedron Lett.* ***1976***, 4605, 4767; Queen, A.; Matts, T.C. *Tetrahedron Lett.* ***1975***, 1503; Stein, A.R. *J. Org. Chem.* ***1976***, *41*, 519; Stephan, E. *Bull. Soc. Chim. Fr.* ***1977***, 779; Katritzky, A.R.; Musumarra, G.; Sakizadeh, K. *J. Org. Chem.* ***1981***, *46*, 3831. For a reply to some of these objections, see Sneen, R.A.; Robbins, H.M. *J. Am. Chem. Soc.* ***1972***, *94*, 7868. For a discussion, see Klumpp, G.W. *Reactivity in Organic Chemistry*, Wiley, NY, ***1982***, pp. 442–450.

[80]For ion-molecule pairs in other solvolysis reactions, see Thibblin, A. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 1629.

and co-workers found that when such a reaction was run at varying high pressures, there was a minimum in the plot of rate constant versus pressure.[81] A minimum of this sort usually indicates a change in mechanism, and the interpretation in this case was that the normal S_N2 mechanism operates at higher pressures and the cation–molecule mechanism at lower pressures.

An alternative view that also favors an intermediate mechanism is that of Schleyer and co-workers,[82] who believe that the key to the problem is varying degrees of nucleophilic solvent assistance to ion-pair formation. They have proposed an S_N2(intermediate) mechanism.[83]

Among the experiments that have been cited for the viewpoint that borderline behavior results from simultaneous S_N1 and S_N2 mechanisms is the behavior of 4-methoxybenzyl chloride in 70% aqueous acetone.[84] In this solvent, hydrolysis (that is, conversion to 4-methoxybenzyl alcohol) occurs by an S_N1 mechanism. When azide ions are added, the alcohol is still a product, but now 4-methoxybenzyl azide is another product. Addition of azide ions increases the rate of ionization (by the salt effect) but *decreases* the rate of hydrolysis. If more carbocations are produced but fewer go to the alcohol, then some azide must be formed by reaction with carbocations: an S_N1 process. However, the rate of ionization is always *less* than the total rate of reaction, so some azide must also form by an S_N2 mechanism.[84] Thus, the conclusion is that S_N1 and S_N2 mechanisms operate simultaneously.[85]

Some nucleophilic substitution reactions that seem to involve a "borderline" mechanism actually do not. Thus, one of the principal indications that a "borderline" mechanism is taking place has been the finding of partial racemization and partial inversion. However, Weiner and Sneen have demonstrated that this type of stereochemical behavior is quite consistent with a strictly S_N2 process. These workers studied the reaction of optically active 2-octyl brosylate in 75% aqueous dioxane, under which conditions inverted 2-octanol was obtained in 77% optical purity.[86] When

[81]Katritzky, A.R.; Sakizadeh, K.; Gabrielsen, B.; le Noble, W.J. *J. Am. Chem. Soc.* ***1984***, *106*, 1879.

[82]Bentley, T.W.; Bowen, C.T.; Morten, D.H.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1981***, *103*, 5466.

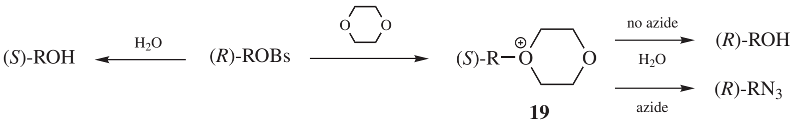
[83]For additional evidence for this view, see Laureillard, J.; Casadevall, A.; Casadevall, E. *Tetrahedron* ***1984***, *40*, 4921; *Helv. Chim. Acta* ***1984***, *67*, 352; McLennan, D.J. *J. Chem. Soc. Perkin Trans. 2* ***1981***, 1316. For evidence against the S_N2 (intermediate) mechanism, see Allen, A.D.; Kanagasabapathy, V.M.; Tidwell, T.T. *J. Am. Chem. Soc.* ***1985***, *107*, 4513; Fǎrcaşiu, D.; Jähme, J.; Rüchardt, C. *J. Am. Chem. Soc.* ***1985***, *107*, 5717; Dietze, P.E.; Jencks, W.P. *J. Am. Chem. Soc.* ***1986***, *108*, 4549; Dietze, P.E.; Hariri, R.; Khattak, J. *J. Org. Chem.* ***1989***, *54*, 3317; Coles, C.J.; Maskill, H. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 1083; Richard, J.P.; Amyes, T.L.; Vontor, T. *J. Am. Chem. Soc.* ***1991***, *113*, 5871.

[84]Kohnstam, G.; Queen, A.; Shillaker, B. *Proc. Chem. Soc.* ***1959***, 157; Amyes, T.L.; Richard, J.P. *J. Am. Chem. Soc.* ***1990***, *112*, 9507. For other evidence supporting the concept of simultaneous mechanisms, see Pocker, Y. *J. Chem. Soc.* ***1959***, 3939, 3944; Casapieri, P.; Swart, E.R. *J. Chem. Soc.* ***1963***, 1254; Ceccon, A.; Papa, I.; Fava, A. *J. Am. Chem. Soc.* ***1966***, *88*, 4643; Okamoto, K.; Uchida, N.; Saitô, S.; Shingu, H. *Bull. Chem. Soc. Jpn.* ***1966***, *39*, 307; Guinot, A.; Lamaty, G. *Chem. Commun.* ***1967***, 960; Queen, A. *Can. J. Chem.* ***1979***, *57*, 2646; Richard, J.P.; Rothenberg, M.E.; Jencks, W.P. *J. Am. Chem. Soc.* ***1984***, *106*, 1361; Richard, J.P.; Jencks, W.P. *J. Am. Chem. Soc.* ***1984***, *106*, 1373, 1383; Katritzky, A.R.; Brycki, B.E. *J. Phys. Org. Chem.* ***1988***, *1*, 1; Stein, A.R. *Can. J. Chem.* ***1989***, *67*, 297.

[85]These data have also been explained as being in accord with the ion-pair mechanism: Sneen, R.A.; Larsen, J.W. *J. Am. Chem. Soc.* ***1969***, *91*, 6031.

[86]Weiner, H.; Sneen, R.A. *J. Am. Chem. Soc.* ***1965***, *87*, 287.

sodium azide was added, 2-octyl azide was obtained along with the 2-octanol, *but the latter was now 100% inverted.* It is apparent that, in the original case, 2-octanol was produced by two different processes: an S_N2 reaction leading to inverted product, and another process in which some intermediate leads to racemization or retention. When azide ions were added, they scavenged this intermediate, so that the entire second process now went to produce azide, while the S_N2 reaction, unaffected by addition of azide, still went on to give inverted 2-octanol. What is the nature of the intermediate in the second process? At first thought we might suppose that it is a carbocation, so that this would be another example of simultaneous S_N1 and S_N2 reactions. However, solvolysis of 2-octyl brosylate in pure methanol or of 2-octyl methanesulfonate in pure water, in the absence of azide ions, gave methyl 2-octyl ether or 2-octanol, respectively, *with 100% inversion of configuration*, indicating that the mechanism in these solvents was pure S_N2. Since methanol and water are more polar than 75% aqueous dioxane and since an increase in polarity of solvent increases the rate of S_N1 reactions at the expense of S_N2 (p. 500), it is extremely unlikely that any S_N1 process could occur in 75% aqueous dioxane. The intermediate in the second process is thus not a carbocation. It's nature is suggested by the fact that, in the absence of azide ions, the amount of inverted 2-octanol decreased with an increasing percentage of dioxane in the solvent. Thus the intermediate is an oxonium ion (**19**) formed by an S_N2 attack *by dioxane*. This ion is not a stable product but reacts with water in another S_N2 process to produce 2-octanol with retained configuration.



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That part of the original reaction that resulted in retention of configuration[87] is thus seen to stem from two successive S_N2 reactions and not from any "borderline" behavior.[88]

SET MECHANISMS

In certain reactions where nucleophilic substitutions would seem obviously indicated, there is evidence that radicals and/or radical ions are actually involved.[89]

[87]According to this scheme, the configuration of the isolated RN_3 should be retained. It was, however, largely inverted, owing to a competing S_N2 reaction where N_3^- directly attacks ROBs.

[88]For other examples, see Streitwieser, Jr., A.; Walsh, T.D.; Wolfe, Jr., J.R. *J. Am. Chem. Soc.* ***1965***, *87*, 3682; Streitwieser, Jr., A.; Walsh, T.D. *J. Am. Chem. Soc.* ***1965***, *87*, 3686; Beronius, P.; Nilsson, A.; Holmgren, A. *Acta Chem. Scand.* ***1972***, *26*, 3173. See also, Knier, B.L.; Jencks, W.P. *J. Am. Chem. Soc.* ***1980***, *102*, 6789.

[89]Kornblum, N.; Michel, R.E.; Kerber, R.C. *J. Am. Chem. Soc.* ***1966***, *88*, 5660, 5662; Russell, G.A.; Danen, W.C. *J. Am. Chem. Soc.* ***1966***, *88*, 5663; Bank, S.; Noyd, D.A. *J. Am. Chem. Soc.* ***1973***, *95*, 8203; Ashby, E.C.; Goel, A.B.; Park, W.S. *Tetrahedron Lett.* ***1981***, *22*, 4209. For discussions of the relationship between S_N2 and SET mechanisms, see Lewis, E.S. *J. Am. Chem. Soc.* ***1989***, *111*, 7576; Shaik, S.S. *Acta Chem. Scand.* ***1990***, *44*, 205.

The first step in such a process is transfer of an electron from the nucleophile to the substrate to form a radical anion:

$$\text{Step 1} \qquad \text{R–X} + \bar{\text{Y}}^- \longrightarrow \text{R–X}^{\bullet -} + \text{Y}^\bullet$$

Mechanisms that begin this way are called SET *(single electron transfer) mechanisms.*[90] Once formed, the radical ion cleaves:

$$\text{Step 2} \qquad \text{R–X}^{\bullet -} \longrightarrow \text{R}^\bullet + \bar{\text{X}}^-$$

The radicals formed in this way can go on to product by reacting with the Y• produced in Step 1 or with the original nucleophilic ion Y^-, in which case an additional step is necessary:

$$\text{Step 3} \qquad \text{R}^\bullet + \text{Y}^\bullet \longrightarrow \text{R–Y}$$

or

$$\text{Step 3} \qquad \text{R}^\bullet + \bar{\text{Y}}^- \longrightarrow \text{R–Y}^{\bullet -}$$

$$\text{Step 4} \qquad \text{R–Y}^{\bullet -} + \text{R–X} \longrightarrow \text{R–Y} + \text{R–X}^{\bullet -}$$

In the latter case, the radical ion $R–X^{\bullet -}$ is formed by Step 4 as well as by Step 1, so that a chain reaction (p. 936) can take place.

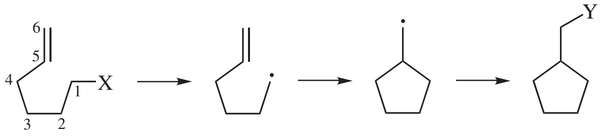
One type of evidence for an SET mechanism is the finding of some racemization. A totally free radical would of course result in a completely racemized product RY, but it has been suggested[91] that inversion can also take place in some SET processes. The suggestion is that in Step 1 the Y^- still approaches from the back side, even although an ordinary S_N2 mechanism will not follow, and that the radical R•, once formed, remains in a solvent cage with Y• still opposite X^-, so that Steps 1, 2, and 3 can lead to inversion.

$$\bar{\text{Y}}^- + \text{R–X} \longrightarrow \underbrace{[\text{Y}^\bullet\ \text{R–X}^{\bullet -}]}_{\text{Solvent cage}} \longrightarrow \underbrace{[\text{Y}^\bullet\ \text{R}^\bullet\ \text{X}^-]}_{\text{Solvent cage}} \longrightarrow \text{Y–R} + \bar{\text{X}}^-$$

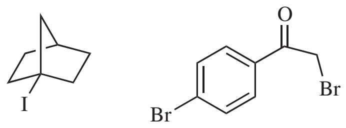
Reactions with SET mechanisms typically show predominant, although not 100%, inversion.

[90]For reviews, see Savéant, J. *Adv. Phys. Org. Chem.* ***1990***, *26*, 1; Rossi, R.A.; Pierini, A.B.; Palacios, S.M. *J. Chem. Educ.* ***1989***, *66*, 720; Ashby, E.C. *Acc. Chem. Res.* ***1988***, *21*, 414; Chanon, M.; Tobe, M.L. *Angew. Chem. Int. Ed.* ***1982***, *21*, 1. See also, Pross, A. *Acc. Chem. Res.* ***1985***, *18*, 212; Chanon, M. *Acc. Chem. Res.* ***1987***, *20*, 214. See Rossi, R.A.; Pierini, A.B.; Peñéñory, A.B. *Chem. Rev.* ***2003***, *103*, 71.
[91]Ashby, E.C.; Pham, T.N. *Tetrahedron Lett.* ***1987***, *28*, 3183; Daasbjerg, K.; Lund, T.; Lund, H. *Tetrahedron Lett.* ***1989***, *30*, 493.

Other evidence cited[92] for SET mechanisms has been detection of radical or radical ion intermediates by esr[93] or CIDNP; the finding that such reactions can take place at 1-norbornyl bridgeheads;[94] and the formation of cyclic side products when the substrate has a double bond in the 5,6 position (such substrates are called *radical probes*).



Free radicals with double bonds in this position are known to cyclize readily (p. 1011).[95]



20 **21**

The SET mechanism is chiefly found, where X = I or NO_2 (see **10-67**). A closely related mechanism, the $S_{RN}1$, takes place with aromatic substrates (Chapter 13).[96] In that mechanism, the initial attack is by an electron donor, rather than a nucleophile. The $S_{RN}1$ mechanism has also been invoked for reactions of enolate anions with 2-iodobicyclo[4.1.0]heptane.[97] An example is the reaction of 1-iodobicyclo[2.2.1]heptane (**20**) with $NaSnMe_3$ or $LiPPh_2$, and some other nucleophiles, to give the substitution product.[98] Another is the reaction of bromo 4-bromoacetophenone (**21**) with Bu_4NBr in cumene.[99] The two mechanisms, S_N2 versus SET, have been compared and contrasted.[100] There are also reactions where it is reported that radical, carbanion, and carbene pathways occur simultaneously.[101]

[92]See also, Chanon, M.; Tobe, M.L. *Angew. Chem. Int. Ed.* ***1982***, *21*, 1; Fuhlendorff, R.; Lund, T.; Lund, H.; Pedersen, J.A. *Tetrahedron Lett.* ***1987***, *28*, 5335.

[93]See, for example Russell, J.A.; Pecoraro, J.M. *J. Am. Chem. Soc.* ***1979***, *101*, 3331.

[94]Santiago, A.N.; Morris, D.G.; Rossi, R.A. *J. Chem. Soc., Chem. Commun.* ***1988***, 220.

[95]For criticisms of this method for demonstrating SET mechanisms, see Newcomb, M.; Kaplan, J. *Tetrahedron Lett.* ***1988***, *29*, 3449; Newcomb, M.; Curran, D.P. *Acc. Chem. Res.* ***1988***, *21*, 206; Newcomb, M. *Acta Chem. Scand.* ***1990***, *44*, 299. For replies to the criticism, see Ashby, E.C. *Acc. Chem. Res.* ***1988***, *21*, 414; Ashby, E.C.; Pham, T.N.; Amrollah-Madjdabadi, A.A. *J. Org. Chem.* ***1991***, *56*, 1596.

[96]In this book, we make the above distinction between the SET and $S_{RN}1$ mechanisms. However, many workers use the designation SET to refer to the $S_{RN}1$, the chain version of the SET, or both.

[97]Nazareno, M.A.; Rossi, R.A. *Tetrahedron* ***1994***, *50*, 9267; Nazareno, M.A.; Rossi, R.A. *J. Org. Chem.* ***1996***, *61*, 1645.

[98]Ashby, E.C.; Sun, X.; Duff, J.L. *J. Org. Chem.* ***1994***, *59*, 1270.

[99]Haberfield, P. *J. Am. Chem. Soc.* ***1995***, *117*, 3314.

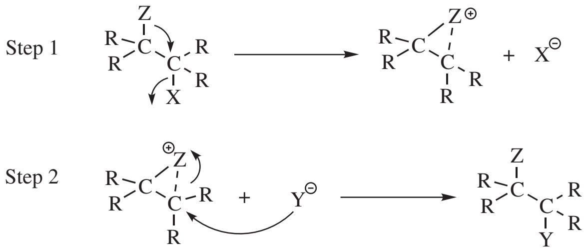
[100]Shaik, S.S. *Acta Chem. Scand.* ***1990***, *44*, 205.

[101]Ashby, E.C.; Park, B.; Patil, G.S.; Gadru, K.; Gurumurthy, R. *J. Org. Chem.* ***1993***, *58*, 424.

The mechanisms so far considered can, in theory at least, operate on any type of saturated (or for that matter unsaturated) substrate. There are other mechanisms that are more limited in scope.

The Neighboring-Group Mechanism[102]

It is occasionally found with certain substrates that (*1*) the rate of reaction is greater than expected, and (*2*) the configuration at a chiral carbon is *retained* and not inverted or racemized. In these cases, there is usually a group with an unshared pair of electrons β to the leaving group (or sometimes farther away). The mechanism operating in such cases is called the *neighboring-group mechanism* and consists essentially of two S_N2 substitutions, each causing an inversion so the net result is retention of configuration.[103] In the first step of this reaction, the neighboring group acts as a nucleophile, pushing out the leaving group but still retaining attachment to the molecule. In the second step, the external nucleophile displaces the neighboring group by a backside attack:



The reaction obviously must go faster than if Y were attacking directly, since if the latter process were faster, *it* would be happening. The neighboring group Z is said to be lending *anchimeric assistance*. The rate law followed in the neighboring-group mechanism is the first-order law shown in Eq. (10.2) or (10.3); that is, Y does not take part in the rate-determining step.

The reason attack by Z is faster than that by Y is that the group Z is more available. In order for Y to react, it must collide with the substrate, but Z is immediately available by virtue of its position. A reaction between the substrate and Y involves a large decrease in entropy of activation ($\Delta S^{\ddagger}$), since the reactants are far less free in the transition state than before. Reaction of Z involves a much smaller loss of $\Delta S^{\ddagger}$ (see p. 303).[104]

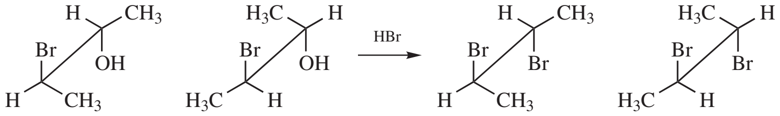
[102]For a monograph, see Capon, B.; McManus, S. *Neighboring Group Participation*, Vol. 1, Plenum, NY, ***1976***.

[103]There is evidence that this kind of process can happen intermolecularly (e.g., $RX + Z^- \rightarrow RZ + Y^-$). In this case Z^- acts as a catalyst for the reaction $RX + Y^- \rightarrow RY$: McCortney, B.A.; Jacobson, B.M.; Vreeke, M.; Lewis, E.S. *J. Am. Chem. Soc.* ***1990***, *112*, 3554.

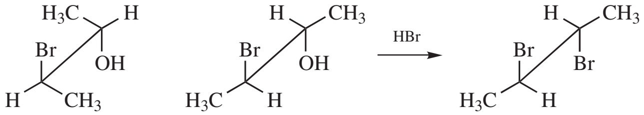
[104]For a review of the energetics of neighboring-group participation, see Page, M.I. *Chem. Soc. Rev.* ***1973***, *2*, 295.

It is not always easy to determine when a reaction rate has been increased by anchimeric assistance. In order to be certain, it is necessary to know what the rate would be without participation by the neighboring group. The obvious way to examine this question is to compare the rates of the reaction with and without the neighboring group, for example, $HOCH_2CH_2Br$ versus CH_3CH_2Br. However, this will certainly not give an accurate determination of the extent of participation, since the steric and field effects of H and OH are not the same. Furthermore, no matter what the solvent, the shell of solvent molecules that surrounds the polar protic OH group must differ greatly from that which surrounds the nonpolar H. Because of these considerations, it is desirable to have a large increase in the rate, preferably >50-fold, before a rate increase is attributed to neighboring-group participation.

The first important evidence for the existence of this mechanism was the demonstration that retention of configuration can occur if the substrate is suitable. It was shown that the threo *dl* pair of 3-bromo-2-butanol when treated with HBr gave *dl*-2,3-dibromobutane, while the erythro pair gave the meso isomer (**22**).[105]

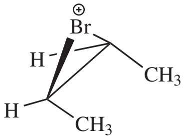


threo *dl* Pair *dl* Pair



erythro *dl* Pair **22** (meso)

This indicated that retention had taken place. Note that both products are optically inactive and so cannot be told apart by differences in rotation. The meso and *dl* dibromides have different boiling points and indexes of refraction and were identified by these properties. Even more convincing evidence was that either of the two threo isomers alone gave not just one of the enantiomeric dibromides, but the *dl* pair. The reason for this is that the intermediate present after the attack by the neighboring group (**23**) is symmetrical, so the external nucleophile Br^- can attack

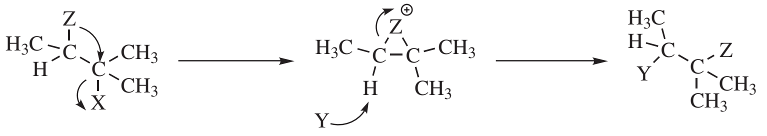


23

both carbon atoms equally well. Intermediate **23** is a bromonium ion, the existence of which has been demonstrated in several types of reactions.

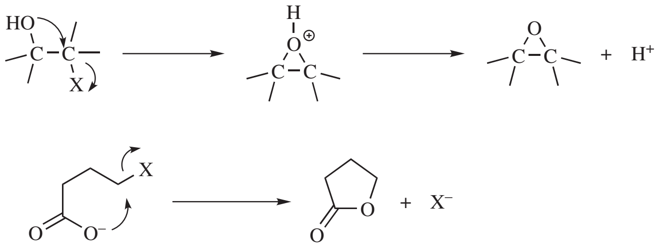
[105]Winstein, S.; Lucas, H.J. *J. Am. Chem. Soc.* ***1939***, *61*, 1576, 2845.

Although **23** is symmetrical, intermediates in most neighboring-group mechanisms are not, and it is therefore possible to get not a simple substitution product but a rearrangement. This will happen if Y attacks not the carbon atom from which X left, but the one to which Z was originally attached:

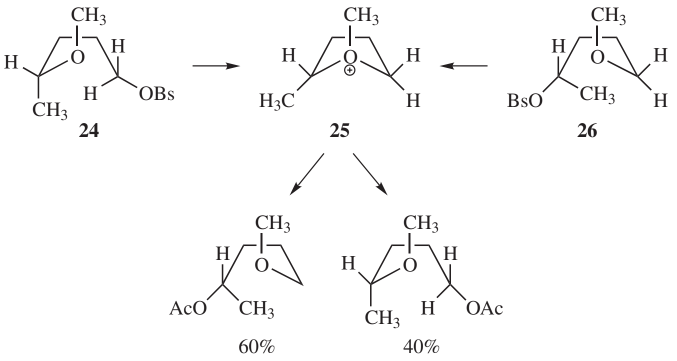


In such cases, substitution and rearrangement products are often produced together. For a discussion of rearrangements, see Chapter 18.

Another possibility is that the intermediate may be stable or may find some other way to stabilize itself. In such cases, Y never attacks at all and the product is cyclic. These are simple internal S_N2 reactions. Two examples are formation of epoxides and lactones:



The fact that acetolysis of both 4-methoxy-1-pentyl brosylate (**24**) and 5-methoxy-2-pentyl brosylate (**25**) gave the same mixture of products is further evidence for participation by a neighboring group.[106] In this case, the intermediate **26** is common to both substrates.

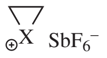


The neighboring-group mechanism operates only when the ring size is right for a particular type of Z. For example, for $MeO(CH_2)_nOBs$, neighboring-group

[106]Allred, E.L.; Winstein, S. *J. Am. Chem. Soc.* ***1967***, *89*, 3991, 3998.

participation was important for $n = 4$ or 5 (corresponding to a five- or six-membered intermediate), but not for $n = 2$, 3, or 6.[107] However, optimum ring size is not the same for all reactions, even with a particular Z. In general, the most rapid reactions occur when the ring size is three, five, or six, depending on the reaction type. The likelihood of four-membered ring neighboring-group participation is increased when there are alkyl groups a or β to the neighboring group.[108]

The following are some of the more important neighboring groups: COO^- (but not COOH), COOR, COAr, OCOR,[109] OR, OH, O^-,[110] NH_2, NHR, NR_2, NHCOR, SH, SR, S^-,[111] SO_2Ph,[112] I, Br, and Cl. The effectiveness of halogens as neighboring groups decreases in the order I > Br > Cl.[113] The Cl is a very weak neighboring group and can be shown to act in this way only when the solvent does not interfere. For example, when 5-chloro-2-hexyl tosylate is solvolyzed in acetic acid, there is little participation by the Cl, but when the solvent is changed to trifluoroacetic acid, which is much less nucleophilic, neighboring-group participation by the Cl becomes the major reaction pathway.[114] Thus, Cl acts as a neighboring group *only when there is need for it* (for other examples of the *principle of increasing electron demand*, see below; p. 454).



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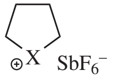

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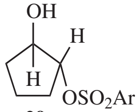
X = Br, Cl, or I



29

A number of intermediates of halogen participation (halonium ions),[115] for example, **27** and **28**, have been prepared as stable salts in SbF_5-SO_2 or SbF_5-SO_2ClF solutions.[116] Some have even been crystallized. Attempts to prepare

[107]Allred, E.L.; Winstein, S. *J. Am. Chem. Soc.* ***1967***, *89*, 4012.

[108]Eliel, E.L.; Clawson, L.; Knox, D.E. *J. Org. Chem.* ***1985***, *50*, 2707; Eliel, E.L.; Knox, D.E. *J. Am. Chem. Soc.* ***1985***, *107*, 2946.

[109]For an example of OCOR as a neighboring group where the ring size is seven membered, see Wilen, S.H.; Delguzzo, L.; Saferstein, R. *Tetrahedron* ***1987***, *43*, 5089.

[110]For a review of oxygen functions as neighboring groups, see Perst, H. *Oxonium Ions in Organic Chemistry*; Verlag Chemie, Deerfield Beach, FL, ***1971***, pp. 100–127. There is evidence that the oxygen in an epoxy group can also act as a neighboring group: Francl, M.M.; Hansell, G.; Patel, B.P.; Swindell, C.S. *J. Am. Chem. Soc.* ***1990***, *112*, 3535.

[111]For a review of sulfur-containing neighboring groups, see Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***, pp. 141–145.

[112]Lambert, J.B.; Beadle, B.M.; Kuang, K. *J. Org. Chem.* ***1999***, *64*, 9241.

[113]Peterson, P.E. *Acc. Chem. Res.* ***1971***, *4*, 407, and references cited therein.

[114]Peterson, P.E.; Bopp, R.J.; Chevli, D.M.; Curran, E.L.; Dillard, D.E.; Kamat, R.J. *J. Am. Chem. Soc.* ***1967***, *89*, 5902. See also, Reich, I.L.; Reich, H.J. *J. Am. Chem. Soc.* ***1974***, *96*, 2654.

[115]For a monograph, see Olah, G.A. *Halonium Ions*, Wiley, NY, ***1975***. For a review, see Koster, G.F., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups*, *Supplement D*, pt. 2, Wiley, NY, ***1983***, pp. 1265–1351.

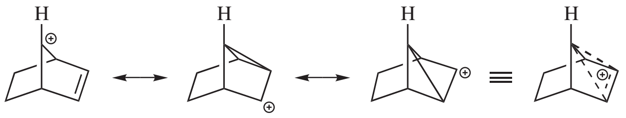
[116]See, for example Olah, G.A.; Peterson, P.E. *J. Am. Chem. Soc.* ***1968***, *90*, 4675; Henrichs, P.M.; Peterson, P.E. *J. Am. Chem. Soc.* ***1973***, *95*, 7449, *J. Org. Chem.* ***1976***, *41*, 362; Olah, G.A.; Liang, G.; Staral, J. *J. Am. Chem. Soc.* ***1974***, *96*, 8112; Vančik, H.; Percač, K.; Sunko, D.E. *J. Chem. Soc., Chem. Commun.* ***1991***, 807.

four-membered homologs of **27** and **28** were not successful.[117] There is no evidence that F can act as a neighboring group.[113]

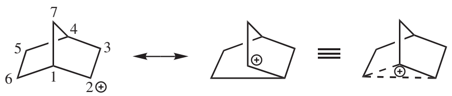
The principle that a neighboring group lends assistance in proportion to the need for such assistance also applies to differences in leaving-group ability. Thus, p-$NO_2C_6H_4SO_2O$ (the nosylate group) is a better leaving group than p-MeC_6H_4-SO_2O (the tosylate group). Experiments have shown that the OH group in *trans*-2-hydroxycyclopentyl arenesulfonates **29** acts as a neighboring group when the leaving group is tosylate but not when it is nosylate, apparently because the nosylate group leaves so rapidly that it does not require assistance.[118]

Neighboring-Group Participation by π and σ Bonds: Nonclassical Carbocations[119]

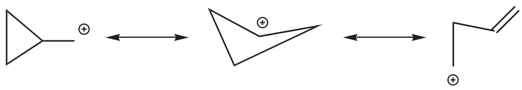
For all the neighboring groups listed in the preceding section, the nucleophilic attack is made by an atom with an unshared pair of electrons. In this section, we consider neighboring-group participation by C=C π bonds and C—C and C—H σ bonds. There has been a great deal of controversy over whether such bonds can act as neighboring groups and about the existence and structure of the intermediates involved. These intermediates are called *nonclassical* (or *bridged*) carbocations. In classical carbocations (Chapter 5) the positive charge is localized on one carbon atom or delocalized by resonance involving an unshared pair of electrons or a double or triple bond in the allylic position. In a nonclassical carbocation, the positive charge is delocalized by a double or triple bond that is not in the allylic position or by a single bond. Examples are the 7-norbornenyl cation (**30**), the norbornyl cation



30a **30b** **30c** **30d**



31a **31b** **31c**



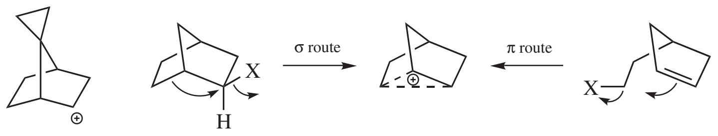
32a **32b** **32c**

[117]Olah, G.A.; Bollinger, J.M.; Mo, Y.K.; Brinich, J.M. *J. Am. Chem. Soc.* ***1972***, *94*, 1164.

[118]Haupt, F.C.; Smith, M.R. *Tetrahedron Lett.* ***1974***, 4141.

[119]For monographs, see Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, ***1972***; Bartlett, P.D. *Nonclassical Ions*, W.A. Benjamin, NY, ***1965***. For reviews, see Barkhash, V.A. *Top. Curr. Chem.* ***1984***, *116/117*, 1; Kirmse, W. *Top. Curr. Chem.* ***1979***, *80*, 125, pp. 196–288; McManus, S.P.; Pittman, Jr., C.U., in McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, ***1973***, pp. 302–321; Bethell, D.; Gold, V. *Carbonium Ions*, Academic Press, NY, ***1967***; pp. 222–282. For a related review, see Prakash, G.K.S.; Iyer, P.S. *Rev. Chem. Intermed.* ***1988***, *9*, 65.

(**31**),[120] and the cyclopropylmethyl cation (**32**). A cyclopropyl group (as in **33**) is capable of stabilizing the norbornyl cation, inhibiting this rearrangement.[121] Carbocation **30** is called a *homoallylic* carbocation, because in **30a** there is one carbon atom between the positively charged carbon and the double bond. Many of these carbocations can be produced in more than one way if the proper substrates are chosen. For example, **31** can be generated by the departure of a leaving group from



33 **34** **31** **35**

34 or from **35**.[122] The first of these pathways is called the σ route to a nonclassical carbocation, because participation of a σ bond is involved. The second is called the π route.[123] The argument against the existence of nonclassical carbocations is essentially that the structures **30a–c** (or **31a**, **31b**, etc.) are not canonical forms but real structures and that there is rapid equilibration among them. This debate remains an active area of interest for some reactions.[124] In one study, the solvolysis and rearrangement of 2-bicyclo[3.2.2]nonanyl tosylate in methanol generated ethers derived from the 2-bicyclo[3.2.2]nonanyl and 2-bicyclo[3.3.1]nonanyl systems that were rationalized in terms of a classical carbocation.[125] Density functional and *ab initio* calculations indicated that the products of the 2-bicyclo[3.2.2]nonanyl tosylate solvolysis were found to have nonclassical structures.[126]

In discussing nonclassical carbocations, we must be careful to make the distinction between neighboring-group participation and the existence of nonclassical carbocations.[127] If a nonclassical carbocation exists in any reaction, then an ion with electron delocalization, as shown in the above examples, is a discrete reaction intermediate. If a carbon–carbon double or single bond participates in the departure of the leaving group to form a carbocation, it may be that a nonclassical carbocation is involved, but there is no necessary relation. In any particular case either or both of these possibilities can be taking place.

In the following pages, we consider some of the evidence bearing on the questions of the participation of π and s bonds and on the existence of nonclassical

[120]Sieber, S.; Schleyer, P.v.R.; Vančik, H.; Mesić, M.; Sunko, D.E. *Angew. Chem. Int. Ed.* ***1993***, *32*, 1604; Schleyer, P.v.R.; Sieber, S. *Angew. Chem. Int. Ed.* ***1993***, *32*, 1606.

[121]Herrmann, R.; Kirmse, W. *Liebigs Ann. Chem.* ***1995***, 703.

[122]Lawton, R.G. *J. Am. Chem. Soc.* ***1961***, *83*, 2399; Bartlett, P.D.; Bank, S.; Crawford, R.J.; Schmid, G.H. *J. Am. Chem. Soc.* ***1965***, *88*, 1288.

[123]Winstein, S.; Carter, P. *J. Am. Chem. Soc.* ***1961***, *83*, 4485.

[124]For example see Brunelle, P.; Sorensen, T.S.; Taeschler, C. *J. Org. Chem.* ***2001***, *66*, 7294.

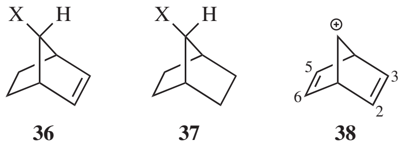
[125]Okazaki, T.; Terakawa, E.; Kitagawa, T.; Takeuchi, K. *J. Org. Chem.* ***2000***, *65*, 1680.

[126]Smith, W. B. *J. Org. Chem.* ***2001***, *66*, 376.

[127]This was pointed out by Cram, D.J. *J. Am. Chem. Soc.* ***1964***, *86*, 3767.

carbocations,[128] although a thorough discussion is beyond the scope of this book.[89]

1. C=C *as a Neighboring Group*.[129] The most striking evidence that C=C can act as a neighboring group is that acetolysis of **36**-OTs is 10^{11} times faster than that of **37**-OTs and *proceeds with retention of configuration*.[130] The rate data alone do not necessarily prove that acetolysis of **36**-OTs involves a



nonclassical intermediate (**30d**), but it is certainly strong evidence that the C=C group assists in the departure of the OTs. Evidence that **30** is indeed a nonclassical ion comes from an NMR study of the relatively stable norbornadienyl cation (**38**). The spectrum shows that the 2 and 3 protons are not equivalent to the 5 and 6 protons.[131] Thus there is interaction between the charged carbon and one double bond, which is evidence for the existence of **30d**.[132] In the case of **36**, the double bond is geometrically fixed in an especially favorable position for backside attack on the carbon bearing the leaving group (hence the very large rate enhancement), but there is much evidence that other double bonds in the homoallylic position,[133] as well as in

[128]The arguments against nonclassical ions are summed up in Brown, H.C. *The Nonclassical Ion Problem*; Plenum, NY, ***1977***. This book also includes rebuttals by Schleyer, P.v.R. See also, Brown, H.C. *Pure Appl. Chem.* ***1982***, *54*, 1783.

[129]For reviews, see Story, P.R.; Clark, Jr., B.C., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, ***1972***, pp. 1007–1060; Richey, Jr., H.G., in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2; Wiley, NY, ***1970***, pp. 77–101.

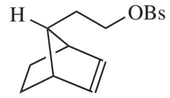
[130]Winstein, S.; Shatavsky, M. *J. Am. Chem. Soc.* ***1956***, *78*, 592.

[131]Story, P.R.; Snyder, L.C.; Douglass, D.C.; Anderson, E.W.; Kornegay, R.L. *J. Am. Chem. Soc.* ***1963***, *85*, 3630. For a discussion, see Story, P.R.; Clark, Jr., B.C., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, ***1972***, pp. 1026–1041. See also, Lustgarten, R.K.; Brookhart, M.; Winstein, S. *J. Am. Chem. Soc.* ***1972***, *94*, 2347.

[132]For further evidence for the nonclassical nature of **30**, see Brookhart, M.; Diaz, A.; Winstein, S. *J. Am. Chem. Soc.* ***1966***, *88*, 3135; Richey, Jr., H.G.; Lustgarten, R.K. *J. Am. Chem. Soc.* ***1966***, *88*, 3136; Gassman, P.G.; Doherty, M.M. *J. Am. Chem. Soc.* ***1982***, *104*, 3742 and references cited therein; Laube, T. *J. Am. Chem. Soc.* ***1989***, *111*, 9224.

[133]For examples, see Shoppee, C.W. *J. Chem. Soc.* ***1946***, 1147; LeBel, N.A.; Huber, J.E. *J. Am. Chem. Soc.* ***1963***, *85*, 3193; Closson, W.D.; Kwiatkowski, G.T. *Tetrahedron* ***1965***, *21*, 2779; Brown, H.C.; Peters, E.N.; Ravindranathan, M. *J. Am. Chem. Soc.* ***1975***, *97*, 7449; Schleyer, P.v.R.; Bentley, T.W.; Koch, W.; Kos, A.J.; Schwarz, H. *J. Am. Chem. Soc.* ***1987***, *109*, 6953; Fernández-Mateos, A.; Rentzsch, M.; Sánchez, L.R.; González, R.R. *Tetrahedron* ***2001***, *57*, 4873.

positions farther away,[134] can also lend anchimeric assistance, although generally with much lower rate ratios. One example of the latter is the compound β-(*syn*-7-norbornenyl)ethyl brosylate (**39**), which at 25°C undergoes acetolysis ~140,000 times faster than the saturated analog **40**.[135] Triple bonds[136] and allenes[137] can also act as neighboring groups.



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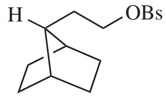

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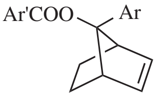
We have already seen evidence that participation by a potential neighboring group can be reduced or eliminated if an outside nucleophile is present that is more effective than the neighboring group in attacking the central carbon (p. 450), or if a sufficiently good leaving group is present (p. 450). In another example of the principle of increasing electron demand, Gassman and co-workers have shown that neighboring-group participation can also be reduced if the stability of the potential carbocation is increased. They found that the presence of a *p*-anisyl group at the 7 position of **36** and **37** exerts a powerful leveling effect on the rate differences. Thus, solvolysis in acetone–water at 85°C of **38** was only ~2.5 times faster than that of the saturated



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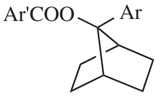

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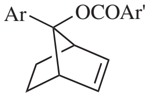


43

Ar = *p*-$MeOC_6H_4$
Ar' = *p*-$NO_2C_6H_4$

compound **42**.[138] Furthermore, both **41** and its stereoisomer **43** gave the same mixture of solvolysis products, showing that the stereoselectivity in the solvolysis of **36** is not present here. The difference between **41** and **36** is that in the case of **41** the positive charge generated at the 7 position in the transition state is greatly stabilized by the *p*-anisyl group. Apparently, the stabilization by the *p*-anisyl group is so great that further stabilization that would come from

[134]For examples, see LeNy, G. *C. R. Acad. Sci.* ***1960***, *251*, 1526; Goering, H.L.; Closson, W.D. *J. Am. Chem. Soc.* ***1961***, *83*, 3511; Bartlett, P.D.; Trahanovsky, W.S.; Bolon, D.A.; Schmid, G.H. *J. Am. Chem. Soc.* ***1965***, *87*, 1314; Bly, R.S.; Swindell, R.T. *J. Org. Chem.* ***1965***, *30*, 10; Marvell, E.N.; Sturmer, D.; Knutson, R.S. *J. Org. Chem.* ***1968***, *33*, 2991; Cogdell, T.J. *J. Org. Chem.* ***1972***, *37*, 2541; Ferber, P.H.; Gream, G.E. *Aust. J. Chem.* ***1981***, *34*, 1051; Orlović, M.; Borčić, S.; Humski, K.; Kronja, O.; Imper, V.; Polla, E.; Shiner, Jr., V.J. *J. Org. Chem.* ***1991***, *56*, 1874; Winstein, S.; Carter, P. *J. Am. Chem. Soc.* ***1961***, *83*, 4485.

[135]Bly, R.S.; Bly, R.K.; Bedenbaugh, A.O.; Vail, O.R. *J. Am. Chem. Soc.* ***1967***, *89*, 880.

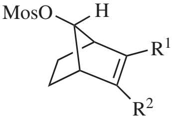
[136]See, for example, Closson, W.D.; Roman, S.A. *Tetrahedron Lett.* ***1966***, 6015; Hanack, M.; Herterich, I.; Vött, V. *Tetrahedron Lett.* ***1967***, 3871; Lambert, J.B.; Papay, J.J.; Mark, H.W. *J. Org. Chem.* ***1975***, *40*, 633; Peterson, P.E.; Vidrine, D.W. *J. Org. Chem.* ***1979***, *44*, 891. For a review of participation by triple bonds and allylic groups, see Rappoport, Z. *React. Intermed. (Plenum)* ***1983***, *3*, 440.

[137]Bly, R.S.; Koock, S.U. *J. Am. Chem. Soc.* ***1969***, *91*, 3292, 3299; Von Lehman, T.; Macomber, R. *J. Am. Chem. Soc.* ***1975***, *97*, 1531.

[138]Gassman, P.G.; Zeller, J.; Lamb, J.T. *Chem. Commun.* ***1968***, 69.

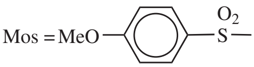
participation by the C=C bond is not needed.[139] The use of a phenyl instead of a *p*-anisyl group is not sufficient to stop participation by the double bond completely, although it does reduce it.[140] These results permit us to emphasize our previous conclusion that *a neighboring group lends anchimeric assistance only when there is sufficient demand for it.*[141] The π-bond of a neighboring alkene group can assist solvolysis via π-participation.[142]

The ability of C=C to serve as a neighboring group can depend on its electron density. When the strongly electron-withdrawing CF_3 group was attached to a double bond carbon of **44**, the solvolysis rate was lowered by a factor of about 10^6.[143]



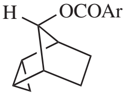
44

Relative Rates	
$R^1 = R^2 = H$	1.4×10^{12}
$R^1 = H, R^2 = CF_3$	1.5×10^6
$R^1 = R^2 = CF_3$	1



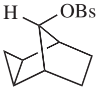
A second CF_3 group had an equally strong effect. In this case, two CF_3 groups decrease the electron density of the C=C bond to the point that the solvolysis rate for **44** ($R^1 = R^2 = CF_3$) was about the same as (actually ~17 times slower than) the rate for the saturated substrate **37** (X = OMos). Thus, the two CF_3 groups completely remove the ability of the C=C bond to act as a neighboring group.

2. *Cyclopropyl*[144] *as a Neighboring Group.*[145] On p. 217 we saw that the properties of a cyclopropane ring are in some ways similar to those of a double bond. Therefore it is not surprising that a suitably placed cyclopropyl ring can



Ar = *p*-$NO_2C_6H_4$

45



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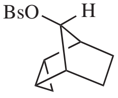


47

[139]Nevertheless, there is evidence from ^{13}C NMR spectra that some π participation is present, even in the cation derived from **38:** Olah, G.A.; Berrier, A.L.; Arvanaghi, M.; Prakash, G.K.S. *J. Am. Chem. Soc.* ***1981***, *103*, 1122.

[140]Gassman, P.G.; Fentiman, Jr., A.F. *J. Am. Chem. Soc.* ***1969***, *91*, 1545; ***1970***, *92*, 2549.

[141]For a discussion of the use of the tool of increasing electron demand to probe neighboring-group activity by double bonds, sigma bonds, and aryl rings, see Lambert, J.B.; Mark, H.W.; Holcomb, A.G.; Magyar, E.S. *Acc. Chem. Res.* ***1979***, *12*, 317.

[142]Malnar, I.; Jurić, S.; Vrček, V.; Gjuranovič, Ž.; Mihalič, Z.; Kronja, O. *J. Org. Chem.* ***2002***, *67*, 1490.

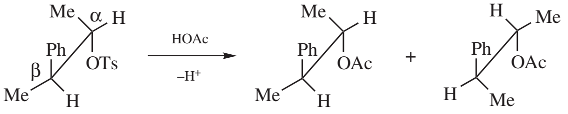
[143]Gassman, P.G.; Hall, J.B. *J. Am. Chem. Soc.* ***1984***, *106*, 4267.

[144]In this section, we consider systems in which at least one carbon separates the cyclopropyl ring from the carbon bearing the leaving group. For a discussion of systems in which the cyclopropyl group is directly attached to the leaving-group carbon, see p. $$$.

[145]For a review, see Haywood-Farmer, J. *Chem. Rev.* ***1974***, *74*, 315.

also be a neighboring group. Thus *endo-anti*-tricyclo[3.2.1.$0^{2,4}$]octan-8-yl *p*-nitrobenzoate (**45**) solvolyzed $\sim 10^{14}$ times faster that the *p*-nitrobenzoate of **37**-OH.[146] Obviously, a suitably placed cyclopropyl ring can be even more effective[147] as a neighboring group than a double bond.[148] The need for suitable placement is emphasized by the fact that **47** solvolyzed only about five times faster than **37**-OBs,[149] while **46** solvolyzed three times *slower* than **37**-OBs.[150] In the case of **45** and of all other cases known where cyclopropyl lends considerable anchimeric assistance, the developing *p* orbital of the carbocation is orthogonal to the participating bond of the cyclopropane ring.[151] An experiment designed to test whether a developing *p* orbital that would be parallel to the participating bond would be assisted by that bond showed no rate enhancement.[151] This is in contrast to the behavior of cyclopropane rings directly attached to positively charged carbons, where the *p* orbital is parallel to the plane of the ring (pp. 241, 464). Rate enhancements, although considerably smaller, have also been reported for suitably placed cyclobutyl rings.[152]

3. *Aromatic Rings as Neighboring Groups*.[153] There is a great deal of evidence that aromatic rings in the β position can function as neighboring



48 **49** **50**

[146]Tanida, H.; Tsuji, T.; Irie, T. *J. Am. Chem. Soc.* ***1967***, *89*, 1953; Battiste, M.A.; Deyrup, C.L.; Pincock, R.E.; Haywood-Farmer, J. *J. Am. Chem. Soc.* ***1967***, *89*, 1954.

[147]For a competitive study of cyclopropyl versus double-bond participation, see Lambert, J.B.; Jovanovich, A.P.; Hamersma, J.W.; Koeng, F.R.; Oliver, S.S. *J. Am. Chem. Soc.* ***1973***, *95*, 1570.

[148]For other evidence for anchimeric assistance by cyclopropyl, see Sargent, G.D.; Lowry, N.; Reich, S.D. *J. Am. Chem. Soc.* ***1967***, *89*, 5985; Battiste, M.A.; Haywood-Farmer, J.; Malkus, H.; Seidl, P.; Winstein, S. *J. Am. Chem. Soc.* ***1970***, *92*, 2144; Coates, R.M.; Yano, K. *Tetrahedron Lett.* ***1972***, 2289; Masamune, S.; Vukov, R.; Bennett, M.J.; Purdham, J.T. *J. Am. Chem. Soc.* ***1972***, *94*, 8239; Gassman, P.G.; Creary, X. *J. Am. Chem. Soc.* ***1973***, *95*, 2729; Costanza, A.; Geneste, P.; Lamaty, G.; Roque, J. *Bull. Soc. Chim. Fr.* ***1975***, 2358; Takakis, I.M.; Rhodes, Y.E. *Tetrahedron Lett.* ***1983***, *24*, 4959.

[149]Battiste, M.A.; Deyrup, C.L.; Pincock, R.E.; Haywood-Farmer, J. *J. Am. Chem. Soc.* ***1967***, *89*, 1954; Haywood-Farmer, J.; Pincock, R.E. *J. Am. Chem. Soc.* ***1969***, *91*, 3020; Haywood-Farmer, J. *Chem. Rev.* ***1974***, *74*, 315; Haywood-Farmer, J. *Chem. Rev.* ***1974***, *74*, 315.

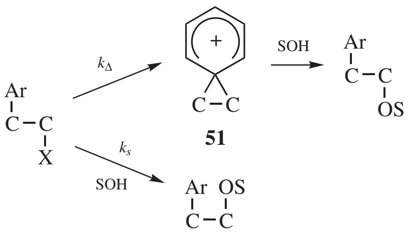
[150]Haywood-Farmer, J.; Pincock, R.E.; Wells, J.I. *Tetrahedron* ***1966***, *22*, 2007; Haywood-Farmer, J.; Pincock, R.E. *J. Am. Chem. Soc.* ***1969***, *91*, 3020. For some other cases where there was little or no rate enhancement by cyclopropyl, see Wiberg, K.B.; Wenzinger, G.R. *J. Org. Chem.* ***1965***, *30*, 2278; Sargent, G.D.; Taylor, R.L.; Demisch, W.H. *Tetrahedron Lett.* ***1968***, 2275; Rhodes, Y.E.; Takino, T. *J. Am. Chem. Soc.* ***1970***, *92*, 4469; Hanack, M.; Krause, P. *Liebigs Ann. Chem.* ***1972***, *760*, 17.

[151]Gassman, P.G.; Seter, J.; Williams, F.J. *J. Am. Chem. Soc.* ***1971***, *93*, 1673. For a discussion, see Haywood-Farmer, J.; Pincock, R.E. *J. Am. Chem. Soc.* ***1969***, *91*, 3020. See also, Chenier, P.J.; Jenson, T.M.; Wulff, W.D. *J. Org. Chem.* ***1982***, *47*, 770.

[152]For example, see Sakai, M.; Diaz, A.; Winstein, S. *J. Am. Chem. Soc.* ***1970***, *92*, 4452; Battiste, M.A.; Nebzydoski, J.W. *J. Am. Chem. Soc.* ***1970***, *92*, 4450; Schipper, P.; Driessen, P.B.J.; de Haan, J.W.; Buck, H.M. *J. Am. Chem. Soc.* ***1974***, *96*, 4706; Ohkata, K.; Doecke, C.W.; Klein, G.; Paquette, L.A. *Tetrahedron Lett.* ***1980***, *21*, 3253.

[153]For a review, see Lancelot, L.A.; Cram, D.J.; Schleyer, P.v.R., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3; Wiley, NY, ***1972***, pp. 1347–1483.

groups.[154] Stereochemical evidence was obtained by solvolysis of L-*threo*-3-phenyl-2-butyl tosylate (**48**) in acetic acid.[155] Of the acetate product 96% was the threo isomer and only about 4% was erythro. Moreover, both the (+) and (−) threo isomers (**49** and **50**) were produced in approximately equal amounts (a racemic mixture). When solvolysis was conducted in formic acid, even less erythro isomer was obtained. This result is similar to that found on reaction of 3-bromo-2-butanol with HBr (p. 446) and leads to the conclusion that configuration is retained because phenyl acts as a neighboring group. However, evidence from rate studies is not so simple. If β-aryl groups assist the departure of the leaving group, solvolysis rates should be enhanced. In general, they are not. However, solvolysis rate studies in 2-arylethyl systems are complicated by the fact that, for primary and secondary systems, two pathways can exist.[156] In one of these (designated k_Δ), the aryl, behaving as a neighboring group, pushes out the leaving group to give a bridged ion, called a *phenonium ion* (**51**), and is in turn pushed out by the solvent SOH, so



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the net result is substitution with retention of configuration (or rearrangement, if **51** is opened from the other side). The other pathway (k_s) is simple S_N2 attack by the solvent at the leaving-group carbon. The net result here is substitution with inversion and no possibility of rearrangement. Whether the leaving group is located at a primary or a secondary carbon, there is no crossover between these pathways; they are completely independent.[157] (Both the k_Δ and k_s pathways are unimportant when the leaving group is at a tertiary carbon.) In these cases, the mechanism is S_N1 and open carbocations $ArCH_2CR_2^+$ are intermediates. This pathway is designated k_c. Which of the two pathways (k_s or k_Δ) predominates in any given case depends on the solvent and on the nature of the aryl group. As expected from the results we have seen for Cl as a neighboring group (p. 450), the k_Δ/k_s ratio is highest for solvents that are poor nucleophiles and so compete very poorly with the aryl

[154]Kevill, D.N.; D'Souza, M.J. *J. Chem. Soc. Perkin Trans. 2* ***1997***, 257; Fujio, M.; Goto, N.; Dairokuno, T.; Goto, M.; Saeki, Y.; Okusako, Y.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* ***1992***, *65*, 3072.

[155]Cram, D.J. *J. Am. Chem. Soc.* ***1949***, *71*, 3863; ***1952***, *74*, 2129.

[156]Brookhart, M.; Anet, F.A.L.; Cram, D.J.; Winstein, S. *J. Am. Chem. Soc.* ***1966***, *88*, 5659; Lee, C.C.; Unger, D.; Vassie, S. *Can. J. Chem.* ***1972***, *50*, 1371.

[157]Brown, H.C.; Kim, C.J.; Lancelot, C.J.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1970***, *92*, 5244; Brown, H.C.; Kim, C.J. *J. Am. Chem. Soc.* ***1971***, *93*, 5765.

group. For several common solvents the k_{Δ}/k_s ratio increases in the order EtOH < CH_3COOH < HCOOH < CF_3COOH.[158] In accord with this, the following percentages of retention were obtained in solvolysis of 1-phenyl-2-propyl tosylate at 50°C: solvolysis in EtOH 7%, CH_3COOH 35%, HCOOH 85%.[158] This indicates that k_s predominates in EtOH (phenyl participates very little), while k_{Δ} predominates in HCOOH. Trifluoroacetic acid is a solvent of particularly low nucleophilic power, and in this solvent the reaction proceeds entirely by k_{Δ};[159] deuterium labeling showed 100% retention.[160] This case provides a clear example of neighboring-group rate enhancement by phenyl: The rate of solvolysis of $PhCH_2CH_2OTs$ at 75°C in CF_3COOH is 3040 times the rate for CH_3CH_2OTs.[159]

With respect to the aromatic ring, the k_{Δ} pathway is electrophilic aromatic substitution (Chapter 11). We predict that groups on the ring that activate that reaction (p. 665) will increase, and deactivating groups will decrease, the rate of this pathway. This prediction has been borne out by several investigations. The *p*-nitro derivative of **48** solvolyzed in acetic acid 190 times slower than **48**, and there was much less retention of configuration; the acetate produced was only 7% threo and 93% erythro.[161] At 90°C, acetolysis of *p*-$ZC_6H_4CH_2CH_2OTs$ gave the rate ratios shown in Table 10.1.[162] Throughout this series k_s is fairly constant, as it should be since it is affected only by the rather remote field effect of Z. It is k_{Δ} that changes substantially as Z is changed from activating to deactivating. The evidence is thus fairly clear that participation by aryl groups depends greatly on the nature of the group. For some groups (e.g., *p*-nitrophenyl), in some solvents (e.g., acetic acid), there is essentially no neighboring-group participation at all,[163] while for others (e.g., *p*-methoxyphenyl), neighboring-group participation is substantial. The combined effect of solvent and structure is shown in Table 10.2, where the figures shown were derived by three different methods.[164] The decrease in neighboring-group effectiveness when aromatic rings are substituted by electron-withdrawing groups is reminiscent of the similar case of C=C bonds substituted by CF_3 groups (p. 454).

[158]Diaz, A.; Winstein, S. *J. Am. Chem. Soc.* ***1969***, *91*, 4300. See also, Schadt, F.L.; Lancelot, C.J.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1978***, *100*, 228.

[159]Nordlander, J.E.; Kelly, W.J. *J. Am. Chem. Soc.* ***1969***, *91*, 996.

[160]Jablonski, R.J.; Snyder, E.I. *J. Am. Chem. Soc.* ***1969***, *91*, 4445.

[161]Thompson, J.A.; Cram, D.J. *J. Am. Chem. Soc.* ***1969***, *91*, 1778. See also, Tanida, H.; Tsuji, T.; Ishitobi, H.; Irie, T. *J. Org. Chem.* ***1969***, *34*, 1086; Kingsbury, C.A.; Best, D.C. *Bull. Chem. Soc. Jpn.* ***1972***, *45*, 3440.

[162]Coke, J.L.; McFarlane, F.E.; Mourning, M.C.; Jones, M.G. *J. Am. Chem. Soc.* ***1969***, *91*, 1154; Jones, M.G.; Coke, J.L. *J. Am. Chem. Soc.* ***1969***, *91*, 4284. See also, Harris, J.M.; Schadt, F.L.; Schleyer, P.v.R.; Lancelot, C.J. *J. Am. Chem. Soc.* ***1969***, *91*, 7508.

[163]The k_{Δ} pathway is important for *p*-nitrophenyl in CF_3COOH: Ando, T.; Shimizu, N.; Kim, S.; Tsuno, Y.; Yukawa, Y. *Tetrahedron Lett.* ***1973***, 117.

[164]Lancelot, C.J.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1969***, *91*, 4291, 4296; Lancelot, C.J.; Harper, J.J.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1969***, *91*, 4294; Schleyer, P.v.R.; Lancelot, C.J. *J. Am. Chem. Soc.* ***1969***, *91*, 4297.

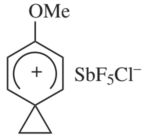
TABLE 10.1. Approximate k_Δ/k_s Ratios for Acetolysis of *p*-$ZC_6H_4CH_2CH_2OTs$ at 90°C[162]

Z	k_Δ/k_s
MeO	30
Me	11
H	1.3
Cl	0.3

TABLE 10.2. Percent of Product Formed by the k_Δ Pathway in Solvolysis of *p*-$ZC_6H_4CH_2CH_2OTs$[164]

Z	Solvent	Percent by k_Δ
H	CH_3COOH	35–38
H	HCOOH	72–79
MeO	CH_3COOH	91–93
MeO	HCOOH	99

Several phenonium ions have been prepared as stable ions in solution where they can be studied by NMR, among them **52**,[165] **53**,[166] and the unsubstituted **51**.[167] These were prepared[168] by the method shown for **51**: treatment of the corresponding β-arylethyl chloride with SbF_5—SO_2 at low temperatures. These conditions are even more extreme than the solvolysis in CF_3COOH mentioned earlier. The absence of any nucleophile at all eliminates



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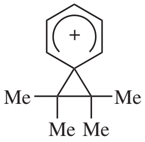
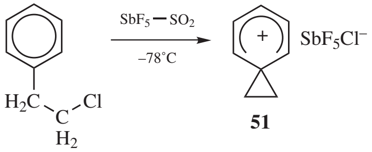


53

not only the k_s pathways, but also nucleophilic attack on **51**. Although **51** is not in equilibrium with the open-chain ion $PhCH_2CH_2^+$ (which is primary



51

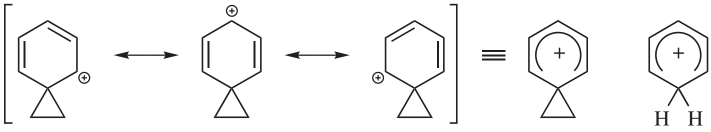
[165]Olah, G.A.; Comisarow, M.B.; Namanworth, E.; Ramsey, B. *J. Am. Chem. Soc.* ***1967***, *89*, 5259; Ramsey, B.; Cook, Jr., J.A.; Manner, J.A. *J. Org. Chem.* ***1972***, *37*, 3310.

[166]Olah, G.A.; Comisarow, M.B.; Kim, C.J. *J. Am. Chem. Soc.* ***1969***, *91*, 1458. See, however, Ramsey, B.; Cook, Jr., J.A.; Manner, J.A. *J. Org. Chem.* ***1972***, *37*, 3310.

[167]Olah, G.A.; Spear, R.J.; Forsyth, D.A. *J. Am. Chem. Soc.* ***1976***, *98*, 6284.

[168]For some others, see Olah, G.A.; Singh, B.P.; Liang, G. *J. Org. Chem.* ***1984***, *49*, 2922; Olah, G.A.; Singh, B.P. *J. Am. Chem. Soc.* ***1984***, *106*, 3265.

and hence unstable), **53** is in equilibrium with the open-chain tertiary ions $PhCMe_2C^+Me_2$ and PhC^+MeCMe_3, although only **53** is present in appreciable concentration. Proton and ^{13}C NMR show that **51**, **52**, and **53** are classical carbocations where the only resonance is in the six-membered ring. The three-membered ring is a normal cyclopropane ring that is influenced only to a relatively small extent by the positive charge on the adjacent ring. Nuclear magnetic resonance spectra show that the six-membered rings have no aromatic character, but are similar in structure to the arenium ions, for example,



54

54, that are intermediates in electrophilic aromatic substitution (Chapter 11). A number of phenonium ions, including **51**, have also been reported to be present in the gas phase, where their existence has been inferred from reaction products and from ^{13}C labeling.[169]

It is thus clear that β-aryl groups can function as neighboring groups.[170] Much less work has been done on aryl groups located in positions farther away from the leaving group, but there is evidence that these too can lend anchimeric assistance.[171]

4. *The Carbon–Carbon Single Bond as a Neighboring Group.*[172]

a. *The 2-Norbornyl System.* In the investigations to determine whether a C–C σ bond can act as a neighboring group, by far the greatest attention

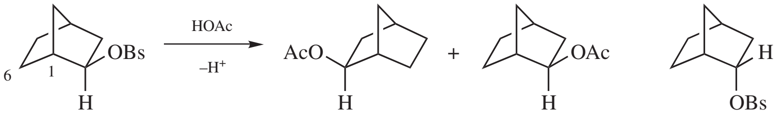
[169]Fornarini, S.; Muraglia, V. *J. Am. Chem. Soc.* ***1989***, *111*, 873; Mishima, M.; Tsuno, Y.; Fujio, M. *Chem. Lett.* ***1990***, 2277.

[170]For additional evidence, see Tanida, H. *Acc. Chem. Res.* ***1968***, *1*, 239; Kingsbury, C.A.; Best, D.C. *Tetrahedron Lett.* ***1967***, 1499; Braddon, D.V.; Wiley, G.A.; Dirlam, J.; Winstein, S. *J. Am. Chem. Soc.* ***1968***, *90*, 1901; Tanida, H.; Ishitobi, H.; Irie, T. *J. Am. Chem. Soc.* ***1968***, *90*, 2688; Brown, H.C.; Tritle, G.L. *J. Am. Chem. Soc.* ***1968***, *90*, 2689; Bentley, M.D.; Dewar, M.J.S. *J. Am. Chem. Soc.* ***1970***, *92*, 3996; Raber, D.J.; Harris, J.M.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1971***, *93*, 4829; Shiner, Jr., V.J.; Seib, R.C. *J. Am. Chem. Soc.* ***1976***, *98*, 862; Faïn, D.; Dubois, J.E. *Tetrahedron Lett.* ***1978***, 791; Yukawa, Y.; Ando, T.; Token, K.; Kawada, M.; Matsuda, K.; Kim, S.; Yamataka, H. *Bull. Chem. Soc. Jpn.* ***1981***, *54*, 3536; Ferber, P.H.; Gream, G.E. *Aust. J. Chem.* ***1981***, *34*, 2217; Fujio, M.; Goto, M.; Seki, Y.; Mishima, M.; Tsuno, Y.; Sawada, M.; Takai, Y. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 1097. For a discussion of evidence obtained from isotope effects, see Scheppele, S.E. *Chem. Rev.* ***1972***, *72*, 511, p. 522.

[171]Heck, R.; Winstein, S. *J. Am. Chem. Soc.* ***1957***, *79*, 3105; Muneyuki, R.; Tanida, H. *J. Am. Chem. Soc.* ***1968***, *90*, 656; Ouellette, R.J.; Papa, R.; Attea, M.; Levin, C. *J. Am. Chem. Soc.* ***1970***, *92*, 4893; Jackman, L.M.; Haddon, V.R. *J. Am. Chem. Soc.* ***1974***, *96*, 5130; Gates, M.; Frank, D.L.; von Felten, W.C. *J. Am. Chem. Soc.* ***1974***, *96*, 5138; Ando, T.; Yamawaki, J.; Saito, Y. *Bull. Chem. Soc. Jpn.* ***1978***, *51*, 219.

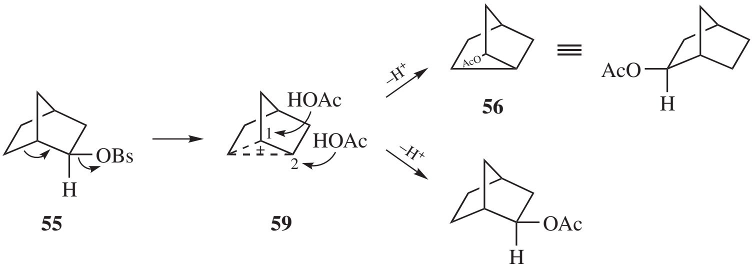
[172]For a review pertaining to studies of this topic at low temperatures, see Olah, G.A. *Angew. Chem. Int. Ed.* ***1973***, *12*, 173, pp. 192–198.

has been paid to the 2-norbornyl system.[173] Winstein and Trifan found that solvolysis in acetic acid of optically active *exo*-2-norbornyl brosylate (**55**) gave a racemic mixture of the two exo acetates; no endo isomers were formed:[174]



55 **56** **57** **58**

Furthermore, **55** solvolyzed ~350 times faster than its endo isomer **58**. Similar high exo/endo rate ratios have been found in many other [2.2.1] systems. These two results—(*1*) that solvolysis of an optically active exo isomer gave only racemic exo isomers and (*2*) the high exo/endo rate ratio—were interpreted by Winstein and Trifan as indicating that the 1,6 bond assists in the departure of the leaving group and that a nonclassical intermediate (**59**) is involved. They reasoned that solvolysis of the endo isomer **58** is not assisted by the 1,6 bond because it is not in a favorable position for backside attack,



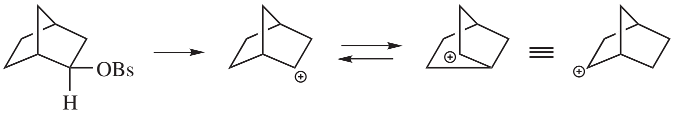
55 **59** **56** **57**

and that consequently solvolysis of **58** takes place at a "normal" rate. Therefore the much faster rate for the solvolysis of **55** must be caused by anchimeric assistance. The stereochemistry of the product is also explained by the intermediacy of **59**, since in **59** the 1 and 2 positions are equivalent and would be attacked by the nucleophile with equal facility, but only from the exo direction in either case. Incidentally, acetolysis of **58** also leads exclusively to the exo acetates (**56** and **57**), so that in this case Winstein and Trifan postulated that a classical ion (**60**)

[173]For reviews, see Olah, G.A.; Prakash, G.K.S.; Williams, R.E. *Hypercarbon Chemistry*, Wiley, NY, ***1987***, pp. 157–170; Grob, C.A. *Angew. Chem. Int. Ed.* ***1982***, *21*, 87; Sargent, G.D., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, ***1972***, pp. 1099–1200; Sargent, G.D. *Q. Rev. Chem. Soc.* ***1966***, *20*, 301; Gream, G.E. *Rev. Pure Appl. Chem.* ***1966***, *16*, 25. For a closely related review, see Kirmse, W. *Acc. Chem. Res.* ***1986***, *19*, 36. See also, Ref. 177.
[174]Winstein, S.; Clippinger, E.; Howe, R.; Vogelfanger, E. *J. Am. Chem. Soc.* ***1965***, *87*, 376.

is first formed, and then converted to the more stable **59**. Evidence for this interpretation is that the product from solvolysis of **58** is not racemic but contains somewhat more **57** than **56** (corresponding to 3–13% inversion, depending on the solvent),[174] suggesting that when **60** is formed, some of it goes to give **57** before it can collapse to **59**.

The concepts of σ participation and the nonclassical ion **59** were challenged by H.C. Brown,[128] who suggested that the two results can also be explained by postulating that **55** solvolyzes without participation of the 1,6 bond to give the classical ion **60**, which is in rapid equilibrium with **61**. This



55 **60** **61**

rapid interconversion has been likened to the action of a windshield wiper.[175] Obviously, in going from **60** to **61** and back again, **59** must be present, but in Brown's view it is a transition state and not an intermediate. Brown's explanation for the stereochemical result was that exclusive exo attack is a property to be expected from any 2-norbornyl system, not only for the cation but even for reactions not involving cations, because of steric hindrance to attack from the endo side. There is a large body of data that shows that exo attack on norbornyl systems is fairly general in many reactions. A racemic mixture will be obtained if **60** and **61** are present in equal amounts, since they are equivalent and exo attack on **60** and **61** gives, respectively, **57** and **56**. Brown explained the high exo/endo rate ratios by contending that it is not the endo rate that is normal and the exo rate abnormally high, but the exo rate that is normal and the endo rate abnormally *low*, because of steric hindrance to removal of the leaving group in that direction.[176]

A vast amount of work has been done[177] on solvolysis of the 2-norbornyl system in an effort to determine whether the 1,6 bond

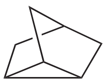
[175]Another view is somewhere in between: There are two interconverting ions, but each is asymmetrically bridged: Bielmann, R.; Fuso, F.; Grob, C.A. *Helv. Chim. Acta* ***1988***, *71*, 312; Flury, P.; Grob, C.A.; Wang, G.Y.; Lennartz, H.; Roth, W.R. *Helv. Chim. Acta* ***1988***, *71*, 1017.

[176]For evidence against steric hindrance as the only cause of this effect, see Menger, F.M.; Perinis, M.; Jerkunica, J.M.; Glass, L.E. *J. Am. Chem. Soc.* ***1978***, *100*, 1503.

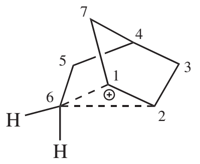
[177]For thorough discussions, see Lenoir, D.; Apeloig, Y.; Arad, D.; Schleyer, P.v.R. *J. Org. Chem.* ***1988***, *53*, 661; Grob, C.A. *Acc. Chem. Res.* ***1983***, *16*, 426; Brown, H.C. *Acc. Chem. Res.* ***1983***, *16*, 432; Walling, C. *Acc. Chem. Res.* ***1983***, *16*, 448; Allred, E.L.; Winstein, S. *J. Am. Chem. Soc.* ***1967***, *89*, 3991, 3998; Nordlander, J.E.; Kelly, W.J. *J. Am. Chem. Soc.* ***1969***, *91*, 996. For commentary on the controversy, see Arnett, E.M.; Hofelich, T.C.; Schriver, G.W. *React. Intermed. (Wiley)* ***1985***, *3*, 189, pp. 193–202.

participates and whether **59** is an intermediate. Most,[178] although not all,[179] chemists now accept the intermediacy of **59**.

Besides the work done on solvolysis of 2-norbornyl compounds, the 2-norbornyl cation has also been extensively studied at low temperatures; there is much evidence that under these conditions the ion is definitely nonclassical. Olah and co-workers have prepared the 2-norbornyl cation in stable solutions at temperatures below $-150°C$ in SbF_5—SO_2 and FSO_3H—SbF_5—SO_2, where the structure is static and hydride shifts are absent.[180] Studies by proton and ^{13}C NMR, as well as by laser Raman spectra and X-ray electron spectroscopy, led to the conclusion[181] that under these conditions the ion is nonclassical.[182] A similar result has been reported for the 2-norbornyl cation in the solid state where at 77 and even 5 K, ^{13}C NMR spectra gave no evidence of the freezing out of a single classical ion.[183]



Nortricyclane



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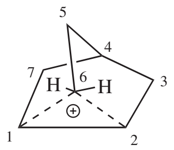

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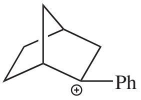

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[178]For some recent evidence in favor of a nonclassical **59**, see Arnett, E.M.; Petro, C.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1979***, *101*, 522: Albano, C.; Wold, S. *J. Chem. Soc. Perkin Trans. 2* ***1980***, 1447; Wilcox, C.F.; Tuszynski, W.J. *Tetrahedron Lett.* ***1982***, *23*, 3119; Kirmse, W.; Siegfried, R. *J. Am. Chem. Soc.* ***1983***, *105*, 950; Creary, X.; Geiger, C.C. *J. Am. Chem. Soc.* ***1983***, *105*, 7123; Chang, S.; le Noble, W.J. *J. Am. Chem. Soc.* ***1984***, *106*, 810; Kirmse, W.; Brandt, S. *Chem. Ber.* ***1984***, *117*, 2510; Wilcox, C.F.; Brungardt, B. *Tetrahedron Lett.* ***1984***, *25*, 3403; Lajunen, M. *Acc. Chem. Res.* ***1985***, *18*, 254; Sharma, R.B.; Sen Sharma, D.K.; Hiraoka, K.; Kebarle, P. *J. Am. Chem. Soc.* ***1985***, *107*, 3747; Servis, K.L.; Domenick, R.L.; Forsyth, D.A.; Pan, Y. *J. Am. Chem. Soc.* ***1987***, *109*, 7263; Lenoir, D.; Apeloig, Y.; Arad, D.; Schleyer, P.v.R. *J. Org. Chem.* ***1988***, *53*, 661.

[179]For some evidence against a nonclassical **59** see Dewar, M.J.S.; Haddon, R.C.; Komornicki, A.; Rzepa, H. *J. Am. Chem. Soc.* ***1977***, *99*, 377; Lambert, J.B.; Mark, H.W. *J. Am. Chem. Soc.* ***1978***, *100*, 2501; Christol, H.; Coste, J.; Pietrasanta, F.; Plénat, F.; Renard, G. *J. Chem. Soc. (S)* ***1978***, 62; Brown, H.C.; Rao, C.G. *J. Org. Chem.* ***1979***, *44*, 133, 3536; ***1980***, *45*, 2113; Liu, K.; Yen, C.; Hwang, H. *J. Chem. Res.(S)* ***1980***, 152; Werstiuk, N.H.; Dhanoa, D.; Timmins, G. *Can. J. Chem.* ***1983***, *61*, 2403; Brown, H.C.; Ikegami, S.; Vander Jagt, D.L. *J. Org. Chem.* ***1985***, *50*, 1165; Nickon, A.; Swartz, T.D.; Sainsbury, D.M.; Toth, B.R. *J. Org. Chem.* ***1986***, *51*, 3736. See also, Brown, H.C. *Top. Curr. Chem.* ***1979***, *80*, 1.

[180]The presence of hydride shifts (p. $$$) under solvolysis conditions has complicated the interpretation of the data.

[181]Olah, G.A. *Acc. Chem. Res.* ***1976***, *9*, 41; Olah, G.A.; Liang, G.; Mateescu, G.D.; Riemenschneider, J.L. *J. Am. Chem. Soc.* ***1973***, *95*, 8698; Saunders, M.; Kates, M.R. *J. Am. Chem. Soc.* ***1980***, *102*, 6867; ***1983***, *105*, 3571; Olah, G.A.; Prakash, G.K.S.; Saunders, M. *Acc. Chem. Res.* ***1983***, *16*, 440. See also, Schleyer, P.v.R.; Lenoir, D.; Mison, P.; Liang, G.; Prakash, G.K.S.; Olah, G.A. *J. Am. Chem. Soc.* ***1980***, *102*, 683; Johnson, S.A.; Clark, D.T. *J. Am. Chem. Soc.* ***1988***, *110*, 4112.

[182]This conclusion has been challenged: Fong, F.K. *J. Am. Chem. Soc.* ***1974***, *96*, 7638; Kramer, G.M. *Adv. Phys. Org. Chem.* ***1975***, *11*, 177; Brown, H.C.; Periasamy, M.; Kelly, D.P.; Giansiracusa, J.J. *J. Org. Chem.* ***1982***, *47*, 2089; Kramer, G.M.; Scouten, C.G. *Adv. Carbocation Chem.* ***1989***, *1*, 93. See, however, Olah, G.A.; Prakash, G.K.S.; Farnum, D.G.; Clausen, T.P. *J. Org. Chem.* ***1983***, *48*, 2146.

[183]Yannoni, C.S.; Macho, V.; Myhre, P.C. *J. Am. Chem. Soc.* ***1982***, *104*, 907, 7380; *Bull. Soc. Chim. Belg.* ***1982***, *91*, 422; Myhre, P.C.; Webb, G.G.; Yannoni, C.S. *J. Am. Chem. Soc.* ***1990***, *112*, 8991.

Olah and co-workers represented the nonclassical structure as a corner-protonated nortricyclane (**62**); the symmetry is better seen when the ion is drawn as in **63**. Almost all the positive charge resides on C-1 and C-2 and very little on the bridging carbon C-6. Other evidence for the nonclassical nature of the 2-norbornyl cation in stable solutions comes from heat of reaction measurements that show that the 2-norbornyl cation is more stable (by ~6–10 kcal mol^{-1} or 25–40 kJ mol^{-1}) than would be expected without the bridging.[184] Studies of ir spectra of the 2-norbornyl cation in the gas phase also show the nonclassical structure.[185] *Ab initio* calculations show that the nonclassical structure corresponds to an energy minimum.[186]

The spectra of other norbornyl cations have also been investigated at low temperatures. Spectra of the tertiary 2-methyl- and 2-ethylnorbornyl cations show less delocalization,[187] and the 2-phenylnorbornyl cation (**64**) is essentially classical,[188] as are the 2-methoxy-[189] and 2-chloronorbornyl cations.[190] We may recall (p. 242) that methoxy and halo groups also stabilize a positive charge. The ^{13}C NMR data show that electron-withdrawing groups on the benzene ring of **64** cause the ion to become less classical, while electron-donating groups enhance the classical nature of the ion.[191]

b. *The Cyclopropylmethyl System.* Apart from the 2-norbornyl system, the greatest amount of effort in the search for C—C participation has been devoted to the cyclopropylmethyl system.[192] It has long been known that cyclopropylmethyl substrates solvolyze with abnormally high rates and

[184]For some examples, see Hogeveen, H.; Gaasbeek, C.J. *Recl. Trav. Chim. Pays-Bas* ***1969***, *88*, 719; Hogeveen, H. *Recl. Trav. Chim. Pays-Bas* ***1970***, *89*, 74; Solomon, J.J.; Field, F.H. *J. Am. Chem. Soc.* ***1976***, *98*, 1567; Staley, R.H.; Wieting, R.D.; Beauchamp, J.L. *J. Am. Chem. Soc.* ***1977***, *99*, 5964; Arnett, E.M.; Pienta, N.; Petro, C. *J. Am. Chem. Soc.* ***1980***, *102*, 398; Saluja, P.P.S.; Kebarle, P. *J. Am. Chem. Soc.* ***1979***, *101*, 1084; Schleyer, P.v.R.; Chandrasekhar, J. *J. Org. Chem.* ***1981***, *46*, 225; Lossing, F.P.; Holmes, J.L. *J. Am. Chem. Soc.* ***1984***, *106*, 6917.

[185]Koch, W.; Liu, B.; DeFrees, D.J.; Sunko, D.E.; Vančik, H. *Angew. Chem. Int. Ed.* ***1990***, *29*, 183.

[186]See, for example Koch, W.; Liu, B.; DeFrees, D.J. *J. Am. Chem. Soc.* ***1989***, *111*, 1527.

[187]Olah, G.A.; DeMember, J.R.; Lui, C.Y.; White, A.M. *J. Am. Chem. Soc.* ***1969***, *91*, 3958. See also, Laube, T. *Angew. Chem. Int. Ed.* ***1987***, *26*, 560; Forsyth, D.A.; Panyachotipun, C. *J. Chem. Soc., Chem. Commun.* ***1988***, 1564.

[188]Olah, G.A. *Acc. Chem. Res.* ***1976***, *9*, 41; Farnum, D.G.; Mehta, G. *J. Am. Chem. Soc.* ***1969***, *91*, 3256. See also, Schleyer, P.v.R.; Kleinfelter, D.C.; Richey, Jr., H.G. *J. Am. Chem. Soc.* ***1963***, *85*, 479; Farnum, D.G.; Wolf, A.D. *J. Am. Chem. Soc.* ***1974***, *96*, 5166.

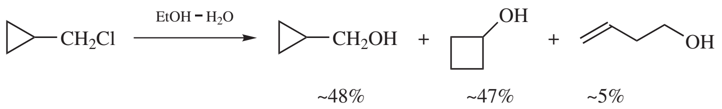
[189]Nickon, A.; Lin, Y. *J. Am. Chem. Soc.* ***1969***, *91*, 6861. See also, Montgomery, L.K.; Grendze, M.P.; Huffman, J.C. *J. Am. Chem. Soc.* ***1987***, *109*, 4749.

[190]Fry, A.J.; Farnham, W.B. *J. Org. Chem.* ***1969***, *34*, 2314.

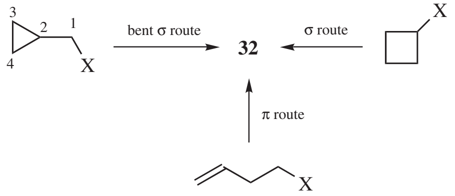
[191]Olah, G.A.; Prakash, G.K.S.; Liang, G. *J. Am. Chem. Soc.* ***1977***, *99*, 5683; Farnum, W.B.; Botto, R.E.; Chambers, W.T.; Lam, B. *J. Am. Chem. Soc.* ***1978***, *100*, 3847. See also, Olah, G.A.; Berrier, A.L.; Prakash, G.K.S. *J. Org. Chem.* ***1982***, *47*, 3903.

[192]For reviews, see, in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, ***1972***, the articles by Richey, Jr., H.G. pp. 1201–1294, and by Wiberg, K.B.; Hess, Jr., B.A.; Ashe III, A.J. pp. 1295–1345; Hanack, M.; Schneider, H. *Fortschr. Chem. Forsch.* ***1967***, *8*, 554, *Angew. Chem. Int. Ed.* ***1967***, *6*, 666; Sarel, S.; Yovell, J.; Sarel-Imber, M. *Angew. Chem. Int. Ed.* ***1968***, *7*, 577.

that the products often include not only unrearranged cyclopropylmethyl, but also cyclobutyl and homoallylic compounds. An example is[193]

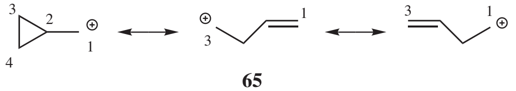


Cyclobutyl substrates also solvolyze abnormally rapidly and give similar products. Furthermore, when the reactions are carried out with labeled substrates, considerable, although not complete, scrambling is observed. For these reasons, it has been suggested that a common intermediate (some kind of nonclassical intermediate, e.g., **32**, p. 450) is present in these cases. This common intermediate could then be obtained by three routes:



In recent years, much work has been devoted to the study of these systems, and it is apparent that matters are not so simple. Although there is much that is still not completely understood, some conclusions can be drawn.

i. In solvolysis of simple primary cyclopropylmethyl systems the rate is enhanced because of participation by the σ bonds of the ring.[194] The ion that forms initially is an unrearranged cyclopropylmethyl cation[195] that is *symmetrically* stabilized, that is, both the 2,3 and 2,4 σ bonds help stabilize the positive charge. We have already seen (p. 240) that a cyclopropyl group stabilizes an adjacent positive charge even better than a phenyl group. One way of representing the structure of this cation is as shown in **65**. Among the



65

evidence that **65** is a symmetrical ion is that substitution of one or more methyl groups in the 3 and 4 positions increases the rate of solvolysis of cyclopropylcarbinyl 3,5-dinitrobenzoates by approximately a factor of 10 for *each* methyl group.[196] If only one of the σ bonds (say, the 2,3 bond)

[193]Roberts, D.D.; Mazur, R.H. *J. Am. Chem. Soc.* ***1951***, *73*, 2509.

[194]See, for example, Roberts, D.D.; Snyder, Jr., R.C. *J. Org. Chem.* ***1979***, *44*, 2860, and references cited therein.

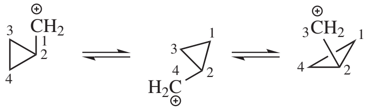
[195]Wiberg, K.B.; Ashe III, A.J. *J. Am. Chem. Soc.* ***1968***, *90*, 63.

[196]Schleyer, P.v.R.; Van Dine, G.W. *J. Am. Chem. Soc.* ***1966***, *88*, 2321. See also, Kevill, D.N.; Abduljaber, M.H. *J. Org. Chem.* ***2000***, *65*, 2548.

stabilizes the cation, then methyl substitution at the 3 position should increase the rate, and a second methyl group at the 3 position should increase it still more, but a second methyl group at the 4 position should have little effect.[197]

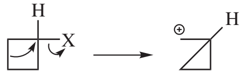
ii. The most stable geometry of simple cyclopropylmethyl cations is the bisected one shown on p. 240. There is much evidence that in systems where this geometry cannot be obtained, solvolysis is greatly slowed.[198]

iii. Once a cyclopropylmethyl cation is formed, it can rearrange to two other cyclopropylmethyl cations:



This rearrangement, which accounts for the scrambling, is completely stereospecific.[199] The rearrangements probably take place through a nonplanar cyclobutyl cation intermediate or transition state. The formation of cyclobutyl and homoallylic products from a cyclopropylmethyl cation is also completely stereospecific. These products may arise by direct attack of the nucleophile on **65** or on the cyclobutyl cation intermediate.[200] A planar cyclobutyl cation is ruled out in both cases because it would be symmetrical and the stereospecificity would be lost.

iv. The rate enhancement in the solvolysis of secondary cyclobutyl substrates is probably caused by participation by a bond leading directly to **65**, which accounts for the fact that solvolysis of cyclobutyl and of cyclopropylmethyl



substrates often gives similar product mixtures. There is no evidence that requires the cyclobutyl cations to be intermediates in most secondary cyclobutyl systems, although tertiary cyclobutyl cations can be solvolysis intermediates.

v. The unsubstituted cyclopropylmethyl cation has been generated in super acid solutions at low temperatures, where ^{13}C NMR spectra have led to

[197]For a summary of additional evidence for the symmetrical nature of cyclopropylmethyl cations, see Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, ***1972***, the article by Wiberg, K.B.; Hess, Jr., B.A.; Ashe III, A.J. pp. 1300–1303.

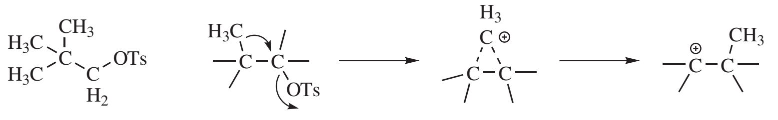
[198]For example, see Ree, B.; Martin, J.C. *J. Am. Chem. Soc.* ***1970***, *92*, 1660; Rhodes, Y.E.; DiFate, V.G. *J. Am. Chem. Soc.* ***1972***, *94*, 7582. See, however, Brown, H.C.; Peters, E.N. *J. Am. Chem. Soc.* ***1975***, *97*, 1927.

[199]Wiberg, K.B.; Szeimies, G. *J. Am. Chem. Soc.* ***1968***, *90*, 4195; ***1970***, *92*, 571; Majerski, Z.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1971***, *93*, 665.

[200]Koch, W.; Liu, B.; DeFrees, D.J. *J. Am. Chem. Soc.* ***1988***, *110*, 7325; Saunders, M.; Laidig, K.E.; Wiberg, K.B.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1988***, *110*, 7652.

the conclusion that it consists of a mixture of the bicyclobutonium ion **32** and the bisected cyclopropylmethyl cation **65**, in equilibrium with **32**.[201] Molecular-orbital calculations show that these two species are energy minima, and that both have nearly the same energy.[200]

c. *Methyl as a Neighboring Group*. Both the 2-norbornyl and cyclopropylmethyl system contain a σ bond that is geometrically constrained to be in a particularly favorable position for participation as a neighboring group. However, there have been a number of investigations to determine whether a C—C bond can lend anchimeric assistance even in a simple open-chain compound, such as neopentyl tosylate. On solvolysis, neopentyl systems undergo almost exclusive rearrangement and **66** must lie on the reaction path, but the two questions that have been asked are (*1*) Is the departure of the


Neopentyl tosylate
66

leaving group concerted with the formation of the CH_3—C bond (i.e., does the methyl participate)? (*2*) Is **66** an intermediate or only a transition state? With respect to the first question, there is evidence, chiefly from isotope effect studies, that indicates that the methyl group in the neopentyl system does indeed participate,[202] although it may not greatly enhance the rate. As to the second question, evidence that **66** is an intermediate is that small amounts of cyclopropanes (10–15%) can be isolated in these reactions.[203] Cation **66** is a protonated cyclopropane and would give cyclopropane on loss of a proton.[204] In an effort to isolate a species that has structure **66**, the 2,3,3-trimethyl-2-butyl cation was prepared in super acid solutions at low temperatures.[205] However, ^{1}H and ^{13}C NMR, as well as Raman spectra,

[201] Staral, J.S.; Yavari, I.; Roberts, J.D.; Prakash, G.K.S.; Donovan, D.J.; Olah, G.A. *J. Am. Chem. Soc.* ***1978***, *100*, 8016. See also, Olah, G.A.; Spear, R.J.; Hiberty, P.C.; Hehre, W.J. *J. Am. Chem. Soc.* ***1976***, *98*, 7470; Saunders, M.; Siehl, H. *J. Am. Chem. Soc.* ***1980***, *102*, 6868; Brittain, W.J.; Squillacote, M.E.; Roberts, J.D. *J. Am. Chem. Soc.* ***1984***, *106*, 7280; Siehl, H.; Koch, E. *J. Chem. Soc., Chem. Commun.* ***1985***, 496; Prakash, G.K.S.; Arvanaghi, M.; Olah, G.A. *J. Am. Chem. Soc.* ***1985***, *107*, 6017; Myhre, P.C.; Webb, G.G.; Yannoni, C.S. *J. Am. Chem. Soc.* ***1990***, *112*, 8992.

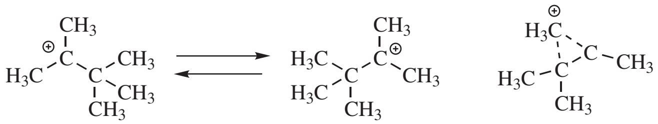
[202] For example, see Dauben, W.G.; Chitwood, J.L. *J. Am. Chem. Soc.* ***1968***, *90*, 6876; Ando, T.; Morisaki, H. *Tetrahedron Lett.* ***1979***, 121; Shiner, V.J.; Tai, J.J. *J. Am. Chem. Soc.* ***1981***, *103*, 436; Yamataka, H.; Ando, T.; Nagase, S.; Hanamura, M.; Morokuma, K. *J. Org. Chem.* ***1984***, *49*, 631. For an opposing view, see Zamashchikov, V.V.; Rudakov, E.S.; Bezbozhnaya, T.V.; Matveev, A.A. *J. Org. Chem. USSR* ***1984***, *20*, 11.

[203] Skell, P.S.; Starer, I. *J. Am. Chem. Soc.* ***1960***, *82*, 2971; Silver, M.S. *J. Am. Chem. Soc.* ***1960***, *82*, 2971; Friedman, L.; Bayless, J.H. *J. Am. Chem. Soc.* ***1969***, *91*, 1790; Friedman, L.; Jurewicz, A.T. *J. Am. Chem. Soc.* ***1969***, *91*, 1800, 1803; Dupuy, W.E.; Hudson, H.R.; Karam, P.A. *Tetrahedron Lett.* ***1971***, 3193; Silver, M.S.; Meek, A.G. *Tetrahedron Lett.* ***1971***, 3579; Dupuy, W.E.; Hudson, H.R. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 1715.

[204] For further discussions of protonated cyclopropanes, see pp. $$$, $$$.

[205] Olah, G.A.; DeMember, J.R.; Commeyras, A.; Bribes, J.L. *J. Am. Chem. Soc.* ***1971***, *93*, 459.

showed this to be a pair of rapidly equilibrating open ions.

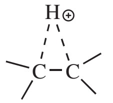


67

Of course, **67** must lie on the reaction path connecting the two open ions, but it is evidently a transition state and not an intermediate. However, evidence from X-ray photoelectron spectroscopy (ESCA) has shown that the 2-butyl cation is substantially methyl bridged.[206]

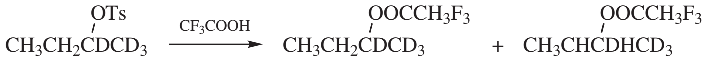
d. *Silylalkyl as a Neighboring Group.* Rates of solvolysis are enhanced in molecules that contain a silylalkyl or silylaryl group β- to the carbon bearing the leaving group. This is attributed to formation of a cyclic transition state involving the silicon.[207]

5. *Hydrogen as a Neighboring Group.* The questions relating to hydrogen are similar to those relating to methyl. There is no question that hydride can migrate, but the two questions are (*1*) Does the hydrogen participate in the



68

departure of the leaving group? (*2*) Is **68** an intermediate or only a transition state? There is some evidence that a β hydrogen can participate.[208] Evidence that **68** can be an intermediate in solvolysis reactions comes from



69 **70** **71**

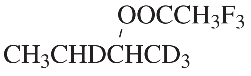
a study of the solvolysis in trifluoroacetic acid of deuterated *sec*-butyl tosylate **69**. In this solvent of very low nucleophilic power, the products were

[206]Johnson, S.A.; Clark, D.T. *J. Am. Chem. Soc.* ***1988***, *110*, 4112. See also, Carneiro, J.W.; Schleyer, P.v.R.; Koch, W.; Raghavachari, K. *J. Am. Chem. Soc.* ***1990***, *112*, 4064.

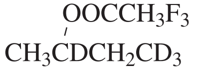
[207]Fujiyama, R.; Munechika, T. *Tetrahedron Lett.* ***1993***, *34*, 5907.

[208]See, for example, Shiner, Jr., V.J.; Jewett, J.G. *J. Am. Chem. Soc.* ***1965***, *87*, 1382; Tichy, M.; Hapala, J.; Sicher, J. *Tetrahedron Lett.* ***1969***, 3739; Myhre, P.C.; Evans, E. *J. Am. Chem. Soc.* ***1969***, *91*, 5641; Inomoto, Y.; Robertson, R.E.; Sarkis, G. *Can. J. Chem.* ***1969***, *47*, 4599; Shiner, V.J.; Stoffer, J.O. *J. Am. Chem. Soc.* ***1970***, *92*, 3191; Krapcho, A.P.; Johanson, R.G. *J. Org. Chem.* ***1971***, *36*, 146; Chuit, C.; Felkin, H.; Le Ny, G.; Lion, C.; Prunier, L. *Tetrahedron* ***1972***, *28*, 4787; Stéhelin, L.; Kanellias, L.; Ourisson, G. *J. Org. Chem.* ***1973***, *38*, 847, 851; Hirsl-Staršević, S.; Majerski, Z.; Sunko, D.E. *J. Org. Chem.* ***1980***, *45*, 3388; Buzek, P.; Schleyer, P.v.R.; Sieber, S.; Koch, W.; Carneiro, J.W. de M.; Vančik, H.; Sunko, D.E. *J. Chem. Soc., Chem. Commun.* ***1991***, 671; Imhoff, M.A.; Ragain, R.M.; Moore, K.; Shiner, V.J. *J. Org. Chem.* ***1991***, *56*, 3542.

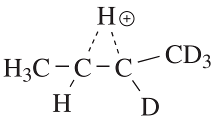
an equimolar mixture of **70** and **71**,[209] but *no* **72** or **73** was found. If this



72

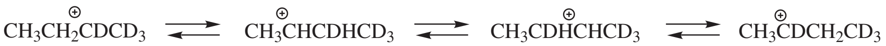


73



74

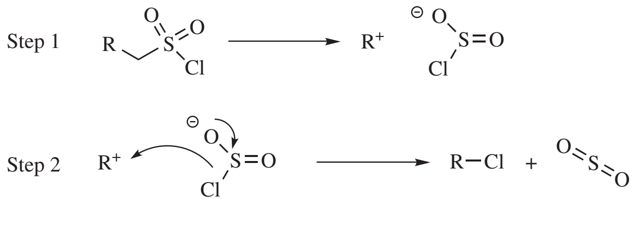
reaction did not involve neighboring hydrogen at all (pure S_N2 or S_N1), the product would be only **70**. On the other hand, if hydrogen does migrate, but only open cations are involved, then there should be an equilibrium among these four cations:



leading not only to **70** and **71**, but also to **72** and **73**. The results are most easily compatible with the intermediacy of the bridged ion **74**, which can then be attacked by the solvent equally at the 2 and 3 positions. Attempts to prepare **68** as a stable ion in super acid solutions at low temperatures have not been successful.[208]

The S_Ni Mechanism

In a few reactions, nucleophilic substitution proceeds with retention of configuration, even where there is no possibility of a neighboring-group effect. In the S_Ni mechanism (*substitution nucleophilic internal*), part of the leaving group must be able to attack the substrate, detaching itself from the rest of the leaving group in the process. The IUPAC designation is $D_N + A_ND_e$. The first step is the same as the very first step of the S_N1 mechanism dissociation into an intimate ion pair.[210] But in the second step part of the leaving group attacks, necessarily from the front since it is unable to get to the rear, which results in retention of configuration.



[209]Dannenberg, J.J.; Goldberg, B.J.; Barton, J.K.; Dill, K.; Weinwurzel, D.H.; Longas, M.O. *J. Am. Chem. Soc.* ***1981***, *103*, 7764. See also, Dannenberg, J.J.; Barton, J.K.; Bunch, B.; Goldberg, B.J.; Kowalski, T. *J. Org. Chem.* ***1983***, *48*, 4524; Allen, A.D.; Ambidge, I.C.; Tidwell, T.T. *J. Org. Chem.* ***1983***, *48*, 4527.

[210]Lee, C.C.; Finlayson, A.J. *Can. J. Chem.* ***1961***, *39*, 260; Lee, C.C.; Clayton, J.W.; Lee, C.C.; Finlayson, A.J. *Tetrahedron* ***1962***, *18*, 1395.

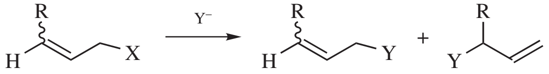
The example shown is the most important case of this mechanism yet discovered, since the reaction of alcohols with thionyl chloride to give alkyl halides usually proceeds in this way, with the first step in this case being $ROH + SOCl_2 \rightarrow ROSOCl$ (these alkyl chlorosulfites can be isolated).

Evidence for this mechanism is as follows: the addition of pyridine to the mixture of alcohol and thionyl chloride results in the formation of alkyl halide with *inverted* configuration. Inversion results because the pyridine reacts with ROSOCl to give $ROSONC_5H_5$ before anything further can take place. The Cl^- freed in this process now attacks from the rear. The reaction between alcohols and thionyl chloride is second order, which is predicted by this mechanism, but the decomposition by simple heating of ROSOCl is first order.[211]

The S_Ni mechanism is relatively rare. Another example is the decomposition of ROCOCl (alkyl chloroformates) into RCl and CO_2.[212]

Nucleophilic Substitution at an Allylic Carbon: Allylic Rearrangements

Allylic substrates rapidly undergo nucleophilic substitution reactions (see p. 482), but we discuss them in a separate section because they are commonly accompanied by a certain kind of rearrangement known as an *allylic rearrangement*.[213] When allylic substrates are treated with nucleophiles under S_N1 conditions, two products are usually obtained: the normal one and a rearranged one.



Two products are formed because an allylic type of carbocation is a resonance hybrid

$$R{-}CH{=}CH{-}\overset{\oplus}{C}H_2 \longleftrightarrow R{-}\overset{\oplus}{C}H{-}CH{=}CH_2$$

so that C-1 and C-3 each carry a partial positive charge and both are attacked by Y. Of course, an allylic rearrangement is undetectable in the case of symmetrical allylic cations, as in the case where $R = H$, unless isotopic labeling is used. This mechanism has been called the S_N1' mechanism. The IUPAC designation is $1/D_N + 3/A_N$, the numbers 1 and 3 signifying the *relative* positions where the nucleophile attacks and from which the nucleofuge leaves.

[211]Lewis, E.S.; Boozer, C.E. *J. Am. Chem. Soc.* ***1952***, *74*, 308.

[212]Lewis, E.S.; Herndon, W.C.; Duffey, D.C. *J. Am. Chem. Soc.* ***1961***, *83*, 1959; Lewis, E.S.; Witte, K. *J. Chem. Soc. B* ***1968***, 1198. For other examples, see Hart, H.; Elia, R.J. *J. Am. Chem. Soc.* ***1961***, *83*, 985; Stevens, C.L.; Dittmer, H.; Kovacs, J. *J. Am. Chem. Soc.* ***1963***, *85*, 3394; Kice, J.L.; Hanson, G.C. *J. Org. Chem.* ***1973***, *38*, 1410; Cohen, T.; Solash, J. *Tetrahedron Lett.* ***1973***, 2513; Verrinder, D.J.; Hourigan, M.J.; Prokipcak, J.M. *Can. J. Chem.* ***1978***, *56*, 2582.

[213]For a review, see DeWolfe, R.H., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 417–437. For comprehensive older reviews, see DeWolfe, R.H.; Young, W.G. *Chem. Rev.* ***1956***, *56*, 753; in Patai, S. *The Chemistry of Alkenes*, Wiley, NY, **1964**, the sections by Mackenzie, K. pp. 436–453 and DeWolfe, R.H.; Young, W.G. pp. 681–738.

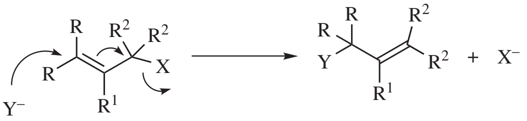
As with other S_N1 reactions, there is clear evidence that S_N1' reactions can involve ion pairs. If the intermediate attacked by the nucleophile is a completely free carbocation, then, say,

$$\underset{\mathbf{75}}{CH_3CH{=}CHCH_2Cl} \qquad \text{and} \qquad \underset{\mathbf{76}}{CH_3CHClCH{=}CH_2}$$

should give the same mixture of alcohols when reacting with hydroxide ion, since the carbocation from each should be the same. When treated with 0.8 *M* aq. NaOH at 25°C, **75** gave 60% $CH_3CH{=}CHCH_2OH$ and 40% $CH_3CHOHCH{=}CH_2$, while **76** gave the products in yields of 38 and 62%, respectively.[214] This phenomenon is called the *product spread*. In this case, and in most others, the product spread is in the direction of the starting compound. With increasing polarity of solvent,[215] the product spread decreases and in some cases is entirely absent. It is evident that in such cases the high polarity of the solvent stabilizes completely free carbocations. There is other evidence for the intervention of ion pairs in many of these reactions. When $H_2C{=}CHCMe_2Cl$ was treated with acetic acid, both acetates were obtained, but also some $ClCH_2CH{=}CMe_2$,[216] and the isomerization was faster than the acetate formation. This could not have arisen from a completely free Cl^- returning to the carbon, since the rate of formation of the rearranged chloride was unaffected by the addition of external Cl^-. All these facts indicate that the first step in these reactions is the formation of an unsymmetrical intimate ion pair that undergoes a considerable amount of internal return and in which the counterion remains close to the carbon from which it departed. Thus, **75** and **76**, for example, give rise to two *different* intimate ion pairs. The field of the anion polarizes the allylic cation, making the nearby carbon atom more electrophilic, so that it has a greater chance of attracting the nucleophile.[217]

Nucleophilic substitution at an allylic carbon can also take place by an S_N2 mechanism, in which case no allylic rearrangement usually takes place. However, allylic rearrangements can also take place under S_N2 conditions, by the following mechanism, in which the nucleophile attacks at the γ carbon rather than the usual position:[218]

S_N2' Mechanism



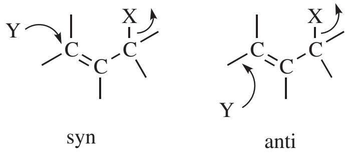
The IUPAC designation is $3/1/A_ND_N$. This mechanism is a second-order allylic rearrangement; it usually comes about where S_N2 conditions hold but where

[214]DeWolfe, R.H.; Young, W.G. *Chem. Rev.* ***1956***, *56*, 753 give several dozen such examples.
[215]Katritzky, A.R.; Fara, D.C.; Yang, H.; Tämm, K.; Tamm, T.; Karelson, M. *Chem. Rev.* ***2004***, *104*, 175.
[216]Young, W.G.; Winstein, S.; Goering, H.L. *J. Am. Chem. Soc.* ***1951***, *73*, 1958.
[217]For additional evidence for the involvement of ion pairs in S_N1' reactions, see Goering, H.L.; Linsay, E.C. *J. Am. Chem. Soc.* ***1969***, *91*, 7435; d'Incan, E.; Viout, P. *Bull. Soc. Chim. Fr.* ***1971***, 3312; Astin, K.B.; Whiting, M.C. *J. Chem. Soc. Perkin Trans. 2* ***1976***, 1157; Kantner, S.S.; Humski, K.; Goering, H.L. *J. Am. Chem. Soc.* ***1982***, *104*, 1693; Thibblin, A. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 313; Ref. 77.
[218]For a review of the S_N2' mechanism, see Magid, R.M. *Tetrahedron* ***1980***, *36*, 1901, see pp. 1901–1910.

a substitution sterically retards the normal S_N2 mechanism. There are few well-established cases of the S_N2' mechanism on substrates of the type C=C–CH_2X, but compounds of the form C=C–CR_2X give the S_N2' rearrangement almost exclusively[219] when they give bimolecular reactions at all. Increasing the size of the nucleophile can also increase the extent of the S_N2' reaction at the expense of the S_N2.[219] In certain cases, the leaving group can also have an affect on whether the rearrangement occurs. Thus PhCH=$CHCH_2$X, treated with $LiAlH_4$, gave 100% S_N2 reaction (no rearrangement) when X = Br or Cl, but 100% S_N2' when $X = PPh_3^+ Br^-$.[220] The solvent also plays a role in some cases, with more polar solvents giving more S_N2' product.[221]

The S_N2' mechanism as shown above involves the simultaneous movement of three pairs of electrons. However, Bordwell has contended that there is no evidence that requires that this bond making and bond breaking be in fact concerted,[222] and that a true S_N2' mechanism is a myth. There is evidence both for[223] and against[224] this proposal. There is also a review of the S_N' reaction.[225]

The stereochemistry of S_N2' reactions has been investigated. It has been found that both syn[226] (the nucleophile enters on the side from which the leaving group departs) and anti[227] reactions can take place, depending on the nature of X and Y,[228] although the syn pathway predominates in most cases.



[219]Bordwell, F.G.; Clemens, A.H.; Cheng, J. *J. Am. Chem. Soc.* ***1987***, *109*, 1773. Also see, Young, J.-j; Jung, L.-j.; Cheng, K.-m. *Tetrahedron Lett.* ***2000***, *41*, 3411.

[220]Hirab, T.; Nojima, M.; Kusabayashi, S. *J. Org. Chem.* ***1984***, *49*, 4084.

[221]Hirashita, T.; Hayashi, Y.; Mitsui, K.; Araki, S. *Tetrahedron Lett.* ***2004***, *45*, 3225.

[222]Bordwell, F.G.; Mecca, T.G. *J. Am. Chem. Soc.* ***1972***, *94*, 5829; Bordwell, F.G. *Acc. Chem. Res.* ***1970***, *3*, 281, pp. 282–285. See also, de la Mare, P.B.D.; Vernon, C.A. *J. Chem. Soc. B* ***1971***, 1699; Dewar, M.J.S. *J. Am. Chem. Soc.* ***1984***, *106*, 209.

[223]See Uebel, J.J.; Milaszewski, R.F.; Arlt, R.E. *J. Org. Chem.* ***1977***, *42*, 585.

[224]See Fry, A. *Pure Appl. Chem.* ***1964***, *8*, 409; Georgoulis, C.; Ville, G. *J. Chem. Res. (S)* ***1978***, 248; *Bull. Soc. Chim. Fr.* ***1985***, 485; Meislich, H.; Jasne, S.J. *J. Org. Chem.* ***1982***, *47*, 2517.

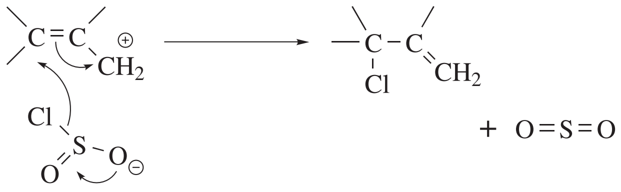
[225]Paquette, L.A.; Stirling, C.J.M. *Tetrahedron* ***1992***, *48*, 7383.

[226]See, for example, Stork, G.; White, W.N. *J. Am. Chem. Soc.* ***1956***, *78*, 4609; Jefford, C.W.; Sweeney, A.; Delay, F. *Helv. Chim. Acta* ***1972***, *55*, 2214; Kirmse, W.; Scheidt, F.; Vater, H. *J. Am. Chem. Soc.* ***1978***, *100*, 3945; Gallina, C.; Ciattini, P.G. *J. Am. Chem. Soc.* ***1979***, *101*, 1035; Magid, R.M.; Fruchey, O.S. *J. Am. Chem. Soc.* ***1979***, *101*, 2107; Bäckvall, J.E.; Vågberg, J.O.; Genêt, J.P. *J. Chem. Soc., Chem. Commun.* ***1987***, 159.

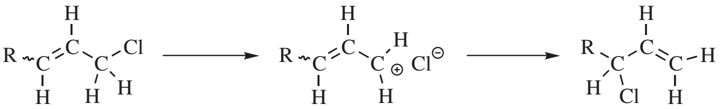
[227]See, for example, Borden, W.T.; Corey, E.J. *Tetrahedron Lett.* ***1969***, 313; Takahashi, T.T.; Satoh, J.Y. *Bull. Chem. Soc. Jpn.* ***1975***, *48*, 69; Staroscik, J.; Rickborn, B. *J. Am. Chem. Soc.* ***1971***, *93*, 3046; See also, Liotta, C. *Tetrahedron Lett.* ***1975***, 523; Stork, G.; Schoofs, A.R. *J. Am. Chem. Soc.* ***1979***, *101*, 5081.

[228]Stork, G.; Kreft III, A.F. *J. Am. Chem. Soc.* ***1977***, *99*, 3850, 3851; Oritani, T.; Overton, K.H. *J. Chem. Soc., Chem. Commun.* ***1978***, 454; Bach, R.D.; Wolber, G.J. *J. Am. Chem. Soc.* ***1985***, *107*, 1352. See also, Chapleo, C.B.; Finch, M.A.W.; Roberts, S.M.; Woolley, G.T.; Newton, R.F.; Selby, D.W. *J. Chem. Soc. Perkin Trans. 1* ***1980***, 1847; Stohrer, W. *Angew. Chem. Int. Ed.* ***1983***, *22*, 613.

When a molecule has in an allylic position a nucleofuge capable of giving the S_Ni reaction, it is possible for the nucleophile to attack at the γ position instead of the α position. This is called the S_Ni' mechanism and has been demonstrated on 2-buten-1-ol and 3-buten-2-ol, both of which gave 100% allylic rearrangement

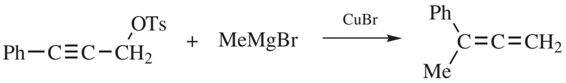


when treated with thionyl chloride in ether.[229] Ordinary allylic rearrangements (S_N1') or S_N2' mechanisms could not be expected to give 100% rearrangement in *both* cases. In the case shown, the nucleophile is only part of the leaving group, not the whole. But it is also possible to have reactions in which a simple leaving group, such as Cl, comes off to form an ion pair and then returns not to the position whence it came, but to the allylic position:



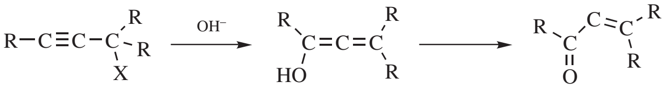
Most S_Ni' reactions are of this type.

Allylic rearrangements have also been demonstrated in propargyl systems, for example,[230]



(Reaction 19-67)

The product in this case is an allene,[231] but such shifts can also give triple-bond compounds or, if Y = OH, an enol will be obtained that tautomerizes to an α,β-unsaturated aldehyde or ketone.



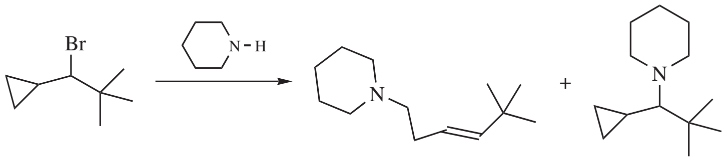
[229]Young, W.G. *J. Chem. Educ.* ***1962***, *39*, 456. For other examples, see Mark, V. *Tetrahedron Lett.* ***1962***, 281; Czernecki, S.; Georgoulis, C.; Labertrande, J.; Prévost, C. *Bull. Soc. Chim. Fr.* ***1969***, 3568; Lewis, E.S.; Witte, K. *J. Chem. Soc. B* ***1968***, 1198; Corey, E.J.; Boaz, N.W. *Tetrahedron Lett.* ***1984***, *25*, 3055.

[230]Vermeer, P.; Meijer, J.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* ***1975***, *94*, 112.

[231]For reviews of such rearrangements, see Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis*, Wiley, NY, ***1984***, pp. 12–19, 26–30; Taylor, D.R. *Chem. Rev.* ***1967***, *67*, 317, pp. 324–328. For a palladium-catalyzed variation of this transformation see Larock, R.C.; Reddy, Ch.K. *Org. Lett.* ***2000***, *2*, 3325.

When X = OH, this conversion of acetylenic alcohols to unsaturated aldehydes or ketones is called the *Meyer–Schuster rearrangement*.[232] The propargyl rearrangement can also go the other way; that is, 1-haloalkenes, treated with organocopper compounds, give alkynes.[233]

The S_N2' reaction has been shown to predominate in reactions of mixed cuprates (**10-57**) with allylic mesylates,[234] and in ring opening reactions of aziridines.[235] A related reaction is the opening of cyclopropylcarbinyl halides with organocuprates where the cyclopropane ring reacts similarly to the C=C unit of an alkene to give a homoallylic substituted product.[236] This latter reaction is interesting since the reaction of **77** with piperidine leads to the S_N2' product (**78**) in ~87% yield, but there is ~8% of the direct substitution product, **79**. Since the carbon bearing the bromine is very hindered, formation of **72** is somewhat unusual under these conditions. As Bordwell has suggested (see above), this may not be a true S_N2 process.



77 **78** **79**

Nucleophilic Substitution at an Aliphatic Trigonal Carbon: The Tetrahedral Mechanism

All the mechanisms so far discussed take place at a saturated carbon atom. Nucleophilic substitution is also important at trigonal carbons, especially when the carbon is double bonded to an oxygen, a sulfur, or a nitrogen. These reactions are discussed in Chapter 16. Nucleophilic substitution at vinylic carbons is considered in the next section; at aromatic carbons in Chapter 13.

Nucleophilic Substitution at a Vinylic Carbon

Nucleophilic substitution at a vinylic carbon[237] is difficult (see p. 481), but many examples are known. The most common mechanisms are the tetrahedral mechanism

[232]For a review, see Swaminathan, S.; Narayanan, K.V. *Chem. Rev.* ***1971***, *71*, 429. For discussions of the mechanism, see Edens, M.; Boerner, D.; Chase, C.R.; Nass, D.; Schiavelli, M.D. *J. Org. Chem.* ***1977***, *42*, 3403; Andres, J.; Cardenas, R.; Silla, E.; Tapi, O. *J. Am. Chem. Soc.* ***1988***, *110*, 666.

[233]Corey, E.J.; Boaz, N.W. *Tetrahedron Lett.* ***1984***, *25*, 3059, 3063.

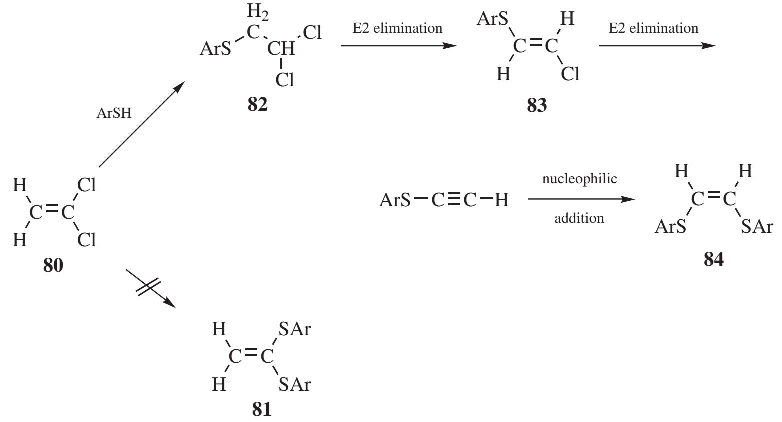
[234]Ibuka, T.; Taga, T.; Habashita, H.; Nakai, K.; Tamamura, H.; Fujii, N.; Chounan, Y.; Nemoto, H.; Yamamoto, Y. *J. Org. Chem.* ***1993***, *58*, 1207.

[235]Wipf, P.; Fritch, P.C. *J. Org. Chem.* ***1994***, *59*, 4875.

[236]Smith, M.B.; Hrubiec, R.T. *Tetrahedron* ***1984***, *40*, 1457; Hrubiec, R.T.; Smith, M.B. *J. Org. Chem.* ***1984***, *49*, 385; Hrubiec, R.T.; Smith, M.B. *Tetrahedron Lett.* ***1983***, *24*, 5031.

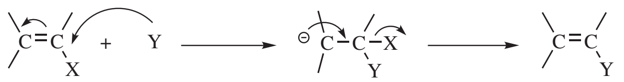
[237]For reviews, see Rappoport, Z. *Recl. Trav. Chim. Pays-Bas* ***1986***, *104*, 309; *React. Intermed. (Plenum)* ***1983***, *3*, 427, *Adv. Phys. Org. Chem.* ***1969***, *7*, 1; Shainyan, B.A. *Russ. Chem. Rev.* ***1986***, *55*, 511; Modena, G. *Acc. Chem. Res.* ***1971***, *4*, 73.

and the closely related *addition–elimination mechanism*. Both of these mechanisms are impossible at a saturated substrate. The addition–elimination mechanism

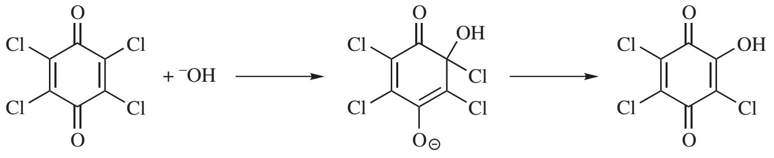


has been demonstrated for the reaction between 1,1-dichloroethene (**80**) and ArS^- catalyzed by ^-OEt.[238] The product was not the 1,1-dithiophenoxy compound **81** but the "rearranged" compound **84**. Isolation of **82** and **83** showed that an addition–elimination mechanism had taken place. In the first step, ArSH adds to the double bond (nucleophilic addition, p. 1007) to give the saturated **82**. The second step is an E2 elimination reaction (p. 1478) to give the alkene **83**. A second elimination and addition give **84**.

The tetrahedral mechanism, often also called addition–elimination (AdN-E), takes place with much less facility than with carbonyl groups, since the negative charge of the intermediate must be borne by a carbon, which is less electronegative than oxygen, sulfur, or nitrogen:



Such an intermediate can also stabilize itself by combining with a positive species. When it does, the reaction is nucleophilic addition to a C=C double bond (see Chapter 15). It is not surprising that with vinylic substrates addition and substitution often compete. For chloroquinones, where the charge is spread by resonance, tetrahedral intermediates have been isolated:[239]



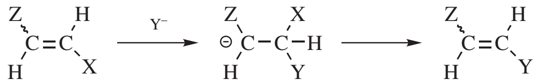
Isolated

[238]Truce, W.E.; Boudakian, M.M. *J. Am. Chem. Soc.* ***1956***, *78*, 2748.
[239]Hancock, J.W.; Morrell, C.E.; Rhom, D. *Tetrahedron Lett.* ***1962***, 987.

In the case of $Ph(MeO)C{=}C(NO_2)Ph + RS^-$, the intermediate lived long enough to be detected by UV spectroscopy.[240]

Since both the tetrahedral and addition–elimination mechanisms begin the same way, it is usually difficult to tell them apart, and often no attempt is made to do so. The strongest kind of evidence for the addition–elimination sequence is the occurrence of a "rearrangement," but of course the mechanism could still take place even if no rearrangement is found. Evidence[241] that a tetrahedral or an addition–elimination mechanism takes place in certain cases (as opposed, e.g., to an S_N1 or S_N2 mechanism) is that the reaction rate increases when the leaving group is changed from Br to Cl to F (this is called the *element effect*).[242] This clearly demonstrates that the carbon–halogen bond does not break in the rate-determining step (as it would in both the S_N1 and S_N2 mechanisms), because fluorine is by far the poorest leaving group among the halogens in both the S_N1 and S_N2 reactions (p. 496). The rate is faster with fluorides in the cases cited, because the superior electron-withdrawing character of the fluorine makes the carbon of the C—F bond more positive, and hence more susceptible to nucleophilic attack.

Ordinary vinylic substrates react very poorly if at all by these mechanisms, but substitution is greatly enhanced in substrates of the type ZCH=CHX, where Z is an electron-withdrawing group, such as HCO, RCO,[243] EtOOC, $ArSO_2$, NC, and F, since these β groups stabilize the carbanion:



Many such examples are known. In most cases where the stereochemistry has been investigated, retention of configuration is observed,[244] but stereoconvergence [the same product mixture from an (*E*) or (*Z*) substrate] has also been observed,[245] especially where the carbanionic carbon bears two electron-withdrawing groups. Although rare, nucleophilic substitution with inversion has also been reported as in the intramolecular substitution of the C—Br bond of 2-bromobut-2-enylamines by the pendant nitrogen atom, giving 2-ethylene aziridines by way of stereochemical inversion.[246] It is not immediately apparent why the tetrahedral mechanism

[240]Bernasconi, C.F.; Fassberg, J.; Killion, Jr., R.B.; Rappoport, Z. *J. Am. Chem. Soc.* ***1989***, *112*, 3169; *J. Org. Chem.* ***1990***, *55*, 4568.

[241]Additional evidence comes from the pattern of catalysis by amines, similar to that discussed for aromatic substrates on p. 856. See Rappoport, Z.; Peled, P. *J. Am. Chem. Soc.* ***1979***, *101*, 2682, and references cited therein.

[242]Beltrame, P.; Favini, G.; Cattania, M.G.; Guella, F. *Gazz. Chim. Ital.* ***1968***, *98*, 380. See also, Solov'yanov, A.A.; Shtern, M.M.; Beletskaya, I.P.; Reutov, O.A. *J. Org. Chem. USSR* ***1983***, *19*, 1945; Avramovitch, B.; Weyerstahl, P.; Rappoport, Z. *J. Am. Chem. Soc.* ***1987***, *109*, 6687.

[243]For a review, see Rybinskaya, M.I.; Nesmeyanov, A.N.; Kochetkov, N.K. *Russ. Chem. Rev.* ***1969***, *38*, 433.

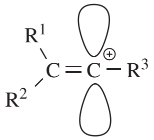
[244]Rappoport, Z. *Adv. Phys. Org. Chem.* ***1969***, *7*, see pp. 31–62; Shainyan, B.A. *Russ. Chem. Rev.* ***1986***, *55*, 516. See also, Rappoport, Z.; Gazit, A. *J. Am. Chem. Soc.* ***1987***, *109*, 6698.

[245]See Rappoport, Z.; Gazit, A. *J. Org. Chem.* ***1985***, *50*, 3184, *J. Am. Chem. Soc.* ***1986***, *51*, 4112; Park, K.P.; Ha, H. *Bull. Chem. Soc. Jpn.* ***1990***, *63*, 3006.

[246]Shiers, J.J.; Shipman, M.; Hayes, J.-F.; Slawin, A.M.Z. *J. Am. Chem. Soc.* ***2004***, *126*, 6868.

should lead to retention, but this behavior has been ascribed, on the basis of molecular orbital calculations, to hyperconjugation involving the carbanionic electron pair and the substituents on the adjacent carbon.[247]

Vinylic substrates are in general very reluctant to undergo S_N1 reactions, but they can be made to do so in two ways:[248] (*1*) By the use of an a group that stabilizes the vinylic cation. For example, α-aryl vinylic halides $ArCBr{=}CR'_2$ have often been shown to give S_N1 reactions.[249] The S_N1 reactions have also been demonstrated with other stabilizing groups: cyclopropyl,[250] vinylic,[251] alkynyl,[252] and an adjacent double bond ($R_2C{=}C{=}CR'X$).[253] (*2*) Even without a stabilization, by the use of a very good leaving group, OSO_2CF_3 (triflate).[254] The stereochemical outcome of S_N1 reactions at a vinylic substrate is often randomization,[255] that is, either a cis or a trans substrate gives a 1:1 mixture of cis and trans products, indicating that vinylic cations are linear. Another indication that vinylic cations prefer to be linear is the fact that reactivity in cycloalkenyl systems decreases with decreasing ring size.[256] However, a linear vinylic cation need not give random products.[257] The empty *p* orbital lies in the plane of the double bond,



so entry of the nucleophile can be and often is influenced by the relative size of R^1 and R^2.[258] It must be emphasized that even where vinylic substrates do give S_N1

[247]Apeloig, Y.; Rappoport, Z. *J. Am. Chem. Soc.* ***1979***, *101*, 5095.

[248]For reviews of the S_N1 mechanism at a vinylic substrate, see Stang, P.J.; Rappoport, Z.; Hanack, H.; Subramanian, L.R. *Vinyl Cations*, Chapt. 5; Academic Press, NY, ***1979***; Stang, P.J. *Acc. Chem. Res.* ***1978***, *11*, 107; Rappoport, Z. *Acc. Chem. Res.* ***1976***, *9*, 265; Subramanian, L.R.; Hanack, M. *J. Chem. Educ.* ***1975***, *52*, 80; Hanack, M. *Acc. Chem. Res.* ***1970***, *3*, 209; Modena, G.; Tonellato, U. *Adv. Phys. Org. Chem.* ***1971***, *9*, 185, 231–253; Grob, C.A. *Chimia* ***1971***, *25*, 87; Rappoport, Z.; Bässler, T.; Hanack, M. *J. Am. Chem. Soc.* ***1970***, *92*, 4985.

[249]For a review, see Stang, P.J.; Rappoport, Z.; Hanack, H.; Subramanian, L.R. *Vinyl Cations*, Chapt. 6, Academic Press, NY, ***1979***.

[250]Kelsey, D.R.; Bergman, R.G. *J. Am. Chem. Soc.* ***1970***, *92*, 238; ***1971***, *93*, 1941; Hanack, M.; Bässler, T.; Eymann, W.; Heyd, W.E.; Kopp, R. *J. Am. Chem. Soc.* ***1974***, *96*, 6686.

[251]Grob, C.A.; Spaar, R. *Tetrahedron Lett.* ***1969***, 1439; *Helv. Chim. Acta* ***1970***, *53*, 2119.

[252]Hassdenteufel, J.R.; Hanack, M. *Tetrahedron Lett.* ***1980***, 503. See also, Kobayashi, S.; Nishi, T.; Koyama, I.; Taniguchi, H. *J. Chem. Soc., Chem. Commun.* ***1980***, 103.

[253]Schiavelli, M.D.; Gilbert, R.P.; Boynton, W.A.; Boswell, C.J. *J. Am. Chem. Soc.* ***1972***, *94*, 5061.

[254]See, for example, Clarke, T.C.; Bergman, R.G. *J. Am. Chem. Soc.* ***1972***, *94*, 3627; ***1974***, *96*, 7934; Summerville, R.H.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1972***, *94*, 3629; ***1974***, *96*, 1110; Hanack, M.; Märkl, R.; Martinez, A.G. *Chem. Ber.* ***1982***, *115*, 772.

[255]Rappoport, Z.; Apeloig, Y. *J. Am. Chem. Soc.* ***1969***, *91*, 6734; Kelsey, D.R.; Bergman, R.G. *J. Am. Chem. Soc.* ***1970***, *92*, 238; ***1971***, *93*, 1941.

[256]Pfeifer, W.D.; Bahn, C.A.; Schleyer, P.v.R.; Bocher, S.; Harding, C.E.; Hummel, K.; Hanack, M.; Stang, P.J. *J. Am. Chem. Soc.* ***1971***, *93*, 1513.

[257]For examples of inversion, see Clarke, T.C.; Bergman, R.G. *J. Am. Chem. Soc.* ***1972***, *94*, 3627; ***1974***, *96*, 7934; Summerville, R.H.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1972***, *94*, 3629; ***1974***, *96*, 1110.

[258]Maroni, R.; Melloni, G.; Modena, G. *J. Chem. Soc., Chem. Commun.* ***1972***, 857.

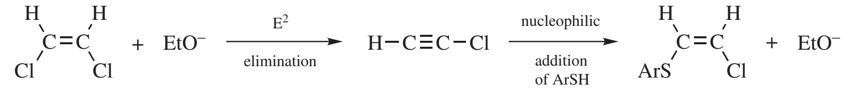
reactions, the rates are generally lower than those of the corresponding saturated compounds.

Alkynyl cations are so unstable that they cannot be generated even with very good leaving groups. However, one way in which they have been generated was by formation of a tritiated substrate.

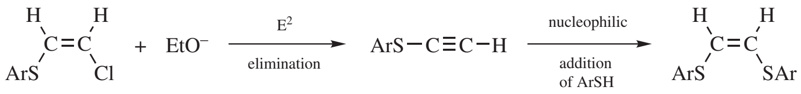
$$R{-}C{\equiv}C{-}T \xrightarrow{\beta\ \text{decay}} R{-}C{\equiv}C{-}^{3}He \xrightarrow[\text{fast}]{\text{very}} R{-}C{\equiv}C^{\oplus} + {}^{3}He$$

When the tritium (half-life 12.26 years) decays it is converted to the helium-3 isotope, which, of course, does not form covalent bonds, and so immediately departs, leaving behind the alkynyl cation. When this was done in the presence of benzene, $RC{\equiv}CC_6H_5$ was isolated.[259] The tritium-decay technique has also been used to generate vinylic and aryl cations.[260]

Besides the mechanisms already discussed, another mechanism, involving an *elimination–addition* sequence, has been observed in vinylic systems (a similar mechanism is known for aromatic substrates, p. 859). An example of a reaction involving this mechanism is the reaction of 1,2-dichloroethane with ArS^- and ^-OEt to produce **84**. The mechanism may be formulated as:



85



84

The steps are the same as in the addition–elimination mechanism, but in reverse order. Evidence for this sequence[261] is as follows: (*1*) The reaction does not proceed without ethoxide ion, and the rate is dependent on the concentration of this ion and not on that of ArS^-. (*2*) Under the same reaction conditions, chloroacetylene gave **85** and **84**. (*3*) Compound **85**, treated with ArS^-, gave no reaction but, when EtO^- was added, **84** was obtained. It is interesting that the elimination–addition mechanism has even been shown to occur in five- and six-membered cyclic systems, where triple bonds are greatly strained.[262] Note that both the addition–elimination and elimination–addition sequences, as shown above, lead to overall retention of configuration, since in each case both addition and elimination are anti.

[259]Angelini, G.; Hanack, M.; Vermehren, J.; Speranza, M. *J. Am. Chem. Soc.* ***1988***, *110*, 1298.

[260]For a review, see Cacace, F. *Adv. Phys. Org. Chem.* ***1970***, *8*, 79. See also, Fornarini, S.; Speranza, M. *J. Am. Chem. Soc.* ***1985***, *107*, 5358.

[261]Flynn, Jr., J.; Badiger, V.V.; Truce, W.E. *J. Org. Chem.* ***1963***, *28*, 2298. See also, Shainyan, B.A.; Mirskova, A.N. *J. Org. Chem. USSR* ***1984***, *20*, 885, 1989; ***1985***, *21*, 283.

[262]Montgomery, L.K.; Clouse, A.O.; Crelier, A.M.; Applegate, L.E. *J. Am. Chem. Soc.* ***1967***, *89*, 3453; Caubere, P.; Brunet, J. *Tetrahedron* ***1971***, *27*, 3515; Bottini, A.T.; Corson, F.P.; Fitzgerald, R.; Frost II, K.A. *Tetrahedron* ***1972***, *28*, 4883.

The elimination–addition sequence has also been demonstrated for certain reactions of saturated substrates, for example, $ArSO_2CH_2CH_2SO_2Ar$.[263] Treatment of this with ethoxide proceeds as follows:

$$ArSO_2CH_2CH_2SO_2Ar \xrightarrow[E^2\text{ elimination}]{EtO^-} ArSO_2CH{=}CH_2 \xrightarrow[\text{addition}]{EtO^-} ArSO_2CH_2CH_2OEt$$

Mannich bases (see **16-19**) of the type $RCOCH_2CH_2NR_2$ similarly undergo nucleophilic substitution by the elimination–addition mechanism.[264] The nucleophile replaces the NR_2 group.

The simple S_N2 mechanism has never been convincingly demonstrated for vinylic substrates.[265]

Vinylic halides can react by a $S_{RN}1$ mechanism (p. 862) in some cases. An example is the $FeCl_2$-catalyzed reaction of 1-bromo-2-phenylethene and the enolate anion of pinacolone (t-$BuCOCH_2^-$), which gave a low yield of substitution products along with alkynes.[266]

REACTIVITY

A large amount of work has been done on this subject. although a great deal is known, much is still poorly understood, and many results are anomalous and hard to explain. In this section, only approximate generalizations are attempted. The work discussed here, and the conclusions reached, pertain to reactions taking place in solution. Some investigations have also been carried out in the gas phase.[267]

The Effect of Substrate Structure

The effect on the reactivity of a change in substrate structure depends on the mechanism.

1. *Branching at the α and β Carbons*. For the S_N2 mechanism, branching at either the α or the β carbon decreases the rate. Tertiary systems seldom[268]

[263]Kader, A.T.; Stirling, C.J.M. *J. Chem. Soc.* ***1962***, 3686. For another example, see Popov, A.F.; Piskunova, Z.; Matvienko, V.N. *J. Org. Chem. USSR* ***1986***, *22*, 1299.

[264]For an example, see Andrisano, R.; Angeloni, A.S.; De Maria, P.; Tramontini, M. *J. Chem. Soc. C* ***1967***, 2307.

[265]For discussions, see Miller, S.I. *Tetrahedron* ***1977***, *33*, 1211; Texier, F.; Henri-Rousseau, O.; Bourgois, J. *Bull. Soc. Chim. Fr.* ***1979***, II-11; Rappoport, Z. *Acc. Chem. Res.* ***1981***, *14*, 7; Rappoport, Z.; Avramovitch, B. *J. Org. Chem.* ***1982***, *47*, 1397.

[266]Galli, C.; Gentili, P.; Rappoport, Z. *J. Org. Chem.* ***1994***, *59*, 6786; Galli, C.; Gentili, P. *J. Chem. Soc., Chem. Commun.* ***1993***, 570.

[267]See, for example, DePuy, C.H.; Gronert, S.; Mullin, A.; Bierbaum, V.M. *J. Am. Chem. Soc.* ***1990***, *112*, 8650.

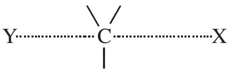
[268]For a reported example, see Edwards, O.E.; Grieco, C. *Can. J. Chem.* ***1974***, *52*, 3561.

TABLE 10.3. Average Relative S_N2 Rates for Some Alkyl Substrates[270]

R	Relative rate	R	Relative rate
Methyl	30	Isobutyl	0.03
Ethyl	1	Neopentyl	10^{-5}
Propyl	0.4	Allyl	40
Butyl	0.4	Benzyl	120
Isopropyl	0.025		

react by the S_N2 mechanism and neopentyl systems react so slowly as to make such reactions, in general, synthetically useless.[269] Table 10.3 shows average relative rates for some alkyl substrates.[270] The reason for these low rates is almost certainly steric.[271] The transition state **1** is more crowded when larger groups are close to the central carbon.

The tetrahedral mechanism for substitution at a carbonyl carbon is also slowed or blocked completely by α or β branching for similar reasons. Solvolysis in such systems is linked to relief of B-strain, but solvent participation can overshadow this as steric hindrance increases.[272] Severe steric strain can cause distortion from coplanarity in the carbocation intermediate,[273] although there seems to be no loss of resonance stability.[274] Adding electron-donating substituents to such molecules improves coplanarity in the cation.[275] For example, esters of the formula R_3CCOOR' cannot generally be hydrolyzed by the tetrahedral mechanism (see **16-59**), nor can acids R_3CCOOH be easily esterified.[276] Synthetic advantage can be taken of this fact, for example, when in a molecule containing two ester groups only the less hindered one is hydrolyzed.



1

[269]The S_N2 reactions on neopentyl tosylates have been conveniently carried out in the solvents HMPA and DMSO: Lewis, R.G.; Gustafson, D.H.; Erman, W.F. *Tetrahedron Lett.* ***1967***, 401; Paquette, L.A.; Philips, J.C. *Tetrahedron Lett.* ***1967***, 4645; Anderson, P.H.; Stephenson, B.; Mosher, H.S. *J. Am. Chem. Soc.* ***1974***, *96*, 3171.

[270]This table is from Streitwieser, A. *Solvolytic Displacement Reactions*, McGraw-Hill, NY, ***1962***, p. 13. Also see, Table 9.2.

[271]For evidence, see Caldwell, G.; Magnera, T.F.; Kebarle, P. *J. Am. Chem. Soc.* ***1984***, *106*, 959.

[272]Liu, K.-T.; Hou, S.-J.; Tsao, K.-L. *J. Org. Chem.* ***1998***, *63*, 1360.

[273]Fujio, M.; Nomura, H.; Nakata, K.; Saeki, Y.; Mishima, M.; Kobayashi, S.; Matsushita, T.; Nishimoto, K.; Tsuno, Y. *Tetrahedron Lett.* ***1994***, *35*, 5005.

[274]Fujio, M.; Nakata, K.; Kuwamura, T.; Nakamura, H.; Saeki, Y.; Mishima, M.; Kobayashi, S.; Tsuno, Y. *Tetrahedron Lett.* ***1992***, *34*, 8309.

[275]Liu, K.T.; Tsao, M.-L.; Chao, I. *Tetrahedron Lett.* ***1996***, *37*, 4173.

[276]For a molecular mechanics study of this phenomenon, see DeTar, D.F.; Binzet, S.; Darba, P. *J. Org. Chem.* ***1987***, *52*, 2074.

TABLE 10.4. Relative Rates of Solvolysis of RBr in Two Solvents[277]

RBr Substrate	In 60% Ethanol at 55°C	In Water at 50°C
MeBr	2.08	1.05
EtBr	1.00	1.00
*i*PrBr	1.78	11.6
t-BuBr	2.41×10^4	1.2×10^6

For the S_N1 mechanism, a branching increases the rate, as shown in Table 10.4.[277] We can explain this by the stability order of alkyl cations (tertiary > secondary > primary). Of course, the rates are not actually dependent on the stability of the ions, but on the difference in free energy between the starting compounds and the transition states. We use the Hammond postulate (p. 308) to make the assumption that the transition states resemble the cations and that anything (e.g., a branching) that lowers the free energy of the ions also lowers it for the transition states. For simple alkyl groups, the S_N1 mechanism is important under all conditions only for tertiary substrates.[278] As previously indicated (p. 440), secondary substrates generally react by the S_N2 mechanism,[279] except that the S_N1 mechanism may become important at high solvent polarities. Table 10.4 shows that isopropyl bromide reacts less than twice as fast as ethyl bromide in the relatively nonpolar 60% ethanol (compare this with the 10^4 ratio for *tert*-butylbromide, where the mechanism is certainly S_N1), but in the more polar water the rate ratio is 11.6. The 2-adamantyl system is an exception; it is a secondary system that reacts by the S_N1 mechanism because backside attack is hindered for steric reasons.[280] Because there is no S_N2 component, this system provides an opportunity for comparing the pure S_N1 reactivity of secondary and tertiary substrates. It has been found that substitution of a methyl group for the a

[277]These values are from Streitwieser, A. *Solvolytic Displacement Reactions*, McGraw-Hill, NY, ***1962***, p. 43, where values are also given for other conditions. Methyl bromide reacts faster than ethyl bromide (and in the case of 60% ethanol, ispropyl bromide) because most of it (probably all) reacts by the S_N2 mechanism.

[278]For a report of an S_N1 mechanism at a primary carbon, see Zamashchikov, V.V.; Bezbozhnaya, T.V.; Chanysheva, I.R. *J. Org. Chem. USSR* ***1986***, *22*, 1029.

[279]See Raber, D.J.; Harris, J.M. *J. Chem. Educ.* ***1972***, *49*, 60; Lambert, J.B.; Putz, G.J.; Mixan, C.E. *J. Am. Chem. Soc.* ***1972***, *94*, 5132; Nordlander, J.E.; McCrary, Jr., T.J. *J. Am. Chem. Soc.* ***1972***, *94*, 5133; Fry, J.L.; Lancelot, C.J.; Lam, L.K.M.; Harris, J.M.; Bingham, R.C.; Raber, D.J.; Hall, R.E.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1970***, *92*, 2538; Dietze, P.E.; Jencks, W.P. *J. Am. Chem. Soc.* ***1986***, *108*, 4549; Dietze, P.E.; Hariri, R.; Khattak, J. *J. Org. Chem.* ***1989***, *54*, 3317.

[280]Fry, J.L.; Harris, J.M.; Bingham, R.C.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1970***, *92*, 2540; Schleyer, P.v.R.; Fry, J.L.; Lam, L.K.M.; Lancelot, C.J. *J. Am. Chem. Soc.* ***1970***, *92*, 2542. See also, Pritt, J.R.; Whiting, M.C. *J. Chem. Soc. Perkin Trans. 2* ***1975***, 1458. For an *ab initio* molecular-orbital study of the 2-adamantyl cation, see Dutler, R.; Rauk, A.; Sorensen, T.S.; Whitworth, S.M. *J. Am. Chem. Soc.* ***1989***, *111*, 9024.

hydrogen of 2-adamantyl substrates (thus changing a secondary to a tertiary system) increases solvolysis rates by a factor of $\sim 10^8$.[281] Simple primary substrates react by the S_N2 mechanism (or with participation by neighboring alkyl or hydrogen), but not by the S_N1 mechanism, even when solvolyzed in solvents of very low nucleophilicity[282] (e.g., trifluoroacetic acid or trifluoroethanol[283]), and even when very good leaving groups (e.g., OSO_2F) are present[284] (see, however, p. 497).

For some tertiary substrates, the rate of S_N1 reactions is greatly increased by the relief of B strain in the formation of the carbocation (see p. 398). Except where B strain is involved, β branching has little effect on the S_N1 mechanism, except that carbocations with β branching undergo rearrangements readily. Of course, isobutyl and neopentyl are primary substrates, and for this reason react very slowly by the S_N1 mechanism, but not more slowly than the corresponding ethyl or propyl compounds.

To sum up, primary and secondary substrates generally react by the S_N2 mechanism and tertiary by the S_N1 mechanism. However, tertiary substrates seldom undergo nucleophilic substitution at all. Elimination is always a possible side reaction of nucleophilic substitutions (wherever a β hydrogen is present), and with tertiary substrates it usually predominates. With a few exceptions, nucleophilic substitutions at a tertiary carbon have little or no preparative value. However, tertiary substrates that can react by the SET mechanism (e.g., p-$NO_2C_6H_4CMe_2Cl$) give very good yields of substitution products when treated with a variety of nucleophiles.[285]

2. *Unsaturation at the α Carbon*. Vinylic, acetylenic,[286] and aryl substrates are very unreactive toward nucleophilic substitutions. For these systems, both the S_N1 and S_N2 mechanisms are greatly slowed or stopped altogether. One reason that has been suggested for this is that sp^2 (and even more, sp) carbon atoms have a higher electronegativity than sp^3 carbons and thus a greater attraction for the electrons of the bond. As we have seen (p. 388), an sp–H bond has a higher acidity than an sp^3—H bond, with that of an sp^2 H bond in

[281]Fry, J.L.; Engler, E.M.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1972***, *94*, 4628. See also, Gassman, P.G.; Pascone, J.M. *J. Am. Chem. Soc.* ***1973***, *95*, 7801.

[282]For discussions and attempts to develop quantitative scales of solvent nucleophilicity see Minegishi, S.; Kobayashi, S.; Mayr, H. *J. Am. Chem. Soc.* ***2004***, *126*, 5174; Catalan, J.; Diaz, C.; Garcia-Blanco, F. *J. Org. Chem.* ***1999***, *64*, 6512; Bentley, T.W.; Llewellyn, G. *Prog. Phys. Org. Chem.* ***1990***, *17*, 121; Kevill, D.N., in Charton, M. *Advances in Quantitative Structure-Property Relationships*, Vol. 1, JAI Press, Greenwich, CT, ***1996***, pp. 81–115; Grunwald, E.; Winstein, S. *J. Am. Chem. Soc.* ***1948***, *70*, 846; Winstein, S.; Fainberg, A.H.; Grunwald, E. *J. Am. Chem. Soc.* ***1957***, *79*, 4146; Peterson, P.E.; Waller, F.J. *J. Am. Chem. Soc.* ***1972***, *94*, 991; Schadt, F.L.; Bentley, T.W.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1976***, *98*, 7667.

[283]Dafforn, G.A.; Streitwieser, Jr., A. *Tetrahedron Lett.* ***1970***, 3159.

[284]Cafferata, L.F.R.; Desvard, O.E.; Sicre, J.E. *J. Chem. Soc. Perkin Trans. 2* ***1981***, 940.

[285]Kornblum, N.; Cheng, L.; Davies, T.M.; Earl, G.W.; Holy, N.L.; Kerber, R.C.; Kestner, M.M.; Manthey, J.W.; Musser, M.T.; Pinnick, H.W.; Snow, D.H.; Stuchal, F.W.; Swiger, R.T. *J. Org. Chem.* ***1987***, *52*, 196.

[286]For a discussion of S_N reactions at acetylenic substrates, see Miller, S.I.; Dickstein, J.I. *Acc. Chem. Res.* ***1976***, *9*, 358.

between. This is reasonable; the carbon retains the electrons when the proton is lost and an *sp* carbon, which has the greatest hold on the electrons, loses the proton most easily. But in nucleophilic substitution, the leaving group *carries off* the electron pair, so the situation is reversed and it is the sp^3 carbon that loses the leaving group and the electron pair most easily. It may be recalled (p. 24) that bond distances decrease with increasing *s* character. Thus the bond length for a vinylic or aryl C—Cl bond is 1.73 Å compared with 1.78 Å for a saturated C—Cl bond. Other things being equal, a shorter bond is a stronger bond.

Of course, we have seen (p. 476) that S_N1 reactions at vinylic substrates can be accelerated by α substituents that stabilize that cation, and that reactions by the tetrahedral mechanism can be accelerated by β substituents that stabilize the carbanion. Also, reactions at vinylic substrates can in certain cases proceed by addition–elimination or elimination–addition sequences (pp. 473, 476).

In contrast to such systems, substrates of the type RCOX are usually much *more* reactive than the corresponding RCH_2X. Of course, the mechanism here is almost always the tetrahedral one. Three reasons can be given for the enhanced reactivity of RCOX: (*1*) The carbonyl carbon has a sizable partial positive charge that makes it very attractive to nucleophiles. (*2*) In an S_N2 reaction, a σ bond must break in the rate-determining step, which requires more energy than the shift of a pair of π electrons, which is what happens in a tetrahedral mechanism. (*3*) A trigonal carbon offers less steric hindrance to a nucleophile than a tetrahedral carbon.

For reactivity in aryl systems, see Chapter 13.

3. *Unsaturation at the* β *Carbon*. The S_N1 rates are increased when there is a double bond in the β position, so that allylic and benzylic substrates react rapidly (Table 10.5).[287] The reason is that allylic (p. 239) and benzylic[288]

TABLE 10.5. Relative Rates for the S_N1 Reaction between ROTs and Ethanol at 25°C[285]

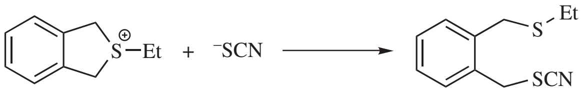
Group	Relative Rate
Et	0.26
*i*Pr	0.69
$CH_2{=}CHCH_2$	8.6
$PhCH_2$	100
Ph_2CH	$\sim 10^5$
Ph_3C	$\sim 10^{10}$

[287]Streitwieser, A. *Solvolytic Displacement Reactions*, McGraw-Hill, NY, ***1962***, p. 75. Actually, the figures for Ph_2CHOTs and Ph_3COTs are estimated from the general reactivity of these substrates.

[288]For a Grunwald-Winstein correlation analysis of the solvolysis of benzyl bromide, see Liu, K.-T.; Hou, I.-J. *Tetrahedron* ***2001***, *57*, 3343.

(p. 240) cations are stabilized by resonance. As shown in Table 10.5, a second and a third phenyl group increase the rate still more, because these carbocations are more stable yet. Remember that allylic rearrangements are possible with allylic systems.

In general, S_N1 rates at an allylic substrate are increased by any substituent in the 1 or 3 position that can stabilize the carbocation by resonance or hyperconjugation.[289] Among these are alkyl, aryl, and halo groups.



86

The S_N2 rates for allylic and benzylic systems are also increased (see Table 10.3), probably owing to resonance possibilities in the transition state. Evidence for this in benzylic systems is that the rate of the reaction was 8000 times slower than the rate with $(PhCH_2)_2SEt^+$.[290] The cyclic **86** does not have the proper geometry for conjugation in the transition state.

Triple bonds in the β position (in propargyl systems) have about the same effect as double bonds.[291] Alkyl, aryl, halo, and cyano groups, among others, in the 3 position of allylic substrates increase S_N2 rates, owing to increased resonance in the transition state, but alkyl and halo groups in the 1 position decrease the rates because of steric hindrance.

4. α *Substitution*. Compounds of the formula ZCH_2X, where Z = RO, RS, or R_2N undergo S_N1 reactions very rapidly,[292] because of the increased resonance in the carbocation. These groups have an unshared pair on an atom directly attached to the positive carbon, which stabilizes the carbocation (p. 242). The field effects of these groups would be expected to decrease S_N1 rates (see Section 6, p. 485), so the resonance effect is far more important.

When Z in ZCH_2X is RCO,[293] HCO, ROCO, NH_2CO, NC, or F_3C,[294] S_N1 rates are decreased compared to CH_3X, owing to the electron-withdrawing field

[289]For a discussion of the relative reactivities of different allylic substrates, see DeWolfe, R.H.; Young, W.G., in Patai, S. *The Chemistry of Alkenes*, Wiley, NY, **1964**, pp. 683–688, 695–697.

[290]King, J.F.; Tsang, G.T.Y.; Abdel-Malik, M.M.; Payne, N.C. *J. Am. Chem. Soc.* ***1985***, *107*, 3224.

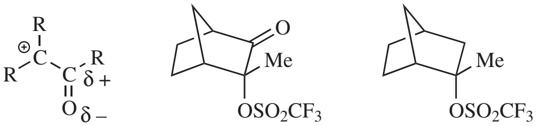
[291]Hatch, L.F.; Chiola, V. *J. Am. Chem. Soc.* ***1951***, *73*, 360; Jacobs, T.L.; Brill, W.F. *J. Am. Chem. Soc.* ***1953***, *75*, 1314.

[292]For a review of the reactions of α-haloamines, sulfides, and ethers, see Gross, H.; Höft, E. *Angew. Chem. Int. Ed.* ***1967***, *6*, 335.

[293]For a review of α-halo ketones, including reactivity, see Verhé, R.; De Kimpe, N., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups*, *Supplement D*, pt. 1, Wiley, NY, ***1983***, pp. 813–931. This review has been reprinted, and new material added, in De Kimpe, N.; Verhé, R. *The Chemistry of α-Haloketones*, *α-Haloaldehydes*, *and α-Haloimines*, Wiley, NY, ***1988***, pp. 225–368.

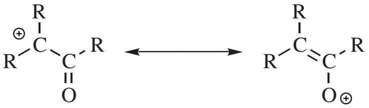
[294]Liu, K.; Kuo, M.; Shu, C. *J. Am. Chem. Soc.* ***1982***, *104*, 211; Gassman, P.G.; Harrington, C.K. *J. Org. Chem.* ***1984***, *49*, 2258; Allen, A.D.; Girdhar, R.; Jansen, M.P.; Mayo, J.D.; Tidwell, T.T. *J. Org. Chem.* ***1986***, *51*, 1324; Allen, A.D.; Kanagasabapathy, V.M.; Tidwell, T.T. *J. Am. Chem. Soc.* ***1986***, *108*, 3470; Richard, J.P. *J. Am. Chem. Soc.* ***1989***, *111*, 1455.

effects of these groups. Furthermore, carbocations[295] with an a CO or CN group are greatly destabilized because of the partial positive charge on the adjacent carbon (**87**). The S_N1 reactions have been carried out on such compounds,[296] but the rates are very low. For example, from a comparison of the solvolysis rates of **88** and **89**, a rate-retarding effect of $10^{7.3}$



87 **88** **89**

was estimated for the C=O group.[297] However, when a different kind of comparison is made: $RCOCR'_2X$ versus HCR'_2X (where X = a leaving group), the RCO had only a small or negligible rate-retarding effect, indicating that resonance stabilization[298]



C **D**

may be offsetting the inductive destabilization for this group.[299] For a CN group also, the rate-retarding effect is reduced by this kind of resonance.[300] A carbocation with an a COR group has been isolated.[301]

When S_N2 reactions are carried out on these substrates, rates are greatly increased for certain nucleophiles (e.g., halide or halide-like ions), but decreased or essentially unaffected by others.[302] For example, α-chloroacetophenone ($PhCOCH_2Cl$) reacts with KI in acetone at 75°C ~32,000 times faster than 1-chlorobutane,[303] but α-bromoacetophenone reacts with the nucleophile triethylamine 0.14 times as fast as iodomethane.[302] The reasons

[295]For reviews of such carbocations, see Bégué, J.; CharpentierMorize, M. *Acc. Chem. Res.* ***1980***, *13*, 207; Charpentier-Morize, M. *Bull. Soc. Chim. Fr.* ***1974***, 343.

[296]For reviews, see Creary, X. *Acc. Chem. Res.* ***1985***, *18*, 3; Creary, X.; Hopkinson, A.C.; Lee-Ruff, E. *Adv. Carbocation Chem.* ***1989***, *1*, 45; Charpentier-Morize, M.; Bonnet-Delpon, D. *Adv. Carbocation Chem.* ***1989***, *1*, 219.

[297]Creary, X. *J. Org. Chem.* ***1979***, *44*, 3938.

[298]**D**, which has the positive charge on the more electronegative atom, is less stable than **C**, according to rule c on p. 47, but it nevertheless seems to be contributing in this case.

[299]Creary, X. *J. Am. Chem. Soc.* ***1984***, *106*, 5568. See, however, Takeuchi, K.; Yoshida, M.; Ohga,Y.; Tsugeno, A.; Kitagawa, T. *J. Org. Chem.* ***1990***, *55*, 6063.

[300]Gassman, P.G.; Saito, K.; Talley, J.J. *J. Am. Chem. Soc.* ***1980***, *102*, 7613.

[301]Takeuchi, K.; Kitagawa, T.; Okamoto, K. *J. Chem. Soc., Chem. Commun.* ***1983***, 7. See also, Dao, L.H.; Maleki, M.; Hopkinson, A.C.; Lee-Ruff, E. *J. Am. Chem. Soc.* ***1986***, *108*, 5237.

[302]Halvorsen, A.; Songstad, J. *J. Chem. Soc., Chem. Commun.* ***1978***, 327.

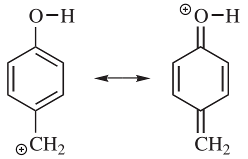
[303]Bordwell, F.G.; Brannen, Jr., W.T. *J. Am. Chem. Soc.* ***1964***, *86*, 4645. For some other examples, see Conant, J.B.; Kirner, W.R.; Hussey, R.E. *J. Am. Chem. Soc.* ***1925***, *47*, 488; Sisti, A.J.; Lowell, S. *Can. J. Chem.* ***1964***, *42*, 1896.

for this varying behavior are not clear, but those nucleophiles that form a "tight" transition state (one in which bond making and bond breaking have proceeded to about the same extent) are more likely to accelerate the reaction.[304]

When Z is SOR or SO_2R (e.g., α-halo sulfoxides and sulfones), nucleophilic substitution is retarded.[305] The S_N1 mechanism is slowed by the electron-withdrawing effect of the SOR or SO_2R group,[306] and the S_N2 mechanism presumably by the steric effect.

5. β *Substitution*. For compounds of the type ZCH_2CH_2X, where Z is any of the groups listed in the previous section as well as halogen[307] or phenyl, S_N1 rates are lower than for unsubstituted systems, because the resonance effects mentioned in Section 4 are absent, but the field effects are still there, although smaller. These groups in the β position do not have much effect on S_N2 rates unless they behave as neighboring groups and enhance the rate through anchimeric assistance,[308] or unless their size causes the rates to decrease for steric reasons.[309] It has been shown that silicon exerts a β-effect, and that tin exerts a γ-effect.[310] Silcon also exerts a γ-effect.[311]

6. *The Effect of Electron-Donating and Electron-Withdrawing Groups*. If substitution rates of series of compounds p-$ZC_6H_4CH_2X$ are measured, it is possible to study the electronic effects of groups Z on the reaction. Steric effects of Z are minimized or eliminated, because Z is so far from the reaction site. For S_N1 reactions electron-withdrawing Z decrease the rate and electron-donating Z increase it,[312] because the latter decrease the energy of the transition state (and of the carbocation) by spreading the positive charge, for example,



[304]For discussions of possible reasons, see McLennan, D.J.; Pross, A. *J. Chem. Soc. Perkin Trans. 2* ***1984***, 981; Yousaf, T.I.; Lewis, E.S. *J. Am. Chem. Soc.* ***1987***, *109*, 6137; Lee, I.; Shim, C.S.; Chung, S.Y.; Lee, I. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 975; Yoh, S.; Lee, H.W. *Tetrahedron Lett.* ***1988***, *29*, 4431.

[305]Bordwell, F.G.; Jarvis, B.B. *J. Org. Chem.* ***1968***, *33*, 1182; Loeppky, R.N.; Chang, D.C.K. *Tetrahedron Lett.* ***1968***, 5414; Cinquini, M.; Colonna, S.; Landini, D.; Maia, A.M. *J. Chem. Soc. Perkin Trans. 2* ***1976***, 996.

[306]See, for example, Creary, X.; Mehrsheikh-Mohammadi, M.E.; Eggers, M.D. *J. Am. Chem. Soc.* ***1987***, *109*, 2435.

[307]See Gronert, S.; Pratt, L.M.; Mogali, S. *J. Am. Chem. Soc.* ***2001***, *123*, 3081.

[308]For example, substrates of the type $RSCH_2CH_2X$ are so prone to the neighboring-group mechanism that ordinary S_N2 reactions have only recently been observed: Sedaghat-Herati, M.R.; McManus, S.P.; Harris, J.M. *J. Org. Chem.* ***1988***, *53*, 2539.

[309]See, for example, Okamoto, K.; Kita, T.; Araki, K.; Shingu, H. *Bull. Chem. Soc. Jpn.* ***1967***, *40*, 1913.

[310]Sugawara, M.; Yoshida, J.-i. *Bull. Chem. Soc. Jpn.* ***2000***, *73*, 1253.

[311]Nakashima, T.; Fujiyama, R.; Fujio, M.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* ***1999***, *72*, 741, 1043; Nakashima, T.; Fujiyama, R.; Kim, H.-J.; Fujio, M.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* ***2000***, *73*, 429.

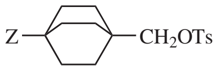
[312]Jorge, J.A.L.; Kiyan, N.Z.; Miyata, Y.; Miller, J. *J. Chem. Soc. Perkin Trans. 2* ***1981***, 100; Vitullo, V.P.; Grabowski, J.; Sridharan, S. *J. Chem. Soc., Chem. Commun.* ***1981***, 737.

while electron-withdrawing groups concentrate the charge. The Hammett $\sigma\rho$ relationship (p. 402) correlates fairly successfully the rates of many of these reactions (with σ^+ instead of σ). ρ values are generally about -4, which is expected for a reaction where a positive charge is created in the transition state.

For S_N2 reactions, no such simple correlations are found.[313] In this mechanism, bond breaking is about as important as bond making in the rate-determining step, and substituents have an effect on both processes, often in opposite directions. The unsubstituted benzyl chloride and bromide solvolyze by the S_N2 mechanism.[306]

For Z = alkyl, the Baker–Nathan order (p. 96) is usually observed both for S_N1 and S_N2 reactions.

In para-substituted benzyl systems, steric effects have been removed, but resonance and field effects are still present. However, Holtz and Stock studied a system that removes not only steric effects, but also resonance effects. This is the 4-substituted bicyclo[2.2.2]octylmethyl tosylate system (**90**).[314] In



90

this system, steric effects are completely absent owing to the rigidity of the molecules, and only field effects operate. By this means, Holtz and Stock showed that electron-withdrawing groups increase the rate of S_N2 reactions. This can be ascribed to stabilization of the transition state by withdrawal of some of the electron density.

For substrates that react by the tetrahedral mechanism, electron-withdrawing groups increase the rate and electron-donating groups decrease it.

7. *Cyclic Substrates*. Cyclopropyl substrates are extremely resistant to nucleophilic attack.[315] For example, cyclopropyl tosylate solvolyzes $\sim10^6$ times more slowly than cyclobutyl tosylate in acetic acid at 60°C.[316] When such attack does take place, the result is generally not normal substitution (though exceptions are known,[317] especially when an a stabilizing group, such as aryl

[313]See Sugden, S.; Willis, J.B. *J. Chem. Soc.* ***1951***, 1360; Baker, J.W.; Nathan, W.S. *J. Chem. Soc.* ***1935***, 1840; Hayami, J.; Tanaka, N.; Kurabayashi, S.; Kotani, Y.; Kaji, A. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 3091; Westaway, K.C.; Waszczylo, Z. *Can. J. Chem.* ***1982***, *60*, 2500; Lee, I.; Sohn, S.C.; Oh, Y.J.; Lee, B.C. *Tetrahedron* ***1986***, *42*, 4713.

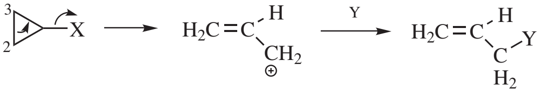
[314]Holtz, H.D.; Stock, L.M. *J. Am. Chem. Soc.* ***1965***, *87*, 2404.

[315]For reviews, see Friedrich, E.C., in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 1; Wiley, NY, ***1987***, pp. 633–700; Aksenov, V.S.; Terent'eva, G.A.; Savinykh, Yu.V. *Russ. Chem. Rev.* ***1980***, *49*, 549.

[316]Roberts, J.D.; Chambers, V.C. *J. Am. Chem. Soc.* ***1951***, *73*, 5034.

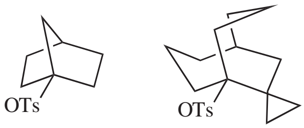
[317]For example, see Kirmse, W.; Schütte, H. *J. Am. Chem. Soc.* ***1967***, *89*, 1284; Landgrebe, J.A.; Becker, L.W. *J. Am. Chem. Soc.* ***1967***, *89*, 2505; Howell, B.A.; Jewett, J.G. *J. Am. Chem. Soc.* ***1971***, *93*, 798; van der Vecht, J.R.; Steinberg, H.; de Boer, T.J. *Recl. Trav. Chim. Pays-Bas* ***1978***, *96*, 313; Engbert, T.; Kirmse, W. *Liebigs Ann. Chem.* ***1980***, 1689; Turkenburg, L.A.M.; de Wolf, W.H.; Bickelhaupt, F.; Stam, C.H.; Konijn, M. *J. Am. Chem. Soc.* ***1982***, *104*, 3471; Banert, K. *Chem. Ber.* ***1985***, *118*, 1564; Vilsmaier, E.; Weber, S.; Weidner, J. *J. Org. Chem.* ***1987***, *52*, 4921.

or alkoxy is present), but ring opening:[310]



There is much evidence that the ring opening is usually concerted with the departure of the leaving group[318] (as in the similar case of cyclobutyl substrates, p. 465), from which we can conclude that if the 2,3 bond of the cyclopropane ring did not assist, the rates would be lower still. Strain plays a role in the ring-opening process.[319] It has been estimated[320] that without this assistance the rates of these already slow reactions would be further reduced by a factor of perhaps 10^{12}. For a discussion of the stereochemistry of the ring opening, see p. 1644. For larger rings, we have seen (p. 399) that, because of I strain, cyclohexyl substrates solvolyze slower than analogous compounds in which the leaving group is attached to a ring of 5 or of from 7 to 11 members.

8. *Bridgeheads.*[11] The S_N2 mechanism is impossible at most bridgehead compounds (p. 429). Nucleophilic attack in [1.1.1]-propellane has been reported, however.[321] In general, a relatively large ring is required for an S_N1 reaction to take place (p. 435).[322] The S_N1 reactions have been claimed to occur for 1-iodobicyclo[1.1.1]pentane via the bicyclo[1.1.1]pentyl cation,[323] but this has been disputed and the bicyclo[1.1.0]butyl carbinyl cation was calculated to be the real intermediate.[324] Solvolytic reactivity at bridgehead positions spans a wide range; for example, from $k = 4 \times 10^{-17}\ s^{-1}$



91 92

for **91** (very slow) to $3 \times 10^6\ s^{-1}$ for the [3.3.3] compound **92** (very fast);[325] a range of 22 orders of magnitude. Molecular mechanics calculations show that

[318]For example, see Schleyer, P.v.R.; Van Dine, G.W.; Schöllkopf, U.; Paust, J. *J. Am. Chem. Soc.* ***1966***, *88*, 2868; DePuy, C.H.; Schnack, L.G.; Hausser, J.W. *J. Am. Chem. Soc.* ***1966***, *88*, 3343; Jefford, C.W.; Wojnarowski, W. *Tetrahedron* ***1969***, *25*, 2089; Hausser, J.W.; Uchic, J.T. *J. Org. Chem.* ***1972***, *37*, 4087.

[319]See Wolk, J.L.; Hoz, T.; Basch, H.; Hoz, S. *J. Org. Chem.* ***2001***, *66*, 915.

[320]Sliwinski, W.F.; Su, T.M.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1972***, *94*, 133; Brown, H.C.; Rao, C.G.; Ravindranathan, M. *J. Am. Chem. Soc.* ***1978***, *100*, 7946.

[321]Sella, A.; Basch, H.; Hoz, S. *Tetrahedron Lett.* ***1996***, *37*, 5573.

[322]For a review of organic synthesis using bridgehead carbocations, see Kraus, G.A.; Hon, Y.; Thomas, P.J.; Laramay, S.; Liras, S.; Hanson, J. *Chem. Rev.* ***1989***, *89*, 1591.

[323]Adcock, J.L.; Gakh, A.A. *Tetrahedron Lett.* ***1992***, *33*, 4875.

[324]Wiberg, K.B.; McMurdie, N. *J. Org. Chem.* ***1993***, *58*, 5603.

[325]Bentley, T.W.; Roberts, K. *J. Org. Chem.* ***1988***, *50*, 5852.

TABLE 10.6. List of Groups in Approximately Descending Order of Reactivity Toward S_N1 and S_N2 Reactions[a]

S_N1 Reactivity	S_N2 Reactivity
Ar_3CX	Ar_3CX
Ar_2CHX	Ar_2CHX
$ROCH_2X$, $RSCH_2X$, R_2NCH_2X	$ArCH_2X$
R_3CX	ZCH_2X
	$-\overset{|}{C}=\overset{|}{C}-CH_2X$
$ArCH_2X$	
$-\overset{|}{C}=\overset{|}{C}-CH_2X$	
	$RCH_2X \sim RCHDX \sim RCHDCH_2X$
R_2CHX	R_2CHX
$RCH_2X \sim R_3CCH_2X$	R_3CX
$RCHDX$	ZCH_2CH_2X
$RCHDCH_2X$	R_3CCH_2X
$-\overset{|}{C}=\overset{|}{C}-X$	$-\overset{|}{C}=\overset{|}{C}-X$
ZCH_2X	
ZCH_2CH_2X	ArX
ArX	Bridgehead-X
[2.2.1] Bridgehead-X	

[a]The Z group is RCO, HCO, ROCO, NH_2CO, NC, or a similar one.

S_N1 bridgehead reactivity is determined by strain changes between the substrate and the carbocation intermediate.[326]

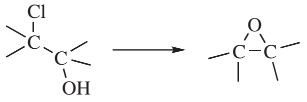
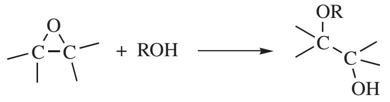
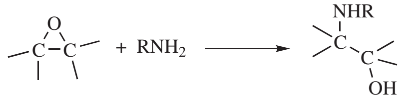
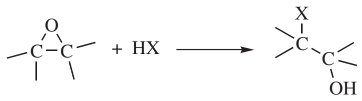
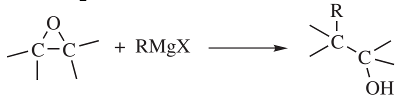
9. *Deuterium Substitution*. Both α and β secondary isotope effects affect the rate in various ways (p. 324). The measurement of a secondary isotope effects provides a means of distinguishing between S_N1 and S_N2 mechanisms, since for S_N2 reactions the values range from 0.95 to 1.06 per α D, while for S_N1 reactions the values are higher.[327] This method is especially good because it provides the minimum of perturbation of the system under study; changing from α H to α D hardly affects the reaction, while other probes, such as changing a substituent or the polarity of the solvent, may have a much more complex effect.

Table 10.6 is an approximate listing of groups in order of S_N1 and S_N2 reactivity. Table 10.7 shows the main reactions that proceed by the S_N2 mechanism (if R = primary or, often, secondary alkyl).

[326]Bingham, R.C.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1971***, *93*, 3189; Müller, P.; Blanc, J.; Mareda, J. *Chimia* ***1987***, *41*, 399; Müller, P.; Mareda, J. *Helv. Chim. Acta* ***1987***, *70*, 1017; Bentley, T.W.; Roberts, K. *J. Org. Chem.* ***1988***, *50*, 5852.

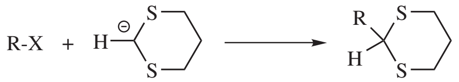
[327]Shiner, Jr., V.J.; Fisher, R.D. *J. Am. Chem. Soc.* ***1971***, *93*, 2553. For a review of secondary isotope effects in S_N2 reactions, see Westaway, K.C. *Isot. Org. Chem.* ***1987***, *7*, 275.

TABLE 10.7. The More Important Synthetic Reactions of Chapter 10 That Take Place by an S_N2 Mechanism.[a] Catalysts are not shown[b]

10-1	$RX + OH^- \longrightarrow ROH$
10-8	$RX + OR' \longrightarrow ROR'$
10-9	
10-10	$R{-}OSO_2OR'' + OR' \longrightarrow ROR'$
10-12	$2\ ROH \longrightarrow ROR$
10-14	
10-15	$R_3O^+ + R'OH \longrightarrow ROR'$
10-17	$RX + R'COO^- \longrightarrow R'COOR$
10-21	$RX + OOH^- \longrightarrow ROOH$
10-25	$RX + SH^- \longrightarrow RSH$
10-26	$RX + R'S^- \longrightarrow RSR'$
10-27	$RX + S_2^{2-} \longrightarrow RSSR$
10-30	$RX + SCN^- \longrightarrow RSCN$
10-31	$RX + R'_2NH \longrightarrow RR'_2N$
10-31	$RX + R'_3N \longrightarrow RR'_3N^+\ X^-$
10-35	
10-41	$RX + R'CONH^- \longrightarrow RNHCOR'$
10-42	$RX + NO_2^- \longrightarrow RNO_2 + RONO$
10-43	$RX + N_3^- \longrightarrow RN_3$
10-44	$RX + NCO^- \longrightarrow RNCO$
10-44	$RX + NCS^- \longrightarrow RNCS$
10-46	$RX + X' \longrightarrow RX'$
10-47	$R{-}OSO_2OR' + X^- \longrightarrow RX$
10-48	$ROH + PCl_5 \longrightarrow RCl$
10-49	$ROR' + 2HI \longrightarrow RI + R'I$
10-50	
10-51	$R{-}O{-}COR' + LiI \longrightarrow RI + R'COO^-$
10-57	$RX + R'_2CuLi \longrightarrow RR'$
10-65	
10-67	$RX + HC^-(CO_2R')_2 \longrightarrow RCH(CO_2R')_2$

(*continued*)

TABLE 10.7. (*Continued*)

10-68	RX + R″$\overset{\ominus}{\text{C}}$H–COR′ ⟶ RCR″–COR′
10-70	RX + R′$\overset{\ominus}{\text{C}}$HCOO$^-$ ⟶ RR′CHCOO$^-$
10-71	
10-74	RX + RC≡C$^{\ominus}$ ⟶ RC≡CR′
10-75	RX + CN$^-$ ⟶ RCN

[a](R = primary, often secondary, alkyl).
[b]This is a schematic list only. Some of these reactions may also take place by other mechanisms and the scope may vary greatly. See the discussion of each reaction for details.

The Effect of the Attacking Nucleophile[328]

Any species that has an unshared pair (i.e., any Lewis base) can be a nucleophile, whether it is neutral or has a negative charge. The rates of S_N1 reactions are independent of the identity of the nucleophile, since it does not appear in the rate-determining step.[329] This may be illustrated by the effect of changing the nucleophile from H_2O to ^-OH for a primary and a tertiary substrate. For methyl bromide, which reacts by an S_N2 mechanism, the rate is multiplied >5000 by the change to the more powerful nucleophile ^-OH, but for *tert*-butylbromide, which reacts by an S_N1 mechanism, the rate is unaffected.[330] A change in nucleophile can, however, change the *product* of an S_N1 reaction. Thus solvolysis of benzyl tosylate in methanol gives benzyl methyl ether (the nucleophile is the solvent methanol). If the more powerful nucleophile Br^- is added, the rate is unchanged, but the product is now benzyl bromide.

For S_N2 reactions in solution, there are four main principles that govern the effect of the nucleophile on the rate, although the nucleophilicity order is not invariant, but depends on substrate, solvent, leaving group, and so on.

1. A nucleophile with a negative charge is always a more powerful nucleophile than its conjugate acid (assuming the latter is also a nucleophile). Thus ^-OH is more powerful than H_2O, $^-NH_2$ more powerful than NH_3, and so on.
2. In comparing nucleophiles whose attacking atom is in the same row of the periodic table, nucleophilicity is approximately in order of basicity, although

[328]For a monograph, see Harris, J.M.; McManus, S.P. *Nucleophilicity*, American Chemical Society, Washington, DC, ***1987***. For reviews, see Klumpp, G.W. *Reactivity in Organic Chemistry*; Wiley, NY, ***1982***, pp. 145–167, 181–186; Hudson, R.F., in Klopman, G. *Chemical Reactivity and Reaction Paths*; Wiley, NY, ***1974***, pp. 167–252.

[329]It is, however, possible to measure the rates of reaction of nucleophiles with fairly stable carbocations: see Ritchie, C.D. *Acc. Chem. Res.* ***1972***, *5*, 348; Ritchie, C.D.; Minasz, R.J.; Kamego, A.A.; Sawada, M. *J. Am. Chem. Soc.* ***1977***, *99*, 3747; McClelland, R.A.; Banait, N.; Steenken, S. *J. Am. Chem. Soc.* ***1986***, *108*, 7023.

[330]Bateman, L.C.; Cooper, K.A.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1940***, 925.

basicity is thermodynamically controlled and nucleophilicity is kinetically controlled. So an approximate order of nucleophilicity is $^{-}NH_2^- > RO^- >$ $^{-}OH > R_2NH > ArO^- > NH_3 >$ pyridine $> F^- > H_2O > ClO_4^-$, and another is $R_3C^- > R_2N^- > RO^- > F^-$ (see Table 8.1). This type of correlation works best when the structures of the nucleophiles being compared are similar, as with a set of substituted phenoxides. Within such a series, linear relationships can often be established between nucleophilic rates and p*K* values.[331]

3. Going down the Periodic table, nucleophilicity increases, although basicity decreases. Thus the usual order of halide nucleophilicity is $I^- > Br^- >$ $Cl^- > F^-$ (as we will see below, this order is solvent dependent). Similarly, any sulfur nucleophile is more powerful than its oxygen analog, and the same is true for phosphorus versus nitrogen. The main reason for this distinction between basicity and nucleophilic power is that the smaller negatively charged nucleophiles are more solvated by the usual polar protic solvents; that is, because the negative charge of Cl^- is more concentrated than the charge of I^-, the former is more tightly surrounded by a shell of solvent molecules that constitute a barrier between it and the substrate. This is most important for protic polar solvents in which the solvent may be hydrogen bonded to small nucleophiles. Evidence for this is that many nucleophilic substitutions with small negatively charged nucleophiles are much more rapid in aprotic polar solvents than in protic ones[332] and that, in DMF, an aprotic solvent, the order of nucleophilicity was $Cl^- > Br^- > I^-$.[333] Another experiment was the use of $Bu_4N^+\ X^-$ and LiX as nucleophiles in acetone, where X^- was a halide ion. The halide ion in the former salt is much less associated than in LiX. The relative rates with LiX were Cl^-, 1; Br^-, 5.7; I^-, 6.2, which is in the normal order, while with $Bu_4N^+\ X^-$, where X^- is much freer, the relative rates were Cl^-, 68; Br^-, 18; I^-, 3.7.[334] In a further experiment, halide ions were allowed to react with the molten salt $(n\text{-}C_5H_{11})_4N^+\ X^-$ at 180°C in the absence of a solvent.[335] Under these conditions, where the ions are unsolvated and unassociated, the relative rates were Cl^-, 620; Br^-, 7.7; I^-, 1. In the gas phase, where no solvent is present, an approximate order of nucleophilicity was found to be $^{-}OH > F^- \approx MeO^- > MeS^- \gg Cl^- > CN^- > Br^-$,[336]

[331]See, for example, Jokinen, S.; Luukkonen, E.; Ruostesuo, J.; Virtanen, J.; Koskikallio, J. *Acta Chem. Scand.* ***1971***, *25*, 3367; Bordwell, F.G.; Hughes, D.L. *J. Org. Chem.* ***1983***, *48*, 2206; *J. Am. Chem. Soc.* ***1984***, *106*, 3234.

[332]Parker, A.J. *J. Chem. Soc.* ***1961***, 1328 has a list of ~20 such reactions.

[333]Weaver, W.M.; Hutchison, J.D. *J. Am. Chem. Soc.* ***1964***, *86*, 261; See also, Fuchs, R.; Mahendran, K. *J. Org. Chem.* ***1971***, *36*, 730; Müller, P.; Siegfried, B. *Helv. Chim. Acta* ***1971***, *54*, 2675; Liotta, C.; Grisdale, E.E.; Hopkins, Jr., H.P. *Tetrahedron Lett.* ***1975***, 4205; Bordwell, F.G.; Hughes, D.L. *J. Org. Chem.* ***1981***, *46*, 3570. For a contrary result in liquid SO_2, see Lichtin, N.N.; Puar, M.S.; Wasserman, B. *J. Am. Chem. Soc.* ***1967***, *89*, 6677.

[334]Winstein, S.; Savedoff, L.G.; Smith, S.G.; Stevens, I.D.R.; Gall, J.S. *Tetrahedron Lett.* ***1960***, no. 9, 24.

[335]Gordon, J.E.; Varughese, P. *Chem. Commun.* ***1971***, 1160. See also, Ford, W.T.; Hauri, R.J.; Smith, S.G. *J. Am. Chem. Soc.* ***1974***, *96*, 4316.

[336]Olmstead, W.N.; Brauman, J.I. *J. Am. Chem. Soc.* ***1977***, *99*, 4219. See also, Tanaka, K.; Mackay, G.I.; Payzant, J.D.; Bohme, D.K. *Can. J. Chem.* ***1976***, *54*, 1643.

providing further evidence that solvation[337] is responsible for the effect in solution.

However, solvation is not the entire answer since, even for *uncharged* nucleophiles, nucleophilicity increases going down a column in the periodic table. These nucleophiles are not so greatly solvated and changes in solvent do not greatly affect their nucleophilicity.[338] To explain these cases we may use the principle of hard and soft acids and bases (p. 375).[339] The proton is a hard acid, but an alkyl substrate (which may be considered to act as a Lewis acid toward the nucleophile considered as a base) is a good deal softer. According to the principle given on p. 380, we may then expect the alkyl group to prefer softer nucleophiles than the proton does. Thus the larger, more polarizable (softer) nucleophiles have a greater (relative) attraction toward an alkyl carbon than toward a proton.

4. The freer the nucleophile, the greater the rate.[340] We have already seen one instance of this.[334] Another is that the rate of attack by $(EtOOC)_2CBu^-\ Na^+$ in benzene was increased by the addition of substances (e.g., 1,2-dimethoxyethane, adipamide) that specifically solvated the Na^+ and thus left the anion freer.[341] In a nonpolar solvent, such as benzene, salts, such as $(EtOOC)_2CBu^-\ Na^+$, usually exist as ion-pair aggregations of large molecular weights.[342] Similarly, it was shown that the half-life of the reaction between $C_6H_5COCHEt^-$ and ethyl bromide depended on the positive ion: K^+, 4.5×10^{-3}; Na^+, 3.9×10^{-5}; Li^+, 3.1×10^{-7}.[343] Presumably, the potassium ion leaves the negative ion most free to attack most rapidly. Further evidence is that in the gas phase,[344] where nucleophilic ions are completely free, without solvent or counterion, reactions take place orders of magnitude faster than the same reactions in solution.[345] It has proven possible to measure the rates of reaction of ^-OH with methyl bromide in the gas phase, with ^-OH either unsolvated or solvated with one, two, or three molecules of water.[346] The rates were, with the number of water molecules

[337]See Kormos, B.L.; Cramer, C.J. *J. Org. Chem.* ***2003***, *68*, 6375.

[338]Parker, A.J. *J. Chem. Soc.* ***1961***, 4398.

[339]Pearson, R.G. *Surv. Prog. Chem.* ***1969***, *5*, 1, pp. 21–38.

[340]For a review of the effect of nucleophile association on nucleophilicity, see Guibe, F.; Bram, G. *Bull. Soc. Chim. Fr.* ***1975***, 933.

[341]Zaugg, H.E.; Leonard, J.E. *J. Org. Chem.* ***1972***, *37*, 2253. See also, Solov'yanov, A.A.; Ahmed, E.A.A.; Beletskaya, I.P.; Reutov, O.A. *J. Org. Chem. USSR* ***1987***, *23*, 1243; Jackman, L.M.; Lange, B.C. *J. Am. Chem. Soc.* ***1981***, *103*, 4494.

[342]See, for example Williard, P.G.; Carpenter, G.B. *J. Am. Chem. Soc.* ***1986***, *108*, 462.

[343]Zook, H.D.; Gumby, W.L. *J. Am. Chem. Soc.* ***1960***, *82*, 1386. See also, Cacciapaglia, R.; Mandolini, L. *J. Org. Chem.* ***1988***, *53*, 2579.

[344]For some other measurements of rates of S_N2 reactions in the gas phase, see Barlow, S.E.; Van Doren, J.M.; Bierbaum, V.M. *J. Am. Chem. Soc.* ***1988***, *110*, 7240; Merkel, A.; Havlas, Z.; Zahradník, R. *J. Am. Chem. Soc.* ***1988***, *110*, 8355.

[345]Olmstead, W.N.; Brauman, J.I. *J. Am. Chem. Soc.* ***1977***, *99*, 4219.

[346]Bohme, D.K.; Raksit, A.B. *J. Am. Chem. Soc.* ***1984***, *106*, 3447. See also, Hierl, P.M.; Ahrens, A.F.; Henchman, M.; Viggiano, A.A.; Paulson, J.F.; Clary, D.C. *J. Am. Chem. Soc.* ***1986***, *108*, 3142.

in parentheses: (0) 1.0×10^{-9}; (1) 6.3×10^{-10}; (2) 2×10^{-12}; (3) 2×10^{-13} cm^3 $molecule^{-1}$ s^{-1}. This provides graphic evidence that solvation of the nucleophile decreases the rate. The rate of this reaction in aqueous solution is 2.3×10^{-25} cm^3 $molecule^{-1}$ s^{-1}. Similar results were found for other nucleophiles and other solvents.[347] In solution too, studies have been made of the effect of solvation of the nucleophile by a specific number of water molecules. When the salt $(n\text{-}C_6H_{13})_4N^+$ F^- was allowed to react with *n*-octyl methanesulfonate, the relative rate fell from 822 for no water molecules to 96 for 1.5 water molecules to 1 for 6 water molecules.[348]

In Chapter 3, we saw that cryptands specifically solvate the alkali metal portion of salts like KF, KOAc, and so on. Synthetic advantage can be taken of this fact to allow anions to be freer, thus increasing the rates of nucleophilic substitutions and other reactions (see p. 509).

However, the four rules given above do not always hold. One reason is that steric influences often play a part. For example, the *tert*-butoxide ion Me_3CO^- is a stronger base than ^-OH or ^-OEt, but a much poorer nucleophile because its large bulk hinders it from closely approaching a substrate.

The following overall nucleophilicity order for S_N2 mechanisms (in protic solvents) was given by Edwards and Pearson:[349] $RS^- > ArS^- > I^- > CN^- > {}^-OH > N_3^- > Br^- > ArO^- > Cl^- > \text{pyridine} > AcO^- > H_2O$. A quantitative relationship[350] (the *Swain–Scott equation*) has been worked out similar to the linear free-energy equations considered in Chapter 9:[351]

$$\log \frac{k}{k_0} = sn$$

where n is the nucleophilicity of a given group, s is the sensitivity of a substrate to nucleophilic attack, and k_0 is the rate for H_2O, which is taken as the standard and for which n is assigned a value of zero. The parameter s is defined as 1.0 for methyl bromide. Table 10.8 contains values of n for some common nucleophiles.[352] The order is similar to that of Edwards and Pearson. The Swain–Scott equation can be derived from Marcus theory.[353]

[347]Bohme, D.K.; Raksit, A.B. *Can. J. Chem.* ***1985***, *63*, 3007.

[348]Landini, D.; Maia, A.; Rampoldi, A. *J. Org. Chem.* ***1989***, *54*, 328.

[349]Edwards, J.O.; Pearson, R.G. *J. Am. Chem. Soc.* ***1962***, *84*, 16.

[350]Swain, C.G.; Scott, C.B. *J. Am. Chem. Soc.* ***1953***, *75*, 141.

[351]This is not the only equation that has been devised in an attempt to correlate nucleophilic reactivity. For reviews of attempts to express nucleophilic power quantitatively, see Ritchie, C.D. *Pure Appl. Chem.* ***1978***, *50*, 1281; Duboc, C., in Chapman, N.B.; Shorter, J. *Correlation Analysis in Chemistry: Recent Advances*, Plenum, NY, ***1978***, pp. 313–355; Ibne-Rasa, K.M. *J. Chem. Educ.* ***1967***, *44*, 89. See also, Hoz, S.; Speizman, D. *J. Org. Chem.* ***1983***, *48*, 2904; Kawazoe, Y.; Ninomiya, S.; Kohda, K.; Kimoto, H. *Tetrahedron Lett.* ***1986***, *27*, 2897; Kevill, D.N.; Fujimoto, E.K. *J. Chem. Res. (S)* ***1988***, 408.

[352]From Wells, P.R. *Chem. Rev.* ***1963***, *63*, 171, p. 212. See also, Koskikallio, J. *Acta Chem. Scand.* ***1969***, *23*, 1477, 1490.

[353]Albery, W.J.; Kreevoy, M.M. *Adv. Phys. Org. Chem.* ***1978***, *16*, 87, pp. 113–115.

TABLE 10.8. Nucleophilicities of Some Common Reagents[352]

Nucleophile	*n*	Nucleophile	*n*
^{-}SH	5.1	Br^-	3.5
^{-}CN	5.1	PhO^-	3.5
I^-	5.0	AcO^-	2.7
$PhNH_2$	4.5	Cl^-	2.7
^{-}OH	4.2	F^-	2.0
N_3^-	4.0	NO_3^-	1.0
Pyridine	3.6	H_2O	0.0

It is now evident that an absolute order of either nucleophilicity[354] or leaving-group ability, even in the gas phase where solvation is not a factor, does not exist, because they have an effect on each other. When the nucleophile and leaving group are both hard or both soft, the reaction rates are relatively high, but when one is hard and the other soft, rates are reduced.[344] Although this effect is smaller than the effects in paragraphs one and four above, it still prevents an absolute scale of either nucleophilicity or leaving-group ability.[355] There has been controversy as to whether the selectivity of a reaction should increase with decreasing reactivity of a series of nucleophiles, or whether the opposite holds. There is evidence for both views.[356]

For substitution at a carbonyl carbon, the nucleophilicity order is not the same as it is at a saturated carbon, but follows the basicity order more closely. The reason is presumably that the carbonyl carbon, with its partial positive charge, resembles a proton more than does the carbon at a saturated center. That is, a carbonyl carbon is a much harder acid than a saturated carbon. The following nucleophilicity order for these substrates has been determined:[357] $Me_2C{=}NO^- > EtO^- > MeO^- > {}^{-}OH > OAr^- > N_3^- > F^- > H_2O > Br^- \sim I^-$. Soft bases are ineffective at a carbonyl carbon.[358] In a reaction carried out in the gas phase with alkoxide nucleophiles OR^- solvated by only one molecule of an alcohol R′OH, it was found that both RO^- and $R'O^-$ attacked the formate substrate (HCOOR″) about equally, although in the unsolvated case, the more basic alkoxide is the better nucleophile.[359] In this study, the product ion R^2O^- was also solvated by one molecule of ROH or R′OH.

[354]However, for a general model of intrinsic nucleophilicity in the gas phase, see Pellerite, M.J.; Brauman, J.I. *J. Am. Chem. Soc.* ***1983***, *105*, 2672.

[355]For reference scales for the characterization of cationic electrophiles and neutral nucleophiles see Mayr, H.; Bug, T.; Gotta, M.F.; Hering, N.; Irrgang, B.; Janker, B.; Kempf, B.; Loos, R.; Ofial, A.R.; Remennikov, G.; Schimmel, H. *J. Am. Chem. Soc.* ***2001***, *123*, 9500.

[356]For discussions, see Dietze, P.; Jencks, W.P. *J. Am. Chem. Soc.* ***1989***, *111*, 5880.

[357]Hudson, R.F.; Green, M. *J. Chem. Soc.* ***1962***, 1055; Bender, M.L.; Glasson, W.A. *J. Am. Chem. Soc.* ***1959***, *81*, 1590; Jencks, W.P.; Gilchrist, M. *J. Am. Chem. Soc.* ***1968***, *90*, 2622.

[358]For theoretical treatments of nucleophilicity at a carbonyl carbon, see Buncel, E.; Shaik, S.S.; Um, I.; Wolfe, S. *J. Am. Chem. Soc.* ***1988***, *110*, 1275, and references cited therein.

[359]Baer, S.; Stoutland, P.O.; Brauman, J.I. *J. Am. Chem. Soc.* ***1989***, *111*, 4097.

If an atom containing one or more unshared pairs is adjacent to the attacking atom on the nucleophile, the nucleophilicity is enhanced.[360] Examples of such nucleophiles are HO_2^-, $Me_2C{=}NO^-$, NH_2NH_2, and so on. This is called the *alpha effect* (α-effect),[361] and a broader definition is a positive deviation exhibited by an α-nucleophile from a Brønsted type nucleophilicity plot, [362] where the reference (or normal) nucleophile is one that possesses the same basicity as the α-nucleophile, but does not deviate from the Brønsted-type plot. Several reviews of the α-effect have been published previously,[362,363]

Several possible explanations have been offered.[364] One is that the ground state of the nucleophile is destabilized by repulsion between the adjacent pairs of electrons;[365] another is that the transition state is stabilized by the extra pair of electrons;[366] a third is that the adjacent electron pair reduces solvation of the nucleophile.[367] Evidence supporting the third explanation is that there was no alpha effect in the reaction of HO_2^- with methyl formate in the gas phase,[368] although HO_2^- shows a strong alpha effect in solution. The α-effect has been demonstrated to be remarkably dependent on the nature of the solvent. [369] The α-effect is substantial for substitution at a carbonyl or other unsaturated carbon, at some inorganic atoms,[370] and for reactions of a nucleophile with a carbocation,[371] but is generally smaller or absent entirely for substitution at a saturated carbon.[372]

[360]Definition in the *Glossary of Terms used in Physical Organic Chemistry, Pure & Appl. Chem.* ***1979***, *51*, 1731.

[361]For reviews, see Grekov, A.P.; Veselov, V.Ya. *Russ. Chem. Rev.* ***1978***, *47*, 631; Fina, N.J.; Edwards, J.O. *Int. J. Chem. Kinet.* ***1973***, *5*, 1.

[362]Hoz, S.; Buncel, E. *Israel J. Chem.* ***1985***, *26*, 313.

[363]Grekov, A.P.; Veselov, V.Ya. *Russ. Chem. Rev.* ***1978***, *47*, 631; Fina, N.J.; Edwards, J.O. *Int. J. Chem. Kinet.* ***1973***, *5*, 1; Jencks, W.P. *Catalysis in Chemistry and Enzymology*, McGraw-Hill, New York, ***1969***; pp. 107–111.

[364]For discussions, see Wolfe, S.; Mitchell, D.J.; Schlegel, H.B.; Minot, C.; Eisenstein, O. *Tetrahedron Lett.* ***1982***, *23*, 615; Ho, S.; Buncel, E. *Isr. J. Chem.* ***1985***, *26*, 313.

[365]Buncel, E.; Hoz, S. *Tetrahedron Lett.* ***1983***, *24*, 4777. For evidence that this is not the sole cause, see Oae, S.; Kadoma, Y. *Can. J. Chem.* ***1986***, *64*, 1184.

[366]See Hoz, S. *J. Org. Chem.* ***1982***, *47*, 3545; Laloi-Diard, M.; Verchere, J.; Gosselin, P.; Terrier, F. *Tetrahedron Lett.* ***1984***, *25*, 1267.

[367]For other explanations, see Hudson, R.F.; Hansell, D.P.; Wolfe, S.; Mitchell, D.J. *J. Chem. Soc., Chem. Commun.* ***1985***, 1406; Shustov, G.V. *Doklad. Chem.* ***1985***, *280*, 80. For a discussion, see Herschlag, D.; Jencks, W.P. *J. Am. Chem. Soc.* ***1990***, *112*, 1951.

[368]DePuy, C.H.; Della, E.W.; Filley, J.; Grabowski, J.J.; Bierbaum, V.M. *J. Am. Chem. Soc.* ***1983***, *105*, 2481; Buncel, E.; Um, I. *J. Chem. Soc., Chem. Commun.* ***1986***, 595; Terrier, F.; Degorre, F.; Kiffer, D.; Laloi, M. *Bull. Soc. Chim. Fr.* ***1988***, 415. For some evidence against this explanation, see Moss, R.A.; Swarup, S.; Ganguli, S. *J. Chem. Soc., Chem. Commun.* ***1987***, 860.

[369]Buncel, E.; Um, I.-H. *Tetrahedron* ***2004***, *60*, 7801.

[370]For example, see Kice, J.L.; Legan, E. *J. Am. Chem. Soc.* ***1973***, *95*, 3912.

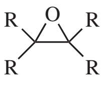
[371]Dixon, J.E.; Bruice, T.C. *J. Am. Chem. Soc.* ***1971***, *93*, 3248, 6592.

[372]Gregory, M.J.; Bruice, T.C. *J. Am. Chem. Soc.* ***1967***, *89*, 4400; Oae, S.; Kadoma, Y.; Yano, Y. *Bull. Chem. Soc. Jpn.* ***1969***, *42*, 1110; McIsaac, Jr., J.E.; Subbaraman, L.R.; Subbaraman, J.; Mulhausen, H.A.; Behrman, E.J. *J. Org. Chem.* ***1972***, *37*, 1037. See, however, Beale, J.H. *J. Org. Chem.* ***1972***, *37*, 3871; Buncel, E.; Wilson, H.; Chuaqui, C. *J. Am. Chem. Soc.* ***1982***, *104*, 4896; *Int. J. Chem. Kinet.* ***1982***, *14*, 823.

The Effect of the Leaving Group

1. *At a Saturated Carbon*. The leaving group comes off more easily the more stable it is as a free entity. This is usually inverse to its basicity, and the best leaving groups are the weakest bases. Thus iodide is the best leaving group among the halides and fluoride the poorest. Since XH is always a weaker base than X^-, nucleophilic substitution is always easier at a substrate RXH^+ than at RX. An example of this effect is that OH and OR are not leaving groups from ordinary alcohols and ethers, but can come off when the groups are protonated, that is, converted to ROH_2^+ or $RORH^+$.[373] Reactions in which the leaving group does not come off until it has been protonated have been called S_N1cA or S_N2cA, depending on whether after protonation the reaction is an S_N1 or S_N2 process (these designations are often shortened to A1 and A2). The cA stands for conjugate acid, since the substitution takes place on the conjugate acid of the substrate. The IUPAC designations for these mechanisms are, respectively, $A_h + D_N + A_N$ and $A_h + A_ND_N$; that is, the same designations as S_N1 and S_N2, with A_h to show the preliminary step. When another electrophile assumes the role of the proton, the symbol A_e is used instead. The ions ROH_2^+ and $RORH^+$ can be observed as stable entities at low temperatures in super acid solutions.[374] At higher temperatures they cleave to give carbocations.

It is obvious that the best nucleophiles (e.g., NH_2^-, ^-OH) cannot take part in S_N1cA or S_N2cA processes, because they would be converted to their conjugate acids under the acidic conditions necessary to protonate the leaving groups.[375] Because S_N1 reactions do not require powerful nucleophiles, but do require good leaving groups, most of them take place under acidic conditions. In contrast, S_N2 reactions, which do require powerful nucleophiles (which are generally strong bases), most often take place under basic or neutral conditions.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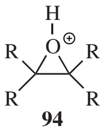
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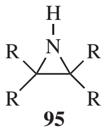
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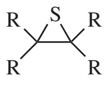
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Another circumstance that increases leaving-group power is ring strain. Ordinary ethers do not cleave at all and protonated ethers only under

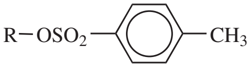
[373] For a review of ORH^+ as a leaving group, see Staude, E.; Patat, F., in Patai, S. *The Chemistry of the Ether Linkage*, Wiley, NY, ***1967***, pp. 22–46.

[374] Olah, G.A.; O'Brien, D.H. *J. Am. Chem. Soc.* ***1967***, *89*, 1725; Olah, G.A.; Sommer, J.; Namanworth, E. *J. Am. Chem. Soc.* ***1967***, *89*, 3576; Olah, J.A.; Olah, G.A., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, pp. 743–747.

[375] Even in the gas phase, NH_3 takes a proton from $CH_3OH_2^+$ rather than acting as a nucleophile: Okada, S.; Abe, Y.; Taniguchi, S.; Yamabe, S. *J. Chem. Soc., Chem. Commun.* ***1989***, 610.

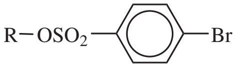
strenuous conditions, but epoxides[376] (**93**) are cleaved quite easily and protonated epoxides (**94**) even more easily. Aziridines (**95**)[377] and episulfides (**96**) are also easily cleaved (see p. 518).[378]

Although halides are common leaving groups in nucleophilic substitution for synthetic purposes, it is often more convenient to use alcohols. Since OH does not leave from ordinary alcohols, it must be converted to a group that does leave. One way is protonation, mentioned above. Another is conversion to a reactive ester, most commonly a sulfonic ester. The sulfonic ester groups *tosylate*, *brosylate*, *nosylate*, and *mesylate* are better leaving groups



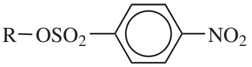
ROTs

p-Toluenesulfonates
Tosylates



ROBs

p-Bromobenzenesulfonates
Brosylates



RONs

p-Nitrobenzenesulfonates
Nosylates

$R{-}OSO_2CH_3$

ROMs

Methanesulfonates
Mesylates

than halides and are frequently used.[379] Other leaving groups are still better, and compounds containing these groups make powerful alkylating agents. Among them are oxonium ions (ROR_2^+),[380] and the fluorinated compounds

$R{-}OSO_2CF_3$	$R{-}OSO_2C_4F_9$	$R{-}OSO_2CCH_2F_3$
ROTf Trifluoromethanesulfonates Triflates	Nonafluorobutanesulfonates Nonaflates	2,2,2-Trifluoroethanesulfonates Tresylates

[376]For a review of the reactions of epoxides, see Smith, J.G. *Synthesis* ***1984***, 629. For a review of their synthesis and reactions, see Bartók, M.; Láng, K.L., in Patai, S. *The Chemistry of Functional Groups, Supplement E*, Wiley, NY, ***1980***, pp. 609–681.

[377]See Kametani, T.; Honda, T. *Adv. Heterocycl. Chem.* ***1986***, *39*, 181; Hu, X.E. *Tetrahedron* ***2004***, *60*, 2701.

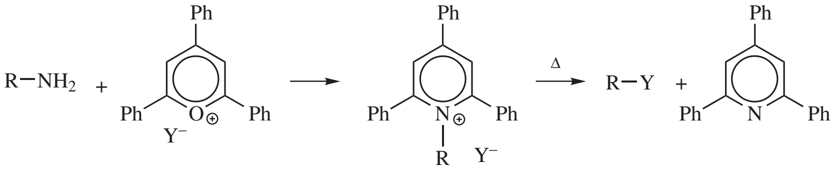
[378]There is evidence that relief of ring strain is not the only factor responsible for the high rates of ring opening of three-membered rings: Di Vona, M.L.; Illuminati, G.; Lillocci, C. *J. Chem. Soc. Perkin Trans. 2* ***1985***, 1943; Bury, A.; Earl, H.A.; Stirling, C.J.M. *J. Chem. Soc., Chem. Commun.* ***1985***, 393.

[379]Bentley, T.W.; Christl, M.; Kemmer, R.; Llewellyn, G.; Oakley, J.E. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 2531.

[380]For a monograph, see Perst, H. *Oxonium Ions in Organic Chemistry*; Verlag Chemie: Deerfield Beach, FL, ***1971***, pp. 100–127. For reviews, see Perst, H., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 5, Wiley, NY, ***1976***, pp. 1961–2047; Granik, V.G.; Pyatin, B.M.; Glushkov, R.G. *Russ. Chem. Rev.* ***1971***, *40*, 747. For a discussion of their use, see Curphey, T.J. *Org. Synth.* ***VI***, 1021.

triflates[381] and *nonaflates*.[381] *Tresylates* are ~400 times less reactive than triflates, but still ~100 times more reactive than tosylates.[382] Halonium ions ($RClR^+$, $RBrR^+$, RIR^+), which can be prepared in super acid solutions (p. 236) and isolated as solid SbF_6^- salts, are also extremely reactive in nucleophilic substitution.[383] Of the above types of compound, the most important in organic synthesis are tosylates, mesylates, oxonium ions, and triflates. The others have been used mostly for mechanistic purposes.

The leaving group ability of NH_2, NHR, and NR_2 are extremely poor,[384] but the leaving-group ability of NH_2 can be greatly improved by converting a primary amine RNH_2 to the ditosylate $RNTs_2$. The NTs_2 group has been successfully replaced by a number of nucleophiles.[385] Another way of converting NH_2 into a good leaving group has been extensively developed by Katritzky and co-workers.[386] In this method the amine is converted to a



97 **98**

pyridinium compound (**98**) by treatment with a pyrylium salt (frequently a 2,4,6-triphenylpyrylium salt, **97**).[387] When the salt is heated, the counterion acts as a nucleophile. In some cases, a non-nucleophilic ion, such as BF_4^-, is used as the counterion for the conversion **97** → **98**, and then Y^- is added to **98**. Among the nucleophiles that have been used successfully in this reaction are I^-, Br^-, Cl^-, F^-, ^-OAc, N_3^-, NHR_2, and H^-. Ordinary NR_2 groups are good leaving groups when the substrate is a Mannich base (these are compounds of the form $RCOCH_2CH_2NR_2$; see reaction **16-19**).[388] The elimination–addition mechanism applies in this case.

[381]For reviews of triflates, nonaflates, and other fluorinated ester leaving groups, see Stang, P.J.; Hanack, M.; Subramanian, L.R. *Synthesis* ***1982***, 85; Howells, R.D.; McCown, J.D. *Chem. Rev.* ***1977***, *77*, 69, pp. 85–87.

[382]Crossland, R.K.; Wells, W.E.; Shiner, Jr., V.J. *J. Am. Chem. Soc.* ***1971***, *93*, 4217.

[383]Peterson, P.E.; Clifford, P.R.; Slama, F.J. *J. Am. Chem. Soc.* ***1970***, *92*, 2840; Peterson, P.E.; Waller, F.J. *J. Am. Chem. Soc.* ***1972***, *94*, 5024; Olah, G.A.; Mo, Y.K. *J. Am. Chem. Soc.* ***1974***, *96*, 3560.

[384]For a review of the deamination of amines, see Baumgarten, R.J.; Curtis, V.A., in Patai, S. *The Chemistry of Functional Groups*, *Supplement F*, pt. 2, Wiley, NY, ***1982***, pp. 929–997.

[385]For references, see Müller, P.; Thi, M.P.N. *Helv. Chim. Acta* ***1980***, *63*, 2168; Curtis, V.A.; Knutson, F.J.; Baumgarten, R.J. *Tetrahedron Lett.* ***1981***, *22*, 199.

[386]For reviews, see Katritzky, A.R.; Marson, C.M. *Angew. Chem. Int. Ed.* ***1984***, *23*, 420; Katritzky, A.R. *Tetrahedron* ***1980***, *36*, 679. For reviews of the use of such leaving groups to study mechanistic questions, see Katritzky, A.R.; Sakizadeh, K.; Musumarra, G. *Heterocycles* ***1985***, *23*, 1765; Katritzky, A.R.; Musumarra, G. *Chem. Soc. Rev.* ***1984***, *13*, 47.

[387]For discussions of the mechanism, see Katritzky, A.R.; Brycki, B. *J. Am. Chem. Soc.* ***1986***, *108*, 7295, and other papers in this series.

[388]For a review of Mannich bases, see Tramontini, M. *Synthesis* ***1973***, 703.

Probably the best leaving group is N_2 from the species RN_2^+, which can be generated in several ways,[389] of which the two most important are the treatment of primary amines with nitrous acid (see p. $$$ for this reaction)

$$RNH_2 + HONO \longrightarrow RN_2^+$$

and the protonation of diazo compounds[390]

$$R_2C{=}\overset{\oplus}{N}{=}\overset{\ominus}{N} + H^+ \longrightarrow R_2CHN_2^+$$

No matter how produced, RN_2^+ are usually too unstable to be isolable,[391] reacting presumably by the S_N1 or S_N2 mechanism.[392] Actually, the exact mechanisms are in doubt because the rate laws, stereochemistry, and products have proved difficult to interpret.[393] If there are free carbocations they should give the same ratio of substitution to elimination to rearrangements, and so on, as carbocations generated in other S_N1 reactions, but they often do not. "Hot" carbocations (unsolvated and/or chemically activated) that can hold their configuration have been postulated,[394] as have ion pairs, in which ^-OH (or ^-OAc, and so on, depending on how the diazonium ion is generated) is the counterion.[395] One class of aliphatic diazonium salts of which several

[389]For reviews, see Kirmse, W. *Angew. Chem. Int. Ed.* ***1976***, *15*, 251; Collins, C.J. *Acc. Chem. Res.* ***1971***, *4*, 315; Moss, R.A. *Chem. Eng. News* ***1971***, *49*, 28 (No. 48, Nov. 22).

[390]For a treatise, see Regitz, M.; Maas, G. *Diazo Compounds*, Academic Press, NY, ***1986***. For reviews of the reactions of aliphatic diazo compounds with acids, see Hegarty, A.F., in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 2, Wiley, NY, 1978, pp. 511–591, 571–575; More O'Ferrall, R.A. *Adv. Phys. Org. Chem.* ***1967***, *5*, 331. For review of the structures of these compounds, see Studzinskii, O.P.; Korobitsyna, I.K. *Russ. Chem. Rev.* ***1970***, *39*, 834.

[391]Aromatic diazonium salts can, of course, be isolated (see Chapter 13), but only a few aliphatic diazonium salts have been prepared (see also, Weiss, R.; Wagner, K.; Priesner, C.; Macheleid, J. *J. Am. Chem. Soc.* ***1985***, *107*, 4491). For reviews see Laali, K.; Olah, G.A. *Rev. Chem. Intermed.* ***1985***, *6*, 237; Bott, K., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups*, *Supplement C*, pt. 1, Wiley, NY, ***1983***, pp. 671–697; Bott, K. *Angew. Chem. Int. Ed.* ***1979***, *18*, 259. The simplest aliphatic diazonium ion $CH_3N_2^+$ has been prepared at $-120°C$ in superacid solution, where it lived long enough for an nmr spectrum to be taken: Berner, D.; McGarrity, J.F. *J. Am. Chem. Soc.* ***1979***, *101*, 3135.

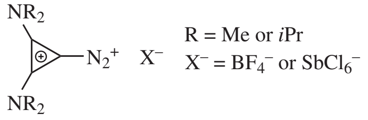
[392]For an example of a diazonium ion reacting by an S_N2 mechanism, see Mohrig, J.R.; Keegstra, K.; Maverick, A.; Roberts, R.; Wells, S. *J. Chem. Soc., Chem. Commun.* ***1974***, 780.

[393]For reviews of the mechanism, see Manuilov, A.V.; Barkhash, V.A. *Russ. Chem. Rev.* ***1990***, *59*, 179; Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***, pp. 280–317; in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, the articles by Keating, J.T.; Skell, P.S. pp. 573–653; and by Friedman, L. pp. 655–713; White, E.H.; Woodcock, D.J., in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, pp. 440–483; Ref. 389.

[394]Semenow, D.; Shih, C.; Young, W.G. *J. Am. Chem. Soc.* ***1958***, *80*, 5472. For a review of "hot" or "free" carbocations, see Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, the articles by Keating, J.T.; Skell, P.S. pp. 573–653.

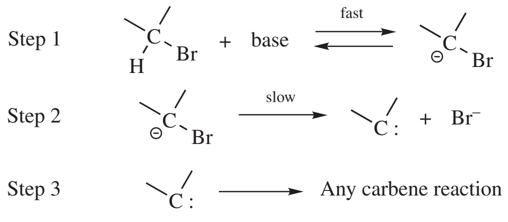
[395]Collins, C.J. *Acc. Chem. Res.* ***1971***, *4*, 315; Collins, C.J.; Benjamin, B.M. *J. Org. Chem.* ***1972***, *37*, 4358; White, E.H.; Field, K.W. *J. Am. Chem. Soc.* ***1975***, *97*, 2148; Cohen, T.; Daniewski, A.R.; Solash, J. *J. Org. Chem.* ***1980***, *45*, 2847; Maskill, H.; Thompson, J.T.; Wilson, A.A. *J. Chem. Soc. Perkin Trans. 2* ***1984***, 1693; Connor, J.K.; Maskill, H. *Bull. Soc. Chim. Fr.* ***1988***, 342.

members have been isolated as stable salts are the cyclopropeniumyldiazonium salts:[396]



Diazonium ions generated from ordinary aliphatic primary amines are usually useless for preparative purposes, since they lead to a mixture of products giving not only substitution by any nucleophile present, but also elimination and rearrangements if the substrate permits. For example, diazotization of *n*-butylamine gave 25% 1-butanol, 5.2% 1-chlorobutane, 13.2% 2-butanol, 36.5% butenes (consisting of 71% 1-butene, 20% *trans*-2-butene, and 9% *cis*-2-butene), and traces of butyl nitrites.[397]

In the S_N1cA and S_N2cA mechanisms (p. 496) there is a preliminary step, the addition of a proton, before the normal S_N1 or S_N2 process occurs. There are also reactions in which the substrate *loses* a proton in a preliminary step. In these reactions, there is a carbene intermediate.



Once formed by this process, the carbene may undergo any of the normal carbene reactions (see p. 287). When the net result is substitution, this mechanism has been called the S_N1cB (for conjugate base) mechanism.[398] Although the slow step is an S_N1 step, the reaction is second order; first order in substrate and first order in base.

Table 10.9 lists some leaving groups in approximate order of ability to leave. The order of leaving-group ability is about the same for S_N1 and S_N2 reactions.

2. *At a Carbonyl Carbon*. This reaction is discussed in Chapter 16.

[396]Weiss, R.; Wagner, K.; Priesner, C.; Macheleid, J. *J. Am. Chem. Soc.* ***1985***, *107*, 4491.
[397]Whitmore, F.C.; Langlois, D.P. *J. Am. Chem. Soc.* ***1932***, *54*, 3441; Streitwieser, Jr., A.; Schaeffer, W.D. *J. Am. Chem. Soc.* ***1957***, *79*, 2888.
[398]Pearson, R.G.; Edgington, D.N. *J. Am. Chem. Soc.* ***1962***, *84*, 4607.

TABLE 10.9. Leaving Groups Listed in Approximate Order of Decreasing Ability to Leave[a]

	Common Leaving Groups	
Substrate RX	At Saturated Carbon	At Carbonyl Carbon
RN_2^+	x	
$ROR_2'^+$		
$ROSO_2C_4F_9$		
$ROSO_2CF_3$	x	
$ROSO_2F$		
ROTs, etc.[b]	x	
RI	x	
RBr	x	
ROH_2^+	x (conjugate acid of alcohol)	
RCl	x	x (acyl halides)
$RORH^+$	x (conjugate acid of ether)	
$RONO_2$, etc.[b]		
$RSR_2'^+$[400]		
$RNR_3'^+$	x	
RF		
ROCOR′[401]	x	x (anhydrides)
RNH_3^+		
ROAr[402]		x (aryl esters)

(*continued*)

The Effect of the Reaction Medium[399]

The effect of solvent polarity[403] on the rate of S_N1 reactions depends on whether the substrate is neutral or positively charged.[404] For neutral substrates, which constitute the majority of cases, the more polar the solvent, the faster the reaction, since there is a greater charge in the transition state than in the starting compound (Table 10.10[405]) and the energy of an ionic transition state is reduced by polar solvents.

[399]For a monograph, see Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed., VCH, NY, ***1988***. For reviews, see Klumpp, G.W. *Reactivity in Organic Chemistry*, Wiley, NY, ***1982***, pp. 186–203; Bentley, T.W.; Schleyer, P.v.R. *Adv. Phys. Org. Chem.* ***1977***, *14*, 1.

[400]For a review of the reactions of sulfonium salts, see Knipe, A.C., in Stirling, C.J.M. *The Chemistry of the Sulphonium Group*, pt. 1, Wiley, NY, ***1981***, pp. 313–385. See also, Badet, B.; Julia, M.; Lefebvre, C. *Bull. Soc. Chim. Fr.* ***1984***, II-431.

[401]For a review of S_N2 reactions of carboxylic esters, where the leaving group is OCOR′, see McMurry, J.E. *Org. React.* ***1976***, *24*, 187.

[402]Nitro substitution increases the leaving-group ability of ArO groups, and alkyl picrates [2,4,6-$ROC_6H_2(NO_2)_3$] react at rates comparable to tosylates: Sinnott, M.L.; Whiting, M.C. *J. Chem. Soc. B* ***1971***, 965. See also, Page, I.D.; Pritt, J.R.; Whiting, M.C. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 906.

[403]Mu, L.; Drago, R.S.; Richardson, D.E. *J. Chem. Soc. Perkin Trans. 2*, ***1998***, 159; Fujio, M.; Saeki, Y.; Nakamoto, K.; Kim, S.H.; Rappoport, Z.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* ***1996***, *69*, 751.

[404]Mitsuhashi, T.; Hirota, H.; Yamamoto, G. *Bull. Chem. Soc. Jpn.* ***1994***, *67*, 824; Bentley, T.W.; Llewellyn, G.; Ryu, Z.H. *J. Org. Chem.* ***1998***, *63*, 4654.

[405]This analysis is due to Ingold, C.K. *Structure and Mechanism in Organic Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, ***1969***, pp. 457–463.

TABLE 10.9. (*Continued*)

	Common Leaving Groups	
Substrate RX	At Saturated Carbon	At Carbonyl Carbon
ROH		x (carboxylic acids)
ROR		x (alkyl esters)
RH		
RNH_2		x (amides)
RAr		
RR		

[a]Groups that are common leaving groups at saturated and carbonyl carbons are indicated.
[b]The substrates ROTs, and so on, includes esters of sulfuric and sulfonic acids in general, for example, $ROSO_2OH$, $ROSO_2OR$, $ROSO_2R$. The substrate $RONO_2$, and so on, includes inorganic ester leaving groups, such as $ROPO(OH)_2$ and $ROB(OH)_2$.

TABLE 10.10. Transition States for S_N1 Reactions of Charged and Uncharged Substrates, and for S_N2 Reactions of the Four Charge Types[405]

	Reactants and Transition States	Charge in the Transition State Relative to Starting Materials	How an Increase in Solvent Polarity Affects the Rate
S_N2	Type I $RX + Y^- \rightarrow Y^{\delta-}\cdots R\cdots X^{\delta-}$	Dispersed	Small decrease
	Type II $RX + Y^- \rightarrow Y^{\delta+}\cdots R\cdots X^{\delta-}$	Increased	Large increase
	Type III $RX + Y^- \rightarrow Y^{\delta-}\cdots R\cdots X^{\delta+}$	Decreased	Large decrease
	Type IV $RX + Y^- \rightarrow Y^{\delta+}\cdots R\cdots X^{\delta+}$	Dispersed	Small decrease
S_N1	$RX \rightarrow R^{\delta+}\cdots X^{\delta-}$	Increased	Large increase
	$RX^- \rightarrow R^{\delta-}\cdots X^{\delta-}$	Dispersed	Small decrease

However, when the substrate is positively charged, the charge is more spread out in the transition state than in the starting ion, and a greater solvent polarity slows the reaction. Even for solvents with about the same polarity, there is a difference between protic and aprotic solvents.[406] The S_N1 reactions of un-ionized substrates are more rapid in protic solvents, which can form hydrogen bonds with the leaving group. Examples of protic solvents are water,[407] alcohols, and carboxylic acids, while some polar aprotic solvents are DMF, dimethyl sulfoxide (DMSO),[408] acetonitrile, acetone, sulfur dioxide, and

[406]See, for example, Ponomareva, E.A.; Dvorko, G.F.; Kulik, N.I.; Evtushenko, N.Yu. *Doklad. Chem.* ***1983***, *272*, 291.
[407]For a study of nucleophilic reactivities in water, see Bug, T.; Mayr, H. *J. Am. Chem. Soc.* ***2003***, *125*, 12980. For a correlation of the Hammett equation and micellar effects see Brinchi, L.; DiProfio, P.; Germani, R.; Savelli, G.; Spreti, N.; Bunton, L.A. *Eur. J. Org. Chem.* ***2000***, 3849.
[408]For reviews of reactions in dimethyl sulfoxide, see Buncel, E.; Wilson, H. *Adv. Phys. Org. Chem.* ***1977***, *14*, 133; Martin, D.; Weise, A.; Niclas, H. *Angew. Chem. Int. Ed.* ***1967***, *6*, 318.

hexamethylphosphoramide [$(Me_2N)_3PO$], HMPA.[409] An algorithm has been developed to accurately calculate dielectric screening effects in solvents.[410] S_N2 reactions have been done in ionic liquids (see p. 415),[411] and in supercritical carbon dioxide (see p. 414).[412]

For S_N2 reactions, the effect of the solvent[413] depends on which of the four charge types the reaction belongs to (p. 425). In types I and IV, an initial charge is dispersed in the transition state, so the reaction is hindered by polar solvents. In type III, initial charges are *decreased* in the transition state, so that the reaction is even more hindered by polar solvents. Only type II, where the reactants are uncharged but the transition state has built up a charge, is aided by polar solvents. These effects are summarized in Table 10.10.[405] Westaway has proposed a "solvation rule" for S_N2 reactions, which states that changing the solvent will not change the structure of the transition state for type I reactions, but will change it for type II reactions.[414] For S_N2 reactions also, the difference between protic and aprotic solvents must be considered.[415] For reactions of types I and III the transition state is more solvated in polar aprotic solvents than in protic ones,[416] while (as we saw on p. 490) the original charged nucleophile is less solvated in aprotic solvents[417] (the second factor is generally much greater than the first[418]). So the change from, say, methanol to DMSO should greatly increase the rate. As an example, the relative rates at 25°C for the reaction between MeI and Cl^- were[332] in MeOH, 1; in $HCONH_2$ (still protic although a weaker acid), 12.5; in HCONHMe, 45.3; and $HCONMe_2$, 1.2×10^6. The change in rate in going from a protic to an aprotic solvent is also related to the *size* of the attacking anion. Small ions are solvated best in protic solvents, since hydrogen bonding is most important for them, while large anions are solvated best in aprotic solvents (protic solvents have highly developed structures held together by hydrogen bonds; aprotic solvents have much looser structures, and it is easier for a large anion to be fitted in). So the rate of attack by small anions is most greatly increased by the change from a protic to an aprotic solvent. This may have preparative significance. The review articles in Ref. 400 have lists of several dozen reactions of charge types I and III in which

[409]For reviews of HMPA, see Normant, H. *Russ. Chem. Rev.* ***1970***, *39*, 457; *Bull. Soc. Chim. Fr.* ***1968***, 791; *Angew. Chem. Int. Ed.* ***1967***, *6*, 1046.

[410]Klamt, A.; Schüürmann, G. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 799.

[411]Wheeler, C.; West, K.N.; Liotta, C.L.; Eckert, C.A. *Chem. Commun.* ***2001***, 887; Kim, D.W.; Song, C.E.; Chi, D.Y. *J. Org. Chem.* ***2003***, *68*, 4281; Chiappe, C.; Pieraccini, D.; Saullo, P. *J. Org. Chem.* ***2003***, *68*, 6710.

[412]DeSimone, J.; Selva, M.; Tundo, P. *J. Org. Chem.* ***2001***, *66*, 4047.

[413]For microsolvation of S_N2 transition states see Craig, S.L.; Brauman, J.I. *J. Am. Chem. Soc.* ***1999***, *121*, 6690.

[414]Westaway, K.C. *Can. J. Chem.* ***1978***, *56*, 2691; Westaway, K.C.; Lai, Z. *Can. J. Chem.* ***1989***, *67*, 345.

[415]For reviews of the effects of protic and aprotic solvents, see Parker, A.J. *Chem. Rev.* ***1969***, *69*, 1; *Adv. Phys. Org. Chem.* ***1967***, *5*, 173; *Adv. Org. Chem.* ***1965***, *5*, 1; Madaule-Aubry, F. *Bull. Soc. Chim. Fr.* ***1966***, 1456.

[416]However, even in aprotic solvents, the transition state is less solvated than the charged nucleophile: Magnera, T.F.; Caldwell, G.; Sunner, J.; Ikuta, S.; Kebarle, P. *J. Am. Chem. Soc.* ***1984***, *106*, 6140.

[417]See, for example, Fuchs, R.; Cole, L.L. *J. Am. Chem. Soc.* ***1973***, *95*, 3194.

[418]See, however, Haberfield, P.; Clayman, L.; Cooper, J.S. *J. Am. Chem. Soc.* ***1969***, *91*, 787.

TABLE 10.11. Relative Rates of Ionization of *p*-Methoxyneophyl Toluenesulfonate in Various Solvents[419]

Solvent	Relative Rate	Solvent	Relative Rate
HCOOH	153	Ac_2O	0.020
H_2O	39	Pyridine	0.013
80% EtOH–H_2O	1.85	Acetone	0.0051
AcOH	1.00	EtOAc	6.7×10^{-4}
MeOH	0.947	THF	5.0×10^{-4}
EtOH	0.370	Et_2O	3×10^{-5}
Me_2SO	0.108	$CHCl_3$	Lower still
Octanoic acid	0.043	Benzene	Lower still
MeCN	0.036	Alkanes	Lower still
$HCONMe_2$	0.029		

yields are improved and reaction times reduced in polar aprotic solvents. Reaction types II and IV are much less susceptible to the difference between protic and aprotic solvents.

Since for most reactions S_N1 rates go up and S_N2 rates go down in solvents of increasing polarity, it is quite possible for the same reaction to go by the S_N1 mechanism in one solvent and the S_N2 in another. Table 10.11 is a list of solvents in order of ionizing power;[419] a solvent high on the list is a good solvent for S_N1 reactions. Trifluoroacetic acid, which was not studied by Smith, Fainberg, and Winstein, has greater ionizing power than any solvent listed in Table 10.11.[420] Because it also has very low nucleophilicity, it is an excellent solvent for S_N1 solvolyses. Other good solvents for this purpose are 1,1,1-trifluoroethanol CF_3CH_2OH, and 1,1,1,3,3,3-hexafluoro-2-propanol, $(F_3C)_2CHOH$.[421]

We have seen how the polarity of the solvent influences the rates of S_N1 and S_N2 reactions. The ionic strength of the medium has similar effects. In general, the addition of an external salt affects the rates of S_N1 and S_N2 reactions in the same way as an increase in solvent polarity, although this is not quantitative; different salts have different effects.[422] However, there are exceptions: although the rates of S_N1 reactions are usually increased by the addition of salts (this is called the *salt effect*), addition of the leaving-group ion often decreases the rate (the common-ion effect, p. 434). There is also the special salt effect of $LiClO_4$, mentioned on p. 439. In addition to these effects, S_N1 rates are also greatly accelerated when there are ions present that specifically help in pulling off the leaving group.[423] Especially

[419]Smith, S.G.; Fainberg, A.H.; Winstein, S. *J. Am. Chem. Soc.* ***1961***, *83*, 618.

[420]Capon, B.; McManus, S. *Neighboring Group Participation*, Vol. 1; Plenum, NY, ***1976***; Haywood-Farmer, J. *Chem. Rev.* ***1974***, *74*, 315; Streitwieser, Jr., A.; Dafforn, G.A. *Tetrahedron Lett.* ***1969***, 1263.

[421]Schadt, F.L.; Schleyer, P.v.R.; Bentley, T.W. *Tetrahedron Lett.* ***1974***, 2335.

[422]See, for example, Duynstee, E.F.J.; Grunwald, E.; Kaplan, M.L. *J. Am. Chem. Soc.* ***1960***, *82*, 5654; Bunton, C.A.; Robinson, L. *J. Am. Chem. Soc.* ***1968***, *90*, 5965.

[423]For a review, see Kevill, D.N., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement D*, pt. 2, Wiley, NY, ***1983***, pp. 933–984.

important are Ag^+, Hg^{2+}, and Hg_2^{2+}, but H^+ helps to pull off F (hydrogen bonding).[424] Even primary halides have been reported to undergo S_N1 reactions when assisted by metal ions.[425] This does not mean, however, that reactions in the presence of metallic ions invariably proceed by the S_N1 mechanism. It has been shown that alkyl halides can react with $AgNO_2$ and $AgNO_3$ by the S_N1 or S_N2 mechanism, depending on the reaction conditions.[426]

The effect of solvent has been treated quantitatively (for S_N1 mechanisms, in which the solvent pulls off the leaving group) by a linear free-energy relationship[427]

$$\log \frac{k}{k_0} = mY$$

where *m* is characteristic of the substrate (defined as 1.00 for *t*-BuCl) and is usually near unity, *Y* is characteristic of the solvent and measures its "ionizing power," and k_0 is the rate in a standard solvent, 80% aqueous ethanol at 25°C. This is known as the Grunwald–Winstein equation, and its utility is at best limited. The *Y* values can of course be measured for solvent *mixtures* too, and this is one of the principal advantages of the treatment, since it is not easy otherwise to assign a polarity arbitrarily to a given mixture of solvents.[428] The treatment is most satisfactory for different proportions of a given solvent pair. For wider comparisons, the treatment is not so good quantitatively, although the *Y* values do give a reasonably good idea of solvolyzing power.[429] Table 10.12 contains a list of some *Y* values.[430]

Ideally, *Y* should measure only the ionizing power of the solvent, and should not reflect any backside attack by a solvent molecule in helping the nucleofuge

[424] For a review of assistance by metallic ions, see Rudakov, E.S.; Kozhevnikov, I.V.; Zamashchikov, V.V. *Russ. Chem. Rev.* ***1974***, *43*, 305. For an example of assistance in removal of F by H^+, see Coverdale, A.K.; Kohnstam, G. *J. Chem. Soc.* ***1960***, 3906.

[425] Zamashchikov, V.V.; Rudakov, E.S.; Bezbozhnaya, T.V.; Matveev, A.A. *J. Org. Chem. USSR* ***1984***, *20*, 424. See, however, Kevill, D.N.; Fujimoto, E.K. *J. Chem. Soc., Chem. Commun.* ***1983***, 1149.

[426] Kornblum, N.; Jones, W.J.; Hardies, D.E. *J. Am. Chem. Soc.* ***1966***, *88*, 1704; Kornblum, N.; Hardies, D.E. *J. Am. Chem. Soc.* ***1966***, *88*, 1707.

[427] Grunwald, E.; Winstein, S. *J. Am. Chem. Soc.* ***1948***, *70*, 846.

[428] For reviews of polarity scales of solvent mixtures, see Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed., VCH, NY, ***1988***, pp. 339–405; Langhals, H. *Angew. Chem. Int. Ed.* ***1982***, *21*, 724.

[429] For a criticism of the *Y* scale, see Abraham, M.H.; Doherty, R.M.; Kamlet, M.J.; Harris, J.M.; Taft, R.W. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 1097.

[430] *Y* values are from Fainberg, A.H.; Winstein, S. *J. Am. Chem. Soc.* ***1956***, *78*, 2770, except for the value for CF_3CH_2OH, which is from Shiner, Jr., V.J.; Dowd, W.; Fisher, R.D.; Hartshorn, S.R.; Kessick, M.A.; Milakofsky, L.; Rapp, M.W. *J. Am. Chem. Soc.* ***1969***, *91*, 4838. Y_{OTs} values are from Bentley, T.W.; Llewellyn, G. *Prog. Phys. Org. Chem.* ***1990***, *17*, 143–144. *Z* values are from Kosower, E.M.; Wu, G.; Sorensen, T.S. *J. Am. Chem. Soc.* ***1961***, *83*, 3147. See also, Larsen, J.W.; Edwards, A.G.; Dobi, P. *J. Am. Chem. Soc.* ***1980***, *102*, 6780. $E_T(30)$ values are from Reichardt, C.; Dimroth, K. *Fortschr. Chem. Forsch.* ***1969***, *11*, 1; Reichardt, C. *Angew. Chem. Int. Ed.* ***1979***, *18*, 98; Laurence, C.; Nicolet, P.; Reichardt, C. *Bull. Soc. Chim. Fr.* ***1987***, 125; Laurence, C.; Nicolet, P.; Lucon, M.; Reichardt, C. *Bull. Soc. Chim. Fr.* ***1987***, 1001; Reichardt, C.; Eschner, M.; Schäfer, G. *Liebigs Ann. Chem.* ***1990***, 57. Values for many additional solvents are given, in the last five papers. Many values from all of these scales are given, in Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH, NY, ***1988***.

TABLE 10.12. The Y, Y_{OTs}, Z, and E_T (30) Values for Some Solvents[430]

Solvent	Y	Y_{OTs}	Z	E_T (30)
CF_3COOH		4.57		
H_2O	3.5	4.1	94.6	63.1
$(CF_3)_2CHOH$		3.82		65.3
HCOOH	2.1	3.04		
H_2O—EtOH (1:1)	1.7	1.29	90	55.6
CF_3CH_2OH	1.0	1.77		59.8
$HCONH_2$	0.6		83.3	56.6
80% EtOH	0.0	0.0	84.8	53.7
MeOH	−1.1	−0.92	83.6	55.4
AcOH	−1.6	−0.9	79.2	51.7
EtOH	−2.0	−1.96	79.6	51.9
90% dioxane	−2.0	−2.41	76.7	46.7
*i*PrOH	−2.7	−2.83	76.3	48.4
95% acetone	−2.8	−2.95	72.9	48.3
t-BuOH	−3.3	−3.74	71.3	43.9
MeCN		−3.21	71.3	45.6
Me_2SO			71.1	45.1
$HCONMe_2$		−4.14	68.5	43.8
Acetone			65.7	42.2
HMPA				40.9
CH_2Cl_2				40.7
Pyridine			64.0	40.5
$CHCl_3$			63.2	39.1
PhCl				37.5
THF				37.4
Dioxane				36.0
Et_2O				34.5
C_6H_6			54	34.3
PhMe				33.9
CCl_4				32.4
n-Octane				31.1
n-Hexane				31.0
Cyclohexane				30.9

to leave (nucleophilic assistance; k_s, p. 456). Actually, there is evidence that many solvents do lend some nucleophilic assistance,[431] even with tertiary substrates.[432] It was proposed that a better measure of solvent "ionizing power" would be a relationship based on 2-adamantyl substrates, rather than *t*-BuCl, since the structure of this system completely prevents backside nucleophilic assistance (p. 480). Such a

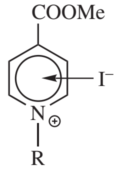
[431]A scale of solvent nucleophilicity (as opposed to ionizing power), called the N_T scale, has been developed: Kevill, D.N.; Anderson, S.W. *J. Org. Chem.* ***1991***, *56*, 1845.

[432]For discussions, with references, see Kevill, D.N.; Anderson, S.W. *J. Am. Chem. Soc.* ***1986***, *108*, 1579; McManus, S.P.; Neamati-Mazreah, N.; Karaman, R.; Harris, J.M. *J. Org. Chem.* ***1986***, *51*, 4876; Abraham, M.H.; Doherty, R.M.; Kamlet, M.J.; Harris, J.M.; Taft, R.W. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 913.

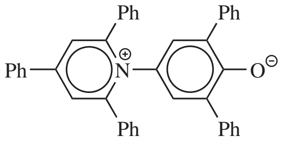
scale, called Y_{OTs}, was developed, with m defined as 1.00 for 2-adamantyl tosylate.[433] Some values of Y_{OTs} are given in Table 10.12. These values, which are actually based on both 1- and 2-adamantyl tosylates (both are equally impervious to nucleophilic assistance and show almost identical responses to solvent ionizing power[434]) are called Y_{OTs} because they apply only to tosylates. It has been found that solvent "ionizing power" depends on the leaving group, so separate scales[435] have been set up for OTf,[436] Cl,[402] Br,[437] I,[438] and other nucleofuges,[439] all based on the corresponding adamantyl compounds. A new Y scale has been established based on benzylic bromides.[440] In part, this was done because benzylic tosylates did not give a linear correlation with the 2-adamantyl Y_{OTs} parameter.[441] This is substrate dependent, since solvolysis of 2,2,-dimethyl-1-phenyl-1-propanol tosylate showed no nucleophilic solvent participation.[442]

In order to include a wider range of solvents than those in which any of the Y values can be conveniently measured, other attempts have been made at correlating solvent polarities.[443] Kosower found that the position of the charge-transfer peak (see p. 115) in the UV spectrum of the complex (**99**) between iodide ion and

R = Me or Et



99



100

[433] Schadt, F.L.; Bentley, T.W.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1976***, *98*, 7667.

[434] Bentley, T.W.; Carter, G.E. *J. Org. Chem.* ***1983***, *48*, 579.

[435] For a review of these scales, see Bentley, T.W.; Llewellyn, G. *Prog. Phys. Org. Chem.* ***1990***, *17*, 121.

[436] Kevill, D.N.; Anderson, S.W. *J. Org. Chem.* ***1985***, *50*, 3330. See also, Creary, X.; McDonald, S.R. *J. Org. Chem.* ***1985***, *50*, 474.

[437] Bentley, T.W.; Carter, G.E. *J. Am. Chem. Soc.* ***1982***, *104*, 5741. See also, Liu, K.; Sheu, H. *J. Org. Chem.* ***1991***, *56*, 3021.

[438] Bentley, T.W.; Carter, G.E.; Roberts, K. *J. Org. Chem.* ***1984***, *49*, 5183.

[439] See Bentley, T.W.; Roberts, K. *J. Org. Chem.* ***1985***, *50*, 4821; Takeuchi, K.; Ikai, K.; Shibata, T.; Tsugeno, A. *J. Org. Chem.* ***1988***, *53*, 2852; Kevill, D.N.; Hawkinson, D.C. *J. Org. Chem.* ***1990***, *55*, 5394 and references cited therein.

[440] Fujio, M.; Saeki, Y.; Nakamoto, K.; Yatsugi, K.-i.; Goto, N.; Kim, S.H.; Tsuji, Y.; Rappoport, Z.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* ***1995***, *68*, 2603; Liu, K.-T.; Chin, C.-P.; Lin, Y.-S.; Tsao, M.-L. *J. Chem. Res. (S)* ***1997***, 18.

[441] Fujio, M.; Susuki, T.; Goto, M.; Tsuji, Y.; Yatsugi, K.; Saeki, Y.; Kim, S.H.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* ***1994***, *67*, 2233.

[442] Tsuji, Y.; Fujio, M.; Tsuno, Y. *Tetrahedron Lett.* ***1992***, *33*, 349.

[443] For reviews of solvent polarity scales, see Abraham, M.H.; Grellier, P.L.; Abboud, J.M.; Doherty, R.M.; Taft, R.W. *Can. J. Chem.* ***1988***, *66*, 2673; Kamlet, M.J.; Abboud, J.M.; Taft, R.W. *Prog. Phys. Org. Chem.* ***1981***, *13*, 485; Shorter, J. *Correlation Analysis of Organic Reactivity*, Wiley, NY, ***1982***, pp. 127–172; Reichardt, C.; Dimroth, K. *Fortschr. Chem. Forsch.* ***1969***, *11*, 1; Reichardt, C. *Angew. Chem. Int. Ed.* ***1979***, *18*, 98; Abraham, M.H. *Prog. Phys. Org. Chem.* ***1974***, *11*, 1; Koppel, I.A.; Palm, V.A., in Chapman, N.B.; Shorter, J. *Advances in Linear Free Energy Relationships*, Plenum, NY, ***1972***, pp. 203–280; Ref. 443. See also, Chastrette, M.; Rajzmann, M.; Chanon, M.; Purcell, K.F. *J. Am. Chem. Soc.* ***1985***, *107*, 1.

1-methyl- or 1-ethyl-4-carbomethoxypyridinium ion was dependent on the polarity of the solvent.[444] From these peaks, which are very easy to measure, Kosower calculated transition energies that he called *Z* values. These values are thus measures of solvent polarity analogous to *Y* values. Another scale is based on the position of electronic spectra peaks of the pyridinium-*N*-phenolbetaine (**100**) in various solvents.[445] Solvent polarity values on this scale are called $E_T(30)$[446] values. The $E_T(30)$ values are related to *Z* values by the expression[447]

$$Z = 1.41\,E_T(30) + 6.92$$

Table 10.12 shows that *Z* and $E_T(30)$ values are generally in the same order as *Y* values. Other scales, the π^* scale,[448] the π^*_{azo} scale,[449] and the Py scale,[450] are also based on spectral data.[451]

Carbon dioxide can be liquefied under high pressure (supercritical CO_2). Several reactions have been done using supercritical CO_2 as the medium, but special apparatus is required. This medium offers many advantages,[452] and some disadvantages, but is an interesting new area of research.

The effect of solvent on nucleophilicity has already been discussed (pp. 490–495).

Phase-Transfer Catalysis

A difficulty that occasionally arises when carrying out nucleophilic substitution reactions is that the reactants do not mix. For a reaction to take place the reacting molecules must collide. In nucleophilic substitutions the substrate is usually insoluble in water and other polar solvents, while the nucleophile is often an anion, which is soluble in water but not in the substrate or other organic solvents. Consequently, when the two reactants are brought together, their concentrations in the same phase are too low for convenient reaction rates. One way to overcome this

[444]Kosower, E.M.; Wu, G.; Sorensen, T.S. *J. Am. Chem. Soc.* ***1961***, *83*, 3147. See also, Larsen, J.W.; Edwards, A.G.; Dobi, P. *J. Am. Chem. Soc.* ***1980***, *102*, 6780.

[445]Dimroth, K.; Reichardt, C. *Liebigs Ann. Chem.* ***1969***, *727*, 93. See also, Haak, J.R.; Engberts, J.B.F.N. *Recl. Trav. Chim. Pays-Bas* ***1986***, *105*, 307.

[446]The symbol E_T comes from *energy, transition*. The (30) is used because the ion **100** bore this number in Dimroth, K.; Reichardt, C. *Liebigs Ann. Chem.* ***1969***, *727*, 93. Values based on other ions have also been reported: See, for example, Reichardt, C.; Harbusch-Görnert, E.; Schäfer, G. *Liebigs Ann. Chem.* ***1988***, 839.

[447]Reichardt, C.; Dimroth, K. *Fortschr. Chem. Forsch.* ***1969***, *11*, p. 32.

[448]Kamlet, M.J.; Abboud, J.M.; Taft, R.W. *J. Am. Chem. Soc.* ***1977***, *99*, 6027; Doherty, R.M.; Abraham, M.H.; Harris, J.M.; Taft, R.W.; Kamlet, M.J. *J. Org. Chem.* ***1986***, *51*, 4872; Kamlet, M.J.; Doherty, R.M.; Abboud, J.M.; Abraham, M.H.; Taft, R.W. *CHEMTECH* ***1986***, 566, and other papers in this series. See also, Doan, P.E.; Drago, R.S. *J. Am. Chem. Soc.* ***1982***, *104*, 4524; Kamlet, M.J.; Abboud, J.M.; Taft, R.W. *Prog. Phys. Org. Chem.* ***1981***, *13*, 485; Bekárek, V. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 1425; Abe, T. *Bull. Chem. Soc. Jpn.* ***1990***, *63*, 2328.

[449]Buncel, E.; Rajagopal, S. *J. Org. Chem.* ***1989***, *54*, 798.

[450]Dong, D.C.; Winnik, M.A. *Can. J. Chem.* ***1984***, *62*, 2560.

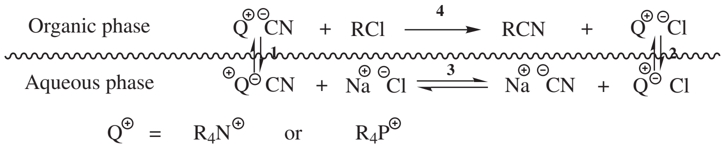
[451]For a review of such scales, see Buncel, E.; Rajagopal, S. *Acc. Chem. Res.* ***1990***, *23*, 226.

[452]Kaupp, G. *Angew. Chem. Int. Ed.* ***1994***, *33*, 1452.

difficulty is to use a solvent that will dissolve both species. As we saw on p. 501, a dipolar aprotic solvent may serve this purpose. Another way, which is used very often, is *phase-transfer catalysis*.[453]

In this method, a catalyst is used to carry the nucleophile from the aqueous into the organic phase. As an example, simply heating and stirring a two-phase mixture of 1-chlorooctane for several days with aqueous NaCN gives essentially no yield of 1-cyanooctane. But if a small amount of an appropriate quaternary ammonium salt is added, the product is quantitatively formed in ~2 h.[454] There are two principal types of phase-transfer catalyst, although the action of the two types is somewhat different, the effects are the same. Both get the anion into the organic phase and allow it to be relatively free to react with the substrate.

1. *Quaternary Ammonium or Phosphonium Salts*. In the above-mentioned case of NaCN, the uncatalyzed reaction does not take place because the ^{-}CN ions cannot cross the interface between the two phases, except in very low concentration. The reason is that the Na^+ ions are solvated by the water, and this solvation energy would not be present in the organic phase. The CN^- ions cannot cross without the Na^+ ions because that would destroy the electrical neutrality of each phase. In contrast to Na^+ ions, quaternary ammonium (R_4N^+)[455] and phosphonium (R_4P^+) ions with sufficiently large R groups are poorly solvated in water and prefer organic solvents. If a small amount of such a salt is added, three equilibria are set up:



The Na^+ ions remain in the aqueous phase; they cannot cross. The Q^+ ions do cross the interface and carry an anion with them. At the beginning of the reaction the chief anion present is ^{-}CN. This gets carried into the organic phase (equilibrium 1) where it reacts with RCl to produce RCN and Cl^-. The Cl^- then gets carried into the aqueous phase (equilibrium 2). Equilibrium 3, taking place entirely in the aqueous phase, allows $Q^{+-}CN$ to be regenerated.

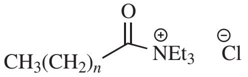
[453]For monographs, see Dehmlow, E.V.; Dehmlow, S.S. *Phase Transfer Catalysis*, 2nd ed., Verlag Chemie, Deerfield Beach, FL, ***1983***; Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Academic Press, NY, ***1978***; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, ***1977***. For reviews, see Makosza, M. *Pure Appl. Chem.* ***2000***, *72*, 1399; Montanari, F.; Landini, D.; Rolla, F. *Top. Curr. Chem.* ***1982***, *101*, 147; Alper, H. *Adv. Organomet. Chem.* ***1981***, *19*, 183; Dehmlow, E.V. *Chimia* ***1980***, *34*, 12; Makosza, M. *Surv. Prog. Chem.* ***1980***, *9*, 1; Sjöberg, K. *Aldrichimica Acta* ***1980***, *13*, 55; Brändström, A. *Adv. Phys. Org. Chem.* ***1977***, *15*, 267; Dockx, J. *Synthesis* ***1973***, 441.

[454]Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Academic Press, NY, ***1978***, p. 2.

[455]Bis-quaternary ammonium salts have also been used: Lissel, M.; Feldman, D.; Nir, M.; Rabinovitz, M. *Tetrahedron Lett.* ***1989***, *30*, 1683.

All the equilibria are normally reached much faster than the actual conversion of RCl to RCN, so the latter is the rate-determining step.

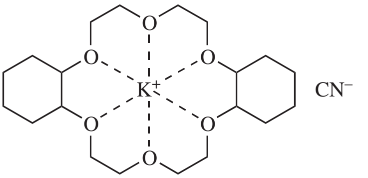
In some cases, the Q^+ ions have such a low solubility in water that virtually all remain in the organic phase.[456] In such cases the exchange of ions (equilibrium 3) takes place across the interface. Still another mechanism (*the interfacial mechanism*) can operate where ^-OH extracts a proton from an organic substrate.[457] In this mechanism, the ^-OH ions remain in the aqueous phase and the substrate in the organic phase; the deprotonation takes place at the interface.[458] Thermal stability of the quaternary ammonium salt is a problem, limiting the use of some catalysts. The trialkylacyl ammonium halide **101** is thermally stable, however, even at high reaction temperatures.[459] The use of molten quaternary ammonium salts as ionic reaction media for substitution reactions has also been reported.[460]



$n = 8–14$

101

2. *Crown Ethers and Other Cryptands*.[461] We saw in Chapter 3 that certain cryptands are able to surround certain cations. In effect, a salt-like KCN is converted by dicyclohexano-18-crown-6 into a new salt (**102**) whose anion is the same, but whose cation is now a much larger species with the positive



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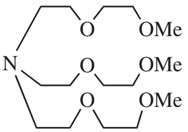

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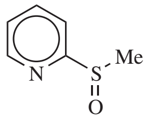


104

charge spread over a large volume and hence much less concentrated. This larger cation is much less solubilized by water than K^+ and much more attracted to organic solvents, although KCN is generally insoluble in organic solvents, the cryptate salt is soluble in many of them. In these cases we do not need an aqueous phase at all but simply add the salt to the organic phase.

[456]Landini, D.; Maia, A.; Montanari, F. *J. Chem. Soc., Chem. Commun.* ***1977***, 112; *J. Am. Chem. Soc.* ***1978***, *100*, 2796.

[457]For a review, see Rabinovitz, M.; Cohen, Y.; Halpern, M. *Angew. Chem. Int. Ed.* ***1986***, *25*, 960.

[458]This mechanism was proposed by Makosza, M. *Pure Appl. Chem.* ***1975***, *43*, 439. See also, Dehmlow, E.V.; Thieser, R.; Sasson, Y.; Pross, E. *Tetrahedron* ***1985***, *41*, 2927; Mason, D.; Magdassi, S.; Sasson, Y. *J. Org. Chem.* ***1990***, *55*, 2714.

[459]Bhalerao, U.T.; Mathur, S.N.; Rao, S.N. *Synth. Commun.* ***1992***, *22*, 1645.

[460]Badri, M.; Brunet, J.-J.; Perron, R. *Tetrahedron Lett.* ***1992***, *33*, 4435.

[461]For a review of this type of phase-transfer catalysis, see Liotta, C., in Patai, S. *The Chemistry of Functional Groups*, *Supplement E*, Wiley, NY, ***1980***, pp. 157–174.

Suitable cryptands have been used to increase greatly the rates of reactions where F^-, Br^-, I^-, ^-OAc, and ^-CN are nucleophiles.[462] Certain compounds that are not cryptands can act in a similar manner. One example is the podand tris(3,6-dioxaheptyl)amine (**103**), also called TDA-1.[463] Another, not related to the crown ethers, is the pyridyl sulfoxide **104**.[464]

Both of the above-mentioned catalyst types get the anions into the organic phase, but there is another factor as well. There is evidence that sodium and potassium salts of many anions, even if they could be dissolved in organic solvents, would undergo reactions very slowly (dipolar aprotic solvents are exceptions) because in these solvents the anions exist as ion pairs with Na^+ or K^+ and are not free to attack the substrate (p. 492). Fortunately, ion pairing is usually much less with the quaternary ions and with the positive cryptate ions, so the anions in these cases are quite free to attack. Such anions are sometimes referred to as "naked" anions.

Not all quaternary salts and cryptands work equally well in all situations. Some experimentation is often required to find the optimum catalyst.

Although phase-transfer catalysis has been most often used for nucleophilic substitutions, it is not confined to these reactions. Any reaction that needs an insoluble anion dissolved in an organic solvent can be accelerated by an appropriate phase-transfer catalyst. We will see some examples in later chapters. In fact, in principle, the method is not even limited to anions, and a small amount of work has been done in transferring cations,[465] radicals, and molecules.[466] The reverse type of phase-transfer catalysis has also been reported: transport into the aqueous phase of a reactant that is soluble in organic solvents.[467] Microwave activated phase-transfer catalysis has been reported.[468]

The catalysts mentioned above are soluble. Certain cross-linked polystyrene resins, as well as alumina[469] and silica gel, have been used as insoluble phase-transfer catalysts. These, called *triphase catalysts*,[470] have the advantage of

[462]See, for example, Liotta, C.; Harris, H.P.; McDermott, M.; Gonzalez, T.; Smith, K. *Tetrahedron Lett.* ***1974***, 2417; Sam, D.J.; Simmons, H.E. *J. Am. Chem. Soc.* ***1974***, *96*, 2252; Durst, H.D. *Tetrahedron Lett.* ***1974***, 2421.

[463]Soula, G. *J. Org. Chem.* ***1985***, *50*, 3717.

[464]Furukawa, N.; Ogawa, S.; Kawai, T.; Oae, S. *J. Chem. Soc. Perkin Trans. 1* ***1984***, 1833. See also, Fujihara, H.; Imaoka, K.; Furukawa, N.; Oae, S. *J. Chem. Soc. Perkin Trans. 1* ***1986***, 333.

[465]See Armstrong, D.W.; Godat, M. *J. Am. Chem. Soc.* ***1979***, *101*, 2489; Iwamoto, H.; Yoshimura, M.; Sonoda, T.; Kobayashi, H. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 796.

[466]See, for example, Dehmlow, E.V.; Slopianka, M. *Chem. Ber.* ***1979***, *112*, 2765.

[467]Mathias, L.J.; Vaidya, R.A. *J. Am. Chem. Soc.* ***1986***, *108*, 1093; Fife, W.K.; Xin, Y. *J. Am. Chem. Soc.* ***1987***, *109*, 1278.

[468]Deshayes, S.; Liagre, M.; Loupy, A.; Luche, J.-L.; Petit, A. *Tetrahedron* ***1999***, *55*, 10851.

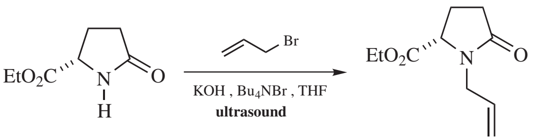
[469]Quici, S.; Regen, S.L. *J. Org. Chem.* ***1979***, *44*, 3436.

[470]For reviews, see Regen, S.L. *Nouv. J. Chim.* ***1982***, *6*, 629; *Angew. Chem. Int. Ed.* ***1979***, *18*, 421. See also, Molinari, H.; Montanari, F.; Quici, S.; Tundo, P. *J. Am. Chem. Soc.* ***1979***, *101*, 3920; Bogatskii, A.V.; Luk'yanenko, N.G.; Pastushok, V.N.; Parfenova, M.N. *Doklad. Chem.* ***1985***, *283*, 210; Pugia, M.J.; Czech, B.P.; Czech, B.P.; Bartsch, R.A. *J. Org. Chem.* ***1986***, *51*, 2945.

simplified product work-up and easy and quantitative catalyst recovery, since the catalyst can easily be separated from the product by filtration.

Influencing Reactivity by External Means

In many cases, reactions are slow. This is sometimes due to poor mixing or the aggregation state of one or more reactants. A powerful technique used to increase reaction rates is *ultrasound* (see p. 349). In this technique, the reaction mixture is subjected to high-energy sound waves, most often 20 KHz, but sometimes higher (a frequency of 20 KHz is about the upper limit of human hearing). When these waves are passed through a mixture, small bubbles form (*cavitation*). Collapse of these bubbles produces powerful shock waves that greatly increase the temperatures and pressures within these tiny regions, resulting in an increased reaction rate.[471] In the common instance where a metal, as a reactant or catalyst, is in contact with a liquid phase, a further effect is that the surface of the metal is cleaned and/or eroded by the ultrasound, allowing the liquid-phase molecules to come into closer contact with the metal atoms. Among the advantages of ultrasound is that it may increase yields, reduce side reactions, and permit the use of lower temperatures and/or pressures. The reaction of pyrrolidinone **105** with allyl bromide, under phase-transfer conditions, gave <10% of the *N*-allyl product, **106**. When the reaction was done under identical conditions, but with exposure to ultrasound (in an ultrasonic bath), the yield of **106** was 78%.[472] It has been postulated that ultrasound has its best results with reactions that proceed, at least partially, through free-radical intermediates.[473]



105 **106**

As noted in Chapter 7 (see p. 352), microwave irradiation is used extensively. Reaction times are greatly accelerated in many reactions, and reactions that took hours to be complete in refluxing solvents are done in minutes. Benzyl alcohol was converted to benzyl bromide, for example, using microwave irradiation (650 W) in only 9 min on a doped K10 Montmorillonite clay.[474] This is a growing and very useful technique.

The rate of many reactions can be increased by application of high pressure.[475] In solution, the rate of a reaction can be expressed in terms of the activation

[471]Reaction rates can also be increased by running reactions in a microwave oven. For reviews, see Mingos, D.M.P.; Baghurst, D.R. *Chem. Soc. Rev.* ***1991***, *20*, 1; Giguere, R.J. *Org. Synth. Theory Appl.* ***1989***, *1*, 103.

[472]Keusenkothen, P.F.; Smith, M.B. *Tetrahedron Lett.* ***1989***, *30*, 3369.

[473]See Einhorn, C.; Einhorn, J.; Dickens, M.J.; Luche, J. *Tetrahedron Lett.* ***1990***, *31*, 4129.

[474]Kad, G.-L.; Singh, V.; Kuar, K.P.; Singh, J. *Tetrahedron Lett.* ***1997***, *38*, 1079.

[475]Matsumoto, K.; Morris, A.R. *Organic Synthesis at High Pressure*, Wiley, NY, ***1991***; Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* ***1985***, 1; Matsumoto, K.; Sera, A. *Ibid.*, ***1985***, 999.

volume, $\Delta V^{\ddagger}$.[476]

$$\frac{\delta \ln k}{\delta p} = \frac{\Delta V^{\ddagger}}{RT}$$

The value of $\Delta V^{\ddagger}$ is the difference in partial molal volume between the transition state and the initial state, but it can be approximated by the molar volume.[476] Increasing pressure decreases the value of $\Delta V^{\ddagger}$ decreases and it $\Delta V^{\ddagger}$ is negative the reaction rate is accelerated. This equation is not strictly obeyed above 10 kbar. If the transition state of a reaction involves bond formation, concentration of charge, or ionization, a negative volume of activation often results. Cleavage of a bond, dispersal of charge, neutralization of the transition state and diffusion control lead to a positive volume of activation. Reactions for which rate enhancement is expected at high pressure include:[476]

1. Reactions in which the number of molecules decreases when starting materials are converted to products: cycloadditions, such as the Diels–Alder (**15-60**); condensations, such as the Knoevenagel condensation (**16-38**).
2. Reactions that proceed via cyclic transition states: Claisen (**18-33**) and Cope (**18-32**) rearrangements.
3. Reactions that take place through dipolar transition states: Menschutkin reaction (**10-31**), electrophilic aromatic substitution.
4. Reactions with steric hindrance.

Many high pressure reactions are done neat, but if a solvent is used, the influence of pressure on that solvent is important. The melting point generally increases at elevated pressures, which influences the viscosity of the medium (viscosity of liquids increases approximately two times per kilobar increase in pressure). Controlling the rate of diffusion of reactants in the medium is also important.[477] In most reactions, pressure is applied (5–20 kbar) at room temperature and then the temperature is increased until reaction takes place.

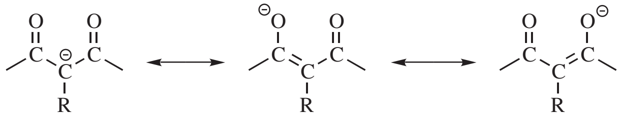
Ambident (Bidentant) Nucleophiles: Regioselectivity

Some nucleophiles have a pair of electrons on each of two or more atoms, or canonical forms can be drawn in which two or more atoms bear an unshared pair. In these cases, the nucleophile may attack in two or more different ways to give different products. Such reagents are called *ambident nucleophiles*.[478] In most cases, a nucleophile with two potentially attacking atoms can attack with either of them,

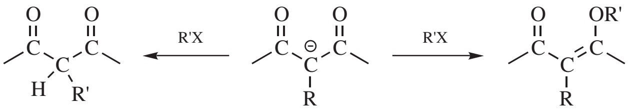
[476]le Noble, W.J. *Progr. Phys. Org. Chem.* ***1967***, *5*, 207; Isaacs, N.S. *Liquid Phase High Pressure Chemistry*, Wiley, Chichester, ***1981***; Asano, T.; le Noble, W.J. *Chem. Rev.* ***1978***, *78*, 407.
[477]Firestone, R.A.; Vitale, M.A. *J. Org. Chem.* ***1981***, *46*, 2160.
[478]For a monograph, see Reutov, O.A.; Beletskaya, I.P.; Kurts, A.L. *Ambident Anions*, Plenum, NY, ***1983***. For a review, see Black, T.H. *Org. Prep. Proced. Int.* ***1989***, *21*, 179.

depending on conditions, and mixtures are often obtained, although this is not always the case. For example, the nucleophile NCO^- usually gives only isocyanates RNCO and not the isomeric cyanates ROCN.[479] When a reaction can potentially give rise to two or more structural isomers (e.g., ROCN or RNCO), but actually produces only one, the reaction is said to be *regioselective*[480] (cf. the definitions of stereoselective, p. 194 and enantioselective, p. 171). Some important ambident nucleophiles are

1. *Ions of the Type* —CO—$\overset{\ominus}{C}$R—CO— . These ions, which are derived by removal of a proton from malonic esters, β-keto esters, β-diketones, and so on, are resonance hybrids:



They can thus attack a saturated carbon with their carbon atoms (*C*-alkylation) or with their oxygen atoms (*O*-alkylation):



With unsymmetrical ions, three products are possible, since either oxygen can attack. With a carbonyl substrate the ion can analogously undergo *C*-acylation or *O*-acylation.

2. *Compounds of the Type* CH_3CO—CH_2—CO— *Can Give Up Two Protons*, if treated with 2 equivalents of a strong enough base, to give dicarbanions:

$$CH_3\text{—CO—}CH_2\text{—CO—} \xrightarrow{\text{2 equivalents of base}} \overset{\ominus}{C}H_2\text{—CO—}\overset{\ominus}{C}H\text{—CO—}$$

107

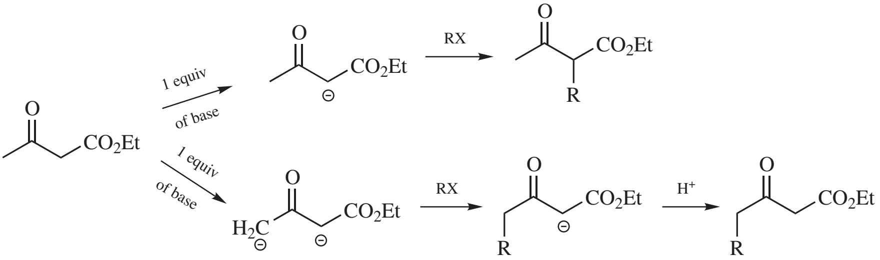
Such ions are ambident nucleophiles, since they have two possible attacking carbon atoms, aside from the possibility of attack by oxygen. In such cases, the attack is virtually always by the more basic carbon.[481] Since the hydrogen of a carbon bonded to two carbonyl groups is more acidic than that of a carbon bonded to just one (see Chapter 8), the CH group of **107** is less basic than the CH_2 group, so the latter attacks the substrate. This gives rise to a useful general principle: whenever we desire to remove a proton at a given

[479]Both cyanates and isocyanates have been isolated in treatment of secondary alkyl iodides with NCO^-: Holm, A.; Wentrup, C. *Acta Chem. Scand.* ***1966***, *20*, 2123.

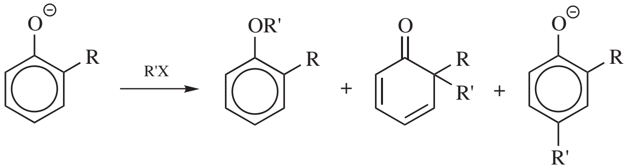
[480]This term was introduced by Hassner, A. *J. Org. Chem.* ***1968***, *33*, 2684.

[481]For an exception, see Trimitsis, G.B.; Hinkley, J.M.; TenBrink, R.; Faburada, A.L.; Anderson, R.; Poli, M.; Christian, B.; Gustafson, G.; Erdman, J.; Rop, D. *J. Org. Chem.* ***1983***, *48*, 2957.

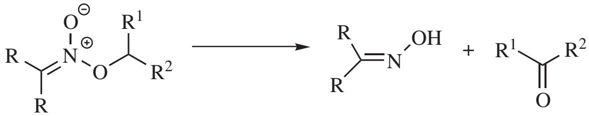
position for use as a nucleophile, but there is a stronger acidic group in the molecule, it may be possible to take off both protons; if it is, then attack is always by the desired position since it is the ion of the weaker acid. On the other hand, if it is desired to attack with the more acidic position, all that is necessary is to remove just one proton.[482] For example, ethyl acetoacetate can be alkylated at either the methyl or the methylene group (**10-67**):



3. *The CN⁻ Ion*. This nucleophile can give nitriles RCN (**10-75**) or isocyanides RN≡C.
4. *The Nitrite Ion*. This ion can give nitrite esters R—O—N=O (**10-22**) or nitro compounds RNO_2 (**10-76**), which are not esters.
5. Phenoxide ions (which are analogous to enolate anions) can undergo *C*-alkylation or *O*-alkylation:



6. Removal of a proton from an aliphatic nitro compound gives a carbanion ($R_2\bar{C}^{\ominus}$—NO_2) that can be alkylated at oxygen or carbon.[483] *O*-Alkylation gives nitronic esters, which are generally unstable to heat but break down to give an oxime and an aldehyde or ketone.



There are many other ambident nucleophiles.

[482]The use of this principle was first reported by Hauser, C.R.; Harris, C.M. *J. Am. Chem. Soc.* ***1958***, *80*, 6360. It has since been applied many times. For reviews, see Thompson, C.M.; Green, D.L.C. *Tetrahedron* ***1991***, *47*, 4223; Kaiser, E.M.; Petty, J.D.; Knutson, P.L.A. *Synthesis* ***1977***, 509; Harris, T.M.; Harris, C.M. *Org. React.* ***1969***, *17*, 155.

[483]For a review, see Erashko, V.I.; Shevelev, S.A.; Fainzil'berg, A.A. *Russ. Chem. Rev.* ***1966***, *35*, 719.

It would be useful to have general rules as to which atom of an ambident nucleophile will attack a given substrate under a given set of conditions.[484] Unfortunately, the situation is complicated by the large number of variables. It might be expected that the more electronegative atom would always attack, but this is often not the case. Where the products are determined by thermodynamic control (p. 307), the principal product is usually the one in which the atom of higher basicity has attacked (i.e., $C > N > O > S$).[485] However, in most reactions, the products are kinetically controlled and matters are much less simple. Nevertheless, the following generalizations can be made, while recognizing that there are many exceptions and unexplained results. As in the discussion of nucleophilicity in general (p. 490), there are two major factors: the polarizability (hard–soft character) of the nucleophile and solvation effects.

1. The principle of hard and soft acids and bases states that hard acids prefer hard bases and soft acids prefer soft bases (p. 375). In an S_N1 mechanism, the nucleophile attacks a carbocation, which is a hard acid. In an S_N2 mechanism, the nucleophile attacks the carbon atom of a molecule, which is a softer acid. The more electronegative atom of an ambident nucleophile is a harder base than the less electronegative atom. We may thus make the statement: As the character of a given reaction changes from S_N1- to S_N2-like, an ambident nucleophile becomes more likely to attack with its less electronegative atom.[486] Therefore, changing from S_N1 to S_N2 conditions should favor C attack by ^{-}CN, N attack by NO_2^-, C attack by enolate or phenoxide ions, etc. As an example, primary alkyl halides are attacked (in protic solvents) by the carbon atom of the anion of CH_3COCH_2COOEt, while α-chloro ethers, which react by the S_N1 mechanism, are attacked by the oxygen atom. However, this does not mean that attack is by the less electronegative atom in all S_N2 reactions and by the more electronegative atom in all S_N1 reactions. The position of attack also depends on the nature of the nucleophile, the solvent, the leaving group, and other conditions. The rule merely states that increasing the S_N2 character of the transition state makes attack by the less electronegative atom more likely.
2. All negatively charged nucleophiles must of course have a positive counterion. If this ion is Ag^+ (or some other ion that specifically helps in removing the leaving group, p. 504), rather than the more usual Na^+ or K^+, then the transition state is more S_N1-like. Therefore the use of Ag^+ promotes attack at the more electronegative atom. For example, alkyl halides treated with NaCN

[484] For reviews, see Jackman, L.M.; Lange, B.C. *Tetrahedron* ***1977***, *33*, 2737; Reutov, O.A.; Kurts, A.L. *Russ. Chem. Rev.* ***1977***, *46*, 1040; Gompper, R.; Wagner, H. *Angew. Chem. Int. Ed.* ***1976***, *15*, 321.

[485] For an example, see Bégué, J.; Charpentier-Morize, M.; Née, G. *J. Chem. Soc., Chem. Commun.* ***1989***, 83.

[486] This principle, sometimes called *Kornblum's rule*, was first stated by Kornblum, N.; Smiley, R.A.; Blackwood, R.K.; Iffland, D.C. *J. Am. Chem. Soc.* ***1955***, *77*, 6269.

generally give mostly RCN, but the use of AgCN increases the yield of isocyanides RNC.[487]

3. In many cases, the solvent influences the position of attack. The freer the nucleophile, the more likely it is to attack with its more electronegative atom, but the more this atom is encumbered by either solvent molecules or positive counterions, the more likely is attack by the less electronegative atom. In protic solvents, the more electronegative atom is better solvated by hydrogen bonds than the less electronegative atom. In polar aprotic solvents, neither atom of the nucleophile is greatly solvated, but these solvents are very effective in solvating cations. Thus in a polar aprotic solvent the more electronegative end of the nucleophile is freer from entanglement by both the solvent and the cation, so that a change from a protic to a polar aprotic solvent often increases the extent of attack by the more electronegative atom. An example is attack by sodium β-naphthoxide on benzyl bromide, which resulted in 95% *O*-alkylation in dimethyl sulfoxide and 85% *C*-alkylation in 2,2,2-trifluoroethanol.[488] Changing the cation from Li^+ to Na^+ to K^+ (in nonpolar solvents) also favors *O*- over *C*-alkylation[489] for similar reasons (K^+ leaves the nucleophile much freer than Li^+), as does the use of crown ethers, which are good at solvating cations (p. 119).[490] Alkylation of the enolate anion of cyclohexanone in the gas phase, where the nucleophile is completely free, showed only *O*-alkylation and no *C*-alkylation.[491]
4. In extreme cases, steric effects can govern the regioselectivity.[492]

Ambident Substrates

Some substrates (e.g., 1,3-dichlorobutane) can be attacked at two or more positions. We may call these *ambident substrates*. In the example given, there happen to be

[487]Actually, this reaction is more complicated than it seems on the surface; see Austad, T.; Songstad, J.; Stangeland, L.J. *Acta Chem. Scand.* ***1971***, *25*, 2327; Carretero, J.C.; García Ruano, J.L. *Tetrahedron Lett.* ***1985***, *26*, 3381.

[488]Kornblum, N.; Berrigan, P.J.; le Noble, W.J. *J. Chem. Soc.* ***1963***, *85*, 1141; Kornblum, N.; Seltzer, R.; Haberfield, P. *J. Am. Chem. Soc.* ***1963***, *85*, 1148. For other examples, see le Noble, W.J.; Puerta, J.E. *Tetrahedron Lett.* ***1966***, 1087; Brieger, G.; Pelletier, W.M. *Tetrahedron Lett.* ***1965***, 3555; Heiszwolf, G.J.; Kloosterziel, H. *Recl. Trav. Chim. Pays-Bas* ***1970***, *89*, 1153, 1217; Kurts, A.L.; Masias, A.; Beletskaya, I.P.; Reutov, O.A. *J. Org. Chem. USSR* ***1971***, *7*, 2323; Schick, H.; Schwarz, H.; Finger, A.; Schwarz, S. *Tetrahedron* ***1982***, *38*, 1279.

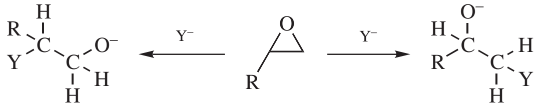
[489]Kornblum, N.; Seltzer, R.; Haberfield, P. *J. Am. Chem. Soc.* ***1963***, *85*, 1148; Kurts, A.L.; Beletskaya, I.P.; Masias, A.; Reutov, O.A. *Tetrahedron Lett.* ***1968***, 3679. See, however, Sarthou, P.; Bram, G.; Guibe, F. *Can. J. Chem.* ***1980***, *58*, 786.

[490]Smith, S.G.; Hanson, M.P. *J. Org. Chem.* ***1971***, *36*, 1931; Kurts, A.L.; Dem'yanov, P.I.; Beletskaya, I.P.; Reutov, O.A. *J. Org. Chem. USSR* ***1973***, *9*, 1341; Cambillau, C.; Sarthou, P.; Bram, G. *Tetrahedron Lett.* ***1976***, 281; Akabori, S.; Tuji, H. *Bull. Chem. Soc. Jpn.* ***1978***, *51*, 1197. See also, Zook, H.D.; Russo, T.J.; Ferrand, E.F.; Stotz, D.S. *J. Org. Chem.* ***1968***, *33*, 2222; le Noble, W.J.; Palit, S.K. *Tetrahedron Lett.* ***1972***, 493.

[491]Jones, M.E.; Kass, S.R.; Filley, J.; Barkley, R.M.; Ellison, G.B. *J. Am. Chem. Soc.* ***1985***, *107*, 109.

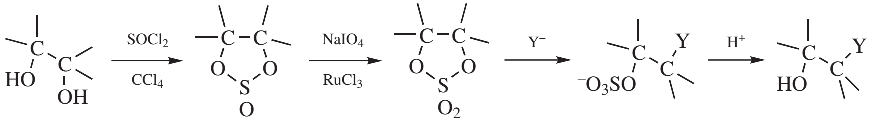
[492]See, for example, O'Neill, P.; Hegarty, A.F. *J. Org. Chem.* ***1987***, *52*, 2113.

two leaving groups in the molecule, but there are two kinds of substrates that are inherently ambident (unless symmetrical). One of these, the allylic type, has already been discussed (p. 469). The other is the epoxy (or the similar aziridine[493] or episulfide) substrate.[494]



Substitution of the free epoxide, which generally occurs under basic or neutral conditions, usually involves an S_N2 mechanism. Since primary substrates undergo S_N2 attack more readily than secondary, unsymmetrical epoxides are attacked in neutral or basic solution at the less highly substituted carbon, and stereospecifically, with inversion at that carbon. Under acidic conditions, it is the protonated epoxide that undergoes the reaction. Under these conditions the mechanism can be either S_N1 or S_N2. In S_N1 mechanisms, which favor tertiary carbons, we might expect that attack would be at the more highly substituted carbon, and this is indeed the case. However, even when protonated epoxides react by the S_N2 mechanism, attack is usually at the more highly substituted position.[495] Thus, it is often possible to change the direction of ring opening by changing the conditions from basic to acidic or vice versa. In the ring opening of 2,3-epoxy alcohols, the presence of $Ti(O\text{-}i\text{Pr})_4$ increases both the rate and the regioselectivity, favoring attack at C-3 rather than C-2.[496] When an epoxide ring is fused to a cyclohexane ring, S_N2 ring opening invariably gives diaxial rather than diequatorial ring opening.[497]

Cyclic sulfates (**108**), prepared from 1,2-diols, react in the same manner as epoxides, but usually more rapidly:[498]



108

[493]Chechik, V.O.; Bobylev, V.A. *Acta Chem. Scand. B* ***1994***, *48*, 837.

[494]For reviews of S_N reactions at such substrates, see Rao, A.S.; Paknikar, S.K.; Kirtane, J.G. *Tetrahedron* ***1983***, *39*, 2323; Behrens, C.H.; Sharpless, K.B. *Aldrichimica Acta* ***1983***, *16*, 67; Enikolopiyan, N.S. *Pure Appl. Chem.* ***1976***, *48*, 317; Fokin, A.V.; Kolomiets, A.F. *Russ. Chem. Rev.* ***1976***, *45*, 25; Dermer, O.C.; Ham, G.E. *Ethylenimine and Other Aziridines*; Academic Press, NY, ***1969***, pp. 206–273; Akhrem, A.A.; Moiseenkov, A.M.; Dobrynin, V.N. *Russ. Chem. Rev.* ***1968***, *37*, 448; Gritter, R.J., in Patai, S. *The Chemistry of the Ether Linkage*, Wiley, NY, ***1967***, pp. 390–400.

[495]Addy, J.K.; Parker, R.E. *J. Chem. Soc.* ***1963***, 915; Biggs, J.; Chapman, N.B.; Finch, A.F.; Wray, V. *J. Chem. Soc. B* ***1971***, 55.

[496]Caron M.; Sharpless, K.B. *J. Org. Chem.* ***1985***, *50*, 1557. See also, Chong, J.M.; Sharpless, K.B. *J. Org. Chem.* ***1985***, *50*, 1560; Behrens, C.H.; Sharpless, K.B. *J. Org. Chem.* ***1985***, *50*, 5696.

[497]Murphy, D.K.; Alumbaugh, R.L.; Rickborn, B. *J. Am. Chem. Soc.* ***1969***, *91*, 2649. For a method of overriding this preference, see McKittrick, B.A.; Ganem, B. *J. Org. Chem.* ***1985***, *50*, 5897.

[498]Gao, Y.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1988***, *110*, 7538; Kim, B.M.; Sharpless, K.B. *Tetrahedron Lett.* ***1989***, *30*, 655.

Reactions

The reactions in this chapter are classified according to the attacking atom of the nucleophile in the order O, S, N, halogen, H, C. For a given nucleophile, reactions are classified by the substrate and leaving group, with alkyl substrates usually considered before acyl ones. Nucleophilic substitutions at a sulfur atom are treated at the end.

Not all the reactions in this chapter are actually nucleophilic substitutions. In some cases, the mechanisms are not known with enough certainty even to decide whether a nucleophile, an electrophile, or a free radical is attacking. In other cases, conversion of one compound to another can occur by two or even all three of these possibilities, depending on the reagent and the reaction conditions. However, one or more of the nucleophilic mechanisms previously discussed do hold for the overwhelming majority of the reactions in this chapter. For the alkylations, the S_N2 is by far the most common mechanism, as long as R is primary or secondary alkyl. For the acylations, the tetrahedral mechanism is the most common.

OXYGEN NUCLEOPHILES

A. Attack by OH at an Alkyl Carbon

10-1 Hydrolysis of Alkyl Halides

Hydroxy-de-halogenation

$$RX + H_2O \longrightarrow ROH_2^+ \xrightarrow{-H^+} ROH + H^+$$

$$RX + OH^- \longrightarrow ROH$$

Alkyl halides can be hydrolyzed to alcohols. Hydroxide ion is usually required, although particularly active substrates such as allylic or benzylic alcohols can be hydrolyzed by water. Ordinary halides can also be hydrolyzed by water,[499] if the solvent is HMPA or *N*-methyl-2-pyrrolidinone,[500] or if the reaction is done in an ionic solvent.[501] In contrast to most nucleophilic substitutions at saturated carbons, this reaction can be performed on tertiary substrates without significant interference from elimination side reactions. Tertiary alkyl α-halocarbonyl compounds can be converted to the corresponding alcohol with silver oxide in aqueous acetonitrile.[502] The

[499]It has been proposed that the mechanism of the reaction of primary halides with water is not the ordinary S_N2 mechanism, but that the rate-determining process involves a fluctuation of solvent configuration: Kurz, J.L.; Kurz, L.C. *Isr. J. Chem.* ***1985***, *26*, 339; Kurz, J.L.; Lee, J.; Love, M.E.; Rhodes, S. *J. Am. Chem. Soc.* ***1986***, *108*, 2960.

[500]Hutchins, R.O.; Taffer, I.M. *J. Org. Chem.* ***1983***, *48*, 1360.

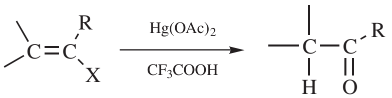
[501]Kim, D.W.; Hong, D.J.; Seo, J.W.; Kim, H.S.; Kim, H.K.; Song, C.E.; Chi, D.Y. *J. Org. Chem.* ***2004***, *69*, 3186.

[502]Cavicchioni, G. *Synth. Commun.* ***1994***, *24*, 2223.

reaction is not frequently used for synthetic purposes, because alkyl halides are usually obtained from alcohols.

An indirect conversion of halides to alcohols involved triethylborane. The reaction of an α-iodo ester with BEt_3, followed by reaction with dimethyl sulfide in methanol, gave an α-hydroxy ester.[503]

Vinylic halides are unreactive (p. 473), but they can be hydrolyzed to ketones at room temperature with mercuric trifluoroacetate, or with mercuric acetate in either

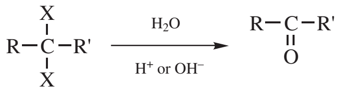


trifluoroacetic acid or acetic acid containing BF_3 etherate.[504] Primary bromides and iodides give alcohols when treated with bis(tributyltin)oxide Bu_3Sn—O—$SnBu_3$ in the presence of silver salts.[505]

OS **II**, 408; **III**, 434; **IV**, 128; **VI**, 142, 1037.

10-2 Hydrolysis of *gem*-Dihalides

Oxo-de-dihalo-bisubstitution



gem-Dihalides can be hydrolyzed with either acid or basic catalysis to give aldehydes or ketones.[506] Formally, the reaction may be regarded as giving R—C(OH)XR′, which is unstable and loses HX to give the carbonyl compound. For aldehydes derived from $RCHX_2$, strong bases cannot be used, because the product undergoes the aldol reaction (**16-34**) or the Cannizzaro reaction (**19-81**). A mixture of calcium carbonate and sodium acetate is effective,[507] and heating to 100°C in DMSO gives good yields.[508] Heating 1,1-dihaloalkenes ($C{=}CX_2$) with zinc and water leads to the corresponding methyl ketone.[509]

OS **I**, 95; **II**, 89, 133, 244, 549; **III**, 538, 788; **IV**, 110, 423, 807. Also see, OS **III**, 737.

[503]Kihara, N.; Ollivier, C.; Renaud, P. *Org. Lett.* ***1999***, *1*, 1419.

[504]Martin, S.F.; Chou, T. *Tetrahedron Lett.* ***1978***, 1943; Yoshioka, H.; Takasaki, K.; Kobayashi, M.; Matsumoto, T. *Tetrahedron Lett.* ***1979***, 3489.

[505]Gingras, M.; Chan, T.H. *Tetrahedron Lett.* ***1989***, *30*, 279.

[506]For a review, see Salomaa, P., in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 177–210.

[507]Mataka, S.; Liu, G.-B.; Sawada, T.; Tori-i, A.; Tashiro, M. *J. Chem. Res. (S)* ***1995***, 410.

[508]Li, W.; Li, J.; DeVincentis, D.; Masour, T.S. *Tetrahedron Lett.* ***2004***, *45*, 1071.

[509]Wang, L.; Li, P.; Yan, J.; Wu, Z. *Tetrahedron Lett.* ***2003***, *44*, 4685.

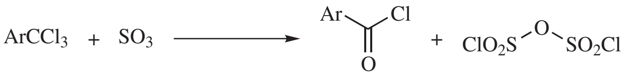
10-3 Hydrolysis of 1,1,1-Trihalides

Hydroxy,oxo-de-trihalo-tersubstitution

$$RCX_3 + H_2O \longrightarrow RCOOH$$

This reaction is similar to the previous one. The utility of the method is limited by the lack of availability of trihalides, although these compounds can be prepared by addition of CCl_4 and similar compounds to double bonds (**15-38**) and by the free-radical halogenation of methyl groups on aromatic rings (**14-1**). When the hydrolysis is carried out in the presence of an alcohol, a carboxylic ester can be obtained directly.[510] 1,1-Dichloroalkenes can also be hydrolyzed to carboxylic acids, by treatment with H_2SO_4. In general 1,1,1-trifluorides do not undergo this reaction,[511] although exceptions are known.[512]

Aryl 1,1,1-trihalomethanes can be converted to acyl halides by treatment with sulfur trioxide.[513]



Chloroform is more rapidly hydrolyzed with base than dichloromethane or carbon tetrachloride and gives not only formic acid, but also carbon monoxide.[514] Hine[515] has shown that the mechanism of chloroform hydrolysis is quite different from that of dichloromethane or carbon tetrachloride, although superficially the three reactions appear similar. The first step is the loss of a proton to give CCl_3^-, which then loses Cl^- to give dichlorocarbene CCl_2, which is hydrolyzed to formic acid or carbon monoxide.

$$HCCl_3 \xrightleftharpoons{OH^-} \bar{C}Cl_3 \xrightarrow{-Cl^-} \bar{C}Cl_2 \xrightarrow{H_2O} HCOOH \text{ or } CO$$

This is an example of an S_N1cB mechanism (p. 500). The other two compounds react by the normal mechanisms. Carbon tetrachloride cannot give up a proton and dichloromethane is not acidic enough.

OS **III**, 270; **V**, 93. Also see, OS **I**, 327.

[510]See, for example, Le Fave, G.M.; Scheurer, P.G. *J. Am. Chem. Soc.* ***1950***, *72*, 2464.

[511]Sheppard, W.A.; Sharts, C.M. *Organic Fluorine Chemistry*, W.A. Benjamin, NY, ***1969***, pp. 410–411; Hudlický, M. *Chemistry of Organic Fluorine Compounds*, 2nd ed., Ellis Horwood, Chichester, ***1976***, pp. 273–274.

[512]See, for example, Kobayashi, Y.; Kumadaki, I. *Acc. Chem. Res.* ***1978***, *11*, 197.

[513]Rondestvedt Jr., C.S. *J. Org. Chem.* ***1976***, *41*, 3569, 3574, 3576. For another method, see Nakano, T.; Ohkawa, K.; Matsumoto, H.; Nagai, Y. *J. Chem. Soc., Chem. Commun.* ***1977***, 808.

[514]For a review, see Kirmse, W. *Carbene Chemistry*, 2nd ed., Academic Press, NY, ***1971***, pp. 129–141.

[515]Hine, J. *J. Am. Chem. Soc.* ***1950***, *72*, 2438. Also, see le Noble, W.J. *J. Am. Chem. Soc.* ***1965***, *87*, 2434.

10-4 Hydrolysis of Alkyl Esters of Inorganic Acids

Hydroxy-de-sulfonyloxy-substitution, and so on.

$$\mathbf{R{-}X \longrightarrow R{-}OH}$$

$$\mathbf{X = OSO_2R', OSO_2OH, OSO_2OR, OSO_2R', OSOR'}$$
$$\mathbf{= ONO_2, ONO, OPO(OH)_2, OPO(OR')_2, OB(OH)_2 \quad \text{and others}}$$

Esters of inorganic acids, including those given above and others, can be hydrolyzed to alcohols. The reactions are most successful when the ester is that of a strong acid, but it can be done for esters of weaker acids by the use of hydroxide ion (a more powerful nucleophile) or acidic conditions (which make the leaving group come off more easily). When vinylic substrates are hydrolyzed, the products are aldehydes or ketones.

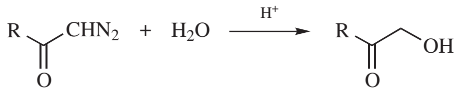
$$R_2C{=}CH{-}X \xrightarrow{H_2O} R_2C{=}CH{-}OH \rightleftharpoons R_2CH{-}CHO$$

These reactions are all considered at one place because they are formally similar, but although some of them involve R—O cleavage and are thus nucleophilic substitutions at a saturated carbon, others involve cleavage of the bond between the inorganic atom and oxygen and are thus nucleophilic substitutions at a sulfur, nitrogen, etc. It is even possible for the same ester to be cleaved at either position, depending on the conditions. Thus benzhydryl *p*-toluenesulfinate ($Ph_2CHOSOC_6H_4CH_3$) was found to undergo C—O cleavage in $HClO_4$ solutions and S—O cleavage in alkaline media.[516] In general, the weaker the corresponding acid, the less likely is C—O cleavage. Thus, sulfonic acid esters $ROSO_2R'$ generally give C—O cleavage,[517] while nitrous acid esters RONO usually give N—O cleavage.[518] Esters of sulfonic acids that are frequently hydrolyzed are mentioned on p. 497. For hydrolysis of sulfonic acid esters, see also **16-100**.

OS **VI**, 852. See also, **VIII**, 50.

10-5 Hydrolysis of Diazoketones

Hydro,hydroxy-de-diazo-bisubstitution



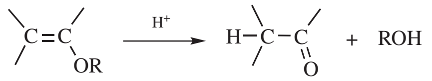
[516]Bunton, C.A.; Hendy, B.N. *J. Chem. Soc.* ***1963***, 627. For another example, see Batts, B.D. *J. Chem. Soc. B* ***1966***, 551.

[517]Barnard, P.W.C.; Robertson, R.E. *Can. J. Chem.* ***1961***, *39*, 881. See also, Drabicky, M.J.; Myhre, P.C.; Reich, C.J.; Schmittou, E.R. *J. Org. Chem.* ***1976***, *41*, 1472.

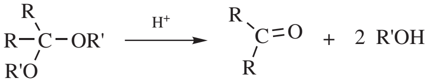
[518]For a discussion of the mechanism of hydrolysis of alkyl nitrites, see Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, ***1988***, pp. 162–163.

Diazoketones are relatively easy to prepare (see **16-89**). When treated with acid, they add a proton to give α-keto diazonium salts, which are hydrolyzed to the alcohols by the S_N1 or S_N2 mechanism.[519] Relatively good yields of α-hydroxy ketones can be prepared in this way, since the diazonium ion is somewhat stabilized by the presence of the carbonyl group, which discourages N_2 from leaving because that would result in an unstable α-carbonyl carbocation.

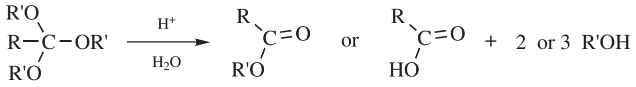
10-6 Hydrolysis of Acetals, Enol Ethers, and Similar Compounds[520]



3/Hydro-de-*O*-alkylation



***O*-Alkyl-*C*-alkoxy-elimination**



The alkoxyl group OR is not a leaving group, so these compounds must be converted to the conjugate acids before they can be hydrolyzed. Although 100% sulfuric acid and other concentrated strong acids readily cleave simple ethers,[521] the only acids used preparatively for this purpose are HBr and HI (**10-49**). However, acetals, ketals, and ortho esters[522] are easily cleaved by dilute acids. These compounds are hydrolyzed with greater facility because carbocations of the type RO—CH— are greatly stabilized by resonance (p. 242). The reactions therefore

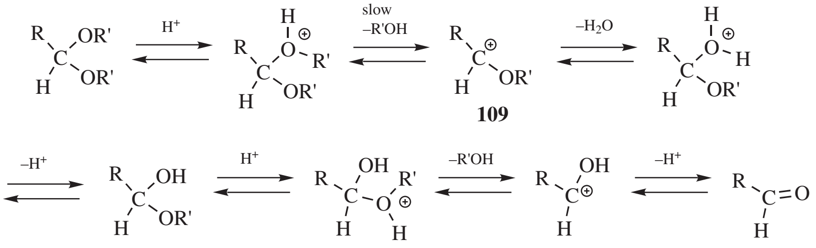
[519]Dahn, H.; Gold, H. *Helv. Chim. Acta* ***1963***, *46*, 983; Thomas, C.W.; Leveson, L.L. *Int. J. Chem. Kinet.*, ***1983***, *15*, 25. For a review of the acidpromoted decomposition of diazoketones, see Smith III, A.B; Dieter, R.K. *Tetrahedron* ***1981***, *37*, 2407.

[520]For reviews, see Bergstrom, R.G., in Patai, S. *The Chemistry of Functional Groups, Supplement E*, Wiley, NY, ***1980***, pp. 881–902; Cockerill, A.F.; Harrison, R.G., in Patai, S. *The Chemistry of Functional Groups, Supplement A*, pt. 1, Wiley, NY, ***1977***, pp. 149–329; Cordes, E.H.; Bull, H.G. *Chem. Rev.* ***1974***, *74*, 581; Cordes, E.H. *Prog. Phys. Org. Chem.* ***1967***, *4*, 1; Salomaa, P., in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 184–198; Pindur, U.; Müller, J.; Flo, C.; Witzel, H. *Chem. Soc. Rev.* ***1987***, *16*, 75 (ortho esters); Cordes, E.H., in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 632–656 (ortho esters); DeWolfe, R.H. *Carboxylic Ortho Acid Derivatives*, Academic Press, NY, ***1970***, pp. 134–146 (ortho esters); Rekasheva, A.F. *Russ. Chem. Rev.* ***1968***, *37*, 1009 (enol ethers).

[521]Jaques, D.; Leisten, J.A. *J. Chem. Soc.* ***1964***, 2683. See also, Olah, G.A.; O'Brien, D.H. *J. Am. Chem. Soc.* ***1967***, *89*, 1725.

[522]For a review of the reactions of ortho esters, see Pavlova, L.A.; Davidovich, Yu.A.; Rogozhin, S.V. *Russ. Chem. Rev.* ***1986***, *55*, 1026.

proceed by the S_N1 mechanism,[523] as shown for acetals:[524]



109

Hemiacetal

This mechanism (which is an S_N1cA or A1 mechanism) is the reverse of that for acetal formation by reaction of an aldehyde and an alcohol (**16-5**). Among the facts supporting the mechanism are[525] (*1*) The reaction proceeds with *specific* H_3O^+ catalysis (see p. 373). (*2*) It is faster in D_2O. (*3*) Optically active ROH are not racemized. (*4*) Even with *tert*-butylalcohol the R—O bond does not cleave, as shown by ^{18}O labeling.[526] (*5*) In the case of acetophenone ketals, the intermediate corresponding to **109** [$ArCMe(OR)_2$] could be trapped with sulfite ions (SO_3^{2-}).[527] (*6*) Trapping of this ion did not affect the hydrolysis rate,[527] so the rate-determining step must come earlier. (*7*) In the case of 1,1-dialkoxyalkanes, intermediates corresponding to **109** were isolated as stable ions in super acid solution at −75°C, where their spectra could be studied.[528] (*8*) Hydrolysis rates greatly increase in the order $CH_2(OR')_2 < RCH(OR')_2 < R_2C(OR')_2 < RC(OR')_3$, as would be expected for a carbocation intermediate.[529] Formation of **109** is usually the rate-determining step (as marked above), but there is evidence that at least in some cases this step is fast, and the rate-determining step is loss of R′OH from the protonated hemiacetal.[530] Rate-determining addition of water to **109** has also been reported.[531]

[523]For a review of the mechanisms of hydrolysis of acetals and thioacetals, see Satchell, D.P.N.; Satchell, R.S. *Chem. Soc. Rev.* ***1990***, *19*, 55.

[524]Kreevoy, M.M.; Taft, R.W. *J. Am. Chem. Soc.* ***1955***, *77*, 3146, 5590.

[525]For a discussion of these, and of other evidence, see Cordes, E.H. *Prog. Phys. Org. Chem.* ***1967***, *4*, 1.

[526]Cawley, J.J.; Westheimer, F.H. *Chem. Ind. (London)* ***1960***, 656.

[527]Young, P.R.; Jencks, W.P. *J. Am. Chem. Soc.* ***1977***, *99*, 8238. See also, Jencks, W.P. *Acc. Chem. Res.* ***1980***, *13*, 161; McClelland, R.A.; Ahmad, M. *J. Am. Chem. Soc.* ***1978***, *100*, 7027, 7031; Young, P.R.; Bogseth, R.C.; Rietz, E.G. *J. Am. Chem. Soc.* ***1980***, *102*, 6268. However, in the case of simple aliphatic acetals, **103** could not be trapped: Amyes, T.L.; Jencks, W.P. *J. Am. Chem. Soc.* ***1988***, *110*, 3677.

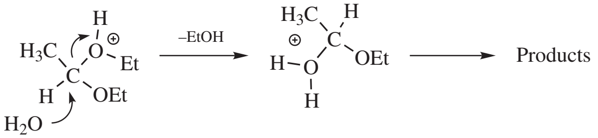
[528]See White, A.M.; Olah, G.A. *J. Am. Chem. Soc.* ***1969***, *91*, 2943; Akhmatdinov, R.T.; Kantor, E.A.; Imashev, U.B.; Yasman, Ya.B.; Rakhmankulov, D.L. *J. Org. Chem. USSR* ***1981***, *17*, 626.

[529]For the influence of alkyl group size on the mechanism see Belarmino, A.T.N.; Froehner, S.; Zanette, D.; Farah, J.P.S.; Bunton, C.A.; Romsted, L.S. *J. Org. Chem.* ***2003***, *68*, 706.

[530]Jensen, J.L.; Lenz, P.A. *J. Am. Chem. Soc.* ***1978***, *100*, 1291; Finley, R.L.; Kubler, D.G.; McClelland, R.A. *J. Org. Chem.* ***1980***, *45*, 644; Przystas, T.J.; Fife, T.H. *J. Am. Chem. Soc.* ***1981***, *103*, 4884; Chiang, Y.; Kresge, A.J. *J. Org. Chem.* ***1985***, *50*, 5038; Fife, T.H.; Natarajan, R. *J. Am. Chem. Soc.* ***1986***, *108*, 2425, 8050; McClelland, R.A.; Sørensen, P.E. *Acta Chem. Scand.* ***1990***, *44*, 1082.

[531]Toullec, J.; El-Alaoui, M. *J. Org. Chem.* ***1985***, *50*, 4928; Fife, T.H.; Natarajan, R. *J. Am. Chem. Soc.* ***1986***, *108*, 2425, 8050.

While the A1 mechanism shown above operates in most acetal hydrolyses, it has been shown that at least two other mechanisms can take place with suitable substrates.[532] In one of these mechanisms the second and third of the above steps are concerted, so that the mechanism is S_N2cA (or A2). This has been shown, for example, in the hydrolysis of 1,1-diethoxyethane, by isotope effect studies:[533]



In the second mechanism, the first and second steps are concerted. In the case of hydrolysis of 2-(*p*-nitrophenoxy)tetrahydropyran, *general* acid catalysis was shown[534] demonstrating that the substrate is protonated in the rate-determining step (p. 373). Reactions in which a substrate is protonated in the rate-determining step are called AS_E2 reactions.[535] However, if protonation of the substrate were all that happens in the slow step, then the proton in the transition state would be expected to lie closer to the weaker base (p. 373). Because the substrate is a much weaker base than water, the proton should be largely transferred. Since the Brønsted coefficient was found to be 0.5, the proton was actually transferred only about halfway. This can be explained if the basicity of the substrate is increased by partial breaking of the C—O bond. The conclusion drawn is that steps 1 and 2 are concerted. The hydrolysis of ortho esters in most cases is also subject to general acid catalysis.[536]

The hydrolysis of acetals and ortho esters is governed by the stereoelectronic control factor discussed on p. 1258,[537] although the effect can generally be seen only in systems where conformational mobility is limited, especially in cyclic systems. There is evidence for synplanar stereoselection in the acid hydrolysis of

[532]For a review, see Fife, T.H. *Acc. Chem. Res.* ***1972***, *5*, 264. For a discussion, see Wann, S.R.; Kreevoy, M.M. *J. Org. Chem.* ***1981***, *46*, 419.

[533]Kresge, A.J.; Weeks, D.P. *J. Am. Chem. Soc.* ***1984***, *106*, 7140. See also, Fife, T.H. *J. Am. Chem. Soc.* ***1967***, *89*, 3228; Craze, G.; Kirby, A.J.; Osborne, R. *J. Chem. Soc. Perkin Trans. 2* ***1978***, 357; Amyes, T.L.; Jencks, W.P. *J. Am. Chem. Soc.* ***1989***, *111*, 7888, 7900.

[534]Fife, T.H.; Brod, L.H. *J. Am. Chem. Soc.* ***1970***, *92*, 1681. For other examples, see Kankaanperä, A.; Lahti, M. *Acta Chem. Scand.* ***1969***, *23*, 2465; Mori, A.L.; Schaleger, L.L. *J. Am. Chem. Soc.* ***1972***, *94*, 5039; Capon, B.; Nimmo, K. *J. Chem. Soc. Perkin Trans. 2* ***1975***, 1113; Eliason, R.; Kreevoy, M.M. *J. Am. Chem. Soc.* ***1978***, *100*, 7037; Jensen, J.L.; Herold, L.R.; Lenz, P.A.; Trusty, S.; Sergi, V.; Bell, K.; Rogers, P. *J. Am. Chem. Soc.* ***1979***, *101*, 4672.

[535]For a review of A-S_E2 reactions, see Williams Jr., J.M.; Kreevoy, M.M. *Adv. Phys. Org. Chem.* ***1968***, *6*, 63.

[536]Chiang, Y.; Kresge, A.J.; Lahti, M.O.; Weeks, D.P. *J. Am. Chem. Soc.* ***1983***, *105*, 6852, and references cited therein; Santry, L.J.; McClelland, R.A. *J. Am. Chem. Soc.* ***1983***, *105*, 6138; Fife, T.H.; Przystas, T.J. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 143.

[537]See, for example, Kirby, A.J. *Acc. Chem. Res.* ***1984***, *17*, 305; Bouab, O.; Lamaty, G.; Moreau, C. *Can. J. Chem.* ***1985***, *63*, 816. See, however, Ratcliffe, A.J.; Mootoo, D.R.; Andrews, C.W.; Fraser-Reid, B. *J. Am. Chem. Soc.* ***1989***, *111*, 7661.

acetals.[538] The mechanism of Lewis acid-mediated cleavage of chiral acetals is also known.[539]

Convenient reagents for acetals are wet silica gel[540] and Amberlyst-15 (a sulfonic acid-based polystyrene cation exchange resin).[541] Both cyclic and acyclic acetals and ketals can be converted to aldehydes or ketones under nonaqueous conditions by treatment with Montmorillonite K10 clay in various solvents,[542] with Lewis acids, such as $FeCl_3{\bullet}6\ H_2O$ in chloroform,[543] $Bi(OTf)_3{\bullet}xH_2O$,[544] or 5% $Ce(OTf)_3$ in wet nitromethane.[545] Hydrolysis techniques include treatment with β-cyclodextrin in water,[546] Me_3SiI in CH_2Cl_2, or $CHCl_3$,[547] $LiBF_4$,[548] ceric ammonium nitirate in aqueous acetonitrile,[549] DDQ[550] in wet MeCN, or Magtrieve in chloroform.[551]

Although acetals, ketals, and ortho esters are easily hydrolyzed by acids, they are extremely resistant to hydrolysis by bases. An aldehyde or ketone can therefore be protected from attack by a base by conversion to the acetal or ketal (**16-5**), and then can be cleaved with acid. Pyridine–HF has also been used for this conversion.[552] Thioacetals, thioketals, *gem*-diamines, and other compounds that contain any two of the groups OR, OCOR, NR_2, NHCOR, SR, and halogen on the same carbon can also be hydrolyzed to aldehydes or ketones, in most cases, by acid treatment. Several $ArCH(OAc)_2$ derivatives were hydrolyzed to the aldehyde using Montmorillonite K10,[553] alumina with microwaves,[554] ceric ammonium nitrate on silica gel,[555] or by heating with CBr_4 in acetonitirle.[556] Thioacetals $RCH(SR')_2$ and thioketals

[538]Li, S.; Kirby, A.J.; Deslongchamps, P. *Tetrahedron Lett.* ***1993***, *34*, 7757.

[539]Sammakia, T.; Smith, R.S. *J. Org. Chem.* ***1992***, *57*, 2997.

[540]Huet, F.; Lechevallier, A.; Pellet, M.; Conia, J.M. *Synthesis* ***1978***, 63. See Caballero, G.M.; Gros, E.G. *Synth. Commun.* ***1995***, *25*, 395 for hydrolysis of hindered ketals with $CuSO_4$ on silica gel.

[541]Coppola, G.M. *Synthesis* ***1984***, 1021.

[542]Li, T.-S.; Li, S.-H. *Synth. Commun.* ***1997***, *27*, 2299; Gautier, E.C.L.; Graham, A.E.; McKillop, A.; Standen, S.T.; Taylor, R.J.K. *Tetrahedron Lett.* ***1997***, *38*, 1881.

[543]Sen, S.E.; Roach, S.L.; Boggs, J.K.; Ewing, G.J.; Magrath, J. *J. Org. Chem.* ***1997***, *62*, 6684.

[544]Carringan, M.D.; Sarapa, D.; Smith, R.C.; Wieland, L.C.; Mohan, R.S. *J. Org. Chem.* ***2002***, *67*, 1027.

[545]Dalpozzo, R.; De Nino, A.; Maiuolo, L.; Procopio, A.; Tagarelli, A.; Sindona, G.; Bartoli, G. *J. Org. Chem.* ***2002***, *67*, 9093.

[546]Krishnaveni, N. S.; Surendra, K.; Reddy, M. A.; Nageswar, Y. V. D.; Rao, K. R. *J. Org. Chem.* ***2003***, *68*, 2018.

[547]Jung, M.E.; Andrus, W.A.; Ornstein, P.L. *Tetrahedron Lett.* ***1977***, 4175. See also, Balme, G.; Goré, J. *J. Org. Chem.* ***1983***, *48*, 3336.

[548]Lipshutz, B.H.; Harvey, D.F. *Synth. Commun.* ***1982***, *12*, 267.

[549]Ates, A.; Gautier, A.; Leroy, B.; Plancher, J.M.; Quesnel, Y.; Markó, I.E. *Tetrahedron Lett.* ***1999***, *40*, 1799.

[550]Tanemura, K.; Suzuki, T.; Horaguchi, T. *J. Chem. Soc., Chem. Commun.* ***1992***, 979.

[551]Ko, J.-y.; Park, S.-T. *Tetrahedron Lett.* ***1999***, *40*, 6025.

[552]Watanabe, Y.; Kiyosawa, Y.; Tatsukawa, A.; Hayashi, M. *Tetrahedron Lett.* ***2001***, *42*, 4641.

[553]Li, T.-S.; Zhang, Z.-H.; Fu, C.-G. *Tetrahedron Lett.* ***1997***, *38*, 3285.

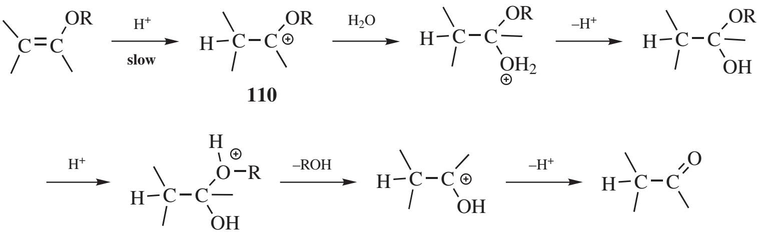
[554]Varma, R.S.; Chatterjee, A.K.; Varma, M. *Tetrahedron Lett*, ***1993***, *34*, 3207.

[555]Cotelle, P.; Catteau, J.-P. *Tetrahedron Lett.* ***1992***, *33*, 3855.

[556]Ramalingam, T.; Srinivas, R.; Reddy, B.V.S.; Yadav, J.S. *Synth. Commun.* ***2001***, *31*, 1091.

$R_2C(SR')_2$ are among those compounds generally resistant to acid hydrolysis.[557] Because conversion to these compounds (**16-11**) serves as an important method for protection of aldehydes and ketones, many methods have been devised to cleave them to the parent carbonyl compounds. Among reagents[558] used for this purpose are $HgCl_2$,[559] $FeCl_3$•6 H_2O,[560] cetyltrimethylammonium tribromide in dichloromethane,[561] *m*-chloroperoxybenzoic acid, and CF_3COOH in CH_2Cl_2,[562] Oxone® on wet alumina,[563] the Dess–Martin periodinane,[564] and DDQ in water under photolysis conditions,[565] and sodium nitrite in aqueous acetyl chloride.[566] Electrochemical methods have also been used.[567] Mixed acetals and ketals (RO—C—SR) can be hydrolyzed with most of the reagents mentioned above, including *N*-bromosuccinimide (NBS) in aqueous acetone,[568] and glyoxylic acid on Amberlyst 15 with microwave irradiation.[569]

Enol ethers are readily hydrolyzed by acids; the rate-determining step is protonation of the substrate.[570] However, protonation does not take place at the oxygen, but at the β carbon,[571] because that gives rise to the stable carbocation **110**.[572] After that the mechanism is similar to the A1 mechanism given above for the hydrolysis of acetals.



[557]Ali, M.; Satchell, D.P.N. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 219; ***1993***, 1825; Ali, M.; Satchell, D.P.N.; Le, V.T. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 917.

[558]For references to other reagents, see Gröbel, B.; Seebach, D. *Synthesis* ***1977***, 357, see pp. 359–367; Cussans, N.J.; Ley, S.V.; Barton, D.H.R. *J. Chem. Soc. Perkin Trans. 1* ***1980***, 1654.

[559]Corey, E.J.; Erickson, B.W. *J. Org. Chem.* ***1971***, *36*, 3553. For a mechanistic study, see Satchell, D.P.N.; Satchell, R.S. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 513.

[560]Kamal, A.; Laxman, E.; Reddy, P.S.M.M. *Synlett* ***2000***, 1476.

[561]Mondal, E.; Bose, G.; Khan, A.T. *Synlett* ***2001***, 785.

[562]Cossy, J. *Synthesis* ***1987***, 1113.

[563]Ceccherelli, P.; Curini, M.; Marcotullio, M.C.; Epifano, F.; Rosati, O. *Synlett*, ***1996***, 767.

[564]Langille, N.F.; Dakin, L.A.; Panek, J.S. *Org. Lett.* ***2003***, *5*, 575. See also, Stork, G.; Zhao, K. *Tetrahedron Lett.* ***1989***, *30*, 287.

[565]Mathew, L.; Sankararaman, S. *J. Org. Chem.* ***1993***, *58*, 7576.

[566]Khan, A.T.; Mondal, E.; Sahu, P.R. *Synlett* ***2003***, 377.

[567]See Schulz-von Itter, N.; Steckhan, E. *Tetrahedron* ***1987***, *43*, 2475; Suda, K.; Watanabe, J.; Takanami, T. *Tetrahedron Lett.* ***1992***, *33*, 1355.

[568]Karimi, B.; Seradj, H.; Tabaei, M.H. *Synlett* ***2000***, 1798.

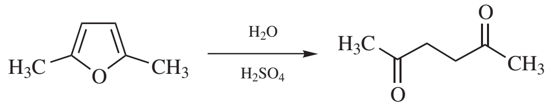
[569]Chavan, S.P.; Soni, P.; Kamat, S.K. *Synlett* ***2001***, 1251.

[570]Jones, J.; Kresge, A. J. *Can. J. Chem.* ***1993***, *71*, 38.

[571]Jones, D.M.; Wood, N.F. *J. Chem. Soc.* ***1964***, 5400; Okuyama, T.; Fueno, T.; Furukawa, J. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 3256; Kreevoy, M.M.; Eliason, R. *J. Phys. Chem.* ***1969***, *72*, 1313; Lienhard, G.; Wang, T.C. *J. Am. Chem. Soc.* ***1969***, *91*, 1146; Burt, R.A.; Chiang, Y.; Kresge, A.J.; Szilagyi, S. *Can. J. Chem.* ***1984***, *62*, 74.

[572]See Chwang, W.K.; Kresge, A.J.; Wiseman, J.R. *J. Am. Chem. Soc.* ***1979***, *101*, 6972.

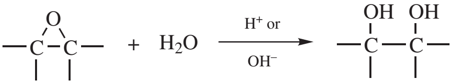
Among the facts supporting this mechanism (which is an A-S_E2 mechanism because the substrate is protonated in the rate-determining step) are (*1*) the ^{18}O labeling shows that in $ROCH{=}CH_2$ it is the vinyl–oxygen bond and not the RO bond that cleaves;[573] (*2*) the reaction is subject to general acid catalysis;[574] (*3*) there is a solvent isotope effect when D_2O is used.[574] Enamines are also hydrolyzed by acids (see **16-2**); the mechanism is similar. Ketene dithioacetals $R_2C{=}C(SR')_2$ also hydrolyze by a similar mechanism, except that the initial protonation step is partially reversible.[575] Furans represent a special case of enol ethers that are cleaved by acid to give 1,4-diones.[576] Thus oxonium ions are cleaved by water to give an alcohol and an ether:



OS **I**, 67, 205; **II**, 302, 305, 323; **III**, 37, 127, 465, 470, 536, 541, 641, 701, 731, 800; **IV**, 302, 499, 660, 816, 903; **V**, 91, 292, 294, 703, 716, 937, 967, 1088; **VI**, 64, 109, 312, 316, 361, 448, 496, 683, 869, 893, 905, 996; **VII**, 12, 162, 241, 249, 251, 263, 271, 287, 381, 495; **VIII**, 19, 155, 241, 353, 373

10-7 Hydrolysis of Epoxides

(3)*OC-seco*-hydroxy-de-alkoxy-substitution



The hydrolysis of epoxides is a convenient method for the preparation of *vic*-diols. The reaction is catalyzed by acids or bases (see discussion of the mechanism on p. 518). Among acid catalysts, perchloric acid leads to minimal side reactions,[577] and 10% Bu_4NHSO_4 in water is effective.[578] Water reacts with epoxides in the presence of β-cyclodextrin to give the corresponding diol.[579] Dimethyl sulfoxide is a superior solvent for the alkaline hydrolysis of epoxides.[580] Water at 10 kbar and 60°C opens epoxides with high stereoselectivity,[581] and epoxide hydrolase

[573]Kiprianova, L.A.; Rekasheva, A.F. *Dokl. Akad. Nauk SSSR*, ***1962***, *142*, 589.

[574]Fife, T.H. *J. Am. Chem. Soc.* ***1965***, *87*, 1084; Salomaa, P.; Kankaanperä, A.; Lajunen, M. *Acta Chem. Scand.* ***1966***, *20*, 1790; Kresge, A.J.; Yin, Y. *Can. J. Chem.* ***1987***, *65*, 1753.

[575]For a review, see Okuyama, T. *Acc. Chem. Res.* ***1986***, *19*, 370.

[576]Enzymatic hydrolysis of 2,5-dimethylfuran gave hex-3-en-2,5-dione. See Finlay, J.; McKervey, M.A.; Gunaratne, H.Q.N. *Tetrahedron Lett.* ***1998***, *39*, 5651.

[577]Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis* Vol. 1, Wiley, NY, ***1967***, p. 796.

[578]Fan, R.-H.; Hou, X.-L. *Org. Biomol. Chem.* ***2003***, *1*, 1565.

[579]Reddy, M.A.; Reddy, L.R.; Bhanumthi, N.; Rao, K.R. *Org. Prep. Proceed. Int.* ***2002***, *34*, 537.

[580]Berti, G.; Macchia, B.; Macchia, F. *Tetrahedron Lett.* ***1965***, 3421.

[581]Kotsuki, H.; Kataoka, M.; Nishizawa, H. *Tetrahedron Lett.* ***1993***, *34*, 4031.

opens epoxides with high enantioselectivity.[582] Cobalt salen [salen = bis(salicylidene)ethylenediamine] catalysts, in the presence of water, open epoxides with high stereoselectivity.[583] Photolysis of epoxy-ketones in the presence of 1,3-dimethylbenzimidazoline in AcOH/THF leads to β-hydroxy ketones.[584]

OS **V**, 414.

B. Attack by OR at an Alkyl Carbon

10-8 Alkylation With Alkyl Halides: The Williamson Reaction

Alkoxy-de-halogenation

$$RX + OR'^{-} \longrightarrow ROR'$$

The *Williamson reaction*, discovered in 1850, is still the best general method for the preparation of unsymmetrical or symmetrical ethers.[585] The reaction can also be carried out with aromatic R′, although *C*-alkylation is sometimes a side reaction (see p. 515).[586] The normal method involves treatment of the halide with alkoxide or aroxide ion prepared from an alcohol or phenol, although methylation using dimethyl carbonate has been reported.[587] It is also possible to mix the halide and alcohol or phenol directly with Cs_2CO_3 in acetonitrile,[588] or with solid KOH in Me_2SO.[589] The reaction can also be carried out in a dry medium,[590] on zeolite–HY[591] or neat[592] or in solvents[593] using microwave irradiation. Williamson ether synthesis in ionic liquids has also been reported.[594] The reaction is not successful for tertiary R (because of elimination), and low yields are often obtained with secondary R. Mono-ethers can be formed from diols and alkyl halides.[595] Many other

[582]Zhao, L.; Han, B.; Huang, Z.; Miller, M.; Huang, H.; Malashock, D.S.; Zhu, Z.; Milan, A.; Robertson, D.E.; Weiner, D.P.; Burk, M. J. *J. Am. Chem. Soc.* ***2004***, *126*, 11156; See also, Pedragosa-Moreau, S.; Archelas, A.; Furstoss, R. *Tetrahedron Lett.* ***1996***, *37*, 3319.

[583]Ready, J.M.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2001***, *123*, 2687.

[584]Hasegawa, E.; Chiba, N.; Nakajima, A.; Suzuki, K.; Yoneoka, A.; Iwaya, K. *Synthesis* ***2001***, 1248. For a related reaction with NO, see Liu, Z.; Li, R.; Yang, D.; Wu, L. *Tetrahedron Lett.* ***2004***, *45*, 1565.

[585]For a review, see Feuer, H.; Hooz, J., in Patai, S. *The Chemistry of the Ether Linkage*, Wiley, NY, ***1967***, pp. 446–450, 460–468.

[586]For a list of reagents used to convert alcohols and phenols to ethers, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 890–893.

[587]Ouk, S.; Thiebaud, S.; Borredon, E.; Legars, P.; Lecomte, L. *Tetrahedron Lett.* ***2002***, *43*, 2661.

[588]Lee, J.C.; Yuk, J.Y.; Cho, S.H. *Synth. Commun.* ***1995***, *25*, 1367.

[589]Benedict, D.A.; Bianchi, T.A.; Cate, L.A. *Synthesis* ***1979***, 428; Johnstone, R.A.W.; Rose, M.E. *Tetrahedron* ***1979***, *35*, 2169. See also, Loupy, A.; Sansoulet, J.; Vaziri-Zand, F. *Bull. Soc. Chim. Fr.* ***1987***, 1027.

[590]Bogdal, D.; Pielichowski, J.; Jaskot, K. *Org. Prep. Proceed. Int.* ***1998***, *30*, 427.

[591]Gadhwal, S.; Boruah, A.; Prajapati, D.; Sandhu, J.S. *Synth. Commun.* ***1999***, *29*, 1921.

[592]Yuncheng, Y.; Yulin, J.; Jun, P.; Xiaohui, Z.; Conggui, Y. *Gazz. Chim. Ital.*, ***1993***, *123*, 519.

[593]Paul, S.; Gupta, M. *Tetrahedron Lett.* ***2004***, *45*, 8825.

[594]In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Xu, Z.Y.; Xu, D.Q.; Liu, B.Y. *Org. Prep. Proceed. Int.* ***2004***, *36*, 156.

[595]For an example, see Jha, S.C.; Joshi, N.N. *J. Org. Chem.* ***2002***, *67*, 3897.

functional groups can be present in the molecule without interference. Ethers with one tertiary group *can* be prepared by treatment of an alkyl halide or sulfate ester (**10-10**) with a tertiary alkoxide $R'O^-$. Di-*tert*-butylether was prepared in high yield by direct attack by *t*-BuOH on the *tert*-butylcation (at −80°C in SO_2ClF).[596] Di-*tert*-alkyl ethers in general have proved difficult to make, but they can be prepared in low-to-moderate yields by treatment of a tertiary halide with Ag_2CO_3 or Ag_2O.[597] Active halides, such as Ar_3CX, may react directly with the alcohol without the need for the more powerful nucleophile alkoxide ion.[598] Even tertiary halides have been converted to ethers in this way, with no elimination,[599] and hindered alcohols react as well.[600] Treatment of tertiary halides ($R_3C{-}Cl$) with zinc acetate and ultrasound leads to the corresponding acetate ($R_3C{-}OAc$) in a related reaction.[601] The mechanism is these cases is of course S_N1. *tert*-Butyl halides can be converted to aryl *tert*-butylethers by treatment with phenols and an amine, such as pyridine.[602] Aryl alkyl ethers can be prepared from alkyl halides by treatment with an aryl acetate (instead of a phenol) in the presence of K_2CO_3 and a crown ether.[603] It is possible to selectively alkylate the primary hydroxyl in a diol $HOCH_2CH(OH)R$ using a tin complex.[604] It is also possible to hydrogenate aldehydes and ketones (**19-36**) and trap the intermediate with an alcohol to form an ether.[605] The palladium-catalyzed displacement of allylic acetates with aliphatic alcohols has been shown to give the corresponding alkyl allyl ether.[606] The rhodium-catalyzed conversion of allylic carbonates to allylic benzyl ethers has also been reported.[607] Aryl ethers have been prepared using Mitsunobu conditions (see **10-17**).[608]

gem-Dihalides react with alkoxides to give acetals, and 1,1,1-trihalides give ortho esters.[609] Both aryl alkyl and dialkyl ethers can be efficiently prepared with

[596]Olah, G.A.; Halpern, Y.; Lin, H.C. *Synthesis* ***1975***, 315. For another synthesis of di-*tert*-butyl ether, see Masada, H.; Yonemitsu, T.; Hirota, K. *Tetrahedron Lett.* ***1979***, 1315.

[597]Masada, H.; Sakajiri, T. *Bull. Chem. Soc. Jpn.* ***1978***, *51*, 866.

[598]For a review of reactions in which alcohols serve as nucleophiles, see Salomaa, P.; Kankaanperä, A.; Pihlaja, K., in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, ***1971***, pp. 454–466.

[599]Biordi, J.; Moelwyn-Hughes, E.A. *J. Chem. Soc.* ***1962***, 4291.

[600]Aspinall, H.C.; Greeves, N.; Lee, W.-M.; McIver, E.G.; Smith, P.M. *Tetrahedron Lett.* ***1997***, *38*, 4679.

[601]Jayasree, J.; Rao, J.M. *Synth. Commun.* ***1996***, *26*, 1103.

[602]Masada, H.; Oishi, Y. *Chem. Lett.* ***1978***, 57. For another method, see Camps, F.; Coll, J.; Moretó, J.M. *Synthesis* ***1982***, 186.

[603]Banerjee, S.K.; Gupta, B.D.; Singh, K. *J. Chem. Soc., Chem. Commun.* ***1982***, 815.

[604]Boons, G.-J.; Castle, G.H.; Clase, J.A.; Grice, P.; Ley, S.V.; Pinel, C. *Synlett*, ***1993***, 913.

[605]Bethmont, V.; Fache, F.; LeMaire, M. *Tetrahedron Lett.* ***1995***, *36*, 4235.

[606]Nakagawa, H.; Hirabayashi, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* ***2004***, *69*, 3474; Haight, A.R.; Stoner, E.J.; Peterson, M.J.; Grover, V.K. *J. Org. Chem.* ***2003***, *68*, 8092.

[607]Evans, P.A.; Leahy, D.K. *J. Am. Chem. Soc.* ***2002***, *124*, 7882.

[608]Lepore, S.D.; He, Y. *J. Org. Chem.* ***2003***, *68*, 8261.

[609]For a review of the formation of ortho esters by this method, see DeWolfe, R.H. *Carboxylic Ortho Acid Derivatives*, Academic Press, NY, ***1970***, pp. 12–18.

the use of phase transfer catalysis (p. 511)[610] and with micellar catalysis.[611] Symmetrical benzylic ethers have been prepared by reaction of benzylic alcohols with Mg/I_2 followed by triflic anhydride.[612]

Hydroxy groups can be protected[613] by reaction of their salts with chloromethyl methyl ether.

$$RO^- + CH_3OCH_2Cl \longrightarrow ROCH_2OCH_3$$

This protecting group is known as MOM (methoxymethyl) and such compounds are called MOM ethers. The resulting acetals are stable to bases and are easily cleaved with mild acid treatment (**10-7**). Another protecting group, the 2-methoxyethoxymethyl group (the MEM group), is formed in a similar manner. Both MOM and MEM groups can be cleaved with dialkyl- and diarylboron halides, such as Me_2BBr.[614]

Aryl cyanates[615] can be prepared by reaction of phenols with cyanogen halides in the presence of a base: $ArO^- + ClCN \rightarrow ArOCN + Cl^-$.[616] This reaction has also been applied to certain alkyl cyanates.[617]

Most Williamson reactions proceed by the S_N2 mechanism, but there is evidence (see p. 446) that in some cases the SET mechanism can take place, especially with alkyl iodides.[618] Secondary alcohols have been converted to the corresponding methyl ether by reaction with methanol in the presence of ferric nitrate nonahydrate.[619] Vinyl ethers have been formed by coupling tetravinyl tin with phenols, in the presence of cupric acetate and oxygen.[620] The palladium-catalyzed coupling of vinyl triflates and phenols has also been reported.[621]

[610]For reviews, see Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Springer, NY, ***1978***, pp. 128–138; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, ***1977***, pp. 73–84. See also, Dueno, E.E.; Chu, F.; Kim, S.-I.; Jung, K.W. *Tetrahedron Lett.* ***1999***, *40*, 1843; Eynde, J.J.V.; Mailleux, I. *Synth. Commun.* ***2001***, *31*, 1. For the use of phase-transfer catalysis to convert one OH group of a diol or triol to a mono ether with selectivity, see de la Zerda, J.; Barak, G.; Sasson, Y. *Tetrahedron* ***1989***, *45*, 1533.

[611]Juršić, B. *Tetrahedron* ***1988***, *44*, 6677.

[612]Nishiyama, T.; Kameyama, H.; Maekawa, H.; Watanuki, K. *Can. J. Chem.* ***1999***, *77*, 258.

[613]For other protecting groups for OH, see Wuts, P.G.M.; Greene, T.W. *Protective Groups in Organic Synthesis Vol. II*, Wiley, NY, ***1991***, pp. 15–104; Wuts, P.G.M.; Greene, T.W. *Protective Groups in Organic Synthesis*, 3rd ed., Wiley, New York, ***1999***. pp. 23–127; Corey, E.J.; Gras, J.; Ulrich, P. *Tetrahedron Lett.* ***1976***, 809 and references cited therein.

[614]Guindon, Y.; Yoakim, C.; Morton, H.E. *J. Org. Chem.* ***1984***, *49*, 3912. For other methods, see Williams, D.R.; Sakdarat, S. *Tetrahedron Lett.* ***1983***, *24*, 3965; Hanessian, S.; Delorme, D.; Dufresne,Y. *Tetrahedron Lett.* ***1984***, *25*, 2515; Rigby, J.H.; Wilson, J.Z. *Tetrahedron Lett.* ***1984***, *25*, 1429.

[615]For reviews of alkyl and aryl cyanates, see Jensen, K.A.; Holm, A., in Patai, S. *The Chemistry of Cyanates and Their Thio Derivatives*, pt. 1, Wiley, NY, ***1977***, pp. 569–618; Grigat, E.; Pütter, R. *Angew. Chem. Int. Ed.* ***1967***, *6*, 206.

[616]Grigat, E.; Pütter, R. *Chem. Ber.* ***1964***, *97*, 3012; Martin, D.; Bauer, M. *Org. Synth.* ***VII***, 435.

[617]Kauer, J.C.; Henderson, W.W. *J. Am. Chem. Soc.* ***1964***, *86*, 4732.

[618]Ashby, E.C.; Bae, D.; Park, W.; Depriest, R.N.; Su, W. *Tetrahedron Lett.* ***1984***, *25*, 5107.

[619]Namboodiri, V.V.; Varma, R.S. *Tetrahedron Lett.* ***2002***, *43*, 4593.

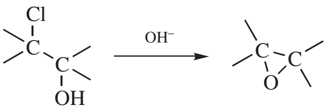
[620]Blouin, M.; Frenette, R. *J. Org. Chem.* ***2001***, *66*, 9043.

[621]Willis, M.C.; Taylor, D.; Gillmore, A.T. *Chem. Commun.* ***2003***, 2222.

OS **I**, 75, 205, 258, 296, 435; **II**, 260; **III**, 127, 140, 209, 418, 432, 544; **IV**, 427, 457, 558, 590, 836; **V**, 251, 258, 266, 403, 424, 684; **VI**, 301, 361, 395, 683; **VII**, 34, 386, 435; **VIII**, 26, 161, 155, 373; **80**, 227.

10-9 Epoxide Formation (Internal Williamson Ether Synthesis)

(3)*OC-cyclo*-Alkoxy-de-halogenation



This is a special case of **10-8**. The base removes the proton from the OH group and the resulting alkoxide subsequently attacks in an internal S_N2 reaction.[622] Many epoxides have been made in this way.[623] The course of the reaction can be influenced by neighboring group effects.[624] The method can also be used to prepare larger cyclic ethers: five- and six-membered rings.[625] Additional treatment with base yields the glycol (**10-7**). Thiiranes can be prepared by the reaction of α-chloro ketones with $(EtO)_2P(=O)$—SH and $NaBH_4$—Al_2O_3 with microwave irradiation.[626]

OS **I**, 185, 233; **II**, 256; **III**, 835; **VI**, 560; **VII**, 164, 356; **VIII**, 434.

10-10 Alkylation With Inorganic Esters

Alkoxy-de-sulfonyloxy-substitution

$$R{-}OSO_2OR'' + R'O^- \longrightarrow ROR$$

The reaction of alkyl sulfates with alkoxide ions is quite similar to **10-8** in mechanism and scope. Other inorganic esters can also be used. Methyl ethers of alcohols and phenols are commonly formd by treatment of alkoxides or aroxides with methyl sulfate. The alcohol or phenol can be methylated directly with dimethyl sulfate under various conditions.[627] Carboxylic esters sometimes give ethers when treated with alkoxides ($B_{AL}2$ mechanism, p. 1403) in a very similar process (see also, **16-64**). A related reaction heated **111** with alumina to give the corresponding benzofuran, **112**.[628]

[622]See, for example, Swain, C.G.; Ketley, A.D.; Bader, R.F.W. *J. Am. Chem. Soc.* ***1959***, *81*, 2353; Knipe, A.C. *J. Chem. Soc. Perkin Trans. 2* ***1973***, 589.

[623]For a review, see Berti, G. *Top. Stereochem.* ***1973***, *7*, 93, pp. 187.

[624]Lang, F.; Kassab, D.J.; Ganem, B. *Tetrahedron Lett.* ***1998***, *39*, 5903.

[625]See Kim, K.M.; Jeon, D.J.; Ryu, E.K. *Synthesis* ***1998***, 835 for cyclization to an alkene in the presence of a catalytic amount of iodine. See Marek, I.; Lefrançois, J.-M.; Normant, J.-F. *Tetrahedron Lett.* ***1992***, *33*, 1747 for a related reaction.

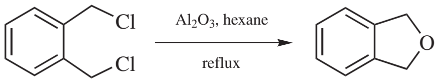
[626]Yadav, L.D.S.; Kapoor, R. *Synthesis* ***2002***, 2344.

[627]Ogawa, H.; Ichimura, Y.; Chihara, T.; Teratani, S.; Taya, K. *Bull. Chem. Soc. Jpn.* ***1986***, *59*, 2481; Cao, Y.-Q.; Pei, B.-G. *Synth. Commun.* ***2000***, *30*, 1759.

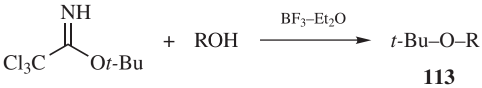
[628]Mihara, M.; Ishino, Y.; Minakata, S.; Komatsu, M. *Synlett* ***2002***, 1526.

The reaction of aliphatic alcohols and potassium organotrifluoroborate salts also gives ethers.[629]

tert-Butyl ethers (**113**) can be prepared by treating the compound *tert*-butyl2,2,2-trichloroacetimidate with an alcohol or phenol in the presence of boron trifluoride etherate.[630] Trichloroimidates can be used to prepare other ethers as well.[631] *tert*-Butyl ethers can be cleaved by acid-catalyzed hydrolysis.[632]



111 **112**



113

OS **I**, 58, 537; **II**, 387, 619; **III**, 127, 564, 800; **IV**, 588; **VI**, 737, 859, **VII**, 41. Also see, OS **V**, 431.

10-11 Alkylation With Diazo Compounds

Hydro,alkoxy-de-diazo-bisubstitution

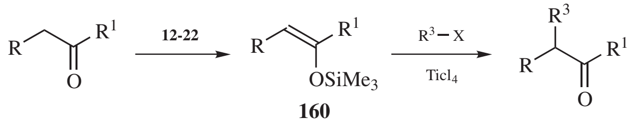
$$CH_2N_2 \;+\; ROH \xrightarrow{HBF_4} CH_3OR$$

$$R_2CN_2 \;+\; ArOH \longrightarrow R_2CHOAr$$

Alcohols react with diazo compounds to form ethers, but diazomethane and diazo ketones are most readily available, giving methyl ethers or α-keto ethers,[633] respectively. With diazomethane[634] the method is expensive and requires great caution, but the conditions are mild and high yields are obtained. Diazomethane is used chiefly to methylate alcohols and phenols that are expensive or available in small amounts. Hydroxy compounds react better as their acidity increases; ordinary alcohols do not react at all unless a catalyst, such as HBF_4[635] or silica gel,[636] is present. The more acidic phenols react very well in the absence of a catalyst. The reaction of oximes, and ketones that have substantial enolic contributions,

[629] Quach, T.D.; Batey, R.A. *Org. Lett.* ***2003***, *5*, 1381.
[630] Armstrong, A.; Brackenridge, I.; Jackson, R.F.W.; Kirk, J.M. *Tetrahedron Lett.* ***1988***, *29*, 2483.
[631] Rai, A.N.; Basu, A. *Tetrahedron Lett.* ***2003***, *44*, 2267.
[632] Lajunen, M.; Ianskanen-Lehti, K. *Acta Chem. Scand. B*, ***1994***, *48*, 861.
[633] Pansare, S.V.; Jain, R.P.; Bhattacharyya, A. *Tetrahedron Lett.* ***1999***, *40*, 5255.
[634] For a review of diazomethane, see Pizey, J.S. *Synthetic Reagents*, Vol. 2, Wiley, NY, ***1974***, pp. 65–142.
[635] Neeman, M.; Caserio, M.C.; Roberts, J.D.; Johnson, W.S. *Tetrahedron* ***1959***, *6*, 36.
[636] Ohno, K.; Nishiyama, H.; Nagase, H. *Tetrahedron Lett.* ***1979***, 4405; Ogawa, H.; Hagiwara, H.; Chihara, T.; Teratani, S.; Taya, K. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 627.

give *O*-alkylation to form, respectively, *O*-alkyl oximes and enol ethers. The mechanism[637] is as in **10-5**:



160

Diazoalkanes can also be converted to ethers by thermal or photochemical cleavage in the presence of an alcohol. These are carbene or carbenoid reactions.[638] Similar intermediates are involved when diazoalkanes react with alcohols in the presence of *t*-BuOCl to give acetals.[639]

$$R_2CN_2 \; + \; 2\,R'OH \xrightarrow{t\text{-BuOCl}} R_2C(OR')_2$$

OS **V**, 245. Also see, OS **V**, 1099.

10-12 Dehydration of Alcohols

Alkoxy-de-hydroxylation

$$2\ ROH \xrightarrow{H_2SO_4} ROR \; + \; H_2O$$

The dehydration of alcohols to form symmetrical ethers[640] is analogous to **10-8** and **10-10**, but the species from which the leaving group departs is ROH_2^+ or $ROSO_2OH$. The former is obtained directly on treatment of alcohols with sulfuric acid and may go, by an S_N1 or S_N2 pathway, directly to the ether if attacked by another molecule of alcohol. On the other hand, it may, again by either an S_N1 or S_N2 route, be attacked by the nucleophile HSO_4^-, in which case it is converted to $ROSO_2OH$, which in turn may be attacked by an alcohol molecule to give ROR. Elimination is always a side reaction and, in the case of tertiary alkyl substrates, completely predominates. Good yields of ethers were obtained by heating diarylcarbinols [ArAr′CHOH → $(ArAr'CH)_2O$] with TsOH in the solid state.[641] Acids, such as Nafion-H with silyl ethers,[642] can be used in this transformation, and Lewis acids can be used with alcohols in some cases.[643]

[637]Kreevoy, M.M.; Thomas, S.J. *J. Org. Chem.* ***1977***, *42*, 3979. See also, McGarrity, J.F.; Smyth, T. *J. Am. Chem. Soc.* ***1980***, *102*, 7303.

[638]Bethell, D.; Newall, A.R.; Whittaker, D. *J. Chem. Soc. B* ***1971***, 23; Noels, A.F.; Demonceau, A.; Petiniot, N.; Hubert, A.J.; Teyssié, P. *Tetrahedron* ***1982***, *38*, 2733.

[639]Baganz, H.; May, H. *Angew. Chem. Int. Ed.* ***1966***, *5*, 420.

[640]For a review, see Feuer, H.; Hooz, J., in Patai, S. *The Chemistry of the Ether Linkage*, Wiley, NY, ***1967***, pp.457–460, 468–470.

[641]Toda, F.; Takumi, H.; Akehi, M. *J. Chem. Soc. Perkin Trans. 2* ***1990***, 1270.

[642]Zolfigol, M.A.; Mohammadpoor-Baltork, I.; Habibi, D.; Mirjalili, B.B.F.; Bamoniri, A. *Tetrahedron Lett.* ***2003***, *44*, 8165.

[643]For a reaction that used $MeAl(NTf)_2$, see Ooi, T.; Ichikawa, H.; Itagaki, Y.; Maruoka, K. *Heterocycles* ***2000***, *52*, 575.

Mixed (unsymmetrical) ethers can be prepared if one group is tertiary alkyl and the other primary or secondary, since the latter group is not likely to compete with the tertiary group in the formation of the carbocation, while a tertiary alcohol is a very poor nucleophile.[644] If one group is not tertiary, the reaction of a mixture of two alcohols leads to all three possible ethers. Unsymmetrical ethers have been formed by treatment of two different alcohols with $MeReO_3$[645] or with $BiBr_3$.[646] Unsymmetrical ethers have been prepared under Mitsunobu conditions (**10-17**) with a polymer-supported phosphine and diethyl azodicarboxylate (DEAD).[647] Diols can be converted to cyclic ethers,[648] although the reaction is most successful for five-membered rings, but five-, six-, and seven-membered rings have been prepared.[649] Thus, 1,6-hexanediol gives mostly 2-ethyltetrahydrofuran. This reaction is also important in preparing furfural derivatives from aldoses, with concurrent elimination:

Phenols and primary alcohols form ethers when heated with dicyclohexylcarbodiimide[650] (see **16-63**). 1,2-Diols can be converted to epoxides by treatment with DMF dimethyl acetal, $(MeO)_2CHNMe_2$,[651] with diethyl azodicarboxylate, EtOOCN=NCOOEt, and Ph_3P,[652] with a dialkoxytriphenylphosphorane,[653] or with $TsCl^-Na^-OHPhCH_2NEt_3^+\ Cl^-$.[654]

OS **I**, 280; **II**, 126; **IV**, 25, 72, 266, 350, 393, 534; **V**, 539, 1024; **VI**, 887; **VIII**, 116. Also see, OS **V**, 721.

10-13 Transetherification

Hydroxy-de-alkoxylation and **Alkoxy-de-hydroxylation**

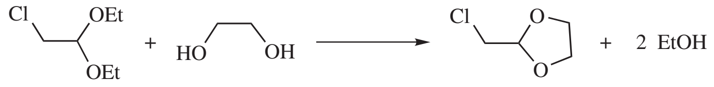
$$ROR' + R''OH \longrightarrow ROR'' + R'OH$$

The exchange of one alkoxy group for another is rare for *ethers* without a reactive R group, such as diphenylmethyl,[655] or by treatment of alkyl aryl ethers with

[644]See, for example, Jenner, G. *Tetrahedron Lett.* ***1988***, *29*, 2445.
[645]Zhu, Z.; Espenson, J.H. *J. Org. Chem.* ***1996***, *61*, 324.
[646]Boyer, B.; Keramane, E.-M.; Roque, J.-P.; Pavia, A.A. *Tetrahedron Lett.* ***2000***, *41*, 2891.
[647]Lizarzaburu, M.E.; Shuttleworth, S. *Tetrahedron Lett.* ***2002***, *43*, 2157.
[648]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 893–894.
[649]For an example, see Olah, G.A.; Fung, A.P.; Malhotra, R. *Synthesis* ***1981***, 474.
[650]Vowinkel, E. *Chem. Ber.* ***1962***, *95*, 2997; ***1963***, *96*, 1702; ***1966***, *99*, 42.
[651]Neumann, H. *Chimia*, ***1969***, *23*, 267.
[652]Guthrie, R.D.; Jenkins, I.D.; Yamasaki, R.; Skelton, B.W.; White, A.H. *J. Chem. Soc. Perkin Trans. 1* ***1981***, 2328 and references cited therein. For a review of diethyl azodicarboxylate-Ph_3P, see Mitsunobu, O. *Synthesis* ***1981***, 1.
[653]Kelly, J.W.; Evans, Jr., S.A. *J. Org. Chem.* ***1986***, *51*, 5490. See also, Hendrickson, J.B.; Hussoin, M.S. *Synlett*, ***1990***, 423.
[654]Szeja, W. *Synthesis* ***1985***, 983.
[655]Pratt, E.F.; Draper, J.D. *J. Am. Chem. Soc.* ***1949***, *71*, 2846. Transetherification using $Fe(ClO_4)_3$ was reported. See Salehi, P.; Irandoost, M.; Seddighi, B.; Behbahani, F.K.; Tahmasebi, D.P. *Synth. Commun.* ***2000***, *30*, 1743.

alkoxide ions: $ROAr + R'O^- \rightarrow ROR' + ArO^-$.[656] 3-(2-Benzyloxyethyl)-3-methyloxetane was transformed into 3-benzyloxymethyl-3-methyltetrahydrofuran by an internal transetherification catalyzed by BF_3•OEt_2.[657]

Acetals and ortho esters undergo transetherification readily,[658] as with the trasnfomraton of **114** to **115**.[659]



114 **115**

As seen in **10-6**, departure of the leaving group from an acetal gives a particularly stable carbocation. It is also possible to convert a dimethylketal directly to a dithiane by reaction with butane 1,4-dithiol on clay.[660] These are equilibrium reactions, and most often the equilibrium is shifted by removing the lower-boiling alcohol by distillation. Enol ethers can be prepared by treating an alcohol with an enol ester or a different enol ether, with mercuric acetate as a catalyst,[661] for example,

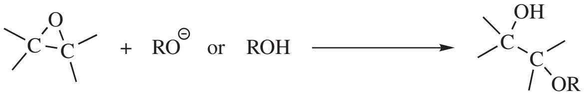
$$ROCH{=}CH_2 + R'OH \xrightarrow{Hg(OAc)_2} R'OCH{=}CH_2 + ROH$$

1,2-Diketones can be converted to α-keto enol ethers by treatment with an alkoxytrimethylsilane ($ROSiMe_3$).[662]

OS **VI**, 298, 491, 584, 606, 869; **VII**, 334; **VIII**, 155, 173. Also see, OS **V**, 1080, 1096.

10-14 Alcoholysis of Epoxides

(3)*OC-seco*-alkoxy-de-alkoxylation



[656]Zoltewicz, J.A.; Sale, A.A. *J. Org. Chem.* ***1970***, *35*, 3462.

[657]Itoh, A.; Hirose, Y.; Kashiwagi, H.; Masaki, Y. *Heterocycles* ***1994***, *38*, 2165.

[658]For reviews, see Salomaa, P.; Kankaanperä, A.; Pihlaja, K., in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, ***1971***, pp. 458–463; DeWolfe, R.H. *Carboxylic Ortho Acid Derivatives*, Academic Press, NY, ***1970***, pp. 18–29, 146–148.

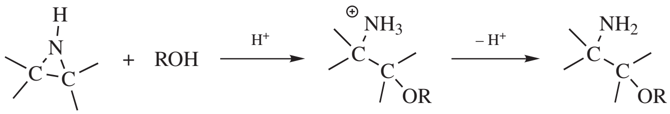
[659]McElvain, S.M.; Curry, M.J. *J. Am. Chem. Soc.* ***1948***, *70*, 3781.

[660]Jnaneshwara, G.K.; Barahate, N.B.; Sudalai, A.; Deshpande, V.H.; Wakharkar, R.D.; Gajare, A.S.; Shingare, M.S.; Sukumar, R. *J. Chem. Soc. Perkin Trans. 1* ***1998***, 965.

[661]Watanabe, W.H.; Conlon, L.E. *J. Am. Chem. Soc.* ***1957***, *79*, 2828; Büchi, G.; White, J.D. *J. Am. Chem. Soc.* ***1964***, *86*, 2884. For a review, see Shostakovskii, M.F.; Trofimov, B.A.; Atavin, A.S.; Lavrov, V.I. *Russ. Chem. Rev.* ***1968***, *37*, 907. For a discussion of the mechanism, see Gareev, G.A. *J. Org. Chem. USSR* ***1982***, *18*, 36.

[662]Ponaras, A.A.; Meah, M.Y. *Tetrahedron Lett.* ***1986***, *27*, 4953.

This reaction is analogous to **10-7**. It may be acid (including Lewis acids[663]), base, or alumina[664] catalyzed, occur with electrolysis,[665] and may occur by either an S_N1 or S_N2 mechanism. Catalysts, such as $[Rh(CO)_2Cl]_2$,[666] $TiCl_3$ (OTf),[667] $Fe(ClO_4)_3$,[668] $Cu(BF_4)_2 \bullet n\ H_2O$,[669] or $BiCl_3$,[670] have been used. β-Cyclodextrin has been used to promote the reaction with phenoxides in aqueous media.[671] Many of the β-hydroxy ethers produced in this way are valuable solvents, for example, diethylene glycol and Cellosolve. Reaction with thiols leads to hydroxy thioethers.[672] The reaction of alcohols with aziridines leads to β-amino ethers,[673] and reaction with thiols gives β-amino thioethers.[674] It has been shown that ring-opening of aziridines by phenols is promoted by tributylphosphine.[675]



Opening an epoxide by an alkoxide moiety can be done intramolecularly, and a new cyclic ether is generated. Ethers of various ring sizes can be produced depending on the length of the tether between the alkoxide unit and the epoxide. Specialized conditions are common, as in the conversion of **116** to **117**.[676] Another variant of this transformation used a cobalt–salen catalyst.[677] A specialized version has the alkoxide moiety on the carbon adjacent to the epoxide, leading to the *Payne rearrangement*, where a 2,3-epoxy alcohol is converted to an isomeric one, by treatment

[663]Iranpoor, N.; Tarrian, T.; Movahedi, Z. *Synthesis* ***1996***, 1473; Iranpoor, N.; Salehi, P. *Synthesis* ***1994***, 1152. See Moberg, C.; Rákos, L.; Tottie, L. *Tetrahedron Lett.* ***1992***, *33*, 2191 for an example that generates a hydroxy ether with high enantioselectivity. Also see, Chini, M.; Crotti, P.; Gardelli, C.; Macchia, F. *Synlett*, ***1992***, 673.

[664]See Posner, G.H.; Rogers, D.Z. *J. Am. Chem. Soc.* ***1977***, *99*, 8208, 8214.

[665]Safavi, A.; Iranpoor, N.; Fotuhi, L. *Bull. Chem. Soc. Jpn.* ***1995***, *68*, 2591.

[666]Fagnou, K.; Lautens, M. *Org. Lett.* ***2000***, *2*, 2319.

[667]Iranpoor, N.; Zeynizadeh, B. *Synth. Commun.* ***1999***, *29*, 1017.

[668]Salehi, P.; Seddighi, B.; Irandoost, M.; Behbahani, F.K. *Synth. Commun.* ***2000***, *30*, 2967.

[669]Barluenga, J.; Vázquez-Villa, H.; Ballesteros, A.; González, J.M. *Org. Lett.* ***2002***, *4*, 2817.

[670]Mohammadpoor-Baltork, I.; Tangestaninejad, S.; Aliyan, H.; Mirkhani, V. *Synth. Commun.*, ***2000***, *30*, 2365.

[671]Surendra, K.; Krishnaveni, N.; Nageswar, Y.V.D.; Rao, K.R. *J. Org. Chem.* ***2003***, *68*, 4994.

[672]Iida, T.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* ***1997***, *119*, 4783; Kesavan, V.; Bonnet-Delpon, D.; Bégué, J.-P. *Tetrahedron Lett.* ***2000***, *41*, 2895; Fringuelli, F.; Pizzo, F.; Toroioli, S.; Vaccaro, L. *J. Org. Chem.* ***2003***, *68*, 8248; Amantini, D.; Friguelli, F.; Pizzo, F.; Tortioli, S.; Vaccaro, L. *Synlett* ***2003***, 2292.

[673]For a review, see Dermer, O.C.; Ham, G.E. *Ethlenimine and Other Aziridines*, Academic Press, NY, ***1969***, pp. 224–227, 256–257.

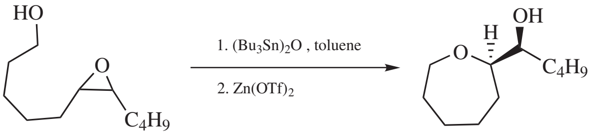
[674]Wu, J.; Hou, X.-L.; Dai, L.-X. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 1314.

[675]Hou, X.-L.; Fan, R.-H.; Dai, L.-X. *J. Org. Chem.* ***2002***, *67*, 5295.

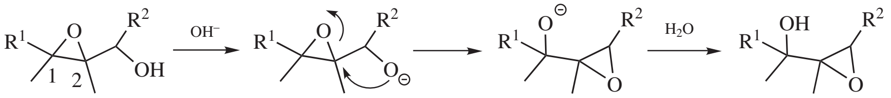
[676]Matsumura, R.; Suzuki, T.; Sato, K.; Oku, K.-i.; Hagiwara, H.; Hoshi, T.; Ando, M.; Kamat, V.P. *Tetrahedron Lett.* ***2000***, *41*, 7701. See also, Karikomi, M.; Watanabe, S.; Kimura, Y.; Uyehara, T. *Tetrahedron Lett.* ***2002***, *43*, 1495.

[677]Wu, M.H.; Hansen, K.B.; Jacobsen, E.N. *Angew. Chem. Int. Ed.* ***1999***, *38*, 2012.

with aqueous base:[678]



116 **117**



The reaction results in inverted configuration at C-2. Of course, the product can also revert to the starting material by the same pathway, so a mixture of epoxy alcohols is generally obtained.

Other nucleophilic oxygen or sulfur species have been shown to open epoxides. Examples include thiocyanate[679] and acetate via acetic anhydride and zeolite HY.[680] Epoxide react with sodium acetate and a cerium catalyst in detergent solutions to give hydroxy acetates.[681] In addition, *N*-tosylaziridines are opened by acetic acid in the presence of $In(OTf)_3$ to give *N*-tosylamino acetates.[682] The reaction of *N*-tosyl aziridines with 10% ceric ammonium nitrate in aqueous methanol leads to *N*-tosylamino alcohols,[683] and reaction with ethanol and 10% BF_3•OEt_2 gives *N*-tosyl ethers.[684] In the presence of Amberlyst 15, *N*-Boc (Boc = *tert*-butoxycarboxyl, —CO_2*t*-Bu) aziridines react with LiBr to give the corresponding bromo amide.[685]

10-15 Alkylation With Onium Salts

Alkoxy-de-hydroxylation

$$R_3O^+ + R'OH \longrightarrow ROR' + R_2O$$

Oxonium ions are excellent alkylating agents, and ethers can be conveniently prepared by treating them with alcohols or phenols.[686] Quaternary ammonium salts can sometimes also be used.[687]

OS **VIII**, 536.

[678]Payne, G.B. *J. Org. Chem.* ***1962***, *27*, 3819; Behrens, C.H.; Ko, S.Y.; Sharpless, K.B.; Walker, F.J. *J. Org. Chem.* ***1985***, *50*, 5687. See Yamazaki, T.; Ichige, T.; Kitazume, T. *Org. Lett.* ***2004***, *6*, 4073.
[679]Sharghi, H.; Nasserri, M.A.; Niknam, K. *J. Org. Chem.* ***2001***, *66*, 7287.
[680]Ramesh, P.; Reddy, V.L.N.; Venugopal, D.; Subrahmanya, M.; Venkateswarlu, Y. *Synth. Commun.* ***2001***, *31*, 2599.
[681]Iranpoor, N.; Firouzabadi, H.; Safavi, A.; Shekarriz, M. *Synth. Commun.* ***2002***, *32*, 2287.
[682]Yadav, J.S.; Reddy, B.V.S.; Sadashiv, K.; Harikishan, K. *Tetrahedron Lett.* ***2002***, *43*, 2099.
[683]Chandrasekhar, S.; Narshihmulu, Ch.; Sultana, S.S. *Tetrahedron Lett.* ***2002***, *43*, 7361.
[684]Prasad, B.A.B.; Sekar, G.; Singh, V.K. *Tetrahedron Lett.* ***2000***, *41*, 4677.
[685]Righi, G.; Potini, C.; Bovicelli, P. *Tetrahedron Lett.* ***2002***, *43*, 5867.
[686]Granik, V.G.; Pyatin, B.M.; Glushkov, R.G. *Russ. Chem. Rev.*, ***1971***, *40*, 747, see p. 749.
[687]For an example, see Vogel, D.E.; Büchi, G.H. *Org. Synth.*, ***66***, 29.

10-16 Hydroxylation of Silanes

Hydroxy-de-silylalkylation

$$R{-}SiR^1{}_2Ar \xrightarrow{F^-} R{-}SiR^{1'}{}_2F \xrightarrow{\text{oxidation}} R{-}OH$$

$$R{-}SiR^1{}_2SiR^2{}_3 \xrightarrow{F^-} R{-}SiR^1{}_2F \xrightarrow{\text{oxidation}} R{-}OH$$

Alkylsilanes can be oxidized, with the silyl unit converted to a hydroxy unit. This usually requires either an aryl group[688] or another silyl group[689] attached to silicon. It has been shown that a strained four-membered ring silane (a siletane) also gives the corresponding alcohol upon oxidation.[690] Treatment with a fluorinating agent, such as tetrabutylammonium fluoride or CsF replaces Ar or SiR_3 with F, which is oxidized with hydrogen peroxide or a peroxy acid to give the alcohol. This sequence is often called the *Tamao–Fleming oxidation*.[688] There are several variation in substrate that allow versatility in the initial incorporation of the silyl unit.[691] Hydroperoxide oxidation of a cyclic silane leads to a diol.[692]

C. Attack by OCOR at an Alkyl Carbon

10-17 Alkylation of Carboxylic Acid Salts

Acyloxy-de-halogenation

$$RX \; + \; R'COO^- \xrightarrow{\text{HMPA}} R'COOR$$

Sodium salts of carboxylic acids, including hindered acids, such as mesitoic, rapidly react with primary and secondary bromides and iodides at room temperature in dipolar aprotic solvents, especially HMPA, to give high yields of carboxylic esters.[693] The mechanism is S_N2. Several bases or basic media have been used to generate the carboxylate salt.[694] Sodium salts are often used, but potassium, silver, cesium,[695] and substituted ammonium salts have also been used. An important

[688]Kumada, M.; Tamao, K.; Yoshida, J.I. *J. Organomet. Chem.* ***1982***, *239*, 115; Tamao, K.; Kakui, T.; Akita, M.; Iwahara, T.; Kanatani, R.; Yoshida, J.; Kumada, M. *Tetrahedron* ***1983***, *39*, 983; Fleming, I.; Henning, R.; Plaut, H. *J. Chem. Soc., Chem. Commun.* ***1984***, 29. For the protodesilylation step see Häbich, D.; Effenberger, F. *Synthesis* ***1979***, 841. For the peroxyacid reaction see Buncel, E.; Davies, A.G. *J. Chem. Soc.* ***1958***, 1550.

[689]Suginome, M.; Matsunaga, S.; Ito, Y. *Synlett*, ***1995***, 941.

[690]Sunderhaus, J.D.; Lam, H.; Dudley, G.B. *Org. Lett.* ***2003***, *5*, 4571.

[691]For examples see Matsumoto, Y.; Hayashi, T.; Ito, Y. *Tetrahedron* ***1994***, *50*, 335; Uozumi, Y.; Kitayama, K.; Hayashi, T.; Yanagi, K.; Fukuyo, E. *Bull. Chem. Soc. Jpn.* ***1995***, *68*, 713.

[692]Liu, D.; Kozmin, S.A. *Angew. Chem. Int. Ed.* ***2001***, *40*, 4757.

[693]Parker, A.J. *Adv. Org. Chem.* ***1965***, *5*, 1, 37; Alvarez, F.S.; Watt, A.N. *J. Org. Chem.* ***1968***, *33*, 2143; Mehta, G. *Synthesis* ***1972***, 262; Shaw, J.E.; Kunerth, D.C. *J. Org. Chem.* ***1974***, *39*, 1968; Larock, R.C. *J. Org. Chem.* ***1974***, *39*, 3721; Pfeffer, P.E.; Silbert, L.S. *J. Org. Chem.* ***1976***, *41*, 1373.

[694]Bases include DBU (p. $$$): See Mal, D. *Synth. Commun.* ***1986***, *16*, 331. Cs_2CO_3: Lee, J.C.; Oh, Y.S.; Cho, S.H.; Lee, J.I. *Org. Prep. Proceed. Int.* ***1996***, *28*, 480. CsF-Celite: Lee, J.C.; Choi, Y. *Synth. Commun.* ***1998***, *28*, 2021.

[695]See Dijkstra, G.; Kruizinga, W.H.; Kellogg, R.M. *J. Org. Chem.* ***1987***, *52*, 4230.

variation uses phase-transfer catalysis,[696] and good yields of esters have been obtained from primary, secondary, benzylic, allylic, and phenacyl halides.[697] Without phase-transfer catalysts and in protic solvents, the reaction is useful only for fairly active R, such as benzylic and allylic, (S_N1 mechanism), but not for tertiary alkyl, since elimination occurs instead.[698] Solid-state procedures are available. Addition of the dry carboxylate salt and the halide to alumina as a solid support, and microwave irradiation gives the ester in a procedure that is applicable to long-chain primary halides.[699] A similar reaction of hexanoic acid and benzyl bromide on solid benzyltributylammonium chloride gave the ester with microwave irradiation.[700] Ionic liquid solvents have been shown to facilitate this alkylation reaction.[701]

The reaction of an alcohol and a carboxylate anion with diethyl azodicarboxylate EtOOCN=NCOOEt and Ph_3P[702] is called the *Mitsunobu esterification reaction*.[703] This reaction can also be considered as an S_N2. Other Mitsunobu catalysts are available,[704] and a polymer-bound phosphine has been used.[705] A renewable phosphine ligand has been developed.[706] Note that other functional groups, including azides[707] and thiocyanates[708] can be generated from alcohols using Mitsunobu conditions.

Lactones can be prepared from halo acids by treatment with base (see **16-63**). This has most often been accomplished with γ and δ lactones, but macrocyclic

[696]For reviews of phase-transfer catalysis of this reaction, see Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Acaemic Press, NY, ***1978***, pp. 140–155; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, ***1977***, pp. 85–95.

[697]For an alternative method for phenacyl halides, see Clark, J.H.; Miller, J.M. *Tetrahedron Lett.* ***1977***, 599.

[698]See, however, Moore, G.G.; Foglia, T.A.; McGahan, T.J. *J. Org. Chem.* ***1979***, *44*, 2425.

[699]Bram, G.; Loupy, A.; Majdoub, M.; Gutierrez, E.; Ruiz-Hitzky, E. *Tetrahedron* ***1990***, *46*, 5167. See Arrad, O.; Sasson, Y. *J. Am. Chem. Soc.* ***1988***, *110*, 185; Dakka, J.; Sasson, Y.; Khawaled, K.; Bram, G.; Loupy, A. *J. Chem. Soc., Chem. Commun.* ***1991***, 853.

[700]Yuncheng, Y.; Yulin, J.; Dabin, G. *Synth. Commun.* ***1992***, *22*, 3109.

[701]Brinchi, L.; Germani, R.; Savelli, G. *Tetraheron Lett.* ***2003***, *44*, 2027, 6583. In bmim BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate: Liu, Z.; Chen, Z.-C.; Zheng, Q.-G. *Synthesis* ***2004***, 33.

[702]Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* ***1967***, *40*, 2380; Camp, D.; Jenkins, I.D. *Aust. J. Chem.* ***1988***, *41*, 1835.

[703]For discussions of the mechanism, see Ahn, C.; Correia, R.; DeShong, P. *J. Org. Chem.* ***2002***, *67*, 1751 and references cited therein. See also, Hughes, D.L. *Org. Prep. Proceed. Int.* ***1996***, *28*, 127; Dembinski, R. *Eur. J. Org. Chem.* ***2004***, 2763; Dandapani, S.; Curran, D.P. *Chem. Eur. J.* ***2004***, *10*, 3131. For a discussion of microwave-promoted Mitsunobu reactions, see Steinreiber, A.; Stadler, A.; Mayer, S.F.; Faber, K.; Kappe, C.O. *Tetrahedron Lett.* ***2001***, *42*, 6283.

[704]See Tsunoda, T.; Yamamiya, Y.; Kawamura, Y.; Itô, S. *Tetrahedron Lett.* ***1995***, *36*, 2529; Tsunoda, T.; Nagaku, M.; Nagino, C.; Kawamura, Y.; Ozaki, F.; Hioki, H.; Itô, S. *Tetrahedron Lett.* ***1995***, *36*, 2531; Walker, M.A. *Tetrahedron Lett.* ***1994***, *35*, 665. For fluorous reactions and reagents, see Dandapani, S.; Curran, D.P. *Tetrahedron* ***2002***, *58*, 3855.

[705]Charette, A.B.; Janes, M.K.; Boezio, A.A. *J. Org. Chem.* ***2001***, *66*, 2178. See also, Elson, K.E.; Jenkins, I.D.; Loughlin, W.A. *Tetrahedron Lett.* ***2004***, *45*, 2491.

[706]Yoakim, C.; Guse, I.; O'Meara, J.A.; Thavonokham, B. *Synlett* ***2003***, 473.

[707]For an example, see Papeo, G.; Poster, H.; Vianello, P.; Varasi, M. *Synthesis* ***2004***, 2886.

[708]Iranpoor, N.; Firouzabadi, H.; Akhlaghinia, B.; Azadi, R. *Synthesis* ***2004***, 92.

lactones (e.g., 11–17 members) have also been prepared in this way.[709] An interesting variation treated 2-ethylbenzoic acid with hypervalent iodine and then $I_2/h\nu$ to give the five-membered ring lactone.[710]

Copper(I) carboxylates give esters with primary (including neopentyl without rearrangement), secondary, and tertiary alkyl, allylic, and vinylic halides.[711] A simple S_N mechanism is obviously precluded in this case. Vinylic halides can be converted to vinylic acetates by treatment with sodium acetate if palladium(II) chloride is present.[712]

A carboxylic acid (not the salt) can be the nucleophile if F^- is present.[713] Mesylates are readily displaced, for example, by benzoic acid/CsF.[714] Dihalides have been converted to diesters by this method.[713] A COOH group can be conveniently protected by reaction of its ion with a phenacyl bromide ($ArCOCH_2Br$).[715] The resulting ester is easily cleaved when desired with zinc and acetic acid. Dialkyl carbonates can be prepared without phosgene (see **16-61**) by phase-transfer catalyzed treatment of primary alkyl halides with dry $KHCO_3$ and K_2CO_3.[716]

Other leaving groups can also be replaced by OCOR. Alkyl chlorosulfites (ROSOCl) and other derivatives of sulfuric, sulfonic, and other inorganic acids can be treated with carboxylate ions to give the corresponding esters. Treatment with oxalyl chloride allows displacement by carboxylate salts.[717] The use of dimethyl sulfate[718] or trimethyl phosphate[719] allows sterically hindered COOH groups to be methylated. The reaction of benzoic acid with aqueous lithium hydroxide and then dimethyl sulfate gave methyl benzoate.[720] Dimethyl carbonate in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) has been used to prepare methyl esters.[721] With certain substrates, carboxylic acids are strong enough nucleophiles

[709]For example, see Galli, C.; Mandolini, L. *Org. Synth. **VI***, 698; Kruizinga, W.H.; Kellogg, R.M. *J. Am. Chem. Soc.* ***1981***, *103*, 5183; Kimura, Y.; Regen, S.L. *J. Org. Chem.* ***1983***, *48*, 1533.

[710]Togo, H.; Muraki, T.; Yokoyama, M. *Tetrahedron Lett.* ***1995***, *36*, 7089.

[711]Lewin, A.H.; Goldberg, N.L. *Tetrahedron Lett.* ***1972***, 491; Klumpp, G.W.; Bos, H.; Schakel, M.; Schmitz, R.F.; Vrielink, J.J. *Tetrahedron Lett.* ***1975***, 3429.

[712]Kohll, C.F.; van Helden, R. *Recl. Trav. Chim. Pays-Bas* ***1968***, *87*, 481; Volger, H.C. *Recl. Trav. Chim. Pays-Bas* ***1968***, *87*, 501; Yamaji, M.; Fujiwara, Y.; Asano, R.; Teranishi, S. *Bull. Chem. Soc. Jpn.* ***1973***, *46*, 90.

[713]Clark, J.H.; Emsley, J.; Hoyte, O.P.A. *J. Chem. Soc. Perkin Trans. 1* ***1977***, 1091; Ooi, T.; Sugimoto, H.; Doda, K.; Maruoka, K. *Tetrahedron Lett.* ***2001***, *42*, 9245.

[714]Sato, T.; Otera, J. *Synlett*, ***1995***, 336.

[715]Hendrickson, J.B.; Kandall, L.C. *Tetrahedron Lett.* ***1970***, 343.

[716]Lissel, M.; Dehmlow, E.V. *Chem. Ber.* ***1981***, *114*, 1210; Verdecchia, M.; Frochi, M.; Palombi, L.; Rossi, L. *J. Org. Chem.* ***2002***, *67*, 8287. See also, Kadokawa, J.-i.; Habu, H.; Fukamachi, S.; Karasu, M.; Tagaya, H.; Chiba, K. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 2205.

[717]Barrett, A.G.M.; Braddock, D.C.; James, R.A.; Koike, N.; Procopiou, P.A. *J. Org. Chem.* ***1998***, *63*, 6273.

[718]Grundy, J.; James, B.G.; Pattenden, G. *Tetrahedron Lett.* ***1972***, 757.

[719]Harris, M.M.; Patel, P.K. *Chem. Ind. (London)* ***1973***, 1002.

[720]Chakraborti, A.K.; Basak, A.; Grover, V. *J. Org. Chem.* ***1999***, *64*, 8014. See also, Avila-Zárraga, J.G.; Martínez, R. *Synth. Commun.* ***2001***, *31*, 2177.

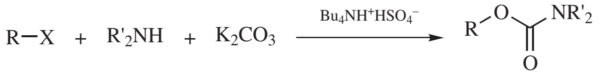
[721]Shieh, W.-C.; Dell, S.; Repič, O. *Tetrahedron Lett.* ***2002***, *43*, 5607.

for the reaction. Examples of such substrates are trialkyl phosphites $P(OR)_3$[722] and acetals of DMF.[723]

$$(RO)_2CHNMe_2 + R'COOH \longrightarrow R'COOR + ROH + HCONMe_2$$

This is an S_N2 process, since inversion is found at R. Another good leaving group is NTs_2 and ditosylamines react quite well with acetate ion in dipolar aprotic solvents:[724] $RNTs_2 + OAc^- \rightarrow ROAc$. Ordinary primary amines have been converted to acetates and benzoates by the Katritzky pyrylium–pyridinium method (p. 498).[725] Quaternary ammonium salts can be cleaved by heating with AcO^- in an aprotic solvent.[726] Oxonium ions can also be used as substrates:[727] $R_3O^+ + R'COO^- \rightarrow R'COOR + R_2O$. The reaction of potassium thioacetate with alkyl halides give dithiocarboxylic esters.[728]

In a variation of this reaction, alkyl halides can be converted to carbamates, by treatment with a secondary amine and K_2CO_3 under phase-transfer conditions.[729] The reaction of alcohols and alkyl halides can lead to carbonates.[730]



OS **II**, 5; **III**, 650; **IV**, 582; **V**, 580; **VI**, 273, 576, 698.

10-18 Cleavage of Ethers With Acetic Anhydride or Acid Halides

Acyloxy-de-alkoxylation

$$R{-}O{-}R' + Ac_2O \xrightarrow{FeCl_3} ROAc + R'OAc$$

Dialkyl ethers can be cleaved by treatment with anhydrous ferric chloride in acetic anhydride,[731] or with Me_3SiOTf in acetic anhydride.[732] In this reaction both R groups are converted to acetates and yields are moderate to high. Ethers

[722]Szmuszkovicz, J. *Org. Prep. Proceed. Int.* ***1972***, *4*, 51.

[723]Vorbrüggen, H. *Angew. Chem. Int. Ed.* ***1963***, *2*, 211; Brechbühler, H.; Büchi, H.; Hatz, E.; Schreiber, J.; Eschenmoser, A. *Angew. Chem. Int. Ed.* ***1963***, *2*, 212.

[724]Andersen, N.H.; Uh, H. *Synth. Commun.* ***1972***, *2*, 297; Curtis, V.A.; Schwartz, H.S.; Hartman, A.F.; Pick, R.M.; Kolar, L.W.; Baumgarten, R.J. *Tetrahedron Lett.* ***1977***, 1969.

[725]See Katritzky, A.R.; Gruntz, U.; Kenny, D.H.; Rezende, M.C.; Sheikh, H. *J. Chem. Soc. Perkin Trans. 1* ***1979***, 430.

[726]Wilson, N.D.V.; Joule, J.A. *Tetrahedron* ***1968***, *24*, 5493.

[727]Raber, D.J.; Gariano Jr., P.; Brod, A.O.; Gariano, A.; Guida, W.C.; Guida, A.R.; Herbst, M.D. *J. Org. Chem.* ***1979***, *44*, 1149.

[728]Zheng, T.-C.; Burkart, M.; Richardson, D.E. *Tetrahedron Lett.* ***1999***, *40*, 603.

[729]Gómez-Parra, V.; Sánchez, F.; Torres, T. *Synthesis* ***1985***, 282; *J. Chem. Soc. Perkin Trans. 2* ***1987***, 695. For another method, with lower yields, see Yoshida, Y.; Ishii, S.; Yamashita, T. *Chem. Lett.* ***1984***, 1571.

[730]Dueno, E.E.; Chu, F.; Kim, S.-I.; Jung, K.W. *Tetrahedron Lett.* ***1999***, *40*, 1843. For the synthesis of cyclic carbonates see Yoshida, M.; Fujita, M.; Ishii, T.; Ihara, M. *J. Am. Chem. Soc.* ***2003***, *125*, 4874.

[731]Ganem, B.; Small, Jr., V.M. *J. Org. Chem.* ***1974***, *39*, 3728.

[732]Procopiou, P.A.; Baugh, S.P.D.; Flack, S.S.; Inglis, G.G.A. *Chem. Commun.* ***1996***, 2625.

can also be cleaved by the mixed anhydride acetyl tosylate:[733]

Epoxides give β-hydroxyalkyl carboxylates when treated with a carboxylic acid or a carboxylate ion and a suitable catalyst.[734] Tetrahydrofuran was opened to give *O*-acyl-4-iodo-1-butanol by treatment with acid chlorides and samarium halides[735] or BCl_3.[736] In a highly specialized transformation, the reaction of an epoxide with carbon dioxide and $ZnCl_2$ in an ionic liquid leads to a cyclic carbonate.[737] Epoxides react with CO and methanol in the presence of 10% of 3-hydroxypyridine and 5% of $Co_2(CO)_8$ to give a β-hydroxy methyl ester.[738]

OS **VIII**, 13.

10-19 Alkylation of Carboxylic Acids With Diazo Compounds

Hydro, acyloxy-de-diazo-bisubstitution

$$R_2CN_2 + R'COOH \longrightarrow R'COOCHR_2$$

Carboxylic acids can be converted to esters with diazo compounds in a reaction essentially the same as **10-11**. In contrast to alcohols, carboxylic acids undergo the reaction quite well at room temperature, since the reactivity of the reagent increases with acidity. The reaction is used where high yields are important or where the acid is sensitive to higher temperatures. Because of availability diazomethane (CH_2N_2)[634] is commonly used to prepare methyl esters, and diazo ketones are common. The mechanism is as shown in **10-11**.

OS **V**, 797.

D. Other Oxygen Nucleophiles

10-20 Formation of Oxonium Salts

$$RX + R_2O \longrightarrow R_3\overset{\oplus}{O}\ \overset{\ominus}{B}F_4 + AgX$$ **Dialkyloxonio-de-halogenation**

$$RX + R_2'CO \longrightarrow R_2'C{=}\overset{\oplus}{O}{-}R\ \overset{\ominus}{B}F_4 + AgX$$

Alkyl halides can be alkylated by ethers or ketones to give oxonium salts, if a very weak, negatively charged nucleophile is present to serve as a counterion and a

[733]Karger, M.H.; Mazur, Y. *J. Am. Chem. Soc.* ***1968***, *90*, 3878. See also, Coffi-Nketsia, S.; Kergomard, A.; Tautou, H. *Bull. Soc. Chim. Fr.* ***1967***, 2788.

[734]See Otera, J.; Matsuzaki, S. *Synthesis* ***1986***, 1019; Deardorff, D.R.; Myles, D.C. *Org. Synth.*, ***67***, 114.

[735]Yu, Y.; Zhang, Y.; Ling, R. *Synth. Commun.* ***1993***, *23*, 1973; Kwon, D.W.; Kim, Y.H.; Lee, K. *J. Org. Chem.* ***2002***, *67*, 9488.

[736]Malladi, R.R.; Kabalka, G.W. *Synth. Commun.* ***2002***, *32*, 1997.

[737]Li, F.; Xiao, L.; Xia, C.; Hu, B. *Tetrahedron Lett.* ***2004***, *45*, 8307.

[738]Hinterding, K.; Jacobsen, E.N. *J. Org. Chem.* ***1999***, *64*, 2164.

Lewis acid is present to combine with X^-.[739] A typical procedure consists of treating the halide with the ether or the ketone in the presence of $AgBF_4$ or $AgSbF_6$. The Ag^+ serves to remove X^- and the BF_4^- or SbF_6^- acts as the counterion. Another method involves treatment of the halide with a complex formed between the oxygen compound and a Lewis acid, for example, $R_2O{\bullet}BF_3 + RX \rightarrow R_3O^+\ BF_4^-$, although this method is most satisfactory when the oxygen and halogen atoms are in the same molecule so that a cyclic oxonium ion is obtained. Ethers and oxonium ions also undergo exchange reactions:

$$2\,R_3O^+\,BF_4^- \quad + \quad 3\,R_2'O \rightleftharpoons 2\,R_3'O^+\,BF_4^- \quad + \quad 3\,R_2O$$

OS **V**, 1080, 1096, 1099; **VI**, 1019.

10-21 Preparation of Peroxides and Hydroperoxides

Hydroperoxy-de-halogenation

$$RX \quad + \quad {}^-OOH \longrightarrow ROOH$$

Hydroperoxides can be prepared by treatment of alkyl halides, esters of sulfuric or sulfonic acids, or alcohols with hydrogen peroxide in basic solution, where it is actually HO_2^+.[740] Sodium peroxide is similarly used to prepare dialkyl peroxides ($2\,RX + Na_2O_2 \rightarrow ROOR$). Another method, which gives primary, secondary, or tertiary hydroperoxides and peroxides, involves treatment of the halide with H_2O_2 or a peroxide in the presence of silver trifluoroacetate.[741] Peroxides can also be prepared[742] by treatment of alkyl bromides or tosylates with potassium superoxide KO_2 in the presence of crown ethers (though alcohols may be side products[743]) and by the reaction between alkyl triflates and germanium or tin peroxide.[744] However, alkyl halides can be converted to symmetrical ethers by treatment with oxide ion generated *in situ* by a reaction between an organotin oxide and fluoride ion in the presence of a quaternary ammonium iodide or a crown ether.[745]

[739]Meerwein, H.; Hederich, V.; Wunderlich, K. *Arch. Pharm.* ***1958***, *291/63*, 541. For a review, see Perst, H.*Oxonium Ions in Organic Chemistry*, Verlag Chemie, Deerfield Beach, VA, ***1971***, pp. 22–39.

[740]For a review, see Hiatt, R., in Swern, D. *Organic Peroxides*, Vol. 2, Wiley, NY, ***1971***, pp. 1–151. For a review of hydrogen peroxide, see Pandiarajan, K., in Pizey, J.S. *Synthetic Reagents*, Vol. 6, Wiley, NY, ***1985***, pp. 60–155.

[741]Cookson, P.G.; Davies, A.G.; Roberts, B.P. *J. Chem. Soc., Chem. Commun.* ***1976***, 1022. For another preparation of unsymmetrical peroxides, see Bourgeois, M.; Montaudon, E.; Maillard, B. *Synthesis* ***1989***, 700.

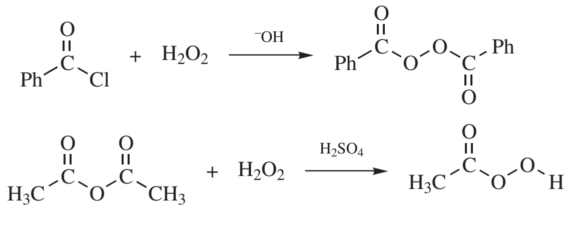
[742]Johnson, R.A.; Nidy, E.G.; Merritt, M.V. *J. Am. Chem. Soc.* ***1978***, *100*, 7960.

[743]Alcohols have also been reported to be the main products: San Filippo, Jr., J.; Chern, C.; Valentine, J.S. *J. Org. Chem.* ***1975***, *40*, 1678; Corey, E.J.; Nicolaou, K.C.; Shibasaki, M.; Machida, Y.; Shiner, C.S. *Tetrahedron Lett.* ***1975***, 3183.

[744]Salomon, M.F.; Salomon, R.G. *J. Am. Chem. Soc.* ***1979***, *101*, 4290.

[745]Harpp, D.N.; Gingras, M. *J. Am. Chem. Soc.* ***1988***, *110*, 7737.

Diacyl peroxides and acyl hydroperoxides can similarly be prepared[746] from acyl halides or anhydrides and from carboxylic acids.[747] Diacyl peroxides can



also be prepared by the treatment of carboxylic acids with hydrogen peroxide in the presence of dicyclohexylcarbodiimide,[748] H_2SO_4, methanesulfonic acid, or some other dehydrating agent. Mixed alkyl–acyl peroxides (peresters) can be made from acyl halides and hydroperoxides.

OS **III**, 619, 649; **V**, 805, 904; **VI**, 276.

10-22 Preparation of Inorganic Esters

Nitrosooxy-de-hydroxylation, and so on.

$$\mathrm{ROH + HONO \xrightarrow{H+} RONO}$$
$$\mathrm{ROH + HONO_2 \xrightarrow{H+} RONO_2}$$
$$\mathrm{ROH + SOCl_2 \longrightarrow ROSOOR}$$
$$\mathrm{ROH + POCl_3 \longrightarrow PO(OR)_3}$$
$$\mathrm{ROH + SO_3 \longrightarrow ROSO_2OH}$$
$$\mathrm{ROH + (CF_3SO_2)_2O \longrightarrow ROSO_2CF_3}$$

The above transformations show a few of the many inorganic esters that can be prepared by the reaction of an alcohol with an inorganic acid or, better, its acid halide or anhydride[749] These similar reactions are grouped together for convenience, but not all involve nucleophilic substitutions at R. The other possible pathway

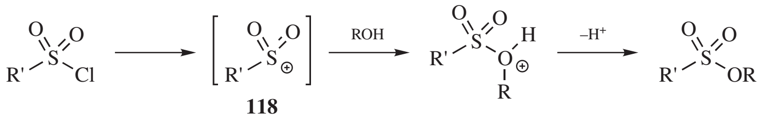
[746]For a review of the synthesis and reactions of acyl peroxides and peresters, see Bouillon, G.; Lick, C.; Schank, K., in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, ***1983***, pp. 279–309. For a review of the synthesis of acyl peroxides, see Hiatt, R. Swern, D. *Organic Peroxides*, Vol. 2, Wiley, NY, ***1971***, pp. 799–929.

[747]See Silbert, L.S.; Siegel, E.; Swern, D. *J. Org. Chem.* ***1962***, *27*, 1336.

[748]Greene, F.D.; Kazan, J. *J. Org. Chem.* ***1963***, *28*, 2168.

[749]For a review, see Salomaa, P.; Kankaanperä, A.; Pihlaja, K., in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, ***1971***, pp. 481–497.

is nucleophilic substitution at the inorganic central atom, such as the attack of the alcohol oxygen at the electrophilic sulfur atom in **118**,[750] or a corresponding



S_N2-type process (see p. 1470). In such cases, there is no alkyl-*O* cleavage. Mono esters of sulfuric acid (alkylsulfuric acids), which are important industrially because their salts are used as detergents, can be prepared by treating alcohols with SO_3, H_2SO_4, $ClSO_2OH$, or SO_3 complexes.[751] It is possible to prepare a primary sulfonate ester such as tosylate, in the presence of a secondary alcohol unit when tosic acid reacts with a 1,2-diol in the presence of Fe^{3+}-Montmorillonite.[752] Polymer-bound reagents have been used to prepared sulfonate esters.[753] Phenolic triflate have been prepared using *N,N*-ditrifylaniline and K_2CO_3 under microwave irradiation.[754] Alkyl nitrites[755] can be conveniently prepared by an exchange reaction $ROH + R'ONO \rightarrow RONO + R'OH$, where $R = t$-Bu.[756] Primary amines can be converted to alkyl nitrates ($RNH_2 \rightarrow RONO_2$) by treatment with N_2O_4 at $-78°C$ in the presence of an excess of amidine base.[757] Mitsunobu conditions (**10-17**) can be used to prepare phosphate ester or phosphonate esters. The reaction can be done intramolecularly for prepare cyclic phosphonate esters.[758]

Alkyl halides are often used as substrates instead of alcohols. In such cases, the *salt* of the inorganic acid is usually used and the mechanism is nucleophilic substitution at the carbon atom. An important example is the treatment of alkyl halides with silver nitrate to form alkyl nitrates. This is used as a test for alkyl halides. In some cases, there is competition from the central atom. Thus nitrite ion is an ambident nucleophile that can give nitrites or nitro compounds (see **10-42**).[759] Dialkyl or aryl alkyl ethers can be cleaved with anhydrous sulfonic acids.[760]

$$ROR' + R''SO_2OH \longrightarrow ROSO_2R'' + R'OH$$

[750]For an example involving nitrite formation, see Aldred, S.E.; Williams, D.L.H.; Garley, M. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 777.

[751]For a review, see Sandler, S.R.; Karo, W. *Organic Functional Group Preparations*, 2nd ed., Vol 3; Academic Press, NY, ***1989***, pp. 129–151.

[752]Choudary, B.M. Chowdari, N.S.; Kantam, M.L. *Tetraheron* ***2000***, *56*, 7291.

[753]Vignola, N.; Dahmen, S.; Enders, D.; Bräse, S. *Tetrahedron Lett.* ***2001***, *42*, 7833.

[754]Bengtson, A.; Hallberg, A.; Larhed, M. *Org. Lett.* ***2002***, *4*, 1231.

[755]For a review of alkyl nitrites, see Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, ***1988***, pp. 150–172.

[756]Doyle, M.P.; Terpstra, J.W.; Pickering, R.A.; LePoire, D.M. *J. Org. Chem.* ***1983***, *48*, 3379. For a review of the nitrosation of alcohols, see Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, ***1988***, pp. 150–156.

[757]Barton, D.H.R.; Narang, S.C. *J. Chem. Soc. Perkin Trans. 1* ***1977***, 1114.

[758]Pungente, M.D.; Weiler, L. *Org. Lett.* ***2001***, *3*, 643.

[759]For a review of formation of nitrates from alkyl halides, see Boguslavskaya, L.S.; Chuvatkin, N.N.; Kartashov, A.V. *Russ. Chem. Rev.* ***1988***, *57*, 760.

[760]Klamann, D.; Weyerstahl, P. *Chem. Ber.* ***1965***, *98*, 2070.

R″ may be alkyl or aryl. For dialkyl ethers, the reaction does not end as indicated above, since R′OH is rapidly converted to R′OR′ by the sulfonic acid (reaction **10-12**), which in turn is further cleaved to $R'OSO_2R''$ so that the product is a mixture of the two sulfonates. For aryl alkyl ethers, cleavage always takes place to give the phenol, which is not converted to the aryl ether under these conditions. Ethers can also be cleaved in a similar manner by mixed anhydrides of sulfonic and carboxylic acids[761] (prepared as in **16-68**). β-Hydroxyalkyl perchlorates[762] and sulfonates can be obtained from epoxides.[763] Epoxides and oxetanes give α,ω-dinitrates when treated with N_2O_5.[764] Aziridines and azetidines react similarly, giving nitramine nitrates; for example, *N*-butylazetidine gave $NO_2OCH_2CH_2CH_2$-N(Bu)NO_2.[764]

OS **II**, 106, 108, 109, 112, 204, 412; **III**, 148, 471; **IV**, 955; **V**, 839; **VIII**, 46, 50, 616. Also see, OS **II**, 111.

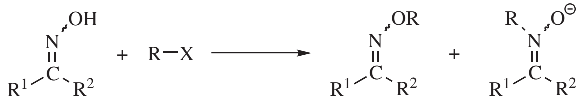
10-23 Alcohols from Amines

Hydroxy-de-amination

$$RNH_2 \longrightarrow ROH$$

This is a rare transformation. A rather direct method was reported whereby a primary amine reacted with KOH in diethylene glycol at 210°C.[765] The reaction of *S*-phenethylamine and the bis(sulfonyl chloride) of 1,2-benzenesulfonic acid, followed by KNO_2 and 18-crown-6 gave (*R*)-phenethyl alcohol in 70% yield and 40% enantiomeric excess (ee).[766]

10-24 Alkylation of Oximes[767]



A nitrone

Oximes can be alkylated by alkyl halides or sulfates. *N*-Alkylation is a side reaction, yielding a nitrone.[768] The relative yield of oxime ether and nitrone depends on the nature of the reagents, including the configuration of the oxime,

[761]Karger, M.H.; Mazur, Y. *J. Org. Chem.* ***1971***, *36*, 532, 540.

[762]For a review of the synthesis and reactions of organic perchlorates, see Zefirov, N.S.; Zhdankin, V.V.; Koz'min, A.S. *Russ. Chem. Rev.* ***1988***, *57*, 1041.

[763]Zefirov, N.S.; Kirin, V.N.; Yur'eva, N.M.; Zhdankin, V.V.; Kozmin, A.S. *J. Org. Chem. USSR* ***1987***, *23*, 1264.

[764]Golding, P.; Millar, R.W.; Paul, N.C.; Richards, D.H. *Tetrahedron Lett.* ***1988***, *29*, 2731, 2735.

[765]Rahman, S.M.A.; Ohno, H.; Tanaka, T. *Tetrahedron Lett.* ***2001***, *42*, 8007.

[766]Sørbye, K.; Tautermann, C.; Carlsen, P.; Fiksdahl, A. *Tetraheron Asymmetry*, ***1998***, *9*, 681.

[767]For a review of the chemistry of oximes see Ãbele, E.; Lukevics, E. *Org. Prep. Proceed. Int.* ***2000***, *32*, 235.

[768]For a review of nitrones, see Torssell, K.B.G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*, VCH, NY, ***1988***, pp. 75–93. For the synthesis of nitrones see Katritzky, A.R.; Cui, X.; Long, Q.; Yanga, B.; Wilcox, A.L.; Zhang, Y.-K. *Org. Prep. Proceed. Int.* ***2000***, *32*, 175.

and on the reaction conditions.[769] For example, *anti*-benzaldoximes give nitrones, while the syn isomers give oxime ethers.[770]

OS **III**, 172; **V**, 1031. Also see, OS **V**, 269; **VI**, 199.

SULFUR NUCLEOPHILES

Sulfur compounds[771] are better nucleophiles than their oxygen analogs (p. 491), so in most cases these reactions take place faster and more smoothly than the corresponding reactions with oxygen nucleophiles. There is evidence that some of these reactions take place by SET mechanisms.[772]

10-25 Attack by SH at an Alkyl Carbon: Formation of Thiols[773]

Mercapto-de-halogenation

$$RX + H_2S \longrightarrow RSH_2^+ \longrightarrow RSH + H^+$$

$$RX + HS^- \longrightarrow RSH$$

Sodium sulfhydride (NaSH) is a much better reagent for the formation of thiols (mercaptans) from alkyl halides than H_2S and is used much more often. It is easily prepared by bubbling H_2S into an alkaline solution, but hydrosulfide on a supported polymer resin has also been used.[774] The reaction is most useful for primary halides. Secondary substrates give much lower yields, and the reaction fails completely for tertiary halides because elimination predominates. Sulfuric and sulfonic esters can be used instead of halides. Thioethers (RSR) are often side products.[775] The conversion can also be accomplished under neutral conditions by treatment of a primary halide with F^- and a tin sulfide, such as $Ph_3SnSSnPh_3$.[776] An indirect method for the preparation of a thiol is the reaction of an alkyl halide with thiourea to give an isothiuronium salt (**119**), and subsequent treatment with alkali or a

[769]For a review, see Reutov, O.A.; Beletskaya, I.P.; Kurts, A.L. *Ambident Anions*, Plenum, NY, ***1983***, pp. 262–272.

[770]Buehler, E. *J. Org. Chem.* ***1967***, *32*, 261.

[771]For monographs on sulfur compounds, see Bernardi, F.; Csizmadia, I.G.; Mangini, A. *Organic Sulfur Chemistry*, Elsevier, NY, ***1985***; Oae, S. *Organic Chemistry of Sulfur*, Plenum, NY, ***1977***. For monographs on selenium compounds, see Krief, A.; Hevesi, L. *Organoselenium Chemistry I*, Springer, NY, ***1988***; Liotta, D. *Organoselenium Chemistry*, Wiley, NY, ***1987***.

[772]See Ashby, E.C.; Park, W.S.; Goel, A.B.; Su, W. *J. Org. Chem.* ***1985***, *50*, 5184.

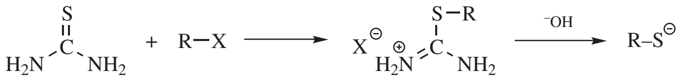
[773]For a review, see Wardell, J.L., in Patai, S. *The Chemistry of the Thiol Group*, pt. 1; Wiley, NY, ***1974***, pp. 179–211.

[774]Bandgar, B.P.; Sadavarte, V.S.; Uppalla, L.S. *Chem. Lett.* ***2000***, 1304.

[775]For a method of avoiding thioether formation, see Vasil'tsov, A.M.; Trofimov, B.A.; Amosova, S.V. *J. Org. Chem. USSR* ***1983***, *19*, 1197.

[776]Gingras, M.; Harpp, D.N. *Tetrahedron Lett.* ***1990***, *31*, 1397.

high-molecular-weight amine gives cleavage to the thiol.



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Other indirect methods are treatment of the halide with silyl-thiols and KH, followed by treatment with fluoride ion and water,[777] and hydrolysis of Bunte salts (see **10-28**) is another method.

Thiols have also been prepared from alcohols. One method involves treatment with H_2S and a catalyst, such as Al_2O_3,[778] but this is limited to primary alcohols. Another method involves treatment with Lawesson's reagent (see **16-10**).[779] When epoxides are substrates, the products are β-hydroxy thiols.[780] Tertiary nitro compounds give thiols ($RNO_2 \rightarrow RSH$) when treated with sulfur and sodium sulfide, followed by amalgamated aluminum.[781]

OS **III**, 363, 440; **IV**, 401, 491; **V**, 1046; **VIII**, 592. Also see, OS **II**, 345, 411, 573; **IV**, 232; **V**, 223; **VI**, 620.

10-26 Attack by S at an Alkyl Carbon: Formation of Thioethers

Alkylthio-de-halogenation; Alkylthio-de-hydroxylation

$$R{-}X \; + \; R'{-}S^- \longrightarrow R{-}S{-}R'$$

$$R{-}OH \; + \; R'{-}SH \xrightarrow{\text{additives}} R{-}S{-}R'$$

Thioethers (sulfides) can be prepared by treatment of alkyl halides with salts of thiols (thiolate ions).[782] The R′ groups may be alkyl or aryl, and organolithium bases can be used to deprotonate the thiol.[783] As in **10-25**, RX cannot be a tertiary halide, and sulfuric and sulfonic esters can be used instead of halides. As in the Williamson reaction (**10-8**), yields are improved by phase-transfer catalysis.[784] Thiols can be reacted directly with alkyl halides in the presence of bases such as

[777]Miranda, E.I.; Díaz, M.J.; Rosado, I.; Soderquist, J.A. *Tetrahedron Lett.* ***1994***, *35*, 3221; Rane, A.M.; Miranda, E.I.; Soderquist, J. *Tetrahedron Lett.* ***1994***, *35*, 3225.

[778]Lucien, J.; Barrault, J.; Guisnet, M.; Maurel, R. *Nouv. J. Chim.* ***1979***, *3*, 15.

[779]Nishio, T. *J. Chem. Soc., Chem. Commun.* ***1989***, 205; Nishio, T. *J. Chem. Soc. Perkin Trans. 1* ***1993***, 1113.

[780]For a review, see Wardell, J.L., in Patai, S. *The Chemistry of the Thiol Groups*, pt. 1, Wiley, NY, ***1974***, pp. 246–251.

[781]Kornblum, N.; Widmer, J. *J. Am. Chem. Soc.* ***1978***, *100*, 7086.

[782]For a review, see Peach, M.E., in Patai, S. *The Chemistry of the Thiol Groups*, pt. 2, Wiley, NY, ***1974***, pp. 721–735.

[783]Yin, J.; Pidgeon, C. *Tetrahedron Lett.* ***1997***, *38*, 5953.

[784]For a review of the use of phase transfer catalysis to prepare sulfur-containing compounds, see Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, ***1977***, pp. 221–233.

DBU (p. 1531)[785] or CsF.[786] Neopentyl bromide was converted to Me_3CCH_2SPh in good yield by treatment with PhS^- in liquid NH_3 at $-33°C$ under the influence of light.[787] This probably takes place by an $S_{RN}1$ mechanism (see p. 862). Leaving groups other than chloride can be used, as in the ruthenium-catalyzed reaction of thiols with propargylic carbonates.[788] Vinylic sulfides can be prepared by treating vinylic bromides with PhS^- in the presence of a nickel complex,[789] with R_3SnSPh[790] or with PhSLi[791] in the presence of $Pd(PPh_3)_4$.

In some cases, alcohols can be converted to thioethers by reaction with thiols. Tertiary alcohols react with thiols in the presence of sulfuric acid to give thioethers, and the reaction works best with tertiary substrates.[792] This reaction is analogous to **10-12**. Thiophenol reacts with propargylic alcohols in the presence of a ruthenium catalysts to give propargylic thioethers.[793] Primary and secondary alcohols can be converted to alkyl aryl sulfides (ROH → RSAr) in high yields by treatment with Bu_3P and an *N*-(arylthio)succinimide in benzene.[794] Primary alcohols reacted with benzylic thiols in the presence of PMe_3, 1,1′(azodicarbonyl)dipyridine (ADDP) and imidazole to give the thioether.[795] Thioethers RSR′ can be prepared from an alcohol ROH and a halide R′Cl by treatment with tetramethylthiourea $Me_2NC(=S)NMe_2$ followed by NaH.[796]

Thiolate ions are also useful for the demethylation of certain ethers,[797] esters, amines, and quaternary ammonium salts. Aryl methyl ethers[798] can be cleaved by heating with EtS^- in the dipolar aprotic solvent DMF: $ROAr + EtS^- \rightarrow ArO^- + EtSR$.[799] Carboxylic esters and lactones are cleaved (the lactones give ω-alkylthio carboxylic acids) with a thiol and $AlCl_3$ or $AlBr_3$.[800] Esters and lactones

[785]Ono, N.; Miyake, H.; Saito, T.; Kaji, A. *Synthesis* ***1980***, 952. See also, Ferreira, J.T.B.; Comasseto, J.V.; Braga, A.L. *Synth. Commun.* ***1982***, *12*, 595; Ando, W.; Furuhata, T.; Tsumaki, H.; Sekiguchi, A. *Synth. Commun.* ***1982***, *12*, 627.; Feroci, M.; Inesi, A.; Rossi, L. *Synth. Commun.* ***1999***, *29*, 2611.

[786]Shah, S.T.A.; Khan, K.M.; Heinich, A.M.; Voelter, W. *Tetrahedron Lett.* ***2002***, *43*, 8281.

[787]Pierini, A.B.; Peñéñory, A.B.; Rossi, R.A. *J. Org. Chem.* ***1985***, *50*, 2739.

[788]Kondo, T.; Kanda, Y.; Baba, A.; Fukuda, K.; Nakamura, A.; Wada, K.; Morisaki, Y.; Mitsudo, T.-a. *J. Am. Chem. Soc.* ***2002***, *124*, 12960.

[789]Cristau, H.J.; Chabaud, B.; Labaudiniere, R.; Christol, H. *J. Org. Chem.* ***1986***, *51*, 875.

[790]Carpita, A.; Rossi, R.; Scamuzzi, B. *Tetrahedron Lett.* ***1989***, *30*, 2699. For another method, see Ogawa, T.; Hayami, K.; Suzuki, H. *Chem. Lett.* ***1989***, 769.

[791]Martínez, A.G.; Barcina, J.O.; Cerezo, A. de F.; Subramanian, L.R. *Synlett*, ***1994***, 561.

[792]See Cain, M.E.; Evans, M.B.; Lee, D.F. *J. Chem. Soc.* ***1962***, 1694.

[793]Inada, Y.; Nishibayashi, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* ***2002***, *124*, 15172.

[794]Walker, K.A.M. *Tetrahedron Lett.* ***1977***, 4475. See the references in this paper for other methods of converting alcohols to sulfides. See also, Cleary, D.G. *Synth. Commun.* ***1989***, *19*, 737.

[795]Falck, J.R.; Lai, J.-Y.; Cho, S.-D.; Yu, J. *Tetrahedron Lett.* ***1999***, *40*, 2903.

[796]Fujisaki, S.; Fujiwara, I.; Norisue, Y.; Kajigaeshi, S. *Bull. Chem. Soc. Jpn.* ***1985***, *58*, 2429.

[797]For a review, see Evers, M. *Chem. Scr.* ***1986***, *26*, 585.

[798]Certain other sulfur-containing reagents also cleave methyl and other ethers: see Hanessian, S.; Guindon, Y. *Tetrahedron Lett.* ***1980***, *21*, 2305; Williard, P.G.; Fryhle, C.B. *Tetrahedron Lett.* ***1980***, *21*, 3731; Node, M.; Nishide, K.; Fuji, K.; Fujita, E. *J. Org. Chem.* ***1980***, *45*, 4275. For cleavage with selenium-containing reagents, see Evers, M.; Christiaens, L. *Tetrahedron Lett.* ***1983***, *24*, 377. For a review of the cleavage of aryl alkyl ethers, see Tiecco, M. *Synthesis* ***1988***, 749.

[799]Feutrill, G.I.; Mirrington, R.N. *Tetrahedron Lett.* ***1970***, 1327, *Aust. J. Chem.* ***1972***, *25*, 1719, 1731.

[800]Node, M.; Nishide, K.; Ochiai, M.; Fuji, K.; Fujita, E. *J. Org. Chem.* ***1981***, *46*, 5163.

are similarly cleaved in high yield by phenyl selenide ion $PhSe^-$.[801] Allylic sulfides have been prepared by treating allylic carbonates ROCOOMe (R = an allylic group) with a thiol and a Pd(0) catalyst.[802] A good method for the demethylation of quaternary ammonium salts consists of refluxing them with PhS^- in butanone:[803]

$$R_3\overset{\oplus}{N}Me \quad + \quad Ph\overset{\ominus}{S} \xrightarrow{\text{MeCOEt}} R_3N \quad + \quad PhSMe$$

A methyl group is cleaved more readily than other simple alkyl groups (such as ethyl), although loss of these groups competes, but benzylic and allylic groups cleave even more easily, and this is a useful procedure for the cleavage of benzylic and allylic groups from quaternary ammonium salts, even if methyl groups are also present.[804]

Symmetrical thioethers can also be prepared by treatment of an alkyl halide with sodium sulfide.[805] Symmetrical thioethers have also been prepared by the reaction of $S(MgBr)_2$ with allylic halides.[806]

$$2\,RX \quad + \quad Na_2S \longrightarrow RSR$$

This reaction can be carried out internally, by treatment of sulfide ions with 1,4-, 1,5-, or 1,6-dihalides, to prepare five-, six-, and seven-membered[807] sulfur-containing heterocyclic rings. Certain larger rings have also been closed in this way.[808] A related variation converts epxoides to thiiranes with thiourea and $LiBF_4$ in acetonitrile.[809]

gem-Dihalides can be converted to dithioacetals $RCH(SR')_2$,[810] and acetals have been converted to monothioacetals $R_2C(OR')(SR^2)$,[811] and to dithioacetals.[812] The combination of carbon disulfide and $NaBH_4$ converted 1,3-dibromopropane to 1,3-dithiane.[813]

[801]Scarborough, Jr., R.M.; Smith III, A.B. *Tetrahedron Lett.* ***1977***, 4361; Liotta, D.; Sunay, U.; Santiesteban, H.; Markiewicz, W. *J. Org. Chem.* ***1981***, *46*, 2605; Kong, F.; Chen, J.; Zhou, X. *Synth. Commun.* ***1988***, *18*, 801.

[802]Trost, B.M.; Scanlan, T.S. *Tetrahedron Lett.* ***1986***, *27*, 4141; Goux, C.; Lhoste, P.; Sinou, D. *Tetrahedron Lett.* ***1992***, *33*, 8099; *Tetrahedron* ***1994***, *50*, 10321.

[803]Shamma, M.; Deno, N.C.; Remar, J.F. *Tetrahedron Lett.* ***1966***, 1375. For alternative procedures, see Hutchins, R.O.; Dux, F.J. *J. Org. Chem.* ***1973***, *38*, 1961; Posner, G.H.; Ting, J. *Synth. Commun.* ***1974***, *4*, 355.

[804]Kametani, T.; Kigasawa, T.; Hiiragi, M.; Wagatsuma, N.; Wakisaka, K. *Tetrahedron Lett.* ***1969***, 635.

[805]For another reagent, see Harpp, D.N.; Gingras, M.; Aida, T.; Chan, T.H. *Synthesis* ***1987***, 1122.

[806]Nedugov, A.N.; Pavlova, N.N. *Zhur. Org. Khim.*, ***1992***, *28*, 1401 (Engl. 1103).

[807]Tan, L.C.; Pagni, R.M.; Kabalka, G.W.; Hillmyer, M.; Woosley, J. *Tetrahedron Lett.* ***1992***, *33*, 7709.

[808]See Hammerschmidt, E.; Bieber, W.; Vögtle, F. *Chem. Ber.* ***1978***, *111*, 2445; Singh, A.; Mehrotra, A.; Regen, S.L. *Synth. Commun.* ***1981***, *11*, 409.

[809]Kazemi, F.; Kiasat, A.R.; Ebrahimi, S. *Synth. Commun.* ***2003***, *33*, 595.

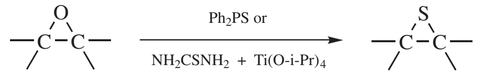
[810]See, for example, Wähälä, K.; Ojanperä, I.; Häyri, L.; Hase, T.A. *Synth. Commun.* ***1987***, *17*, 137.

[811]Masaki, Y.; Serizawa, Y.; Kaji, K. *Chem. Lett.* ***1985***, 1933; Sato, T.; Kobayashi, T.; Gojo, T.; Yoshida, E.; Otera, J.; Nozaki, H. *Chem. Lett.* ***1987***, 1661.

[812]Firouzabadi, H.; Iranpoor, N.; Hazarkhami, H. *J. Org. Chem.* ***2001***, *66*, 7527, and references cited therein; Ranu, B.C.; Das, A.; Samanta, S. *Synlett.* ***2002***, 727.

[813]Wan,Y.; Kurchan, A.N.; Barnhurst, L.A.; Kutateladze, A.G. *Org. Lett.* ***2000***, *2* , 1133.

When epoxides are substrates,[814] reaction with $PhSeSnBu_3/BF_3{\bullet}OEt_2$[815] gives the corresponding β-hydroxy selenide in a manner analogous to that mentioned in **10-25**. Reaction of an epoxide with Ph_3SiSH followed by treatment with Bu_4NF gives hydroxy-thiols.[816] Epoxides can also be directly converted to episulfides[817] by treatment with a phosphine sulfide, such as Ph_3PS,[818] with thiourea and titanium tetraisopropoxide,[819] with NH_4SCN and $TiO(tfa)_2$,[820] with $(EtO)_2P(=O)H/S/Al_2O_3$,[821] with KSCN and $InBr_3$,[822] and with KSCN in ionic liquids.[823]



Alkyl halides, treated with thioethers, give sulfonium salts.[824] Other leaving groups have also been used for this purpose.[825]

Selenides (selenoethers)and tellurides can be prepared via RSe^- and RTe^- species,[826] and selenium and borohydride exchange resin followed by the halide give the selenoether.[827] The La/I_2-catalyzed reaction of diphenyl diselenide with primary alkyl iodides gave arylalkyl selenides,[828] and InI has been used with benzyl halides.[829] Diaryl selenides (Ar—Se—Ar′) have been prepared by coupling aryl iodides with tin reagents ($ArSeSnR_3$) with a palladium(0) catalyst.[830]

[814]Chini, M.; Crotti, P.; Giovani, E.; Macchia, F.; Pineschi, M. *Synlett*, ***1992***, 303.

[815]Nishiyama, Y.; Ohashi, H.; Itoh, K.; Sonoda, N. *Chem. Lett.* ***1998***, 159.

[816]Brittain, J.; Gareau, Y. *Tetrahedron Lett.* ***1993***, *34*, 3363.

[817]For a review of episulfides, see Fokin, A.V.; Kolomiets, A.F. *Russ. Chem. Rev.* ***1975***, *44*, 138.

[818]Chan, T.H.; Finkenbine, J.R. *J. Am. Chem. Soc.* ***1972***, *94*, 2880.

[819]Gao, Y.; Sharpless, K.B. *J. Org. Chem.* ***1988***, *53*, 4114. For other methods, see Calō, V.; Lopez, L.; Marchese, L.; Pesce, G. *J. Chem. Soc., Chem. Commun.* ***1975***, 621; Takido, T.; Kobayashi, Y.; Itabashi, K. *Synthesis* ***1986***, 779; Bouda, H.; Borredon, M.E.; Delmas, M.; Gaset, A. *Synth. Commun.* ***1987***, *17*; 943, ***1989***, *19*, 491.

[820]Iranpoor, N.; Zeynizadeh, B. *Synth. Commun.* ***1998***, *28*, 3913. See also, Tamami, B.; Kolahdoozan, M. *Tetrahedron Lett.* ***2004***, *45*, 1535.

[821]Kaboudin, B.; Norouzi, H. *Tetrahedron Lett.* ***2004***, *45*, 1283.

[822]Yadav, J.S.; Reddy, B.V.S.; Baishya, G. *Synlett.* ***2003***, 396.

[823]Yadav, J.S.; Reddy, B.V.S.; Reddy, Ch.S.; Rajasekhar, K. *J. Org. Chem.* ***2003***, *68*, 2525.

[824]For a review of the synthesis of sulfonium salts, see Lowe, P.A., in Stirling, C.J.M. *The Chemistry of the Sulphonium Group*, pt. 1, Wiley, NY, ***1981***, pp. 267–312.

[825]See Badet, B.; Jacob, L.; Julia, M. *Tetrahedron* ***1981***, *37*, 887; Badet, B.; Julia, M. *Tetrahedron Lett.* ***1979***, 1101, and references cited in the latter paper.

[826]Brandsma, L.; Wijers, H.E. *Recl. Trav. Chim. Pays-Bas* ***1963***, *82*, 68; Clarembeau, M.; Krief, A. *Tetrahedron Lett.* ***1984***, *25*, 3625; Cohen, R.J.; Fox, D.L.; Salvatore, R.N. *J. Og. Chem.* ***2004***, *69*, 4265. For a review of nucleophilic selenium, see Monahan, R.; Brown, D.; Waykole, L.; Liotta, D., in Liotta, D.C. *Organoselenium Chemistry*, Wiley, NY, ***1987***, pp. 207–241.

[827]Yanada, K.; Fujita, T.; Yanada, R. *Synlett*, ***1998***, 971.

[828]Nishino, T.; Okada, M.; Kuroki, T.; Watanabe, T.; Nishiyama, Y.; Sonoda, N. *J. Org. Chem.* ***2002***, *67*, 8696. Zinc in aqueous media has also been used: see Bieber, L.W.; de Sá, A.C.P.F.; Menezes, P.H. Gonçalves, S.M.C. *Tetrahedron Lett.* ***2001***, *42*, 4597.

[829]Ranu, B.C.; Mandal, T.; Samanta, S. *Org. Lett.* ***2003***, *5*, 1439.; Ranu, B.C.; Mandal, T. *J. Org. Chem.* ***2004***, *69*, 5793.

[830]Nishiyama, Y.; Tokunaga, K.; Sonoda, N. *Org. Lett.* ***1999***, *1*, 1725.

OS **II**, 31, 345, 547, 576; **III**, 332, 751, 763; **IV**, 396, 667, 892, 967; **V**, 562, 780, 1046; **VI**, 5, 31, 268, 364, 403, 482, 556, 601, 683, 704, 737, 833, 859; **VII**, 453; **VIII**, 592. See also, OS **VI**, 776.

$$RI + R_2'S \longrightarrow R_2'\overset{\oplus}{S}R \; I^{\ominus}$$

10-27 Formation of Disulfides[831]

Dithio-de-dihalo-*aggre*-substitution

$$2\,RX + S_2^{2-} \longrightarrow RSSR + 2\,X^-$$

Disulfides can be prepared by treatment of alkyl halides with disulfide ions and also indirectly by the reaction of Bunte salts (see **10-28**) with acid solutions of iodide, thiocyanate ion, or thiourea,[832] or by pyrolysis or treatment with hydrogen peroxide. Alkyl halides also give disulfides when refluxed with sulfur and NaOH,[833] and with piperidinium tetrathiotungstate or piperidinium tetrathiomolybdate.[834] Other molybdenum compounds convert alkyl halides to disulfides, including $(BnNEt_3)_6Mo_7S_{24}$.[835]

There are no OS references, but a similar preparation of a polysulfide may be found in OS **IV**, 295.

10-28 Formation of Bunte Salts

Sulfonatothio-de-halogenation

$$RX + S_2O_3^{2-} \longrightarrow R{-}S{-}SO_3^- + X^-$$

Primary and secondary, but not tertiary, alkyl halides are easily converted to Bunte salts ($RSSO_3^-$) by treatment with thiosulfate ion.[836] Bunte salts can be hydrolyzed with acids to give the corresponding thiols[837] or converted to disulfides, tetrasulfides, or pentasulfides.[838]

OS **VI**, 235.

[831]For a discussion of disulfide exchange reactions, see Arisawa, M.; Yamaguchi, M. *J. Am. Chem. Soc.* ***2004***, *125*, 6624.

[832]Milligan, B.; Swan, J.M. *J. Chem. Soc.* ***1962***, 2712.

[833]Chorbadjiev, S.; Roumian, C.; Markov, P. *J. Prakt. Chem.* ***1977***, *319*, 1036. For an example using microwave irradiation, see Wang, J.-X.; Gao, L.; Huang, D. *Synth. Commun.* ***2002***, *32*, 963.

[834]Dhar, P.; Chandrasekaran, S. *J. Org. Chem.* ***1989***, *54*, 2998.

[835]Polshettiwar, V.; Nivsarkar, M.; Acharya, J.; Kaushik, M.P. *Tetrahedron Lett.* ***2003***, *44*, 887.

[836]For a review of Bunte salts, see Distler, H. *Angew. Chem. Int. Ed.* ***1967***, *6*, 544–553.

[837]Kice, J.L. *J. Org. Chem.* ***1963***, *28*, 957.

[838]Milligan, B.; Saville, B.; Swan, J.M. *J. Chem. Soc.* ***1963***, 3608.

10-29 Alkylation of Sulfinic Acid Salts

Alkylsulfonyl-de-halogenation

$$RX + R'SO_2^- \longrightarrow R{-}SO_2{-}R' + X^-$$

Alkyl halides or alkyl sulfates, treated with the salts of sulfinic acids, give sulfones.[839] A palladium catalyzed reaction with a chiral complexing agent led to sulfones with modest asymmetric induction.[840] Alkyl sulfinates R′SO—OR may be side products.[841] Sulfonic acids themselves can be used, if DBU (p. 1530) is present.[842] Sulfonyl halides react with allylic halides in the presence of $AlCl_3^-$Fe[843] and wit benzyl hlaides in the presence of Sm/$HgCl_2$.[844] Sulfones have also been prepared by treatment of alkyl halides with tosylhydrazide.[845]

Vinyl sulfones were prepared from $PhSO_2Na$ and vinyl iodinium salts C=C—I^+Ph BF_4^-.[846] Sulfinate esters (RS(=O)OR′ were prepared from alcohols and sulfinyl chlorides, in the presence of Proton Sponge®.[847]

OS **IV**, 674; **IX**, 497. See also, OS **VI**, 1016.

10-30 Formation of Alkyl Thiocyanates

Thiocyanato-de-halogenation

$$RX + SCN^- \longrightarrow RSCN + X^-$$

Alkyl halides[848] or sulfuric or sulfonic esters can be heated with sodium or potassium thiocyanate to give alkyl thiocyanates,[849] although the attack by the analogous cyanate ion (**10-44**) gives exclusive *N*-alkylation. Primary amines can be converted to thiocyanates by the Katritzky pyrylium–pyridinium method (p. 498).[850] Tertiary

839For a review, see Schank, K., in Patai, S.; Rappoport, Z.; Stirling, C. *The Chemistry of Sulphones and Sulphoxides*, Wiley, NY, ***1988***, pp. 165–231, 177–188.

840Eichelmann, H.; Gais, H.-J. *Tetrahedron Asymmetry*, ***1995***, *6*, 643.

841See, for example Meek, J.S.; Fowler, J.S. *J. Org. Chem.* ***1968***, *33*, 3422; Kiełbasiński, P.; Żurawiński, R.; Drabowicz, J.; Mikołajczyk, M. *Tetrahedron* ***1988***, *44*, 6687.

842Biswas, G.; Mal, D. *J. Chem. Res. (S)* ***1988***, 308.

843Saikia, P.; Laskar, D.D.; Prajapati, D.; Sandhu, J.S. *Chem. Lett.* ***2001***, 512.

844Zhang, J.; Zhang, Y. *J. Chem. Res. (S)* ***2001***, 516.

845Ballini, R.; Marcantoni, E.; Petrini, M. *Tetrahedron* ***1989***, *45*, 6791.

846Ochiai, M.; Oshima, K.; Masaki, Y.; Kunishima, M.; Tani, S. *Tetrahedron Lett.* ***1993***, *34*, 4829.

847Evans, J.W.; Fierman, M.B.; Miller, S.J.; Ellman, J.A. *J. Am. Chem. Soc.* ***2004***, *126*, 8134.

848Renard, P.-Y.; Schwebel, H.; Vayron, P.; Leclerc, E.; Dias, S.; Mioskowski, C. *Tetrahedron Lett.* ***2001***, *42*, 8479. For a variation involving *in situ* halogenation of active methylene compounds with formation of the thiocyanate, see Prakash, O.; Kaur, H.; Batra, H.; Rani, N.; Singh, S.P.; Moriarty, R.M. *J. Org. Chem.* ***2001***, *66*, 2019. The reagent $Ph_3P(SCN)_2$ has also been used: see Iranpoor, N.; Firouzabadi, H.; Shaterian, H.R. *Tetrahedron Lett.* ***2002***, *43*, 3439.

849For a review of thiocyanates, see Guy, R.G., in Patai, S. *The Chemistry of Cyanates and Their Thio Derivatives*, pt. 2; pp. 819–886, Wiley, NY, ***1977***, pp. 819–886.

850Katritzky, A.R.; Gruntz, U.; Mongelli, N.; Rezende, M.C. *J. Chem. Soc. Perkin Trans. 1* ***1979***, 1953. For the conversion of primary alcohols to thiocyanates, see Tamura, Y.; Kawasaki, T.; Adachi, M.; Tanio, M.; Kita, Y. *Tetrahedron Lett.* ***1977***, 4417.

chlorides are converted to tertiary thiocyanates with $Zn(SCN)_2$ in pyridine and ultrasound.[851]

OS **II**, 366.

NITROGEN NUCLEOPHILES

A. Attack by NH_2, NHR, or NR_2 at an Alkyl Carbon

10-31 Alkylation of Amines

Amino-de-halogenation (alkyl)

$$3\,RX + NH_3 \longrightarrow R_3N + RX \longrightarrow R_4N^+\ X^-$$
$$2\,RX + R'NH_2 \longrightarrow R_2R'N + RX \longrightarrow R_3R'N^+\ X^-$$
$$RX + R''R'NH_2 \longrightarrow RR'R''N + RX \longrightarrow R_2R'R''N^+\ X^-$$
$$RX + RR'R''N \longrightarrow RR'R''R''N^+\ X^-$$

The reaction between alkyl halides and ammonia or primary amines is not usually a feasible method for the preparation of primary or secondary amines, since they are stronger bases than ammonia and preferentially attack the substrate. However, the reaction is very useful for the preparation of tertiary amines[852] and quaternary ammonium salts. If ammonia is the nucleophile,[853] the three or four alkyl groups on the nitrogen of the product must be identical. If a primary, secondary, or tertiary amine is used, then different alkyl groups can be placed on the same nitrogen atom. The conversion of tertiary amines to quaternary salts is called the *Menshutkin reaction*.[854] It is sometimes possible to use this method for the preparation of a primary amine by the use of a large excess of ammonia or a secondary amine by the use of a large excess of primary amine. The use of ammonia in methanol with microwave irradiation has also been effective.[855] Microwave irradiation has also been used in reactions of aniline with allyl iodides.[856] A base other than the amine

[851]Bettadaiah, B.K.; Gurudutt, K.N.; Srinivas, P. *Synth. Commun.* ***2003***, *33*, 2293.

[852]For reviews of this reaction, see Gibson, M.S., in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, pp. 45–55; Spialter, L.; Pappalardo, J.A. *The Acyclic Aliphatic Tertiary Amines*, Macmillan, NY, ***1965***, pp. 14–29.

[853]For a review of ammonia as a synthetic reagent, see Jeyaraman, R., in Pizey, J.S. *Synthetic Reagents*, Vol. 5, Wiley, NY, ***1983***, pp. 9–83.

[854]For a discussion of solvent effects see Deleuze, M.S.; Leigh, D.A.; Zerbetto, F. *J. Am. Chem. Soc.* ***1999***, *121*, 2364. For a review of stereoselectivity in this reaction see Bottini, A.T. *Sel. Org. Transform.* ***1970***, *1*, 89. For a discussion of steric effects, see Persson, J.; Berg, U.; Matsson, O. *J. Org. Chem.* ***1995***, *60*, 5037. For a review of quaternization of heteroaromatic rings, see Zoltewicz, J.A.; Deady, L.W. *Adv. Heterocycl. Chem.* ***1978***, *22*, 71. See Shaik, S.; Ioffe, A.; Reddy, A.C.; Pross, A. *J. Am. Chem. Soc.* ***1994***, *116*, 262 for a discussion of the transition state for this reaction.

[855]Saulnier, M.G.; Zimmermann, K.; Struzynski, C.P.; Sang, X.; Velaparthi, U.; Wittman, M.; Frennesson, D.B. *Tetrahedron Lett.* ***2004***, *45*, 397.

[856]Romera, J.L.; Cid, J.M.; Trabanco, A.A. *Tetrahedron Lett.* ***2004***, *45*, 8797.

can be added to facilitate the reaction. Sodium carbonate has been used,[857] as has lithium hydroxide.[858] Cesium hydroxide was successfully used as a base in the presence of molecular sieve 4 Å,[859] and cesium fluoride has been used with benzylic halides.[860] Potassium carbonate in DMSO has been used for the alkylation of aniline.[861] Bromides react faster than chlorides, and secondary amines reaction with 3-chloro-1-bromopropane via the bromide, in the presence of Zn and THF.[862]

The limitations of this approach can be seen in the reaction of a saturated solution of ammonia in 90% ethanol with ethyl bromide in a 16:1 molar ratio, under which conditions the yield of primary amine was 34.2% (at a 1:1 ratio the yield was 11.3%).[863] Alkyl amines can be one type of substrate that does give reasonable yields of primary amine (provided a large excess of NH_3 is used) are α-halo acids, which are converted to amino acids. *N*-Chloromethyl lactams also react with amines to give good yields to the *N*-aminomethyl lactam.[864] Primary amines can be prepared from alkyl halides by **10-43**, followed by reduction of the azide (**19-32**),[865] or by the Gabriel synthesis (**10-41**).

The immediate product in any particular step is the protonated amine, but it rapidly loses a proton to another molecule of ammonia or amine in an equilibrium process, for example,

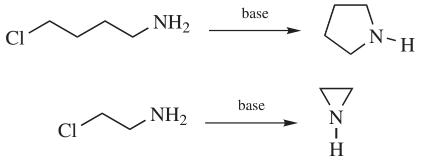
$$RX + R_2NH \longrightarrow R_3\overset{\oplus}{N}H + R_2NH \rightleftharpoons R_3N + R_2\overset{\oplus}{N}H_2$$

When it is desired to convert a primary or secondary amine directly to the quaternary salt (*exhaustive alkylation*), the rate can be increased by the addition of a non-nucleophilic strong base that serves to remove the proton from $RR'NH_2^+$ or $RR'R^2NH^+$ and thus liberates the amine to attack another molecule of RX.[866]

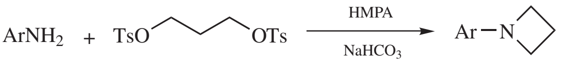
The conjugate bases of ammonia and of primary and secondary amines (NH_2^-, RNH^- R_2N^-) are sometimes used as nucleophiles,[867] including amide bases generated from organolithium reagents and amines (R_2NLi).[868] This is in contrast to the

[857]Faul, M.M.; Kobierski, M.E.; Kopach, M.E. *J. Org. Chem.* ***2003***, *68*, 5739.
[858]Cho, J.H.; Kim, B.M. *Tetrahedron Lett.* ***2002***, *43*, 1273.
[859]Salvatore, R.N.; Nagle, A.S.; Schmidt, S.E.; Jung, K.W. *Org. Lett.* ***1999***, *1*, 1893; Salvatore, R.N.; Schmidt, S.E.; Shin, S.I.; Nagle, A.S.; Worrell, J.H.; Jung, K.W. *Tetrahedron Lett.* ***2000***, *41*, 9705.
[860]Hayat, S.; Rahman, A.-U.; Choudhary, M.I.; Khan, K.M.; Schumann, W.; Bayer, E. *Tetrahedron* ***2001***, *57*, 9951.
[861]Srivastava, S.K.; Chauhan, P.M.S.; Bhaduri, A.P. *Synth. Commun.* ***1999***, *29*, 2085; Jaisinghani, H.G.; Khadilkar, B.M. *Synth. Commun.* ***1999***, *29*, 3693; Salvatore, R.N.; Nagle, A.S.; Jung, K.W. *J. Org. Chem.* ***2002***, *67*, 674.
[862]Murty, M.S.R.; Jyothirmai, B.; Krishna, P.R.; Yadav, J.S. *Synth. Commun.* ***2003***, *33*, 2483.
[863]Werner, E.A. *J. Chem. Soc.* ***1918***, *113*, 899.
[864]Chen, P.; Suh, D.J.; Smith, M.B. *J. Chem. Soc. Perkin Trans. 1* ***1995***, 1317; Deskus, J.; Fan, D.-p.; Smith. M.B. *Synth. Commun.* ***1998***, *28*, 1649.
[865]See Kumar, H.M.S.; Anjaneyulu, S.; Reddy, B.V.S.; Yadav, J.S. *Synlett.* ***1999***, 551.
[866]Sommer, H.Z.; Jackson, L.L. *J. Org. Chem.* ***1970***, *35*, 1558; Sommer, H.Z.; Lipp, H.I.; Jackson, L.L. *J. Org. Chem.* ***1971***, *36*, 824. See also, Chuang, T.-H.; Sharpless, K.B. *Org. Lett.* ***2000***, *2*, 3555.
[867]For a discussion of the mechanism of the reaction between a primary halide and Ph_2NLi, see DePue, J.S.; Collum, D.B. *J. Am. Chem. Soc.* ***1988***, *110*, 5524.
[868]Vitale, A.A.; Chiocconi, A.A. *J. Chem. Res. (S)* ***1996***, 336.

analogous methods **10-1**, **10-8**, **10-25**, and **10-26**. Pyrrole is converted to *N*-methylpyrrole with KOH, iodomethane in ionic liquids.[869] Primary alkyl, allylic, and benzylic bromides, iodides, and tosylates react with sodium bis(trimethylsilyl) amide to give derivatives that are easily hydrolyzed to produce amine salts in high overall yields.[870] Primary arylamines are easily alkylated, but diaryl- and triarylamines are very poor nucleophiles. However, the reaction has been carried out with diarylamines.[871] Sulfates or sulfonates can be used instead of halides. The reaction can be carried out intramolecularly to give cyclic amines, with three-, five-, and six-membered (but not four-membered) rings being easily prepared. Thus, 4-chloro-1-aminobutane treated with base gives pyrrolidine, and 2-chloroethylamine gives aziridine[872] (analogous to **10-9**):



Reduction of *N*-(3-bromopropyl) imines gives a bromo-amine *in situ*, which cyclizes to the aziridine.[873] Five-membered ring amines (pyrrolidines) can be prepared from alkenyl amines via treatment with *N*-chlorosuccinimide and then Bu_3SnH.[874] Internal addition of amine to allylic acetates, catalyzed by $Pd(PPh_3)_4$, leads to cyclic products via a S_N2' reaction.[875] Three-membered cyclic amines (aziridines) can be prepared from chiral conjugated amides via bromination and reaction with an amine.[876] Four-membered cyclic amines (azetidines) have been prepared in a different way:[877]



This reaction was also used to close five-, six-, and seven-membered rings.

As usual, tertiary substrates do not give the reaction at all but undergo preferential elimination. However, tertiary (but not primary or secondary) halides R_3CCl can be converted to primary amines R_3CNH_2 by treatment with NCl_3 and $AlCl_3$[878] in a reaction related to **10-39**.

[869]In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Le, Z.-G.; Chen, Z.-C.; Hu, Y.; Zheng, Q.-G. *Synthesis* ***2004***, 1951.

[870]Bestmann, H.J.; Wölfel, G. *Chem. Ber.* ***1984***, *117*, 1250.

[871]Patai, S.; Weiss, S. *J. Chem. Soc.* ***1959***, 1035.

[872]For a review of aziridine formation by this method, see Dermer, O.C.; Ham, G.E. *Ethylenimine and Other Aziridines*, Academc Press, NY, ***1969***, pp. 1–59.

[873]DeKimpe, N.; DeSmaele, D. *Tetrahedron Lett.*, ***1994***, *35*, 8023. Also see, De Kimpe, N.; Boelens, M.; Piqueur, J.; Baele, J. *Tetrahedron Lett.* ***1994***, *35*, 1925.

[874]Tokuda, M.; Fujita, H.; Suginome, H. *J. Chem. Soc. Perkin Trans. 1* ***1994***, 777.

[875]Grellier, M.; Pfeffer, M.; van Koten, G. *Tetrahedron Lett.* ***1994***, *35*, 2877.

[876]Garner, P.; Dogan, O.; Pillai, S. *Tetrahedron Lett.*,**1994**, 35, 1653.

[877]Juaristi, E.; Madrigal, D. *Tetrahedron* ***1989***, *45*, 629.

[878]Strand, J.W.; Kovacic, M.K. *J. Am. Chem. Soc.* ***1973***, *95*, 2977.

Amines can be *N*-alkylated by reaction with alcohols, in a sealed tube with microwave irradiation,[879] by ruthenium-catalyzed,[880] palladium-[881] or iridium-catalyzed[882] reactions. Heating indoles with benzylic alcohols in the presence of $Me_3P{=}CH(CN)$ give the *N*-benzylindole.[883] Heating an alcohol on γ-Al_2O_3 leads to an amine,[884] as does treatment with the amine, $SnCl_2$ and $Pd(PPh_3)_4$.[885] The palladium-catalyzed displacement of allylic acetates leads to allylic amines.[886] Chlorodiethylaluminum (Et_2AlCl), with a Cu(II) catalysts can be used to prepare *N*-ethylaniline derivatives.[887] *tert*-Butylamines can be prepared from isobutylene, HBr and the amine by heating a sealed tube.[888]

Phosphines behave similarly, and compounds of the type R_3P and R_4P^+ X^- can be so prepared.[889] The reaction between triphenylphosphine and quaternary salts of nitrogen heterocycles in an aprotic solvent is probably the best way of dealkylating the heterocycles, for example,[890]

Primary amines can be prepared from alkyl halides by the use of hexamethylenetetramine[891] followed by cleavage of the resulting salt with ethanolic HCl. The method, called the *Delépine reaction*, is most successful for active halides such as allylic and benzylic halides and α-halo ketones, and for primary

A convenient way of obtaining secondary amines without contamination by primary or tertiary amines involves treatment of alkyl halides with the sodium or

[879] Jiang, Y.-L.; Hu, Y.-Q.; Feng, S.-Q.; Wu, J.-S.; Wu, Z.-W.; Yuan, Y.-C.; Liu, J.-M.; Hao, Q.-S.; Li, D.-P. *Synth. Commun.* ***1996***, *26*, 161.

[880] Watanabe, Y.; Morisaki, Y.; Kondo, T.; Mitsudo, T. *J. Org. Chem.* ***1996***, *61*, 4214.

[881] Yang, S.-C.; Yu, C.-L.; Tsai, Y.-C. *Tetrahedron Lett.* ***2000***, *41*, 7097; Shue, Y.-J.; Yang, S.-C.; Lai, H.-C. *Tetrahedron Lett.* ***2003***, *44*, 1481; Kimura, M.; Futamata, M.; Shibata, K.; Tamaru, Y. *Chem. Commun.* ***2003***, 234.

[882] Takeuchi, R.; Ue, N.; Tanabe, K.; Yamashita, K.; Shiga, N. *J. Am. Chem. Soc.* ***2001***, *123*, 9525; Fujita, K.-i.; Li, Z.; Ozeki, N.; Yamaguchi, R. *Tetrahedron Lett.* ***2003***, *44*, 2687.

[883] Bombrun, A.; Casi, G. *Tetrahedron Lett.* ***2002***, *43*, 2187.

[884] Valot, F.; Fache, F.; Jacquot, R.; Spagnol, M.; Lemaire, M. *Tetrahedron Lett.* ***1999***, *40*, 3689. For a zeolite mediated reaction that uses methyl acetate, see Selva, M.; Tundo, P.; Perosa, A. *J. Org. Chem.* ***2003***, *68*, 7374.

[885] Masuyama, Y.; Kagawa, M.; Kurusu, Y. *Chem. Lett.* ***1995***, 1121.

[886] Kodama, H.; Taiji, T.; Ohta, T.; Furukawa, I. *Synlett* ***2001***, 385; Feuerstein, M.; Laurenti, D.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* ***2001***, *42*, 2313; Watson, I.D.G.; Styler, S.A.; Yudin, A.K. *J. Am. Chem. Soc.* ***2004***, *126*, 5086; Ohta, T.; Sasayama, H.; Nakajima, O.; Kurahashi, N.; Fujii, J.; Furukawa, I. *Tetrahedron Asymmetry* ***2003***, *14*, 537. See also, Evans, P.A.; Robinson, J.E.; Moffett, K.K. *Org. Lett.* ***2001***, *3*, 3269. For a titanium-catalyzed variation see Mahrwald, R.; Quint, S. *Tetrahedron Lett.* ***2001***, *42*, 1655.

[887] Barton, D.H.R.; Doris, E. *Tetrahedron Lett.* ***1996***, *37*, 3295.

[888] Gage, J.R.; Wagner, J.M. *J. Org. Chem.* ***1995***, *60*, 2613.

[889] See Honaker, M.T.; Sandefur, B.J.; Hargett, J.L.; McDaniel, A.L.; Salvatore, R.N. *Tetrahedron Lett.* ***2003***, *44*, 8373.

[890] For example, see Deady, L.W.; Finlayson, W.L.; Korytsky, O.L. *Aust. J. Chem.* ***1979***, *32*, 1735.

[891] For a review of the reactions of this reagent, see Blažević, N.; Kolbah, D.; Belin, B.; Śunjić, V.; Kajfež, F. *Synthesis* ***1979***, 161.

calcium salt of cyanamide NH_2—CN to give disubstituted cyanamides, which are then hydrolyzed and decarboxylated to secondary amines. Good yields are obtained when the reaction is carried out under phase-transfer conditions.[892] The R group may be primary, secondary, allylic, or benzylic. 1,ω-Dihalides give cyclic secondary amines. Aminoboranes react with sulfonate esters to give a derivative that can be hydrolyzed to a tertiary amine.[893] An aminyl-radical cyclization process was used to prepare cyclic amines.[894]

N-Silylalkyl amines are formed from amines by reaction with halotrialkylsilanes and a suitable base.[895] Amines react directly with triarylsilanes in the presence of Yb catalysts.[896]

OS **I**, 23, 48, 102, 300, 488; **II**, 85, 183, 290, 328, 374, 397, 419, 563; **III**, 50, 148, 254, 256, 495, 504, 523, 705, 753, 774, 813, 848; **IV**, 84, 98, 383, 433, 466, 582, 585, 980; **V**, 88, 124, 306, 361, 434, 499, 541, 555, 608, 736, 751, 758, 769, 825, 883, 985, 989, 1018, 1085, 1145; **VI**, 56, 75, 104, 106, 175, 552, 652, 704, 818, 967; **VIII**, 9, 152, 231, 358. Also see, OS **II**, 395; **IV**, 950; OS **V**, 121; OS **I**, 203.

For *N*-arylation of amines see **13-5**.

10-32 Replacement of a Hydroxy or Alkoxy by an Amino Group

Amino-de-hydroxylation and Amino-de-alkoxylation

$$\text{R—OH} \longrightarrow \text{R—NH}_2$$
$$\text{Ar—OR}' \longrightarrow \text{R}'\text{—NH}_2 + \text{ArOH}$$

Alcohols can be converted to alkyl halides, which then react with amines (**10-43**). Alcohols react with various amine reagents that give products convertible to the amine.[897] The conversion ROH → RNH_2 can be accomplished for primary and secondary alcohols by treatment with hydrazoic acid (HN_3), diisopropyl azodicarboxylate (*i*Pr—OOCN=NCOO—*i*Pr), and excess Ph_3P in THF, followed by water or aqueous acid.[898] This is a type of Mitsunobu reaction (see **10-17**). Other

[892] Jończyk, A.; Ochal, Z.; Makosza, M. *Synthesis* ***1978***, 882.

[893] Thomas, S.; Huynh, T.; Enriquez-Rios, V.; Singaram, B. *Org. Lett.* ***2001***, *3*, 3915.

[894] Crich, D.; Shirai, M.; Rumthao, S. *Org. Lett.* ***2003***, *5*, 3767.

[895] Greene, T.W. *Protective Groups in Organic Synthesis* Wiley, NY, ***1980***, p. 283; Wuts, P.G.M.; Greene, T.W. *Protective Groups in Organic Synthesis 2nd ed.*, Wiley, NY, ***1991***, pp. 69–71; Wuts, P.G.M.; Greene, T.W. *Protective Groups in Organic Synthesis 3rd ed.*, Wiley, NY, ***1999***; Pratt, J.R.; Massey, W.D.; Pinkerton, F.H.; Thames, S.F. *J. Org. Chem.* ***1975***, *40*, 1090.

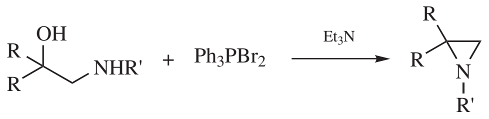
[896] Takaki, K.; Kamata, T.; Miura, Y.; Shishido, T.; Takehira, K. *J. Org. Chem.* ***1999***, *64*, 3891.

[897] See Laurent, M.; Marchand-Brynaert, J. *Synthesis* ***2000***, 667; Jirgensons, A.; Kauss, V.; Kalvinsh, I.; Gold, M.R. *Synthesis* ***2000***, 1709; Katritzky, A.R.; Huang, T.-B.; Voronkov, M.V. *J. Org. Chem.* ***2001***, *66*, 1043; Cami-Kobeci, G.; Williams, J.M.J. *Chem. Commun.* ***2004***, 1072. See also, Salehi, P.; Motlagh, A.R. *Synth. Commun.* ***2000***, *30*, 671; Lakouraj. M.M.; Movassagh, B.; Fasihi, J. *Synth. Commun.* ***2000***, *30*, 821.

[898] Fabiano, E.; Golding, B.T.; Sadeghi, M.M. *Synthesis* ***1987***, 190. See also, Klepacz, A.; Zwierzak, A. *Synth. Commun.* ***2001***, *31*, 1683.

alcohol-to-amine Mitsunobu reactions have also been reported.[899] Primary and secondary alcohols ROH (but not methanol) can be converted to tertiary amines,[900] R'_2NR, by treatment with the secondary amine R'_2NH and $(t\text{-BuO})_3Al$ in the presence of Raney nickel.[901] The use of aniline gives secondary amines PhNHR. Allylic alcohols ROH react with primary ($R'NH_2$) or secondary (R'_2NH) amines in the presence of platinum or palladium complexes, to give secondary (RNHR′) or tertiary (RNR'_2) allylic amines.[902] Conversion of an allyic alcohol to the corresp-sodning allylic crbonate, foolwed by reacatin with an *N*-tosylamine and lihtium hexamethyldisilazide, followedby by $Rh(PPh_3)_3Cl$ and $P(OMe)_3$, gives the *N*-tosylallylic amine.[903] α-Hydroxy phosphonates react with aniline on alumina with microwave irradiation.[904] The ruthenium-catalyzed reaction of amines and diols leads to cyclic amines.[905]

β-Amino alcohols give aziridines (**120**) when treated with triphenylphosphine dibromide in the presence of triethylamine.[906] The fact that inversion takes place at the OH carbon indicates that an S_N2 mechanism is involved, with $OPPh_3$ as the leaving group.



120

Alcohols can be converted to amines in an indirect manner.[907] The alcohols are converted to alkyloxyphosphonium perchlorates which in DMF successfully

[899]See, for example, Henry, J.R.; Marcin, L.R.; McIntosh, M.C.; Scola, P.M.; Harris Jr., G.D.; Weinreb, S.M. *Tetrahedron Lett.* ***1989***, *30*, 5709; Edwards, M.L.; Stemerick, D.M.; McCarthy, J.R. *Tetrahedron Lett.* ***1990***, *31*, 3417.

[900]For other methods of converting certain alcohols to secondary and tertiary amines, see Murahashi, S.; Kondo, K.; Hakata, T. *Tetrahedron Lett.* ***1982***, *23*, 229; Baiker, A.; Richarz, W. *Tetrahedron Lett.* ***1977***, 1937; *Helv. Chim. Acta* ***1978***, *61*, 1169; *Synth. Commun.* ***1978***, *8*, 27; Grigg, R.; Mitchell, T.R.B.; Sutthivaiyakit, S.; Tongpenyai, N. *J. Chem. Soc., Chem. Commun.* ***1981***, 611; Arcelli, A.; Bui-The-Khai; Porzi, G. *J. Organomet. Chem.* ***1982***, *235*, 93; Kelly, J.W.; Eskew, N.L.; Evans, Jr., S.A. *J. Org. Chem.* ***1986***, *51*, 95; Huh, K.; Tsuji, Y.; Kobayashi, M.; Okuda, F.; Watanabe, Y. *Chem. Lett.* ***1988***, 449.

[901]Botta, M.; De Angelis, F.; Nicoletti, R. *Synthesis* ***1977***, 722.

[902]Atkins, K.E.; Walker, W.E.; Manyik, R.M. *Tetrahedron Lett.* ***1970***, 3821; Tsuji, Y.; Takeuchi, R.; Ogawa, H.; Watanabe, Y. *Chem. Lett.* ***1986***, 293.

[903]Evans, P.A.; Robinson, J.E.; Nelson, J.D. *J. Am. Chem. Soc.* ***1999***, *121*, 6761.

[904]Kaboudin, B. *Tetrahedron Lett.* ***2003***, *44*, 1051.

[905]Fujita, K.-i.; Fujii, T.; Yamaguchi, R. *Org. Lett.* ***2004***, *6*, 3525.

[906]Okada, I.; Ichimura, K.; Sudo, R. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 1185. See also, Pfister, J.R. *Synthesis* ***1984***, 969; Suzuki, H.; Tani, H. *Chem. Lett.* ***1984***, 2129; Marsella, J.A. *J. Org. Chem.* ***1987***, *52*, 467.

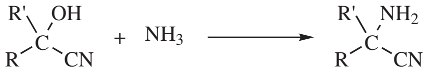
[907]For some other indirect methods, see White, E.H.; Ellinger, C.A. *J. Am. Chem. Soc.* ***1965***, *87*, 5261; Burgess, E.M.; Penton Jr., H.R.; Taylor, E.A. *J. Am. Chem. Soc.* ***1970***, *92*, 5224; Hendrickson, J.B.; Joffee, I. *J. Am. Chem. Soc.* ***1973***, *95*, 4083; Trost, B.M.; Keinan, E. *J. Org. Chem.* ***1979***, *44*, 3451; Koziara, A.; Osowska-Pacewicka, K.; Zawadzki, S.; Zwierzak, A. *Synthesis* ***1985***, 202; ***1987***, 487.

monoalkylate not only secondary but also primary amines.[908]

$$\mathrm{ROH} \xrightarrow[\text{2. } NH_4ClO_4]{\text{1. } CCl_4\text{–}P(NMe_2)_3} \mathrm{RO}^{\oplus}\mathrm{P(NMe_2)_3}\ {}^{\ominus}\mathrm{ClO_4} \xrightarrow[R'R''NH]{DMF} \mathrm{RR'R''N} + \mathrm{OP(NMe_2)_3}$$

Thus by this means secondary as well as tertiary amines can be prepared in good yields. Benzylic alcohols can be converted to an azide and then treated with triphenylphosphine to give the amine (**19-50**).[909]

Cyanohydrins can be converted to amines by treatment with ammonia. The use of primary or secondary amines instead of ammonia leads to secondary and tertiary cyanoamines, respectively. It is more common to perform the conversion of an aldehyde or ketone directly to the cyanoamine without isolation of the cyanohydrin (see **16-52**). α-Hydroxy ketones (acyloins and benzoins) behave similarly.[910]



A solution of the sodium salt of *N*-methylaniline in HMPA can be used to cleave the methyl group from aryl methyl ethers:[911] $ArOMe + PhNMe^- \rightarrow ArO^- + PhNMe_2$. This reagent also cleaves benzylic groups. In a similar reaction, methyl groups of aryl methyl ethers can be cleaved with lithium diphenylphosphide, Ph_2PLi.[912] This reaction is specific for methyl ethers and can be carried out in the presence of ethyl ethers with high selectivity. Phenyl allyl ethers react with secondary amines in the presence of a palladium catalyst to give phenol and the tertiary allyl amine.[913]

OS **II**, 29, 231; **IV**, 91, 283; **VI**, 567, 788; **VII**, 501. Also see, OS **I**, 473; **III**, 272, 471.

10-33 Transamination

Alkylamino-de-amination

$$RNH_2 + R'NH^- \longrightarrow RR'NH + NH_2^-$$

Where the nucleophile is the conjugate base of a primary amine, NH_2 can be a leaving group. The method has been used to prepare secondary amines.[914] In another process, primary amines are converted to secondary amines in which

[908]Castro, B.; Selve, C. *Bull. Soc. Chim. Fr.* ***1971***, 4368. For a similar method, see Tanigawa, Y.; Murahashi, S.; Moritani, I. *Tetrahedron Lett.* ***1975***, 471.

[909]Reddy, G.V.S.; Rao, G.V.; Subrmanyam, R.V.K.; Iyengar, D.S. *Synth. Commun.* ***2000***, *30*, 2233.

[910]For example, see Klemmensen, P.; Schroll, G.; Lawesson, S. *Ark. Kemi*, ***1968***, *28*, 405.

[911]Loubinoux, B.; Coudert, G.; Guillaumet, G. *Synthesis* ***1980***, 638.

[912]Ireland, R.E.; Walba, D.M. *Org. Synth.* ***VI***, 567.

[913]Widehem, R.; Lacroix, T.; Bricout, H.; Monflier, E. *Synlett* ***2000***, 722.

[914]Baltzly, R.; Blackman, S.W. *J. Org. Chem.* ***1963***, *28*, 1158.

both R groups are the same (2 $RNH_2 \rightarrow R_2NH + NH_3$)[915] by refluxing in xylene in the presence of Raney nickel.[916] Quaternary salts can be dealkylated with ethanolamine.[917]

$$R_4N^+ + NH_2CH_2CH_2OH \longrightarrow R_3N + R\overset{\oplus}{N}H_2CH_2CH_2OH$$

In this reaction, methyl groups are cleaved in preference to other saturated alkyl groups. A similar reaction takes place between a Mannich base (see **16-19**) and a secondary amine, where the mechanism is elimination–addition (see p. 477). See also, **19-5**.

OS **V**, 1018.

10-34 Alkylation of Amines With Diazo Compounds

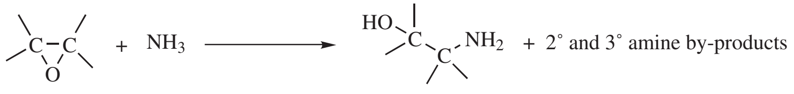
Hydro,dialkylamino-de-diazo-bisubstitution

$$CR_2N_2 + R'_2NH \xrightarrow{BF_3} CHR_2NR'_2$$

The reaction of diazo compounds with amines is similar to **10-11**.[918] The acidity of amines is not great enough for the reaction to proceed without a catalyst, but BF_3, which converts the amine to the $F_3B{-}NHR'_2$ complex, enables the reaction to take place. Cuprous cyanide can also be used as a catalyst.[919] The most common substrate is diazomethane,[630] in which case this is a method for the methylation of amines. Ammonia has been used as the amine but, as in the case of **10-31**, mixtures of primary, secondary, and tertiary amines are obtained. Primary aliphatic amines give mixtures of secondary and tertiary amines. Secondary amines give successful alkylation. Primary aromatic amines also give the reaction, but diaryl or arylalkylamines react very poorly.

10-35 Reaction of Epoxides With Nitrogen Reagents

(3)*OC-seco*-Amino-de-alkoxylation



[915]In a similar manner, a mixture of primary amines can be converted to a mixed secondary amine. For a review of the mechanism, see Geller, B.A. *Russ. Chem. Rev.* ***1978***, *47*, 297.

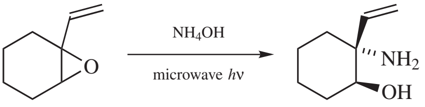
[916]De Angelis, F.; Grgurina, I.; Nicoletti, R. *Synthesis* ***1979***, 70; See also, Ballantine, J.A.; Purnell, H.; Rayanakorn, M.; Thomas, J.M.; Williams, K.J. *J. Chem. Soc., Chem. Commun.* ***1981***, 9; Arcelli, A.; Bui-The-Khai; Porzi, G. *J. Organomet. Chem.* ***1982***, *231*, C31; Jung, C.W.; Fellmann, J.D.; Garrou, P.E. *Organometallics* ***1983***, *2*, 1042; Tsuji, Y.; Shida, J.; Takeuchi, R.; Watanabe, Y. *Chem. Lett.* ***1984***, 889; Bank, S.; Jewett, R. *Tetrahedron Lett.* ***1991***, *32*, 303.

[917]Hünig, S.; Baron W. *Chem. Ber.* ***1957***, *90*, 395, 403.

[918]Müller, E.; Huber-Emden, H.; Rundel, W. *Liebigs Ann. Chem.* ***1959***, *623*, 34.

[919]Saegusa, T.; Ito, Y.; Kobayashi, S.; Hirota, K.; Shimizu, T. *Tetrahedron Lett.* ***1966***, 6131.

The reaction between epoxides and ammonia[920] (or ammonium hydroxide)[921] is a general and useful method for the preparation of β-hydroxyamines. With epoxide derived from terminal alkenes, the reaction with ammonia gives largely the primary amine, but secondary and tertiary amine products are possible from the appropriate epoxide. The reaction of **121** with ammonium hydroxide with microwave irradiation, for example, gave **122**.[922] Ethanolamines, which are useful solvents



121 **122**

as well as synthetic precursors, are prepared by this reaction. Similar ring opening occurs with alkyl and aromatic amines.[923] For another way of accomplishing this conversion, see **10-40**. The reaction can be catalyzed with $Yb(OTf)_3$ and in the presence of (*R*)-BINOL (BINOL = 1,1′-bi-2-naphthol) gives amino alcohols with high asymmetric induction.[924] Many other metal-catalyzed ring-opening reactions have been reported.[925] Ring opening has been accomplished with aniline on silica gel.[926]

Primary and secondary amines give, respectively, secondary and tertiary amines (**121**). Aniline reacts with epoxides in the presence of aqueous β-cyclodextrin[927] in 5 *M* $LiClO_4$ in ether,[928] or in fluoro-alcohol solvents.[929] Aniline reacts with epoxides in the presence of a VCl_3 catalyst.[930] *N*-Boc-amine ($H_2N—CO_2$*t*-Bu) reacted

[920]For an example, see McManus, S.P.; Larson, C.A.; Hearn, R.A. *Synth. Commun.* ***1973***, *3*, 177; Charrada, B.; Hedhli, A.; Baklouti, A. *Tetrahedron Lett.* ***2000***, *41*, 7347.

[921]Pastó, M.; Rodríguez, B.; Riera, A.; Pericàs, M.A. *Tetrahedron Lett.* ***2003***, *44*, 8369.

[922]Lindström, U.M.; Olofsson, B.; Somfai, P. *Tetrahedron Lett.* ***1999***, *40*, 9273.

[923]See Harrack, Y.; Pujol, M.D. *Tetrahedron Lett.* ***2002***, *43*, 819; Steiner, D.; Sethofer, S.G.; Goralski, C.T.; Singaram, B. *Tetrahedron Asymmetry* ***2002***, *13*, 1477. For a reaction catalyzed by LiBr, see Chakraborti, A.K.; Rudrawar, S.; Kondaskar, A. *Eur. J. Org. Chem.* ***2004***, 3597.

[924]Hou, X.-L.; Wu, J.; Dai, L.-X.; Xia, L.-J.; Tang, M.-H. *Tetrahedron Asymmetry* ***1998***, *9*, 1747.

[925]Examples include, **$Sn(OTf)_2$**: Sekar, G.; Singh, V.K. *J. Org. Chem.* ***1999***, *64*, 287; **$CeCl_3$-NaI**: Reddy, L.R.; Reddy, M.A.; Bhanumathi, N.; Rao, K.R. *Synthesis* ***2001***, 831; **Zr catalysts**: Curini, M.; Epifano, F.; Marcotullio, M.C.; Rosati, O. *Eur. J. Org. Chem.* ***2001***, 4149 and Charkraborti, A.K.; Kondaskar, A. *Tetrahedron Lett.* ***2003***, *44*, 8315; **$LiNTf_2$**: Cossy, J.; Bellosta, V.; Hamoir, C.; Desmurs, J.-R. *Tetrahedron Lett.* ***2002***, *43*, 7083; **Bi compounds**: Ollevier, T.; Lavie-Compin, G. *Tetrahedron Lett.* ***2002***, *43*, 7891 and ***2004***, *45*, 49; **$ZnCl_2$:** Pachón, L.D.; Gamez, P.; van Brussel, J.J.M.; Reedijk, J. *Tetrahedron Lett.* ***2003***, *44*, 6025; **$InBr_3$:** Rodríguez, J.R.; Navarro, A. *Tetrahedron Lett.* ***2004***, *45*, 7495; **$SmI_2(thf)_2$:** Carrée, F.; Gil, R.; Collin, J. *Tetrahedron Lett.* ***2004***, *45*, 7749; **$CoCl_2$**: Sundararajan, G.; Viyayakrishna, K.; Varghese, B. *Tetrahedron Lett.* ***2004***, *45*, 8253.

[926]Chakraborti, A.K.; Rudrawar, S.; Kondaskar, A. *Org. Biomol. Chem.* ***2004***, *2*, 1277.

[927]Reddy, L.R.; Reddy, M.A.; Chanumathi, N.; Rao, K.R. *Synlett* ***2000***, 339.

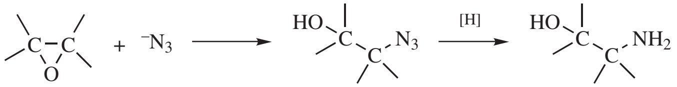
[928]Heydar, A.; Mehrdad, M.; Malecki, A.; Ahmadi, N. *Synthesis* ***2004***, 1563.

[929]Das, U.; Crousse, B.; Kesavan, V.; Bonnet-Delpon, D.; Bégue, J.P. *J. Org. Chem.* ***2000***, *65*, 6749.

[930]Sabitha, G.; Reddy, G.S.K.K.; Reddy, K.B.; Yadav, J.S. *Synthesis* ***2003***, 2298.

with epoxides in the presence of a cobalt–salen catalyst to give the amido alcohol.[931] Solvent free reactions using a catalytic amount of $SnCl_4$ are known.[932] Tetrahydropyrimidones can be used to mediate the addition of indole to epoxides.[933] Amide bases react differently with epoxides. Lithium tetramethylpiperidide (LTMP), for example, reacted with epoxides, but the product was the corresponding enamine.[934] This latter reaction follows a very different mechanism. Initial formation of the lithio-epoxide is followed by rearrangement to give the aldehyde,[935] and subsequent reaction with the amine by-product of the lithiation leads to the enamine.

An indirect method for generating an amino alcohol (**124**) is to open an epoxide with azide to give the azido-alcohol **123**,[936] and subsequent reduction (**19-50**) gives the amine group.[937] Sodium azide and Oxone® react with epoxides to give an azido-alcohol.[938] Under Mitsunobu conditions (**10-17**), epoxides are converted to 1,2-diazides with HN_3.[939] The reaction of trimethylsilyl azide and an epoxide was reported using an ionic solvent.[940] The cerium ammonium nitrate catalyzed reaction of epoxides and sodium azide, for example, gave the azido alcohol with selectivity for the azide group on the more substituted position.[941] Cerium chloride has also been used, giving the azide on the less substituted carbon.[942] Manganese–salen complexes, immobilized on mesoporous material has also been used to mediate the ring opening of epoxides by azide.[943] In the presence of $AlCl_3$ in water at pH 4, sodium azide reacts with epxoy acids to give the β-azido-α-hydroxycarboxylic acid.[944] Silylazides can be used as well.[945]



123 **124**

[931]Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Mechiorre, P.; Sambri, L. *Org. Lett.* ***2004***, *6*, 3973.
[932]Zhao, P.-Q.; Xu, L.-W.; Xia, C.-G. *Synlett* ***2004***, 846.
[933]Fink, D.M. *Synlett* ***2004***, 2394.
[934]Hodgson, D.M.; Bray, C.D.; Kindon, N.D. *J. Am. Chem. Soc.* ***2004***, *126*, 6870.
[935]Yanagisawa, A.; Yasue, K.; Yamamoto, H. *J. Chem. Soc., Chem. Commun.* ***1994***, 2103.
[936]Kazemi, F.; Kiasat, A.R.; Ebrahimi, S. *Synth. Commun.* ***2003***, *33*, 999. For a reaction done under phase-transfer conditions, see Tamami, B.; Mahdavi, H. *Tetrahedron Lett.* ***2001***, *42*, 8721.
[937]Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, p. 815.
[938]Sabitha, G.; Babu, R.S.; Reddy, M.S.K.; Yadav, J.S. *Synthesis* ***2002***, 2254.
[939]Göksu, S.; Soçen, H.; Sütbeyaz, Y. *Synthesis* ***2002***, 2373.
[940]In emim, 1-ethyl-3-methylimidazolium: Song, C.E.; Oh, C.R.; Roh, E.J.; Choo, D.J. *Chem. Commun.* ***2000***, 1743.
[941]Iranpoor, N.; Kazemi, F. *Synth. Commun.* ***1999***, *29*, 561.
[942]Sabitha, G.; Babu, R.S.; Rajkumar, M.; Yadav, J.S. *Org. Lett.* ***2002***, *4*, 343.
[943]Kantam, M.L.; Choudary, B.M.; Bharathi, B. *Synth. Commun.* ***1999***, *29*, 1121.
[944]Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Tetrahedron Lett.* ***2001***, *42*, 1131.
[945]Schneider, C. *Synlett* ***2000***, 1840.

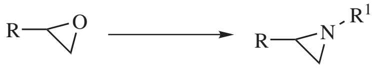
Sodium nitrate ($NaNO_2$) reacts with epoxides in the presence of $MgSO_4$ to give the nitro alcohol.[946] The nitro group can also be reduced to give the amine (**19-45**).[947]

Episulfides, which can be generated *in situ* in various ways, react similarly to give β-amino thiols,[948] and aziridines react with amines to give 1,2-diamines (**10-38**). Triphenylphosphine similarly reacts with epoxides to give an intermediate that undergoes elimination to give alkenes (see the Wittig reaction, **16-44**).

OS **X**, 29. See OS **VI**, 652 for a related reaction.

10-36 Formation of Aziridines from Epoxides

Amino-de-alkoxylation



It is possible to prepare aziridines, which are synthetically important molecules, directly from the corresponding epoxide. Reaction of $Ph_3P{=}NPh$ with an epoxide in the presence of $ZnCl_2$ gives the *N*-phenyl aziridine.[949] Guanidines have also been used to prepare aziridnes from epoxides.[950] Tosylamines react with epoxides to give the *N*-tosylaziridine.[951]

Various methods are available to convert an aminomethyl epoxide to a hydroxymethyl aziridine, **125**[952]

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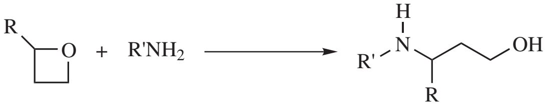
10-37 Amination of Oxetanes

(4)*OC-homoseco*-Amino-de-alkoxylation



Oxetanes are significantly less reactive with nucleophiles due to diminished ring strain. Under certain conditions, however, amines can open oxetanes to give amino

[946]Kalita, B.; Barua, N.C.; Bezbarua, M.; Bez, G. *Synlett* ***2001***, 1411.

[947]Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, p. 821.

[948]Dong, Q.; Fang, X.; Schroeder, J.D.; Garvey, D.S. *Synthesis* ***1999***, 1106.

[949]Kühnau, D.; Thomsen, I.; Jørgensen, K.A. *J. Chem. Soc. Perkin Trans. 1*, ***1996***, 1167.

[950]Tsuchiya, Y.; Kumamoto, T.; Ishikawa, T. *J. Org. Chem.* ***2004***, *69*, 8504.

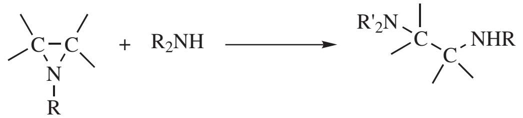
[951]Albanese, D.; Landini, D.; Penso, M.; Petricci, S. *Tetrahedron* ***1999***, *55*, 6387.

[952]Najime, R.; Pilard, S.; Vaultier, M. *Tetrahedron Lett.* ***1992***, *33*, 5351; Moulines, J.; Bats, J.-P.; Hautefaye, P.; Nuhrich, A.; Lamidey, A.-M. *Tetrahedron Lett.* ***1993***, *34*, 2315; Moulines, J.; Charpentier, P.; Bats, J.-P.; Nuhrich, A.; Lamidey, A.-M. *Tetrahedron Lett.* ***1992***, *33*, 487.

alcohols. *tert*-Butylamine reacts with oxetanes in the presence of $Yb(OTf)_3$, for example, to give 3-hydroxy amines.[953] Lithium tetrafluoroborate has also been used for this purpose.[954]

10-38 Reaction of Aziridines With Nitrogen

(3)*NC-seco*-Amino-de-aminoalkylation



Just as epoxides can be opened by amines to give hydroxy amines, aziridines can be opened to give diamines.[955] With bicyclic aziridines, the major product is usually the trans diamine. *N*-Aryl or *N*-alkyl aziridines react with amines in the presence of $Sn(OTf)_2$[956] or $B(C_6F_5)_3$[957] to give the diamine. Amines react with *N*-tosylaziridines, in the presence of various catalysts or additives to give the corresponding diamine.[958] This reaction also takes place on activated silica.[959] The reaction of $LiNTf_2$ and an amine, in the presence of an *N*-alkyl aziridine gives the diamine.[960]

As with epoxides, tosyl-aziridines react with azide to generate azido tosylamines.[961] Reduction of the azide (**19-50**) gives the diamine. Silylazides, such as Me_3SiN_3, also react with aziridine derivatives to give the azidoamine.[962] This latter reaction can be catalyzed by $InCl_3$.[963]

[953]Crotti, P.; Favero, L.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* ***1994***, *35*, 7089.

[954]Chini, M.; Crotti, P.; Favero, L.; Macchia, F. *Tetrahedron Lett.* ***1994***, *35*, 761.

[955]For a review, see Dermer, O.C.; Ham, G.E. *Ethylenimine and Other Aziridines*, Academic Press, NY, ***1969***, pp. 262–268. See also, Scheuermann, J.E.W.; Ilyashenko, G.; Griffiths, D.V.; Watkinson, M. *Tetrahedron Asymmetry* ***2002***, *13*, 269.

[956]Sekar, G.; Singh, V.K. *J. Org. Chem.* ***1999***, *64*, 2537.

[957]Watson, I.D.G.; Yudin, A.K. *J. Org. Chem.* ***2003***, *68*, 5160.

[958]Examples include **$Yb(OTf)_3$**: Meguro, M.; Yamamoto, Y. *Heterocycles* ***1996***, *43*, 2473. **PBu_3**: Fan, R.-H.; Hou, X-L. *J. Org. Chem.* ***2003***, *68*, 726. **Aqueous media with β-cyclodextrin:** Reddy, M.A.; Reddy, L.R.; Bhanamathi, N.; Rao, K.R. *Chem. Lett.* ***2001***, 246. **$TaCl_5/SiO_2$:** Chandrasekhar, S.; Prakash, S.J.; Shyamsunder, T.; Ramachandar, T. *Synth. Commun.* ***2004***, *34*, 3865. **$InCl_3$**: Yadav, J.S.; Reddy, B.V.S.; Abraham, S.; Sabitha, G. *Tetrahedron Lett.* ***2002***, *43*, 1565; **$InBr_3$:** Yadav, J.S.; Reddy, B.V.S.; Rao, K.; Raj, K.S.; Prasad, A.R. *Synthesis* ***2002***, 1061. **$BiCl_3$:** Swamy, N.R.; Venkateswarlu, Y. *Synth. Commun.* ***2003***, *33*, 547. **$LiClO_4$**: Yadav, J.S.; Reddy, B.V.S.; Jyothivmai, B.; Murty, M.S.R. *Synlett* ***2002***, 53; Yadav, J.S.; Reddy, B.V.S.; Parimala, G.; Reddy, P.V. *Synthesis* ***2002***, 2383.

[959]Anand, R.V.; Pandey, G.; Singh, V.K. *Tetrahedron Lett.* ***2002***, *43*, 3975; Kumar, G.D.K.; Baskaran, S. *Synlett* ***2004***, 1719.

[960]Cossy, J.; Bellosta, V.; Alauze, V.; Desmurs, J.-R. *Synthesis* ***2002***, 2211.

[961]Bisai, A.; Pandey, G.; Pandey, M.K.; Singh, V.K. *Tetrahedron Lett.* ***2003***, *44*, 5839.

[962]Chandrasekhar, M.; Sekar, G.; Singh, V.K. *Tetrahedron Lett.* ***2000***, *41*, 10079.

[963]Yadav, J.S.; Reddy, B.V.S.; Kumar, G.M.; Murthy, Ch.V.S.R. *Synth. Commun.* ***2002***, *32*, 1797.

10-39 Amination of Alkanes

Amino-de-hydrogenation or Amination

$$R_3CH \quad + \quad NCl_3 \xrightarrow[0-10^{\circ}C]{AlCl_3} R_3CNH_2$$

Alkanes, arylalkanes, and cycloalkanes can be aminated, at tertiary positions only, by treatment with trichloroamine and aluminum chloride at 0–10°C.[964] For example, *p*-$MeC_6H_4CHMe_2$ gives *p*-$MeC_6H_4CMe_2NH_2$, methylcyclopentane gives 1-amino-1-methylcyclopentane, and adamantane gives 1-aminoadamantane, all in good yields. This is a useful reaction, since there are not many other methods for the preparation of *tert*-alkyl amines. The mechanism has been rationalized as an S_N1 process with H^- as the leaving group:[964]

$$NCl_3 \quad + \quad AlCl_3 \longrightarrow (Cl_2N{-}AlCl_3)^- \; Cl^+$$

$$R_3CH \xrightarrow{Cl+} R_3C^{\oplus} \xrightarrow{NCl_2^-} R_3CNCl_2 \xrightarrow[2\,H^+]{-2\,Cl^+} R_3CNH_2$$

It is noted than under photochemical conditions, ammonia opens cyclopropane derivatives to give the corresponding alkyl amine.[965] See also, **12-12**.

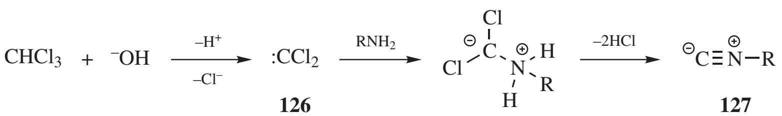
OS **V**, 35.

10-40 Formation of Isocyanides (Isonitriles)

Haloform-isocyanide transformation

$$CHCl_3 \quad + \quad RNH_2 \xrightarrow{-OH} R{-}\overset{\oplus}{N}{\equiv}C^{\ominus}$$

Reaction with chloroform under basic conditions is a common test for primary amines, both aliphatic and aromatic, since isocyanides (**126**) have very strong bad odors. The reaction probably proceeds by an S_N1cB mechanism with dichlorocarbene (**127**) as an intermediate.



126 **127**

The reaction can also be used synthetically for the preparation of isocyanides, although yields are generally not high.[966] An improved procedure has been reported.[967] When

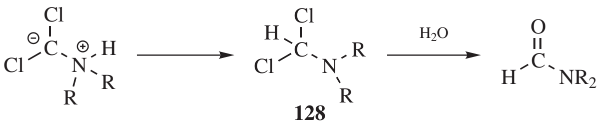
[964]Wnuk, T.A.; Chaudhary, S.S.; Kovacic, P. *J. Am. Chem. Soc.* ***1976***, *98*, 5678, and references cited therein.

[965]Yasuda, M.; Kojima, R.; Tsutsui, H.; Utsunomiya, D.; Ishii, K.; Jinnouchi, K.; Shiragami, T.; Yamashita, T. *J. Org. Chem.* ***2003***, *68*, 7618.

[966]For a review of isocyanides, see Periasamy, M.P.; Walborsky, H.M. *Org. Prep. Proced. Int.* ***1979***, *11*, 293.

[967]Weber, W.P.; Gokel, G.W. *Tetrahedron Lett.* ***1972***, 1637; Weber, W.P.; Gokel, G.W.; Ugi, I. *Angew. Chem. Int. Ed.* ***1972***, *11*, 530.

secondary amines are involved, the adduct **128** cannot lose 2 mol of HCl. Instead it is hydrolyzed to an *N,N*-disubstituted formamide.[968]



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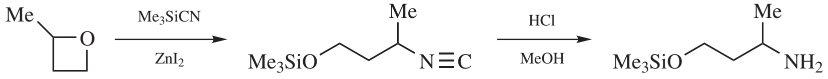
A completely different way of preparing isocyanides involves the reaction of epoxides or oxetanes with trimethylsilyl cyanide and zinc iodide to give the isocyanide **129**.[969]



129 **130**

The products can be hydrolyzed to protected hydroxy-amines, such as **130**.

OS **VI**, 232.

B. Attack by NHCOR

10-41 *N*-Alkylation or *N*-Arylation of Amides and Imides

Acylamino-de-halogenation

$$RX + {}^{\ominus}NHCOR' \longrightarrow RNHCOR'$$
$$ArX + {}^{\ominus}NHCOR' \longrightarrow ArNHCOR'$$

Amides are very weak nucleophiles,[970] far too weak to attack alkyl halides, so they must first be converted to their conjugate bases. By this method, unsubstituted amides can be converted to *N*-substituted, or *N*-substituted to *N,N*-disubstituted, amides.[971] Esters of sulfuric or sulfonic acids can also be substrates. Tertiary substrates give elimination. *O*-Alkylation is at times a side reaction.[972] Both amides and sulfonamides have been alkylated under phase-transfer conditions.[973] Lactams can be alkylated using similar procedures. Ethyl pyroglutamate (5-carboethoxy

[968]Saunders, M.; Murray, R.W. *Tetrahedron* ***1959***, *6*, 88; Frankel, M.B.; Feuer, H.; Bank, J. *Tetrahedron Lett.* ***1959***, no. 7, 5.

[969]Gassman, P.G.; Haberman, L.M. *Tetrahedron Lett.* ***1985***, *26*, 4971, and references cited therein.

[970]Brace, N.O. *J. Org. Chem.* ***1993***, *58*, 1804.

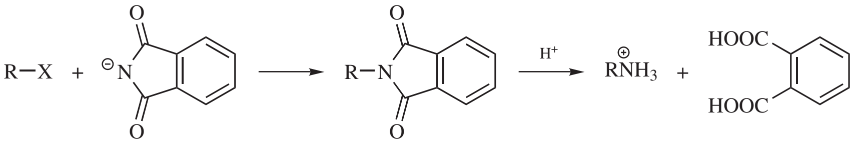
[971]For procedures, see Zawadzki, S.; Zwierzak, A. *Synthesis* ***1979***, 549; Yamawaki, J.; Ando, T.; Hanafusa, T. *Chem. Lett.* ***1981***, 1143; Sukata, K. *Bull. Chem. Soc. Jpn.* ***1985***, *58*, 838.

[972]For a review of alkylation of amides, see Challis, B.C.; Challis, J.A., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 734–754.

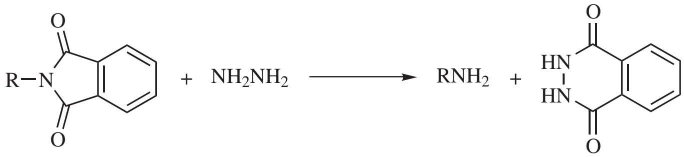
[973]Loupy, A.; Sansoulet, J.; Díez-Barra, E.; Carrillo, J.R. *Synth. Commun.* ***1992***, *22*, 1661; Salvatore, R.N.; Shin, S.I.; Flanders, V.L.; Jung, K.w. *Tetrahedron Lett.* ***2001***, *42*, 1799.

2-pyrrolidinone) and related lactams were converted to *N*-alkyl derivatives via treatment with NaH (short contact time) followed by addition of the halide.[974] 2-Pyrrolidinone derivatives can be alkylated using a similar procedure.[975] Lactams can be reductively alkylated using aldehydes under catalytic hydrogenation conditions (reductive alkylation).[976] *N*-Aryl lactams can be prepared using Ph_3Bi and $Cu(OAc)_2$.[977] *N*-Arylation of sulfonamides has been reported using a palladium catalysis.[978] *N*-Alkenyl amides have been prepared from vinyl iodides and primary amides, using 10% CuI and two equivalents of cesium carbonate.[979] A related palladium-catalyzed vinylation of lactams was repeated using vinyl ethers as a substrate.[980] Oxazolidin-2-ones (a cyclic carbamate) can be *N*-alkylated using an alkyl halide with KF/Al_2O_3.[981]

The *Gabriel synthesis*[982] for converting halides to primary amines is based on this reaction. The halide is treated with potassium phthalimide and the product hydrolyzed (**16-60**):



It is obvious that the primary amines formed in this reaction will be uncontaminated by secondary or tertiary amines (unlike **10-31**). The reaction is usually rather slow, but can be conveniently speeded by the use of a dipolar aprotic solvent, such as DMF[983] or with a crown ether.[984] Hydrolysis of the phthalimide, whether acid or base catalyzed (acid catalysis is used far more frequently), is also usually very slow, and better procedures are generally used. A common one is the *Ing–Manske procedure*,[985] in which the phthalimide is heated with hydrazine in an exchange



[974]Simandan, T.; Smith, M.B. *Synth. Commun.* ***1996***, *26*, 1827; Keusenkothen, P.F.; Smith, M.B. *Synth. Commun.* ***1992***, *22*, 2935.

[975]Liu, H.; Ko, S.-B.; Josien, H.; Curran, D.P. *Tetrahedron Lett.* ***1995***, *36*, 8917.

[976]Fache, F.; Jacquot, L.; Lemaire, M. *Tetrahedron Lett.* ***1994***, *35*, 3313.

[977]Chan, D.M.T. *Tetrahedron Lett.* ***1996***, *37*, 9013.

[978]Burton, G.; Cao, P.; Li, G.; Rivero, R. *Org. Lett.* ***2003***, *5*, 4373.

[979]Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* ***2004***, *6*, 1809.

[980]Brice, J.L.; Meerdink, J.E.; Stahl, S.S. *Org. Lett.* ***2004***, *6*, 1845.

[981]Blass, B.E.; Drowns, M.; Harris, C.L.; Liu, S.; Portlock, D.E. *Tetrahedron Lett.* ***1999***, *40*, 6545.

[982]For a review, see Gibson, M.S.; Bradshaw, R.W. *Angew. Chem. Int. Ed.* ***1968***, *7*, 919.

[983]For example, see Sheehan, J.C.; Bolhofer, W.A. *J. Am. Chem. Soc.* ***1950***, *72*, 2786. See also, Landini, D.; Rolla, F. *Synthesis* ***1976***, 389.

[984]Soai, K.; Ookawa, A.; Kato, K. *Bull. Chem. Soc. Jpn.* ***1982***, *55*, 1671.

[985]Ing, H.R.; Manske, R.H.F. *J. Chem. Soc.* ***1926***, 2348.

reaction,[986] but other methods have been introduced, using Na_2S in aqueous THF or acetone,[987] $NaBH_4$-2-propanol followed by acetic acid;[988] and 40% aqueous methylamine.[989] *N*-aryl imides can be prepared from $ArPb(OAc)_3$ and NaH.[990]

An alternative to the Gabriel synthesis, in which alkyl halides can be converted to primary amines in good yields, involves treatment of the halide with the strong base guanidine followed by alkaline hydrolysis.[991] There are several alternative procedures.[992]

N-Alkyl amides or imides can also be prepared starting from alcohols by treatment of the latter with equimolar amounts of the amide or imide, Ph_3P, and diethyl azodicarboxylate (EtOOCN=NCOOEt) at room temperature (the Mitsunobu reaction, **10-17**).[993] A related reaction treats the alcohol with $ClCH{=}NMe_2^+Cl^-$, followed by potassium phthalimide and treatment with hydrazine give the amine.[994]

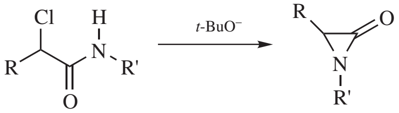
Amides can also be alkylated with diazo compounds, as in **10-34**. Salts of sulfonamides ($ArSO_2NH^-$) can be used to attack alkyl halides to prepare *N*-alkyl sulfonamides ($ArSO_2NHR$) that can be further alkylated to $ArSO_2NRR'$. Hydrolysis of the latter is a good method for the preparation of secondary amines. Secondary amines can also be made by crown ether assisted alkylation of $F_3CCONHR$ (R = alkyl or aryl) and hydrolysis of the resulting $F_3CCONRR'$.[995]

The reaction of a primary amide and benzaldehyde, in the presence of a silane and trifluoroacetic acid, leads to the corresponding *N*-benzylamide.[996] This transformation is a reductive alkylation. *N*-Alkynyl amides have been prepared by the copper-catalyzed reaction of 1-bromoalkynes and secondary amides.[997] 1-Haloalkynes

[986]See Khan, M.N. *J. Org. Chem.* ***1995***, *60*, 4536 for the kinetics of hydrazinolysis of phthalimides.
[987]Kukolja, S.; Lammert, S.R. *J. Am. Chem. Soc.* ***1975***, *97*, 5582.
[988]Osby, J.O.; Martin, M.G.; Ganem, B. *Tetrahedron Lett.* ***1984***, *25*, 2093.
[989]Wolfe, S.; Hasan, S.K. *Can. J. Chem.* ***1970***, *48*, 3572.
[990]López-Alvarado, P.; Avendaño, C.; Menéndez, J.C. *Tetrahedron Lett.* ***1992***, *33*, 6875.
[991]Hebrard, P.; Olomucki, M. *Bull. Soc. Chim. Fr.* ***1970***, 1938.
[992]For other methods, see Mukaiyama, T.; Taguchi, T.; Nishi, M. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 2797; Hendrickson, J.B.; Bergeron R.; Sternbach, D.D. *Tetrahedron* ***1975***, *31*, 2517; Clarke, C.T.; Elliott, J.D.; Jones, J.H. *J. Chem. Soc. Perkin Trans 1*, ***1978***, 1088; Mukaiyama, T.; Tsuji, T.; Watanabe, Y. *Chem. Lett.* ***1978***, 1057; Zwierzak, A.; Pilichowska, S. *Synthesis* ***1982***, 922; Calverley, M.J. *Synth. Commun.* ***1983***, *13*, 601; Harland, P.A.; Hodge, P.; Maughan, W.; Wildsmith, E. *Synthesis* ***1984***, 941; Grehn, L.; Ragnarsson, U. *Synthesis* ***1987***, 275; Dalla Croce, P.; La Rosa, C.; Ritieni, A. *J. Chem. Res. (S)* ***1988***, 346; Yinglin, H.; Hongwen, H. *Synthesis* ***1990***, 122.
[993]Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* ***1972***, *94*, 679; Grunewald, G.L.; Paradkar, V.M.; Pazhenchevsky, B.; Pleiss, M.A.; Sall, D.J.; Seibel, W.L.; Reitz, T.J. *J. Org. Chem.* ***1983***, *48*, 2321; Ślusarska, E.; Zwierzak, A. *Liebigs Ann. Chem.* ***1986***, 402; Kolasa, T.; Miller, M.J. *J. Org. Chem.* ***1987***, *52*, 4978; Sammes, P.G.; Thetford, D. *J. Chem. Soc. Perkin Trans. 1* ***1989***, 655.
[994]Barrett, A.G.M.; Braddock, D.C.; James, R.A.; Procopiou, P.A. *Chem. Commun.* ***1997***, 433.
[995]Nordlander, J.E.; Catalane, D.B.; Eberlein, T.H.; Farkas, L.V.; Howe, R.S.; Stevens, R.M.; Tripoulas, N.A. *Tetrahedron Lett.* ***1978***, 4987. For other methods, see Zwierzak, A.; Brylikowska-Piotrowicz, J. *Angew. Chem. Int. Ed.* ***1977***, *16*, 107; Briggs, E.M.; Brown, G.W.; Jiricny, J.; Meidine, M.F. *Synthesis* ***1980***, 295; Zwierzak, A.; Brylikowska-Piotrowicz, J. *Synthesis* ***1982***, 922
[996]Dubé, D.; Scholte, A.A. *Tetrahedron Lett.* ***1999***, *40*, 2295.
[997]Zhang, Y.; Hsung, R.P.; Tracey, M.R.; Kurtz, K.C.M.; Vera, E.L. *Org. Lett.* ***2004***, *6*, 1151; Frederick, M.O.; Mulder, J.A.; Tracey, M.R.; Hsung, R.P.; Huang, J.; Kurtz, K.C.M.; Shen, L.; Douglas, C.J. *J. Am. Chem. Soc.* ***2003***, *125*, 2368.

are typically prepared by base-induced elimination of 1,1-dihaloalkenes[998] or by direct halogenation of an alkyne with sodium or potassium hypohalite, prepared by reaction of the appropriate base with the halogen.[999]

Internal *N*-alkylation has been used to prepare the highly strained compounds α-lactams.[1000]



OS **I**, 119, 203, 271; **II**, 25, 83, 208; **III**, 151; **IV**, 810; **V**, 1064; **VI**, 951; **VII**, 501.

C. Other Nitrogen Nucleophiles

10-42 Formation of Nitro Compounds[1001]

Nitro-de-halogenation

$$RX + NO_2^- \longrightarrow RNO_2$$

Sodium nitrite can be used to prepare nitro compounds from primary or secondary alkyl bromides or iodides, but the method is of limited scope. Silver nitrite gives nitro compounds only when RX is a primary bromide or iodide.[1002] Nitrite esters are an important side product in all these cases (**10-22**) and become the major product (by an S_N1 mechanism) when secondary or tertiary halides are treated with silver nitrite. Alkyl nitro compounds can be prepared from the alkyl halide via the corresponding azide, by treatment with HOF in acetonitrile.[1003]

Nitro compounds can be prepared from alcohols using $NaNO_2$/AcOH/HCl.[1004]

OS **I**, 410; **IV**, 368, 454, 724.

10-43 Formation of Azides

Azido-de-halogenation

$$RX + N_3^- \longrightarrow RN_3$$
$$RCOX + N_3^- \longrightarrow RCON_3$$

[998]For an example involving bromine see Bestmann, H.-J.; Frey, H. *Liebigs Ann. Chem.* ***1980***, *12*, 2061.

[999]For examples with hypobromite, see Mozūraitis, R.; Būda, V.; Liblikas, I.; Unelius, C.R.; Borg-Karlson, A.-K. *J. Chem. Ecol.* ***2002***, *28*, 1191; Barbu, E.; Tsibouklis, J. *Tetrahedron Lett.* ***1996***, *37*, 5023; Brandsma, L.; Verkruijsse, H.D *Synthesis* ***1990***, 984.

[1000]See Quast, H.; Leybach, H. *Chem. Ber.* ***1991***, *124*, 849. For a review of α-lactams, see Lengyel, I.; Sheehan, J.C. *Angew. Chem. Int. Ed.* ***1968***, *7*, 25.

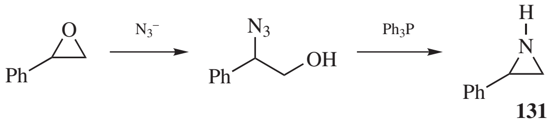
[1001]For reviews, see Larson, H.O. in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, pt. 1, Wiley, NY, ***1969***, pp. 325–339; Kornblum, N. *Org. React.* ***1962***, *12*, 101.

[1002]See Ballini, R.; Barboni, L.; Giarlo, G. *J. Org. Chem.* ***2004***, *69*, 6907.

[1003]Rozen, S.; Carmeli, M. *J. Am. Chem. Soc.* ***2003***, *125*, 8118.

[1004]Baruah, A.; Kalita, B.; Barua, N.C. *Synlett* ***2000***, 1064.

Alkyl azides can be prepared by treatment of the appropriate halide with azide ion.[1005] Phase-transfer catalysis,[1006] ultrasound,[1007] and the use of reactive clays[1008] are important variations. Substrates other than alkyl halides have been used,[1009] including OH,[1010] OMs, OTs,[1011] and OAc.[1012] Epoxides react with NaN_3 (**10-35**), $SnCl_2$/Mg with NaN_3,[1013] $TMSN_3$ and Ph_4SbOH[1014] or SmI_2,[1015] or $(i\text{-}Bu)_2AlHN_3Li$[1016] to give β-azido alcohols; these are easily converted to aziridines, **131**.[1017]



131

This conversion has been used as a key step in the preparation of optically active aziridines from optically active 1,2-diols (prepared by **15-48**).[1018] Even hydrogen can be the leaving group. Benzylic hydrogens have been replaced by N_3 by treatment with HN_3 in $CHCl_3$ in the presence of DDQ (p. 1710).[1019]

Tertiary alkyl azides can be prepared by stirring tertiary alkyl chlorides with NaN_3 and $ZnCl_2$ in CS_2[1020] or by treating tertiary alcohols with NaN_3 and CF_3COOH[1021] or with HN_3 and $TiCl_4$[1022] or BF_3.[1023] Aryl azides can be prepared from aniline and aniline derivatives.[1024] Acyl azides, which can be used in the Curtius reaction (**18-14**),

[1005]For reviews, see Scriven, E.F.V.; Turnbull, K. *Chem. Rev.* ***1988***, *88*, 297; Biffin, M.E.C.; Miller, J.; Paul, D.B., in Patai, S. *The Chemistry of the Azido Group*, Wiley, NY, ***1971***, pp. 57–119; Alvarez, S.G.; Alvarez, M.T. *Synthesis* ***1997***, 413.

[1006]See Reeves, W.P.; Bahr, M.L. *Synthesis* ***1979***, 823; Marti, M.J.; Rico, I.; Ader, J.C.; de Savignac, A.; Lattes, A. *Tetrahedron Lett.* ***1989***, *30*, 1245.

[1007]Priebe, H. *Acta Chem. Scand. Ser. B*, ***1984***, *38*, 895.

[1008]See, for example, Varma, R.S.; Naicker, K.P.; Aschberger, J. *Synth. Commun.* ***1999***, *29*, 2823.

[1009]See, for example, Hojo, K.; Kobayashi, S.; Soai, K.; Ikeda, S.; Mukaiyama, T. *Chem. Lett.* ***1977***, 635; Murahashi, T.; Tanigawa, Y.; Imada, Y.; Taniguchi, Y. *Tetrahedron Lett.* ***1986***, *27*, 227.

[1010]See, for example, Yu, C.; Liu, B.; Hu, L. *Org. Lett.* ***2000***, *2*, 1959.

[1011]Scriven, E.F.V.; Turnbull, K. *Chem. Rev.* ***1988***, *88*, 297, see p. 306.

[1012]Murahashi, S.; Taniguchi, Y.; Imada, Y.; Tanigawa, Y. *J. Org. Chem.* ***1989***, *54*, 3292.

[1013]Sarangi, C.; Das, N.B.; Nanda, B.; Nayak, A.; Sharma, R.P. *J. Chem. Res. (S)* ***1997***, 378.

[1014]Fujiwara, M.; Tanaka, M.; Baba, A.; Ando, H.; Souma, Y. *Tetrahedron Lett.* ***1995***, *36*, 4849.

[1015]Van de Weghe, P.; Collin, J. *Tetrahedron Lett.* ***1995***, *36*, 1649.

[1016]Youn, Y.S.; Cho, I.S.; Chung, B.Y. *Tetrahedron Lett.* ***1998***, *39*, 4337.

[1017]See, for example, Ittah, Y.; Sasson, Y.; Shahak, I.; Tsaroom, S.; Blum, J. *J. Org. Chem.* ***1978***, *43*, 4271. For the mechanism of the conversion to aziridines, see Pöchlauer, P.; Müller, E.P.; Peringer, P. *Helv. Chim. Acta* ***1984***, *67*, 1238.

[1018]Lohray, B.B.; Gao, Y.; Sharpless, K.B. *Tetrahedron Lett.* ***1989***, *30*, 2623.

[1019]Guy, A.; Lemor, A.; Doussot, J.; Lemaire, M. *Synthesis* ***1988***, 900.

[1020]Miller, J.A. *Tetrahedron Lett.* ***1975***, 2959. See also, Koziara, A.; Zwierzak, A. *Tetrahedron Lett.* ***1987***, *28*, 6513.

[1021]Balderman, D.; Kalir, A. *Synthesis* ***1978***, 24.

[1022]Hassner, A.; Fibiger, R.; Andisik, D. *J. Org. Chem.* ***1984***, *49*, 4237.

[1023]See, for example, Adam, G.; Andrieux, J.; Plat, M. *Tetrahedron* ***1985***, *41*, 399.

[1024]Liu, Q.; Tor, Y. *Org. Lett.* ***2003***, *5*, 2571.

can be similarly prepared from acyl halides, anhydrides,[1025] esters,[1026] or other acyl derivatives.[1027] Acyl azides can also be prepared form aldehydes using $SiCl_4$/NaN_3—MnO_2,[1028] $TMSN_3$/CrO_3[1029] or the Dess–Martiin periodinane (see p. 1723) with NaN_3.[1030]

α-Azido ketones have been prepared from ketones via reaction with [hydroxy (*p*-nitrobenzenesulfonyloxy)iodo]benzene followed by reaction with sodium azide.[1031]

OS **III**, 846; **IV**, 715; **V**, 273, 586; **VI**, 95, 207, 210, 910; **VII**, 433; **VIII**, 116; **IX**, 220; **X**, 378. See also, OS **VII**, 206.

10-44 Formation of Isocyanates and Isothiocyanates

Isocyanato-de-halogenation

Isothiocyanato-de-halogenation

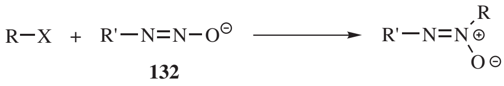
$$RX + NCO^- \longrightarrow RNCO$$
$$RX + NCS^- \longrightarrow RNCS$$

When the reagent is the thiocyanate ion, *S*-alkylation is an important side reaction (**10-30**), but the cyanate ion practically always gives exclusive *N*-alkylation.[478] Primary alkyl halides have been converted to isocyanates by treatment with sodium nitrocyanamide ($NaNCNNO_2$) and *m*-chloroperoxybenzoic acid, followed by heating of the initially produced $RN(NO_2)CN$.[1032] When alkyl halides are treated with NCO^- in the presence of ethanol, carbamates can be prepared directly (see **16-8**).[1033] Acyl halides give the corresponding acyl isocyanates and isothiocyanates.[1034] For the formation of isocyanides, see **10-75**.

OS **III**, 735.

10-45 Formation of Azoxy Compounds

Alkyl-*NNO*-azoxy-de-halogenation



132

[1025]For a review of acyl azides, see Lwowski, W., in Patai, S. *The Chemistry of the Azido Group*, Wiley, NY, ***1971***, pp. 503–554.

[1026]Rawal, V.H.; Zhong, H.M. *Tetrahedron Lett.* ***1994***, *35*, 4947.

[1027]Affandi, H.; Bayquen, A.V.; Read, R.W. *Tetrahedron Lett.* ***1994***, *35*, 2729. For a preparation using triphosgene, see Gumaste, V.K.; Bhawal, B.M.; Deshmukh, A.R.A.S. *Tetrahedron Lett.* ***2002***, *43*, 1345.

[1028]Elmorsy, S.S. *Tetrahedron Lett.* ***1995***, *36*, 1341.

[1029]Lee, J.G.; Kwak, K.H. *Tetrahedron Lett.* ***1992***, *33*, 3165.

[1030]Bose, D.S.; Reddy, A.V.N. *Tetrahedron Lett.* ***2003***, *44*, 3543.

[1031]Lee, J.C.; Kim, S.; Shin, W.C. *Synth. Commun.* ***2000***, *30*, 4271.

[1032]Manimaran, T.; Wolford, L.T.; Boyer, J.H. *J. Chem. Res. (S)* ***1989***, 331.

[1033]Argabright, P.A.; Rider, H.D.; Sieck, R. *J. Org. Chem.* ***1965***, *30*, 3317; Effenberger, F.; Drauz, K.; Förster, S.; Müller, W. *Chem. Ber.* ***1981***, *114*, 173.

[1034]For reviews of acyl isocyanates, see Tsuge, O., in Patai, S. *The Chemistry of Cyanates and Their Thio Derivatives*, pt. 1, Wiley, NY, ***1977***, pp. 445–506; Nuridzhanyan, K.A. *Russ. Chem. Rev.* ***1970***, *39*, 130; Lozinskii, M.O.; Pel'kis, P.S. *Russ. Chem. Rev.* ***1968***, *37*, 363.

The reaction between alkyl halides and alkanediazotates (**132**) gives azoxyalkanes.[1035] The R and R′ groups may be the same or different, but neither may be aryl or tertiary alkyl. The reaction is regioselective; only the isomer shown is obtained.

HALOGEN NUCLEOPHILES[1036]

10-46 Halide Exchange.

Halo-de-halogenation

$$RX + X'^- \rightleftharpoons RX' + X^-$$

Halide exchange, sometimes call the *Finkelstein reaction*, is an equilibrium process, but it is often possible to shift the equilibrium.[1037] The reaction is most often applied to the preparation of iodides and fluorides. Iodides can be prepared from chlorides or bromides by taking advantage of the fact that sodium iodide, but not the bromide or chloride, is soluble in acetone. When an alkyl chloride or bromide is treated with a solution of sodium iodide in acetone, the equilibrium is shifted by the precipitation of sodium chloride or bromide. Since the mechanism is S_N2, the reaction is much more successful for primary halides than for secondary or tertiary halides; sodium iodide in acetone can be used as a test for primary bromides or chlorides. Tertiary chlorides can be converted to iodides by treatment with excess NaI in CS_2, with $ZnCl_2$ as catalyst.[1038] Vinylic bromides give vinylic iodides with retention of configuration when treated with KI and a nickel bromide-zinc catalyst,[1039] or with KI and CuI in hot HMPA.[1040]

Fluorides[1041] are prepared by treatment of other alkyl halides with any of a number of fluorinating agents,[1042] among them anhydrous HF (which is useful only for

[1035]For reviews, see Yandovskii, V.N.; Gidaspov, B.V.; Tselinskii, I.V. *Russ. Chem. Rev.* ***1980***, *49*, 237; Moss, R.A. *Acc. Chem. Res.* ***1974***, *7*, 421.

[1036]For a review of the formation of carbon-halogen bonds, see Hudlický, M.; Hudlicky, T., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement D*, pt. 2, Wiley, NY, ***1983***, pp. 1021–1172.

[1037]For a list of reagents for alkyl halide interconversion, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 667–671.

[1038]Miller, J.A.; Nunn, M.J. *J. Chem. Soc. Perkin Trans. 1* ***1976***, 416.

[1039]Takagi, K.; Hayama, N.; Inokawa, S. *Chem. Lett.* ***1978***, 1435.

[1040]Suzuki, H.; Aihara, M.; Yamamoto, H.; Takamoto, Y.; Ogawa, T. *Synthesis* ***1988***, 236.

[1041]For reviews of the introduction of fluorine into organic compounds, see Mann, J. *Chem. Soc. Rev.* ***1987***, *16*, 381; Rozen, S.; Filler, R. *Tetrahedron* ***1985***, *41*, 1111; Hudlický, M. *Chemistry of Organic Fluorine Compounds*, pt. 2, Ellis Horwood, Chichester, ***1976***, pp. 24–169; Sheppard, W.A.; Sharts, C.M., *Organic Fluorine Chemistry*, W.A. Benjamin, NY, ***1969***, pp. 52–184, 409–430.

[1042]For reviews of the use of halogen exchange to prepare alkyl fluorides, see Sharts, C.M.; Sheppard, W.A. *Org. React.* ***1974***, *21*, 125; Hudlický, M. *Chemistry of Organic Fluorine Compunds*, pt. 2, Ellis Horwood, Chichester, ***1976***, pp. 91–136.

reactive substrates, e.g., benzylic or allylic), AgF, KF,[1043] HgF_2, Et_3N•2HF,[1044] 4-Me-$C_6H_4IF_2$,[1045] and $Me_2SiF_2Ph^+$ $^-NBu_4$.[1046] The equilibria in these cases are shifted because the alkyl fluoride once formed has little tendency to react, owing to the extremely poor leaving-group ability of fluorine. Phase-transfer catalysis of the exchange reaction is a particularly effective way of preparing both fluorides and iodides.[1047]

Primary alkyl chlorides can be converted to bromides with ethyl bromide, *N*-methyl-2-pyrrolidinone and a catalytic amount of NaBr,[1048] with LiBr under phase-transfer conditions,[1049] and with Bu_4N^+ Br^-.[1050] Primary bromides were converted to chlorides with TMSCl/imidazole in hot DMF.[1051] For secondary and tertiary alkyl chlorides, treatment in CH_2Cl_2 with excess gaseous HBr and an anhydrous $FeBr_3$ catalyst has given high yields[1052] (this procedure is also successful for chloride-to-iodide conversions). Alkyl chlorides or bromides can be prepared from iodides by treatment with HCl or HBr in the presence of HNO_3, making use of the fact that the leaving I^- is oxidized to I_2 by the HNO_3.[1053] Primary iodides give the chlorides when treated with PCl_5 in $POCl_3$.[1054] Alkyl fluorides and chlorides are converted to the bromides and iodides (and alkyl fluorides to the chlorides) by heating with the corresponding HX in excess amounts.[1055]

OS **II**, 476; **IV**, 84, 525; **VIII**, 486; **IX**, 502.

10-47 Formation of Alkyl Halides from Esters of Sulfuric and Sulfonic Acids

Halo-de-sulfonyloxy-substitution, and so on

$$ROSO_2R' + X^- \longrightarrow RX$$

[1043]See Mąkosza, M.; Bujok, R. *Tetrahedron Lett.* ***2002***, *43*, 2761.
[1044]Giudicelli, M.B.; Picq, D.; Veyron B. *Tetrahedron Lett.* ***1990***, *31*, 6527. For an electrolytic procedure using Et_3•*n* HF see Sawaguchi, M.; Ayuba, S.; Nakamura, Y.; Fukuhara, J.; Hara, S.; Yoneda, N. *Synlett* ***2000***, 999.
[1045]Sawaguchi, M.; Hara, S.; Nakamura, Y.; Ayuba, S.; Kukuhara, T.; Yoneda, N. *Tetrahedron* ***2001***, 57, 3315.
[1046]Kvíala, J.; Mysík, P.; Paleta, O. *Synlett* ***2001***, 547.
[1047]For reviews, see Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Academic Press, NY, ***1978***, pp. 112–125; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, ***1977***, pp. 117–124. See also, Clark, J.H.; Macquarrie, D.J. *Tetrahedron Lett.* ***1987***, *28*, 111; Bram, G.; Loupy, A.; Pigeon, P. *Synth. Commun.* ***1988***, *18*, 1661.
[1048]Willy, W.E.; McKean, D.R.; Garcia, B.A. *Bull. Chem. Soc. Jpn.* ***1976***, *49*, 1989. See also, Babler, J.H.; Spina, K.P. *Synth. Commun.* ***1984***, *14*, 1313.
[1049]Loupy, A.; Pardo, C. *Synth. Commun.* ***1988***, *18*, 1275.
[1050]Bidd, I.; Whiting, M.C. *Tetrahedron Lett.* ***1984***, *25*, 5949.
[1051]Peyrat, J.-F.; Figadère, B.; Cavé, A. *Synth. Commun.* ***1996***, *26*, 4563.
[1052]Yoon, K.B.; Kochi, J.K. *J. Org. Chem.* ***1989***, *54*, 3028.
[1053]Svetlakov, N.V.; Moisak, I.E.; Averko-Antonovich, I.G. *J. Org. Chem. USSR* ***1969***, *5*, 971.
[1054]Bartley, J.P.; Carman, R.M.; Russell-Maynard, J.K.L. *Aust. J. Chem.* ***1985***, *38*, 1879.
[1055]Namavari, M.; Satyamurthy, N.; Phelps, M.E.; Barrio, J.R. *Tetrahedron Lett.* ***1990***, *31*, 4973.

Alkyl sulfates, tosylates, and other esters of sulfuric and sulfonic acids can be converted to alkyl halides with any of the four halide ions.[1056] Neopentyl tosylate reacts with Cl^-, Br^-, or I^- without rearrangement in HMPA.[1057] Similarly, allylic tosylates can be converted to chlorides without allylic rearrangement by reaction with LiCl in the same solvent.[1058] Inorganic esters are intermediates in the conversion of alcohols to alkyl halides with $SOCl_2$, PCl_5, PCl_3, and so on (**10-48**), but are seldom isolated.

OS **I**, 25; **II**, 111, 404; **IV**, 597, 753; **V**, 545.

10-48 Formation of Alkyl Halides from Alcohols

Halo-de-hydroxylation

$$ROH + HX \longrightarrow RX$$
$$ROH + SOCl_2 \longrightarrow RCl$$

Alcohols can be converted to alkyl halides with several reagents,[1059] the most common of which are halogen acids HX and inorganic acid halides, such as $SOCl_2$,[1060] PCl_5, PCl_3, and $POCl_3$.[1061] The reagent HBr is usually used for alkyl bromides[1062] and HI for alkyl iodides. These reagents are often generated *in situ* from the halide ion and an acid such as phosphoric or sulfuric. The use of HI sometimes results in reduction of the alkyl iodide to the alkane (**19–53**) and, if the substrate is unsaturated, can also reduce the double bond.[1063] The reaction can be used to prepare primary, secondary, or tertiary halides, but alcohols of the isobutyl or neopentyl type often give large amounts of rearrangement products.[1064] Tertiary chlorides are easily made with concentrated HCl, but primary and secondary alcohols react with HCl so slowly that a catalyst, usually zinc chloride, is required.[1065] Primary alcohols give good yields of chlorides upon treatment with HCl in

[1056]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 697–700.

[1057]Stephenson, B.; Solladié, G.; Mosher, H.S. *J. Am. Chem. Soc.* ***1974***, *96*, 3171.

[1058]Stork, G.; Grieco, P.A.; Gregson, M. *Tetrahedron Lett.* ***1969***, 1393.

[1059]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 689–697.

[1060]For a review of thionyl chloride ($SOCl_2$), see Pizey, J.S. *Synthetic Reagents*, Vol. 1, Wiley, NY, ***1974***, pp. 321–357. See Mohanazadeh, F.; Momeni, A.R. *Org. Prep. Proceed. Int.* ***1996***, *28*, 492 for the use of $SOCl_2$ on silica gel.

[1061]For a review, see Salomaa, P.; Kankaanperä, A.; Pihlaja, K., in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, ***1971***, pt. 1, pp. 595–622.

[1062]Mas, J.-M.; Metivier, P. *Synth. Commun.* ***1992***, *22*, 2187; Chong, J.M.; Heuft, M.A.; Rabbat, P. *J. Org. Chem.* ***2000***, *65*, 5837.

[1063]Jones, R.; Pattison, J.B. *J. Chem. Soc. C* ***1969***, 1046.

[1064]For a reaction using $CeCl_3 \bullet 7\ H_2O$ and NaI with neopentyl alcohol to give 2-iodo-2-methylbutane see Di Deo, M.; Marcantoni, E.; Torregiani, E.; Bartoli, G.; Bellucci, M. C.; Bosco, M.; Sambri, L. *J. Org. Chem.* ***2000***, *65*, 2830.

[1065]Phase-transfer catalysts have been used instead of $ZnCl_2$; Landini, D.; Montanari, F.; Rolla, F. *Synthesis* ***1974***, 37.

HMPA.[1066] The inorganic acid chlorides $SOCl_2$,[1067] PCl_3, and so on, give primary, secondary, or tertiary alkyl chlorides with much less rearrangement than is observed with HCl. Iodides have been prepared by simply heating the alcohol with iodine.[1068] Trichloroisocyanuric acid (1,3,5-trichlorohexahydrotriazin-2,4,6-trione) and triphenylphosphine converts primary alcohols to the corresponding chloride.[1069]

Analogous bromides and iodides, especially PBr_3, have also been used, but they are more expensive and used less often than HBr or HI, although some of them may also be generated *in situ* (e.g., PBr_3 from phosphorous and bromine). Bromides have also been prepared with NaBr on doped Montmorillonite K10 clay[1070] and iodides were prepared by using NaI on KSF-clay,[1071] both using with microwave irradiation. Secondary alcohols always gives *some* rearranged bromides if another secondary position is available, even with PBr_3, PBr_5, or $SOBr_2$; thus 3-pentanol gives both 2- and 3-bromopentane. Such rearrangement can be avoided by converting the alcohol to a sulfonate and then using **10-47**,[1072] or by the use of phase transfer catalysis.[1073] Tertiary alcohols can be converted to the bromide with BBr_3 at 0°C.[1074] HF does not generally convert alcohols to alkyl fluorides.[1075] The most important reagent for this purpose is the commercially available diethylaminosulfur trifluoride Et_2NSF_3 (DAST),[1076] which converts primary, secondary, tertiary, allylic, and benzylic alcohols to fluorides in high yields under mild conditions.[1077] Fluorides have also been prepared from alcohols by treatment with SF_4,[1078] SeF_4,[1079] TsF,[1080] CsI/BF_3,[1081] and indirectly, by conversion to a sulfate or tosylate, and so on (**10-47**). Sodium iodide and Amberlyst-15[1082] or tosic acid and KI with microwave irradiation[1083] converts primary alcohols to the iodide. A mixture of IF_5, NEt_3

[1066]Fuchs, R.; Cole, L.L. *Can. J. Chem.* ***1975***, *53*, 3620.

[1067]For a transformation involving a primary benzylic alcohol, thionyl chloride and benzotriazole, see Chaudhari, S.S.; Akamanchi, K.G. *Synlett* ***1999***, 1763.

[1068]Joseph, R.; Pallan, P.S.; Sudalai, A.; Ravindranathan, T. *Tetrahedron Lett.* ***1995***, *36*, 609.

[1069]Hiegel, G.A.; Rubino, M. *Synth. Commmun.* ***2002***, *32*, 2691.

[1070]Kad, G.L.; Singh, V.; Kaur, K.P.; Singh. J. *Tetrahedron Lett.* ***1997***, *38*, 1079.

[1071]Kad, G.L.; Kaur, J.; Bansal, P.; Singh, J. *J. Chem. Res. (S)* ***1996***, 188.

[1072]Cason, J.; Correia, J.S. *J. Org. Chem.* ***1961***, *26*, 3645.

[1073]Dakka, G.; Sasson, Y. *Tetrahedron Lett.* ***1987***, *28*, 1223.

[1074]Pelletier, J.D.; Poirier, D. *Tetrahedron Lett.* ***1994***, *35*, 1051.

[1075]For an exception, see Hanack, M.; Eggensperger, H.; Hähnle, R. *Liebigs Ann. Chem.* ***1962***, *652*, 96; See also, Politanskii, S.F.; Ivanyk, G.D.; Sarancha, V.N.; Shevchuk, V.U. *J. Org. Chem. USSR* ***1974***, *10*, 697.

[1076]For a review of this reagent, see Hudlický, M. *Org. React.* ***1988***, *35*, 513.

[1077]Middleton, W.J. *J. Org. Chem.* ***1975***, *40*, 574.

[1078]For reviews, see Wang, C.J. *Org. React.* ***1985***, *34*, 319; Kollonitsch, J. *Isr. J. Chem.* ***1978***, *17*, 53; Boswell, Jr., G.A.; Ripka, W.C.; Scribner, R.M.; Tullock, C.W. *Org. React.* ***1974***, *21*, 1.

[1079]Olah, G.A.; Nojima, M.; Kerekes, I. *J. Am. Chem. Soc.* ***1974***, *96*, 925.

[1080]Shimizu, M.; Nakahara, Y.; Yoshioka, H. *Tetrahedron Lett.* ***1985***, *26*, 4207. For another method, see Olah, G.A.; Li, X. *Synlett*, ***1990***, 267.

[1081]Hayat, S.; Atta-ur-Rahman, Khan, K.M.; Choudhary, M.I.; Maharvi, G.M.; Zia-Ullah; Bayer, E. *Synth. Commun.* ***2003***, *33*, 2531.

[1082]Tajbakhsh, M.; Hosseinzadeh, R.; Lasemi, Z. *Synlett* ***2004***, 635.

[1083]Lee, J.C.; Park, J.Y.; Yoo, E.S. *Synth. Commun.* ***2004***, *34*, 2095.

and excess KF[1084] or $(Cl_3CO)_2C{=}O$, bis(trichloromethyl)carbonate, and KF (which gives COF_2 *in situ*)with 18-crown-6[1085] also converts primary alcohols to primary fluorides.

Primary, secondary, and tertiary alcohols can be converted to any of the four halides by treatment with the appropriate NaX, KX, or NH_4X in polyhydrogen fluoride–pyridine solution.[1086] This method is even successful for neopentyl halides. Another reagent that converts neopentyl alcohol to neopentyl chloride, in 95% yield, is PPh_3—CCl_3CN.[1087] Ionic liquids can be used for halogenation, and bmim-Cl (1-*n*-butyl-3-methylimidazolium chloride) generates the chloride directly from the alcohol without any additional reagent.[1088]

Other reagents[1089] have also been used, including $ZrCl_4$/NaI,[1090] 2,4,6-trichloro [1,3,5]triazine (cyanuric acid) and DMF,[1091] Me_3SiCl and $BiCl_3$[1092] or Me_3SiCl and 5% $InCl_3$[1093] or simply Me_3SiCl in DMSO.[1094] Other specialized reagents include $(RO)_3PRX$[1095] and R_3PX_2[1096] (made from R_3P and X_2), which give good yields for primary (including neopentyl), secondary, and tertiary halides without rearrange-

[1084]Yoneda, N. Fukuhara, T. *Chem. Lett.* ***2001***, 222.

[1085]Flosser, D.A.; Olofson, R.A. *Tetrahedron Lett.* ***2002***, *43*, 4275.

[1086]Olah, G.A.; Welch, J.; Vankar, Y.D.; Nojima, M.; Kerekes, I.; Olah, J.A. *J. Org. Chem.* ***1979***, *44*, 3872. See also, Yin, J.; Zarkowsky, D.S.; Thomas, D.W.; Zhao, M.W.; Huffman, M.A. *Org. Lett.* ***2004***, *6*, 1465.

[1087]Matveeva, E.D.; Yalovskaya, A.I.; Cherepanov, I.A.; Kurts, A.L.; Bundel', Yu.G. *J. Org. Chem. USSR* ***1989***, *25*, 587.

[1088]Ren, R. X.; Wu, J. X. *Org. Lett.* ***2001***, *3*, 3727.

[1089]For some other reagents, not listed here, see Echigo, Y.; Mukaiyama, T. *Chem. Lett.* ***1978***, 465; Barton, D.H.R.; Stick, R.V.; Subramanian, R. *J. Chem. Soc. Perkin Trans. 1* ***1976***, 2112; Savel'yanov, V.P.; Nazarov, V.N.; Savel'yanova, R.T.; Suchkov, V.V. *J. Org. Chem. USSR* ***1977***, *13*, 604; Jung, M.E.; Hatfield, G.L. *Tetrahedron Lett.* ***1978***, 4483; Sevrin, M.; Krief, A. *J. Chem. Soc., Chem. Commun.* ***1980***, 656; Hanessian, S.; Leblanc, Y.; Lavallée, P. *Tetrahedron Lett.* ***1982***, *23*, 4411; Cristol, S.J.; Seapy, D.G. *J. Org. Chem.* ***1982***, *47*, 132; Richter, R.; Tucker, B. *J. Org. Chem.* ***1983***, *48*, 2625; Imamoto, T.; Matsumoto, T.; Kusumoto, T.; Yokoyama, M. *Synthesis* ***1983***, 460; Olah, G.A.; Husain, A.; Singh, B.P.; Mehrotra, A.K. *J. Org. Chem.* ***1983***, *48*, 3667; Toto, S.D.; Doi, J.T. *J. Org. Chem.* ***1987***, *52*, 4999; Camps, F.; Gasol, V.; Guerrero, A. *Synthesis* ***1987***, 511; Schmidt, S.P.; Brooks, D.W. *Tetrahedron Lett.* ***1987***, *28*, 767; Collingwood, S.P.; Davies, A.P.; Golding, B.T. *Tetrahedron Lett.* ***1987***, *28*, 4445; Kozikowski, A.P.; Lee, J. *Tetrahedron Lett.* ***1988***, *29*, 3053; Classon, B.; Liu, Z.; Samuelsson, B. *J. Org. Chem.* ***1988***, *53*, 6126; Munyemana, F.; Frisque-Hesbain, A.; Devos, A.; Ghosez, L. *Tetrahedron Lett.* ***1989***, *30*, 3077; Ernst, B.; Winkler, T. *Tetrahedron Lett.* ***1989***, *30*, 3081.

[1090]Firouzabadi, H.; Iranpoor, N.; Jafarpour, M. *Tetrahedron Lett.* ***2004***, *45*, 7451.

[1091]De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* ***2002***, *4*, 553.

[1092]Labrouillère, M.; LeRoux, C.; Oussaid, A.; Gaspard-Iloughmane, H.; Dubac, J. *Bull. Soc. Chim. Fr.* ***1995*** *132*, 522.

[1093]Yasuda, M.; Yamasaki, S.; Onishi, Y.; Baba, A. *J. Am. Chem. Soc.* ***2004***, *126*, 7186.

[1094]Snyder, D.C. *J. Org. Chem.* ***1995***, *60*, 2638.

[1095]Rydon, H.N. *Org. Synth.* ***VI***, 830.

[1096]Wiley, G.A.; Hershkowitz, R.L.; Rein, B.M.; Chung, B.C. *J. Am. Chem. Soc.* ***1964***, *86*, 964; Wiley, G.A.; Rein, B.M.; Hershkowitz, R.L. *Tetrahedron Lett.* ***1964***, 2509; Schaefer, J.P.; Weinberg, D.S. *J. Org. Chem.* ***1965***, *30*, 2635; Kaplan, L. *J. Org. Chem.* ***1966***, *31*, 3454; Weiss, R.G.; Snyder, E.I. *J. Org. Chem.* ***1971***, *36*, 403; Garegg, P.J.; Johansson, R.; Samuelsson, B. *Synthesis* ***1984***, 168; Sandri, J.; Viala, J. *Synth. Commun.* ***1992***, *22*, 2945.

ments.[1097] Similarly, Me_2SBr_2[1098] (prepared from Me_2S and Br_2), and a mixture of PPh_3 and CCl_4[1099] (or CBr_4[1100]).

$$ROH + Ph_3P + CCl_4 \longrightarrow RCl + Ph_3PO + HCCl_3$$

The last method converts allylic alcohols[1101] to the corresponding halides without allylic rearrangements[1102] and also cyclopropylcarbinyl alcohols to the halides without ring opening.[1103] A simple method that is specific for benzylic and allylic alcohols (and does not give allylic rearrangement) involves reaction with *N*-chloro- or *N*-bromosuccinimide and methyl sulfide.[1104] The specificity of this method is illustrated by the conversion, in 87% yield, of (*Z*)-$HOCH_2CH_2CMe{=}CHCH_2OH$ to (*Z*)-$HOCH_2CH_2Me{=}CHCH_2Cl$. Only the allylic OH group was affected. A mixture of NBS, $Cu(OTf)_2$ and diisopropylcarbodiimide converted primary alcohols to the corresponding bromide.[1105] The use of NCS gave the chloride and NIS gave the iodide under identical conditions. Thiols are converted to alkyl bromides by a similar procedure using PPh_3 and NBS.[1106]

Allylic and benzylic alcohols can also be converted to bromides or iodides with NaX-BF_3 etherate,[1107] and to iodides with AlI_3.[1108] A mixture of methanesulfonic acid and NaI also converts benzylic alcohols to benzylic iodides.[1109] Both (chlorophenylthio-methylene)dimethylammonium chloride[1110] and 2-chloro-1,3-dimethylimidazolinium chloride[1111] react with alcohols to give the corresponding chloride.

[1097]For reviews of reactions with these reagents, see Castro, B.R. *Org. React.* ***1983***, *29*, 1; Mackie, R.K., in Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, ***1979***; pp. 433–466.

[1098]Furukawa, N.; Inoue, T.; Aida, T.; Oae, S. *J. Chem. Soc., Chem. Commun.* ***1973***, 212.

[1099]For reviews, see Appel, R. *Angew. Chem. Int. Ed.* ***1975***, *14*, 801; Appel, R.; Halstenberg, M., in Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, ***1979***, pp. 387–431. For a discussion of the mechanism, see Slagle, J.D.; Huang, T.T.; Franzus, B. *J. Org. Chem.* ***1981***, *46*, 3526. For a similar reaction using hexachloroethane and bis-1,2-diphenylphosphinoethane see Pollastri, M.P.; Sagal, J.F.; Chang, G. *Tetrahedron Lett.* ***2001***, *42*, 2459.

[1100]Wagner, A.; Heitz, M.; Mioskowski, C. *Tetrahedron Lett.* ***1989***, *30*, 557. See also, Desmaris, L.; Percina, N.; Cottier, L.; Sinou, D. *Tetrahedron Lett.* ***2003***, *44*, 7589.

[1101]For a review of the conversion of allylic alcohols to allylic halides, see Magid, R.M. *Tetrahedron* ***1980***, *36*, 1901, pp. 1924–1926.

[1102]Snyder, E.I. *J. Org. Chem.* ***1972***, *37*, 1466; Axelrod, E.H.; Milne, G.M.; van Tamelen, E.E. *J. Am. Chem. Soc.* ***1973***, *92*, 2139.

[1103]Hrubiec, R.T.; Smith, M.B. *Synth. Commun.* ***1983***, *13*, 593.

[1104]Corey, E.J.; Kim, C.U.; Takeda, M. *Tetrahedron Lett.* ***1972***, 4339.

[1105]Li, Z.; Crosignani, S.; Linclau, B. *Tetrahedron Lett.* ***2003***, *44*, 8143; Crosignani, S.; Nadal, B.; Li, Z.; Linclau, B. *Chem. Commun.* ***2003***, 260.

[1106]Iranpoor, N.; Firouzabadi, H.; Aghapour, G. *Synlett* ***2001***, 1176.

[1107]Vankar, Y.D.; Rao, C.T. *Tetrahedron Lett.* ***1985***, *26*, 2717; Mandal, A.K.; Mahajan, S.W. *Tetrahedron Lett.* ***1985***, *26*, 3863; Bandgar, B.P.; Sadavarte, V.S.; Uppalla, L.S. *Tetrahedron Lett.* ***2001***, *42*, 951.

[1108]Sarmah, P.; Barua, N.C. *Tetrahedron* ***1989***, *45*, 3569.

[1109]Kamal, A.; Ramesh, G.; Laxman, N. *Synth. Commun.* ***2001***, *31*, 827.

[1110]Gomez, L.; Gellibert, F.; Wagner, A.; Mioskowski, C. *Tetrahedron Lett.* ***2000***, *41*, 6049.

[1111]Isobe, T.; Ishikawa, T. *J. Org. Chem.* ***1999***, *64*, 5832.

When the reagent is HX, the mechanism is S_N1cA or S_N2cA; that is, the leaving group is not ^-OH, but OH_2 (p. 496). The leaving group is not ^-OH with the other reagents either, since in these cases the alcohol is first converted to an inorganic ester, for example, ROSOCl with $SOCl_2$ (**10-22**). The leaving group is therefore ^-OSOCl or a similar group (**10-47**). These may react by the S_N1 or S_N2 mechanism and, in the case of ROSOCl, by the S_Ni mechanism[1112] (p. 468).

Trialkylsilyl ethers such as $ROSiMe_3$ are converted to the corresponding iodide with SiO_2–Cl/NaI.[1113]

OS **I**, 25, 36, 131, 142, 144, 292, 294, 533; **II**, 91, 136, 159, 246, 308, 322, 358, 399, 476; **III**, 11, 227, 370, 446, 698, 793, 841; **IV**, 106, 169, 323, 333, 576, 681; **V**, 1, 249, 608; **VI**, 75, 628, 634, 638, 781, 830, 835; **VII**, 210, 319, 356; **VIII**, 451. Also see, OS **III**, 818; **IV**, 278, 383, 597.

10-49 Formation of Alkyl Halides from Ethers

Halo-de-alkoxylation

$$ROR' + HI \longrightarrow RI + R'OH$$

Ethers can be cleaved by heating with concentrated HI or HBr.[1114] Hydrogen chloride is seldom successful,[1115] and HBr reacts more slowly than HI, but is often a superior reagent, since it causes fewer side reactions. Phase-transfer catalysis has also been used,[1116] and 47% HBr in ionic liquids has proven effective.[1117] Dialkyl ethers and alkyl aryl ethers can be cleaved. In the latter case the alkyl–oxygen bond is the one broken. As in **10-48**, the actual leaving group is not OR'^-, but OHR'. Although alkyl aryl ethers always cleave so as to give an alkyl halide and a phenol, there is no general rule for dialkyl ethers. Often cleavage occurs from both sides, and a mixture of two alcohols and two alkyl halides is obtained. However, methyl ethers are usually cleaved so that methyl iodide or bromide is a product. An excess of HI or HBr converts the alcohol product into alkyl halide, so that dialkyl ethers (but not alkyl aryl ethers) are converted to 2 equivalents of alkyl halide. This procedure is often carried out so that a mixture of only two products is obtained instead of four. *O*-Benzyl ethers are readily cleaved to the alcohol and the hydrocarbon via hydrogenolysis, and the most common methods are hydrogenation[1118] or

[1112]Schreiner, P.R.; Schleyer, P.v.R.; Hill, R.K. *J. Org. Chem.* ***1993***, *58*, 2822.

[1113]Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H. *Tetrahedron Lett.* ***2002***, *43*, 7139.

[1114]For reviews of ether cleavage in general, see Bhatt, M.V.; Kulkarni, S.U. *Synthesis* ***1983***, 249; Staude, E.; Patat, F., in Patai, S. *The Chemistry of the Ether Linkage*, Wiley, NY, ***1967***, p. 22. For a review of cleavage of aryl alkyl ethers, see Tiecco, M. *Synthesis* ***1988***, 749.

[1115]Cleavage with HCl has been accomplished in the presence of surfactants: Juršić, B. *J. Chem. Res. (S)* ***1989***, 284.

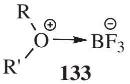
[1116]Landini, D.; Montanari, F.; Rolla, F. *Synthesis* ***1978***, 771.

[1117]In bmim BF_4, 1-*n*-butyl-3-methylimidazolium bromide: Boovanahalli, S.K.; Kim, D.W.; Chi, D.Y. *J. Org. Chem.* ***2004***, *69*, 3340.

[1118]Heathcock, C.H.; Ratcliffe, R. *J. Am. Chem. Soc.* ***1971***, *93*, 1746.

dissolving metal conditions (Na or K in ammonia).[1119] Heating in anisole with 3% $Sc(NTf_2)_3$[1120] or In metal in aqueous ethanol[1121] also cleaves benzyl ethers. Isoprenyl alkyl ethers are cleaved using iodine in dichloromethane,[1122] and allyl alkyl ethers are cleaved with Lewis acids under various conditions.[1123] The $OCH_2CH{=}CHPh$ unit of mixed allyl ethers ($O\text{-}CH_2CH{=}CH_2$ and $OCH_2CH{=}CHPh$) can be cleaved selectively under electrolytic conditions.[1124]

Cyclic ethers (usually tetrahydrofuran derivatives) can be similarly cleaved (see **10-50** for epoxides). Treatment of 2-methyltetrahydrofuran with acetyl chloride and $ZnCl_2$ gave primarily *O*-acetyl-4-chloro-1-pentanol.[1125] A mixture of Et_2NSiMe_3/2 MeI cleaved tetrahydrofuran to give the *O*-trimethylsilyl ether of 4-iodo-1-butanol.[1126] Ethers have also been cleaved with Lewis acids, such as BF_3, $Ce(OTf)_4$,[1127] $SiCl_4$/LiI/BF_3,[1128] BBr_3,[1129] or $AlCl_3$.[1130] In such cases, the departure of the OR is assisted by complex formation with the Lewis acid (see **133**).



133

Lewis acids are also used. The reagent NaI—BF_3 etherate selectively cleaves ethers in the order benzylic ethers > alkyl methyl ethers > aryl methyl ethers.[1131]

Dialkyl and alkyl aryl ethers are cleaved with iodotrimethylsilane:[1132] $ROR' + Me_3SiI \rightarrow RI + Me_3SiOR$.[1133] A more convenient and less expensive alternative, which gives the same products, is a mixture of chlorotrimethylsilane and

[1119]McCloskey, C.M. *Adv. Carbohydr. Chem.* ***1957***, *12*, 137; Reist, E.J.; Bartuska, V.J.; Goodman, L. *J. Org. Chem.* ***1964***, *29*, 3725.

[1120]Ishihara, K.; Hiraiwa, Y.; Yamamoto, H. *Synlett* ***2000***, 80.

[1121]Moody, C.J.; Pitts, M.R. *Synlett* ***1999***, 1575.

[1122]Vatèle, J.-M. *Synlett* ***2001***, 1989. For a procedure using DDQ, see Vatèle, J.-M. *Synlett* ***2002***, 507

[1123]Examples include SmI_2 in the presence of H_2O-*i*$PrNH_2$: Dahlen, A.; Sundgren, A.; Lahmann, M.; Oscarson, S.; Hilmersson, G. *Org. Lett.* ***2003***, *5*, 4085. $CeCl_3$/NaI: Bartoli, G.; Cupone, G.; Dalpozzo, R.; DeNino, A.; Maiuolo, L.; Marcantoni, E.; Procopio, A. *Synlett* ***2001***, 1897. $ZnCl_2$-$Pd(PPh_3)_4$: Chandrasekhar, S.; Reddy, Ch.R.; Rao, R.J. *Tetrahedron* ***2001, 57***, 3435. A ruthenium-catalyzed protocol: Tanaka, S.; Saburi, H.; Ishibashi, Y.; Kitamura, M. *Org. Lett.* ***2004***, *6*, 1873. See also, Murakami, H.; Minami, T.; Ozawa, F. *J. Org. Chem.* ***2004***, *69*, 4482.

[1124]Solis-Oba, A.; Hudlicky, T.; Koroniak, L.; Frey, D. *Tetrahedron Lett.* ***2001***, *42*, 1241.

[1125]Mimero, P.; Saluzzo, C.; Amouroux, R. *Tetrahedron Lett.* ***1994***, *35*, 1553.

[1126]Ohshita, J.; Iwata, A.; Kanetani, F.; Kunai, A.; Yamamoto, Y.; Matui, C. *J. Org. Chem.* ***1999***, *64*, 8024.

[1127]Khalafi-Nezhad, A.; Alamdari, R.F. *Tetrahedron* ***2001***, *57*, 6805.

[1128]Zewge, D.; King, A.; Weissman, S.; Tschaen, D. *Tetrahedron Lett.* ***2004***, *45*, 3729.

[1129]Press, J.B. *Synth. Commun.* ***1979***, *9*, 407; Niwa, H.; Hida, T.; Yamada, K. *Tetrahedron Lett.* ***1981***, *22*, 4239.

[1130]For a review, see Johnson, F., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 4, Wiley, NY, ***1965***, pp. 1–109.

[1131]Vankar, Y.D.; Rao, C.T. *J. Chem. Res. (S)* ***1985***, 232. See also, Mandal, A.K.; Soni, N.R.; Ratnam, K.R. *Synthesis* ***1985***, 274; Ghiaci, M.; Asghari, J. *Synth. Commun.* ***1999***, *29*, 973; Sharma, G.V.M.; Reddy, Ch.G.; Krishna, P.R. *J. Org. Chem.* ***2003***, *68*, 4574.

[1132]For a review of this reagent, see Olah, G.A.; Prakash, G.K.S.; Krishnamurti, R. *Adv. Silicon Chem.* ***1991***, *1*, 1.

[1133]Jung, M.E.; Lyster, M.A. *J. Org. Chem.* ***1977***, *42*, 3761; *Org. Synth.* ***VI***, 353.

NaI.[1134] Triphenyldibromophosphorane (Ph_3PBr_2) cleaves dialkyl ethers to give 2 moles of alkyl bromide.[1135] Alkyl aryl ethers can also be cleaved with LiI to give alkyl iodides and salts of phenols[1136] in a reaction similar to **10-51**. Allyl aryl ethers[1137] are efficiently cleaved with NaI/Me_3SiCl,[1138] $CeCl_3/NaI$[1139] or $ZrCl_4/NaBH_4$.[1140]

A closely related reaction is cleavage of oxonium salts.

$$R_3O^+X^- \longrightarrow RX + R_2O$$

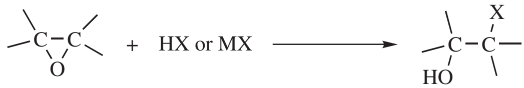
For these substrates, HX is not required, and X can be any of the four halide ions.

tert-Butyldimethylsilyl ethers ($ROSiMe_2CMe_3$) can be converted to bromides RBr by treatment with Ph_3PBr_2,[1141] $Ph_3P–CBr_4$,[1142] or BBr_3.[1143] Alcohols are often protected by conversion to this kind of silyl ether.[1144]

OS **I**, 150; **II**, 571; **III**, 187, 432, 586, 692, 753, 774, 813; **IV**, 266, 321; **V**, 412; **VI**, 353. See also, OS **VIII**, 161, 556.

10-50 Formation of Halohydrins from Epoxides

(3)*OC-seco*-Halo-de-alkoxylation



This is a special case of **10-49** and is frequently used for the preparation of halohydrins. In contrast to the situation with open-chain ethers and with larger rings, many epoxides react with all four hydrohalic acids, although with HF[1145] the reaction is unsuccessful with simple aliphatic and cycloalkyl epoxides.[1146] Hydrogen fluoride does react with more rigid epoxides, such as those in steroid systems. The reaction can applied to simple epoxides[1147] if polyhydrogen fluoride-pyridine

[1134] Morita, T.; Okamoto, Y.; Sakurai, H. *J. Chem. Soc., Chem. Commun.* ***1978***, 874; Olah, G.A.; Narang, S.C.; Gupta, B.G.B.; Malhotra, R. *J. Org. Chem.* ***1979***, *44*, 1247; Amouroux, R.; Jatczak, M.; Chastrette, M. *Bull. Soc. Chim. Fr.* ***1987***, 505.

[1135] Anderson Jr., A.G.; Freenor, F.J. *J. Org. Chem.* ***1972***, *37*, 626.

[1136] Harrison, I.T. *Chem. Commun.* ***1969***, 616.

[1137] For cleavage with Pd/C in KOH/MeOH, see Ishizaki, M.; Yamada, M.; Watanabe, S.-i.; Hoshino, O.; Nishitani, K.; Hayashida, M.; Tanaka, A.; Hara, H. *Tetrahedron* ***2004***, *60*, 7973.

[1138] Kamal, A.; Laxman, E.; Rao, N.V. *Tetrahedron Lett.* ***1999***, *40*, 371.

[1139] Thomas, R.M.; Reddy, G.S.; Iyengar, D.S. *Tetrahedron Lett.* ***1999***, *40*, 7293

[1140] Chary, K.P.; Mohan, G.H.; Iyengar, D.S. *Chem. Lett.* ***1999***, 1223.

[1141] Aizpurua, J.M.; Cossío, F.P.; Palomo, C. *J. Org. Chem.* ***1986***, *51*, 4941.

[1142] Mattes, H.; Benezra, C. *Tetrahedron Lett.* ***1987***, *28*, 1697.

[1143] Kim, S.; Park, J.H. *J. Org. Chem.* ***1988***, *53*, 3111.

[1144] See Corey, E.J.; Venkateswarlu, A. *J. Am. Chem. Soc.* ***1972***, *94*, 6190.

[1145] For a review of reactions HF with epoxides, see Sharts, C.M.; Sheppard, W.A. *Organic Fluorine Chemistry*, W.A. Benjamin, NY, ***1969***, pp. 52–184, 409–430. For a related review, see Yoneda, N. *Tetrahedron* ***1991***, *47*, 5329.

[1146] Shahak, I.; Manor, S.; Bergmann, E.D. *J. Chem. Soc. C* ***1968***, 2129.

[1147] Olah, G.A.; Meidar, D. *Isr. J. Chem.* ***1978***, *17*, 148.

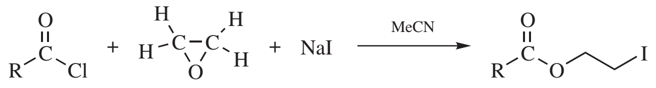
is the reagent. The reagent NEt_3•3 HF converts epoxides to fluorohydrins with microwave irradiation.[1148] The epoxide-to-fluorohydrin conversion has also been carried out with SiF_4 and a tertiary amine.[1149] Chloro-, bromo-, and iodohydrins can also be prepared[1150] by treating epoxides with Ph_3P and X_2,[1151] with $InBr_3$/NaBr/H_2O,[1152] LiBr on Amberlyst-15 resin,[1153] $TiCl_4$-LiCl,[1154] $SiCl_4$,[1155] I_2 with a SmI_2 catalyst,[1156] and LiI on silica gel.[1157] Epoxides can be converted directly to 1,2-dichloro compounds by treatment with $SOCl_2$ and pyridine,[1158] or with Ph_3P and CCl_4.[1159] These are two-step reactions: a halohydrin is formed first and is then converted by the reagents to the dihalide (**10-48**). As expected, inversion is found at both carbons. Meso epoxides were cleaved enantioselectively with the chiral B-halodiisopinocampheylboranes (see **15-16**), where the halogen was Cl, Br, or I.[1160] Diatomic iodine gives an iodohydrin with a 2,6-bis[2-(*o*-aminophenoxy) methyl]-4-bromo-1-methoxybenzene catalyst.[1161]

Bicyclic epoxides are usually opened to the *trans*-halohydrin. Unsymmetrical epoxides are usually opened to give mixtures of regioisomers. In a typical reaction, the halogen is delivered to the less sterically hindered carbon of the epoxide. In the absence of this structural feature, and in the absence of a directing group, relatively equal mixtures of regioisomeric halohydrins are expected. The phenyl is such as group in 1-phenyl-2-alkyl epoxides, where reaction with $POCl_3$/DMAP leads to the chlorohydrin with the chlorine on the carbon bearing the phenyl.[1162]

[1148]Inagaki, T.; Fukuhara, T.; Hara, S. *Synthesis* ***2003***, 1157.
[1149]Shimizu, M.; Yoshioka, H. *Tetrahedron Lett.* ***1988***, *29*, 4101. For other methods, see Muehlbacher, M.; Poulter, C.D. *J. Org. Chem.* ***1988***, *53*, 1026; Ichihara, J.; Hanafusa, T. *J. Chem. Soc., Chem. Commun.* ***1989***, 1848.
[1150]Einhorn, C.; Luche, J. *J. Chem. Soc., Chem. Commun.* ***1986***, 1368; Ciaccio, J.A.; Addess, K.J.; Bell, T.W. *Tetrahedron Lett.* ***1986***, *27*, 3697; Spawn, C.; Drtina, G.J.; Wiemer, D.F. *Synthesis* ***1986***, 315. For reviews, see Bonini, C.; Righi, G. *Synthesis* ***1994***, 225; Chini, M.; Crotti, P.; Gardelli, C.; Macchia, F. *Tetrahedron* ***1992***, *48*, 3805.
[1151]Palumbo, G.; Ferreri, C.; Caputo, R. *Tetrahedron Lett.* ***1983***, *24*, 1307. See Afonso, C.A.M.; Vieira, N.M.L.; Motherwell, W.B. *Synlett* ***2000***, 382.
[1152]Amantini, D.; Fringulli, F.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* ***2001***, *66*, 4463.
[1153]Bonini, C.; Giuliano, C.; Righi, G.; Rossi, L. *Synth. Commun.* ***1992***, *22*, 1863.
[1154]Shimizu, M.; Yoshida, A.; Fujisawa, T. *Synlett*, ***1992***, 204.
[1155]Denmark, S.E.; Barsanti, P.A.; Wong, K.-T.; Stavenger, R. *J. Org. Chem.* ***1998***, *63*, 2428; Tao, B.; Lo, M.M.-C.; Fu, G.C. *J. Am. Chem. Soc.* ***2001***, *123*, 353; Reymond, S.; Legrand, O.; Brunel, J.M.; Buono, G. *Eur. J. Org. Chem.* ***2001***, 2819.
[1156]Kwon, D.W.; Cho, M.S.; Kim, Y.H. *Synlett* ***2003***, 959.
[1157]Kotsuki, H.; Shimanouchi, T. *Tetrahedron Lett.* ***1996***, *37*, 1845.
[1158]Campbell, J.R.; Jones, J.K.N.; Wolfe, S. *Can. J. Chem.* ***1966***, *44*, 2339.
[1159]Isaacs, N.S.; Kirkpatrick, D. *Tetrahedron Lett.* ***1972***, 3869.
[1160]Srebnik, M.; Joshi, N.N.; Brown, H.C. *Isr. J. Chem.* ***1989***, *29*, 229.
[1161]Nikam, K.; Nashi, T. *Tetrahedron*, ***2002***, *58*, 10259. For an alternative reaction of iodine and a pyridine-containing macrocycle, see Sharghi, H.; Niknam, K.; Pooyan, M. *Tetrahedron* ***2001***, *57*, 6057. For the reaction of iodine with a Mn–salen catalyst see Sharghi, H.; Naeimi, H. *Bull. Chem. Soc. Jpn.* ***1999***, *72*, 1525.
[1162]Sartillo-Piscil, F.; Quinero, L.; Villegas, C.; Santacruz-Juárez, E.; de Parrodi, C.A. *Tetrahedron Lett.* ***2002***, *43*, 15.

When done in an ionic liquid with Me_3SiCl, styrene epoxide gives 2-chloro-2-phenylethanol.[1163] The reaction of thionyl chloride and poly(vinylpyrrolidinone) converts epoxides to the corresponding 2-chloro-1-carbinol.[1164] Bromine with a phenylhydrazine catalyst, however, converts epoxides to the 1-bromo-2-carbinol.[1165] An alkenyl group also leads to a halohydrin with the halogen on the carbon bearing the C=C unit.[1166] Epxoy carboxylic acids are another example. When NaI reacts at pH 4, the major regioisomer is the 2-iodo-3-hydroxy compound, but when $InCl_3$ is added, the major product is the 3-iodo-2-hydroxy carboxylic acid.[1167]

Acyl chlorides react with ethylene oxide in the presence of NaI to give 2-iodoethyl esters.[1168]



Acyl chlorides react with epoxides in the presence of a $Eu(dpm)_3$ catalyst[1169] [dpm = 1,1-bis(diphenylphosphino)methane] or a YCp_2Cl catalyst[1170] to give chloro esters.

A related reaction with epi-sulfides leads to 2-chlorothio-esters.[1171] Aziridines have been opened with $MgBr_2$ to give 2-haloamides in a related reaction.[1172] *N*-Tosyl aziridines react with KF•2 H_2O to give the 2-fluorotosylamine product.[1173]

OS **I**, 117; **VI**, 424; **IX**, 220.

10-51 Cleavage of Carboxylic Esters With Lithium Iodide

Iodo-de-acyloxy-substitution

$$\text{R'COOR} + \text{LiI} \xrightarrow[\Delta]{\text{pyridine}} \text{RI} + \text{R'COOLi}$$

[1163]Xu, L.-W.; Li, L.; Xia, C.-G.; Zhao, P.-Q. *Tetrahedron Lett.* ***2004***, *45*, 2435.

[1164]Tamami, B.; Ghazi, I.; Mahdavi, H. *Synth. Commun.* ***2002***, *32*, 3725.

[1165]Sharghi, H.; Eskandari, M.M. *Synthesis* ***2002***, 1519.

[1166]Ha, J.D.; Kim, S.Y.; Lee, S.J.; Kang, S.K.; Ahn, J.H.; Kim, S.S.; Choi, J.-K. *Tetrahedron Lett.* ***2004***, *45*, 5969.

[1167]Fringuelli, F.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* ***2001***, *66*, 4719. For a related SmI_2 ring opening of epoxy amides to give the 3-iodo-2-hydroxy compound, see Concellón, J.M.; Bardales, E.; Concellón, C.; García-Granda, S.; Díaz, M.R. *J. Org. Chem.* ***2004***, *69*, 6923.

[1168]Belsner, K.; Hoffmann, H.M.R. *Synthesis* ***1982***, 239. See also, Roloff, A. *Chimia*, ***1985***, *39*, 392; Iqbal, J.; Khan, M.A.; Srivastava, R.R. *Tetrahedron Lett.* ***1988***, *29*, 4985.

[1169]Taniguchi, Y.; Tanaka, S.; Kitamura, T.; Fujiwara, Y. *Tetrahedron Lett.* ***1998***, *39*, 4559.

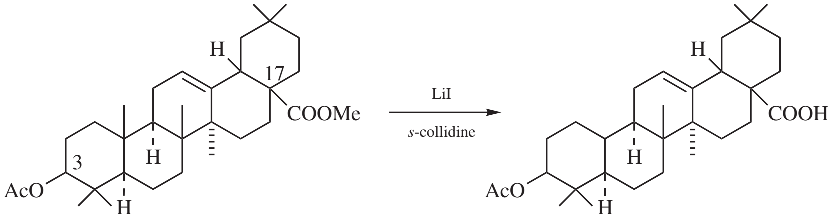
[1170]Qian, C.; Zhu, D. *Synth. Commun.* ***1994***, *24*, 2203.

[1171]Kameyama, A.; Kiyota, M.; Nishikubo, T. *Tetrahedron Lett.* ***1994***, *35*, 4571.

[1172]Righi, G.; D'Achille, R.; Bonini, C. *Tetrahedron Lett.* ***1996***, *37*, 6893.

[1173]Fan, R.-H.; Zhou, Y.-G.; Zhang, W.-X.; Hou, X.-L.; Dai, L.-X. *J. Org. Chem.* ***2004***, *69*, 335.

Carboxylic esters, where R is methyl or ethyl, can be cleaved by heating with lithium iodide in refluxing pyridine or a higher boiling amine.[1174] The reaction is useful where a molecule is sensitive to acid and base (so that **16-59** cannot be used) or where it is desired to cleave selectively only one ester group in a molecule containing two or more. For example, refluxing *O*-acetyloleanolic acid methyl ester



with LiI in *s*-collidine cleaved only the 17-carbomethoxy group, not the 3-acetyl group.[1175] Esters RCOOR′ and lactones can also be cleaved with a mixture of Me_3SiCl and NaI to give R′I and RCOOH.[1176] The reaction of acetyl chloride and allylic acetate leads to the allylic chloride.[1177]

10-52 Conversion of Diazo Ketones to α-halo Ketones

Hydro, halo-de-diazo-bisubstitution

$$RCOCHN_2 + HBr \longrightarrow RCOCH_2Br$$

When diazo ketones are treated with HBr or HCl, they give the respective α-halo ketones. HI does not give the reaction, since it reduces the product to a methyl ketone (**19-67**). α-Fluoro ketones can be prepared by addition of the diazo ketone to polyhydrogen fluoride–pyridine.[1178] This method is also successful for diazoalkanes.

Diazotization of α-amino acids in the above solvent at room temperature gives α-fluoro carboxylic acids.[1179] If this reaction is run in the presence of excess KCl or KBr, the corresponding α-chloro or α-bromo acid is obtained instead.[1180]

OS **III**, 119.

[1174]Taschner, E.; Liberek, B. *Rocz. Chem.* ***1956***, *30*, 323 [*Chem. Abstr.*, ***1957***, *51*, 1039]. For a review, see McMurry, J. *Org. React.* ***1976***, *24*, 187–224.

[1175]Elsinger, F.; Schreiber, J.; Eschenmoser, A. *Helv. Chim. Acta* ***1960***, *43*, 113.

[1176]Olah, G.A.; Narang, S.C.; Gupta, B.G.B.; Malhotra, R. *J. Org. Chem.* ***1979***, *44*, 1247. See also, Kolb, M.; Barth, J. *Synth. Commun.* ***1981***, *11*, 763.

[1177]Yadav, V.K.; Babu, K.G. *Tetrahedron* ***2003***, *59*, 9111.

[1178]Olah, G.A.; Welch, J. *Synthesis* ***1974***, 896; Olah, G.A.; Welch, J.; Vankar, Y.D.; Nojima, M.; Kerekes, I.; Olah, J.A. *J. Org. Chem.* ***1979***, *44*, 3872.

[1179]Olah, G.A.; Prakash, G.K.S.; Chao, Y.L. *Helv. Chim. Acta* ***1981***, *64*, 2528; Faustini, F.; De Munary, S.; Panzeri, A.; Villa, V.; Gandolfi, C.A. *Tetrahedron Lett.* ***1981***, *22*, 4533; Barber, J.; Keck, R.; Rétey, J. *Tetrahedron Lett.* ***1982***, *23*, 1549.

[1180]Olah, G.A.; Shih, J.; Prakash, G.K.S. *Helv. Chim. Acta* ***1983***, *66*, 1028.

10-53 Conversion of Amines to Halides

Halo-de-amination

$$RNH_2 \longrightarrow RNTs_2 \xrightarrow[DMF]{I^-} RI$$

Primary alkyl amines RNH_2 can be converted[1181] to alkyl halides by (*1*) conversion to $RNTs_2$ (p. 498) and treatment of this with I^- or Br^- in DMF,[385] or to N(Ts)—NH_2 derivatives followed by treatment with *N*-bromosuccinimide under photolysis conditions;[1182] (*2*) diazotization with *tert*-butylnitrite and a metal halide such as $TiCl_4$ in DMF;[1183] or (*3*) the Katritzky pyrylium–pyridinium method (p. 498).[1184] Alkyl groups can be cleaved from secondary and tertiary aromatic amines by concentrated HBr in a reaction similar to **10-49**, for example,[1185]

$$ArNR_2 + HBr \longrightarrow RBr + ArNHR$$

Tertiary aliphatic amines are also cleaved by HI, but useful products are seldom obtained. Tertiary amines can be cleaved by reaction with phenyl chloroformate:[1186] $R_3N + ClCOOPh \rightarrow RCl + R_2NCOOPh$. α-Chloroethyl chloroformate behaves similarly.[1187] Alkyl halides may be formed when quaternary ammonium salts are heated: $R_4N^+ X^- \rightarrow R_3N + RX$.[1188]

OS **VIII**, 119. See also, OS **I**, 428.

10-54 Conversion of Tertiary Amines to Cyanamides: The von Braun Reaction

Bromo-de-dialkylamino-substitution

$$R_3NH + BrCN \longrightarrow R_2NCN + RBr$$

The *von Braun reaction* involves the cleavage of tertiary amines by cyanogen bromide to give an alkyl bromide and a disubstituted cyanamide, and can be applied to many tertiary amines.[1189] Usually, the R group that cleaves is the one that gives the most reactive halide (e.g., benzyl or allyl). For simple alkyl groups, the smallest

[1181]For another method, see Lorenzo, A.; Molina, P.; Vilaplana, M.J. *Synthesis* ***1980***, 853.

[1182]Collazo, L.R.; Guziec, Jr., F.S.; Hu, W.-X.; Pankayatselvan, R. *Tetrahedron Lett.* ***1994***, *35*, 7911.

[1183]Doyle, M.P.; Bosch, R.J.; Seites, P.G. *J. Org. Chem.* ***1978***, *43*, 4120.

[1184]Katritzky, A.R.; Chermprapai, A.; Patel, R.C. *J. Chem. Soc. Perkin Trans. 1* ***1980***, 2901.

[1185]Chambers, R.A.; Pearson, D.E. *J. Org. Chem.* ***1963***, *28*, 3144.

[1186]Hobson, J.D.; McCluskey, J.G. *J. Chem. Soc. C* ***1967***, 2015. For a review, see Cooley, J.H.; Evain, E.J. *Synthesis* ***1989***, 1.

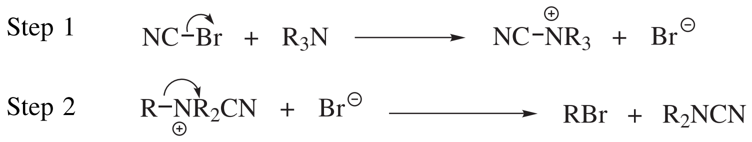
[1187]Olofson, R.A.; Martz, J.T.; Senet, J.; Piteau, M.; Malfroot, T. *J. Org. Chem.* ***1984***, *49*, 2081; Olofson, R.A.; Abbott, D.E. *J. Org. Chem.* ***1984***, *49*, 2795. See also, Campbell, A.L.; Pilipauskas, D.R.; Khanna, I.K.; Rhodes, R.A. *Tetrahedron Lett.* ***1987***, *28*, 2331.

[1188]For examples, see Ko, E.C.F.; Leffek, K.T. *Can. J. Chem.* ***1970***, *48*, 1865; ***1971***, *49*, 129; Deady, L.W.; Korytsky, O.L. *Tetrahedron Lett.* ***1979***, 451.

[1189]For a review, see Cooley, J.H.; Evain, E.J. *Synthesis* ***1989***, 1.

are the most readily cleaved. One or two of the groups on the amine may be aryl, but they do not cleave. Cyclic amines have been frequently cleaved by this reaction. Secondary amines also give the reaction, but the results are usually poor.[1190]

The mechanism consists of two successive nucleophilic substitutions, with the tertiary amine as the first nucleophile and the liberated bromide ion as the second:



The intermediate *N*-cyanoammonium bromide has been trapped, and its structure confirmed by chemical, analytical, and spectral data.[1191] The BrCN in this reaction has been called a *counterattack reagent*; that is, a reagent that accomplishes, in one flask, two transformations designed to give the product.[1192]

OS **III**, 608.

CARBON NUCLEOPHILES

In any heterolytic reaction in which a new carbon–carbon bond is formed,[1193] one carbon atoms attacks as a nucleophile and the other as an electrophile. The classification of a given reaction as nucleophilic or electrophilic is a matter of convention and is usually based on analogy. Although not discussed in this chapter, **11-8–11-25** and **12-16–12-21** are nucleophilic substitutions with respect to one reactant, though, following convention, we classify them with respect to the other. Similarly, all the reactions in this section would be called electrophilic substitution (aromatic or aliphatic) if we were to consider the reagent as the substrate.

In **10-56–10-65** the nucleophile is a "carbanion" part of an organometallic compound, often a Grignard reagent. There is much that is still not known about the mechanisms of these reactions and many of them are not nucleophilic substitutions at all. In those reactions that are nucleophilic substitutions, the attacking carbon brings a pair of electrons with it to the new C—C bond, whether or not free carbanions are actually involved. The connection of two alkyl or aryl groups is called *coupling*. Reactions **10-56–10-65** include both symmetrical and unsymmetrical coupling reactions. The latter are also called *cross-coupling reactions*. Other coupling reactions are considered in later chapters.

[1190]For a detailed discussion of the scope of the reaction and of the ease of cleavage of different groups, see Hageman, H.A. *Org. React.* ***1953***, 205.

[1191]Fodor, G.; Abidi, S. *Tetrahedron Lett.* ***1971***, 1369; Fodor, G.; Abidi, S.; Carpenter, T.C. *J. Org. Chem.* ***1974***, *39*, 1507. See also, Paukstelis, J.V.; Kim, M. *J. Org. Chem.* ***1974***, *39*, 1494.

[1192]For a review of counterattack reagents, see Hwu, J.R.; Gilbert, B.A. *Tetrahedron* ***1989***, *45*, 1233.

[1193]For a monograph that discusses most of the reactions in this section, see Stowell, J.C. *Carbanions in Organic Synthesis*, Wiley, NY, ***1979***. For a review, see Noyori, R., in Alper, H. *Transition Metal Organometallics in Organic Synthesis*, Vol. 1, Academic Press, NY, ***1976***, pp. 83–187.

10-55 Coupling With Silanes

De-silylalkyl-coupling

$$R{-}X + R^1_3Si{-}CH_2CH{=}CH_2 \longrightarrow R{-}CH_2CH{=}CH_2$$

Organosilanes $RSiMe_3$ or $RSiMe_2F$ (where R can be vinylic, allylic, or alkynyl) couple with vinylic, allylic, and aryl bromides and iodides R′X, in the presence of certain catalysts, to give RR′ in good yields.[1194] Allylsilanes react with allylic acetates in the presence of iodine.[1195] The transition-metal catalyzed coupling of silanes, particularly allyl silanes, is a mild method for incorporating alkyl fragments into a molecule.[1196] $PhSiMe_2Cl$ couples to give biphenyl in the presence of CuI and Bu_4NF,[1197] and vinyl silanes react with allylic carbonates and a palladium catalyst to give dienes.[1198] Allylsilanes have been coupled to substrates containing a benzotriazole unit, in the presence of BF_3•etherate.[1199] One variation used a silylmethyltin derivative in a palladium-catalyzed coupling with aryl iodides.[1200] Homoallyl silanes coupled to Ph_3BiF_2 in the presence of BF_3•OEt_2 to give the phenyl coupling product.[1201]

α-Silyloxy methoxy derivatives, $RCH(OMe)OSiR^1_3$, react with allyltrimethylsilane ($Me_3SiCH_2CH{=}CH_2$) in the presence of TiX_4 derivatives to give displacement of the OMe group and $RCH(OSiR^1_3)CH_2CH{=}CH_2$).[1202] A tertiary silyloxy group was displaced by allyl in the presence of $ZnCl_2$.[1203] Electrolysis with allyltrimethylsilane and RCH(OMe)SPh leads to $RCH(OMe)CH_2CH{=}CH_2$.[1204] Similar reaction with a dithioacetal leads to the allylic silane.[1205] Allylic acetates react with $Me_3SiSiMe_3$ and LiCl with a palladium catalyst to give the allyl silane.[1206] $RSiF_3$ reagents can also be used in coupling reaction with aryl halides.[1207]

[1194]Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* ***1988***, *53*, 918; ***1989***, *54*, 268; Cho, Y.S.; Kang, S.-H.; Han, J.-S.; Yoo, B.R.; Jung, I.N. *J. Am. Chem. Soc.* ***2001***, *123*, 5584.

[1195]Yadav, J.S.; Reddy, B.V.S.; Rao, K.V.; Raj, K.S.; Rao, P.P.; Prasad, A.R.; Gunasekar, D. *Tetrahedron Lett.* ***2004***, *45*, 6505.

[1196]For a ruthenium-catalyzed reaction, see Kakiuchi, F.; Tsuchiya, K.; Matsumoto, M.; Mizushima, E.; Chatani, N. *J. Am. Chem. Soc.* ***2004***, *126*, 12792. For a Cp_2TiCl_2-catalyzed reaction with allyl phenyl ether and chlorotrialkylsilanes, see Nii, S.; Terao, J.; Kambe, N. *Tetrahedron Lett.* ***2004***, *45*, 1699.

[1197]Kang, S.-K.; Kim, T.H.; Pyun, S.-J. *J. Chem. Soc. Perkin Trans. 1* ***1997***, 797.

[1198]Matsuhashi, H.; Hatanaka, Y.; Kuroboshi, M.; Hiyama, T. *Tetrahedron Lett.* ***1995***, *36*, 1539; Matsuhashi, H.; Asai, S.; Hirabayashi, K.; Hatanaka, Y.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* ***1997***, *70*, 1943.

[1199]Katritzky, A.R.; Mehta, S.; He, H.-Y.; Cui, X. *J. Org. Chem.* ***2000***, *65*, 4364.

[1200]Itami, K.; Kamei, T.; Yoshida, J.-i. *J. Am. Chem. Soc.* ***2001***, *123*, 8773.

[1201]Matano, Y.; Yoshimune, M.; Suzuki, H. *Tetrahedron Lett.* ***1995***, *36*, 7475.

[1202]Maeda, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* ***1997***, *62*, 6429.

[1203]Yokozawa, T.; Furuhashi, K.; Natsume, H. *Tetrahedron Lett.* ***1995***, *36*, 5243.

[1204]Yoshida, J.; Sugawara, M.; Kise, N. *Tetrahedron Lett.* ***1996***, *37*, 3157.

[1205]Fujiwara, T.; Takamori, M.; Takeda, T. *Chem. Commun.* ***1998***, 51.

[1206]Tsuji, Y.; Funato, M.; Ozawa, M.; Ogiyama, H.; Kajita, S.; Kawamura, T. *J. Org. Chem.* ***1996***, *61*, 5779.

[1207]Hatanaka, Y.; Goda, K.; Hiyama, T. *Tetrahedron Lett.* ***1994***, *35*, 6511; Matsuhashi, H.; Kuroboshi, M.; Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* ***1994***, *35*, 6507.

Allyl silanes react with epoxides, in the presence of BF_3•OEt_2 to give 2-allyl alcohols.[1208] The reaction of α-bromo lactones and $CH_2{=}CHCH_2Si(SiMe_3)_3$ and AIBN leads to the α-allyl lactone.[1209] On the other hand, silyl epoxides have been prepared from epoxides via reaction with *sec*-butyllithium and chlorotrimethylsilane.[1210] α-Silyl-*N*-Boc-amines were prepared in a similar manner from the *N*-Boc-amine.[1211] Arylsilanes were prepared by reaction of an aryllithium intermediate with $TfOSi(OEt)_3$.[1212] In the presence of BF_3•etherate, allyl silane and α-methoxy *N*-Cbz amines were coupled.[1213] Benzyl silanes coupled with allyl silanes to give $ArCH_2$—R derivatives in the presence of $VO(OEt)Cl_2$[1214] and allyltin compounds couple with allyl silanes in the presence of $SnCl_4$.[1215] Allyl silanes couple to the α-carbon of amines under photolysis conditions.[1216]

The reaction of a vinyl iodide with $(EtO)_3SiH$ with a palladium catalyst generated a good yield of the corresponding vinylsilane.[1217]

OSCV 10, 531.

10-56 Coupling of Alkyl Halides: The Wurtz Reaction

De-halogen-coupling

$$2\,RX + Na \longrightarrow RR$$

The coupling of alkyl halides by treatment with sodium to give a symmetrical product is called the *Wurtz reaction*. Side reactions (elimination and rearrangement) are so common that the reaction is seldom used. Mixed Wurtz reactions of two alkyl halides are even less feasible because of the number of products obtained. A somewhat more useful reaction (though still not very good) takes place when a mixture of an alkyl and an aryl halide is treated with sodium to give an alkylated aromatic compound (the *Wurtz–Fittig reaction*).[1218]

[1208]Burgess, L.E.; Gross, E.K.M.; Jurka, J. *Tetrahedron Lett.* ***1996***, *37*, 3255; Prestat, G.; Baylon, C.; Heck, M.-P.; Mioskowski, C. *Tetrahedron Lett.* ***2000***, *41*, 3829.

[1209]Chatgilialoglu, C.; Ferreri, C.; Ballestri, M.; Curran, D.P. *Tetrahedron Lett.* ***1996***, *37*, 6387; Chatgilialoglu, C.; Alberti, A.; Ballestri, M.; Macciantelli, D.; Curran, D.P. *Tetrahedron Lett.* ***1996***, *37*, 6391.

[1210]Hodgson, D.M.; Norsikian, S.L.M. *Org. Lett.* ***2001***, *3*, 461.

[1211]Harrison, J.R.; O'Brien, P.; Porter, D.W.; Smith, N.W. *Chem. Commun.* ***2001***, 1202.

[1212]Seganish, W.M.; DeShong, P. *J. Org. Chem.* ***2004***, *69*, 6790.

[1213]Matos, M.R.P.N.; Afonso, C.A.M.; Batey, R.A. *Tetrahedron Lett.* ***2001***, *42*, 7007.

[1214]Hirao, T.; Fujii, T.; Ohshiro, Y. *Tetrahedron Lett.* ***1994***, *35*, 8005.

[1215]Takeda, T.; Takagi, Y.; Takano, H.; Fujiwara, T. *Tetrahedron Lett.* ***1992***, *33*, 5381.

[1216]Pandey, G.; Rani, K.S.; Lakshimaiah, G. *Tetrahedron Lett.* ***1992***, *33*, 5107. See Gelas-Mialhe, Y.; Gramain, J.-C.; Louvet, A.; Remuson, R. *Tetrahedron Lett.* ***1992***, *33*, 73 for an internal coupling reaction of an allyl silane and an α-hydoxy lactam.

[1217]Murata, M.; Watanabe, S.; Masuda, Y. *Tetrahedron Lett.* ***1999***, *40*, 9255.

[1218]For an example, see Kwa, T.L.; Boelhouwer, C. *Tetrahedron* ***1970***, *25*, 5771.

However, the coupling of two aryl halides with sodium is impractical (but see **13-11**). Other metals have also been used to effect Wurtz reactions,[1219] notably silver, zinc,[1220] iron,[1221] activated copper,[1222] In,[1223] La,[1224] and manganese compounds.[1225] Lithium, under the influence of ultrasound, has been used to couple alkyl, aryl, and benzylic halides.[1226] Metallic nickel, prepared by the reduction of nickel halides with Li, dimerizes benzylic halides to give $ArCH_2CH_2Ar$.[1227] The coupling of alkyl halides has also been achieved electrochemically[1228] and photochemically.[1229] In a related reaction, Grignard reagents (**12-38**) have been coupled in the presence of trifluorosulfonic anhydride.[1230]

Tosylates and other sulfonates and sulfates couple with Grignard reagents,[1231] most often those prepared from aryl or benzylic halides.[1232] Alkyl sulfates and sulfonates generally make better substrates in reactions with Grignard reagents than the corresponding halides (**10-57**). The method is useful for primary and secondary R.

One type of Wurtz reaction that is quite useful is the closing of small rings, especially three-membered rings.[1233] For example, 1,3-dibromopropane can be converted to cyclopropane by Zn and NaI.[1234] Two highly strained molecules that

[1219]For a list of reagents, including metals and other reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 83–84.

[1220]See, for example, Nosek, J. *Collect. Czech. Chem. Commun.* ***1964***, *29*, 597.

[1221]Nozaki, H.; Noyori, R. *Tetrahedron* ***1966***, *22*, 2163; Onsager, O. *Acta Chem. Scand. Ser. B*, ***1978***, *32*, 15.

[1222]Ginah, F.O.; Donovan, T.A.; Suchan, S.D.; Pfennig, D.R.; Ebert, G.W. *J. Org. Chem.* ***1990***, *55*, 584.

[1223]Ranu, B.C.; Dutta, P.; Sarkar, A. *Tetrahedron Lett.* ***1998***, *39*, 9557.

[1224]Nishino, T.; Watanabe, T.; Okada, M.; Nishiyama, Y.; Sonoda, N. *J. Org. Chem.* ***2002***, *67*, 966.

[1225]$Mn/CuCl_2$: Ma, J.; Chan, T.-H. *Tetrahedron Lett.* ***1998***, *39*, 2499. $Mn_2(CO)_{10}/h\nu$: Gilbert, B.C.; Lindsay, C.I.; McGrail, P.T.; Parsons, A.F.; Whittaker, D.T.E. *Synth. Commun.* ***1999***, *29*, 2711.

[1226]Han, B.H.; Boudjouk, P. *Tetrahedron Lett.* ***1981***, *22*, 2757.

[1227]Inaba, S.; Matsumoto, H.; Rieke, R.D. *J. Org. Chem.* ***1984***, *49*, 2093. For some other reagents that accomplish this, see Sayles, D.C.; Kharasch, M.S. *J. Org. Chem.* ***1961***, *26*, 4210; Cooper, T.A. *J. Am. Chem. Soc. 1973*, *95*, 4158; Ho, T.; Olah, G.A. *Synthesis* ***1977***, 170; Ballatore, A.; Crozet, M.P.; Surzur, J. *Tetrahedron Lett.* ***1979***, 3073; Yamada, Y.; Momose, D. *Chem. Lett.* ***1981***, 1277; Iyoda, M.; Sakaitani, M.; Otsuka, H.; Oda, M. *Chem. Lett.* ***1985***, 127.

[1228]Folest, J.C.; Nédélec, J.Y.; Perichon, J. *J. Chem. Res. (S)* ***1989***, 394.

[1229]Ouchi, A.; Yabe, A. *Tetrahedron Lett.* ***1992***, *33*, 5359.

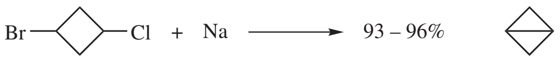
[1230]Nishiyama, T.; Seshita, T.; Shodai, H.; Aoki, K.; Kameyama, H.; Komura, K. *Chem. Lett.* ***1996***, 549.

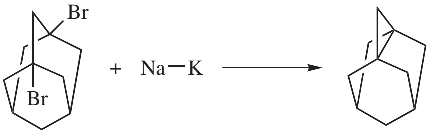
[1231]For a review, see Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 1277–1286.

[1232]For an example involving an allylic rearrangement (conversion of a silylalkyne to a silylallene), see Danheiser, R.L.; Tsai, Y.; Fink, D.M. *Org. Synth. 66*, 1.

[1233]For a review, see Freidlina, R.Kh.; Kamyshova, A.A.; Chukovskaya, E.Ts. *Russ. Chem. Rev.* ***1982***, *51*, 368. For reviews of methods of synthesizing cyclopropane rings, see, in Rappoport *The Chemistry of the Cyclopropyl Group*, pt. 1; Wiley, NY, ***1987***, the reviews by Tsuji, T.; Nishida, S. pp. 307–373, and Verhé, R.; De Kimpe, N. pp. 445–564.

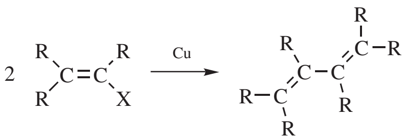
[1234]For a discussion of the mechanism, see Applequist, D.E.; Pfohl, W.F. *J. Org. Chem.* ***1978***, *43*, 867.





Tetracyclo[3.3.1.13,7.01,3]decane

have been prepared this way are bicyclobutane[1235] and tetracyclo[3.3.1.$1^{3,7}$.$0^{1,3}$]decane.[1236] Three- and four-membered rings can also be closed in this manner with certain other reagents,[1237] including benzoyl peroxide,[1238] *t*-BuLi,[1239] and lithium amalgam,[1240] as well as electrochemically.[1241]



134

Vinylic halides can be coupled to give 1,3-butadienes (**134**) by treatment with activated copper powder in a reaction analogous to the Ullmann reaction (**13-11**).[1242] This reaction is stereospecific, with retention of configuration at both carbons. Vinylic halides can also be coupled[1243] with Zn—$NiCl_2$,[1244] and with *n*-BuLi in ether in the presence of $MnCl_2$.[1245] The coupling reaction with vinyltin reagents and vinyl halides occurs with a palladium catalyst.[1246]

[1235]Wiberg, K.B.; Lampman, G.M. *Tetrahedron Lett.* ***1963***, 2173; Lampman, G.M.; Aumiller, J.C. *Org. Synth.* ***VI***, 133.

[1236]Pincock, R.E.; Schmidt, J.; Scott, W.B.; Torupka, E.J. *Can. J. Chem.* ***1972***, *50*, 3958.

[1237]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 175–184.

[1238]Kaplan, L. *J. Am. Chem. Soc.* ***1967***, *89*, 1753; *J. Org. Chem.* ***1967***, *32*, 4059.

[1239]Bailey, W.F.; Gagnier, R.P. *Tetrahedron Lett.* ***1982***, *23*, 5123.

[1240]Connor, D.S.; Wilson, E.R. *Tetrahedron Lett.* ***1967***, 4925.

[1241]Rifi, M.R. *J. Am. Chem. Soc.* ***1967***, *89*, 4442; *Org. Synth.* ***VI***, 153.

[1242]Cohen, T.; Poeth, T. *J. Am. Chem. Soc.* ***1972***, *94*, 4363.

[1243]See Wellmann, J.; Steckhan, E. *Synthesis* ***1978***, 901; Miyahara, Y.; Shiraishi, T.; Inazu, T.; Yoshino, T. *Bull. Chem. Soc. Jpn.* ***1979***, *52*, 953; Grigg, R.; Stevenson, P.; Worakun, T. *J. Chem. Soc., Chem. Commun.* ***1985***, 971; Vanderesse, R.; Fort, Y.; Becker, S.; Caubere, P. *Tetrahedron Lett.* ***1986***, *27*, 3517.

[1244]Takagi, K.; Mimura, H.; Inokawa, S. *Bull. Chem. Soc. Jpn.* ***1984***, *57*, 3517.

[1245]Cahiez, G.; Bernard, D.; Normant, J.F. *J. Organomet. Chem.* ***1976***, *113*, 99.

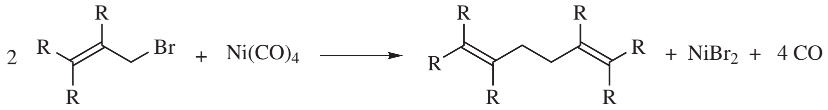
[1246]Paley, R.S.; de Dios, A.; de la Pradilla, R.F. *Tetrahedron Lett.* ***1993***, *34*, 2429.

Treatment of conjugated ketones with SmI_2 in HMPA gave the coupled diketone via Wurtz-type coupling.[1247]

It seems likely that the mechanism of the Wurtz reaction consists of two basic steps. The first is halogen-metal exchange to give an organometallic compound ($RX + M \rightarrow RM$), which in many cases can be isolated (**12-38**). Following this, the organometallic compound reacts with a second molecule of alkyl halide ($RX + RM \rightarrow RR$). This reaction and its mechanism are considered in the next section (**10-57**).

OS **III**, 157; **V**, 328, 1058; **VI**, 133, 153.

A variation of the Wurtz coupling uses other metals to mediate or facilitate the coupling. In certain cases, such variations can be synthetically useful.



Because of the presence of the 1,5-diene moiety in many naturally occurring compounds, methods that couple[1248] allylic groups[1249] are quite important. In one of these methods, allylic halides, tosylates, and acetates can be symmetrically coupled by treatment with nickel carbonyl[1250] at room temperature in a solvent, such as THF or DMF to give 1,5-dienes.[1251] The order of halide reactivity is $I > Br > Cl$. With unsymmetrical allylic substrates, coupling nearly always takes place at the less-substituted end. The reaction can be performed intramolecularly; large (11–20 membered) rings can be made in good yields (60–80%) by the use of high dilution.[1252] The mechanism of coupling likely involves reaction of the allylic compound with $Ni(CO)_4$ to give one or more π-allyl complexes, one of which may be the η^3-complex **135**. Loss of CO to give a π-allylnickel bromide (**136**) and ligand transfer leads to coupling and the final product. In some cases, the η^3-complexes **136** can be isolated from the solution and

[1247]Cabrera, A.; Rosas, N.; Sharma, P.; LeLagadec, R.; Velasco, L.; Salmón, M. *Synth. Commun.* ***1998***, *28*, 1103.

[1248]For a review of some allylic coupling reactions, see Magid, R.M. *Tetrahedron* ***1980***, *36*, 1901, see pp. 1910–1924.

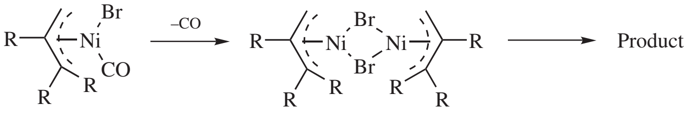
[1249]In this section are discussed methods in which one molecule is a halide. For other allylic coupling reactions, see **10-57**, **10-63**, and **10-60**.

[1250]For a review of the use of organonickel compounds in organic synthesis, see Tamao, K.; Kumada, M., in Hartley, F.R. *The Chemistry of the Metal-Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 819–887.

[1251]For reviews, see Collman, J.P. ; Hegedus, L.; Norton, J.R.; Finke, R. *Principles and Applications of Organotransition Metal Chemsitry*, 2nd ed., University Science Books, Mill Valley, CA, ***1987***, pp. 739–748; Billington, D.C. *Chem. Soc. Rev.* ***1985***, *14*, 93; Kochi, J.K. *Organometallic Mechanisms and Catalysis*, Academic Press, NY, ***1978***, pp. 398–408; Semmelhack, M.F. *Org. React.* ***1972***, *19*, 115, see pp. 162–170; Baker, R. *Chem. Rev.* ***1973***, *73*, 487, see pp. 512–517; Heimbach, P.; Jolly, P.W.; Wilke, G. *Adv. Organomet. Chem.* ***1970***, *8*, 29, see pp. 30–39.

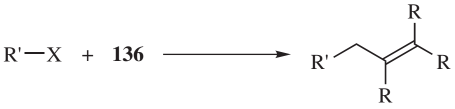
[1252]Corey, E.J.; Wat, E.K.W. *J. Am. Chem. Soc.* ***1967***, *89*, 2757. See also, Corey, E.J.; Helquist, P. *Tetrahedron Lett.* ***1975***, 4091; Reijnders, P.J.M.; Blankert, J.F.; Buck, H.M. *Recl. Trav. Chim. Pays-Bas* ***1978***, *97*, 30.

crystallized as stable solids.



135 **136**

Unsymmetrical coupling can be achieved by treating an alkyl halide directly with **136**, in a polar aprotic solvent,[1253] where coupling occurs at the less substituted end. There is evidence that free radicals are involved in such couplings.[1254] Hydroxy or carbonyl groups in the alkyl halide do not interfere. When **136** reacts with an allylic halide, a mixture of three products is obtained because of halogen–metal interchange. For example, allyl bromide treated with **136** prepared from methallyl bromide gave an approximately statistical mixture of 1,5-hexadiene, 2-methyl-1,5-hexadiene, and 2,5-dimethyl-1,5-hexadiene.[1255] Allylic tosylates can be symmetrically coupled with $Ni(CO)_4$.



Symmetrical coupling of allylic halides can prepared by heating with magnesium in ether,[1256] with a cuprous iodide–dialkylamide complex,[1257] or electrochemically.[1258] The coupling of two different allylic groups has been achieved by treatment of an allylic bromide with an allylic Grignard reagent in THF containing HMPA,[1259] or with an allylic tin reagent.[1260] This type of coupling can be achieved with almost no allylic rearrangement in the substrate (and almost complete allylic rearrangement in the reagent) by treatment of allylic halides with lithium allylic boron ate complexes ($RCH{=}CHCH_2B^{\ominus}\ R^2_3\ Li^+$).[1261] The reaction between primary and secondary halides and allyltributylstannane provides another method for unsymmetrical coupling

[1253]Corey, E.J.; Semmelhack, M.F. *J. Am. Chem. Soc.* ***1967***, *89*, 2755. For a review, see Semmelhack, M.F. *Org. React.* ***1972***, *19*, 115, see pp. 147–162. For a discussion of the preparation and handling of π-allylnickel halides, see Semmelhack, M.F. *Org. React.* ***1972***, *199*, 115, see pp. 144–146.

[1254]Hegedus, L.S.; Thompson, D.H.P. *J. Am. Chem. Soc.* ***1985***, *107*, 5663.

[1255]Corey, E.J.; Semmelhack, M.F.; Hegedus, L.S. *J. Am. Chem. Soc.* ***1968***, *90*, 2416.

[1256]Turk, A.; Chanan, H. *Org. Synth.* ***III***, 121.

[1257]Kitagawa, Y.; Oshima, K.; Yamamoto, H.; Nozaki, H. *Tetrahedron Lett.* ***1975***, 1859.

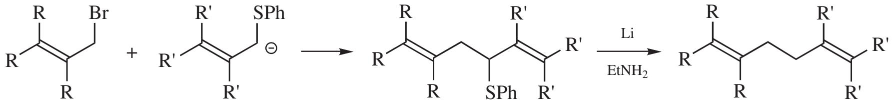
[1258]Tokuda, M.; Endate, K.; Suginome, H. *Chem. Lett.* ***1988***, 945.

[1259]Stork, G.; Grieco, P.A.; Gregson, M. *Tetrahedron Lett.* ***1969***, 1393; Grieco, P.A. *J. Am. Chem. Soc.* ***1969***, *91*, 5660.

[1260]Godschalx, J.; Stille, J.K. *Tetrahedron Lett.* ***1980***, *21*, 2599; ***1983***, *24*, 1905; Hosomi, A.; Imai, T.; Endo, M.; Sakurai, H. *J. Organomet. Chem.* ***1985***, *285*, 95. See also, Yanagisawa, A.; Norikate, Y.; Yamamoto, H. *Chem. Lett.* ***1988***, 1899.

[1261]Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* ***1981***, *103*, 1969.

$RX + CH_2{=}CHCH_2SnBu_3 \rightarrow RCH_2CH{=}CH_2$.[1262]



137

In another method for the coupling of two different allylic groups,[1263] a carbanion derived from a β,γ-unsaturated thioether couples with an allylic halide to give **137**.[1264] The product **137** contains an SPh group that must be removed (with Li in ethylamine) to give the 1,5-diene. Unlike most of the methods previously discussed, this method has the advantage that the coupling preserves the original positions and configurations of the two double bonds; no allylic rearrangements take place.

OS **III**, 121; **IV**, 748; **VI**, 722.

10-57 The Reaction of Alkyl Halides and Sulfonate Esters With Group I and II Organometallic Reagents[1265]

Alkyl-de-halogenation

$$R{-}Na(K)(Li) + R'X \longrightarrow R{-}R'$$

A variety of organometallic compounds[1266] have been used to couple with alkyl halides.[1267] Organosodium and organopotassium compounds are more reactive than Grignard reagents and couple even with less reactive halides. Organolithium reagents react with ether solvents, and their half-life in such solvents is known.[1268] The difficulty is in preparing and keeping them long enough for the alkyl halide to be added. Alkenes can be prepared by the coupling of vinylic lithium compounds with primary halides[1269] or of vinylic halides with alkyllithium reagents in the presence of a Pd or

[1262]See Keck, G.E.; Yates, J.B. *J. Am. Chem. Soc.* ***1982***, *104*, 5829; Migita, T.; Nagai, K.; Kosugi, M. *Bull. Chem. Soc. Jpn* ***1983***, *56*, 2480.

[1263]For other procedures, see Axelrod, E.H.; Milne, G.M.; van Tamelen, E.E. *J. Am. Chem. Soc.* ***1970***, *92*, 2139; Morizawa, Y.; Kanemoto, S.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* ***1982***, *23*, 2953.

[1264]Biellmann, J.F.; Ducep, J.B. *Tetrahedron Lett.* ***1969***, 3707.

[1265]For a review of the reactions in this section, see Naso, F.; Marchese, G., in Patai, S.; Rappoport, Z. *The Chemstry of Functional Groups, Supplement D*, pt. 2, Wiley, NY, ***1983***, pp. 1353–1449.

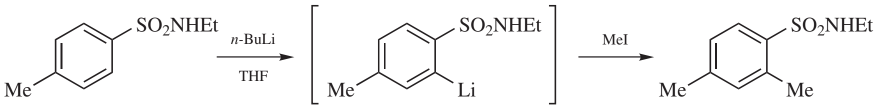
[1266]For lists of reagents and substrates, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 101–127.

[1267]For a review of the coupling of organic halides with organotin, mercury, and copper compounds catalyzed by palladium complexes, see Beletskaya, I.P. *J. Organomet. Chem.* ***1983***, *250*, 551. For a review of palladium-assisted coupling, see Larock, R.C. *Organomercury Compounds in Organic Synthesis*; Springer, NY, ***1985***, pp. 249–262.

[1268]Stanetty, P.; Mihovilovic, M.D. *J. Org. Chem.* ***1997***, *62*, 1514.

[1269]Millon, J.; Lorne, R.; Linstrumelle, G. *Synthesis* ***1975***, 434; Duhamel, L.; Poirier, J. *J. Am. Chem. Soc.* ***1977***, *99*, 8356.

Ru catalyst.[1270] Propargyl lithium reagents formed in the presence of mercuric salts couple with halides.[1271] Coupling of organolithium compounds with alkyl halides[1272] or aryl halides[1273] is possible.[1274] Unactivated aryl halides couple with alkyllithium reagents in THF.[1275] The reaction of *n*-butyllithium–TMEDA with a homoallylic alcohol [$CH_2{=}C(Me)CH_2CH_2OH$] leads to the allyllithium reagent, and subsequent reaction with an alkyl halide gives the substituted homoallylic alcohol [$CH_2{=}C(CH_2R)CH_2CH_2OH$].[1276] α-Lithioepoxides can also be formed, and reaction with an alkyl halide gives the substituted epoxide.[1277] Arylsilanes, such as 2-trimethylsilylpyridine, undergo a deprotonation reaction of a silyl methyl group when treated with *tert*-butyllithium to give the corresponding $ArMe_2SiCH_2Li$ reagent.[1278] Subsequent reaction with an alkyl halide leads to the substituted silane. Organolithium reagents formed by Li—H exchange in the presence of (−)-sparteine couple with alkyl halides with high asymmetric induction.[1279] The dianion of $PhC({=}Se)NHCH_2Ph$ was generated with *n*-butyllithium and reaction with bromocyclohexane gave the C-substituted derivative.[1280] Exchange of organotin compounds with organolithium reagents generates a new organolithium, and in one case intramolecular coupling in the presence of (−)-sparteine led to chiral pyrrolidine derivatives.[1281] It is noted that 1-lithioalkynes were coupled to alkyl halides in the presence of a palladium catalyst.[1282]



138 **139** **140**

Aryllithium reagents are formed by metal–halogen exchange with aryl halides or H-metal exchange with various aromatic compounds, and they react with alkyl halides. The reaction of **138** with *n*-butyllithium, for example, generated the

[1270]Murahashi, S.; Yamamura, M.; Yanagisawa, K.; Mita, N.; Kondo, K. *J. Org. Chem.* ***1979***, *44*, 2408.
[1271]Ma, S.; Wang, L. *J. Org. Chem.* ***1998***, *63*, 3497.
[1272]Snieckus, V.; Rogers-Evans, M.; Beak, P.; Lee, W.K.; Yum, E.K.; Freskos, J. *Tetrahedron Lett.* ***1994***, *35*, 4067.
[1273]Dieter, R.K.; Li, S.J. *J. Org. Chem.* ***1997***, *62*, 7726; Dieter, R.K.; Dieter, J.W.; Alexander, C.W.; Bhinderwala, N.S. *J. Org. Chem.* ***1996***, *61*, 2930. Also see, Beak, P.; Du, H. *J. Am. Chem. Soc.* ***1993***, *115*, 2516; Beak, P.; Wu, S.; Yum, E.K.; Jun, Y.M. *J. Org. Chem.* ***1994***, *59*, 276.
[1274]For example, see Brimble, M.A.; Gorsuch, S. *Aust. J. Chem.* ***1999***, *52*, 965.
[1275]Merrill, R.E.; Negishi, E. *J. Org. Chem.*, ***1974***, *39*, 3452. For another method, see Hallberg, A.; Westerlund, C. *Chem. Lett.*, ***1982***, 1993.
[1276]Yong, K.H.; Lotoski, J.A.; Chong, J.M. *J. Org. Chem.* ***2001***, *66*, 8248.
[1277]Marié, J.-C.; Curillon, C.; Malacria, M. *Synlett* ***2002***, 553.
[1278]Itami, K.; Kamei, T.; Mitsudo, K.; Nokami, T.; Yoshida, J.-i. *J. Org. Chem.* ***2001***, *66*, 3970.
[1279]Basu, A.; Beak, P. *J. Am. Chem. Soc.* ***1996***, *118*, 1575; Wu, S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* ***1996***, *118*, 715; Dieter, R.K.; Sharma, R.R. *Tetrahedron Lett.* ***1997***, *38*, 5937.
[1280]Murai, T.; Aso, H.; Kato, S. *Org. Lett.* ***2002***, *4*, 1407.
[1281]Serino, C.; Stehle, N.; Park, Y.S.; Florio, S.; Beak, P. *J. Org. Chem.* ***1999***, *64*, 1160.
[1282]Yang, L.-M.; Huang, L.-F.; Luh, T.-Y. *Org. Lett.* ***2004***, *6*, 1461.

aryllithium (**139**), which reacted with iodomethane to give **140**.[1283] When an aromatic ring has an attached heteroatom or an heteroatom-containing substituent, reaction with a strong base, such as an organolithium reagent, usually leads to an ortho lithiated species.[1284] Subsequent reaction with an electrophilic species gives the ortho substituted product. This phenomenon is known as *directed ortho metalation* (see **13-17**). This selectivity was discovered independently by Gilman and by Wittig in 1939–1940, when anisole was found to give ortho deprotonation in the presence of butyllithium.[1285] Alkylation ortho to a carbonyl is possible, and treatment of the acyl hydrazide PhC(=O)NHNMe$_2$ with *sec*-butyllithium and then iodoethane gave the ortho ethyl derivative.[1286] It is noted that aminonaphthalene derivatives were reacted with *tert*-butyllithium and aryllithium formation occurred on the ring distal to the amino group, and subsequent reaction with iodomethane gave methylation on that ring.[1287]

$$\mathrm{RX} + \underset{\mathbf{141}}{\mathrm{Li}\overset{3}{\mathrm{C}}\mathrm{H_3{-}C{\equiv}\overset{1}{C}{-}SiMe_3}} \longrightarrow \mathrm{RCH_2{-}C{\equiv}C{-}SiMe_3} \xrightarrow[\text{2. CN}^-]{\text{1. Ag}^+} \mathrm{R{-}CH_2{-}C{\equiv}C{-}H}$$

In a method for propargylating an alkyl halide without allylic rearrangement, the halide is treated with lithio-1-trimethylsilylpropyne (**141**), which is a lithium compound protected by an SiMe$_3$ group.[1288] Attack by the ambident nucleophile at its 1 position (which gives an allene) takes place only to a small extent, because of steric blockage by the large SiMe$_3$ group. The SiMe$_3$ group is easily removed by treatment with Ag$^+$ followed by CN$^-$. **141** is prepared by treating propynyllithium with Me$_3$SiCl to give MeC=CSiMe$_3$ from which a proton is removed with BuLi. R may be primary or allylic.[1289] On the other hand, propargylic halides can be alkylated with essentially complete allylic rearrangement, to give allenes, by treatment with Grignard reagents and metallic salts,[1290] or with dialkylcuprates R$_2$Cu.[1291]

Grignard reagents can be made to couple with alkyl halides in good yields by the use of certain catalysts,[1292] and stereocontrol is possible in these reactions.[1293] Among these are Cu(I) salts (see **10-58**), which permit the coupling of Grignard reagents with

[1283]MacNeil, S.L.; Familoni, O.B.; Snieckus, V. *J. Org. Chem.* ***2001***, *66*, 3662.

[1284]For reviews, see Snieckus, V. *Chem. Rev.* ***1990***, *90*, 879; Gschwend, H.W.; Rodriguez, H.R. *Org. React.* ***1979***, *26*, 1. See also, Green, L.; Chauder, B.; Snieckus, V. *J. Heterocyclic Chem.* ***1999***, *36*, 1453; Puterbaugh, W.H.; Hauser, C.R. *J. Org. Chem.* ***1964***, *29*, 853;

[1285]Gilman, H.; Bebb, R.L. *J. Am. Chem. Soc.* ***1939***, *61*, 109; Wittig, G.; Fuhrman, G. *Chem. Ber.* ***1940***, *73*, 1197.

[1286]McCombie, S.W.; Lin, S.-I.; Vice, S.F. *Tetrahedron Lett.* ***1999***, *40*, 8767.

[1287]Kraus, G.A.; Kim, J. *J. Org. Chem.* ***2002***, *67*, 2358.

[1288]Corey, E.J.; Kirst, H.A.; Katzenellenbogen, J.A. *J. Am. Chem. Soc.* ***1970***, *92*, 6314.

[1289]For an alternative procedure, see Ireland, R.E.; Dawson, M.I.; Lipinski, C.A. *Tetrahedron Lett.* ***1970***, 2247.

[1290]Pasto, D.J.; Chou, S.; Waterhouse, A.; Shults, R.H.; Hennion, G.F. *J. Org. Chem.* ***1978***, *43*, 1385; Jeffery-Luong, T.; Linstrumelle, G. *Tetrahedron Lett.* ***1980***, *21*, 5019.

[1291]Pasto, D.J.; Chou, S.; Fritzen, E.; Shults, R.H.; Waterhouse, A.; Hennion, G.F. *J. Org. Chem.* ***1978***, *43*, 1389. See also, Tanigawa, Y.; Murahashi, S. *J. Org. Chem.* ***1980***, *45*, 4536.

[1292]For reviews, see Erdik, E. *Tetrahedron* ***1984***, *40*, 641; Kochi, J.K. *Organometallic Mechanisms and Catalysis*, Academic Press, NY, ***1978***, pp. 374–398.

[1293]Bäckvall, J.-E.; Persson, E.S.M.; Bombrun, A. *J. Org. Chem.* ***1994***, *59*, 4126.

primary alkyl halides in good yield[1294] (organocopper salts are probably intermediates here). Allylic halides are more reactive than aliphatic alkyl halides, but copper salts have been used to facilitate coupling with alkylmagnesiumhalides.[1295] Iron(III)[1296] or palladium[1297] complexes are also used, and the latter allows the coupling of Grignard reagents and vinylic halides. Vinyl halides[1298] and aryl halides[1299] also couple with alkyl Grignard reagents in the presence of a catalytic amount of $Fe(acac)_3$, where acac = acetylacetonate, as do vinyl triflates with CuI[1300] or vinyl halides with a cobalt catalyst.[1301] Grignard reagents prepared from primary or secondary[1302] alkyl or aryl halides can be coupled with vinylic or aryl halides (see **13-9**) in high yields in the presence of a nickel(II) catalyst.[1303] When a chiral nickel(II) catalyst is used, optically active hydrocarbons can be prepared from achiral reagents.[1304] Neopentyl iodides also couple with aryl Grignard reagents in the presence of a nickel(II) catalyst.[1305]

Aryl halides, even when activated, generally do not couple with Grignard reagents, although certain transition-metal catalysts do effect this reaction in variable yields.[1306] The reaction with Grignard reagents proceeds better when OR can be the leaving group, providing that activating groups are present in the ring. The oxazoline group actives *o*-methoxy and *o*-fluoro groups to reaction with Grignard

[1294]Tamura, M.; Kochi, J.K. *J. Am. Chem. Soc.* ***1971***, *93*, 1485; Derguini-Boumechal, F.; Linstrumelle, G. *Tetrahedron Lett.* ***1976***, 3225; Mirviss, S.B. *J. Org. Chem.* ***1989***, *54*, 1948; Terao, J.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* ***2003***, *125*, 5646.

[1295]Tissot-Croset, K.; Alexakis, A. *Tetrahedron Lett.* ***2004***, *45*, 7375; Tissot-Croset, K.; Polet, D.; Alexakis, A. *Angew. Chem. Int. Ed.* ***2004***, *43*, 2426.

[1296]Smith, R.S.; Kochi, J.K. *J. Org. Chem.* ***1976***, *41*, 502; Walborsky, H.M.; Banks, R.B. *J. Org. Chem.* ***1981***, *46*, 5074; Molander, G.A.; Rahn, B.J.; Shubert, D.C.; Bonde, S.E. *Tetrahedron Lett.* ***1983***, *24*, 5449. An iron–salen catalyst has been used: see Bedford, R.B.; Bruce, D.W.; Frost, R.M.; Goodby, J.W.; Hird, M. *Chem. Commun.* ***2004***, 2822.

[1297]Ratovelomanana, V.; Linstrumelle, G.; Normant, J. *Tetrahedron Lett.* ***1985***, *26*, 2575; Minato, A.; Suzuki, K.; Tamao, K. *J. Am. Chem. Soc.* ***1987***, *109*, 1257; Frisch, A.C.; Shaikh, N.; Zapf, A.; Beller, M. *Angew. Chem. Int. Ed.* ***2002***, *41*, 4056. For other references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 386–392.

[1298]Cahiez, G.; Avedissian, H. *Synthesis* ***1998***, 1199; Nagano, T.; Hayashi, T. *Org. Lett.* ***2004***, *6*, 1297.

[1299]Fürstner, A.; Leitner, A. *Angew. Chem. Int. Ed.* ***2002***, *41*, 609; Martin, R.; Fürstner, A. *Angew. Chem. Int. Ed.* ***2004***, *43*, 3955.

[1300]Karlström, A.S.E.; Rönn, M.; Thorarensen, A. ; Bäckvall, J.-E. *J. Org. Chem.* ***1998***, *63*, 2517.

[1301]Cahiez, G.; Avedissian, H. *Tetrahedron Lett.* ***1998***, *39*, 6159.

[1302]Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* ***1984***, *106*, 158.

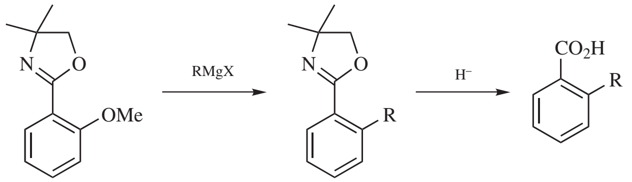
[1303]Corriu, R.J.P.; Masse, J.P. *J. Chem. Soc., Chem. Commun.* ***1972***, 144; Böhm, V.P.W.; Gstöttmayr, C.W.K.; Weskamp, T.; Hermann, W.A. *Angew. Chem. Int. Ed.* ***2001***, *40*, 3387; Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* ***2002***, *124*, 4222. For a review, see Kumada, M. *Pure Appl. Chem.* ***1980***, *52*, 669.

[1304]For a review, see Hayashi, T.; Kumada, M., in Morrison, J.D. *Asymmetic Synthesis*, Vol. 5, Academic Press, NY, ***1985***, pp. 147–169. See also, Cross, G.A.; Kellogg, R.M. *J. Chem. Soc., Chem. Commun.* ***1987***, 1746; Iida, A.; Yamashita, M. *Bull. Chem. Soc. Jpn.* ***1988***, *61*, 2365.

[1305]Yuan, K.; Scott, W.J. *Tetrahedron Lett.* ***1991***, *32*, 189.

[1306]See, for example, Sekiya, A.; Ishikawa, N. *J. Organomet. Chem.*, ***1976***, *118*, 349; ***1977***, *125*, 281; Tiecco, M.; Testaferri, L.; Tingoli, M.; Chianelli, D.; Wenkert, E. *Tetrahedron Lett.*, ***1982***, *23*, 4629; Bell, T.W.; Hu, L.; Patel, S.V. *J. Org. Chem.*, ***1987***, *52*, 3847; Bumagin, N.A.; Andryukhova, N.L.; Beletskaya, I.P. *Doklad. Chem.*, ***1987***, *297*, 524; Ozawa, F.; Kurihara, K.; Fujimori, M.; Hidaka, T.; Toyoshima, T.; Yamamoto, A. *Organometallics* ***1989***, *8*, 180.

reagents and organolithiums; the product **142** can be hydrolyzed after coupling[1307] (see **10-74**):



142

gem-Dichlorides have been prepared by coupling alkyl halides to $RCCl_3$ compounds electrochemically, in an undivided cell with a sacrificial anode:[1308]

$$RCCl_3 + R'X + 2\,e^- \longrightarrow RCCl_2R' + Cl^- + X^-$$

R′ could also be Cl, in which case the product bears a CCl_3 group.[1309]

Much study has been devoted to the mechanisms of these reactions,[1310] but firm conclusions are still lacking, in part because the mechanisms vary depending on the metal, the R group, the catalyst, if any, and the reaction conditions. Two basic pathways can be envisioned: a nucleophilic substitution process (which might be S_N1 or S_N2) and a free-radical mechanism. This could be an SET pathway, or some other route that provides radicals. In either case the two radicals R• and R′• would be in a solvent cage:

$$RX + R'M \longrightarrow \left[\begin{matrix} R\cdot + R'\cdot \\ + MX \end{matrix}\right] \longrightarrow RR'$$

Solvent cage

It is necessary to postulate the solvent cage because, if the radicals were completely free, the products would be about 50% RR′, 25% RR, and 25% R′R′. This is generally not the case; in most of these reactions RR′ is the predominant or exclusive product.[1311] An example where an S_N2 mechanism has been demonstrated (by the finding of inversion of configuration at R) is the reaction between allylic or benzylic lithium reagents with secondary halides.[1312] The fact that in some of these cases the

[1307]For a review of oxazolines in aromatic substitutions, see Reuman, M.; Meyers, A.I. *Tetrahedron*, ***1985***, *41*, 837. For the similar use of oxazoles, see Cram, D.J.; Bryant, J.A.; Doxsee, K.M. *Chem. Lett.*, ***1987***, 19.
[1308]Nédélec, J.; Aït Haddou Mouloud, H.; Folest, J.; Périchon, J. *J. Am. Chem. Soc.* ***1988***, *53*, 4720.
[1309]For the transformation $RX \rightarrow RCF_3$, see Chen, Q.; Wu, S. *J. Chem. Soc., Chem. Commun.* ***1989***, 705.
[1310]For a review, see Beletskaya, I.P.; Artamkina, G.A.; Reutov, O.A. *Russ. Chem. Rev.* ***1976***, *45*, 330.
[1311]When a symmetrical distribution of products *is* found, this is evidence for a free-radical mechanism: the solvent cage is not efficient and breaks down.
[1312]Sauer, J.; Braig, W. *Tetrahedron Lett.* ***1969***, 4275; Sommer, L.H.; Korte, W.D. *J. Org. Chem.* ***1970***, *35*, 22; Korte, W.D.; Kinner, L.; Kaska, W.C. *Tetrahedron Lett.* ***1970***, 603. See also, Schlosser, M.; Fouquet, G. *Chem. Ber.* ***1974***, *107*, 1162, 1171.

reaction can be successfully applied to aryl and vinylic substrates indicates that a simple S_N process cannot be the only mechanism. One possibility is that the reagents first undergo an exchange reaction: ArX + RM → RX + ArM, and then a nucleophilic substitution takes place. On the other hand, there is much evidence that many coupling reactions involving organometallic reagents with simple alkyl groups occur by free-radical mechanisms. Among the evidence[1313] is the observation of CIDNP in reactions of alkyl halides with simple organolithium reagents[1314] (see p. 269), the detection of free radicals by esr spectroscopy[1315] (p. 277), and the formation of 2,3-dimethyl-2,3-diphenylbutane when the reaction was carried out in the presence of cumene[1316] (this product is formed when a free-radical abstracts a hydrogen from cumene to give $PhCMe_2$, which dimerizes). Evidence for free-radical mechanisms has also been found for the coupling of alkyl halides with simple organosodium compounds (Wurtz),[1317] with Grignard reagents,[1318] and with lithium dialkylcopper reagents (see **10-58**).[1319] Free radicals have also been implicated in the metal-ion-catalyzed coupling of alkyl and aryl halides with Grignard reagents.[1320]

A much older reaction is the coupling of alkyl halides with Grignard reagents.[1321] Grignard reagents have the advantage that they are usually simpler to prepare than the corresponding R'_2CuLi (see **10-58**), but the reaction is much narrower in scope. Grignard reagents couple only with active halides: allylic (though allylic rearrangements are common) and benzylic. They also couple with tertiary alkyl halides, but generally in low or moderate yields.[1322]

Aryl Grignard reagents usually give better yields in these reactions than alkyl Grignard reagents. Aryl triflates couple with arylmagnesium halides in the presence

[1313]For other evidence, see Muraoka, K.; Nojima, M.; Kusabayashi, S.; Nagase, S. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 761.

[1314]Ward, H.R.; Lawler, R.G.; Cooper, R.A. *J. Am. Chem. Soc.* ***1969***, *91*, 746; Lepley, A.R.; Landau, R.L. *J. Am. Chem. Soc.* ***1969***, *91*, 748; Podoplelov, A.V.; Leshina, T.V.; Sagdeev, R.Z.; Kamkha, M.A.; Shein, S.M. *J. Org. Chem. USSR* ***1976***, *12*, 488. For a review, see Ward, H.R.; Lawler, R.G.; Cooper, R.A., in Lepley, A.R.; Closs, G.L. *Chemically Induced Magnetic Polarization*, Wiley, NY, ***1973***, pp. 281–322.

[1315]Russell, G.A.; Lamson, D.W. *J. Am. Chem. Soc.* ***1969***, *91*, 3967.

[1316]Bryce-Smith, D. *Bull. Soc. Chim. Fr.* ***1963***, 1418.

[1317]Garst, J.F.; Cox, R.H. *J. Am. Chem. Soc.* ***1970***, *92*, 6389; Kasukhin, L.F.; Gragerov, I.P. *J. Org. Chem. USSR* ***1971***, *7*, 2087; Garst, J.F.; Hart, P.W. *J. Chem Soc. Chem. Commun.* ***1975***, 215.

[1318]Gough, R.G.; Dixon, J.A. *J. Org. Chem.* ***1968***, *33*, 2148; Ward, H.R.; Lawler, R.G.; Marzilli, T.A. *Tetrahedron Lett.* ***1970***, 521; Kasukhin, L.F.; Ponomarchuk, M.P.; Buteiko, Zh.F. *J. Org. Chem. USSR* ***1972***, *8*, 673; Singh, P.R.; Tayal, S.R.; Nigam, A. *J. Organomet. Chem.* ***1972***, *42*, C9.

[1319]Ashby, E.C.; Coleman, D. *J. Org. Chem.* ***1987***, *52*, 4554; Bertz, S.H.; Dabbagh, G.; Mujsce, A.M. *J. Am. Chem. Soc.* ***1991***, *113*, 631.

[1320]Norman, R.O.C.; Waters, W.A. *J. Chem. Soc.* ***1957***, 950; Frey Jr., F.W. *J. Org. Chem.* ***1961***, *26*, 5187; Slaugh, L.H. *J. Am. Chem. Soc.* ***1961***, *83*, 2734; Davies, D.I.; Done, J.N.; Hey, D.H. *J. Chem. Soc. C* ***1969***, 1392, 2021, 2056; Abraham, M.H.; Hogarth, M.J. *J. Organomet. Chem.* ***1968***, *12*, 1, 497; Tamura, M.; Kochi, J.K. *J. Am. Chem. Soc.* ***1971***, *93*, 1483, 1485, 1487; *J. Organomet. Chem.* ***1971***, *31*, 289; ***1972***, *42*, 205; Lehr, G.F.; Lawler, R.G. *J. Am. Chem. Soc.* ***1986***, *106*, 4048.

[1321]For reviews, see Raston, C.L.; Salem, G., in Hartley, F.R. *The Chemistry of the Metal-Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 161–306, 269–283; Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 1046–1165.

[1322]See, for example, Ohno, M.; Shimizu, K.; Ishizaki, K.; Sasaki, T.; Eguchi, S. *J. Org. Chem.* ***1988***, *53*, 729.

of a palladium catalyst,[1323] as do vinyl halides with RMgX with a palladium[1324] or nickel catalyst.[1325] It is also possible to couple alkynylmagnesium halides with aryl iodides in the presence of palladium catalysts.[1326] A silica-supported phosphine–palladium (0) medium was used to couple arylmagnesium halides with aryl iodides.[1327] Aryl Grignard reagents couple with alkyl halides, including neopentyl iodide, in the presence of $ZnCl_2$ and a nickel catalyst.[1328]

In some cases, vinyl halides can be coupled. An aryl Grignard reagent was coupled to a vinyl iodide in the presence of an iron catalyst.[1329] Butylmagnesium chloride was coupled to vinyl triflates with $Fe(acac)_3$.[1330] The palladium-catalyzed coupling of arylmagnesium halides and vinyl bromides has also been reported.[1331]

Because Grignard reagents react with the C=O group (**16-24**, **16-82**), they cannot be used to couple with halides containing ketone, COOR, or amide functions. Although the coupling of Grignard reagents with ordinary alkyl halides is usually not useful for synthetic purposes, small amounts of symmetrical coupling product are commonly formed while Grignard reagents are being prepared.

For symmetrical coupling of organometallic reagents (2RM → RR), see **14-24** and **14-25**.

OS **I**, 186; **III**, 121; **IV**, 748; **VI**, 407; **VII**, 77, 172, 326, 485; **VIII**, 226, 396; **IX**, 530; **X**, 332, 396.

10-58 Reaction of Alkyl Halides and Sulfonate Esters with Organocuprates

Alkyl-de-halogenation

$$RX + R'_2CuLi \longrightarrow R{-}R'$$

The reagents lithium dialkylcopper[1332] (dialkyl cuprates, also called *Gilman reagents*)[1333] react with alkyl bromides, chlorides, and iodides in ether or THF to

[1323]Kamikawa, T.; Hayashi, T. *Synlett*, ***1997***, 163.

[1324]Hoffmann, R.W.; Gieson, V.; Fuest, M. *Liebigs Ann. Chem.* ***1993***, 629.

[1325]Babudri, F.; Fiandanese, V.; Mazzone, L.; Naso, F. *Tetrahedron Lett.* ***1994***, *35*, 8847.

[1326]Negishi, E.; Kotora, M.; Xu, C. *J. Org. Chem.* ***1997***, *62*, 8957.

[1327]Cai, M.-Z.; Song, C.-S.; Huang, X. *J. Chem. Res. (S)* ***1998***, 264.

[1328]Kondo, S.; Ohira, M.; Kawasoe, S.; Kunisada, H.; Yuki, Y. *J. Org. Chem.* ***1993***, *58*, 5003.

[1329]Dohle, W.; Kopp, F.; Cahiez, G.; Knochel, P. *Synlett* ***2001***, 1901.

[1330]Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem.* ***2004***, *69*, 3943.

[1331]Rathore, R.; Deselnicu, M.I.; Burns, C.L. *J. Am. Chem. Soc.* ***2002***, *124*, 14832.

[1332]For the structure of Me_2CuLi (a cyclic dimer), see Pearson, R.G.; Gregory, C.D. *J. Am. Chem. Soc.* ***1976***, *98*, 4098. See also, Lipshutz, B.H.; Kozlowski, J.A.; Breneman, C.M. *Tetrahedron Lett.* ***1985***, *26*, 5911. For a review of the structure and reactions of organocopper compounds, see Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed., University Science Books, Mill Valley, CA, ***1987***, pp. 682–698.

[1333]See Stemmler, T.L.; Barnhart, T.M.; Penner-Hahn, J.E.; Tucker, C.E.; Knochel, P.; Böhme, M.; Frenking, G. *J. Am. Chem. Soc.* ***1995***, *117*, 12489 for a discussion concerning the structure of organocuprate reagents. Solution compositions of Gilman reagents have also been studied. See Lipshutz, B.H.; Kayser, F.; Siegmann, K. *Tetrahedron Lett.* ***1993***, *34*, 6693.

give good yields of the cross-coupling products.[1334] They are prepared (see **12-36**) by the reaction of an organolithium compound with CuI or CuBr, typically, most other Cu(I) compounds can be used. They are usually generated at temperatures <0°C due to the thermal instability of many dialkyl cuprates. The reaction with alkyl halides is of wide scope[1335] and R in R_2CuLi may be primary alkyl, allylic, benzylic, aryl, vinylic, or allenic, and may contain keto, COOH, COOR, or $CONR_2$ groups.[1336] Inversion of configuration has been shown in the reaction of 2-bromobutane with Ph_2CuLi,[1337] but the same reaction with 2-iodobutane has been reported to proceed with racemization.[1338] The reaction at a vinylic substrate occurs stereospecifically, with retention of configuration.[1339] When the reagent and substrate are both vinylic, yields are low, but the reaction can be pushed to give 1,3-butadienes, stereospecifically and in high yields by the use of $ZnBr_2$ and a Pd(0) complex.[1340] Many *gem*-dihalides do not react, but when the two halogens are on a carbon α to an aromatic ring[1341] or on a cyclopropane ring,[1342] both halogens can be replaced by R, for example, $PhCHCl_2 \rightarrow PhCHMe_2$. However, 1,2-dibromides give exclusive elimination[1337] (**17-22**). Vinylmagnesium halides, upon addition of a catalytic amount of Li_2CuCl_4, couple to alkyl halide.[1343]

Lithium dialkylcopper reagents couple with alkyl tosylates.[1344] High yields are obtained with primary tosylates; secondary tosylates give lower yields.[1345] Aryl tosylates do not react. Vinylic triflates[1346] couple very well to give alkenes[1347] and they

[1334]Corey, E.J.; Posner, G.H. *J. Am. Chem. Soc.* ***1968***, *90*, 5615; Bergbreiter, D.E.; Whitesides, G.M. *J. Org. Chem.* ***1975***, *40*, 779. See Bertz, S.H.; Eriksson, M.; Miao, G.; Snyder, J.P. *J. Am. Chem. Soc.* ***1998***, *118*, 10906 for the reactivity of β-silyl organocuprates.

[1335]For reviews see Posner, G.H. *Org. React.* ***1975***, *22*, 253; Normant, J.F. *Synthesis* ***1972***, 63; Lipshutz, B.H. *Accts. Chem. Res.* ***1997***, *30*, 277; Posner, G.H. *An Introduction to Synthesis Using Organocopper Reagents*, Wiley, NY, ***1980***. For lists of substrates and reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 392–399, 599–604, 1564.

[1336]For a discussion of the mechansim of S_N2 alkylation with organocuprates see Mori, S.; Nakamura, E.; Morokuma, K. *J. Am. Chem. Soc.* ***2000***, *122*, 7294.

[1337]Cahiez, G.; Chaboche, C.; Jézéquel, M. *Tetrahedron* ***2000***, *56*, 2733.

[1338]Lipshutz, B.H.; Wilhelm, R.S.; Nugent, S.T.; Little, R.D.; Baizer, M.M. *J. Org. Chem.* ***1983***, *48*, 3306.

[1339]Corey, E.J.; Posner, G.H. *J. Am. Chem. Soc.* ***1967***, *89*, 3911; Klein, J.; Levene, R. *J. Am. Chem. Soc.* ***1972***, *94*, 2520. For a discussion of the mechanism, see Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* ***2004***, *126*, 12264.

[1340]Jabri, N.; Alexakis, A.; Normant, J.F. *Tetrahedron Lett.* ***1981***, *22*, 959; ***1982***, *23*, 1589; *Bull. Soc. Chim. Fr.* ***1983***, II-321, II-332.

[1341]Posner, G.H.; Brunelle, D.J. *Tetrahedron Lett.* ***1972***, 293.

[1342]See, for example, Kitatani, K.; Hiyama, T.; Nozaki, H. *Bull. Chem. Soc. Jpn.* ***1977***, *50*, 1600.

[1343]Posner, G.H.; Ting, J. *Synth. Commun.* ***1973***, *3*, 281.

[1344]Johnson, C.R.; Dutra, G.A. *J. Am. Chem. Soc.* ***1973***, *95*, 7777, 7783. For examples, see Posner, G.H. *An Introduction to Synthesis Using Organocopper Reagents*, Wiley, NY, ***1980***, pp. 85–90.

[1345]Secondary tosylates give higher yields when they contain an O or S atom: Hanessian, S.; Thavonekham, B.; DeHoff, B. *J. Org. Chem.* ***1989***, *54*, 5831.

[1346]For a review of coupling reactions of vinylic triflates, see Scott, W.J.; McMurry, J.E. *Acc. Chem. Res.* ***1988***, *21*, 47.

[1347]McMurry, J.E.; Scott, W.J. *Tetrahedron Lett.* ***1980***, *21*, 4313; Tsushima, K.; Araki, K.; Murai, A. *Chem. Lett.* ***1989***, 1313.

also couple with allylic cuprates, to give 1,4-dienes.[1348] Propargylic tosylates couple with vinylic cuprates to give vinylic allenes.[1349]

The R′ in R'_2CuLi may be primary alkyl, vinylic, allylic, or aryl. Thus, in the reaction as so far described, the alkyl groups on the organocuprate or the alkyl halide may *not* be secondary or tertiary alkyl. However, secondary and tertiary alkyl coupling can be achieved (on primary RX) by the use of $R'_2CuLi•PBu_3$[1350] (though this procedure introduces problems in the workup) or by the use of PhS(R′)CuLi,[1351] which selectively couples a secondary or tertiary R′ with a primary iodide RI to give RR′.[1352] It is possible to prepare mixed cuprates, where one ligand is tightly bound to the copper, allowing the other ligand to be transferred in a coupling reaction. A common example is adds a 2-thienyl group to the cuprate to give R(Th)CuLi, where the R group is transferred in lieu of the thienyl unit.[1353] A lithium neopentyl aryl cuprate selectively transferred to aryl group to an allylic halide.[1354]

Coupling to a secondary alkyl halide (R in RX above = secondary) can be achieved in high yield with the reagents $R'_2Cu(CN)Li_2$,[1355] where R′ is primary alkyl or vinylic (but not aryl).[1356] This modified reagent is commonly known as a higher order mixed cuprate. The reagents $RCu(PPh_2)Li$, $RCu(NR'_2)Li$, and $RCu(PR'_2)Li$ (R′ = cyclohexyl) are more stable than R_2CuLi and can be used at higher temperatures.[1357] However, these reagents are quite reactive. Unactivated aryl triflates[1358] $ArOSO_2CF_3$ react to give ArR in good yields when treated with $R_2Cu(CN)Li_2$,[1359] with R_3Al,[1360] or with R'_3SnR and a Pd complex catalyst.[1361] See section **10-59** for other examples involving Al, Sn and Pd coupling reactions.

[1348]Lipshutz, B.H.; Elworthy, T.R. *J. Org. Chem.* ***1990***, *55*, 1695.

[1349]Baudouy, R.; Goré, J. *J. Chem. Res. (S)* ***1981***, 278. See also, Elsevier, C.J.; Vermeer, P. *J. Org. Chem.* ***1989***, *54*, 3726.

[1350]Whitesides, G.M.; Fischer, Jr., W.F.; San Filippo, Jr., J.; Bashe, R.W.; House, H.O., *J. Am. Chem. Soc.* ***1969***, *91*, 4871.

[1351]Prepared as in Ref. 1371 or treatment of PhSCu with RLi: Posner, G.H.; Brunelle, D.J.; Sinoway, L. *Synthesis* ***1974***, 662.

[1352]Posner, G.H.; Whitten, C.E.; Sterling, J.J. *J. Am. Chem. Soc.* ***1973***, *95*, 7788.

[1353]For an example, see Malmberg, H.; Nilsson, M.; Ullenius, C. *Tetrahedron Lett.* ***1982***, *23*, 3823. For an example involving higher order cuprates, see Lipshutz, B.H.; Kozlowski, J.A.; Parker, D.A.; Nguyen, S.L.; McCarthy, K.E. *J. Organomet. Chem.* ***1985***, *285*, 437.

[1354]Piazza, C.; Knochel, P. *Angew. Chem. Int. Ed.* ***2002***, *41*, 3263.

[1355]For reviews of these and other "higher order" organocuprates, see Lipshutz, B.H.; Wilhelm, R.S.; Kozlowski, J.A. *Tetrahedron* ***1984***, *40*, 5005; Lipshutz, B.H. *Synthesis* ***1987***, 325; *Synlett* ***1990***, 119. See also, Bertz, S.H. *J. Am. Chem. Soc.* ***1990***, *112*, 4031; Lipshutz, B.H.; Sharma, S.; Ellsworth, E.L. *J. Am. Chem. Soc.* ***1990***, *112*, 4032.

[1356]Lipshutz, B.H.; Wilhelm, R.S.; Floyd, D.M. *J. Am. Chem. Soc.* ***1981***, *103*, 7672.

[1357]Bertz, S.H.; Dabbagh, G.; Villacorta, G.M. *J. Am. Chem. Soc.* ***1982***, *104*, 5824; Bertz, S.H.; Dabbagh, G. *J. Org. Chem.* ***1984***, *49*, 1119.

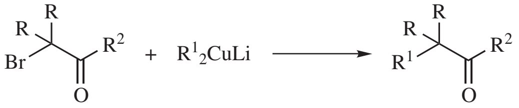
[1358]For another coupling reaction of aryl triflates, see Aoki, S.; Fujimura, T.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.*, ***1988***, *110*, 3296.

[1359]McMurry, J.E.; Mohanraj, S. *Tetrahedron Lett.*, ***1983***, *24*, 2723.

[1360]Hirota, K.; Isobe, Y.; Maki, Y. *J. Chem. Soc.*, *Perkin Trans. 1*, ***1989***, 2513.

[1361]Echevarren, E.M.; Stille, J.K. *J. Am. Chem. Soc.*, ***1987***, *109*, 5478. For a similar reaction with aryl fluorosulfonates, see Roth, G.P.; Fuller, C.E. *J. Org. Chem.*, ***1991***, *56*, 3493.

Both OTf units in $RCH(OTf)_2$ can be replaced with $Me_2(CN)CuLi_2$.[1362] With an allenic substrate, reaction with R(CN)CuLi can give ordinary displacement (with retention of configuration)[1363] or an S_N2' reaction to produce an alkyne.[1364] In the latter case, a chiral allene gave a chiral alkyne. The structures of these "higher order mixed" cuprates has been called into question[1365] by Bertz, who suggested the reagent actually existed as R_2CuLi•LiCN in THF.[1366] This was contradicted by Lipshutz.[1367]



143

The fact that R'_2CuLi do not react with ketones provides a method for the alkylation of ketones via the organocuprate coupling with α-halokeotones, such as **143**[1368] (see also, **10-68** and **10-73**). Note that halogen–metal exchange (**12-39**) is a side reaction and can become the main reaction.[1369] When α,α′-dibromo ketones are treated with Me_2CuLi in ether at −78°C and the mixture quenched with methanol, *mono*methylation takes place[1370] (no dimethylation is observed). It has been suggested that the reaction involves cyclization (**10-56**) to a cyclopropanone followed by nucleophilic attack to give the enolate anion, which is protonated by the methanol. If methyl iodide is added instead of methanol, an α,α′-dimethyl ketone is obtained, presumably from S_N2 attack (**10-68**). Primary, secondary, *and tertiary* monoalkylation can be achieved with a lithium *tert*-butoxy (alkyl)copper reagent[1371] instead of Me_2CuLi, one of the few methods for introducing a tertiary alkyl group a to a carbonyl group.

When dialkylcopperzinc reagents $R_2CuZnCl$ couple with allylic halides, almost complete allylic rearrangement occurs (S_N2'), and the reaction is diastereoselective if the allylic halide contains a δ alkoxy group.[1372] Another type of copper reagent

[1362]Martínez, A.G.; Barcina, J.O.; Díez, B.R.; Subramanian, L.R. *Tetrahedron* ***1994***, *50*, 13231.

[1363]Mooiweer, H.H.; Elsevier, C.J.; Wijkens, P.; Vermeer, P. *Tetrahedron Lett.* ***1985***, *26*, 65.

[1364]Corey, E.J.; Boaz, N.W. *Tetrahedron Lett.* ***1984***, *25*, 3059, 3063. For the reaction of these reagents with haloalkynes, see Yeh, M.C.P.; Knochel, P. *Tetrahedron Lett.* ***1989***, *30*, 4799.

[1365]Bertz, S.H.; Miao, G.; Eriksson, M. *Chem. Commun.* ***1996***, 815; Snyder, J.P.; Bertz, S.H. *J. Org. Chem.* ***1995***, *60*, 4312. Also see, Snyder, J.P.; Tipsword, G.E.; Spangler, D.P. *J. Am. Chem. Soc.* ***1992***, *114*, 1507.

[1366]Bertz, S.H. *J. Am. Chem. Soc.* ***1990***, *112*, 4031.

[1367]Lipshutz, B.H.; James, B. *J. Org. Chem.* ***1994***, *59*, 7585; Lipshutz, B.H.; Sharma, S.; Ellsworth, E.L. *J. Am. Chem. Soc.* ***1990***, *112*, 4032.

[1368]Dubois, J.E.; Lion, C.; Moulineau, C. *Tetrahedron Lett.* ***1971***, 177; Dubois, J.E.; Fournier, P.; Lion, C. *Bull. Soc. Chim. Fr.* ***1976***, 1871.

[1369]See Corey, E.J.; Posner, G.H. *J. Am. Chem. Soc.* ***1967***, *89*, 3911; Wakselman, C.; Mondon, M. *Tetrahedron Lett.* ***1973***, 4285.

[1370]Posner, G.H.; Sterling, J.J. *J. Am. Chem. Soc.* ***1973***, *95*, 3076. See also, Posner, G.H.; Sterling, J.J.; Whitten, C.E.; Lentz, C.M.; Brunelle, D.J. *J. Am. Chem. Soc.* ***1975***, *97*, 107; Lion, C.; Dubois, J.E. *Tetrahedron* ***1975***, *31*, 1223. The compound Ph_2CuLi behaves similarly: see Lei, X.; Doubleday Jr., C.; Turro, N.J. *Tetrahedron Lett.* ***1986***, *27*, 4671.

[1371]Prepared by treating CuI with *t*-BuOLi in THF at 0°C and adding RLi to this solution.

[1372]Nakamura, E.; Sekiya, K.; Arai, M.; Aoki, S. *J. Am. Chem. Soc.* ***1989***, *111*, 3091.

was prepared from RZnI/CuCN, and this was shown to couple with alkenyl halides,[1373] and diethylzinc in the presence of a catalytic amount of CuBr coupled to allylic chlorides.[1374] When treated with organocopper compounds and Lewis acids (e.g., *n*-BuCu•BF_3), allylic halides give substitution with almost complete allylic rearrangement, irrespective of the degree of substitution at the two ends of the allylic system.[1375]

$$\text{ArI} + \text{R}_2\text{CuLi} \longrightarrow \text{ArR}$$

OS **IX**, 502.

10-59 Reaction of Alkyl Halides and Sulfonate Esters With Other Organometallic Reagents

Alkyl-de-halogenation

$$\text{RX} + \text{R}'\text{—M} \longrightarrow \text{R—R}'$$

Many other metals and metal complexes can be used to catalyze or mediate coupling reactions. Organoaluminum compounds couple very well with tertiary (to give products containing a quaternary carbon) and benzylic halides at −78°C.[1376] This reaction can also be applied to allylic, secondary, and some primary halides, but several days standing at room temperature is required (see also **10-63**). Vinylic aluminum compounds (in the presence of a suitable transition-metal catalyst) couple with allylic halides, acetates, and alcohol derivatives to give 1,4-dienes,[1377] and with vinylic and benzylic halides to give 1,3-dienes and allylic arenes, respectively.[1378] An interesting transformation treated a vinyl nitro compound (PhCH=$CHNO_2$) with Et_3Al and a large excess of 2-iodopropane, in the presence of 2 equivalents of dibenzoyl peroxide, to give the coupling product, PhCH=CH*i*-Pr.[1379] Note that alkylboronic acids are coupled in the presence of Ag_2O and a catalytic amount of $CrCl_2$ to give the symmetrical alkyl derivative.[1380]

[1373]Marquais, S.; Cahiez, G.; Knochel, P. *Synlett*, ***1994***, 849.

[1374]Malda, H.; van Zijl, A.W.; Arnold, L.A.; Feringa, B.L. *Org. Lett.* **2001**, *3*, 1169.

[1375]Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* ***1980***, *102*, 2318. See also, Lipshutz, B.H.; Ellsworth, E.L.; Dimock, S.H. *J. Am. Chem. Soc.* ***1990***, *112*, 5869.

[1376]Miller, D.B. *J. Org. Chem.* ***1966***, *31*, 908; Kennedy, J.P. *J. Org. Chem.* ***1970***, *35*, 532. See also, Kennedy, J.P.; Sivaram, S. *J. Org. Chem.* ***1973***, *38*, 2262; Sato, F.; Kodama, H.; Sato, M. *J. Organomet. Chem.* ***1978***, *157*, C30.

[1377]Lynd, R.A.; Zweifel, G. *Synthesis* ***1974***, 658; Matsushita, H.; Negishi, E. *J. Am. Chem. Soc.* ***1981***, *103*, 2882; *J. Chem. Soc., Chem. Commun.* ***1982***, 160. For similar reactions with other metals, see Larock, R.C.; Bernhardt, J.C.; Driggs, R.J. *J. Organomet. Chem.* ***1978***, *156*, 45; Brown, H.C.; Campbell, Jr., J.B. *J. Org. Chem.* ***1980***, *45*, 550; Baeckström, P.; Björkling, F.; Högberg, H.; Norin, T. *Acta Chem. Scand. Ser. B*, ***1984***, *38*, 779.

[1378]Negishi, E.; Takahashi, T.; Baba, S.; Van Horn, D.E.; Okukado, N. *J. Am. Chem. Soc.* ***1987***, *109*, 2393; Negishi, E.; Takahashi, T.; Baba, S. *Org. Synth.* *66*, 60.

[1379]Liu, J.-Y.; Liu, J.-T.; Yao, C.-F. *Tetrahedron Lett.* **2001**, *42*, 3613.

[1380]Falck, J.R.; Mohaptra, S.; Bondlela, M.; Venkataraman, S.K. *Tetrahedron Lett.* **2002**, *43*, 8149.

Products containing a quaternary carbon can also be obtained by treatment of tertiary halides with dialkyl or diaryl zinc reagents in CH_2Cl_2,[1381] with Me_4Si and $AlCl_3$,[1382] or with alkyltitanium reagents $RTiCl_3$ and R_2TiCl_2.[1383] Dialkylzinc compounds can be coupled to alkyl iodides in the presence of a nickel catalyst,[1384] but with geminal diiodo compounds without a catalyst.[1385] Copper compounds can also be used as catalysts with dialkylzinc reagents.[1386] The reaction of aryl halides with Me_4ZnLi_2, and then $VO(OEt)Cl_2$ leads to the methylated aryl.[1387] Isopropylzinc (*i*PrZn) displaces the iodide in γ-iodo ketones to give the alkyl substitution product, without reaction at the carbonyl.[1388] Reactions of organozinc reagents with a carbonyl compound via acyl addition is presented in **16-31**, the Reformatsky reaction. The titanium method can also be used with secondary halides ($R_2CHCl \rightarrow R_2CHMe$), tertiary ethers ($R_3COR' \rightarrow R_3CMe$), and *gem*-dihalides ($R_2CCl_2 \rightarrow R_2CMe_2$).[1389] Tertiary halides have also been coupled to allyltin reagents in the presence of AIBN.[1390] Alkyl halides can be treated with SmI_2 and then CuBr to give a reactive species that couples with other alkyl halides.[1391] Trialkylindium compounds couple to allylic bromides in the presence of $Cu(OTf)_2$•$P(OEt)_3$[1392] and vinyl indium compounds are coupled to α-halo esters with a BEt_3 catalyst.[1393] Arylsulfonyl chlorides couple with allyl halides in the presence of bismuth to give allyl-aryls.[1394] Vinyl iodides couple with RMnCl with an iron catalyst[1395] and $Bu_3MnMgBr$ reacted with a geminal dibromocyclopropane to give a dialkylated cyclopropane.[1396] α-Haloketones are coupled with aryl halides using a nickel catalyst.[1397] Allylgallium reagents have been coupled to α-bromo esters in the presence of BEt_3/O_2.[1398]

Arylpalladium salts "ArPdX" prepared from arylmercury compounds and lithium palladium chloride couple with allylic chlorides in moderate yields,

[1381]Reetz, M.T.; Wenderoth, B.; Peter, R.; Steinbach, R.; Westermann, J. *J. Chem. Soc., Chem. Commun.* ***1980***, 1202. See also, Klingstedt, T.; Frejd, T. *Organometallics* ***1983***, *2*, 598.

[1382]Bolestova, G.I.; Parnes, Z.N.; Latypova, F.M.; Kursanov, D.N. *J. Org. Chem. USSR* ***1981***, *17*, 1203.

[1383]Reetz, M.T.; Westermann, J.; Steinbach, R. *Angew. Chem. Int. Ed.* ***1980***, *19*, 900, 901.

[1384]Giovannini, R.; Stüdemann, T.; Devasagayaraj, A.; Dussin, G.; Knochel, P. *J. Org. Chem.* ***1999***, *64*, 3544; Jensen, A.E.; Knochel, P. *J. Org. Chem.* ***2002***, *67*, 79; Zhou, J.; Fu, G.C. *J. Am. Chem. Soc.* ***2003***, *125*, 14726; Terao, J.; Todo, H.; Watanabe, H.; Ikumi, A.; Kambe, N. *Angew. Chem. Int. Ed.* ***2004***, *43*, 6180.

[1385]Shibli, A.; Varghese, J.P.; Knochel, P.; Marek, I. *Synlett* ***2001***, 818.

[1386]Shi, W.J.; Wang, L.-X.; Fu, Y.; Zhu, S.-F.; Zhou, Q.-L. *Tetrahedron Asymmetry* ***2003***, *14*, 3867.

[1387]Hu, J.-b.; Zhao, G.; Yang, G.-s.; Ding, Z.-d. *J. Org. Chem.* ***2001***, *66*, 303.

[1388]Jensen, A.E.; Knochel, P. *J. Org. Chem.* ***2002***, *67*, 79.

[1389]Reetz, M.T.; Steinbach, R.; Wenderoth, B. *Synth. Commun.* ***1982***, *11*, 261.

[1390]Kraus, G.A.; Ansersh, B.; Su, Q.; Shi, J. *Tetrahedron Lett.* ***1993***, *34*, 1741.

[1391]Berkowitz, W.F.; Wu, Y. *Tetrahedron Lett.* ***1997***, *38*, 3171.

[1392]Rodríguez, D.; Sestelo, J.P.; Sarandeses, L.A. *J. Org. Chem.* ***2003***, *68*, 2518.

[1393]Takami, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* ***2004***, *6*, 4555.

[1394]Baruah, M.; Boruah, A.; Prajapati, D.; Sandu, J.S. *Synlett*, ***1998***, 1083.

[1395]Cahiez, G.; Marquais, S. *Tetrahedron Lett.* ***1996***, *37*, 1773.

[1396]Kakiya, H.; Inoue, R.; Shinokubo, H.; Oshima, K. *Tetrahedron* ***2000***, *56*, 2131.

[1397]Durandetti, M.; Sibille, S.; Nédélec, J.-Y.; Périchon, J. *Synth. Commun.* ***1994***, *24*, 145.

[1398]Usugi, S.-i.; Yorimitsu, H.; Oshima, K. *Tetrahedron Lett.* ***2001***, *42*, 4535.

although allylic rearrangements can occur.[1399] The advantage of this procedure is that the aryl group may contain nitro, ester, or aldehyde groups, and so on, which cannot be present in a Grignard reagent. In most cases, a palladium(0) complex is added to the substrate, sometimes in conjunction with another metal, to facilitate coupling. Any arylpalladium species is therefore generated *in situ*. Allylic, benzylic, vinylic, and aryl halides or triflates (trifluoromethylsulfonates) couple with organotin reagents in a reaction catalyzed by palladium complexes.[1400] Such functional groups as COOR, CN, OH, and CHO may be present in either reagent, but the substrate may not bear a β hydrogen on an sp^3 carbon, because that results in elimination. Indium metal has been used to mediate the coupling of an allylic halide and an arylpalladium complex,[1401] and organoindium compounds were coupled to 1-iodonaphthalene with a palladium catalyst.[1402] Dimethylzinc was coupled to aryl halides with a palladium catalyst,[1403] and Reformatsky-type zinc derivatives (**16–28**) have been coupled to aryl halides using a palladium catalyst and microwave irradiation.[1404]

In many cases, the organometallic reagent is prepared from the corresponding organolithium reagent (**10-57**), as in the conversion of an aryllithium to an arylzirconium reagent, which was subsequently coupled to a aryl halide in the presence of a palladium catalyst.[1405] Alkyl or aryl triflates (halides) couple with alkyl or ArZn(halide) reagents in the presence of a palladium catalyst.[1406] This organozinc coupling reaction has been done in ionic liquids.[1407] Vinyl halides coupled with vinyltin reagents in the presence of CuI,[1408] and aryl tin compounds couple with vinyl halides[1409] or vinyl triflates when a palladium catalyst is present.[1410] When the vinyltin reagent is coupled with a vinyl triflate in the presence of a palladium catalyst, the reaction is known as the *Stille reaction* (**12-15**). These latter reactions are obviously related, but the Stille reaction is placed in Chapter 14 for mechanistic reasons related

[1399]Heck, R.F. *J. Am. Chem. Soc.* ***1968***, *90*, 5531. See **13-10**. For a review of palladium-assisted coupling, see Heck, R.F. *Palladium Reagents in Organic Syntheses*, Academic Press, NY, ***1985***, pp. 208–214, 242–249.

[1400]For a review, see Stille, J.K. *Angew. Chem. Int. Ed.* ***1986***, *25*, 508. For a review of the mechanism, see Bumagin, N.A.; Beletskaya, I.P. *Russ. Chem. Rev.* ***1990***, *59*, 1174. See also, Stille, J.K.; Simpson, J.H. *J. Am. Chem. Soc.* ***1987***, *109*, 2138; Martínez, A.G.; Barcina, J.O.; Heras, Md.R.C.; Cerezo, A.d.F. *Org. Lett.* ***2000***, *2*, 1377.

[1401]Lee, P.H.; Sung, S.-y.; Lee, K. *Org. Lett.* ***2001***, *3*, 3201.

[1402]Lee, P.H.; Lee, S.W.; Seomoon, D. *Org. Lett.* ***2003***, *5*, 4963; Rodríguez, D.; Sestelo, J.P.; Sarandeses, L.A. *J. Org. Chem.* ***2004***, *69*, 8136.

[1403]Herbert, J.M. *Tetrahedron Lett.* ***2004***, *45*, 817.

[1404]Bentz, E.; Moloney, M.G.; Westaway, S.M. *Tetrahedron Lett.* ***2004***, *45*, 7395.

[1405]Frid, M.; Pérez, D.; Peat, A.J.; Buchwald, S.L. *J. Am. Chem. Soc.* ***1999***, *121*, 9469. See also, Villiers, P.; Vicart, N.; Ramondenc, Y.; Plé, G. *Tetrahedron Lett.* ***1999***, *40*, 8781.

[1406]Piber, M.; Jensen, A.E.; Rottländer, M.; Knochel, P. *Org. Lett.* ***1999***, *1*, 1323; Hossain, K.M.; Shibata, T.; Takagi, K. *Synlett* ***2000***, 1137; Zhou, J.; Fu, G.C. *J. Am. Chem. Soc.* ***2003***, *125*, 12527.

[1407]Sirieix, J.; Oßberger, M.; Betzemeier, B.; Knochel, P. *Synlett* ***2000***, 1613.

[1408]Kang, S.-K.; Kim, J.-S.; Choi, S.-C. *J. Org. Chem.* ***1997***, *62*, 4208.

[1409]Shen, W.; Wang, L. *J. Org. Chem.* ***1999***, *64*, 8873.

[1410]Fouquet, E.; Rodriguez, A.L. *Synlett* ***1998***, 1323; Lipshutz, B.H.; Alami, M. *Tetrahedron Lett.* ***1993***, *34*, 1433.

to similar palladium-catalyzed coupling reactions. Vinylic triflates, in the presence of $Pd(Ph_3P)_4$ and LiCl, couple with organotin compounds $R'SnMe_3$, where R′ can be alkyl, allylic, vinylic, or alkynyl.[1411] The reaction has been performed intramolecularly, to prepare large-ring lactones.[1412] Alkyl halides couple with ArMnCl or RMnCl in the presence of a palladium catalyst.[1413] The coupling of aryl substrates to form biaryls is discussed in **13-9**.

Alkenylboranes ($R'_2C{=}CHBZ_2$; Z = various groups) couple in high yields with vinylic,[1414] alkynyl, aryl, benzylic, and allylic halides or triflates in the presence of a palladium catalyst and a base to give $R'_2C{=}CHR$.[1415] 9-Alkyl-9-BBN compounds (**15–16**) also couple with vinylic and aryl halides,[1416] as well as with α-halo ketones, nitriles, and esters.[1417] Another palladium-catalyzed coupling of vinyl halides and alkylboronic acids[1418] gives substituted alkenes, in a reaction that is related to the Suzuki coupling (**13-12**). Arylboronic acids can also be coupled to alkyl halides with a palladium catalyst,[1419] alkylboronic acids can be coupled to aryl halides in a similar manner,[1420] and a cyclopropylboronic acid was coupled to an allylic bromide with silver oxide/KOH and a palladium catalyst.[1421] Vinyl zirconium reagents were coupled to alkyl halides with a palladium catalyst.[1422]

Potassium aryl- and 1-alkenyltrifluoroborates ($ArBF_3K$ and RBF_3K) are easily prepared from organoboronic acids or esters. In general, the trifluoroborates have greater air stability and greater nucleophilicity[1423] when compared to the

[1411]Kwon, H.B.; McKee, B.H.; Stille, J.K. *J. Org. Chem.* ***1990***, *55*, 3114. For discussions of the mechanism, see Stang, P.J.; Kowalski, M.H.; Schiavelli, M.D.; Longford, D. *J. Am. Chem. Soc.* ***1989***, *111*, 3347; Stang, P.J.; Kowalski, M.H. *J. Am. Chem. Soc.* ***1989***, *111*, 3356.

[1412]Stille, J.K.; Tanaka, M. *J. Am. Chem. Soc.* ***1987***, *109*, 3785.

[1413]Riquet, E.; Alami, M.; Cahiez, G. *Tetrahedron Lett.* ***1997***, *38*, 4397; Cahiez, G.; Marquais, S. *Synlett*, ***1993***, 45.

[1414]Occhiato, E.G.; Trabocchi, A.; Guarna, A. *Org. Lett.* ***2000***, *2*, 1241.

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[1416]Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* ***1989***, *111*, 314. See also, Soderquist, J.A.; Santiago, B. *Tetrahedron Lett.* ***1990***, *31*, 5541.

[1417]Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A. *Chem. Lett.* ***1992***, 691; Brown, H.C.; Joshi, N.N.; Pyun, C.; Singaram, B. *J. Am. Chem. Soc.* ***1989***, *111*, 1754. For another such coupling, see Matteson, D.S.; Tripathy, P.B.; Sarkar, A.; Sadhu, K.M. *J. Am. Chem. Soc.* ***1989***, *111*, 4399.

[1418]Bellina, F.; Anselmi, C.; Rossi, R. *Tetrahedron Lett.* ***2001***, *42*, 3851. See also, Yoshida, H.; Yamaryo, Y.; Oshita, J.; Kunai, A. *Tetrahedron Lett.* ***2003***, *44*, 1541.

[1419]Nobre, S.M.; Monteiro, A.L. *Tetrahedron Lett.* ***2004***, *45*, 8225; Liu, X.-x.; Deng, M.-z. *Chem. Commun.* ***2002***, 622; Langle, S.; Abarbri, M.; Duchêne, A. *Tetrahedron Lett.* ***2003***, *44*, 9255.

[1420]Kondolff, I.; Doucet, H.; Santelli, M. *Tetrahedron* ***2004***, *60*, 3813. For a variation involving a borate complex, see Zou, G.; Falck, J.R. *Tetraahedron Lett.* ***2001***, *42*, 5817.

[1421]Chen, H.; Deng, M.-Z. *J. Org. Chem.* ***2000***, *65*, 4444.

[1422]Wiskur, S.L.; Lorte, A.; Fu, G.C. *J. Am. Chem. Soc.* ***2004***, *126*, 82.

[1423]Batey, R.A.; Thadani, A.N.; Smil, D.V.; Lough, A.J. *Synthesis* ***2000***, 990; Batey R.A.; Thadani, A.N.; Smil, D.V. *Org. Lett.* ***1999***, *1*, 1683; Batey, R.A.; Thadani, A.N.; Smil, D.V. *Tetrahedron Lett.* ***1999***, *40*, 4289; Batey, R.A.; MacKay, D.B.; Santhakumar, V. *J. Am. Chem. Soc.* ***1999***, *121*, 5075.

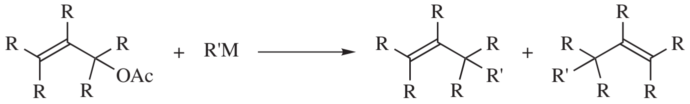
corresponding organoboranes and organoboronic acid derivatives. Potassium alkyltrifluoroborates undergo the palladium-catalyzed coupling reaction with arenediazonium tetrafluoroborates,[1424] diaryliodonium salts,[1425] aryl halides,[1426] as well as with aryl triflates. An example of the latter reaction converted **144** to diphenylmethane via coupling with phenyl triflate.[1427] Alkenyltrifluoroborates can be coupled to aryl halides.[1428]

$$\underset{\mathbf{144}}{PhCH_2BF_3K} + PhOTf \xrightarrow[9\%\ PdCl_2(dppf)\bullet CH_2Cl_2]{3\ equiv\ Cs_2CO_3,\ aq.\ THF} PhCH_2Ph$$

OS **VII**, 245; **VIII**, 295; **X**, 391.

10-60 Coupling of Organometallic Reagents With Carboxylic Esters

Alkyl-de-acyloxy-substitution



Several organometallic reagents react with allylic esters and carbonates to give the coupling product. Lithium dialkylcopper reagents couple with allylic acetates to give normal coupling products or those resulting from allylic rearrangement, depending on the substrate.[1429] A mechanism involving a σ-allylic copper(III) complex has been suggested.[1430] Silyl cuprates have also been used, with benzoate esters, to give allyl silanes.[1431] Interestingly, allylic silanes have been coupled to acetates using $B(C_6F_5)_3$[1432] or BF_3.[1433] With propargyl substrates, the products are allenes.[1434]

$$RC{\equiv}C{-}CR_2{-}OAc + R'_2CuLi \longrightarrow RR'C{=}C{=}CR_2$$

[1424]Darses, S.; Michaud, G.; Genêt, J.-P. *Eur. J. Org. Chem.* ***1999***, 1875; Darses, S.; Michaud, G.; Genêt, J.-P. *Tetrahedron Lett.* ***1998***, *39*, 5045; Darses, S.; Genêt, J.-P.; Brayer, J.-L.; Demoute, J.-P. *Tetrahedron Lett.* ***1997***, *38*, 4393.

[1425]Xia, M.; Chen, Z.-C. *Synth. Commun.* ***1999***, *29*, 2457.

[1426]Ishikura, M.; Agata, I.; Katagiri, N. *J. Heterocylic Chem.* ***1999***, *36*, 873; Molander, G.A.; Biolatto, B. *Org. Lett.* ***2002***, *4*, 1867.

[1427]Molander, G.A.; Ito, T. *Org. Lett.* ***2001***, *3*, 393.

[1428]Molander, G.A.; Rivero, M.R. *Org. Lett.* ***2002***, *4*, 107.

[1429]Rona, P.; Tökes, L.; Tremble, J.; Crabbé, P. *Chem. Commun.* ***1969***, 43; Goering, H.L.; Kantner, S.S. *J. Org. Chem.* ***1984***, *49*, 422; Purpura, M.; Krause, N. *Eur. J. Org. Chem.* ***1999***, 267.

[1430]Goering, H.L.; Kantner, S.S.; Seitz Jr., E.P. *J. Org. Chem.* ***1985***, *50*, 5495.

[1431]Fleming, I.; Higgins, D.; Lawrence, N.J.; Thomas, A.P. *J. Chem. Soc. Perkin Trans. 1* ***1992***, 3331.

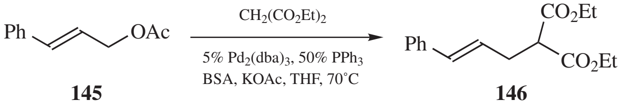
[1432]Rubin, M.; Gevorgyan, V. *Org. Lett.* ***2001***, *3*, 2705. For a reaction of a propargyl ester ($-O_2CCH_2Cl$) with an allylic silane and a catalytic amount of $B(C_6F_5)_3$, see Schwier, T.; Rubin, M.; Gevorgyan, V. *Org. Lett.* ***2004***, *6*, 1999.

[1433]Smith, D.M.; Tran, M.B.; Woerpel, K.A. *J. Am. Chem. Soc.* ***2003***, *125*, 14149; Ayala, L.; Lucero, C.G.; Romero, J.A.C.; Tabacco, S.A.; Woerpel, K.A. *J. Am. Chem. Soc.* ***2003***, *125*, 15521.

[1434]Crabbé, P.; Barreiro, E.; Dollat, J.; Luche, J. *J. Chem. Soc., Chem. Commun.* ***1976***, 183, and references cited therein.

Allenes are also obtained when propargyl acetates are treated with methylmagnesium iodide.[1435] Lithium dialkylcopper reagents also give normal coupling products with enol acetates of β-dicarbonyl compounds.[1436] It is also possible to carry out the coupling of allylic acetates with Grignard reagents, if catalytic amounts of cuprous salts are present.[1437] With this method yields are better and regioselectivity can be controlled by a choice of cuprous salts.

Allylic, benzylic, and cyclopropylmethyl acetates couple with trialkylaluminums,[1438] and allylic acetates couple with aryl and vinylic tin reagents, in the presence of a palladium catalyst[1439] (see below). Allylic acetates can be symmetrically coupled by treatment with $Ni(CO)_4$ (reaction **10-56**) or with Zn and a palladium-complex catalyst,[1440] or converted to unsymmetrical 1,5-dienes by treatment with an allylic stannane $R_2C{=}CHCH_2SnR_3$ in the presence of a palladium complex.[1441] Aryl halides can be coupled to allylic acetates with $CoBr_2$/Mn/$FeBr_2$.[1442] Lactones can be coupled at carbon by an alkylpalladium reagent in the presence of a silane[1443] or by a Grignard reagent with CuBr.[1444]



145 **146**

The most common method now in the literature is the reaction of η^3-π-allyl palladium complexes[1445] (see p. 117) with various nucleophiles,[1446] where the complex is obtained from allylic esters (acetate is the most common) or allylic

[1435]Roumestant, M.; Gore, J. *Bull. Soc. Chim. Fr.* ***1972***, 591, 598.

[1436]Casey, C.P.; Marten, D.F. *Synth. Commun.* ***1973***, *3*, 321, *Tetrahedron Lett.* ***1974***, 925. See also, Posner, G.H.; Brunelle, D.J. *J. Chem. Soc., Chem. Commun.* ***1973***, 907; Kobayashi, S.; Takei, H.; Mukaiyama, T. *Chem. Lett.* ***1973***, 1097.

[1437]Paisley, S.D.; Schmitter, J.; Lesheski, L.; Goering, H.L. *J. Org. Chem.* ***1989***, *54*, 2369; Karlström, A.S.E.; Huerta, F.F.; Muezelaar, G.J.; Bäckvall, J.-E. *Synlett* ***2001***, 923; Alexakis, A.; Malan, C.; Lea, L.; Benhaim, C.; Fournioux, X. *Synlett* ***2001***, 927.

[1438]Itoh, A.; Oshima, K.; Sasaki, S.; Yamamoto, H.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* ***1979***, 4751; Gallina, C. *Tetrahedron Lett.* ***1985***, *26*, 519; Tolstikov, G.A.; Dzhemilev, U.M. *J. Organomet. Chem.* ***1985***, *292*, 133; van Klaveren, M.; Persson, E.S.M.; del Villar, A.; Grove, D.M.; Bäckvall, J.-E.; van Koten, G. *Tetrahedron Lett.* ***1995***, *36*, 3059.

[1439]Del Valle, L.; Stille, J.K.; Hegedus, L.S. *J. Org. Chem.* ***1990***, *55*, 3019. For another method, see Legros, J.; Fiaud, J. *Tetrahedron Lett.* ***1990***, *31*, 7453.

[1440]Sasaoka, S.; Yamamoto, T.; Kinoshita, H.; Inomata, K.; Kotake, H. *Chem. Lett.* ***1985***, 315.

[1441]Trost, B.M.; Keinan, E. *Tetrahedron Lett.* ***1980***, *21*, 2595.

[1442]Gomes, P.; Gosmini, C.; Périchon, J. *Org. Lett.* ***2003***, *5*, 1043.

[1443]Iwata, A.; Ohshita, J.; Tang, H.; Kunai, A.; Yamamoto, Y.; Matui, C. *J. Org. Chem.* ***2002***, *67*, 3927.

[1444]Nelson, S.G.; Wan, Z.; Stan, M.A. *J. Org. Chem.* ***2002***, *67*, 4680.

[1445]For a review of the use of η^3-allylpalladium complexes to form C—C bonds, see Tsuji, J., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 3, Wiley, NY, ***1985***, pp. 163–199.

[1446]For a review related to synthetic applications see Trost, B.M.; Crawley, M.L. *Chem. Rev.* ***2003***, *103*, 2921. For a discussion of the mechanism see Tsurugi, K.; Nomura, N.; Aoi, K. *Tetrahedron Lett.* ***2002***, *43*, 469.

carbonates.[1447] The mechansim of such π-allyl palladium reactions has been discussed.[1448] A typical transformation is shown for the reaction of **145** with diethyl malonate, BSA and potassium acetate, which gives coupling product **146** in the presence of the palladium catalyst.[1449] This reaction is a variation of the basic transformation reported several years ago by Trost.[1450] Sulfone anions were also used as nucleophiles.[1451] The palladium catalyst used, the reaction conditions, and the nature of the organometallic compounds varies widely. Although two allylic coupling products are possible via the π-allyl intermediate, attack at the less substituted position is generally favored. In most reported cases the R′M species is the anion of an active methylene compound (such as sodium, potassium or lithium dimethylmalonate) or Knoevenagel-type carbanions (**16–38**) or amino acid surrogates.[1452] The use of chiral ligands[1453] or chiral additives that may act as ligands[1454]

[1447]For reviews, see Trost, B.M. *Angew. Chem. Int. Ed.* ***1989***, *28*, 1173; *Aldrichimica Acta* ***1981***, *14*, 43; *Acc. Chem. Res.* ***1980***, *13*, 385; *Tetrahedron* ***1977***, *33*, 2615; Tsuji, J.; Minami, I. *Acc. Chem. Res.* ***1987***, *20*, 140; Tsuji, J. *Tetrahedron* ***1986***, *42*, 4361, *Organic Synthesis with Palladium Compounds*, Springer, Berlin, ***1981***, pp. 45, 125; Heck, R.F. *Palladium Reagents in Organic Synthesis*, Academic Press, NY, ***1985***, pp. 130–166; Hegedus, L.S., in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, Vol. 5, pt. B, Elsevier, NY, ***1984***, pp. 30–44.

[1448]Trost, B.M.; Strege, P.E.; Weber, L.; Fullerton, T.J.; Dietsche, T.J. *J. Am. Chem. Soc.* ***1978***, *100*, 3407; Organ, M.G.; Miller, M.; Konstantinou, Z. *J. Am. Chem. Soc.* ***1998***, *120*, 9283; Trost, B.M.; Toste, F.D. *J. Am. Chem. Soc.* ***1999***, *121*, 4545

[1449]Poli, G.; Giambastiani, G.; Mordini, A. *J. Org. Chem.* ***199***, *64*, 2962.

[1450]Trost, B.M.; Weber, L.; Strege, P.E.; Fullerton, T.J.; Dietsche, T.J. *J. Am. Chem. Soc.* ***1978***, *100*, 3416, 3426. These papers include a discussion of the mechanism of this reaction.

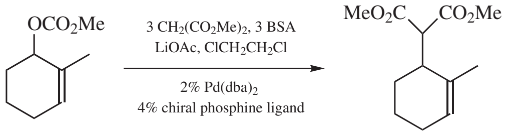
[1451]Manchand, P.S.; Wong, H.S.; Blount, J.F. *J. Org. Chem.* ***1978***, *43*, 4769.

[1452]Nakoji, M.; Kanayama, T.; Okino, T.; Takemoto, Y. *Org. Lett.* ***2001***, *3*, 3329.

[1453]For example see Kodama, H.; Taiji, T.; Ohta, T.; Furkawa, I. *Tetrahedron Asymmetry* ***2000***, *11*, 4009; Gong, L.; Chen, G.; Mi, A.; Jiang, Y.; Fu, F.; Cui, X.; Chan, A.S.C. *Tetrahedron Asymmetry* ***2000***, *11*, 4297; Mino, T.; Shiotsuki, M.; Yamamoto, N.; Suenaga, T.; Sakamoto, M.; Fujita, T.; Yamashita, M. *J. Org. Chem.* ***2001***, *66*, 1795; Zhang, R.; Yu, L.; Xu, L.; Wang, Z.; Ding, K. *Tetrahedron Lett.* ***2001***, *42*, 7659; Arena, C.G.; Drommi, D.; Faraone, F. *Tetrahedron Asymmetry* ***2000***, *11*, 4753; Kang, J.; Lee, J.H.; Choi, J.S. *Tetrahedron Asymmetry* ***2001***, *12*, 33; Mino, T.; Tanaka, Y.; Sakamoto, M.; Fujita, T. *Tetrahedron Asymmetry* ***2001***, *12*, 2435; Hu, X.; Dai, H.; Hu, X.; Chen, H.; Wang, J.; Bai, C.; Zheng, Z. *Tetrahedron Asymmetry* ***2002***, *13*, 1687; Tollabi, M.; Framery, E.; Goux-Henry, C.; Sinou, D. *Tetrahedron Asymmetry* ***2003***, *14*, 3329; Boaz, N.W.; Ponaskik, Jr., J.A.; Large, S.E.; Debenham, S.D. *Tetrahedron Asymmetry* ***2004***, *15*, 2151.

[1454]Rabeyrin, C.; Nguefack, C.; Sinou, D. *Tetrahedron Lett.* ***2000***, *41*, 7461; Jansat, S.; Gómez, M.; Muller, G.; Diéguez, M.; Aghmiz, A.; Claver, C.; Masdeu-Bultó, A.M.; Flores-Santos, L.; Martin, E.; Maestro, M.A.; Mahía, J. *Tetrahedron Asymmetry* ***2001***, *12*, 1469; Fukuda, T.; Takehara, A.; Iwao, M. *Tetrahedron Asymmetry* ***2001***, *12*, 2793; Abrunhosa, I.; Gulea, M.; Levillain, J.; Masson, S. *Tetrahedron Asymmetry* ***2001***, *12*, 2851; Stranne, R.; Moberg, C. *Eur. J. Org. Chem.* ***2001***, 2191; Mancheño, O.G.; Priego, J.; Cabera, S.; Arrayás, R.G.; Llamas, T.; Carretero, J.C. *J. Org. Chem.* ***2003***, *68*, 3679; Molander, G.A.; Burke, J.P.; Carroll, P.J. *J. Org. Chem.* ***2004***, *69*, 8062; Hou, X.-L.; Sun, N. *Org. Lett.* ***2004***, *6*, 4399; Jin, M.-J.; Kim, S.-H.; Lee. S.-J.; Kim, Y.-M. *Tetrahedron Lett.* ***2002***, *43*, 7409; Okuyama, Y.; Nakano, H.; Takahashi, K.; Hongo, H.; Kubuto, C. *Chem. Commun.* ***2003***, 524; Chen, G.; Li, X.; Zhang, H.; Gong, L.; Mi, A.; Cui, X.; Jiang, Y.; Choi, M.C.K.; Chan, A.S.C. *Tetrahedron Asymmetry* ***2002***, *13*, 809; Kloetzing, R.J.; Lotz, M.; Knochel, P. *Tetrahedron Asymmetry* ***2003***, *14*, 255; Nakano, H.; Yokayama, J.-i.; Koiyama, Y.; Fujita, R.; Hongo, H. *Tetrahedron Asymmetry* ***2003***, *14*, 2361; Mercier, F.; Brebion, F.; Dupont, R.; Mathey, F. *Tetrahedron Asymmetry* ***2003***, *14*, 3137.

lead to asymmetric induction in the coupling product.[1455] Enolate anions (see **10–68**) have also been used.[1456] This transformation has been done in ionic liquids[1457] and ionic liquids have been used as additives in catalytic amounts in other solvents.[1458] Palladium nanoparticles have been used to catalyze the reaction.[1459] Other nucleophiles can be used to displace allylic acetates.[1460] S_N2' reactions with allylic acetates have been reported.[1461] Benzoate esters have been used successfully in lieu of the acetate.[1462] Catalyst systems other than palladium have been used for this reaction with allylic acetates.[1463]



147 **148**

As mentioned above, a common variation is to replace the acetate leaving group with a carbonate (—OCO_2R), where methyl carbonate (—OCO_2Me) is most common.[1464] A typical reaction is the transformation of **147** to **148**,[1465] where the use of a chiral ligand led to modest asymmetric induction. As with allylic acetates, chiral ligands and chiral additives lad to asymmetric induction.[1466] A variety of active methylene compounds can be used as nucleophiles,[1467] including enolate anions.[1468] Other nucleophiles can be used to

[1455]For a review, see Consiglio, G.; Waymouth, R.M. *Chem. Rev.* ***1989***, *89*, 257.

[1456]Braun, M.; Laicher, F.; Meier, T. *Angew. Chem. Int. Ed.* ***2000***, *39*, 3494.

[1457]For a reaction in bmim BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate, see Chen, W.; Xu, L.; Chatterton, C.; Xiao, J. *Chem. Commun.* ***1999***, 1247.

[1458]Sato, Y.; Yoshino, T.; Mori, M. *Org. Lett.* ***2003***, *5*, 31.

[1459]Jansat, S.; Gómez, M.; Philippot, K.; Muller, G.; Guiu, E.; Claver, C.; Castillón, S.; Chaudret, B. *J. Am. Chem. Soc.*, ***2004***, *126*, 1592.

[1460]**NaN(CHO)$_2$:** Wang, Y.; Ding, K. *J. Org. Chem.* ***2001***, *66*, 3238. **Indene**: Hayashi, T.; Suzuka, T.; Okada, A.; Kawatsura, M. *Tetrahedron Asymmetry* ***2004***, *15*, 545.

[1461]Belelie, J.L.; Chong, J.M. *J. Org. Chem.* ***2002***, *67*, 3000.

[1462]Krafft, M.E.; Sugiura, M.; Abboud, K.A. *J. Am. Chem. Soc.* ***2001***, *123*, 9174.

[1463]**Pt**: Blacker, A.J.; Clarke, M.L.; Loft, M.S.; Mahon, M.F.; Humphries, M.E.; Williams, J.M.J. *Chem. Eur. J.* ***2000***, *6*, 353. **Ir**: Kinoshita, N.; Marx, K.H.; Tanaka, K.; Tsubaki, K.; Kawabata, T.; Yoshikai, N.; Nakamura, E.; Fuji, K. *J. Org. Chem.* ***2004***, *69*, 7960; Bartels, B.; García-Yebra, C.; Helmchen, G. *Eur. J. Org. Chem.* ***2003***, 1097. **Ru**: Renaud, J.-L.; Bruneau, C.; Demerseman, B. *Synlett* ***2003***, 408.

[1464]For a —OCO_2Ph leaving group, see Ito, K.; Kashiwagi, R.; Hayashi, S.; Uchida, T.; Katsuki, T. *Synlett* ***2001***, 284.

[1465]Hamada, Y.; Sakaguchi, K.-e.; Hatano, K.; Hara, O. *Tetrahedron Lett.* ***2001***, *42*, 1297.

[1466]Kuwano, R.; Kondo, Y.; Matsuyama, Y. *J. Am. Chem. Soc.* ***2003***, *125*, 12104; Faller, J.W.; Wilt, J.C. *Tetrahedron Lett.* ***2004***, *45*, 7613.

[1467]**Amide esters:** Kazmaier, U.; Zumpe, F.L. *Angew. Chem. Int. Ed.* ***1999***, *38*, 1468.

[1468]You, S.-L.; Hou, X.-L.; Dai, L.-X.; Zhu, X.-Z. *Org. Lett.* ***2001***, *3*, 149; Evans, P.A.; Leahy, D.K. *J. Am. Chem. Soc.* ***2003***, *125*, 7882; Evans, P.A.; Lawler, M.J. *J. Am. Chem. Soc.* ***2004***, *126*, 8642. For a reaction of a silyl enol ether, see Muraoka, T.; Matsuda, I.; Itoh, K. *Tetrahedron Lett.* ***2000***, *41*, 8807.

displace allylic carbonates,[1469] often in conjunction with chiral ligands to give the product with enantioselectivity. Polymer-supported phosphine ligands have been used successfully.[1470] Catalyst systems other than palladium have been used for this reaction with allylic carbonates.[1471]

Intramolecular cyclization is possible when the active methylene compound and an allylic acetate or carbonate is incorporated into the same molecule.[1472]

Allylic phosphonates have been used as substrates for displacement by higher order cuprates[1473] (see **10-58**) or dialkylzinc reagents.[1474]

10-61 Coupling of Organometallic Reagents With Esters of Sulfates, Sulfoxides, Sulfones, Nitro, and Acetals

Alkyl-de-sulfonyl and de-sulfonyloxy-substitution, and so on; **Alkyl-de-alkoxy-substitution**, and so on; **Alkyl-de-nitration**, and so on.

$$RSO_2X + R'M \longrightarrow R{-}R'$$

Leaving groups other than halide, esters or carbonate, or sulfonate esters are sometimes used. Sulfates, sulfonates, and epoxides give the expected products. The reaction of sodium sulfonates and alkyl halides in ionic liquids have been reported.[1475] Acetals can behave as substrates, one OR group being replaced by ZCHZ′ in a reaction similar to **10-64**.[1476] Ortho esters behave similarly, but the product loses R′OH to give an enol ether.[1477] The SO_2Ph group of allylic sulfones can

[1469]**Aryllithium reagents:** Evans, P.A.; Uraguchi, D. *J. Am. Chem. Soc.* ***2003***, *125*, 7158. **Alkoxides**: Evans, P.A.; Leahy, D.K.; Slieker, L.M. *Tetrahedron Asymmetry* ***2003***, *14*, 3613. **Phenoxide anions**: Evans, P.A.; Leahy, D.K. *J. Am. Chem. Soc.* ***2000***, *122*, 5012; López, F.; Ohmura, T.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2003***, *125*, 3426. **Secondary amines**: Matsushima, Y.; Onitsuka, K.; Kondo, T.; Mitsudo, T.-A.; Takahashi, S. *J. Am. Chem. Soc.* ***2001***, *123*, 10405. **Primary amines**: Ohmura, T.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2002***, *124*, 15164. ***N*-Lithio-sulfonamides**: Evans, P.A.; Robinson, J.E.; Baum, E.W.; Fazal, A.N. *J. Am. Chem. Soc.* ***2002***, *124*, 8782. ***C*-Alkylation with an indole**: Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Org. Lett.* ***2004***, *6*, 3199. **Michael addition of conjugated esters**: Muraoka, T.; Matsuda, I.; Itoh, K. *J. Am. Chem. Soc.* ***2000***, *122*, 9552.

[1470]Uozumi, Y.; Shibatmoi, K. *J. Am. Chem. Soc.* ***2001***, *123*, 2919.

[1471]**Ruthenium**: Trost, B.M.; Fraisse, P.L.; Ball, Z.T. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1059. **Molybdenum**: Glorius, F.; Pfaltz, A. *Org. Lett.* ***1999***, *1*, 141; Malkov, A.V.; Spoor, P.; Vinader, V.; Kočovský, P. *Tetrahedron Lett.* ***2001***, *42*, 509. **Iridium**: Alexakis, A.; Polet, D. *Org. Lett.* ***2004***, *6*, 3529; Lee, P.H.; Sung, S.-y.; Lee, K.; Chang, S. *Synlett* ***2002***, 146.

[1472]Castaño, A.M.; Méndez, M.; Ruano, M.; Echavarren, A.M. *J. Org. Chem.* ***2001***, *66*, 589. See also, Zhang, Q.; Lu, X.; Han, X. *J. Org. Chem.* ***2001***, *66*, 7676.

[1473]Belelie, J.L.; Chong, J.M. *J. Org. Chem.* ***2001***, *66*, 5552.

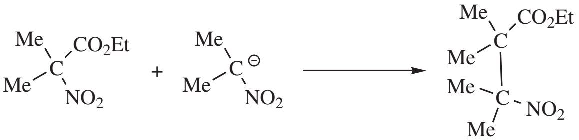
[1474]Kacprzynski, M.A.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2004***, *126*, 10676.

[1475]In bmim BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate: Hu, Y.; Chen, Z.-C.; Le, Z.-G.; Zheng, Q.G. *Synth. Commun.* ***2004***, *34*, 4031.

[1476]Yufit, S.S.; Krasnaya, Zh.A.; Levchenko, T.S.; Kucherov, V.F. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1967***, 123; Aleskerov, M.A.; Yufit, S.S.; Kucherov, V.F. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1972***, *21*, 2279.

[1477]For a review, see DeWolfe, R.H. *Carboxylic Ortho Acid Derivatives*, Academic Press, NY, ***1970***, pp. 231–266.

be a leaving group if a palladium(0) complex is present.[1478] The NR_2 group from Mannich bases, such as $RCOCH_2CH_2NR_2$, can also act as a leaving group in this reaction (elimination–addition mechanism, p. 474). A nitro group can be displaced[1479] from α-nitro esters, ketones, nitriles, and α,α-dinitro compounds,[1480] and even from simple tertiary nitro compounds of the form R_3CNO_2[1481] or $ArR_2C\text{-}NO_2$[1482] by salts of nitroalkanes, for example,



These reactions take place by SET mechanisms.[1483] However, with α-nitro sulfones it is the sulfone group that is displaced, rather than the nitro group.[1484] The SO_2R group of allylic sulfones can be replaced by CHZZ′ (C=CCH$_2$—SO$_2$R → C=CCH$_2$—CHZZ′) if an $Mo(CO)_6$ catalyst is used.[1485]

tert-Butylsulfones react with organolithium reagents, in the presence of a catalytic amount of iron complex, to give coupling.[1486] In this case, the *t*-BuSO$_2$ unit becomes a "leaving group." A sulfoxide was a "leaving group" in the cyclization of a carboxylic acid contain a sulfoxide unit at C-4. Treatment with phenyliodonium bis(trifluoroacetate) gave the five-membered ring lactone.[1487] Similar displacement of TolSO$_2$ was observed with tolylsulfones and diethylzinc.[1488] Biaryl can be prepared by the reaction of diarylsulfones and arylmagnesium halides, n the presence of a nickel catalyst.[1489]

Phosphonic esters, ROPO(OR)$_2$, react with allylic Grignard reagents to give the coupling product.[1490]

OS **I**, 471; **II**, 47, 360; **VII**, 351; **VIII**, 97, 471.

[1478]Trost, B.M.; Schmuff, N.R.; Miller, M.J. *J. Am. Chem. Soc.* ***1980***, *102*, 5979.

[1479]For reviews, see Kornblum, N., in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 1, Wiley, NY, ***1982***, pp. 361–393; Kornblum, N. *Angew. Chem. Int. Ed.* ***1975***, *14*, 734. For reviews of aliphatic S_N reactions in which NO_2 is a leaving group, see Tamura, R.; Kamimura, A.; Ono, N. *Synthesis* ***1991***, 423; Kornblum, N., in Feuer, H.; Nielsen, A.T. *Nitro Compunds: Recent Advances in Synthesis and Chemisry*, VCH, NY, ***1990***, pp. 46–85.

[1480]Kornblum, N.; Kelly, W.J.; Kestner, M.M. *J. Org. Chem.* ***1985***, *50*, 4720.

[1481]Kornblum, N.; Erickson, A.S. *J. Org. Chem.* ***1981***, *46*, 1037.

[1482]Kornblum, N.; Carlson, S.C.; Widmer, J.; Fifolt, M.J.; Newton, B.N.; Smith, R.G. *J. Org. Chem.* ***1978***, *43*, 1394.

[1483]For a review of the mechanism, see Beletskaya, I.P.; Drozd, V.N. *Russ. Chem. Rev.* ***1979***, *48*, 431. See also, Kornblum, N.; Wade, P.A. *J. Org. Chem.* ***1987***, *52*, 5301; Bowman, W.R. *Chem. Soc. Rev.* ***1988***, *17*, 283; Ref. 1479.

[1484]Kornblum, N.; Boyd, S.D.; Ono, N. *J. Am. Chem. Soc.* ***1974***, *96*, 2580.

[1485]Trost, B.M.; Merlic, C.A. *J. Org. Chem.* ***1990***, *55*, 1127.

[1486]Jin, L.; Julia, M.; Verpeaux, J.N. *Synlett* ***1994***, 215.

[1487]Casey, M.; Manage, A.C.; Murphy, P.J. *Tetrahedron Lett.* ***1992***, *33*, 965.

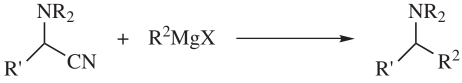
[1488]Dahmen, S.; Bräse, S. *J. Am. Chem. Soc.* ***2002***, *124*, 5940.

[1489]Cho, C.-H.; Yun, H.-S.; Park, K. *J. Org. Chem.* ***2003***, *68*, 3017.

[1490]Yanagisawa, A.; Hibino, H.; Nomura, N.; Yamamoto, H. *J. Am. Chem. Soc.* ***1993***, *115*, 5879.

10-62 The Bruylants Reaction

Alkyl-de-cyanation



The *Bruylants reaction* is the reaction of an aminonitrile with a Grignard reagent to give a substituted amine.[1491] This reaction is most often used for the preparation of aliphatic amines via aliphatic Grignard reagents. In a few cases, vinylic Grignard reagents can be used to prepare allylic amines.[1492] The use of $AgBF_4$ to convert amino nitriles to the corresponding iminium ion facilitates the Bruylants reaction with vinylic Grignard reagents.[1493]

Displacement of a cyano group in α-cyanoketones is possible. Treatment of the α-cyanoketone with SmI_2 followed by addition of an excess of allyl bromide gave the α-allyl ketone derivative.[1494] α-Cyano amines react with allyl bromide and then zinc metal to give homoallylic amines after treatment with dilute acetic acid in THF.[1495]

10-63 Coupling Involving Alcohols

De-hydroxyl-coupling

$$\text{ROH} + \text{R'M} \longrightarrow \text{R–R'}$$

In some cases, it is possible to couple an alcohol with an organometallic compound. Allylic alcohols are coupled with alkylmagnesium bromides in the presence of $Ti(OiPr)_4$, for example.[1496] Allylic alcohols can be coupled with arylboronic acids in ionic liquid solvent and a rhodium catalyst.[1497] The palladium-catalyzed reaction of active methylene compounds with allylic alcohols[1498] or benzylic alcohols[1499] is also known. The coupling of an alcohol to the α-carbon of a ketone

[1491]Bruylants, P. *Bull. Soc. Chem. Belg.* ***1924***, *33*, 467.

[1492]Ahlbrecht, H.; Dollinger, H. *Synthesis* ***1985***, 743; Trost, B.M.; Spagnol, M.D. *J. Chem. Soc., Perkin Trans. 1* ***1995***, 2083.

[1493]Agami, C.; Couty, F.; Evano, G. *Org. Lett.* ***2000***, *2*, 2085.

[1494]Zhu, J.-L.; Shia, K.-S.; Liu, H.-J. *Tetrahedron Lett.* ***1999***, *40*, 7055.

[1495]Bernardi, L.; Bonini, B.F.; Capitò, E.; Dessole, G.; Fochi, M.; Comes-Franchini, M.; Ricci, A. *Synlett* ***2003***, 1778.

[1496]Kulinkovich, O.G.; Epstein, OL.; Isakov, V.E.; Khmel'nitskaya, E.A. *Synlett* ***2001***, 49.

[1497]Kabalka, G.W.; Dong, G.; Venkataish, B. *Org. Lett.* ***2003***, *5*, 893.

[1498]Manabe, K.; Kobayashi, S. *Org. Lett.* ***2003***, *5*, 3241; Kinoshita, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* ***2004***, *6*, 4085; Horino, Y.; Naito, M.; Kimura, M. Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* ***2001***, *42*, 3113.

[1499]Bisaro, F.; Prestat, G.; Vitale, M.; Poli, G. *Synlett* ***2002***, 1823.

(RCOMe + R′OH) to give a β-substituted alcohol (RCH(OH)CH$_2$R′) is possible in the presence of a ruthenium catalyst.[1500]

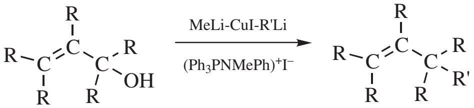
$$2\,\text{ROH} \xrightarrow[-78^\circ\text{C}]{\text{MeLi–TiCl}_3} \text{RR}$$

Allylic or benzylic alcohols can be symmetrically coupled[1501] by treatment with methyllithium and titanium trichloride at −78°C[1502] or by refluxing with TiCl$_3$ and LiAlH$_4$.[1503] When the substrate is an allylic alcohol, the reaction is not regiospecific, but a mixture of normal coupling and allylically rearranged products is found. A free-radical mechanism is involved.[1504] The TiCl$_3$–LiAlH$_4$ reagent can also convert 1,3-diols to cyclopropanes, provided that at least one a phenyl is present.[1505]

Tertiary alcohols react with trimethylaluminum at 80–200°C to give methylation.[1506] The presence of side products from elimination and rearrangement, as well as the lack of stereospecificity,[1507] indicate an

$$\text{R}_3\text{COH} + \text{Me}_3\text{Al} \xrightarrow{80-200^\circ\text{C}} \text{R}_3\text{CMe}$$

S$_N$1 mechanism. The reaction can also be applied to primary and secondary alcohols if these contain an aryl group in the a position. Higher trialkylaluminums are far less suitable, because reduction competes with alkylation (see also, reactions of Me$_3$Al with ketones, **16-24**, and with carboxylic acids, **16-82**). The compound Me$_2$TiCl$_2$ also reacts with tertiary alcohols in the same way.[1508] Allylic alcohols couple with a reagent prepared from MeLi, CuI, and R′Li in the presence of (Ph$_3$PNMePh)$^+$ I$^-$ to give alkenes, such as **149**, that are products of allylic rearrangement.[1509]



149

[1500]Cho, C.S.; Kim, B.T.; Kim. T.-J.; Shim. S.C. *J. Org. Chem.* ***2001***, *66*, 9020.

[1501]For a review, see Lai, Y. *Org. Prep. Proceed. Int.* ***1980***, *12*, 363, pp. 377–388.

[1502]Sharpless, K.B.; Hanzlik, R.P.; van Tamelen, E.E. *J. Am. Chem. Soc.* ***1968***, *90*, 209.

[1503]McMurry, J.E.; Silvestri, M.G.; Fleming, M.P.; Hoz, T.; Grayston, M.W. *J. Org. Chem.* ***1978***, *43*, 3249. For another method, see Nakanishi, S.; Shundo, T.; Nishibuchi, T.; Otsuji, Y. *Chem. Lett.* ***1979***, 955.

[1504]van Tamelen, E.E.; Åkermark, B.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1969***, *91*, 1552.

[1505]Baumstark, A.L.; McCloskey, C.J.; Tolson, T.J.; Syriopoulos, G.T. *Tetrahedron Lett.* ***1977***, 3003; Walborsky, H.M.; Murati, M.P. *J. Am. Chem. Soc.* ***1980***, *102*, 426.

[1506]Meisters, A.; Mole, T. *J. Chem. Soc., Chem. Commun.* ***1972***, 595; Harney, D.W.; Meisters, A.; Mole, T. *Aust. J. Chem.* ***1974***, *27*, 1639.

[1507]Salomon, R.G.; Kochi, J.K. *J. Org. Chem.* ***1973***, *38*, 3715.

[1508]Reetz, M.T.; Westermann, J.; Steinbach, R. *J. Chem. Soc., Chem. Commun.* ***1981***, 237.

[1509]Tanigawa, Y.; Ohta, H.; Sonoda, A.; Murahashi, S. *J. Am. Chem. Soc.* ***1978***, *100*, 4610; Goering, H.L.; Tseng, C.C. *J. Org. Chem.* ***1985***, *50*, 1597. For another procedure, see Yamamoto, Y.; Maruyama, K. *J. Organomet. Chem.* ***1978***, *156*, C9.

The reaction gives good yields with primary, secondary, and tertiary alcohols, and with alkyl and aryllithium reagents.[1510] Allylic alcohols also couple with certain Grignard reagents[1511] in the presence of a nickel complex to give both normal products and the products of allylic rearrangement.

Allenic alcohols couple with allyl indium reagents at 140°C to give allylic alcohol products.[1512] Similarly, ω-hydroxy lactones couple with organoindium reagents.[1513] Phenols react with vinyl boronates and a copper catalyst to give aryl vinyl ethers.[1514]

Alcohols react with allylsilanes, in the presence of an $InCl_3$[1515] or $InBr_3$[1516] catalyst to give the corresponding coupling product ($R_2CHOH \rightarrow R_2CH{-}CH_2CH{=}CH_2$).

10-64 Coupling of Organometallic Reagents With Compounds Containing the Ether Linkage[1517]

Alkyl-de-alkoxy-substitution

$$R_2C(OR')_2 + R''MgX \longrightarrow R_2CR''(OR') + R'OMgX$$

$$RC(OR')_3 + R''MgX \longrightarrow RCR''(OR')_2 + R'OMgX$$

Acetals,[1518] ketals, and ortho esters[1519] react with Grignard reagents to give, respectively, ethers and acetals (or ketals). The latter can be hydrolyzed to aldehydes or ketones (**10-6**). This procedure is a way of converting a halide R″X (which may be alkyl, aryl, vinylic, or alkynyl) to an aldehyde R″CHO, increasing the length of the carbon chain by one carbon (see also, **10-76**). The ketone synthesis generally gives lower yields. Acetals, including allylic acetals, also give this reaction with organocopper compounds and BF_3.[1520] Dihydropyrans react with Grignard reagents in the

[1510]For the allylation of benzylic alcohols, see Cella, J.A. *J. Org. Chem.* ***1982***, *47*, 2125.

[1511]Buckwalter, B.L.; Burfitt, I.R.; Felkin, H.; Joly-Goudket, M.; Naemura, K.; Salomon, M.F.; Wenkert, E.; Wovkulich, P.M. *J. Am. Chem. Soc.* ***1978***, *100*, 6445; Felkin, H.; Joly-Goudket, M.; Davies, S.G. *Tetrahedron Lett.* ***1981***, *22*, 1157; Consiglio, G.; Morandini, F.; Piccolo, O. *J. Am. Chem. Soc.* ***1981***, *103*, 1846, and references cited therein. For a review, see Felkin, H.; Swierczewski, G. *Tetrahedron* ***1975***, *31*, 2735. For other procedures, see Mukaiyama, T.; Imaoka, M.; Izawa, T. *Chem. Lett.* ***1977***, 1257; Fujisawa, T.; Iida, S.; Yukizaki, H.; Sato, T. *Tetrahedron Lett.* ***1983***, *24*, 5745.

[1512]Araki, S.; Usui, H.; Kato, M.; Butsugan, Y. *J. Am. Chem. Soc*, ***1996***, *118*, 4699.

[1513]Bernardelli, P.; Paquette, L.A. *J. Org. Chem.* ***1997***, *62*, 8284.

[1514]McKinley, N.F.; O'Shea, D.F. *J. Org. Chem.* ***2004***, *69*, 5087.

[1515]Yasuda, M.; Saito, T.; Ueba, M.; Baba, A. *Angew. Chem. Int. Ed.* ***2004***, *43*, 1414.

[1516]Kim, S.H.; Shin, C.; Pae, A.N.; Koh, H.Y.; Chang, M.H.; Chung, B.Y.; Cho, Y.S. *Synthesis* ***2004***, 1581.

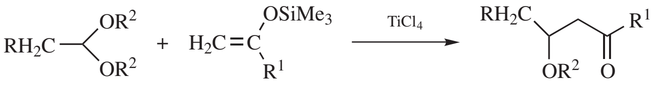
[1517]For a review, see Trofimov, B.A.; Korostova, S.E. *Russ. Chem. Rev.* ***1975***, *44*, 41.

[1518]For a review of coupling reactions of acetals, see Mukaiyama, T.; Murakami, M. *Synthesis* ***1987***, 1043. For a discussion of the mechanism, see Abell, A.D.; Massy-Westropp, R.A. *Aust. J. Chem.* ***1985***, *38*, 1031. For a list of substrates and reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 934–942.

[1519]For a review of the reaction with ortho esters, see DeWolfe, R.H. *Carboxylic Ortho Acid Derivatives*, Academic Press, NY, ***1970***, pp. 44–45, 224–230.

[1520]Normant, J.F.; Alexakis, A.; Ghribi, A.; Mangeney, P. *Tetrahedron* ***1989***, *45*, 507; Alexakis, A.; Mangeney, P.; Ghribi, A.; Marek, I.; Sedrani, R.; Guir, C.; Normant, J.F. *Pure Appl. Chem.* ***1988***, *60*, 49.

presence of a nickel catalyst.[1521] Acetals also undergo substitution when treated with silyl enol ethers or allylic silanes, with a Lewis acid catalyst,[1522] for example,



ω-Ethoxy lactams react with Grignard regents to give ω-substituted lactams.[1523] Tertiary amines can be prepared by the reaction of amino ethers with Grignard reagents,[1524] ($R_2NCH_2{-}OR' + R^2MgX \rightarrow R_2NCH_2{-}R^2$) or with lithium dialkylcopper reagents.[1525]

Ordinary ethers are not cleaved by Grignard reagents (in fact, diethyl ether and THF are the most common solvents for Grignard reagents), although more active organometallic compounds often do cleave them.[1526] Oxetanes have been opened with organolithium reagents and $BF_3{\bullet}OEt_2$[1527] and also with excess lithium metal with a biphenyl catalyst.[1528] Allylic ethers can be cleaved by Grignard reagents in THF if CuBr is present.[1529] The reaction takes place either with or without allylic rearrangement.[1530] Propargylic ethers give allenes.[1531] Vinylic ethers can also be cleaved by Grignard reagents in the presence of a catalyst, in this case, a nickel complex.[1532] Silyl enol ethers $R_2C{=}CROSiMe_3$ behave similarly.[1533] Bicyclic benzofurans can be opened by dialkylzinc reagents in the presence of a palladium catalyst.[1534]

[1521]Ducoux, J.-P.; LeMénez, P.; Kunesch, N.; Wenkert, E. *J. Org. Chem.* ***1993***, *58*, 1290.

[1522]See Mori, I.; Ishihara, K.; Flippen, L.A.; Nozaki, K.; Yamamoto, H.; Bartlett, P.A.; Heathcock, C.H. *J. Org. Chem.* ***1990***, *55*, 6107, and references cited therein.

[1523]Wei, Z.Y.; Knaus, E.E. *Org. Prep. Proceed. Int.* ***1993***, *25*, 255.

[1524]For example, see Miginiac, L.; Mauzé, B. *Bull. Soc. Chim. Fr.* ***1968***, 2544; Eisele, G.; Simchen, G. *Synthesis* ***1978***, 757; Kapnang, H.; Charles, G. *Tetrahedron Lett.* ***1983***, *24*, 1597; Morimoto, T.; Takahashi, T.; Sekiya, M. *J. Chem. Soc., Chem. Commun.* ***1984***, 794; Mesnard, D.; Miginiac, L. *J. Organomet. Chem.* ***1989***, *373*, 1. See also, Bourhis, M.; Bosc, J.; Golse, R. *J. Organomet. Chem.* ***1983***, *256*, 193.

[1525]Germon, C.; Alexakis, A.; Normant, J.F. *Bull. Soc. Chim. Fr.* ***1984***, II-377.

[1526]For a review of the reactions of ethers with Grignard Reagents, see Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 1013–1045.

[1527]Bach, T.; Eilers, F. *Eur. J. Org. Chem.* ***1998***, 2161.

[1528]Rama, K.; Pasha, M.A. *Tetrahedron Lett.* ***2000***, *41*, 1073.

[1529]Commercon, A.; Bourgain, M.; Delaumeny, M.; Normant, J.F.; Villieras, J. *Tetrahedron Lett.* ***1975***, 3837; Claesson, A.; Olsson, L. *J. Chem. Soc., Chem. Commun.* ***1987***, 621.

[1530]Normant, J.F.; Commercon, A.; Gendreau, Y.; Bourgain, M.; Villieras, J. *Bull. Soc. Chim. Fr.* ***1979***, II-309; Gendreau, Y.; Normant, J.F. *Tetrahedron* ***1979***, *35*, 1517; Calo, V.; Lopez, L.; Pesce, G. *J. Chem. Soc. Perkin Trans. 1* ***1988***, 1301. See also, Valverde, S.; Bernabé, M.; Garcia-Ochoa, S.; Gómez, A.M. *J. Org. Chem.* ***1990***, *55*, 2294.

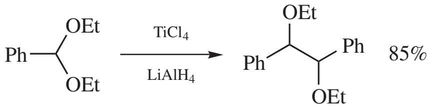
[1531]Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J.F. *Tetrahedron Lett.* ***1989***, *30*, 2387; *J. Am. Chem. Soc.* ***1990***, *112*, 8042.

[1532]Wenkert, E.; Michelotti, E.L.; Swindell, C.S.; Tingoli, M. *J. Org. Chem.* ***1984***, *49*, 4894; Kocieński, P.; Dixon, N.J.; Wadman, S. *Tetrahedron Lett.* ***1988***, *29*, 2353.

[1533]Hayashi, T.; Katsuro, Y.; Kumada, M. *Tetrahedron Lett.* ***1980***, *21*, 3915.

[1534]Lauens, M.; Renaud, J.-L.; Hiebert, S. *J. Am. Chem. Soc.* ***200***, *122*, 1804.

Certain acetals and ketals can be dimerized in a reaction similar to **10-56** by treatment with $TiCl_4$—$LiAlH_4$, for example,[1535]

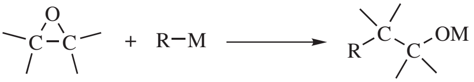


Also see, **10-65**.

OS **II**, 323; **III**, 701. Also see, OS **V**, 431.

10-65 The Reaction of Organometallic Reagents With Epoxides

3(*OC*)-*seco*-Alkyl-de-alkoxy-substitution



The reaction between Grignard reagents or organolithium reagents and epoxides is very valuable and is often used to increase the length of a carbon chain by two carbons.[1536] The Grignard reagent may be aromatic or aliphatic, although tertiary Grignard reagents give low yields. As expected for an S_N2 process, attack is at the less substituted carbon. With allylic Grignard reagents, the addition of a catalytic amount of $Yb(OTf)_3$ facilitated alkylation.[1537] Organolithium reagents,[1538] in the presence of chiral additives lead to the 2-substituted alcohol with good enantioselectivity. Similar reaction with a chiral Schiff base gave the same type of product, with excellent enantioselectivity.[1539]

Lithium dialkylcopper reagents also give the reaction,[1540] as do higher order cuprates,[1541] often producing higher yields. They have the additional advantage that they do not react with ester, ketone, or carboxyl groups so that the epoxide ring of epoxy esters, ketones, and carboxylic acids can be selectively attacked, often

[1535]Ishikawa, H.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* ***1978***, *51*, 2059.

[1536]For a review, see Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 961–1012. For a thorough discussion, see Schaap, A.; Arens, J.F. *Recl. Trav. Chim. Pays-Bas* ***1968***, *87*, 1249. For improved procedures, see Huynh, C.; Derguini-Boumechal, F.; Linstrumelle, G. *Tetrahedron Lett.* ***1979***, 1503; Schrumpf, G.; Grätz, W.; Meinecke, A.; Fellenberger, K. *J. Chem. Res. (S)* ***1982***, 162.

[1537]Likhar, P.R.; Kumar, M.P.; Bandyopadhyay, A.K. *Tetrahedron Lett.* ***2002***, *43*, 3333.

[1538]Harder, S.; van Lenthe, J.H.; van Eikkema Hommes, N.J.R.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1994***, *116*, 2508; Alexakis, A.; Vrancken, E.; Mangeney, P. *Synlett*, ***1998***, 1165.; Hodgson, D.M.; Stent, M.A.H.; Štefane, B.; Wilson, F.X. *Org. Biomol. Chem.* ***2003***, *1*, 1139; Hodgson, D.M.; Maxwell, C.R.; Miles, T.J.; Paruch, E.; Stent, M.A.H.; Matthews, I.R. Wilson, F.X.; Witherington, J. *Angew. Chem. Int. Ed.* ***2002***, *41*, 4313.

[1539]Oguni, N.; Miyagi, Y.; Itoh, K. *Tetrahedron Lett.* ***1998***, *39*, 9023.

[1540]For examples of the use of this reactions, see Posner, G.H. *An Introduction to Synthesis Using Organocopper Reagents*, Wiley, NY, ***1980***, pp. 103–113. See also, Lipshutz, B.H.; Kozlowski, J.; Wilhelm, R.S. *J. Am. Chem. Soc.* ***1982***, *104*, 2305; Blanchot-Courtois, V.; Hanna, I. *Tetrahedron Lett.* ***1992***, *33*, 8087.

[1541]Chauret, D.C.; Chong, J.M. *Tetrahedron Lett.* ***1993***, *34*, 3695.

in a regioselective manner.[1542] The use of BF_3 increases the reactivity of R_2CuLi, enabling it to be used with thermally unstable epoxides.[1543] Lithium diaminocyano cuprates have also been used.[1544]

The reaction has also been performed with other organometallic compounds.[1545] Trialkylaluminum reagents open epoxides with delivery of the alkyl group to carbon.[1546] In the presence of a Lewis acid catalyst, such as BF_3, alkylation can occur at the more substituted carbon.[1547] Friedel–Crafts type alkylation (see **11-11**) is possible when an aromatic compounds reacts with an epoxide and $AlCl_3$.[1548] Epoxides reaction with allyl bromide in the presence of indium metal, with the expected delivery of allyl to the less substituted carbon being the major product.[1549] Other organometallic reagents can be used.[1550] When a substituted epoxide was treated with CO, BF_3•$OEt_2$and a cobalt catalyst, carbonylation occurred and the final product was a β-lactone.[1551] Similar β-lactone forming reactions were reported using substituted epoxides, CO and a metal compound–BF_3 complex.[1552] Five-membered ring lactams were also formed from substituted epoxides using BF_3•OEt_2 followed by treatment with KHF_2.[1553] An interesting variation reacted an epoxy acetate (acetoxy at the 3-position relative to the first epoxy carbon) with Cp_2TiCl_2/Zn, and the product was an allylic alcohol where the epoxide ring was opened with loss of the acetoxy group.[1554]

[1542]Johnson, C.R.; Herr, R.W.; Wieland, D.M. *J. Org. Chem.* ***1973***, *38*, 4263; Hartman, B.C.; Livinghouse, T.; Rickborn, B. *J. Org. Chem.* ***1973***, *38*, 4346; Hudrlik, P.F.; Peterson, D.; Rona, R.J. *J. Org. Chem.* ***1975***, *40*, 2263; Chong, J.M.; Sharpless, K.B. *Tetrahedron Lett.* ***1985***, *26*, 4683; Chong, J.M.; Cyr, D.R.; Mar, E.K. *Tetrahedron Lett.* ***1987***, *28*, 5009; Larchevêque, M.; Petit, Y. *Tetrahedron Lett.* ***1987***, *28*, 1993.

[1543]See, for example, Alexakis, A.; Jachiet, D.; Normant, J.F. *Tetrahedron* ***1986***, *42*, 5607.

[1544]Yamamoto, Y.; Asao, N.; Meguro, M.; Tsukada, N.; Nemoto, H.; Sadayori, N.; Wilson, J.G.; Nakamura, H. *J. Chem. Soc., Chem. Commun.* ***1993***, 1201.

[1545]For lists of organometallic reagents that react with epoxides, see Wardell, J.L.; Paterson, E.S. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 2; Wiley, NY, ***1985***, pp. 307–310; Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1045–1063.

[1546]Schneider, C.; Brauner, J. *Eur. J. Org. Chem.* ***2001***, 4445; Sasaki, M.; Tanino, K.; Miyashita, M. *J. Org. Chem.* ***2001***, *66*, 5388; Sasaki, M.; Tanino, K.; Miyashita, M. *Org. Lett.* ***2001***, *3*, 1765; Shanmugam, P.; Miyashita, M. *Org. Lett.* ***2003***, *5*, 3265 (formation of *O*-silyl ether product). For the reaction in an ionic liquid see Zhou, H.; Campbell, E.J.; Nguyen, S.T. *Org. Lett.* ***2001***, *3*, 2229.

[1547]For an example, see Zhao, H.; Pagenkopf, B.L. *Chem. Commun.* ***2003***, 2592.

[1548]Lin, J.; Kanazaki, S.; Kashino, S.; Tsuboi, S. *Synlett* ***2002***, 899.

[1549]Yadav, J.S.; Anjaneyulu, S.; Ahmed, Md.M.; Subba Reddy, B.V. *Tetrahedron Lett.* ***2001***, *42*, 2557; Oh, B.K.; Cha, J.H.; Cho, Y.S.; Choi, K.I.; Koh, H.Y.; Chang, M.H.; Pae, A.N. *Tetrahedron Lett.* ***2003***, *44*, 2911; Hirashita, T.; Mitsui, K.; Hayashi, Y.; Araki, S. *Tetrahedron Lett.* ***2004***, *45*, 9189. For a reaction using palladium nanoparticles see Jiang, N.; Hu, Q.; Reid, C.S.; Ou, Y.; Li, C.J. *Chem. Commun.* ***2003***, 2318.

[1550]**Ba**: Yasue, K.; Yanagisawa, A.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* ***1997***, *70*, 493. **Mn**: Tang, J.; Yorimitsu, H.; Kakiya, H.; Inoue, R.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* ***1997***, *38*, 9019. **Sn**: Yadav, J.S.; Reddy, B.V.S.; Satheesh, G. *Tetahedron Lett.* ***2003***, *44*, 6501. **Zn**: Equey, O.; Vrancken, E.; Alexakis, A. *Eur. J. Org. Chem.* ***2004***, 2151.

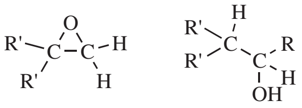
[1551]Lee, J.T.; Thomas, P.J.; Apler, H. *J. Org. Chem.* ***2001***, *66*, 5424.

[1552]Getzler, Y.D.Y.L.; Mahadevan V.; Lobkovsky, E.B.; Coates, G.W. *J. Am. Chem. Soc.* ***2002***, *124*, 1174; Schmidt, J.A.R.; Mahadevan, V.; Getzler, Y.D.Y.L.; Coates, G.W. *Org. Lett.* ***2004***, *6*, 373.

[1553]Movassaghi, M.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2002***, *124*, 2456.

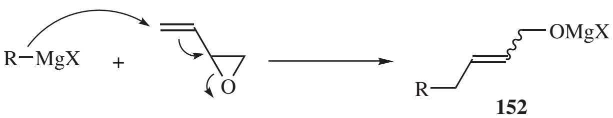
[1554]Bermejo, F.; Sandoval, C. *J. Org. Chem.* ***2004***, *69*, 5275.

In the presence of a scandium catalyst, chiral allylic boranes open epoxides at the less substituted position to generate chiral, homoallylic alcohols.[1555]



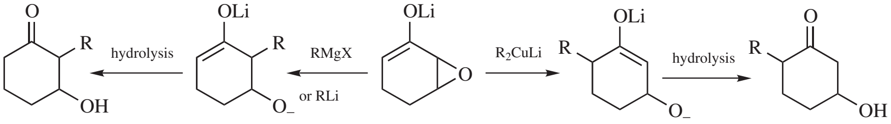
150 **151**

When *gem*-disubstituted epoxides (**150**) are treated with Grignard reagents (and sometimes other epoxides), the product may be **151**, that is, the new alkyl group may appear on the same carbon as the OH. In such cases, the epoxide is isomerized to an aldehyde or a ketone before reacting with the Grignard reagent. Halohydrins are often side products.



152

When the substrate is a vinylic epoxide,[1556] Grignard reagents generally give a mixture of the normal product and the product of allylic rearrangement (**152**).[1557] Butyllithium reacted with a difluoroalkylidene epoxide ($F_2C{=}CR$–epoxide) and S_N2' displacement gave alkylation at the difluoro carbon and opened the epoxide.[1558] The latter often predominates. In the case of R_2CuLi,[1559] acyclic substrates give mostly allylic rearrangement (S_N2').[1556] The double bond of the "vinylic" epoxide can be part of an enolate anion. In this case, R_2CuLi give exclusive allylic rearrangement (S_N2') to **153** after hydrolysis, while Grignard and organolithium reagents opened the epoxide directly (S_N2) to give **154** after hydrolysis.[1560]



154 **153**

[1555]Lautens, M.; Maddess, M.L.; Sauer, E.L.O.; Oullet, S.G. *Org. Lett.* ***2002***, *4*, 83.

[1556]For a list of organometallic reagents that react with vinylic epoxides, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 244–250.

[1557]Anderson, R.J. *J. Am. Chem. Soc.* ***1970***, *92*, 4978; Johnson, C.R.; Herr, R.W.; Wieland, D.M. *J. Org. Chem.* ***1973***, *38*, 4263; Marshall, J.A.; Trometer, J.D.; Cleary, D.G. *Tetrahedron* ***1989***, *45*, 391.

[1558]Ueki, H.; Chiba, T.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* ***2004***, *69*, 7616.

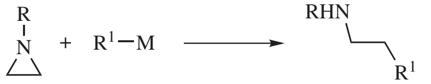
[1559]For a review of the reactions of vinylic epoxides with organocopper reagents, see Marshall, J.A. *Chem. Rev.* ***1989***, *89*, 1503.

[1560]Wender, P.A.; Erhardt, J.M.; Letendre, L.J. *J. Am. Chem. Soc.* ***1981***, *103*, 2114.

An organometallic equivalent that opens epoxides is a hydrosilane, for example, Me_3SiH, and carbon monoxide, catalyzed by dicobalt octacarbonyl:[1561] See **10-55** for other coupling reactions with organosilanes. Silyl enol ethers react with epoxides in a related reaction, but a Lewis acid, such as $TiCl_4$, is required.[1562]

OS **I**, 306; **VII**, 501; **VIII**, 33, 516; **X**, 297.

10-66 Reaction of Organometallics With Aziridines



Aziridines have been opened by organometallic reagents to give amines.[1563] Although less reactive than epoxides, it is also possible to open aziridines[1564] with organometallic reagents particularly when there is a *N*-sulfonyl group such as tosyl (formally making it a sulfonamide). Grignard reagents react with *N*-tosyl 2-phenylaziridine to give the corresponding *N*-tosylamine.[1565] Organocuprates (**10-58**) reaction with *N*-alkylaziridines to give the corresponding amine.[1566] *N*-Tosyl aziridines have also been opened with enolate anions, which led to a pyrroline derivative,[1567] and with $Me_2S{=}CHCO_2Et$ (see **16-46**) to generate a *N*-tosyl azetidine.[1568] In a Friedel–Crafts type reaction (**11-11**), aziridines react with benzene, in the presence of $In(OTf)_3$, to give the β-aryl amine.[1569] Allylic alcohols open *N*-tosylaziridines with KSF–Montmorillonite clay.[1570]

Aziridines react with nucleophiles other than carbon nucleophiles. In the presence of TBAF, trimethylsilyl azide react with *N*-tosylaziridines to give the azido *N*-tosylamine.[1571] *N*-Benzylic aziridines are opened by trimethylsilyl azide in the presence of a chromium catalyst.[1572] Acetic anhydride reacts with *N*-tosylaziridines, in the presence of PBu_3, to give the *N*-tosylamino acetate.[1573] *N*-Tosylaziridines react with $InCl_3$ to give the chloro *N*-tosylamine.[1574]

[1561] Murai, T.; Kato, S.; Murai, T.; Toki, T.; Suzuki, S.; Sonoda, N. *J. Am. Chem. Soc.* ***1984***, *106*, 6093.

[1562] Lalić, G.; Petrovski, Ž.; Galonić, D.; Matović, R.; Saičić, R.N. *Tetrahedron* ***2001***, *57*, 583.

[1563] See, for example Eis, M.J.; Ganem, B. *Tetrahedron Lett.* ***1985***, *26*, 1153; Onistschenko, A.; Buchholz, B.; Stamm, H. *Tetrahedron* ***1987***, *43*, 565.

[1564] Crotti, P.; Favero, L.; Gardelli, C.; Macchia, F.; Pineschi, M. *J. Org. Chem.* ***1995***, *60*, 2514.

[1565] Toshimitsu, A.; Abe, H.; Hirosawa, C.; Tamao, K. *J. Chem. Soc. Perkin Trans. 1* ***1994***, 3465; Müller, P.; Nury, P. *Org. Lett.* ***1999***, *1*, 439; Müller, P.; Nury, P. *Helv. Chim. Acta* ***2001***, *84*, 662.

[1566] Penkett, C.S.; Simpson, I.D. *Tetrahedron Lett.* ***2001***, *42*, 1179.

[1567] Lygo, B. *Synlett*, ***1993***, 764.

[1568] Nadir, U.K.; Arora, A. *J. Chem. Soc. Perkin Trans. 1* ***1995***, 2605.

[1569] Saidi, M.R.; Azizi, N.; Naimi-Jamal, M.R. *Tetrahedron Lett.* ***2001***, *42*, 8111.

[1570] Yadav, J.S.; Reddy, B.V.S.; Balanarsaiah, E.; Raghavendra, S. *Tetrahedron Lett.* ***2002***, *43*, 5105.

[1571] Wu, J.; Hou, X.-L.; Dai, L.-X. *J. Org. Chem.* ***2000***, *65*, 1344.

[1572] Li, Z.; Fernández, M.; Jacobsen, E.N. *Org. Lett.* ***1999***, *1*, 1611.

[1573] Fan, R.-H.; Hou, X.-L. *Tetrahedron Lett.* ***2003***, *44*, 4411.

[1574] Yadav, J.S.; Subba Reddy, B.V.; Kumar, G.M. *Synlett* ***2001***, 1417.

10-67 Alkylation at a Carbon Bearing an Active Hydrogen

Bis(ethoxycarbonyl)methyl-de-halogenation, and so on.

The metal-catalyzed displacement of allylic acetates and carbonates (**10-60**) clearly falls in to this category. However, this section will focus on the more general reaction of active methylene compounds with substrates bearing a leaving group, not necessarily allylic substrates or metal catalyzed. When compounds contain two or three strong electron-withdrawing groups on a carbon atom bearing a proton (the so-called α-proton), that proton is more acidic than compounds without such groups (p. 252). Treatment with a suitable base (a base that has a conjugate acid with a pK_a greater than the α-proton) removes the α-proton and generates the corresponding enolate anion (**10-68**). These enolate anions react as carbon nucleophiles and attack alkyl halides, resulting in their alkylation.[1575] Both Z and Z′ may be COOR′, CHO, COR′,[1576] $CONR'_2$, COO^-, CN,[1577] NO_2, SOR′, SO_2R',[1578] SO_2OR', $SO_2NR'_2$ or similar groups.[1579] Some commonly used bases are sodium ethoxide and potassium *tert*-butoxide, each in its respective alcohol as solvent. With particularly acidic compounds (e.g., β-diketones–Z, Z′ = COR′), sodium hydroxide in water or aqueous alcohol or acetone, or even sodium carbonate,[1580] is a strong enough base for the reaction. If at least one Z group is COOR′, saponification is a possible side reaction. In addition to the groups listed above, Z may also be phenyl, but if two phenyl groups are on the same carbon, the acidity is less than in the other cases and a stronger base must be used. However, the reaction can be successfully carried out with diphenylmethane with $NaNH_2$ as the base.[1581] If the solvent used in the reaction is acidic enough to protonate either the enolate anion or the base, an equilibrium will be established leading to only small amounts of the enolate anion (thermodynamic conditions). Such aprotic solvents include

[1575]For dicussions of reactions **10-67** and **10-68**, see House, H.O. *Modern Synthetic Reactions*, 2nd ed., W. A. Benjamin, NY, ***1972***, pp. 492–570, 586–595; Carruthers, W. *Some Modern Methods of Organic Synthesis* 3rd ed., Cambridge University Press, Cambridge, ***1986***, pp. 1–26.

[1576]For a reaction using n-Bu_4NF as the base in aq. THF, see Christoffers, J. *Synth. Commun.* ***1999***, *29*, 117.

[1577]For reviews of the reactions of malononitrile $CH_2(CN)_2$, see Fatiadi, A.J. *Synthesis* ***1978***, 165, 241; Freeman, F. *Chem. Rev.* ***1969***, *69*, 591.

[1578]For a review of compounds with two SO_2R groups on the same carbon (*gem*-disulfones), see Neplyuev, V.M.; Bazarova, I.M.; Lozinskii, M.O. *Russ. Chem. Rev.* ***1986***, *55*, 883.

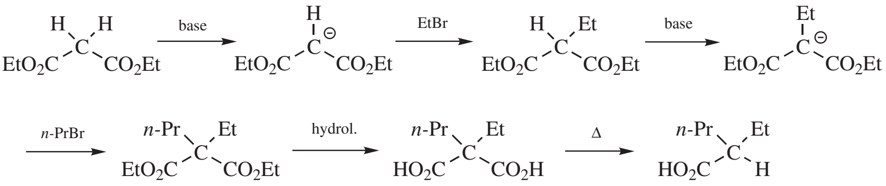
[1579]For lists of examples, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1522–1527 *ff*, 1765–1769.

[1580]See, for example, Fedoryński, M.; Wojciechowski, K.; Matacz, Z.; Makosza, M. *J. Org. Chem.* ***1978***, *43*, 4682.

[1581]Murphy, W.S.; Hamrick, Jr., P.J.; Hauser, C.R. *Org. Synth. V*. 523.

water, alcohols, or amines. In general, solvents that do not contain an acidic proton (aprotic solvents) are used, but protic solvents can be used in some cases. The use of polar aprotic solvents (e.g., DMF or DMSO) markedly increases the rate of alkylation,[1582] but also increases the extent of alkylation at the oxygen rather than the carbon with highly reactive species such as iodomethane (p. 513). In general, enolate anions such as those described here react with alkyl halides via *C*-alkylation, although trialkylsilyl halides and anhydrides tend to react via *O*-alkylation. Phase-transfer catalysis has also been used,[1583] and the use of chiral phase transfer catalysts led to enantioselectivity in the alkylated product.[1584] The reaction is successful for primary and secondary alkyl, allylic (with allylic rearrangement possible), and benzylic RX, but fails for tertiary halides, since these undergo elimination under the reaction conditions (see, however, p. 625). Various functional groups may be present in RX as long as they are not sensitive to base. Side reactions that may cause problems are the above-mentioned competing *O*-alkylation, elimination (if the enolate anion is a strong enough base), and dialkylation.

With substrates, such as ZCH_2Z', it is possible to alkylate twice. Initial removal of the proton with a base followed by alkylation of the resulting enolate anion with RX, can be followed by subsequent removal of the proton from ZCHRZ′ and then alkylation with the same or a different RX. An important example of this reaction is the *malonic ester synthesis*, in which both Z groups are COOEt. The product can be hydrolyzed and decarboxylated (**12-40**) to give a carboxylic acid. An illustration is the preparation of 2-ethylpentanoic acid (**155**) from malonic ester. A variation of this alkylation sequence employs 1,2-dibromoethane as the alkylating agent, and subsequent treatment with DBU leads to incorporation of a vinyl group on the α-carbon.[1585] Another variation involved coupling of a dimalonate with an allylic carbonate (see **10-60**), using a polymer-supported palladium catalyst.[1586]



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It is obvious that many carboxylic acids of the formulas RCH_2COOH and RR′CHCOOH can be synthesized by this method [for some other ways of preparing

[1582]Zaugg, H.E.; Dunnigan, D.A.; Michaels, R.J.; Swett, L.R.; Wang, T.S.; Sommers, A.H.; DeNet, R.W. *J. Org. Chem.* ***1961***, *26*, 644; Johnstone, R.A.W.; Tuli, D.; Rose, M.E. *J. Chem. Res. (S)* ***1980***, 283.

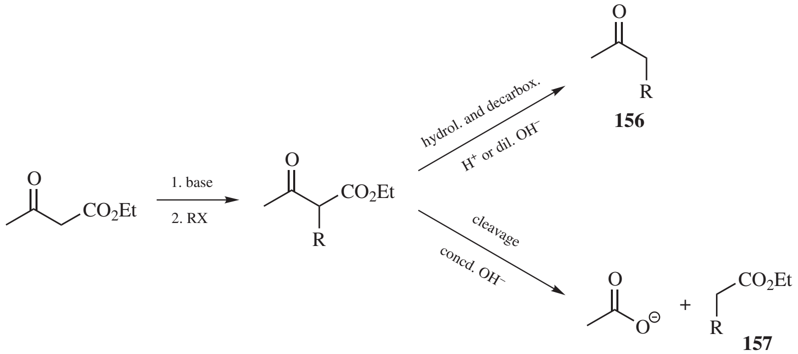
[1583]See Sukhanov, N.N.; Trappel', L.N.; Chetverikov, V.P.; Yanovskaya, L.A. *J. Org. Chem. USSR* ***1985***, *21*, 2288; Tundo, P.; Venturello, P.; Angeletti, E. *J. Chem. Soc. Perkin Trans. 1* ***1987***, 2159.

[1584]Park, E.J.; Kim, M.H.; Kim, D.Y. *J. Org. Chem.* ***2004***, *69*, 6897.

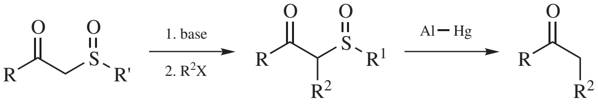
[1585]Bunce, R.A.; Burns, S.E. *Org. Prep. Proceed. Int.* ***1999***, *31*, 99.

[1586]Akiyama, R.; Kobayashi, S. *J. Am. Chem. Soc.* ***2003***, *125*, 3412.

such acids (see **10-70–10-73**)]. Another important example is the *acetoacetic ester synthesis*, in which Z is COOEt and Z′ is $COCH_3$. In this case, the product can be decarboxylated with acid or dilute base (**12-40**) to give a ketone (**156**) or cleaved with concentrated base (**12-43**) to give a carboxylic ester (**157**) and a salt of acetic acid. This reaction has been done in *tert*-butanol in the presence of alumina, *in vacuo*, to give the alkylated keto acid directly from the keto ester.[1587]



Another way of preparing ketones involves alkylation[1588] of β-keto sulfoxides[1589] or sulfones,[1590] to give **158**.



158

The sulfoxide group in the product (**158**) is easily reduced (desulfurized, see p. $$$) to give the ketone in high yields using aluminum amalgam or by electrolysis.[1591] β-Keto sulfoxides, such as **158** or sulfones (—SO_2—), are easily prepared (**16-86**). When one group attached to the sulfur atom is chiral, the alkylation proceeds to with reasonable enantioselectivity.[1592] Alkylation of α-nitrosulfones was reported, using photochemical conditions, $(Me_3Sn)_2$ and a secondary iodide.[1593]

Other examples of the reaction are the *cyanoacetic ester synthesis*, in which Z is COOEt and Z′ is CN (as in the malonic ester synthesis, the product here can be hydrolyzed and decarboxylated), and the *Sorensen* method of amino acid synthesis, in which

[1587]Bhar, S.; Chaudhuri, S.K.; Sahu, S.G.; Panja, C. *Tetrahedron* ***2001***, *57*, 9011.

[1588]For a review of the synthetic uses of β-keto sulfoxides, sulfones, and sulfides, see Trost, B.M. *Chem. Rev.* ***1978***, *78*, 363. For a review of asymmetric synthesis with chiral sulfoxides, see Solladié, G. *Synthesis* ***1981***, 185.

[1589]Gassman, P.G.; Richmond, G.D. *J. Org. Chem.* ***1966***, *31*, 2355. Such sulfoxides can be alkylated on the other side of the C=O group by the use of two moles of base: Kuwajima, I.; Iwasawa, H. *Tetrahedron Lett.* ***1974***, 107.

[1590]House, H.O.; Larson, J.K. *J. Org. Chem.* ***1968***, *33*, 61; Kurth, M.J.; O'Brien, M.J. *J. Org. Chem.* ***1985***, 3846.

[1591]Lamm, B.; Samuelsson, B. *Acta Chem. Scand.* ***1969***, *23*, 691.

[1592]Enders, D.; Harnying, W.; Vignola, N. *Eur. J. Org. Chem.* ***2003***, 3939.

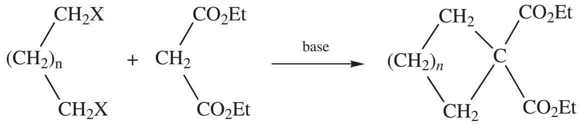
[1593]Kim, S. Yoon, Y.-y.; Lim, C.J. *Synlett* ***2000***, 1151.

the reaction is applied to *N*-acetylaminomalonic ester $(EtOOC)_2CHNHCOCH_3$. Hydrolysis and decarboxylation of the product in this case gives an α-amino acid. The amino group is also frequently protected by conversion to a phthalimido group.

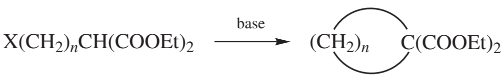
The reaction is not limited to $Z—CH_2—Z'$ compounds. Other compounds have acidic CH hydrogens. Some examples are the methyl hydrogens of α-aminopyridines, the methyl hydrogens of ynamines of the form $CH_3C{\equiv}CNR_2$[1594] (the product in this case can be hydrolyzed to an amide $RCH_2CH_2CONR_2$), the CH_2 hydrogens of cyclopentadiene and its derivatives (p. 63), hydrogens connected to a triple-bond carbon (**10-74**), and the hydrogen of HCN (**10-75**) can also be removed with a base and the resulting ion alkylated (see also, **10-68** to **10-72**). α-Imino esters have been used since treatment with a strong base with a titanium catalyst followed by an aldehyde leads to hydroxy-amino-esters.[1595]

Alkylation takes place at the most acidic position of a reagent molecule; for example, acetoacetic ester (CH_3COCH_2COOEt) is alkylated at the methylene and not at the methyl group, because the former is more acidic than the latter and hence gives up its proton to the base. However, if 2 equivalents of base are used, then not only is the most acidic proton removed, but also the second most acidic. Alkylation of this doubly charged anion (a dianion) occurs at the less acidic position, in this case the second most acidic position[1596] (see p. 513). The first and second ion pair acidities of β-diketones has been studied.[1597]

When ω,ω′-dihalides are used, ring closures can be effected:[1598]



This method has been used to close rings of from three ($n = 0$) to seven members, although five-membered ring closures proceed in highest yields. Another ring-closing method involves internal alkylation.[1599]



[1594]Corey, E.J.; Cane, D.E. *J. Org. Chem.* ***1970***, *35*, 3405.

[1595]Kanemasa, S.; Mori, T.; Wada, E.; Tatsukawa, A. *Tetrahedron Lett.* ***1993***, *34*, 677. See Kotha, S.; Kuki, A. *Tetrahedron Lett.* ***1992***, *33*, 1565 for a related reaction.

[1596]For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1540–1541. Also see, Lu, Y.-Q.; Li, C.-J. *Tetrahedron Lett.* ***1996***, *37*, 471.

[1597]Facchetti, A.; Streitwieser, A. *J. Org. Chem.* ***2004***, *69*, 8345.

[1598]Zefirov, N.S.; Kuznetsova, T.S.; Kozhushkov, S.I.; Surmina, L.S.; Rashchupkina, Z.A. *J. Org. Chem. USSR* ***1983***, *19*, 474.

[1599]For example, see Knipe, A.C.; Stirling, C.J.M. *J. Chem. Soc. B* ***1968***, 67; Gosselck, J.; Winkler, A. *Tetrahedron Lett.* ***1970***, 2437; Walborsky, H.M.; Murari, M.P. *Can. J. Chem.* ***1984***, *62*, 2464. For a review of this method as applied to the synthesis of β-lactams, see Bose, A.K.; Manhas, M.S.; Chatterjee, B.G.; Abdulla, R.F. *Synth. Commun.* ***1971***, *1*, 51. For a list of examples, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 156–157, 165–166.

This method has been shown to be applicable to medium rings (10–14 members) without the use of high-dilution techniques.[1600]

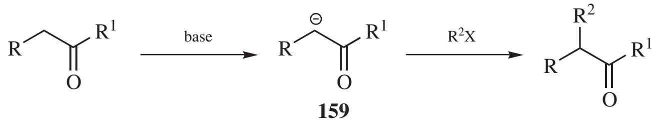
The mechanism of these reactions is usually S_N2 with inversion taking place at a chiral RX, although an SET[1601] mechanism may be involved in certain cases,[1602] especially where the nucleophile is an α-nitro carbanion[1603] and/or the substrate contains a nitro or cyano[1604] group. Tertiary alkyl groups can be introduced by an S_N1 mechanism if the ZCH_2Z' compound (not the enolate anion) is treated with a tertiary carbocation generated *in situ* from an alcohol or alkyl halide and BF_3 or $AlCl_3$,[1605] or with a tertiary alkyl perchlorate.[1606]

Alkylation α to a nitro group can be achieved with the Katritzky pyrylium–pyridinium reagents.[1607] This reaction probably has a free-radical mechanism.[1608]

OS **I**, 248, 250; **II**, 262, 279, 384, 474; **III**, 213, 219, 397, 405, 495, 705; **IV**, 10, 55, 288, 291, 623, 641, 962; **V**, 76, 187, 514, 523, 559, 743, 767, 785, 848, 1013; **VI**, 223, 320, 361, 482, 503, 587, 781, 991; **VII**, 339, 411; **VIII**, 5, 312, 381. See also, OS **VIII**, 235.

10-68 Alkylation of Ketones, Aldehydes, Nitriles, and Carboxylic Esters

α-Acylalkyl-de-halogenation, and so on



159

Ketones,[1609] nitriles,[1610] and carboxylic esters[1611] can be alkylated in the α position in a reaction similar to **10-67**.[1568] The pK_a of the proton α to the carbonyl or

[1600]Deslongchamps, P.; Lamothe, S.; Lin, H. *Can. J. Chem.* ***1984***, *62*, 2395; ***1987***, *65*, 1298; Brillon, D.; Deslongchamps, P. *Can. J. Chem.* ***1987***, *65*, 43, 56.

[1601]These SET mechanisms are often called $S_{RN}1$ mechanisms. See also, Ref. 96.

[1602]Kornblum, N.; Michel, R.E.; Kerber, R.C. *J. Am. Chem. Soc.* ***1966***, *88*, 5660, 5662; Russell, G.A.; Ros, F. *J. Am. Chem. Soc.* ***1985***, *107*, 2506; Ashby, E.C.; Argyropoulos, J.N. *J. Org. Chem.* ***1985***, *50*, 3274; Bordwell, F.G.; Harrelson, Jr., J.A. *J. Am. Chem. Soc.* ***1989***, *111*, 1052.

[1603]For a review of mechanisms with these nucleophiles, see Bowman, W.R. *Chem. Soc. Rev.* ***1988***, *17*, 283.

[1604]Kornblum, N.; Fifolt, M. *Tetrahedron* ***1989***, *45*, 1311.

[1605]For example, see Boldt, P.; Militzer, H. *Tetrahedron Lett.* ***1966***, 3599; Crimmins, T.F.; Hauser, C.R. *J. Org. Chem.* ***1967***, *32*, 2615; Boldt, P.; Militzer, H.; Thielecke, W.; Schulz, L. *Liebigs Ann. Chem.* ***1968***, *718*, 101.

[1606]Boldt, P.; Ludwieg, A.; Militzer, H. *Chem. Ber.* ***1970***, *103*, 1312.

[1607]Katritzky, A.R.; Kashmiri, M.A.; Wittmann, D.K. *Tetrahedron* ***1984***, *40*, 1501.

[1608]Katritzky, A.R.; Chen, J.; Marson, C.M.; Maia, A.; Kashmiri, M.A. *Tetrahedron* ***1986***, *42*, 101.

[1609]For a review of the alkylation and acylation of ketones and aldehydes, see Caine, D., in Augustine, R.L. *Carbon–Carbon Bond Formation*, Vol. 1, Marcel Dekker, NY, ***1979***, pp. 85–352.

[1610]For a review, see Arseniyadis, S.; Kyler, K.S.; Watt, D.S. *Org. React.* ***1984***, *31*, 1. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1801–1808. See Taber, D.F.; Kong, S. *J. Org. Chem.* ***1997***, *62*, 8575.

[1611]For a review, see Petragnani, N.; Yonashiro, M. *Synthesis* ***1982***, 521. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1724–1758*ff.*

CN is in the range of 19–25 (see p. 363), and a base that has a conjugate acid with a pK_a greater than that proton must be employed. Note that since only one activating group is present here, compared with two activating groups for the substrates in **10-67**, the pK_a of the α-proton is higher (a weaker acid) and a stronger base is required. Reaction of the α-proton with the base generates they key nucleophilic intermediate, an enolate anion (**159**). The most common bases[1612] are lithium diethylamide (Et_2NLi), lithium diisopropylamide[(iPr)$_2$NLi, LDA], *t*-BuOK, $NaNH_2$, and KH. A combination of lithium hexamethyldisilazide [$LiN(SiMe_3)_2$] followed by $MnBr_2$ is also effective for alkylation of ketones.[1613] The base lithium *N*-isopropyl-*N*-cyclohexylamide (LICA) is particularly successful for carboxylic esters[1614] and nitriles.[1615] Solid KOH in Me_2SO has been used to methylate ketones, in high yields.[1616] Some of these bases are strong enough to convert the ketone, nitrile, or ester completely to its enolate anion conjugate base; others (especially *t*-BuOK) convert a significant fraction of the molecules. In the latter case, the aldol reaction (**16-34**) or Claisen condensation (**16-85**) may be side reactions, since both the free molecule and its conjugate base are present at the same time. It is therefore important to use a base strong enough to convert the starting compound completely. Both lactones[1617] and lactams are similarly alkylated.[1618] Protic solvents are generally not suitable because they protonate the base (though of course this is not a problem with a conjugate pair, such as *t*-BuOK in *t*-BuOH). Some common solvents are 1,2-dimethoxyethane, THF, DMF, and liquid NH_3. Phase-transfer catalysis has been used to alkylate many nitriles, as well as some esters and ketones.[1619]

Direct alkylation of aldehydes is difficult when bases, such as KOH and NaOMe, are used due to rapid aldol reaction (**16-34**), but aldehydes bearing only one α hydrogen have been alkylated with allylic and benzylic halides in good yields by the use of the base KH to prepare the potassium enolate,[1620] or in moderate yields, by the use of a phase-transfer catalyst.[1621] Even the use of amide bases such as

[1612]For a list of some bases, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1476–1479.

[1613]Reetz, M.T.; Haning, H. *Tetrahedron Lett.* ***1993***, *34*, 7395.

[1614]Rathke, M.W.; Lindert, A. *J. Am. Chem. Soc.* ***1971***, *93*, 2319; Bos, W.; Pabon, H.J.J. *Recl. Trav. Chim. Pays-Bas* ***1980***, *99*, 141. See also, Cregge, R.J.; Herrmann, J.L.; Lee, C.S.; Richman, J.E.; Schlessinger, R.H. *Tetrahedron Lett.* ***1973***, 2425.

[1615]Watt, D.S. *Tetrahedron Lett.* ***1974***, 707.

[1616]Langhals, E.; Langhals, H. *Tetrahedron Lett.* ***1990***, *31*, 859.

[1617]For a discusson of the stereochemistry of lactone alkylation see Ibrahim-Ouali, M.; Parrain, J.-L.; Santelli, M. *Org. Prep. Proceed. Int.* ***1999***, *31*, 467. Enolate anions of β-lactones are subject to ring opening: see Mori, S.; Shindo, M. *Org. Lett.* ***2004***, *6*, 3945.

[1618]Matsuo, J.-i.; Kobayashi, S.; Koga, K. *Tetrahedron Lett.* ***1998***, *39*, 9723.

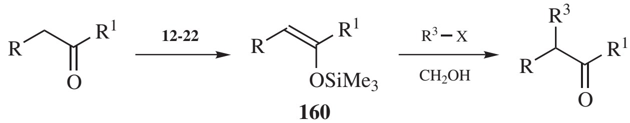
[1619]For reviews, see Makosza, M. *Russ. Chem. Rev.* ***1977***, *46*, 1151; *Pure Appl. Chem.* ***1975***, *43*, 439; Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Acaemic Press, NY, ***1978***, pp. 170–217; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, ***1977***, pp. 136–204.

[1620]Groenewegen, F.; Kallenberg, H.; van der Gen, A. *Tetrahedron Lett.* ***1978***, 491; Artaud, I.; Torossian, G.; Viout, P. *Tetrahedron* ***1985***, *41*, 5031.

[1621]Dietl, H.K.; Brannock, K.C. *Tetrahedron Lett.* ***1973***, 1273; Purohit, V.G.; Subramanian, R. *Chem. Ind. (London)* ***1978***, 731; Buschmann, E.; Zeeh, B. *Liebigs Ann. Chem.* ***1979***, 1585.

lithium diisopropylamide (LDA), lithium hexamethyldisilazide (LHMDS), or lithium tetramethylpiperidide (LTMP) to generate the enolate anion in an aprotic solvent, such as ether or THF, cannot preclude rapid aldol side reactions.

As in **10-67**, the alkyl halide that reacts with the enolate anion may be primary or secondary. Tertiary halides give elimination. Even primary and secondary halides give predominant elimination if the enolate anion is a strong enough base (e.g., the enolate anion from Me_3CCOMe).[1622] Tertiary alkyl groups, as well as other groups that normally give S_N1 reactions, can be introduced if the reaction is performed on a silyl enol ether[1623] of a ketone, aldehyde, or ester (see **160**) with a Lewis acid catalyst.[1624] Tertiary alkyl fluorides were coupled to silyl enol ethers with BF_3•etherate.[1625] An interesting reaction reacted a methyl ketone, such as acetophenone (1-phenyl-1-ethanone) with tributylamine, in the presence of a ruthenium catalyst at 180°C, and the product resulted from *C*-alkylation (1-phenyl-1-hexanone).[1626] Note that tin enolates (C=C—OSnR$_3$) react with halides in the presence of a zinc catalyst.[1627] A chiral variation of this latter reaction was reported involving generation of the enolate anion in the presence of Me_3SnCl, a palladium catalyst and a chiral ligand.[1628]



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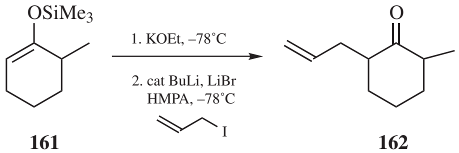
Silyl enol ethers can be converted to the enolate anion, which can then be alkylated in the usual manner. The reaction of silyl enol ether **161** using KOEt followed by LiBr at a catalytic amount of *n*-butyllithium with allyl iodide gave **162**.[1629] Initial conversion of the silyl enol ether to the enolate anion allows the alkylation process to take place.



161 **162**

[1622]Zook, H.D.; Kelly, W.L.; Posey, I.Y. *J. Org. Chem.* ***1968***, *33*, 3477.

[1623]For a list of alkylations of silyl enol ethers, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1494–1505.

[1624]Reetz, M.T.; Sauerwald, M. *J. Organomet. Chem.* ***1990***, *382*, 121; Kad, G.L.; Singh, V.; Khurana, A.; Chaudhary, S.; Singh, J. *Synth. Commun.* ***1999***, *29* , 3439; Kang, S.-K.; Ryu, H.-C.; Hong, Y.-T. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 3350. For a review, see Reetz, M.T. *Angew. Chem. Int. Ed.* ***1982***, *21*, 96.

[1625]Hirano, K.; Fujita, K.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* ***2004***, *45*, 2555.

[1626]Cho, C.S.; Kim, B.T.; Lee, M.J.; Kim, T.-J.; Shim, S.C. *Angew. Chem. Int. Ed.* ***2001***, *40*, 958.

[1627]Yasuda, M.; Tsuji, S.; Shigeyoshi, Y.; Baba, A. *J. Am. Chem Soc.* ***2002***, *124*, 7440.

[1628]Trost, B.M.; Schroeder, G.M. *J. Am. Chem. Soc.* ***1999***, *121*, 6759.

[1629]Yu, W.; Jin, Z. *Tetrahedron Lett.* ***2001***, *42*, 369.

Enol carbonates react with alkylating agents in the presence of a palladium catalyst. The decarboxylative alkylation of allyl enol carbonates to the corresponding allylcyclohexanone derivatives is known as the *Tsuji alkylation.*[1630] An asymmetric version of this reaction has been reported.[1631] The same reaction can be done using enolate anion and allylic acetates with a palladium catalyst.[1632]

Vinylic and aryl halides can be used to vinylate or arylate carboxylic esters (but not ketones) by the use of $NiBr_2$ as a catalyst.[1633] Ketones have been vinylated by treating their enol acetates with vinylic bromides in the presence of a Pd compound catalyst,[1634] but direct reaction of a ketone, a vinyl halide, sodium *tert*-butoxide and a palladium catalyst also give the α-vinyl ketone.[1635] Also as in **10-67**, this reaction can be used to close rings.[1636] Rings have been closed by treating a dianion of a dialkyl succinate with a 1,ω-dihalide or ditosylate.[1637] This was applied to the synthesis of three-, four-, five-, and six-membered rings. When the attached groups were chiral (e.g., menthyl) the product was formed with >90% ee.[1636]

Efficient enantioselective alkylations are known.[1638] In another method enantioselective alkylation can be achieved by using a chiral base to form the enolate.[1639] Alternatively, a chiral auxiliary can be attached. Many auxiliaries are based on the use of chiral amides[1640] or esters.[1641] Subsequent formation of the enolate anion allows alkylation to proceed with high enantioselectivity. A subsequent step is

[1630]Tsuji, J.; Minami, I. *Acc. Chem. Res.* ***1987***, *20*, 140; Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* ***1983***, *24*, 1793; Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y.; Sugiura, T.; Takahashi, K. *J. Org. Chem.* ***1985***, *50*, 1523; Tsuji, J.; Minami, I.; Shimizu, I. *Chem. Lett.* ***1983***, *12*, 1325. See also, Nicolaou, K.C.; Vassilikogiannakis, G.; Mägerlein, W.; Kranich, R. *Angew. Chem. Int. Ed.* ***2001***, *40*, 2482; Herrinton, P.M.; Klotz, K.L.; Hartley, W.M. *J. Org. Chem.* ***1993***, *58*, 678.

[1631]Behenna, D.C.; Stoltz, B.M. *J. Am. Chem. Soc.* ***2004***, *126*, 15044.

[1632]Trost, B.M.; Schroeder, G.M.; Kristensen, J. *Angew. Chem. Int. Ed.* ***2002***, *41*, 3492.

[1633]Millard, A.A.; Rathke, M.W. *J. Am. Chem. Soc.* ***1977***, *99*, 4833.

[1634]Kosugi, M.; Hagiwara, I.; Migita, T. *Chem. Lett.* ***1983***, 839. For other methods, see Negishi, E.; Akiyoshi, K. *Chem. Lett.* ***1987***, 1007; Chang, T.C.T.; Rosenblum, M.; Simms, N. *Org. Synth. 66*, 95.

[1635]Chieffi, A.; Kamikawa, K.; Åhman, J.; Fox, J.M.; Buchwald, S.L *Org. Lett.* ***2001***, *3*, 1897.

[1636]For example, see Etheredge, S.J. *J. Org. Chem.* ***1966***, *31*, 1990; Wilcox, C.F.; Whitney, G.C. *J. Org. Chem.* ***1967***, *32*, 2933; Bird, R.; Stirling, C.J.M. *J. Chem. Soc. B* ***1968***, 111; Stork, G.; Boeckman, Jr., R.K. *J. Am. Chem. Soc.* ***1973***, *95*, 2016; Stork, G.; Cohen, J.F. *J. Am. Chem. Soc.* ***1974***, *96*, 5270. In the last case, the substrate moiety is an epoxide function.

[1637]Misumi, A.; Iwanaga, K.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* ***1985***, *107*, 3343; Furuta, K.; Iwanaga, K.; Yamamoto, H. *Org. Synth. 67*, 76.

[1638]For reviews of stereoselective alkylation of enolates, see Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, ***1986***, pp. 236–245; Evans, D.A. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 3, Academic Press, NY, ***1984***, pp. 1–110.

[1639]For example, see Murakata, M.; Nakajima, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* ***1990***, 1657. For a review, see Cox. P.J.; Simpkins, N.S. *Tetrahedron: Asymmetry* ***1991***, *2*, 1, pp. 6–13.

[1640]Chiral oxazolidinones such as the Evan's auxiliaries derived from chiral amino alcohols: Lafontaine, J.A.; Provencal, D.P.; Gardelli, C.; Leahy, J.W. *J. Org. Chem.* ***2003***, *68*, 4215; Bull, S.D.; Davies, S.G.; Nicholson, R.L.; Sanganee, H.J.; Smith, A.D. *Tetrahedron Asymmetry* ***2000***, *11*, 3475. See Evans, D.A.; Chapman, K.T.; Bisaha, J. *Tetrahedron Lett.* ***1984***, *25*, 4071; Evans, D.A. Chapman, K.T.; Bisaha, J. *J. Am. Chem. Soc.* ***1984***, *106*, 4261. Oppolzer's sultam: Oppolzer, W.; Chapuis, C.; Dupuis, D.; Guo, M. *Helv. Chim. Acta* ***1985***, *68*, 2100. Chiral sulfonamides: Schmierer, R.; Grotemeier, G.; Helmchen, G.; Selim, A. *Angew. Chem. Int. Ed.* ***1981***, *20*, 207.

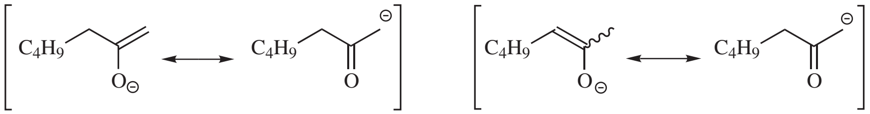
[1641]Oppolzer, W.; Dudfield, P.; Stevenson, T.; Godel, T. *Helv. Chim. Acta* ***1985***, *68*, 212.

required to convert the chiral amide or ester to the corresponding carboxylic acid. Chiral additives can also be used.[1642]

When the compound to be alkylated is an unsymmetrical ketone, the question arises as to which side will be alkylated. If a phenyl or a vinylic group is present on one side, alkylation goes predominantly on that side. When only alkyl groups are present, the reaction is generally not regioselective; mixtures are obtained in which sometimes the more alkylated and sometimes the less alkylated side is predominantly alkylated. Which product is found in higher yield depends on the nature of the substrate, the base,[1643] the cation, and the solvent. In any case, di- and trisubstitution are frequent[1644] and it is often difficult to stop with the introduction of just one alkyl group.[1645]

Several methods have been developed for ensuring that alkylation takes place regioselectively on the *desired* side of a ketone.[1646] Among these are

1. Block one side of the ketone by introducing a removable group. Alkylation takes place on the other side; the blocking group is then removed. A common reaction for this purpose is formylation with ethyl formate (**16-86**); this generally blocks the less hindered side. The formyl group is easily removed by alkaline hydrolysis (**12-43**).
2. Introduce an activating group on one side; alkylation then takes place on that side (**10-67**); the activating group is then removed.
3. Prepare the desired one of the two possible enolate anions.[1647] The two ions, for example, **163** and **164** for 2-heptanone, interconvert rapidly only in



163 **164**

the presence of the parent ketone or any stronger acid.[1648] In the absence of such acids, it is possible to prepare either **163** or **164** and thus achieve

[1642]Denmark, S.E.; Stavenger, R.A. *Acc. Chem. Res.* ***2000***, *33*, 432; Machajewski, T.D.; Wong, C.-H. *Angew. Chem. Int. Ed.* ***2000***, *39*, 1352.

[1643]Sterically hindered bases may greatly favor one enolate over the other. See, for example, Prieto, J.A.; Suarez, J.; Larson, G.L. *Synth. Commun.* ***1988***, *18*, 253; Gaudemar, M.; Bellassoued, M. *Tetrahedron Lett.* ***1989***, *30*, 2779.

[1644]For a procedure for completely methylating the apositions of a ketone, see Lissel, M.; Neumann, B.; Schmidt, S. *Liebigs Ann. Chem.* ***1987***, 263.

[1645]For some methods of reducing dialkylation, see Hooz, J.; Oudenes, J. *Synth. Commun.* ***1980***, *10*, 139; Morita, J.; Suzuki, M.; Noyori, R. *J. Org. Chem.* ***1989***, *54*, 1785.

[1646]For a review, see House, H.O. *Rec. Chem. Prog.* ***1968***, *28*, 99. For a review with respect to cyclohexenones, see Podraza, K.F. *Org. Prep. Proced. Int.* ***1991***, *23*, 217.

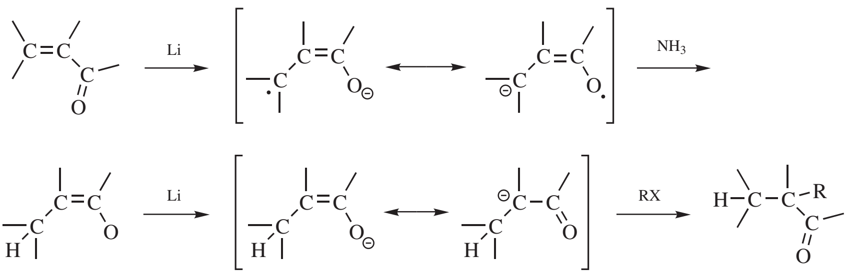
[1647]For reviews, see d'Angelo, J. *Tetrahedron* ***1976***, *32*, 2979; Stork, G. *Pure Appl. Chem.* ***1975***, *43*, 553.

[1648]House, H.O.; Trost, B.M. *J. Org. Chem.* ***1965***, *30*, 1341.

selective alkylation on either side of the ketone.[1649] The desired enolate anion can be obtained by treatment of the corresponding enol acetate with two equivalents of methyllithium in 1,2-dimethoxyethane. Each enol acetate gives the corresponding enolate, for example,

The enol acetates, in turn, can be prepared by treatment of the parent ketone with an appropriate reagent.[1241] Such treatment generally gives a mixture of the two enol acetates in which one or the other predominates, depending on the reagent. The mixtures are easily separable.[1648] An alternate procedure involves conversion of a silyl enol ether[1650] (see **12-17**) or a dialkylboron enol ether[1651] (an enol borinate, see p. 645) to the corresponding enolate anion. If the less hindered enolate anion is desired (e.g., **126**), it can be prepared directly from the ketone by treatment with LDA in THF or 1,2-dimethoxyethane (DME) at −78°C.[1652]

4. Begin not with the ketone itself, but with an α,β-unsaturated ketone in which the double bond is present on the side where alkylation is desired. Upon treatment with lithium in liquid NH_3, such a ketone is reduced to an enolate anion. When the alkyl halide is added, it must react with the enolate anion on



the side where the double bond was.[1653] Of course, this method is not actually an alkylation of the ketone, but of the α,β-unsaturated ketone, although the

[1649]Whitlock Jr., H.W.; Overman, L.E. *J. Org. Chem.* ***1969***, *34*, 1962; House, H.O.; Gall, M.; Olmstead, H.D. *J. Org. Chem.* ***1971***, *36*, 2361. For an improved procedure, see Liotta, C.L.; Caruso, T.C. *Tetrahedron Lett.* ***1985***, *26*, 1599.

[1650]Stork, G.; Hudrlik, P.F. *J. Am. Chem. Soc.* ***1968***, *90*, 4462, 4464. For reviews, see Kuwajima, I.; Nakamura, E. *Acc. Chem. Res.* ***1985***, *18*, 181; Fleming, I. *Chimia*, ***1980***, *34*, 265; Rasmussen, J.K. *Synthesis* ***1977***, 91.

[1651]Pasto, D.J.; Wojtkowski, P.W. *J. Org. Chem.* ***1971***, *36*, 1790.

[1652]House, H.O.; Gall, M.; Olmstead, H.D. *J. Org. Chem.* ***1971***, *36*, 2361. See also, Corey, E.J.; Gross, A.W. *Tetrahedron Lett.* ***1984***, *25*, 495.

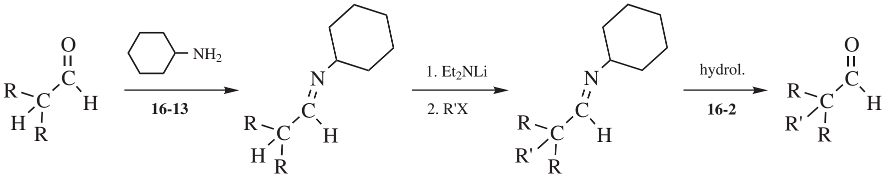
[1653]Stork, G.; Rosen, P.; Goldman, N.; Coombs, R.V.; Tsuji, J. *J. Am. Chem. Soc.* ***1965***, *87*, 275. For a review, see Caine, D. *Org. React.* ***1976***, *23*, 1. For similar approaches, see Coates, R.M.; Sowerby, R.L. *J. Am. Chem. Soc.* ***1971***, *93*, 1027; Näf, F.; Decorzant, R. *Helv. Chim. Acta* ***1974***, *57*, 1317; Wender, P.A.; Eissenstat, M.A. *J. Am. Chem. Soc.* ***1978***, *100*, 292.

product is the same as if the saturated ketone had been alkylated on the desired side.

Both sides of acetone have been alkylated with different alkyl groups, in one operation, by treatment of the *N,N*-dimethylhydrazone of acetone with *n*-BuLi, followed by a primary alkyl, benzylic, or allylic bromide or iodide; then another mole of *n*-BuLi, a second halide, and finally hydrolysis of the hydrazone.[1654] Alkylation of an unsymmetrical ketone at the more substituted position was reported using an alkyl bromide, NaOH, and a calix[*n*]arene catalyst (see p. 122 for calixarenes).[1655]

Among other methods for the preparation of alkylated ketones are (*1*) Alkylation of silyl enol ethers using various reagents as noted above, (*2*) the Stork enamine reaction (**10-69**), (*3*) the acetoacetic ester synthesis (**10-67**), (*4*) alkylation of β-keto sulfones or sulfoxides (**10-67**), (*5*) acylation of $CH_3SOCH_2^-$ followed by reductive cleavage (**16-86**), (*6*) treatment of α-halo ketones with lithium dialkylcopper reagents (**10-57**), and (*7*) treatment of α-halo ketones with trialkylboranes (**10-73**).

Aldehydes can be indirectly alkylated via an imine derivative of the aldehyde.[1656] The derivative is easily prepared (**16-13**) and the product easily hydrolyzed to the aldehyde (**16-2**). Either or both R groups may be hydrogen, so that



mono-, di-, and trisubstituted acetaldehydes can be prepared by this method. R′ may be primary alkyl, allylic, or benzylic. Imine alkylation can also be applied to the preparation of substituted amine derivatives. An amino acid surrogate, such as $Ph_2C{=}NCH_2CO_2R$, when treated with KOH and an alkyl halide gives the *C*-alkylated product.[1657] When a chiral additive is used, good enantioselectivity was observed. This reaction has also been done in the ionic liquid bmim tetrafluoroborate (see p. 415).[1658] It is possible to alkylate α-amino amides directly.[1659]

[1654]Yamashita, M.; Matsuyama, K.; Tanabe, M.; Suemitsu, R. *Bull. Chem. Soc. Jpn.* ***1985***, *58*, 407.

[1655]Shimizu, S.; Suzuki, T.; Sasaki, Y.; Hirai, C. *Synlett* ***2000***, 1664.

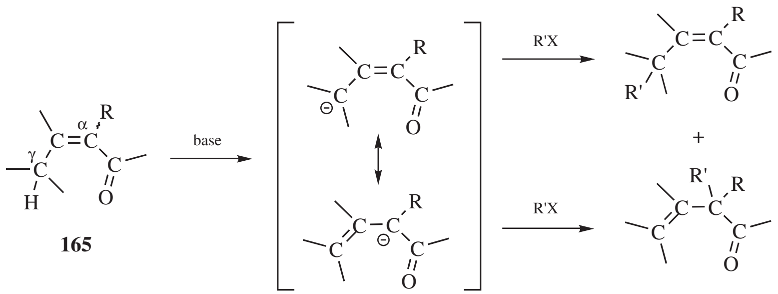
[1656]Cuvigny, T.; Normant, H. *Bull. Soc. Chim. Fr.* ***1970***, 3976. For reviews, see Fraser, R.R., in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, Vol. 5, pt. B, Elsevier, NY, ***1984***, pp. 65–105; Whitesell, J.K.; Whitesell, M.A. *Synthesis* ***1983***, 517. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1513–1518. For a method in which the metalated imine is prepared from a nitrile, see Goering, H.L.; Tseng, C.C. *J. Org. Chem.* ***1981***, *46*, 5250.

[1657]Park, H.-g.; Jeong, B.-s.; Yoo, M.-s.; Park, M.-k.; Huh, H.; Jew, S.-s. *Tetrahedron Lett.* ***2001***, *42*, 4645; Jew, S.-s.; Jeong, B.-s.; Yoo, M.-s.; Huh, H.; Park, H.-g. *Chem. Commun.* ***2001***, 1244.

[1658]Pellissier, H.; Santelli, M. *Tetrahedron* ***2003***, *59*, 701.

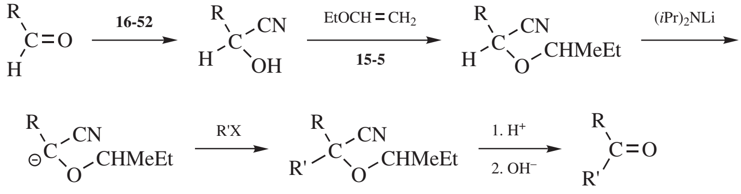
[1659]Myers, A.G.; Schnider, P.; Kwon, S.; Kung, D.W. *J. Org. Chem.* ***1999***, *64*, 3322.

Hydrazones and other compounds with C=N bonds can be similarly alkylated.[1639] The use of chiral amines or hydrazines[1660] (followed by hydrolysis **16-2** of the alkylated imine) can lead to chiral alkylated ketones in high optical yields[1661] (for an example, see p. 170).



165

In α,β-unsaturated ketones, nitriles, and esters (e.g., **165**), the γ hydrogen assumes the acidity normally held by the position α to the carbonyl group, especially when R is not hydrogen and so cannot compete. This principle, called *vinylogy*, operates because the resonance effect is transmitted through the double bond. However, because of the resonance, alkylation at the α position (with allylic rearrangement) competes with alkylation at the γ position and usually predominates.



166

α-Hydroxynitriles (cyanohydrins), protected by conversion to acetals with ethyl vinyl ether (**15-5**), can be easily alkylated with primary or secondary alkyl or allylic halides.[1662] The R group can be aryl or a saturated or unsaturated alkyl. Since the cyanohydrins[1663] are easily formed from aldehydes (**16-52**) and the product is easily hydrolyzed to a ketone, this is a method for converting an aldehyde

[1660]For a review of the alkylation of chiral hydrazones, see Enders, D., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 3, Academic Press, NY, ***1984***, pp. 275–339.

[1661]Meyers, A.I.; Williams, D.R.; Erickson, G.W.; White, S.; Druelinger, M. *J. Am. Chem. Soc.* ***1981***, *103*, 3081; Meyers, A.I.; Williams, D.R.; White, S.; Erickson, G.W. *J. Am. Chem. Soc.* ***1981***, *103*, 3088; Enders, D.; Bockstiegel, B. *Synthesis* ***1989***, 493; Enders, D.; Kipphardt, H.; Fey, P. *Org. Synth. 65*, 183.

[1662]Stork, G.; Maldonado, L. *J. Am. Chem. Soc.* ***1971***, *93*, 5286; Stork, G.; Depezay, J.C.; D'Angelo, J. *Tetrahedron Lett.* ***1975***, 389. See also, Rasmussen, J.K.; Heilmann, S.M. *Synthesis* ***1978***, 219; Ahlbrecht, H.; Raab, W.; Vonderheid, C. *Synthesis* ***1979***, 127; Hünig, S.; Marschner, C.; Peters, K.; von Schnering, H.G. *Chem. Ber.* ***1989***, *122*, 2131, and other papers in this series.

[1663]For a review of **166**, see Albright, J.D. *Tetrahedron* ***1983***, *39*, 3207.

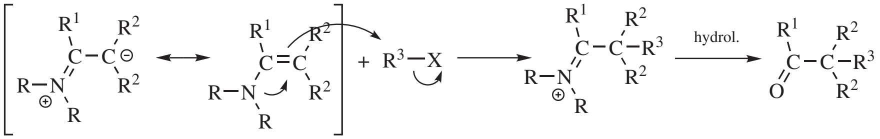
RCHO to a ketone RCOR′[1664] (for other methods, see **10-71**, **16-82**, and **18-9**).[1665] In this procedure the normal mode of reaction of a carbonyl carbon is reversed. The C atom of an aldehyde molecule is normally electrophilic and is attacked by nucleophiles (Chapter 16), but by conversion to the protected cyanohydrin this carbon atom has been induced to perform as a nucleophile.[1666] The German word *Umpolung*[1667] is used to describe this kind of reversal (another example is found in **10-71**). Since the ion **166** serves as a substitute for the unavailable R—$^{\ominus}$ C=O anion, it is often called a "masked" R($^{\ominus}$C=O) ion. This method fails for formaldehyde (R = H), but other masked formaldehydes have proved successful.[1668] In an interesting variation of nitrile alkylation, a quaternary bromide [PhC(Br)(Me)CN] reacted with allyl bromide, in the presence of a Grignard reagent, to give the alkylated product [PhC(CN)(Me)$CH_2CH{=}CH_2$].[1669]

A coupling react of two ketones to form a 1,4-diketone has been reported, using $ZnCl_2/Et_2NH$.[1670]

OS **III**, 44, 219, 221, 223, 397; **IV**, 278, 597, 641, 962; **V**, 187, 514, 559, 848; **VI**, 51, 115, 121, 401, 818, 897, 958, 991; **VII**, 153, 208, 241, 424; **VIII**, 141, 173, 241, 403, 460, 479, 486; **X**, 59, 460; **80**, 31.

10-69 The Stork Enamine Reaction

α-Acylalkyl-de-halogenation[1671]



[1664]For similar methods, see Stetter, H.; Schmitz, P.H.; Schreckenberg, M. *Chem. Ber.* ***1977***, *110*, 1971; Hünig, S. *Chimia*, ***1982***, *36*, 1.

[1665]For a review of methods of synthesis of aldehydes, ketones and carboxylic acids by coupling reactions, see Martin, S.F. *Synthesis* ***1979***, 633.

[1666]For reviews of such reversals of carbonyl group reactivity, see Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***, pp. 56–67; Gröbel, B.; Seebach, D. *Synthesis* ***1977***, 357; Lever, Jr., O.W. *Tetrahedron* ***1976***, *32*, 1943; Seebach, D.; Kolb, M. *Chem. Ind. (London)* ***1974***, 687; Seebach, D. *Angew. Chem. Int. Ed.* ***1969***, *8*, 639. For a compilation of references to masked acyl and formyl anions, see Hase, T.A.; Koskimies, J.K. *Aldrichimica Acta* ***1981***, *14*, 73. For tables of masked reagents, see Hase, T.A. Umpoled Synthons, Wiley, NY, ***1987***, pp. xiii-xiv, 7–18, 219–317. For lists of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1435–1438.

[1667]For a monograph, see Hase, T.A. *Umpoled Synthons*, Wiley, NY, ***1987***. For a review, see Seebach, D. *Angew. Chem. Int. Ed.* ***1979***, *18*, 239.

[1668]Possel, O.; van Leusen, A.M. *Tetrahedron Lett.* ***1977***, 4229; Stork, G.; Ozorio, A.A.; Leong, A.Y.W. *Tetrahedron Lett.* ***1978***, 5175.

[1669]Fleming, F.F.; Zhang, Z.; Knochel, P. *Org. Lett.* ***2004***, *6*, 501.

[1670]Nevar, N.M.; Kel'in, A.V.; Kulinkovich, O.G. *Synthesis* ***2000***, 1259.

[1671]This is the IUPAC name with respect to the halide as substrate.

When enamines are treated with alkyl halides, an alkylation occurs to give an iminium salt via electron transfer from the electron pair on nitrogen, through the C=C to the electrophilic carbon of the alkyl halide.[1672] In effect, an enamine behaves as a "nitrogen enolate" and generally react as carbon nucleophiles.[1673] Hydrolysis of the iminium salt gives a ketone. Since the enamine is normally formed from a ketone (**16-13**), the net result is alkylation of the ketone at the α position. The method, known as the *Stork enamine reaction*,[1674] is an alternative to the ketone alkylation considered in **10-68**, generally giving monoalkylation of the ketone. Alkylation usually takes place on the less substituted side of the original ketone. The most commonly used amines are the cyclic amines piperidine, morpholine, and pyrrolidine.

The method is quite useful for particularly active alkyl halides, such as allylic, benzylic, and propargylic halides, and for α-halo ethers and esters. Other primary and secondary halides can show sluggish reactivity. The react of enamines with benzotriazole derivatives has been reported.[1675] Tertiary halides do not give the reaction at all since, with respect to the halide, this is nucleophilic substitution and elimination predominates. The reaction can also be applied to activated aryl halides (e.g., 2,4-dinitrochlorobenzene; see Chapter 13), to epoxides,[1676] and to activated alkenes, such as acrylonitrile. The latter is a Michael-type reaction (**15–24**) with respect to the alkene.

Acylation[1677] can be accomplished with acyl halides or with anhydrides. Hydrolysis of the resulting iminium salt leads to a 1,3-diketone. A COOEt group can be introduced by treatment of the enamine with ethyl chloroformate ClCOOEt,[1678] a CN group with cyanogen chloride[1679] (not cyanogen bromide or iodide, which leads to halogenation of the enamine), a CHO group with the mixed anhydride of formic and acetic acids[1678] or with DMF and phosgene,[1680] and a C(R)=NR′ group with a nitrilium salt $RC{\equiv}N^{+}R'$.[1681] The acylation of the enamine can take

[1672]See Adams, J.P. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 125.

[1673]For a discussion of structure–nucleophilicity relationships, see Kempf, B.; Hampel, N.; Ofial, A.R.; Mayr, H. *Chem. Eur. J.* ***2003***, *9*, 2209.

[1674]Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.*, ***1963***, *85*, 207. For general reviews of enamines, see Hickmott, P.W. *Tetrahedron*, ***1984***, *40*, 2989; ***1982***, *38*, 1975, 3363; Granik, V.G. *Russ. Chem. Rev.*, ***1984***, *53*, 383. For reviews of this reaction, see, in Cook, A.G. *Enamines*, 2nd ed.; Marcel Dekker, NY, ***1988***, the articles by Alt, G.H.; Cook, A.G. pp. 181–246, and Gadamasetti, G.; Kuehne, M.E. pp. 531–689; Whitesell, J.K.; Whitesell, M.A. *Synthesis*, ***1983***, 517; Kuehne, M.E. *Synthesis*, ***1970***, 510; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 570–582, 766–772; Bláha, K.; Červinka, O. *Adv. Heterocycl. Chem.*, ***1966***, *6*, 147, pp. 186.

[1675]Katritzky, A.R.; Fang, Y.; Silina, A. *J. Org. Chem.* ***1999***, *64*, 7622; Katritzky, A.R.; Huang, Z.; Fang, Y. *J. Org. Chem.* ***1999***, *64*, 7625.

[1676]Britten, A.Z.; Owen, W.S.; Went, C.W. *Tetrahedron* ***1969***, *25*, 3157.

[1677]For reviews, see Hickmott, P.W. *Chem. Ind. (London)* ***1974***, 731; Hünig, S.; Hoch, H. *Fortschr. Chem. Forsch.* ***1970***, *14*, 235.

[1678]Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* ***1963***, *85*, 207.

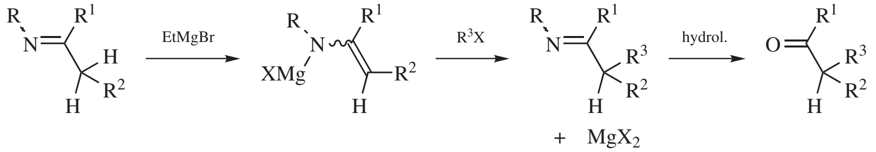
[1679]Kuehne, M.E. *J. Am. Chem. Soc.*, ***1959***, *81*, 5400.

[1680]Ziegenbein, W. *Angew. Chem. Int. Ed. Engl.*, ***1965***, *4*, 358.

[1681]Baudoux, D.; Fuks, R. *Bull. Soc. Chim. Belg.*, ***1984***, *93*, 1009.

place by the same mechanism as alkylation, but another mechanism is also possible, if the acyl halide has an a hydrogen and if a tertiary amine is present, as it often is (it is added to neutralize the HX given off). In this mechanism, the acyl halide is dehydrohalogenated by the tertiary amine, producing a ketene (**17-14**), which adds to the enamine to give a cyclobutanone (**15-63**). This compound can be cleaved in the solution to form the same acylated imine salt (that would form by the more direct mechanism, or it can be isolated (in the case of enamines derived from aldehydes), or it may cleave in other ways.[1682]

N-Alkylation can be a problem, particularly with enamines derived from aldehydes. An alternative method, which gives good yields of alkylation with primary and secondary halides, is alkylation of enamine *salts*, which are prepared by treating an imine with ethylmagnesium bromide in THF:[1683]



The imines are prepared by the reaction of secondary amines with aldehydes or ketones, mainly ketones (**16-13**). The enamine salt method has also been used to give good yields of mono α alkylation of α,β-unsaturated ketones.[1684] Enamines prepared from aldehydes and butylisobutylamine can be alkylated by simple primary alkyl halides in good yields.[1685] *N*-Alkylation in this case is presumably prevented by steric hindrance.

When the nitrogen of the substrate contains a chiral R group, both the Stork enamine synthesis and the enamine salt method can be used to perform enantioselective syntheses.[1686] The use of *S*-proline can generate a chiral enamine *in situ*, thus allowing alkylation to occur, giving alkylated product with good enantioselectivity,. The reaction has been done intramolecularly.[1687]

Conjugate addition (Michael addition) occurs when enamines react with conjugated ketones. This reaction is discussed in Section **15-24**.

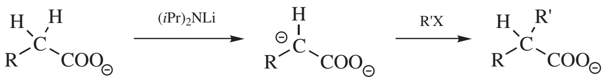
Although not formally the enamine synthesis, reaction of an enamine with methyl bromoacetate in the presence of indium metal leads to α-alkylation: $R_2N{-}CH{=}CHR \rightarrow R_2N{-}CH(R')CHR$.[1688]

OS **V**, 533, 869; **VI**, 242, 496, 526; **VII**, 473.

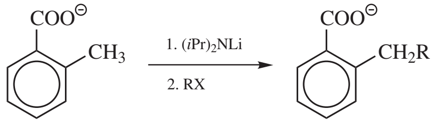
[1682]See Alt, G.H.; Cook, A.G., in Cook, A.G. *Enamines*, 2nd ed., Marcel Dekker, NY, ***1988***, pp. 204–215.
[1683]Stork, G.; Dowd, S.R. *J. Am. Chem. Soc.*, ***1963***, *85*, 2178.
[1684]Stork, G.; Benaim, J. *J. Am. Chem. Soc.*, ***1971***, *93*, 5938.
[1685]Curphey, T.J.; Hung, J.C.; Chu, C.C.C. *J. Org. Chem.*, ***1975***, *40*, 607. See also, Ho, T.; Wong, C.M. *Synth. Commun.*, ***1974***, *4*, 147.
[1686]For reviews, see Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, ***1986***, pp. 248–255; Whitesell, J.K. *Acc. Chem. Res.*, ***1985***, *18*, 280; Bergbreiter, D.E.; Newcomb, M., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 2, Academic Press, NY, ***1983***, pp. 243–273.
[1687]Vignola, N.; List, B. *J. Am. Chem. Soc.* ***2004***, *126*, 450.
[1688]Bossard, F.; Dambrin, V.; Lintanf, V.; Beuchet, P.; Mosset, P. *Tetrahedron Lett.*, ***1995***, *36*, 6055.

10-70 Alkylation of Carboxylic Acid Salts

α-Carboxyalkyl-de-halogenation



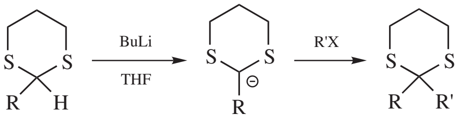
Carboxylic acids can be alkylated in the a position by conversion of their salts to dianions [which have resonance contributors $RCH{=}C(O^-)_2$[1689]] by treatment with a strong base, such as LDA.[1690] The use of Li^+ as the counterion increases the solubility of the dianionic salt. The reaction has been applied[1691] to primary alkyl, allylic, and benzylic halides, and to carboxylic acids of the form RCH_2COOH and $RR^2CHCOOH$.[1610] Allkylation occurs at carbon, the more nucleophilic site relative to the carboxylate oxygen anion (see p. 513). this procedure is an alternative to the malonic ester synthesis (**10-67**) as a means of preparing carboxylic acids and has the advantage that acids of the form $RR'R^2CCOOH$ can also be prepared. In a related reaction, methylated aromatic acids can be alkylated at the methyl group by a similar procedure.[1692]



OS **V**, 526; **VI**, 517; **VII**, 249. See also, OS **VII**, 164.

10-71 Alkylation at a Position α to a Heteroatom.

2-(2-Alkyl-thio)de-halogenation



The presence of a sulfur atom on a carbon enhances the acidity of a proton on that carbon, and in dithioacetals and dithioketals that proton ($RSCH_2SR$) is even more acidic. 1,3-Dithianes can be alkylated[1693] if a proton is first removed by

[1689]Mladenova, M.; Blagoev, B.; Gaudemar, M.; Dardoize, F.; Lallemand, J.Y. *Tetrahedron* ***1981***, *37*, 2153.

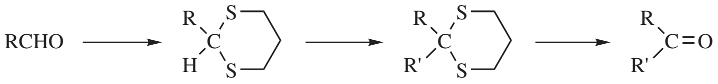
[1690]Cregar, P.L. *J. Am. Chem. Soc.* ***1967***, *89*, 2500; ***1970***, *92*, 1397; Pfeffer, P.E.; Silbert, L.S.; Chirinko, Jr., J.M. *J. Org. Chem.* ***1972***, *37*, 451.

[1691]For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1717–1720*ff.*

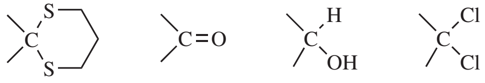
[1692]Cregar, P.L. *J. Am. Chem. Soc.* ***1970***, *92*, 1396.

[1693]Seebach, D.; Corey, E.J. *J. Org. Chem.* ***1975***, *40*, 231. For reviews, see Page, P.C.B.; van Niel, M.B.; Prodger, J.C. *Tetrahedron* ***1989***, *45*, 7643; Ager, D.J., in Hase, T.A. *Umpoled Synthons*, Wiley, NY, ***1987***, pp. 19–37; Seebach, D. *Synthesis* ***1969***, 17, especially pp. 24–27; Olsen, R.K.; Curriev, Jr., Y.O., in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, ***1974***, pp. 536–547.

treatment with butyllithium in THF.[1694] Since 1,3-dithianes can be prepared by treatment of an aldehyde or its acetal (see OS **VI**, 556) with 1,3-propanedithiol (**16-11**) and can be hydrolyzed (**10-7**), this is a method for the conversion of an aldehyde to a ketone[1695] (see also, **10-68** and **18-9**):



This is another example of Umpolung (see **10-68**);[1664] the normally electrophilic carbon of the aldehyde is made to behave as a nucleophile. The reaction can be applied to the unsubstituted dithiane (R = H) and one or two alkyl groups can be introduced, so a wide variety of aldehydes and ketones can be made starting with formaldehyde.[1696] The R′ group may be primary or secondary alkyl or benzylic. Iodides give the best results. The reaction has been used to close rings.[1697] A similar synthesis of aldehydes can be performed starting with ethyl ethylthiomethyl sulfoxide ($EtSOCH_2SEt$).[1698]



A **B** **C** **D**

The group **A** may be regarded as a structural equivalent for the carbonyl group **B**, since introduction of **A** into a molecule is actually an indirect means of introducing **B**. It is convenient to have a word for units within molecules; such a word is *synthon*, introduced by Corey,[1699] which is defined as a structural unit within a molecule that can be formed and/or assembled by known or conceivable synthetic operations. There are many other synthons equivalent to **A** and **B**, for example, **C** (by reactions **19-36** and **19-3**) and **D** (by reactions **10-2** and **16-23**).[1700]

Carbanions generated from 1,3-dithianes also react with epoxides[1701] to give the expected products.

[1694]For an improved method of removing the proton, see Lipshutz, B.H.; Garcia, E. *Tetrahedron Lett.* ***1990***, *31*, 7261.

[1695]For examples of the use of this reaction, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1451–1454.

[1696]For a direct conversion of RX to RCHO, see **10-76**.

[1697]For example, see Seebach, D.; Jones, N.R.; Corey, E.J. *J. Org. Chem.* ***1968***, *33*, 300; Hylton, T.; Boekelheide, V. *J. Am. Chem. Soc.* ***1968***, *90*, 6887; Ogura, K.; Yamashita, M.; Suzuki, M.; Tsuchihashi, G. *Tetrahedron Lett.* ***1974***, 3653.

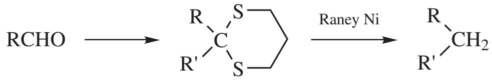
[1698]Richman, J.E.; Herrmann, J.L.; Schlessinger, R.H. *Tetrahedron Lett.* ***1973***, 3267. See also, Ogura, K.; Tsuchihashi, G. *Tetrahedron Lett.* ***1971***, 3151; Schill, G.; Jones, P.R. *Synthesis* ***1974***, 117; Hori, I.; Hayashi, T.; Midorikawa, H. *Synthesis* ***1974***, 705.

[1699]Corey, E.J. *Pure Appl. Chem.* ***1967***, *14*, 19, pp. 20–23.

[1700]For a long list of synthons for RCO, with references, see Hase, T.A.; Koskimies, J.K. *Aldrichimica Acta* ***1982***, *15*, 35.

[1701]For example, see Corey, E.J.; Seebach, D. *J. Org. Chem.* ***1975***, *40*, 231; Jones, J.B.; Grayshan, R. *Chem. Commun.* ***1970***, 141, 741.

Another useful application of this reaction stems from the fact that dithianes can be desulfurated with Raney nickel (**14-27**). Aldehydes can therefore be converted to chain-extended hydrocarbons:[1702]



Similar reactions have been carried out with other thioacetals, as well as with compounds containing three thioether groups on a carbon.[1703]

If a stabilizing group other than sulfur is attached to the S-CH_2 unit of a thioether ($RSCH_2X$, where X is a stabilizing group), formation of the anion and alkylation can be facile. For example, benzylic and allylic thioethers ($RSCH_2Ar$ and $RSCH_2CH{=}CH_2$)[1704] and thioethers of the form $RSCH_3$ (R = tetrahydrofuranyl or 2-tetrahydropyranyl)[1705] have been successfully alkylated at the carbon adjacent to the sulfur atom.[1706] Stabilization by one thioether group has also been used in a method for the homologation of primary halides.[1707] Thioanisole is treated with BuLi to give the corresponding anion,[1708] which reacts with the halide to give the thioether, which is then refluxed with a mixture of methyl iodide and sodium iodide in DMF to give the alkyl iodide as the final product (via an intermediate sulfonium salt). By this sequence an alkyl halide RX is converted to its homolog RCH_2X by a pathway involving two laboratory steps (see also, **10-64**).

Vinylic sulfides containing an a hydrogen can also be alkylated[1709] by alkyl halides or epoxides. This is a method for converting an alkyl halide RX to an α,β-unsaturated aldehyde, which is the synthetic equivalent of the unknown $H^{\ominus}C{=}CH{-}CHO$ ion.[1710] Even simple alkyl aryl sulfides (RCH_2SAr and RR′CHSAr) have been alkylated to the sulfur.[1711]

[1702]For examples, see Hylton, T.; Boekelheide, V. *J. Am. Chem. Soc.* ***1968***, *90*, 6887; Jones, J.B.; Grayshan, R.*Chem. Commun.* ***1970***, 141, 741.

[1703]For example, see Seebach, D. *Angew. Chem. Int. Ed.* ***1967***, *6*, 442; Olsson, K. *Acta Chem. Scand.* ***1968***, *22*, 2390; Mori, K.; Hashimoto, H.; Takenaka, Y.; Takigawa, T. *Synthesis* ***1975***, 720; Lissel, M. *Liebigs Ann. Chem.* ***1982***, 1589.

[1704]Uemoto, K.; Kawahito, A.; Matsushita, N.; Skamoto, I.; Kaku, H.; Tsunoda, T. *Tetrahedron Lett.* ***2001***, *42*, 905.

[1705]Block, E.; Aslam, M. *J. Am. Chem. Soc.* ***1985***, *107*, 6729.

[1706]Biellmann, J.F.; Ducep, J.B. *Tetrahedron Lett.* ***1968***, 5629; ***1969***, 3707; *Tetrahedron* ***1971***, *27*, 5861. See also, Narasaka, K.; Hayashi, M.; Mukaiyama, T. *Chem. Lett.* ***1972***, 259.

[1707]Corey, E.J.; Jautelat, M. *Tetrahedron Lett.* ***1968***, 5787.

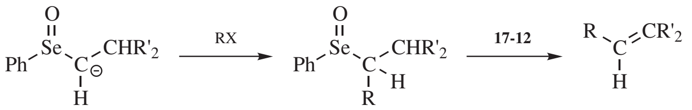
[1708]Corey, E.J.; Seebach, D. *J. Org. Chem.* ***1966***, *31*, 4097.

[1709]Oshima, K.; Shimoji, K.; Takahashi, H.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* ***1973***, *95*, 2694.

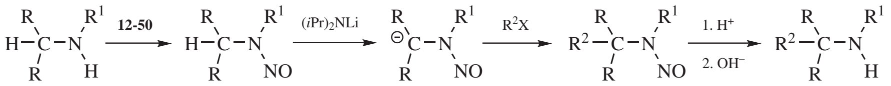
[1710]For references to other synthetic equivalents of this ion, see Funk, R.L.; Bolton, G.L. *J. Am. Chem. Soc.* ***1988***, *110*, 1290.

[1711]Dolak, T.M.; Bryson, T.A. *Tetrahedron Lett.* ***1977***, 1961.

Sulfones[1712] and sulfonic esters can also be alkylated in the a position if strong enough bases are used.[1713] Alkylation at the α position of selenoxides allows the formation of alkenes, since selenoxides easily undergo elimination (**17-12**).[1714]



Alkylation can also be carried out, in certain compounds, at positions α to other heteroatoms,[1715] for example, at a position α to the nitrogen of tertiary amines.[1716] Alkylation α to the nitrogen of primary or secondary amines is not generally feasible because an NH hydrogen is usually more acidic than a CH



hydrogen. α-Lithiation of *N*-Boc amines has been accomplished and these react with halides in the presence of a palladium catalyst.[1717] Alkylation α to the nitrogen atom of a carbamate occurs when the carbamate is treated with a Grignard reagent under electrolysis conditions.[1718] α-Methoxy amides also react with allyl halides and zinc metal to give alkylation via replacement of the OMe unit.[1719] It has been accomplished, however, by replacing the NH hydrogens with other (removable) groups.[1720] In one example, a secondary amine is converted to its *N*-nitroso derivative (**12-50**).[1721] The *N*-nitroso product is easily hydrolyzed to the product

[1712]For a review, see Magnus, P.D. *Tetrahedron* ***1977***, *33*, 2019, 2022–2025. For alkylation of sulfones containing the F_3CSO_2 group, see Hendrickson, J.B.; Sternbach, D.D.; Bair, K.W. *Acc. Chem. Res.* ***1977***, *10*, 306.

[1713]For examples, see Truce, W.E.; Hollister, K.R.; Lindy, L.B.; Parr, J.E. *J. Org. Chem.* ***1968***, *33*, 43; Julia, M.; Arnould, D. *Bull. Soc. Chim. Fr.* ***1973***, 743, 746; Bird, R.; Stirling, C.J.M. *J. Chem. Soc. B* ***1968***, 111.

[1714]Reich, H.J.; Shah, S.K. *J. Am. Chem. Soc.* ***1975***, *97*, 3250.

[1715]For a review of anions α to a selenium atom on small rings, see Krief, A. *Top. Curr. Chem.* ***1987***, *135*, 1. For alkylation α to boron see Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, pp. 336–341.

[1716]Lepley, A.R.; Khan, W.A. *J. Org. Chem.* ***1966***, *31*, 2061, 2064; *Chem. Commun.* ***1967***, 1198; Lepley, A.R.; Giumanini, A.G. *J. Org. Chem.* ***1966***, *31*, 2055; Ahlbrecht, H.; Dollinger, H. *Tetrahedron Lett.* ***1984***, *25*, 1353.

[1717]Dieter, R.K.; Li, S. *Tetrahedron Lett.* ***1995***, *36*, 3613.

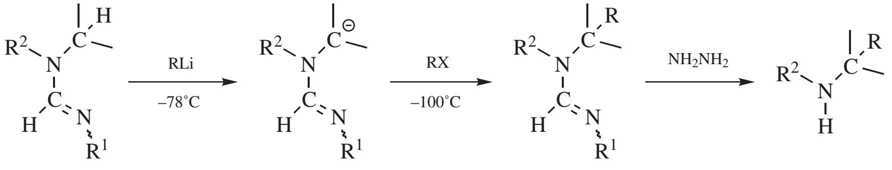
[1718]Suga, S.; Okajima, M.; Yoshida, J.-i. *Tetrahedron Lett.* ***2001***, *42*, 2173.

[1719]Kise, N.; Yamazaki, H.; Mabuchi, T.; Shono, T. *Tetrahedron Lett.* ***1994***, *35*, 1561.

[1720]For a review, see Beak, P.; Zajdel, W.J.; Reitz, D.B. *Chem. Rev.* ***1984***, *84*, 471.

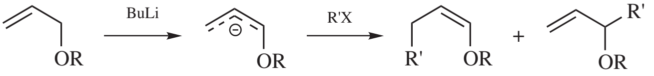
[1721]Seebach, D.; Enders, D.; Renger, B. *Chem. Ber.* ***1977***, *110*, 1852; Renger, B.; Kalinowski, H.; Seebach, D. *Chem. Ber.* ***1977***, *110*, 1866. For a review, see Seebach, D.; Enders, D. *Angew. Chem. Int. Ed.* ***1975***, *14*, 15.

amine (**19-51**).[1722] Alkylation of secondary and primary amines has also been accomplished with >10 other protecting groups, involving conversion of amines to amides, carbamates,[1723] formamidines,[1724] and phosphoramides.[1719] In the case of formamidines (**167**), use of a chiral R′ leads to a chiral amine, in high ee, even when R is not chiral.[1725]



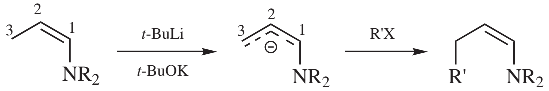
167

A proton can be removed from an allylic ether by treatment with an alkyllithium at about −70°C (at higher temperatures the Wittig rearrangement, **18-22**, takes place) to give the ion **168**, which reacts with alkyl halides to give the two products



168

shown.[1726] Similar reactions[1727] have been reported for allylic[1728] and vinylic tertiary amines. In the latter case, enamines **169**, treated with a strong base, are converted to anions that are then alkylated, generally at C-3.[1729] (For direct alkylation of enamines at C-2, see **10-69**.)



169

[1722]Fridman, A.L.; Mukhametshin, F.M.; Novikov, S.S. *Russ. Chem. Rev.* ***1971***, *40*, 34, pp. 41–42.

[1723]For the use of *tert*-butyl carbamates, see Beak, P.; Lee, W. *Tetrahedron Lett.* ***1989***, *30*, 1197.

[1724]For a review, see Meyers, A.I. *Aldrichimica Acta* ***1985***, *18*, 59.

[1725]Gawley, R.E.; Hart, G.; Goicoechea-Pappas, M.; Smith, A.L. *J. Org. Chem.* ***1986***, *51*, 3076; Gawley, R.E. *J. Am. Chem. Soc.* ***1987***, *109*, 1265; Meyers, A.I.; Miller, D.B.; White, F. *J. Am. Chem. Soc.* ***1988***, *110*, 4778; Gonzalez, M.A.; Meyers, A.I. *Tetrahedron Lett.* ***1989***, *30*, 43, 47, and references cited therein.

[1726]Evans, D.A.; Andrews, G.C.; Buckwalter, B. *J. Am. Chem. Soc.* ***1974***, *96*, 5560; Still, W.C.; Macdonald, T.L. *J. Am. Chem. Soc.* ***1974***, *96*, 5561; Funk, R.L.; Bolton, G.L. *J. Am. Chem. Soc.* ***1988***, *110*, 1290. For a similar reaction with triple-bond compounds, see Hommes, H.; Verkruijsse, H.D.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* ***1980***, *99*, 113, and references cited therein.

[1727]For a review of allylic and benzylic carbanions substituted by heteroatoms, see Biellmann, J.F.; Ducep, J. *Org. React.* ***1982***, *27*, 1.

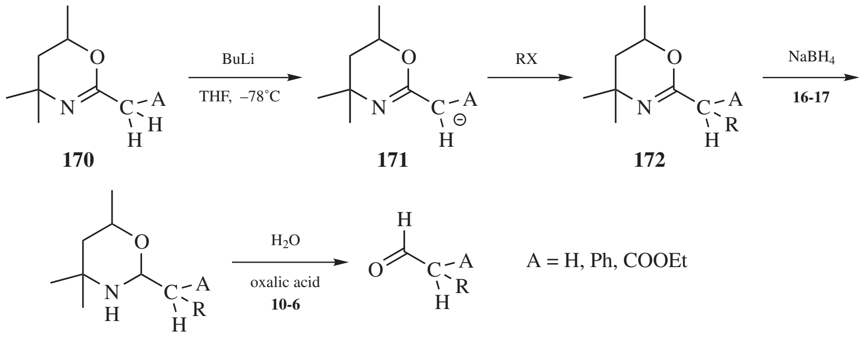
[1728]Martin, S.F.; DuPriest, M.T. *Tetrahedron Lett.* ***1977***, 3925, and references cited therein.

[1729]For a review, see Ahlbrecht, H. *Chimia* ***1977***, *31*, 391.

It is also possible to alkylate a methyl, ethyl, or other primary group of an aryl ester ArCOOR, where Ar is a 2,4,6-trialkylphenyl group.[1730] Since esters can be hydrolyzed to alcohols, this constitutes an indirect alkylation of primary alcohols. Methanol has also been alkylated by converting it to $^{\ominus}CH_2O^{\ominus}$.[1731]

OS **VI**, 316, 364, 542, 704, 869; **VIII**, 573.

10-72 Alkylation of Dihydro-1,3-Oxazine: The Meyers Synthesis of Aldehydes, Ketones, and Carboxylic Acids



A synthesis of aldehydes[1732] developed by Meyers[1733] begins with the commercially available dihydro-1,3-oxazine derivatives **170** (A = H, Ph, or COOEt).[1734] Removal of a proton from the indicated carbon in **170** leads to the resonance stabilized and bidentate anion **172**. Alkylation occurs regioselectively at carbon by a many alkyl bromides and iodides. The R group of RX can be primary or secondary alkyl, allylic, or benzylic and can carry another halogen or a CN group.[1735] The alkylated oxazine **173** is then reduced and hydrolyzed to give an aldehyde containing two more carbons than the starting RX. This method thus complements **10-71**, which converts RX to an aldehyde containing one more carbon. Since A can be H, mono- or disubstituted acetaldehydes can be produced by this method.

The ion **171** also reacts with epoxides, to form γ-hydroxy aldehydes after reduction and hydrolysis,[1736] and with aldehydes and ketones (**16-38**). Similar aldehyde

[1730]Beak, P.; Carter. L.G. *J. Org. Chem.* ***1981***, *46*, 2363.

[1731]Seebach, D.; Meyer, N. *Angew. Chem. Int. Ed.* ***1976***, *15*, 438.

[1732]For examples of the preparation of aldehydes and ketones by the reactions in this section, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1461–1465.

[1733]Meyers, A.I.; Nabeya, A.; Adickes, H.W.; Politzer, I.R.; Malone, G.R.; Kovelesky, A.C.; Nolen, R.L.; Portnoy, R.C. *J. Org. Chem.* ***1973***, *38*, 36.

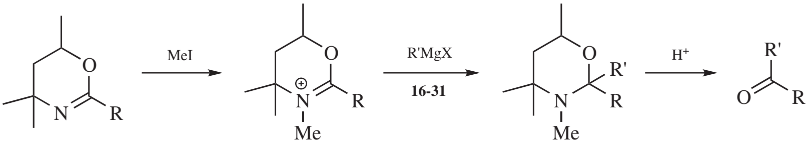
[1734]For reviews of the preparation and reactions of **169**, see Schmidt, R.R. *Synthesis* ***1972***, 333; Collington, E.W. *Chem. Ind. (London)* ***1973***, 987.

[1735]Meyers, A.I.; Malone, G.R.; Adickes, H.W. *Tetrahedron Lett.* ***1970***, 3715.

[1736]Adickes, H.W.; Politzer, I.R.; Meyers, A.I. *J. Am. Chem. Soc.* ***1969***, *91*, 2155.

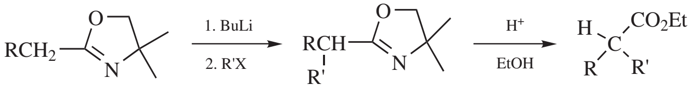
synthesis has also been carried out with thiazoles[1737] and thiazolines[1738] (five-membered rings containing N and S in the 1 and 3 positions).

The reaction has been extended to the preparation of ketones:[1739] Treatment of a dihydro-1,3-oxazine (**172**) with iodomethane forms the iminium salt **173** (**10-31**) which, when treated with a Grignard reagent or organolithium compound (**16-31**)



173 **174**

produces **174**, which can be hydrolyzed to a ketone. The R group can be alkyl, cycloalkyl, aryl, benzylic, and so on, and R′ of the Grignard reagent can be alkyl, aryl, benzylic, or allylic. Note that the hetereocycles **170**, **172**, or **173** do not react directly with Grignard reagents. In another procedure, 2-oxazolines (**175**)[1740] can be alkylated to give **176**,[1741] which are easily converted directly to the esters **177** by heating in 5–7% ethanolic sulfuric acid.



175 **176** **177**

2-Oxazolines **175** and **176** are thus synthons for carboxylic acids; this is another indirect method for the α alkylation of a carboxylic acid,[1742] representing an alternative to the malonic ester synthesis (**10-67**) and to **10-70** and **10-73**. The method can be adapted to the preparation of optically active carboxylic acids by the use of a chiral reagent.[1743] Note that, unlike **170**, **175** can be alkylated even if R is alkyl. However, the C=N bond of **175** and **176** cannot be effectively reduced, so that aldehyde synthesis is not feasible here.[1744]

OS **VI**, 905.

[1737]Altman, L.J.; Richheimer, S.L. *Tetrahedron Lett.* ***1971***, 4709.

[1738]Meyers, A.I.; Durandetta, J.L. *J. Org. Chem.* ***1975***, *40*, 2021.

[1739]Meyers, A.I.; Smith, E.M. *J. Am. Chem. Soc.* ***1970***, *92*, 1084; *J. Org. Chem.* ***1972***, *37*, 4289.

[1740]For a review, see Meyers, A.I.; Mihelich, E.D. *Angew. Chem. Int. Ed.* ***1976***, *15*, 270.

[1741]Meyers, A.I.; Temple, Jr., D.L.; Nolen, R.L.; Mihelich, E.D. *J. Org. Chem.* ***1974***, *39*, 2778; Meyers, A.I.; Mihelich, E.D.; Nolen, R.L. *J. Org. Chem.* ***1974***, *39*, 2783; Meyers, A.I.; Mihelich, E.D.; Kamata, K. *J. Chem. Soc., Chem. Commun.* ***1974***, 768.

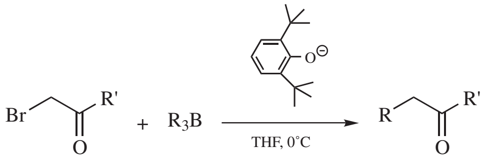
[1742]For reviews, see Meyers, A.I. *Pure Appl. Chem.* ***1979***, *51*, 1255; *Acc. Chem. Res.* ***1978***, *11*, 375. See also, Hoobler, M.A.; Bergbreiter, D.E.; Newcomb, M. *J. Am. Chem. Soc.* ***1978***, *100*, 8182; Meyers, A.I.; Snyder, E.S.; Ackerman, J.J.H. *J. Am. Chem. Soc.* ***1978***, *100*, 8186.

[1743]For a review of asymmetric synthesis via chiral oxazolines, see Lutomski, K.A.; Meyers, A.I., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 3, Academic Press, NY, ***1984***, pp. 213–274.

[1744]Meyers, A.I.; Temple Jr., D.L. *J. Am. Chem. Soc.* ***1970***, *92*, 6644, 6646.

10-73 Alkylation with Trialkylboranes

Alkyl-de-halogenation



Trialkylboranes react rapidly and in high yields with α-halo ketones,[1745] α-halo esters,[1746] α-halo nitriles,[1747] and α-halo sulfonyl derivatives (sulfones, sulfonic esters, sulfonamides)[1748] in the presence of a base to give, respectively, alkylated ketones, esters, nitriles, and sulfonyl derivatives.[1749] Potassium *tert*-butoxide is often a suitable base, but potassium 2,6-di-*tert*-butylphenoxide at 0°C in THF gives better results in most cases, possibly because the large bulk of the two *tert*-butyl groups prevents the base from coordinating with the R_3B.[1750] The trialkylboranes are prepared by treatment of 3 equivalents of an alkene with 1 equivalent of BH_3 (**15-16**).[1751] With appropriate boranes, the R group transferred to α-halo ketones, nitriles, and esters can be vinylic,[1752] or (for α-halo ketones and esters) aryl.[1753]

The reaction can be extended to α,α-dihalo esters[1754] and α,α-dihalo nitriles.[1755] It is possible to replace just one halogen or both. In the latter case the two alkyl groups can be the same or different. When dialkylation is applied to dihalo nitriles, the two alkyl groups can be primary or secondary, but with dihalo esters, dialkylation is limited to primary R. Another extension is the reaction of boranes (BR_3) with γ-halo-α,β-unsaturated esters.[1756] Alkylation takes place in the γ position, but the double bond migrates out of conjugation with the COOEt unit [$BrCH_2CH{=}CHCOOEt \rightarrow RCH{=}CHCH_2COOEt$]. In this case, however, double-bond

[1745]Brown, H.C.; Rogić, M.M.; Rathke, M.W. *J. Am. Chem. Soc.* ***1968***, *90*, 6218.

[1746]Brown, H.C.; Rogić, M.M.; Rathke, M.W.; Kabalka, G.W. *J. Am. Chem. Soc.* ***1968***, *90*, 818.

[1747]Brown, H.C.; Nambu, H.; Rogić, M.M. *J. Am. Chem. Soc.* ***1969***, *91*, 6854.

[1748]Truce, W.E.; Mura, L.A.; Smith, P.J.; Young, F. *J. Org. Chem.* ***1974***, *39*, 1449.

[1749]For reviews, see Negishi, E.; Idacavage, M.J. *Org. React.* ***1985***, *33*, 1, 42–43, 143–150; Weill-Raynal, J. *Synthesis* ***1976***, 633; Brown, H.C.; Rogić, M.M. *Organomet. Chem. Synth.* ***1972***, *1*, 305; Rogić, M.M. *Intra-Sci. Chem. Rep.* ***1973***, *7(2)*, 155; Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, ***1972***, pp. 372–391, 404–409; Cragg, G.M.L. *Organoboranes in Organic Synthesis*, Marcel Dekker, NY, ***1973***, pp. 275–278, 283–287.

[1750]Brown, H.C.; Nambu, H.; Rogić, M.M. *J. Am. Chem. Soc.* ***1969***, *91*, 6852, 6854, 6855.

[1751]For an improved procedure, with B-9-BBN (see p. $$$), see Brown, H.C.; Rogić, M.M. *J. Am. Chem. Soc.* ***1969***, *91*, 2146; Brown, H.C.; Rogić, M.M.; Nambu, H.; Rathke, M.W. *J. Am. Chem. Soc.* ***1969***, *91*, 2147; Katz, J.; Dubois, J.E.; Lion, C. *Bull. Soc. Chim. Fr.* ***1977***, 683.

[1752]Brown, H.C.; Bhat, N.G.; Campbell, Jr., J.B. *J. Org. Chem.* ***1986***, *51*, 3398.

[1753]Brown, H.C.; Rogić, M.M. *J. Am. Chem. Soc.* ***1969***, *91*, 4304.

[1754]Brown, H.C.; Rogić, M.M.; Rathke, M.W.; Kabalka, G.W. *J. Am. Chem. Soc.* ***1968***, *90*, 1911.

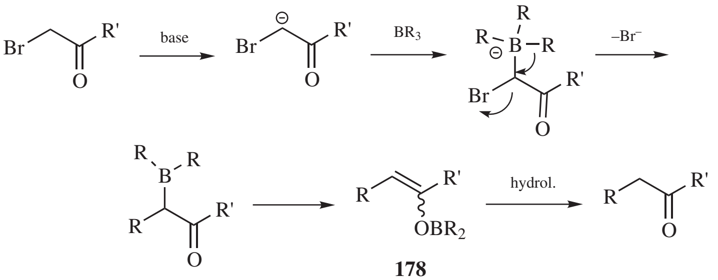
[1755]Nambu, H.; Brown, H.C. *J. Am. Chem. Soc.* ***1970***, *92*, 5790.

[1756]Brown, H.C.; Nambu, H. *J. Am. Chem. Soc.* ***1970***, *92*, 1761.

migration is an advantage, because nonconjugated β,γ-unsaturated esters are usually much more difficult to prepare than their α,β-unsaturated isomers.

The alkylation of activated halogen compounds is one of several reactions of trialkylboranes developed by H.C. Brown[1757] (see also, **15-16**, **15-27**, **18-31-18-40**, and so on). These compounds are extremely versatile and can be used for the preparation of many types of compounds. In this reaction, for example, an alkene (through the BR_3 prepared from it) can be coupled to a ketone, a nitrile, a carboxylic ester, or a sulfonyl derivative. Note that this is still another indirect way to alkylate a ketone (see **10-68**) or a carboxylic acid (see **10-70**), and provides an additional alternative to the malonic ester and acetoacetic ester syntheses (**10-67**).

Although superficially this reaction resembles **10-57** it is likely that the mechanism is quite different, involving migration of an R group from boron to carbon (see also, **18-23–18-26**). The mechanism is not known with certainty,[1758] but it may be tentatively shown as (illustrated for an α-halo ketone):



178

The first step is removal of the acidic proton by the base to give an enolate anion that combines with the borane (Lewis acid–base reaction). An R group then migrates, displacing the halogen leaving group.[1759] Another migration follows, this time of BR_2 from carbon to oxygen to give the enol borinate **178**,[1760] which is hydrolyzed. Configuration at R is retained.[1761]

[1757]Brown, H.C. *Organic Syntheses via Boranes*, Wiley, NY, ***1975***; *Hydroboration*, W.A. Benjamin, NY, ***1962***; *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, ***1972***; Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***.

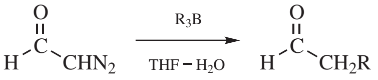
[1758]See Prager, R.H.; Reece, P.A. *Aust. J. Chem.* ***1975***, *28*, 1775.

[1759]It has been shown that this migration occurs stereospecifically with inversion in the absence of a solvent, but nonstereospecifically in the presence of a solvent, such as THF or dimethyl sulfide: Midland, M.M.; Zolopa, A.R.; Halterman, R.I. *J. Am. Chem. Soc.* ***1979***, *101*, 248. See also, Midland, M.M.; Preston, S.B. *J. Org. Chem.* ***1980***, *45*, 747.

[1760]Pasto, D.J.; Wojtkowski, P.W. *Tetrahedron Lett.* ***1970***, 215, Pasto, D.J.; Wojtkowski, P.W. *J. Org. Chem.* ***1971***, *36*, 1790.

[1761]Brown, H.C.; Rogić, M.M.; Rathke, M.W.; Kabalka, G.W. *J. Am. Chem. Soc.* ***1969***, *91*, 2150.

The reaction has also been applied to compounds with other leaving groups. Diazo ketones, diazo esters, diazo nitriles, and diazo aldehydes (**179**)[1762] react with trialkylboranes in a similar manner.



179

The mechanism is probably also similar. In this case a base is not needed, since the carbon already has an available pair of electrons. The reaction with diazo aldehydes[1763] is especially notable, since successful reactions cannot be obtained with α-halo aldehydes.[1764]

OS **VI**, 919; **IX**, 107.

10-74 Alkylation at an Alkynyl Carbon

Alkynyl-de-halogenation

$$\mathrm{RX} + \mathrm{R'C{\equiv}C^-} \longrightarrow \mathrm{RC{\equiv}CR'}$$

The reaction between alkyl halides and acetylide ions is useful but of limited scope.[1765] Only primary halides unbranched in the β-position give good yields, although allylic halides can be used if CuI is present.[1766] If acetylene is the reagent, two different groups can be successively attached. Sulfates, sulfonates, and epoxides[1767] are sometimes used as substrates. The acetylide ion is often prepared by treatment of an alkyne with a strong base such as $NaNH_2$. Magnesium acetylides (ethynyl Grignard reagents; prepared as in **12-22**) are also frequently used, although they react only with active substrates, such as allylic, benzylic, and propargylic halides, and not with primary alkyl halides. Alternatively, the alkyl halide can be treated with a lithium acetylide–ethylenediamine complex.[1768] If 2 equivalents of a very

[1762]Hooz, J.; Gunn, D.M.; Kono, H. *Can. J. Chem.* ***1971***, *49*, 2371; Mikhailov, B.M.; Gurskii, M.E. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1973***, *22*, 2588.

[1763]Hooz, J.; Morrison, G.F. *Can J. Chem.* ***1970***, *48*, 868.

[1764]For an improved procedure, see Hooz, J.; Bridson, J.N.; Calzada, J.G.; Brown, H.C.; Midland, M.M.; Levy, A.B. *J. Org. Chem.* ***1973***, *38*, 2574.

[1765]For reviews, see Ben-Efraim, D.A., in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, Wiley, NY, ***1978***, pp. 790–800; Ziegenbein, W., in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 185–206, 241–244. For a discussion of the best ways of preparing various types of alkyne, see Bernadou, F.; Mesnard, D.; Miginiac, L. *J. Chem. Res. (S)* ***1978***, 106; ***1979***, 190.

[1766]Bourgain, M.; Normant, J.F. *Bull. Soc. Chim. Fr.* ***1973***, 1777; Jeffery, T. *Tetrahedron Lett.* ***1989***, *30*, 2225.

[1767]For example, see Fried, J.; Lin, C.; Ford, S.H. *Tetrahedron Lett.* ***1969***, 1379; Krause, N.; Seebach, D. *Chem. Ber.* ***1988***, *121*, 1315.

[1768]Smith, W.N.; Beumel Jr., O.F. *Synthesis* ***1974***, 441.

strong base are used, alkylation can be effected at a carbon α to a terminal triple bond: $RCH_2C{\equiv}CH + 2BuLi \rightarrow RCHC{\equiv}C^- + R'Br \rightarrow RR'CHC{\equiv}C^-$.[1769] For another method of alkylating at an alkynyl carbon, see **18-26**. An alternative method for generating an alkyne anion treated a trialkylsilyl alkyne with potassium carbonate in methanol, and then methyllithium/LiBr.[1770] In the presence of an alkyl iodide, alkylation at the alkynyl carbon occurred.

Alkynes couple with alkyl halides in the presence of SmI_2/Sm.[1771] Alkynes react with hypervalent iodine compounds[1772] and with reactive alkanes such as adamantane in the presence of AIBN.[1773] The reaction of benzylic amines with terminal alkynes, in the presence of copper triflate and *tert*-butylhydroperoxide leads to incorporation of the alkyne group α to the nitrogen.[1774] A similar reaction occurs at a methyl group of *N,N*-dimethylaniline.[1775] α-Methoxycarbamates (MeO—CHR—NR^1—CO_2R^2) react with terminal alkynes and CuBr to give the alkynylamine.[1776] In the presence of $GaCl_3$, $ClC{\equiv}CSiMe_3$ reacts with silyl enol ethers to give, after treatment with methanolic acid, an α-ethynyl ketone.[1777]

1-Haloalkynes (R—C≡C—X) react with $ArSnBu_3$ and CuI to give R—C≡C—Ar.[1778] Organozirconium compounds react in a similar manner.[1779] Acetylene reacts with 2 equivalents of iodobenzene, in the presence of a palladium catalyst and CuI, to give 1,2-diphenylethyne.[1780] 1-Trialkylsilyl alkynes react with 1-haloalkynes, in the presence of a CuCl catalyst, to give diynes[1781] and with aryl triflates to give 1-aryl alkynes.[1782]

In a related reaction, terminal alkynes react with silanes (R_3SiH) in the presence of an iridium catalyst to give the 1-trialkylsilyl alkyne.[1783] similar products are obtained when terminal alkynes react with *N*-trialkylsilylamines and $ZnCl_2$.[1784]

[1769]Bhanu, S.; Scheinmann, F. *J. Chem. Soc. Perkin Trans.1*, ***1979***, 1218; Quillinan, A.J.; Scheinmann, F. *Org. Synth.* ***VI***, 595.

[1770]Fiandanese, V.; Bottalico, D.; Marchese, G.; Punzi, A. *Tetrahedron Lett.* ***2003***, *44*, 9087.

[1771]Murakami, M.; Hayashi, M.; Ito, Y. *Synlett*, ***1994***, 179.

[1772]Kang, S.-K.; Lim, K.-H.; Ho, P.-S.; Kim, W.-Y. *Synthesis* ***1997***, 874.

[1773]Xiang, J.; Jiang, W.; Fuchs, P.L. *Tetrahedron Lett.* ***1997***, *38*, 6635.

[1774]Li, Z.; Li, C.-J. *Org. Lett.* ***2004***, *6*, 4997.

[1775]Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* ***2004***, *126*, 11810.

[1776]Zhang, J.; Wei, C.; Lei, C.-J. *Tetrahedron Lett.* ***2002***, *43*, 5731.

[1777]Arisawa, M.; Amemiya, R.; Yamaguchi, M. *Org. Lett.* ***2002***, *4*, 2209.

[1778]Kang, S.-K.; Kim, W.-Y.; Jiao, X. *Synthesis* ***1998***, 1252.

[1779]Liu, Y.; Xi, C.; Hara, R.; Nakajima, K.; Yamazaki, A.; Kotora, M.; Takahashi, T. *J. Org. Chem.* ***2000***, *65*, 6951.

[1780]Pal, M.; Kundu, N.G. *J. Chem. Soc. Perkin Trans 1*, ***1996***, 449. Also see, Nguefack, J.-F.; Bolitt, V.; Sinou, D. *Tetrahedron Lett*, ***1996***, *37*, 5527.

[1781]Nishihara, Y.; Ikegashira, K.; Mori, A.; Hiyama, T. *Tetrahedron Lett.* ***1998***, *39*, 4075.

[1782]Bumagin, N.A.; Sukhmolinova, L.I.; Luzikova, E.V.; Tolstaya, T.P.; Beletskaya, I.P. *Tetrahedron Lett.* ***1996***, *37*, 897; Powell, N.A.; Rychnovsky, S.D. *Tetrahedron Lett.* ***1996***, *37*, 7901; Nishihara, Y.; Ikegashira, K.; Mori, A.; Hiyama, T. *Chem. Lett.* ***1997***, 1233.

[1783]Shimizu, R; Fuchikami, T. *Tetrahedron Lett.* ***2000***, *41*, 907.

[1784]Andreev, A.A.; Konshin, V.V.; Komarov, N.V.; Rubin, M.; Brouwer, C.; Gevorgyan, V. *Org. Lett.* ***2004***, *6*, 421.

OS **IV**, 117; **VI**, 273, 564, 595; **VIII**, 415; **IX**, 117, 477, 688; **76**, 263. Also see, OS **IV**, 801; **VI**, 925.

10-75 Preparation of Nitriles

Cyano-de-halogenation

$$RX + {}^{-}CN \longrightarrow RCN$$

The reaction between cyanide ion and alkyl halides is a convenient method for the preparation of nitriles.[1785] Primary, benzylic, and allylic halides give good yields of nitriles; secondary halides give moderate yields. The reaction fails for tertiary halides, which give elimination under these conditions. Many other groups on the molecule do not interfere. A number of solvents have been used, but the high yields and short reaction times observed with DMSO make it a very good solvent for this reaction.[1786] Other ways to obtain high yields under mild conditions are to use a phase-transfer catalyst,[1787] in alternative solvents, such as PEG 400 (a polyethylene glycol),[1788] or with ultrasound.[1789] This is an important way of increasing the length of a carbon chain by one carbon, since nitriles are easily hydrolyzed to carboxylic acids (**16-4**).

The cyanide ion is an ambident nucleophile (it can react via N or via C) and isocyanides (also called isonitriles, R—N≡C) may be side products.[1790] If the preparation of isocyanides is desired, they can be made the main products by the use of reagents with more covalent metal–carbon bonds, such as silver or copper(I) cyanide[1791] (p. 515). However, the use on an excess of LiCN in acetone/THF gave the nitrile as the major product.[1792] Tosyl cyanide ($TolSO_2CN$) has been used in some cases.[1793]

Vinylic bromides can be converted to vinylic cyanides with CuCN,[1794] with KCN, a crown ether, and a Pd(0) complex,[1795] or with KCN and a Ni(0)

[1785]For reviews, see, in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 1, Wiley, NY, ***1983***, the articles by Fatiadi, A.J. pt. 2, pp. 1057–1303, and Friedrich, K. pt. 2, pp. 1343–1390; Friedrich, K.; Wallenfels, K., in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 77–86.

[1786]Smiley, R.A.; Arnold, C. *J. Org. Chem.* ***1960***, *25*, 257; Friedman, L.; Shechter, H. *J. Org. Chem.* ***1960***, *25*, 877.

[1787]For reviews, see Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Acaemic Press, NY, ***1978***, pp. 94–112; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, ***1977***, pp. 96–108. See also, Bram, G.; Loupy, A.; Pedoussaut, M. *Tetrahedron Lett.* ***1986***, *27*, 4171; *Bull. Soc. Chim. Fr.* ***1986***, 124.

[1788]Cao, Y.-Q.; Che, B.-H.; Pei, B.-G. *Synth. Commun.* ***2001***, *31*, 2203.

[1789]Ando, T.; Kawate, T.; Ichihara, J.; Hanafusa, T. *Chem. Lett.* ***1984***, 725.

[1790]For a solid-phase synthesis of isonitriles see Luanay, D.; Booth, S.; Clemens, I.; Merritt, A.; Bradley, M. *Tetrahedron Lett.* ***2002***, *43*, 7201.

[1791]For an example, see Jackson, H.L.; McKusick, B.C. *Org. Synth.* ***IV***, 438.

[1792]Ciaccio, J.A.; Smrtka, M.; Maio, W.A.; Rucando, D. *Tetrahedron Lett.* ***2004***, *45*, 7201.

[1793]Kim, S.; Song, H.-J. *Synlett* ***2002***, 2110.

[1794]For example, see Koelsch, C.F. *J. Am. Chem. Soc.* ***1936***, *58*, 1328; Newman, M.S.; Boden, H. *J. Org. Chem.* ***1961***, *26*, 2525; Lapouyade, R.; Daney, M.; Lapenue, M.; Bouas-Laurent, H. *Bull. Soc. Chim. Fr.* ***1973***, 720.

[1795]Yamamura, K.; Murahashi, S. *Tetrahedron Lett.* ***1977***, 4429.

catalyst.[1796] Halides can be converted to the corresponding nitriles by treatment with trimethylsilyl cyanide in the presence of catalytic amounts of $SnCl_4$: $R_3CCl + Me_3\ SiCN \rightarrow R_3CCN$.[1797] Primary, secondary, and tertiary alcohols are converted to nitriles in good yields by treatment with NaCN, Me_3SiCl, and a catalytic amount of NaI in DMF—MeCN.[1798] Lewis acids have been used in conjunction with NaCN or KCN.[1799] α,β-Epxoy amides were opened to the β-cyano-α-hydroxyamide with Et_2AlCN.[1800] Cyanohydrins react with alkyl halides in some cases to give the nitrile.[1801]

Substrates that react with cyanide may contain leaving groups other than halides, such as esters of sulfuric and sulfonic acids (sulfates and sulfonates, respectively). Vinylic triflates give vinylic cyanides when treated with LiCN, a crown ether, and a palladium catalyst.[1802] Epoxides give β-hydroxy nitriles. The C-2-selectivity was observed when NaCN and $B(OMe)_3$ were reacted with a disubstituted epoxide.[1803] The use of trimethylsilyl cyanide (Me_3SiCN) and a Lewis acid generates the *O*-TMS β-hydroxy nitrile, and the use of $YbCl_3$ and a salen complex gave good enantioselectivity.[1804] One alkoxy group of acetals is replaced by CN [$R_2C(OR')_2 \rightarrow R_2C(OR')CN$] with Me_3SiCN and a catalyst[1805] or with *t*-BuNC and $TiCl_4$.[1806] Tetrabutylammonium cyanide converted a primary alcohol to the corresponding nitrile in the presence of PPh_3/DDQ.[1807]

Sodium cyanide in HMPA selectively cleaves methyl esters in the presence of ethyl esters:

$$RCOOMe + CN^- \longrightarrow MeCN + RCOO^-.$$ [1808]

[1796]Sakakibara, Y.; Yadani, N.; Ibuki, I.; Sakai, M.; Uchino, N. *Chem. Lett.* ***1982***, 1565; Procházka, M.; Siroky, M. *Collect. Czech. Chem. Commun.* ***1983***, *48*, 1765.

[1797]Reetz, M.T.; Chatziiosifidis, I. *Angew. Chem. Int. Ed.* ***1981***, *20*, 1017; Zieger, H.E.; Wo, S. *J. Org. Chem.* ***1994***, *59*, 3838. See Tsuji, Y.; Yamada, N.; Tanaka, S. *J. Org. Chem.* ***1993***, *58*, 16 for a similar reaction with allylic acetates. See Hayashi, M.; Tamura, M.; Oguni, N. *Synlett*, ***1992***, 663 for a similar reaction with epoxides using a titanium catalyst.

[1798]Davis, R.; Untch, K.G. *J. Org. Chem.* ***1981***, *46*, 2985. See also, Mizuno, A.; Hamada, Y.; Shioiri, T. *Synthesis* ***1980***, 1007; Manna, S.; Falck, J.R.; Mioskowski, C. *Synth. Commun.* ***1985***, *15*, 663; Camps, F.; Gasol, V.; Guerrero, A. *Synth. Commun.* ***1988***, *18*, 445.

[1799]$Ce(OTf)_4$: Iranpoor, N.; Shekarriz, M. *Synth. Commun.* ***1999***, *29*, 2249.

[1800]Ruano, J.L.G.; Fernández-Ibáñez, M.Á.; Castro, A.M.M.; Ramos, J.H.R.; Flamarique, A.C.R. *Tetrahedron Asymmetry* ***2002***, *13*, 1321.

[1801]Dowd, P.; Wilk, B.K.; Wlostowski, M. *Synth. Commun.* ***1993***, *23*, 2323; Wilk, B.K. *Synth. Commun.* ***1993***, *23*, 2481 and see Ohno, H.; Mori, A.; Inoue, S. *Chem. Lett.* ***1993***, 975 and Mitchell, D.; Koenig, T.M. *Tetrahedron Lett.* ***1992***, *33*, 3281 for similar reactions with epoxides.

[1802]Piers, E.; Fleming, F.F. *J. Chem. Soc., Chem. Commun.* ***1989***, 756.

[1803]Sasaki, M.; Tanino, K.; Hirai, A.; Miyashita, M. *Org. Lett.* ***2003***, *5*, 1789.

[1804]Schaus, S.E.; Jacobsen, E.N. *Org. Lett.* ***2000***, *2*, 1001.

[1805]Torii, S.; Inokuchi, T.; Kobayashi, T. *Chem. Lett.* ***1984***, 897; Soga, T.; Takenoshita, H.; Yamada, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* ***1990***, *63*, 3122.

[1806]Ito, Y.; Imai, H.; Segoe, K.; Saegusa, T. *Chem. Lett.* ***1984***, 937.

[1807]Iranpoor, N.; Firouzabadi, H.; Akhlaghinia, B.; Nowrouzi, N. *J. Org. Chem.* ***2004***, *69*, 2562.

[1808]Müller, P.; Siegfried, B. *Helv. Chim. Acta* ***1974***, *57*, 987.

OS **I**, 46, 107, 156, 181, 254, 256, 536; **II**, 292, 376; **III**, 174, 372, 557; **IV**, 438, 496, 576; **V**, 578, 614.

10-76 Direct Conversion of Alkyl Halides to Aldehydes and Ketones

Formyl-de-halogenation

$$RX + Na_2Fe(CO)_4 \xrightarrow{PPh_3} \underset{\mathbf{180}}{RCOFe(CO)_3PPh_3^-} \xrightarrow{HOAc} RCHO$$

The direct conversion of alkyl bromides to aldehydes, with an increase in the chain length by one carbon, can be accomplished[1809] by treatment with sodium tetracarbonylferrate(-2)[1810] (*Collman's reagent*) in the presence of triphenylphosphine and subsequent quenching of **180** with acetic acid. The reagent $Na_2Fe(CO)_4$ can be prepared by treatment of iron pentacarbonyl $Fe(CO)_5$ with sodium amalgam in THF. Good yields are obtained from primary alkyl bromides; secondary bromides give lower yields. The reaction is generally not satisfactory for benzylic bromides, but a good yield of the ketone was obtained using benzyl chloride and aryl iodides.[1811] The initial species produced from RX and $Na_2Fe(CO)_4$ is the ion $RFe(CO)_4^-$ (which can be isolated[1812]); it then reacts with Ph_3P to give **180**.[1813]

The synthesis can be extended to the preparation of ketones in six distinct ways.[1814] These include quenching **180** with a second alkyl halide (R′X) rather than acetic acid; omitting PPh_3 with first RX and then adding the second, R′X; treatment with RX in the presence of CO,[1810] followed by treatment with R′X'; treatment with an acyl halide followed by treatment with an alkyl halide or an epoxide, gives an α,β-unsaturated ketone.[1815] The final variations involve reaction of alkyl halides or tosylates with $Na_2Fe(CO)_4$ in the presence of ethylene to give alkyl ethyl ketones;[1816] when 1,4-dihalides are used, five-membered cyclic ketones are prepared.[1817]

[1809]Cooke, Jr., M.P. *J. Am. Chem. Soc.* ***1970***, *92*, 6080.

[1810]For a review of this reagent, see Collman, J.P. *Acc. Chem. Res.* ***1975***, *8*, 342. For a review of the related tetracarbonylhydridoferrates $MHFe(CO)_4$, see Brunet, J. *Chem. Rev.* ***1990***, *90*, 1041.

[1811]Dolhem, E.; Barhdadi, R.; Folest, J.C.; Nédélec, J.Y.; Troupel, M. *Tetrahedron* ***2001***, *57*, 525.

[1812]Siegl, W.O.; Collman, J.P. *J. Am. Chem. Soc.* ***1972***, *94*, 2516.

[1813]For the mechanism of the conversion $RFe(CO)_4^- \rightarrow$ **180**, see Collman, J.P.; Finke, R.G.; Cawse, J.N.; Brauman, J.I. *J. Am. Chem. Soc.* ***1977***, *99*, 2515; ***1978***, *100*, 4766.

[1814]For the first four of these methods, see Collman, J.P.; Winter, S.R.; Clark, D.R. *J. Am. Chem. Soc.* ***1972***, *94*, 1788; Collman, J.P.; Hoffman, N.W. *J. Am. Chem. Soc.* ***1973***, *95*, 2689.

[1815]Yamashita, M.; Yamamura, S.; Kurimoto, M.; Suemitsu, R. *Chem. Lett.* ***1979***, 1067.

[1816]Cooke, Jr., M.P.; Parlman, R.M. *J. Am. Chem. Soc.* ***1975***, *97*, 6863. The reaction was not successful for higher alkenes, except that where the double bond and the tosylate group are in the same molecule, five- and six-membered rings can be closed: see McMurry, J.E.; Andrus, A. *Tetrahedron Lett.* ***1980***, *21*, 4687, and references cited therein.

[1817]Yamashita, M.; Uchida, M.; Tashika, H.; Suemitsu, R. *Bull. Chem. Soc. Jpn.* ***1989***, *62*, 2728.

Yet another approach uses electrolysis conditions with the alkyl chloride, $Fe(CO)_5$ and a nickel catalyst and gives the ketone directly, in one step.[1818] In the first stage of methods 1, 2, and 3, primary bromides, iodides, and tosylates and secondary tosylates can be used. The second stage of the first four methods requires more active substrates, such as primary iodides or tosylates or benzylic halides. Method 5 has been applied to primary and secondary substrates.

Other acyl organometallic reagents are known. An acyl zirconium reagent, such as $RCOZr(Cl)Cp_2$, reacted with allylic bromide in the presence of CuI to give the corresponding ketone, but with allylic rearrangement.[1819]

Symmetrical ketones R_2CO can be prepared by treatment of a primary alkyl or benzylic halide with $Fe(CO)_5$ and a phase transfer catalyst,[1820] or from a halide RX (R = primary alkyl, aryl, allylic, or benzylic) and CO by an electrochemical method involving a nickel complex.[1821] Aryl, benzylic, vinylic, and allylic halides have been converted to aldehydes by treatment with CO and Bu_3SnH, with a Pd(0) catalyst.[1822] Various other groups do not interfere. Several procedures for the preparation of ketones are catalyzed by palladium complexes. Alkyl aryl ketones are formed in good yields by treatment of a mixture of an aryl iodide, an alkyl iodide, and a Zn—Cu couple with CO ($ArI + RI + CO \rightarrow RCOAr$).[1823] Vinylic halides react with vinylic tin reagents in the presence of CO to give unsymmetrical divinyl ketones.[1824] Aryl, vinylic, and benzylic halides can be converted to methyl ketones ($RX \rightarrow RCOMe$) by reaction with (α-ethoxyvinyl)tributyltin Bu_3Sn-$C(OEt){=}CH_2$.[1825] In addition, SmI_2 can be used to convert alkyl chloride to ketones, in the presence of 50 atm of CO.[1826] Carbonylation can also be done with Zn/CuI,[1827] Zn, and then $CoBr_2$,[1828] or with AIBN and $(Me_3Si)_3SiH$.[1829]

[1818]Dolhem, E.; Oçafrain, M.; Nédélec, J.Y.; Troupel, M. *Tetrahedron* ***1997***, *53*, 17089; Yoshida, K.; Kobayashi, M.; Amano, S. *J. Chem. Soc. Perkin Trans. 1* ***1992***, 1127.

[1819]Hanzawa, Y.; Narita, K.; Taguchi, T. *Tetrahedron Lett.* ***2000***, *41*, 109.

[1820]Kimura, Y.; Tomita, Y.; Nakanishi, S.; Otsuji, Y. *Chem. Lett.* ***1979***, 321; des Abbayes, H.; Clément, J.; Laurent, P.; Tanguy, G.; Thilmont, N. *Organometallics* ***1988***, *7*, 2293.

[1821]Garnier, L.; Rollin, Y.; Périchon, J. *J. Organomet. Chem.* ***1989***, *367*, 347.

[1822]Baillargeon, V.P.; Stille, J.K. *J. Am. Chem. Soc.* ***1986***, *108*, 452. See also, Kasahara, A.; Izumi, T.; Yanai, H. *Chem. Ind. (London)* ***1983***, 898; Pri-Bar, I.; Buchman, O. *J. Org. Chem.* ***1984***, *49*, 4009; Takeuchi, R.; Tsuji, Y.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* ***1986***, 351; Ben-David, Y.; Portnoy, M.; Milstein, D. *J. Chem. Soc., Chem. Commun.* ***1989***, 1816.

[1823]Tamaru, Y.; Ochiai, H.; Yamada, Y.; Yoshida, Z. *Tetrahedron Lett.* ***1983***, *24*, 3869.

[1824]Goure, W.F.; Wright, M.E.; Davis, P.D.; Labadie, S.S.; Stille, J.K. *J. Am. Chem. Soc.* ***1984***, *106*, 6417. For a similar preparation of diallyl ketones, see Merrifield, J.H.; Godschalx, J.P.; Stille, J.K. *Organometallics* ***1984***, *3*, 1108.

[1825]Kosugi, M.; Sumiya, T.; Obara, Y.; Suzuki, M.; Sano, H.; Migita, T. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 767.

[1826]Ogawa, A.; Sumino, Y.; Nanke, T.; Ohya, S.; Sonoda, N.; Hirao, T. *J. Am. Chem. Soc.*, ***1997***, *119*, 2745.

[1827]Tsunoi, S.; Ryu, I.; Fukushima, H.; Tanaka, M.; Komatsu, M.; Sonoda, N. *Synlett*, ***1995***, 1249.

[1828]Devasagayaraj, A.; Knochel, P. *Tetrahedron Lett.* ***1995***, *36*, 8411.

[1829]Ryu, I.; Hasegawa, M.; Kurihara, A.; Ogawa, A.; Tsunoi, S.; Sonoda, N. *Synlett*, ***1993***, 143.

The conversion of alkyl halides to aldehydes and ketones can also be accomplished indirectly (**10-71**). See also, **12-33**.

OS **VI**, 807.

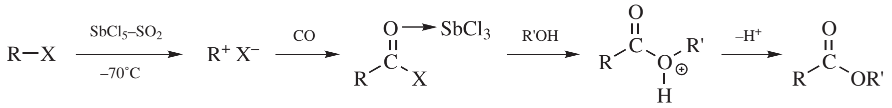
10-77 Carbonylation of Alkyl Halides, Alcohols, or Alkanes

Alkoxycarbonyl-de-halogenation

$$RX + CO + R'OH \xrightarrow[-70^\circ C]{SbCl_5-SO_2} RCOOR'$$

A direct method for preparing a carboxylic acid treats an alkyl halide with $NaNO_2$ in acetic acid and DMSO.[1830] Reaction of an alkyl halide with ClCO-CO_2Me and $(Bu_3Sn)_2$ under photochemical conditions leads to the corresponding methyl ester.[1831]

Several methods, all based on carbon monoxide or metal carbonyls, have been developed for converting an alkyl halide to a carboxylic acid or an acid derivative with the chain extended by one carbon.[1832] When an alkyl halide is treated with $SbCl_5$—SO_2 at −70°C, it dissociates into the corresponding carbocation (p. 236). If carbon monoxide and an alcohol are present, a carboxylic ester is formed by the following route:[1833]



This has also been accomplished with concentrated H_2SO_4 saturated with CO.[1834] Not surprisingly, only tertiary halides perform satisfactorily; secondary halides give mostly rearrangement products. An analogous reaction takes place with alkanes possessing a tertiary hydrogen, using HF—SbF_5—CO.[1835]

Carboxylic acids or esters are the products, depending on whether the reaction mixture is solvolyzed with water or an alcohol. Alcohols with more than seven

[1830]Matt, C.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* ***1997***, *62*, 234.

[1831]Kim, S.; Jon, S.Y. *Tetrahedron Lett.* ***1998***, *39*, 7317.

[1832]For discussions of most of the reactions in this section, see Colquhoun, H.M.; Holton, J.; Thompson, D.J.; Twigg, M.V. *New Pathways for Organic Synthesis*; Plenum, NY, ***1984***, pp. 199–204, 212–220, 234–235. For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1684–1685, 1694–1698, 1702–1704.

[1833]Yoshimura, M.; Nojima, M.; Tokura, N. *Bull. Chem. Soc. Jpn.* ***1973***, *46*, 2164; Puzitskii, K.V.; Pirozhkov, S.D.; Ryabova, K.G.; Myshenkova, T.N.; Éidus, Ya.T. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1974***, *23*, 192.

[1834]Takahashi, Y.; Yoneda, N. *Synth. Commun.* ***1989***, *19*, 1945.

[1835]Paatz, R.; Weisgerber, G. *Chem. Ber.* ***1967***, *100*, 984. For a related reaction using $AlBr_3$ see Akhrem, I.; Afanas'eva, L.; Petrovskii, P.; Vitt, S.; Orlinkov, A. *Tetrahedron Lett.* ***2000***, *41*, 9903.

carbons are cleaved into smaller fragments by this procedure.[1836] Similarly, tertiary alcohols[1837] react with H_2SO_4 and CO (which is often generated from HCOOH and the H_2SO_4 in the solution) to give trisubstituted acetic acids in a process called the *Koch–Haaf reaction* (see also, **15-35**).[1838] If a primary or secondary alcohol is the substrate, the carbocation initially formed rearranges to a tertiary ion before reacting with the CO. Better results are obtained if trifluoromethanesulfonic acid F_3CSO_2OH is used instead of H_2SO_4.[1839] Iodo alcohols were transformed into lactones under radical conditions (AIBN, allyl$SnBu_3$) and 45 atm of CO.[1840]

Another method[1841] for the conversion of alkyl halides to carboxylic esters is treatment of a halide with nickel carbonyl $Ni(CO)_4$ in the presence of an alcohol and its conjugate base.[1842] When R′ is primary, RX may only be a vinylic or an aryl halide; retention of configuration is observed at a vinylic R. Consequently, a carbocation intermediate is not involved here. When R′ is tertiary, R may be primary alkyl as well as vinylic or aryl. This is thus one of the few methods for preparing esters of tertiary alcohols. Alkyl iodides give the best results, then bromides. In the presence of an amine, an amide can be isolated directly, at least in some instances.

$$\mathrm{RX} + \mathrm{Ni(CO)_4} \xrightarrow[\mathrm{R'OH}]{\mathrm{R'O^-}} \mathrm{RCOOR'}$$

Still another method for the conversion of halides to acid derivatives makes use of $Na_2Fe(CO)_4$. As described in **10-76**, primary and secondary alkyl halides and tosylates react with this reagent to give the ion $RFe(CO)_4^-$ or, if CO is present, the ion $RCOFe(CO)_4^-$. Treatment of $RFe(CO)_4^-$ or $RCOFe(CO)_4^-$ with oxygen or sodium hypochlorite gives, after hydrolysis, a carboxylic acid.[1843] Alternatively, $RFe(CO)_4^-$ or $RCOFe(CO)_4^-$ reacts with a halogen (e.g., I_2) in the presence of an

[1836]Yoneda, N.; Takahashi, Y.; Fukuhara, T.; Suzuki, A. *Bull. Chem. Soc. Jpn.* ***1986***, *59*, 2819.

[1837]For reviews of other carbonylation reactions of alcohols and other saturated oxygenated compounds, see Bahrmann, H.; Cornils, B., in Falbe, J. *New Syntheses with Carbon Monoxide*, Springer, NY, ***1980***, pp. 226–241; Piacenti, F.; Bianchi, M. in Wender, I.; Pino, P. *Organic Syntheses via Metal Carbonyls*, Vol. 2, Wiley, NY, ***1977***, pp. 1–42.

[1838]For a review, see Bahrmann, H., in Falbe, J. *New Syntheses with Carbon Monoxide*, Springer, NY, ***1980***, pp. 372–413.

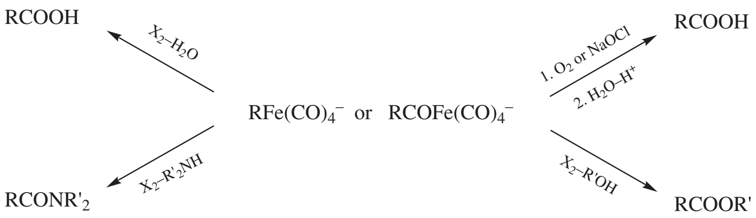
[1839]Booth, B.L.; El-Fekky, T.A. *J. Chem. Soc. Perkin Trans. 1* ***1979***, 2441.

[1840]Kreimerman, S.; Ryu, I.; Minakata, S.; Komatsu, M. *Org. Lett.* ***2000***, *2*, 389.

[1841]For reviews of methods involving transition metals, see Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed., University Science Books, Mill Valley, CA, ***1987***, pp. 749–768; Anderson, G.K.; Davies, J.A., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 3, Wiley, NY, pp. 335–359, pp. 348–356; Heck, R.F. *Adv. Catal.*, ***1977***, *26*, 323, see pp. 323; Cassar, L.; Chiusoli, G.P.; Guerrieri, F. *Synthesis* ***1973***, 509.

[1842]Corey, E.J.; Hegedus, L.S. *J. Am. Chem. Soc.* ***1969***, *91*, 1233. See also, Crandall, J.K.; Michaely, W.J. *J. Organomet. Chem.* ***1973***, *51*, 375.

[1843]Collman, J.P.; Winter, S.R.; Komoto, R.G. *J. Am. Chem. Soc.* ***1973***, *95*, 249.



alcohol to give a carboxylic ester,[1844] or in the presence of a secondary amine or water to give, respectively, the corresponding amide or free acid. The compound $RFe(CO)_4^-$ and $RCOFe(CO)_4^-$, what are prepared from primary R, give high yields. With secondary R, the best results are obtained in the solvent THF by the use of $RCOFe(CO)_4^-$ prepared from secondary tosylates. Ester and keto groups may be present in R without being affected. Carboxylic esters RCO_2R' have also been prepared by treating primary alkyl halides RX with alkoxides $R'O^-$ in the presence of $Fe(CO)_5$.[1845] $RCOFe(CO)_4^-$ is presumably an intermediate.

Palladium complexes also catalyze the carbonylation of halides.[1846] Aryl (see **13-15**),[1847] vinylic,[1848] benzylic, and allylic halides (especially iodides) can be converted to carboxylic esters with CO, an alcohol or alkoxide, and a palladium complex.[1849] Similar reactivity was reported with vinyl triflates.[1850] α-Halo ketones are converted to β-keto esters with CO, an alcohol, NBu_3 and a palladium catalyst at 110°C.[1851] Use of an amine instead of the alcohol or alkoxide leads to an amide.[1852]

[1844]Collman, J.P.; Winter, S.R.; Komoto, R.G. *J. Am. Chem. Soc.* ***1973***, *95*, 249; Masada, H.; Mizuno, M.; Suga, S.; Watanabe, Y.; Takegami, Y. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 3824.

[1845]Yamashita, M.; Mizushima, K.; Watanabe, Y.; Mitsudo, T.; Takegami,Y. *Chem. Lett.* ***1977***, 1355. See also, Tanguy, G.; Weinberger, B.; des Abbayes, H. *Tetrahedron Lett.* ***1983***, *24*, 4005.

[1846]For reviews, see Gulevich, Yu.V.; Bumagin, N.A.; Beletskaya, I.P. *Russ. Chem. Rev.* ***1988***, *57*, 299, 303–309; Heck, R.F. *Palladium Reagents in Organic Synthesis*, Academic Press, NY, ***1985***, pp. 348–356, 366–370.

[1847]For an example, see Bessard, Y; Crettaz, R. *Heterocycles* ***1999***, *51*, 2589.

[1848]For conversion of vinylic triflates to carboxylic esters and amides, see Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* ***1985***, *26*, 1109.

[1849]Tsuji, J.; Kishi, J.; Imamura, S.; Morikawa, M. *J. Am. Chem. Soc.* ***1964***, *86*, 4350; Schoenberg, A.; Bartoletti, I.; Heck, R.F. *J. Org. Chem.* ***1974***, *39*, 3318; Adapa, S.R.; Prasad, C.S.N. *J. Chem. Soc. Perkin Trans. 1* ***1989***, 1706; Kiji, J.; Okano, T.; Higashimae, Y.; Kukui, Y. *Bull. Chem. Soc. Jpn.* ***1996***, *69*, 1029; Okano, T.; Okabe, N.; Kiji, J. *Bull. Chem. Soc. Jpn.* ***1992***, *65*, 2589.

[1850]Jutand, A.; Négri, S. *Synlett*, ***1997***, 719.

[1851]Lapidus, A.L.; Eliseev, O.L.; Bondarenko, T.N.; Sizan, O.E.; Ostapenko, A.G.; Beletskaya, I.P. *Synthesis* ***2002***, 317.

[1852]Schoenberg, A.; Heck, R.F. *J. Org. Chem.* ***1974***, *39*, 3327. See also, Lindsay, L.M.; Widdowson, D.A. *J. Chem. Soc. Perkin Trans. 1* ***1988***, 569; Cai, M.-Z.; Song, C.-S.; Huang, X. *Synth. Commun.* ***1997***, *27*, 361. For a review of some methods of amide formation that involve transition metals, see Screttas, C.G.; Steele, B.R. *Org. Prep. Proceed. Int.* ***1990***, *22*, 271, 288–314. See Satoh, T.; Ikeda, M.; Kushino, Y.; Miura, M.; Nomura, M. *J. Org. Chem.* ***1997***, *62*, 2662 for the carbonylation of an alcohol to give the corresponding ester by a similar method.

Reaction with an amine, AIBN, CO and a tetraalkyltin catalyst also leads to an amide.[1853] Benzylic and allylic halides were converted to carboxylic acids electrocatalytically, with CO and a cobalt imine complex.[1854] Vinylic halides were similarly converted with CO and nickel cyanide, under phase-transfer conditions.[1855] Allylic *O*-phosphates were converted to allylic amides with CO and ClTi=NTMS, in the presence of a palladium catalyst.[1856] Terminal alkynes were converted to the alkynyl ester using CO, $PdBr_2$, $CuBr_2$ in methanol and sodium bicarbonate.[1857]

Other organometallic reagents can be used to convert alkyl halides to carboxylic acid derivatives. Benzylic halides were converted to carboxylic esters with CO in the presence of a rhodium complex.[1858] Variations introduce the R′ group via an ether R'_2O,[1859] a borate ester $B(OR')_3$,[1860] or an Al, Ti, or Zr alkoxide.[1861] The reaction of an alkene, a primary alcohol and CO, in the presence of a rhodium catalyst, led to carbonylation of the alkene and formation of the corresponding ester.[1862] Vinyl triflates were converted to the conjugated carboxylic acid with CO_2 and a nickel catalyst.[1863] Hydrogen peroxide with a catalytic amount of Na_2WO_4•2 H_2O converted benzylic chlorides to the corresponding benzoic acid.[1864] Reaction with an α,ω-diiodide, Bu_4NF and $Mo(CO)_6$ gave the corresponding lactone.[1865]

Reaction of an alkyl halide with $(MeS)_3C$—Li followed by aqueous HBF_4 leads to a thioester.[1866]

A number of double carbonylations have been reported. In these reactions, two molecules of CO are incorporated in the product, leading to α-keto acids or their derivatives.[1867] When the catalyst is a palladium complex, best results are obtained in the formation of α-keto amides.[1868] R is usually aryl or vinylic.[1869] The formation

[1853]Ryu, I.; Nagahara, K.; Kambe, N.; Sonoda, N.; Kreimerman, S.; Komatsu, M. *Chem. Commun.* ***1998***, 1953.

[1854]Folest, J.; Duprilot, J.; Perichon, J.; Robin, Y.; Devynck, J. *Tetrahedron Lett.* ***1985***, *26*, 2633. See also, Miura, M.; Okuro, K.; Hattori, A.; Nomura, M. *J. Chem. Soc. Perkin Trans. 1* ***1989***, 73; Urata, H.; Goto, D.; Fuchikami, T. *Tetrahedron Lett.* ***1991***, *32*, 3091; Isse, A.A.; Gennaro, A. *Chem. Commun.* ***2002***, 2798.

[1855]Alper, H.; Amer, I.; Vasapollo, G. *Tetrahedron Lett.* ***1989***, *30*, 2615. See also, Amer, I.; Alper, H. *J. Am. Chem. Soc.* ***1989***, *111*, 927.

[1856]Ueda, K.; Mori, M. *Tetrahedron Lett.* ***2004***, *45*, 2907. For an intramolecular carbonylation to generate a cyclic amide, see Trost, B.M.; Ameriks, M.K. *Org. Lett.* ***2004***, *6*, 1745.

[1857]Li, J.; Jiang, H.; Chen, M. *Synth. Commun.* ***2001***, *31*, 199.

[1858]For an example, see Giroux, A.; Nadeau, C.; Han, Y. *Tetrahedron Lett.* ***2000***, *41*, 7601.

[1859]Buchan, C.; Hamel, N.; Woell, J.B.; Alper, H. *Tetrahedron Lett.* ***1985***, *26*, 5743.

[1860]Alper, H.; Hamel, N.; Smith, D.J.H.; Woell, J.B. *Tetrahedron Lett.* ***1985***, *26*, 2273.

[1861]Woell, J.B.; Fergusson, S.B.; Alper, H. *J. Org. Chem.* ***1985***, *50*, 2134.

[1862]Yokoa, K.; Tatamidani, H.; Fukumoto, Y.; Chatani, N. *Org. Lett.* ***2003***, *5*, 4329.

[1863]Senboku, H.; Kanaya, H.; Tokuda, M. *Synlett* ***2002***, 140.

[1864]Shi, M.; Feng, Y.-S. *J. Org. Chem.* ***2001***, *66*, 3235.

[1865]Imbeaux, M.; Mestdagh, H.; Moughamir, K.; Rolando, C. *J. Chem. Soc., Chem. Commun.* ***1992***, 1678.

[1866]Barbero, M.; Cadamuro, S.; Degani, I.; Dughera, S.; Fochi, R. *J. Chem. Soc. Perkin Trans. 1* ***1993***, 2075.

[1867]For a review, see Collin, J. *Bull. Soc. Chim. Fr.* ***1988***, 976.

[1868]Kobayashi, T.; Tanaka, M. *J. Organomet. Chem.* ***1982***, *233*, C64; Ozawa, F.; Sugimoto, T.; Yuasa, Y.; Santra, M.; Yamamoto, T.; Yamamoto, A. *Organometallics* ***1984***, *3*, 683.

[1869]Son, T.; Yanagihara, H.; Ozawa, F.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* ***1988***, *61*, 1251.

of α-keto acids[1870] or esters[1871] requires more severe conditions. α-Hydroxy acids were obtained from aryl iodides when the reaction was carried out in the presence of an alcohol, which functioned as a reducing agent.[1872] Cobalt catalysts have also been used and require lower CO pressures.[1867]

OS **V**, 20, 739.

[1870]Tanaka, M.; Kobayashi, T.; Sakakura, T. *J. Chem. Soc., Chem. Commun.* ***1985***, 837.

[1871]See Ozawa, F.; Kawasaki, N.; Okamoto, H.; Yamamoto, T.; Yamamoto, A. *Organometallics* ***1987***, *6*, 1640.

[1872]Kobayashi, T.; Sakakura, T.; Tanaka, M. *Tetrahedron Lett.* ***1987***, *28*, 2721.

CHAPTER 11

Aromatic Substitution, Electrophilic

Most substitutions at an aliphatic carbon are by nucleophiles. In aromatic systems the situation is reversed, because the high electron density at the aromatic ring leads to its reactivity as a Lewis base or a Brønsted–Lowry base, depending on the positive species. In electrophilic substitutions, a positive ion or the positive end of a dipole or induced dipole is attacked by the aromatic ring. The leaving group (the electrofuge) must necessarily depart without its electron pair. In nucleophilic substitutions, the chief leaving groups are those best able to carry the unshared pair: Br^-, H_2O, OTs^-, and so on., that is, the weakest bases. In electrophilic substitutions the most important leaving groups are those that can best exist without the pair of electrons necessary to fill the outer shell, that is, the weakest Lewis acids.

MECHANISMS

Electrophilic aromatic substitutions are unlike nucleophilic substitutions in that the large majority proceed by just one mechanism with respect to the substrate.[1] In this mechanism, which we call the *arenium ion mechanism*, the electrophile (which can be viewed as a Lewis acid) is attacked by the π-electrons of the aromatic ring (behaving as a Lewis base in most cases) in the first step. This reaction leads to formation of a new C—X bond and a new sp^3 carbon in a positively charged intermediate called an arenium ion, where X is the electrophile. The positively charged intermediate (the arenium ion) is resonance stabilized, but not aromatic. Loss of a proton from the sp^3 carbon that is ‘‘adjacent’’ to the positive carbon in the arenium ion, in what is effectively an E1 process (see p. 1487), is driven by rearomatization of the ring from the arenium ion to give the aromatic substitution product. A proton

[1]For monographs, see Taylor, R. *Electrophilic Aromatic Substitution*, Wiley, NY, ***1990***; Katritzky, A.R.; Taylor, R. *Electrophilic Substitution of Heterocycles: Quantitative Aspects* (Vol. 47 of *Adv. Heterocycl. Chem.*), Academic Press, NY, ***1990***. For a review, see Taylor, R., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 1–406.

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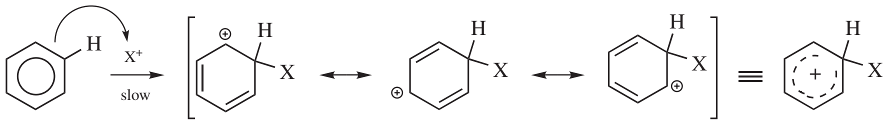
therefore becomes the leaving group in this overall transformation, where X replaces H. The IUPAC designation for this mechanism is $A_E + D_E$. Another mechanism, much less common, consists of the opposite behavior: a leaving group departs *before* the electrophile arrives. In this case, a substituent (*not* H) is attached to the aromatic ring, and the substituent is lost prior to incorporation of the electrophile. This mechanism, the S_E1 mechanism, corresponds to the S_N1 mechanism of nucleophilic substitution. Simultaneous attack and departure mechanisms (corresponding to S_N2) are not found at all. An addition–elimination mechanism has been postulated in one case (see **11-6**).

The Arenium Ion Mechanism[2]

In the arenium ion mechanism the electrophilic species may be produced in various ways, but when H is replaced by X conversion of the aromatic ring to an arenium ion is basically the same in all cases. For this reason, most attention in the study of this mechanism centers around the identity of the electrophilic entity and how it is produced.



1 **2**

The electrophile may be a positive ion or be a molecule that has a positive dipole. If it is a positive ion, it is attacked by the ring (a pair of electrons from the aromatic sextet is donated to the electrophile) to give a carbocation. This intermediate is a resonance hybrid as shown in **1**, but is often represented as in **2**. For convenience, the H atom to be replaced by X is shown in **1**. Ions of this type are called[3] *Wheland intermediates*, *σ complexes*, or *arenium ions*.[4] The inherent stability associated with aromaticity is no longer present in **1**, but the ion is stabilized by resonance. For this reason, the arenium ion is generally a highly reactive intermediate, although there are cases in which it has been isolated (see p. 661).

Carbocations can react in various ways (see p. 247), but for this type of ion the most likely pathway[5] is loss of either X^+ or H^+. In the second step of the

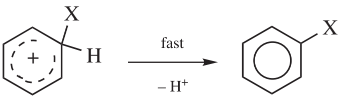
[2]This mechanism is sometimes called the S_E2 mechanism because it is bimolecular, but in this book we reserve that name for aliphatic substrates (see Chapter 12).

[3]General agreement on what to call these ions has not yet been reached. The term σ complex is a holdover from the time when much less was known about the structure of carbocations and it was thought they might be complexes of the type discussed in Chapter 3. Other names have also been used. We will call them arenium ions, following the suggestion of Olah, G.A. *J. Am. Chem. Soc.* ***1971***, *94*, 808.

[4]For reviews of arenium ions formed by addition of a proton to an aromatic ring, see Brouwer, D.M.; Mackor, E.L.; MacLean, C. in Olah, G.A.; Schleyer, P.V.R. *Carbonium Ions*, vol. 2, Wiley, NY, ***1970***, pp. 837–897; Perkampus, H. *Adv. Phys. Org. Chem.* ***1966***, *4*, 195.

[5]For a discussion of cases in which **1** stabilizes itself in other ways, see de la Mare, P.B.D. *Acc. Chem. Res.* ***1974***, *7*, 361.

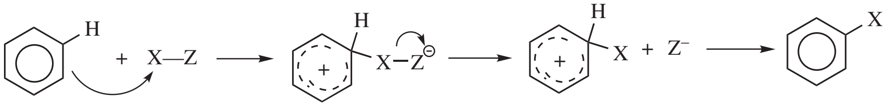
mechanism, the reaction proceeds with loss of the proton and the aromatic sextet is restored in the final product **3**.



3

The second step is nearly always faster than the first, making the first rate determining, and the reaction is second order. If formation of the attacking species is slower still, the aromatic compound does not take part in the rate expression at all. If X^+ is lost, there is no net reaction, but if H^+ is lost, an aromatic substitution has taken place and a base (generally the counterion of the electrophilic species although solvents can also serve this purpose) is necessary to help remove it.

If the attacking species is not an ion, but a dipole, the product must have a negative charge unless part of the dipole, with its pair of electrons, is broken off somewhere in the process, as in the conversion of **4** to **5**. Note that when the aromatic ring attacks X, Z may be lost directly to give **5**.



4 **5**

The electrophilic entities and how they are formed are discussed for each reaction in the reactions section of this chapter.

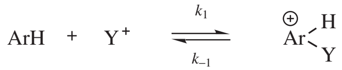
The evidence for the arenium ion mechanism is mainly of two kinds:

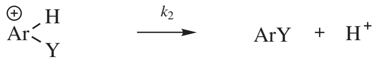
1. *Isotope Effects*. If the hydrogen ion departs before the arrival of the electrophile (S_E1 mechanism) or if the arrival and departure are simultaneous, there should be a substantial isotope effect (i.e., deuterated substrates should undergo substitution more slowly than non-deuterated compounds) because, in each case, the C—H bond is broken in the rate-determining step. However, in the arenium ion mechanism, the C—H bond is not broken in the rate-determining step, so no isotope effect should be found. Many such studies have been carried out and, in most cases, especially in the case of nitrations, there is no isotope effect.[6] This result is incompatible with either the S_E1 or the simultaneous mechanism.

   However, in many instances, isotope effects have been found. Since the values are generally much lower than expected for either the S_E1 or the simultaneous mechanisms (e.g., 1–3 for k_H/k_D instead of 6–7), we must look elsewhere for

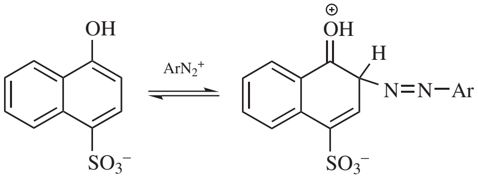
[6]The pioneering studies were by Melander, L. *Ark. Kemi* ***1950***, *2*, 213; Berglund-Larsson, U.; Melander, L. *Ark. Kemi* ***1953***, *6*, 219. See also, Zollinger, H. *Adv. Phys. Org. Chem.* ***1964***, *2*, 163.

the explanation. For the case where hydrogen is the leaving group, the arenium ion mechanism can be summarized:

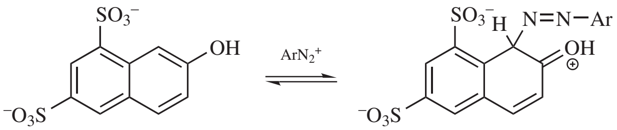
Step 1 

Step 2 

The small isotope effects found most likely arise from the reversibility of step 1 by a *partitioning effect*.[7] The rate at which $ArHY^+$ reverts to ArH should be essentially the same as that at which $ArDY^+$ (or $ArTY^+$) reverts to ArD (or ArT), since the Ar—H bond is not cleaving. However, $ArHY^+$ should go to ArY faster than either $ArDY^+$ or $ArTY^+$, since the Ar—H bond is broken in this step. If $k_2 \gg k_{-1}$, this does not matter; since a large majority of the intermediates go to product, the rate is determined only by the slow step (k_1[ArH][Y^+]) and no isotope effect is predicted. However, if $k_2 \leq k_{-1}$, reversion to starting materials is important. If k_2 for $ArDY^+$ (or $ArTY^+$) is < k_2 for $ArHY^+$, but k_{-1} is the same, then a larger proportion of $ArDY^+$ reverts to starting compounds. That is, k_2/k_{-1} (the *partition factor)* for $ArDY^+$ is less than that for $ArHY^+$. Consequently, the reaction is slower for ArD than for ArH and an isotope effect is observed.



6 **7**



8 **9**

One circumstance that could affect the k_2/k_{-1} ratio is steric hindrance. Thus, diazonium coupling of **6** gave no isotope effect, while coupling of **8** gave a k_H/k_D ratio of 6.55.[8] For steric reasons, it is much more difficult for **9** to lose a proton (it is harder for a base to approach) than it is for **7**, so k_2 is greater for the latter. Since no base is necessary to remove ArN_2^+, k_{-1} does not depend on steric factors[9] and is about the same for each. Thus the partition factor k_2/k_{-1}

[7]For a discussion, see Hammett, L.P. *Physical Organic Chemistry*, 2nd ed., McGraw-Hill, NY, ***1970***, pp. 172–182.

[8]Zollinger, H. *Helv. Chim. Acta* ***1955***, *38*, 1597, 1617, 1623.

[9]Snyckers, F.; Zollinger, H. *Helv. Chim. Acta* ***1970***, *53*, 1294.

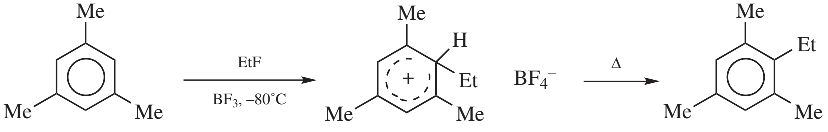
is sufficiently different for **7** and **9** that **8** exhibits a large isotope effect and **6** exhibits none.[10] Base catalysis can also affect the partition factor, since an increase in base concentration increases the rate at which the intermediate goes to product without affecting the rate at which it reverts to starting materials. In some cases, isotope effects can be diminished or eliminated by a sufficiently high concentration of base.

Evidence for the arenium ion mechanism has also been obtained from other kinds of isotope-effect experiments, involving substitutions of the type

$$ArMR_3 + H_3O^+ \longrightarrow ArH + R_3MOH_2^+$$

where M is Si, Ge, Sn, or Pb, and R is methyl or ethyl. In these reactions, the proton is the electrophile. If the arenium ion mechanism is operating, then the use of D_3O^+ should give rise to an isotope effect, since the D–O bond would be broken in the rate-determining step. Isotope effects of 1.55–3.05 were obtained,[11] in accord with the arenium ion mechanism.

2. *Isolation of Arenium Ion Intermediates*. Very strong evidence for the arenium ion mechanism comes from the isolation of arenium ions in a number of instances.[12] For example, **7** was isolated as a solid with a



mesitylene **10** **11**

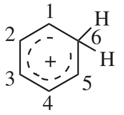
melting point of $-15°C$ from treatment of mesitylene with ethyl fluoride and the catalyst BF_3 at $-80°C$. When **10** was heated, the normal substitution product **11** was obtained.[13] Even the simplest such ion, the benzenonium ion (**12**), has been prepared in HF—SbF_5—SO_2ClF—SO_2F_2 at $-134°C$, where it could be studied

[10]For some other examples of isotope effects caused by steric factors, see Helgstrand, E. *Acta Chem. Scand.* ***1965***, *19*, 1583; Nilsson, A. *Acta Chem. Scand.* ***1967***, *21*, 2423; Baciocchi, E.; Illuminati, G.; Sleiter, G.; Stegel, F. *J. Am. Chem. Soc.* ***1967***, *89*, 125; Myhre, P.C.; Beug, M.; James, L.L. *J. Am. Chem. Soc.* ***1968***, *90*, 2105; Dubois, J.E.; Uzan, R. *Bull. Soc. Chim. Fr.* ***1968***, 3534; Márton, J. *Acta Chem. Scand.* ***1969***, *23*, 3321, 3329.

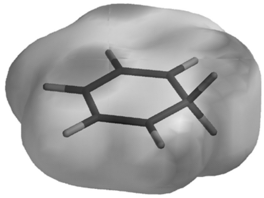
[11]Bott, R.W.; Eaborn, C.; Greasley. P.M. *J. Chem. Soc.* ***1964***, 4803.

[12]For reviews, see Koptyug, V.A. *Top. Curr. Chem.* ***1984***, *122*, 1; *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1974***, *23*, 1031. For a review of polyfluorinated arenium ions, see Shteingarts, V.D. *Russ. Chem. Rev.* ***1981***, *50*, 735. For a review of the protonation of benzene and simple alkylbenzenes, see Fărcaşiu, D. *Acc. Chem. Res.* ***1982***, *15*, 46.

[13]Olah, G.A.; Kuhn, S.J. *J. Am. Chem. Soc.* ***1958***, *80*, 6541. For some other examples, see Ershov, V.V.; Volod'kin, A.A. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1962***, 680; Farrell, P.G.; Newton, J.; White, R.F.M. *J. Chem. Soc. B* ***1967***, 637; Kamshii, L.P.; Koptyug, V.A. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1974***, *23*, 232; Olah, G.A.; Spear, R.J.; Messina, G.; Westerman, P.W. *J. Am. Chem. Soc.* ***1975***, *97*, 4051; Nambu, N.; Hiraoka, N.; Shigemura, K.; Hamanaka, S.; Ogawa, M. *Bull. Chem. Soc. Jpn.* ***1976***, *49*, 3637; Chikinev, A.V.; Bushmelev, V.A.; Shakirov, M.; Shubin, V.G. *J. Org. Chem. USSR* ***1986***, *22*, 1311; Knoche, W.; Schoeller, W.W.; Schomäcker, R.; Vogel, S. *J. Am. Chem. Soc.* ***1988***, *110*, 7484; Effenberger, F. *Acc. Chem. Res.* ***1989***, *22*, 27.



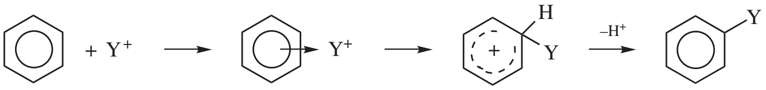
12



13

spectrally.[14] The ^{13}C NMR spectra of the benzenonium ion[15] and the pentamethylbenzenonium ion[16] give graphic evidence for the charge distribution shown in **1** (see the electron density map for the arenium ion, **13**). According to this, the 1, 3, and 5 carbons, each of which bears a positive charge of $+\frac{1}{3}$ [note that C-1,-3,-5 (numbering from **12**) are lighter,indicating less electron density in **13**, whereas C-2,-4 are darker for higher electron density], should have a greater chemical shift in the NMR than the 2 and 4 carbons, which are uncharged. The spectra bear this out. For example, ^{13}C NMR chemical shifts for **12** are C-3: 178.1; C-1 and C-5: 186.6; C-2 and C-4: 136.9, and C-6: 52.2.[15]

In Chapter 3, it was mentioned that positive ions can form addition complexes with π systems. Since the initial step of electrophilic substitution involves attack of a positive ion by an aromatic ring, it has been suggested[17] that such a complex, called a π *complex* (represented as **14**), is formed first, and then is converted to the arenium ion **15**.[18] Stable solutions of arenium ions or π complexes (e.g., with Br_2, I_2,



14 **15**

picric acid, Ag^+, or HCl) can be formed.[19] For example, π complexes are formed when aromatic hydrocarbons are treated with HCl alone, but the use of HCl plus a

[14]Olah, G.A.; Schlosberg, R.H.; Porter, R.D.; Mo, Y.K.; Kelly, D.P.; Mateescu, G.D. *J. Am. Chem. Soc.* ***1972***, *94*, 2034.

[15]Olah, G.A.; Staral, J.S.; Asencio, G.; Liang, G.; Forsyth, D.A.; Mateescu, G.D. *J. Am. Chem. Soc.* ***1978***, *100*, 6299.

[16]Lyerla, J.R.; Yannoni, C.S.; Bruck, D.; Fyfe, C.A. *J. Am. Chem. Soc.* ***1979***, *101*, 4770.

[17]Dewar, M.J.S. *Electronic Theory of Organic Chemistry;* Clarendon Press: Oxford, ***1949***.

[18]For a discussion of both σ- and π-complexes in electrophilic aromatic substitution, see Hubig, S. M.; Kochi, J. K. *J. Org. Chem.* ***2000***, *65*, 6807.

[19]For an *ab initio* study involving the interaction of water and hexafluorobenzene, to determine the efficacy of lone-pair binding to a π-system, see Gallivan, J.P.; Dougherty, D.A. *Org. Lett.* ***1999***, *1*, 103. For a study concerning preorganization and charge-transfer complexes, see Rosokha, S.V.; Kochi, J.K. *J. Org. Chem.* ***2002***, *67*, 1727.

TABLE 11.1. Relative Stabilities of Arenium Ions and π Complexes and Relative Rates of Chlorination and Nitration[a]

Substituents	Relative Arenium Ion Stability[20]	Relative π-Complex Stability[20]	Rate of Chlorination[21]	Rate of Nitration[26]
None (benzene)	0.09	0.61	0.0005	0.51
Me	0.63	0.92	0.157	0.85
p-Me_2	1.00	1.00	1.00	1.00
o-Me_2	1.1	1.13	2.1	0.89
m-Me_2	26	1.26	200	0.84
1,2,4-Me_3	63	1.36	340	
1,2,3-Me_3	69	1.46	400	
1,2,3,4-Me_4	400	1.63	2,000	
1,2,3,5-Me_4	16,000	1.67	240,000	
Me_5	29,900		360,000	

[a]In each case, p-xylene = 1.00.

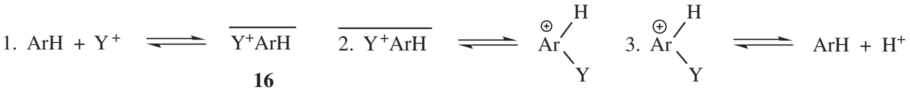
Lewis acid (e.g., $AlCl_3$) gives arenium ions. The two types of solution have very different properties. For example, a solution of an arenium ion is colored and conducts electricity (showing positive and negative ions are present), while a π complex formed from HCl and benzene is colorless and does not conduct a current. Furthermore, when DCl is used to form a π complex, no deuterium exchange takes place (because there is no covalent bond between the electrophile and the ring), while formation of an arenium ion with DCl and $AlCl_3$ gives deuterium exchange. The relative stabilities of some methylated arenium ions and π complexes are shown in Table 11.1. The arenium ion stabilities listed were determined by the relative basicity of the substrate toward HF.[20] The π complex stabilities are relative equilibrium constants for the reaction[21] between the aromatic hydrocarbon and HCl. As shown in Table 11.1, the relative stabilities of the two types of species are very different: the π complex stability changes very little with methyl substitution, but the arenium ion stability changes a great deal. It is noted that stable arenium ions have been obtained from large methylene-bridged polycyclic aromatic hydrocarbons.[22]

How can we tell if **14** is present on the reaction path? If it is present, there are two possibilities: (*1*) The formation of **14** is rate determining (the conversion of **14** to **15** is much faster), or (*2*) the formation of **14** is rapid, and the conversion **14** to **15** is rate determining. One way to ascertain which species is formed in the rate-determining step in a given reaction is to use the stability information given in Table 11.1. We measure the relative rates of reaction of a given electrophile with the series of compounds listed in Table 11.1. If the relative rates resemble the arenium ion stabilities, we conclude that the arenium ion is formed in the slow step; but if they

[20]Kilpatrick, M.; Luborsky, F.E. *J. Am. Chem. Soc.* ***1953***, *75*, 577.
[21]Brown, H.C.; Brady, J.D. *J. Am. Chem. Soc.* ***1952***, *74*, 3570.
[22]Laali, K.K.; Okazaki, T.; Harvey, R.G. *J. Org. Chem.* ***2001***, *66*, 3977.

resemble the stabilities of the π complexes, the latter are formed in the slow step.[23] When such experiments are carried out, it is found in most cases that the relative rates are similar to the arenium ion and not to the π complex stabilities. For example, Table 11.1 lists chlorination rates.[21] Similar results were obtained in room-temperature bromination with Br_2 in acetic acid[24] and in acetylation with CH_3CO^+ SbF_6^-.[25] It is clear that in these cases the π complex either does not form at all, or if it does, its formation is not rate determining (unfortunately, it is very difficult to distinguish between these two possibilities).

On the other hand, in nitration with the powerful electrophile NO_2^+ (in the form of NO_2^+ BF_4^-), the relative rates resembled π complex stabilities much more than arenium ion stabilities (Table 11.1).[26] Similar results were obtained for bromination with Br_2 and $FeCl_3$ in nitromethane. These results were taken to mean[27] that in these cases π complex formation is rate determining. However, graphical analysis of the NO_2^+ data showed that a straight line could not be drawn when the nitration rate was plotted against π complex stability,[28] which casts doubt on the rate-determining formation of a π complex in this case.[29] There is other evidence, from positional selectivities (discussed on p. 682), that *some* intermediate is present before the arenium ion is formed, whose formation can be rate determining with powerful electrophiles. Not much is known about this intermediate, which is given the nondescriptive name *encounter complex* and generally depicted as **16**. The arenium complex mechanism is therefore written as[30]

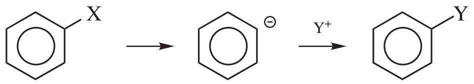


[23]Condon, F.E. *J. Am. Chem. Soc.* ***1952***, *74*, 2528.
[24]Brown, H.C.; Stock, L.M. *J. Am. Chem. Soc.* ***1957***, *79*, 1421.
[25]Olah, G.A.; Kuhn, S.J.; Flood, S.H.; Hardie, B.A. *J. Am. Chem. Soc.* ***1964***, *86*, 2203.
[26]Olah, G.A.; Kuhn, S.J.; Flood, S.H. *J. Am. Chem. Soc.* ***1961***, *83*, 4571, 4581.
[27]Olah, G.A.; Kuhn, S.J.; Flood, S.H.; Hardie, B.A. *J. Am. Chem. Soc.* ***1964***, *86*, 1039, 1044; Olah, G.A.; Kuhn, S.J.; Flood, S.H. *J. Am. Chem. Soc.* ***1961***, *83*, 4571, 4581.
[28]Rys, P.; Skrabal, P.; Zollinger, H. *Angew. Chem. Int. Ed.* ***1972***, *11*, 874. See also, DeHaan, F.P.; Covey, W.D.; Delker, G.L.; Baker, N.J.; Feigon, J.F.; Miller, K.D.; Stelter, E.D. *J. Am. Chem. Soc.* ***1979***, *101*, 1336; Santiago, C.; Houk, K.N.; Perrin, C.L. *J. Am. Chem. Soc.* ***1979***, *101*, 1337.
[29]For other evidence against π complexes, see Tolgyesi, W.S. *Can. J. Chem.* ***1965***, *43*, 343; Caille, S.Y.; Corriu, R.J.P. *Tetrahedron* ***1969***, *25*, 2005; Coombes, R.G.; Moodie, R.B.; Schofield, K. *J. Chem. Soc. B* ***1968***, 800; Hoggett, J.G.; Moodie, R.B.; Schofield, K. *J. Chem. Soc. B* ***1969***, 1; Christy, P.F.; Ridd, J.H.; Stears, N.D. *J. Chem. Soc. B* ***1970***, 797; Ridd, J.H. *Acc. Chem. Res.* ***1971***, *4*, 248; Taylor, R.; Tewson, T.J. *J. Chem. Soc., Chem. Commun.* ***1973***, 836; Naidenov, S.V.; Guk, Yu.V.; Golod, E.L. *J. Org. Chem. USSR* ***1982***, *18*, 1731. For further support for π complexes, see Olah, G.A. *Acc. Chem. Res.* ***1971***, *4*, 240; Olah, G.A.; Lin, H.C. *J. Am. Chem. Soc.* ***1974***, *96*, 2892; Koptyug, V.A.; Rogozhnikova, O.Yu.; Detsina, A.N. *J. Org. Chem. USSR* ***1983***, *19*, 1007; El-Dusouqui, O.M.E.; Mahmud, K.A.M.; Sulfab, Y. *Tetrahedron Lett.* ***1987***, *28*, 2417; Sedaghat-Herati, M.R.; Sharifi, T. *J. Organomet. Chem.* ***1989***, *363*, 39. For an excellent discussion of the whole question, see Banthorpe, D.V. *Chem. Rev.* ***1970***, *70*, 295, especially Sections VI and IX.
[30]For discussions, see Stock, L.M. *Prog. Phys. Org. Chem.* ***1976***, *12*, 21; Ridd, J.H. *Adv. Phys. Org. Chem.* ***1978***, *16*, 1.

For the reason given above and for other reasons, it is unlikely that the encounter complex is a π complex, but just what kind of attraction exists between Y^+ and ArH is not known, other than the presumption that they are together within a solvent cage (see also p. 682). There is evidence (from isomerizations occurring in the alkyl group, as well as other observations) that π complexes are present on the pathway from substrate to arenium ion in the gas-phase protonation of alkylbenzenes.[31]

The S_E1 Mechanism

The S_E1 mechanism (*substitution electrophilic unimolecular*) is rare, being found only in certain cases in which carbon is the leaving atom (see **11-33**, **11-35**) or when a very strong base is present (see **11-1**, **11-10**, and **11-39**).[32] It consists of two steps with an intermediate carbanion. The IUPAC designation is $D_E + A_E$.



Reactions **12-41**, **12-45**, and **12-46** also take place by this mechanism when applied to aryl substrates.

ORIENTATION AND REACTIVITY

Orientation and Reactivity in Monosubstituted Benzene Rings[33]

When an electrophilic substitution reaction is performed on a monosubstituted benzene, the new group may be directed primarily to the ortho, meta, or para position and the substitution may be slower or faster than with benzene itself. The group already on the ring determines which position the new group will take and whether the reaction will be slower or faster than with benzene. Groups that increase the reaction rate are called *activating* and those that slow it *deactivating*. Some groups are predominantly meta directing; all of these are deactivating. Others are mostly ortho-para directing; some of these are deactivating too, but most are activating. Groups direct *predominantly*, but usually not *exclusively*. For example, nitration of nitrobenzene gave 93% *m*-dinitrobenzene, 6% of the ortho, and 1% of the para isomer.

The orientation and reactivity effects are explained on the basis of resonance and field effects of each group on the stability of the intermediate arenium ion. To understand why we can use this approach, it is necessary to know that in these reactions

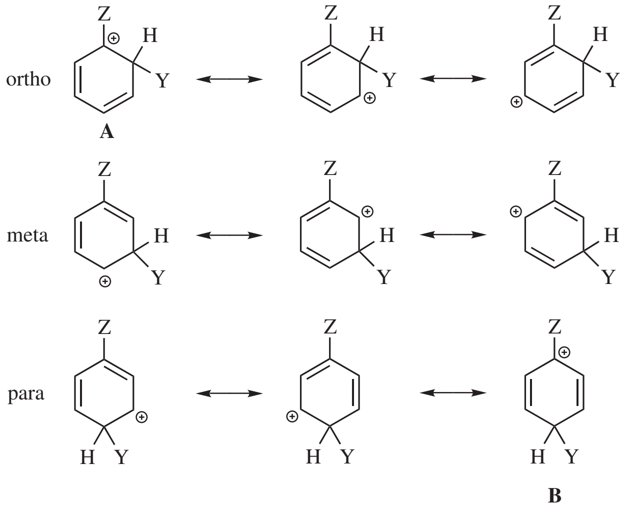
[31]Holman, R.W.; Gross, M.L. *J. Am. Chem. Soc.* ***1989***, *111*, 3560.

[32]It has also been found with a metal ($SnMe_3$) as electrofuge: Eaborn, C.; Hornfeld, H.L.; Walton, D.R.M. *J. Chem. Soc. B* ***1967***, 1036.

[33]For a review of orientation and reactivity in benzene and other aromatic rings, see Hoggett, J.G.; Moodie, R.B.; Penton, J.R.; Schofield, K. *Nitration and Aromatic Reactivity*, Cambridge University Press, Cambridge, ***1971***, pp. 122–145, 163–220.

the product is usually kinetically and not thermodynamically controlled (see p. 307). Some of the reactions are irreversible and the others are usually stopped well before equilibrium is reached. *Therefore, which of the three possible intermediates is formed is dependent not on the thermodynamic stability of the products, but on the activation energy necessary to form each of the three intermediates.* It is not easy to predict which of the three activation energies is lowest, but we make the assumption that the free-energy profile resembles either Fig. 6.2(*a* or *b*). In either case, the transition state is closer in energy to the arenium ion intermediate than to the starting compounds. Invoking the Hammond postulate (p. 308), we can then assume that the geometry of the transition state also resembles that of the intermediate and that anything that increases the stability of the intermediate will also lower the activation energy necessary to attain it. Since the intermediate, once formed, is rapidly converted to products, we can use the relative stabilities of the three intermediates as guides to predict which products will predominantly form. Of course, if reversible reactions are allowed to proceed to equilibrium, we may get product ratios that are quite different. For example, the sulfonation of naphthalene at 80°C, where the reaction does not reach equilibrium, gives mostly α-naphthalenesulfonic acid,[34] while at 160°C, where equilibrium is attained, the β isomer predominates[35] (the α isomer is thermodynamically less stable because of steric interaction between the SO_3H group and the hydrogen at the 8 position).

The three possible ions from incorporation of Y at the ortho, meta, and para positions are shown, and each arenium in obviously has a positive charge in the ring.



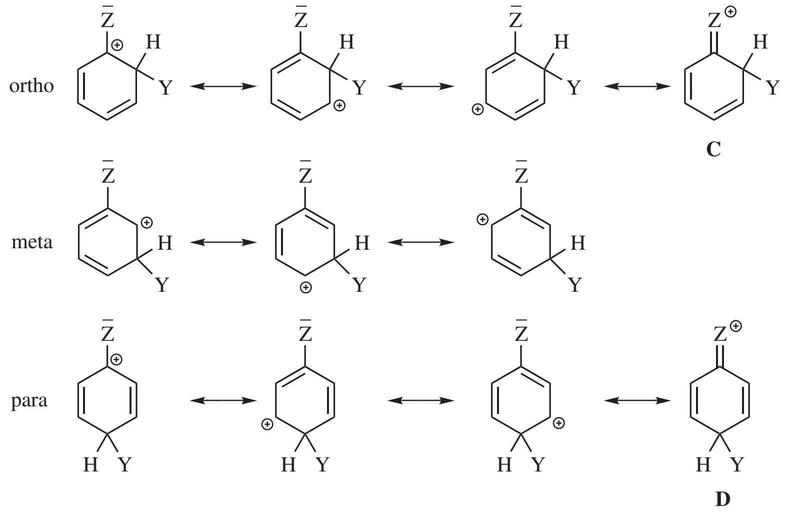
We can therefore predict that any group Z that has an electron-donating field effect (+*I*, Z will have a − charge or a δ− dipole in most cases) should stabilize all three

[34]Fierz, H.E.; Weissenbach, P. *Helv. Chim. Acta* ***1920***, *3*, 312.
[35]Witt, O.N. *Berchti* ***1915***, *48*, 743.

ions (relative to **1**), since electron donation to a positive center is stabilizing. On the other hand, electron-withdrawing groups (*−I*, Z will have a + charge or a δ+ dipole in most cases) will increase the positive charge on the ring (like charges repel), and destabilize the arenium ion. Formation of a stabilized ion should be faster than benzene (which generates **1**), or activating, but formation of a destabilized ion should be slower, or deactivating. Such field effects should taper off with distance and are thus strongest at the carbon connected to the group Z (known as the ipso carbon). Of the three arenium ions, only the ortho and para have any positive charge at this carbon. None of the canonical forms of the meta ion has a positive charge at the ipso carbon. Therefore, *+I* groups should stabilize all three ions but mostly the ortho and para, so they should be not only activating but ortho–para-directing as well. On the other hand, *−I* groups, by removing electron density, should destabilize all three ions but mostly the ortho and para, and should be not only deactivating but also meta-directing.

These conclusions are correct as far as they go, but they do not lead to the proper results in all cases. In many cases, there is *resonance interaction* between Z and the ring; this also affects the relative stability, in some cases in the same direction as the field effect, in others differently.

Some substituents have a pair of electrons (usually unshared) that may be contributed *toward* the ring. The three arenium ions would then look like this:



For each ion the same three canonical forms can be drawn as before, but now we can draw an extra form for the ortho and para ions. The stability of these two ions is increased by the extra form not only because it is another canonical form, but because it is more stable than the others and makes a greater contribution to the hybrid. Every atom (except of course hydrogen) in these forms (**C** and **D**) has a complete octet, while all the other forms have one carbon atom with a sextet. No corresponding form can be drawn for the meta isomer. The inclusion of this form in

the hybrid lowers the energy not only because of rule 6 (p. 47), but also because it spreads the positive charge over a larger area—out onto the group Z. Groups with a pair of electrons (e.g., as the halogens) to contribute would be expected, then, in the absence of field effects, not only to direct ortho and para, but also to activate these positions for electrophilic attack.

On the basis of these discussions, we can distinguish three types of groups.

1. Groups that contain an unshared pair of electrons on the atom connected to the ring. In this category are O^-, NR_2, NHR, NH_2,[36] OH, OR, NHCOR, OCOR, SR, and the four halogens.[37] The halogens deactivate the aromatic ring to substitution (the rate of reaction is slower than that of benzene), and this effect may arise from the unique energy level of the halogen lone-pair orbital, which is higher than the adjacent π-molecular orbital of benzene (π_1).[38] The widely held explanation for this, however, is that the halogens have a $-I$ effect. The SH group would probably belong here too, except that in the case of thiophenols electrophiles usually attack the sulfur rather than the ring, and ring substitution is not feasible with these substrates. [39] The resonance explanation predicts that all these groups should be ortho–para directing, and they are, though all except O^- are electron withdrawing by the field effect (p. 20). Therefore, for these groups, resonance is more important than the field effect. This is especially true for NR_2, NHR, NH_2, and OH, which are *strongly* activating, as is O^-. The other groups are mildly activating, except for the halogens, which are deactivating. Fluorine is the least deactivating, and fluorobenzenes usually show a reactivity approximating that of benzene itself. The other three halogens deactivate about equally. In order to explain why chlorine, bromine, and iodine deactivate the ring, even though they direct ortho–para, we must assume that the canonical forms **C** and **D** make such great contributions to the respective hybrids that they make the ortho and para arenium ions more stable than the meta, even though the $-I$ effect of the halogen is withdrawing sufficient electron density from the ring to deactivate it. The three halogens make the ortho and para ions more stable than the meta, but less stable than the unsubstituted arenium ion (**1**). For the other groups that contain an unshared pair, the ortho and para ions are more stable than either the meta ion or the unsubstituted ion. For most of

[36]It must be remembered that in acid solution amines are converted to their conjugate acids, which for the most part are meta-directing (type 2). Therefore in acid (which is the most common medium for electrophilic substitutions) amino groups may direct meta. However, unless the solution is highly acidic, there will be a small amount of free amine present, and since amino groups are activating and the conjugate acids deactivating, ortho-para direction is often found even under acidic conditions.

[37]For a review of the directing and orienting effects of amino groups, see Chuchani, G., in Patai's. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, pp. 250–265; for ether groups see Kohnstam, G.; Williams, D.L.H., in Patai's. *The Chemistry of the Ether Linkage*, Wiley, NY, ***1967***, pp. 132–150.

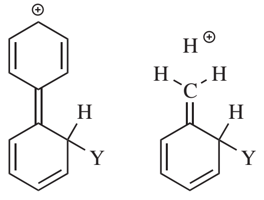
[38]Tomoda, S.; Takamatsu, K.; Iwaoka, M. *Chem. Lett.* ***1998***, 581.

[39]Tarbell, D.S.; Herz, A.H. *J. Am. Chem. Soc.* ***1953***, *75*, 4657. Ring substitution *is* possible if the SH group is protected. For a method of doing this, see Walker, D. *J. Org. Chem.* ***1966***, *31*, 835.

the groups in this category, the meta ion is more stable than **1**, so that groups, such as NH_2 and, OH, activate the meta positions too, but not as much as the ortho and para positions (see also the discussion on pp. 677–679).

2. Groups that lack an unshared pair on the atom connected to the ring and that are *−I*. In this category are, in approximate order of decreasing deactivating ability, NR_3^+, NO_2, CF_3,[40] CN, SO_3H, CHO, COR, COOH, COOR, $CONH_2$, CCl_3, and NH_3^+. Also in this category are all other groups with a positive charge on the atom directly connected to the ring[41] (SR_2^+, PR_3^+, etc.) and many groups with positive charges on atoms farther away, since often these are still powerful *−I* groups. The field-effect explanation predicts that these should all be meta directing and deactivating, and (except for NH_3^+) this is the case. The NH_3^+ group is an anomaly, since this group directs para about as much as or a little more than it directs meta.[42] The NH_2Me^+, $NHMe_2^+$, and NMe_3^+ groups all give more meta than para substitution, the percentage of para product decreasing with the increasing number of methyl groups.[43]

3. Groups that lack an unshared pair on the atom connected to the ring and that are ortho–para directing. In this category are alkyl groups, aryl groups, and the COO^- group,[44] all of which activate the ring. We will discuss them separately. Since aryl groups are *−I* groups, they might seem to belong to category 2. They are nevertheless ortho–para directing and activating. This can be explained in a similar manner as in category 1, with a pair of electrons from the aromatic sextet playing the part played by the unshared pair, so



E **F**

that we have forms like **E**. The effect of negatively charged groups like COO^- is easily explained by the field effect (negatively charged groups are of

[40]For the long-range electron-withdrawing effects of this group, see Castagnetti, E.; Schlosser, M. *Chem. Eur. J.* ***2002***, *8*, 799.

[41]For discussions, see Gastaminza, A.; Ridd, J.H.; Roy, F. *J. Chem. Soc. B* ***1969***, 684; Gilow, H.M.; De Shazo, M.; Van Cleave, W.C. *J. Org. Chem.* ***1971***, *36*, 1745; Hoggett, J.G.; Moodie, R.B.; Penton, J.R.; Schofield, K. *Nitration and Aromatic Reactivity*, Cambridge University Press, Cambridge, ***1971***, pp. 167–176.

[42]Hartshorn, S.R.; Ridd, J.H. *J. Chem. Soc. B* ***1968***, 1063. For a discussion, see Ridd, J.H., in *Aromaticity, Chem. Soc. Spec. Publ., no. 21*, ***1967***, 149–162.

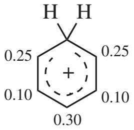
[43]Brickman, M.; Utley, J.H.P.; Ridd, J.H. *J. Chem. Soc.* ***1965***, 6851.

[44]Spryskov, A.A.; Golubkin, L.N. *J. Gen. Chem. USSR* ***1961***, *31*, 833. Since the COO^- group is present only in alkaline solution, where electrophilic substitution is not often done, it is seldom met with.

course electron donating), since there is no resonance interaction between the group and the ring. The effect of alkyl groups can be explained in the same way, but, in addition, we can also draw canonical forms, even though there is no unshared pair. These of course are hyperconjugation forms like **F** (see p. 669). This effect, like the field effect, predicts activation and ortho–para direction, so that it is not possible to say how much each effect contributes to the result. Another way of looking at the effect of alkyl groups (which sums up both field and hyperconjugation effects) is that (for Z = R) the ortho and para arenium ions are more stable because each contains a form (**A** and **B**) that is a tertiary carbocation, while all the canonical forms for the meta ion and for **1** are secondary carbocations. In activating ability, alkyl groups usually follow the Baker–Nathan order (p. 96), but not always.[45]

The Ortho/Para Ratio[46]

When an ortho–para-directing group is on a ring, it is usually difficult to predict how much of the product will be the ortho isomer and how much the para isomer. Indeed, these proportions can depend greatly on the reaction conditions. For example, chlorination of toluene gives an ortho/para ratio anywhere from 62:38 to 34:66.[47] Nevertheless, certain points can be made. On a purely statistical basis there would be 67% ortho and 33% para, since there are two ortho positions and only one para. However, the phenonium ion



12

12, which arises from protonation of benzene, has the approximate charge distribution shown[48] (see **13** as well). If we accept this as a model for the arenium ion in aromatic substitution, a para substituent would have a greater stabilizing effect on the adjacent carbon than an ortho substituent. If other effects are absent, this would mean that >33% para and <67% ortho substitution would be found. In hydrogen exchange (reaction **11-1**), where other effects are absent, it has been found for a number of substituents that the average ratio of the logarithms of the partial rate

[45]For examples of situations where the Baker–Nathan order is not followed, see Eaborn, C.; Taylor, R. *J. Chem. Soc.* ***1961***, 247; Utley, J.H.P.; Vaughan, T.A. *J. Chem. Soc. B* ***1968***, 196; Schubert, W.M.; Gurka, D.F. *J. Am. Chem. Soc.* ***1969***, *91*, 1443; Himoe, A.; Stock, L.M. *J. Am. Chem. Soc.* ***1969***, *91*, 1452.

[46]For a discussion, see Pearson, D.E.; Buehler, C.A. *Synthesis* ***1971***, 455 see pp 455–464. For a discussion of the influence of reaction conditions on the ortho/para ratio, see Effenberger, F.; Maier, A.J. *J. Am. Chem. Soc.* ***2001***, *123*, 3429.

[47]Stock, L.M.; Himoe, A. *J. Am. Chem. Soc.* ***1961***, *83*, 4605.

[48]Olah, G.A. *Acc. Chem. Res.* ***1970***, *4*, 240, p. 248.

factors for these positions (see p. 677 for a definition of partial rate factor) was close to 0.865,[49] which is not far from the value predicted from the ratio of charge densities in **12**. This picture is further supported by the fact that meta-directing groups, which destabilize a positive charge, give ortho/para ratios >67:33[50] (of course the total amount of ortho and para substitution with these groups is small, but the *ratios* are generally >67:33). Another important factor is the steric effect. If either the group on the attacking ring or the group on the electrophile is large, steric hindrance inhibits formation of the ortho product and increases the amount of the para isomer. An example may be seen in the nitration, under the same conditions, of toluene and *tert*-butylbenzene. The former gave 58% of the ortho compound and 37% of the para, while the more bulky *tert*-butyl group gave 16% of the ortho product and 73% of the para.[51] Some groups are so large that they direct almost entirely para.

When the ortho–para-directing group is one with an unshared pair (this of course applies to most of them), there is another effect that increases the amount of para product at the expense of the ortho. A comparison of the intermediates involved (p. 667) shows that **C** is a canonical form with an ortho-quinoid structure, while **D** has a para-quinoid structure. Since we know that para-quinones are more stable than the ortho isomers, it seems reasonable to assume that **D** is more stable than **C**, and therefore contributes more to the hybrid and increases its stability compared to the ortho intermediate.

It has been shown that it is possible to compel regiospecific para substitution by enclosing the substrate molecules in a cavity from which only the para position projects. Anisole was chlorinated in solutions containing a cyclodextrin, a molecule in which the anisole is almost entirely enclosed (see Fig. 3.4). With a high enough concentration of cyclodextrin, it was possible to achieve a para/ortho ratio of 21.6[52] (in the absence of the cyclodextrin the ratio was only 1.48). This behavior is a model for the regioselectivity found in the action of enzymes.

Ipso Attack

We have discussed orientation in the case of monosubstituted benzenes entirely in terms of attachment at the ortho, meta, and para positions, but attachment at the

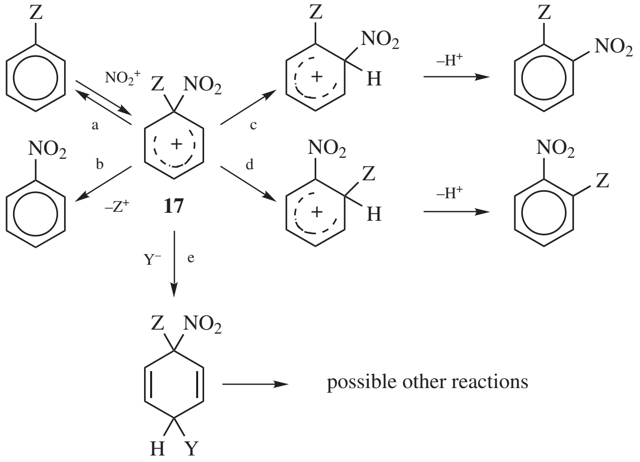
[49]Ansell, H.V.; Le Guen, J.; Taylor, R. *Tetrahedron Lett.* ***1973***, 13.

[50]Hoggett, J.G.; Moodie, R.B.; Penton, J.R.; Schofield, K. *Nitration and Aromatic Reactivity*, Cambridge University Press, Cambridge, ***1971***, pp. 176–180.

[51]Nelson, K.L.; Brown, H.C. *J. Am. Chem. Soc.* ***1951***, *73*, 5605. For product ratios in the nitration of many monoalkylbenzenes, see Baas, J.M.A.; Wepster, B.M. *Recl. Trav. Chim. Pays-Bas* ***1971***, *90*, 1081, 1089;111 ***1972***, *91*, 285, 517, 831.

[52]Breslow, R.; Campbell, P. *J. Am. Chem. Soc.* ***1969***, *91*, 3085; *Bioorg. Chem.* ***1971***, *1*, 140. See also Chen, N.Y.; Kaeding, W.W.; Dwyer, F.G. *J. Am. Chem. Soc.* ***1979***, *101*, 6783; Konishi, H.; Yokota, K.; Ichihashi, Y.; Okano, T.; Kiji, J. *Chem. Lett.* ***1980***, 1423; Komiyama, M.; Hirai, H. *J. Am. Chem. Soc.* ***1983***, *105*, 2018; ***1984***, *106*, 174; Chênevert, R.; Ampleman, G. *Can. J. Chem.* ***1987***, *65*, 307; Komiyama, M. *Polym. J. (Tokyo)* ***1988***, *20*, 439.

position bearing the substituent (called the *ipso position*[53]) can also be important. Ipso attack has mostly been studied for nitration.[54] When attack of NO_2^+ leads to incorporation at the ipso position there are at least five possible fates for the resulting arenium ion (**17**).



Path a. The arenium ion can lose NO_2^+ and revert to the starting compounds. This results in no net reaction and is often undetectable.

Path b. The arenium ion can lose Z^+, in which case this is simply aromatic substitution with a leaving group other than H (see **11-33–11-41**).

Path c. The electrophilic group (in this case NO_2^+) can undergo a 1,2-migration, followed by loss of the proton. The product in this case is the same as that obtained by direct attachment of NO_2^+ at the ortho position of PhZ. It is not always easy to tell how much of the ortho product in any individual case arises from this pathway,[55] though there is evidence that it can be a considerable proportion. Because of this possibility, many of the reported conclusions about the relat'ive reactivity of the ortho, meta, and para positions are cast into doubt, since some of the product may have arisen not from direct attachment at the ortho position, but from attachment at the ipso position followed by rearrangement.[56]

Path d. The ipso substituent (Z) can undergo 1,2-migration, which also produces the ortho product (though the rearrangement would become apparent if there

[53]Perrin, C.L.; Skinner, G.A. *J. Am. Chem. Soc.* ***1971***, *93*, 3389. For a review of ipso substitution, see Traynham, J.G. *J. Chem. Educ.* ***1983***, *60*, 937.

[54]For a review, see Moodie, R.B.; Schofield, K. *Acc. Chem. Res.* ***1976***, *9*, 287. See also, Fischer, A.; Henderson, G.N.; RayMahasay, S. *Can. J. Chem.* ***1987***, *65*, 1233, and other papers in this series.

[55]For methods of doing so, see Gibbs, H.W.; Moodie, R.B.; Schofield, K. *J. Chem. Soc. Perkin Trans. 2* ***1978***, 1145.

[56]This was first pointed out by Myhre, P.C. *J. Am. Chem. Soc.* ***1972***, *94*, 7921.

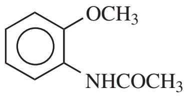
were other substituents present). The evidence is that this pathway is very minor, at least when the electrophile is NO_2^+.[57]

Path e. Attack of a nucleophile on **17**. In some cases, the products of such an attack (cyclohexadienes) have been isolated[58] (this is 1,4-addition to the aromatic ring), but further reactions are also possible.

Orientation in Benzene Rings With More Than One Substituent[59]

It is often possible in these cases to predict the correct isomer. In many cases, the groups already on the ring reinforce each other. Thus, 1,3-dimethylbenzene is substituted at the 4 position (ortho to one group and para to the other), but not at the 5 position (meta to both). Likewise, the incoming group in *p*-chlorobenzoic acid goes to the position ortho to the chloro and meta to the carboxyl group.

When the groups oppose each other, predictions may be more difficult. In a case such as where two



groups of about equal directing ability are in competing positions, all four products can be expected, and it is not easy to predict the proportions, except that steric hindrance should probably reduce the yield of substitution ortho to the acetamido group, especially for large electrophiles. Mixtures of about equal proportions are frequent in such cases. Nevertheless, even when groups on a ring oppose each other, there are some regularities.

1. If a strong activating group competes with a weaker one or with a deactivating group, the former controls. Thus *o*-cresol gives substitution mainly ortho and para to the *hydroxyl* group and not to the methyl. For this purpose we can arrange the groups in the following order: NH_2, OH, NR_2, O^- > OR, OCOR, NHCOR > R, Ar > halogen > meta-directing groups.
2. All other things being equal, a third group is least likely to enter between two groups in the meta relationship. This is the result of steric hindrance and increases in importance with the size of the groups on the ring and with the size of the attacking species.[60]

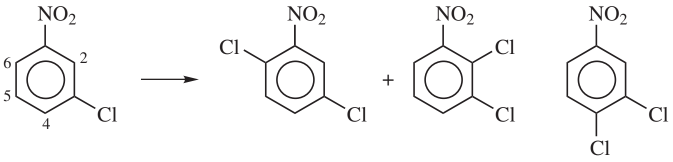
[57]For examples of such migration, where Z = Me, see Hartshorn, M.P.; Readman, J.M.; Robinson, W.T.; Sies, C.W.; Wright, G.J. *Aust. J. Chem.* ***1988***, *41*, 373.

[58]For examples, see Banwell, T.; Morse, C.S.; Myhre, P.C.; Vollmar, A. *J. Am. Chem. Soc.* ***1977***, *99*, 3042; Fischer, A.; Greig, C.C. *Can. J. Chem.* ***1978***, *56*, 1063.

[59]For a quantitative discussion, see pp. 677–678.

[60]In some cases, attack at an electrophile preferentially leads to attachment at the position between two groups in the meta relationship. For a list of some of these cases and a theory to explain them, see Kruse, L.I.; Cha, J.K. *J. Chem. Soc., Chem. Commun.* ***1982***, 1333.

3. When a meta-directing group is meta to an ortho–para-directing group, the incoming group primarily goes ortho to the meta-directing group rather than para. For example, chlorination of **18** gives mostly **19**.



18 **19** **20** **21**

The importance of this effect is underscored by the fact that **20**, which is in violation of the preceding rule, is formed in smaller amounts, but **21** is not formed at all. This is called the *ortho effect*,[61] and many such examples are known.[62] Another is the nitration of *p*-bromotoluene, which gives 2,3-dinitro-4-bromotoluene. In this case, once the first nitro group came in, the second was directed ortho to it rather than para, even though this means that the group has to come in between two groups in the meta position. There is no good explanation yet for the ortho effect, though possibly there is intramolecular assistance from the meta-directing group.

It is interesting that chlorination of **18** illustrates all three rules. Of the four positions open to the electrophile, the 5 position violates rule 1, the 2 position rule 2, and the 4 position rule 3. The principal attachment is therefore at position 6.

Orientation in Other Ring Systems[63]

In fused ring systems, the positions are not equivalent and there is usually a preferred orientation, even in the unsubstituted hydrocarbon. The preferred positions may often be predicted as for benzene rings. Thus it is possible to draw more canonical forms for the arenium ion when attack by naphthalene leads to attachment of the electrophile at the α position than when attack by naphthalene leads to attachment of the electrophile at the β position. Therefore, the α position is the preferred site of attachment,[64] though, as previously mentioned (p. 666), the isomer formed by substitution at the β-position is thermodynamically more stable and is the product if the reaction is reversible and equilibrium is reached. Because of the more extensive delocalization of charges in the corresponding arenium ions, naphthalene is more reactive than benzene and substitution is faster at both positions. Similarly,

[61]This is not the same as the ortho effect mentioned on p. 412.

[62]See Hammond, G.S.; Hawthorne, M.F., in Newman, M.S. *Steric Effects in Organic Chemistry*, Wiley, NY, ***1956***, pp. 164–200, 178–182.

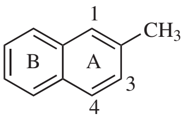
[63]For a review of substitution on nonbenzenoid aromatic systems, see Hafner, H.; Moritz, K.L., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 4, Wiley, NY, ***1965***, pp. 127–183. For a review of aromatic substitution on ferrocenes, see Bublitz, D.E.; Rinehart Jr., K.L. *Org. React.* ***1969***, *17*, 1.

[64]For a discussion on the preferred site of attachment for many ring systems, see de la Mare, P.B.D.; Ridd, J.H. *Aromatic Substitution Nitration and Halogenation*, Academic Press, NY, ***1959***, pp. 169–209.

anthracene, phenanthrene, and other fused polycyclic aromatic hydrocarbons are also substituted faster than benzene.

Heterocyclic compounds, too, have nonequivalent positions, and the principles are similar,[65] in terms of mechanism, and rate data is available.[66] Furan, thiophene, and pyrrole are chiefly substituted at the 2 position, and all are substituted faster than benzene.[67] Pyrrole is particularly reactive, with a reactivity approximating that of aniline or the phenoxide ion. For pyridine,[68] it is not the free base that must attack the electrophile, but the conjugate acid (the pyridinium ion),[69] making the reactivity much less than that of benzene, being similar to that of nitrobenzene. The 3 position is most reactive in electrophilic substitution reactions of pyridine. However, groups can be introduced into the 4 position of a pyridine ring indirectly, by performing the reaction on the corresponding pyridine *N*-oxide.[70] Note that calculations show that the 2-pyridyl and 2-pyrimidyl cations are best represented as *ortho*-hetarynium ions, being more stable than their positional, nonconjugated isomers by as much as 18–28 kcal mol^{-1} (75-11) kJ mol^{-1}.[71]

When fused ring systems contain substituents, successful predictions can often be made by using a combination of the above principles. Thus, ring A of 2-methylnaphthalene (**22**) is activated by the methyl



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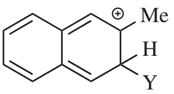

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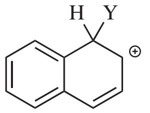


24

group; ring B is not (though the presence of a substituent in a fused ring system affects all the rings,[72] the effect is generally greatest on the ring to which it is attached). We therefore expect substitution in ring A. The methyl group activates positions 1 and 3, which are ortho to itself, but not position 4, which is meta to it.

[65]For a monograph, see Katritzky, A.R.; Taylor, R. *Electrophilic Substitution of Heterocycles: Quantitative Aspects* (Vol. 47 of *Adv. Heterocycl. Chem.*), Academic Press, NY, ***1990***.

[66]Katritzky, A.R.; Fan, W.-Q. *Heterocycles* ***1992***, *34*, 2179.

[67]For a review of electrophilic substitution on five-membered aromatic heterocycles, see Marino, G. *Adv. Heterocycl. Chem.* ***1971***, *13*, 235.

[68]For reviews of substitution on pyridines and other six-membered nitrogen-containing aromatic rings, see Comins, D.L.; O'Connor, S. *Adv. Heterocycl. Chem.* ***1988***, *44*, 199; Aksel'rod, Zh.I.; Berezovskii, V.M. *Russ. Chem. Rev.* ***1970***, *39*, 627; Katritzky, A.R.; Johnson, C.D. *Angew. Chem. Int. Ed.* ***1967***, *6*, 608; Abramovitch, R.A.; Saha, J.G. *Adv. Heterocycl. Chem.* ***1966***, *6*, 229. For a review of methods of synthesizing 3-substituted pyrroles, see Anderson, H.J.; Loader, C.E. *Synthesis* ***1985***, 353.

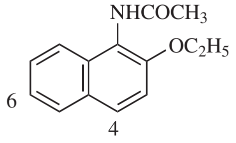
[69]Olah, G.A.; Olah, J.A.; Overchuk, N.A. *J. Org. Chem.* ***1965***, *30*, 3373; Katritzky, A.R.; Kingsland, M. *J. Chem. Soc. B* ***1968***, 862.

[70]Jaffé, H.H. *J. Am. Chem. Soc.* ***1954***, *76*, 3527.

[71]Gozzo, F.C.; Eberlin, M.N. *J. Org. Chem.* ***1999***, *64*, 2188.

[72]See, for example, Ansell, H.V.; Sheppard, P.J.; Simpson, C.F.; Stroud, M.A.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* ***1979***, 381.

However, substitution at the 3 position gives rise to an arenium ion for which it is impossible to write a low-energy canonical form in which ring B has a complete sextet. All we can write are forms like **23**, in which the sextet is no longer intact. In contrast, substitution at the 1 position gives rise to a more stable arenium ion, for which two canonical forms (one of them is **24**) can be written in which ring B is benzenoid. We thus predict predominant substitution at C-1, and that is what is generally found.[73] However, in some cases predictions are much harder to make. For example, chlorination or nitration of **25** gives mainly the 4 derivative, but bromination yields chiefly the 6 compound.[74]



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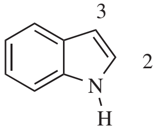
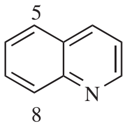
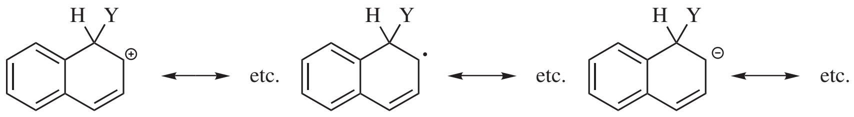


Indole



Quinoline

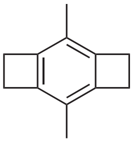
For fused heterocyclic systems too, we can often make predictions based on the above principles, though many exceptions are known. Thus, indole is chiefly substituted in the pyrrole ring (at position 3) and reacts faster than benzene, while quinoline generally reacts in the benzene ring, at the 5 and 8 positions, and slower than benzene, though faster than pyridine.



24 **26** **27**

In alternant hydrocarbons (p. 69), the reactivity at a given position is similar for electrophilic, nucleophilic, and free-radical substitution, because the same kind of resonance can be shown in all three types of intermediate (cf. **24**, **26**, and **27**). Attachment of the electrophile at the position that will best delocalize a positive charge will also best delocalize a negative charge or an unpaired electron. Most results are in accord with these predictions. For example, naphthalene is attacked primarily at the 1 position by NO_2^+, NH_2-, and Ph•, and always more readily than benzene.

[73]For example, see Alcorn, P.G.E.; Wells, P.R. *Aust. J. Chem.* ***1965***, *18*, 1377, 1391; Eaborn, C.; Golborn, P.; Spillett, R.E.; Taylor, R. *J. Chem. Soc. B* ***1968***, 1112; Kim, J.B.; Chen, C.; Krieger, J.K.; Judd, K.R.; Simpson, C.C.; Berliner, E. *J. Am. Chem. Soc.* ***1970***, *92*, 910. For discussions, see Taylor, R. *Chimia* ***1968***, *22*, 1; Gore, P.H.; Siddiquei, A.S.; Thorburn, S. *J. Chem. Soc. Perkin Trans. 1* ***1972***, 1781.
[74]Bell, F. *J. Chem. Soc.* ***1959***, 519.

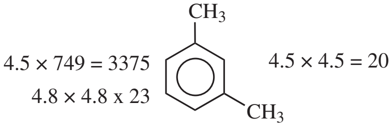


28

When strain due to a ring fused on an aromatic ring deforms that ring out of planarity, the molecule is more reactive to electrophilic aromatic substitution.[75] This has been explained by the presence of a shortened bond for the sp^2 hybridized carbon, increasing the strain at that position, and this is known as the *Mills–Nixon effect.*[76] There is EPR evidence (see p. 267) for 3,6-dimethyl-1,2,4,5-tetrahydrobenzo-bis (cyclobutene) (**28**) that supports the Mills–Nixon effect,[77] and a theoretical study supports this.[78] However, *ab initio* studies of triannelated benzene rings shows *no evidence* for the Mills–Nixon effect, and an new motif for bond-alternating benzenes was proposed.[79] Indeed, it is argued that the Mills–Nixon effect is not real.[80]

Quantitative Treatments of Reactivity in the Substrate

Quantitative rate studies of aromatic substitutions are complicated by the fact that there are usually several hydrogens that can leave, so that measurements of overall rate ratios do not give a complete picture as they do in nucleophilic substitutions, where it is easy to compare substrates that have only one possible leaving group in a molecule. What is needed is not, say, the overall rate ratio for acetylation of toluene versus that for benzene, but the *rate ratio at each position*. These can be calculated from the overall rates and a careful determination of the proportion of isomers formed, provided that the products are kinetically controlled, as is usually the case. We may thus define the *partial rate factor* for a given group and a given reaction as the rate of substitution at a single position relative to a single position in benzene. For example, for acetylation



of toluene the partial rate factors are: for the ortho position $o_f^{\mathrm{Me}} = 4.5$, for the meta $m_f^{\mathrm{Me}} = 4.8$, and for the para $p_f^{\mathrm{Me}} = 749$.[81] This means that toluene is acetylated at

[75]Taylor, R. *Electrophilic Aromatic Substitution*, Wiley, Chichester, ***1990***, pp. 53.
[76]Mills, W.H.; Nixon, I.G. *J. Chem. Soc.* ***1930***, 2510.
[77]Davies, A.G.; Ng, K.M. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 1857.
[78]Eckert-Maksić, M.; Maksić, Z.B.; Klessinger, M. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 285; Eckert-Maksić, M.; Lesar, A.; Maksić, Z.B. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 993.
[79]Baldridge, K.K.; Siegel, J.J. *J. Am. Chem. Soc.* ***1992***, *114*, 9583.
[80]Siegel, J.S. *Angew. Chem. Int. Ed.* ***1994***, *33*, 1721.
[81]Brown, H.C.; Marino, G.; Stock, L.M. *J. Am. Chem. Soc.* ***1959***, *81*, 3310.

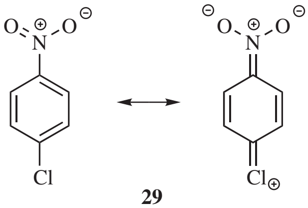
the ortho position 4.5 times as fast as a single position in benzene, or 0.75 times as fast as the overall rate of acetylation of benzene. A partial rate factor >1 for a given position indicates that the group in question activates that position for the given reaction. Partial rate factors differ from one reaction to another and are even different, though less so, for the same reaction under different conditions.

Once we know the partial rate factors, we can predict the proportions of isomers to be obtained when two or more groups are present on a ring, *if we make the assumption that the effect of substituents is independent*. For example, if the two methyl groups in *m*-xylene have the same effect as the methyl group in toluene, we can calculate the theoretical partial rate factors at each position by multiplying those from toluene, so they should be as indicated:

TABLE 11.2. Calculated and Experimental Isomer Distributions in the Acetylation of *m*-Xylene[81]

	Isomer Distribution, %	
Position	Calculated	Observed
2	0.30	0
4	9.36	97.5
5	0.34	2.5

From this, it is possible to calculate the overall theoretical rate ratio for acetylation of *m*-xylene relative to benzene, since this is one-sixth the sum of the partial rate factors (in this case 1130), and the isomer distribution if the reaction is kinetically controlled. The overall rate ratio actually is 347[82] and the calculated and observed isomer distributions are listed in Table 11.2.[76] In this case, and in many others, agreement is fairly good, but many cases are known where the effects are not additive (as on p. 671).[83] For example, this treatment predicts that for 1,2,3-trimethylbenzene



29

[82]Marino, G.; Brown, H.C. *J. Am. Chem. Soc.* ***1959***, *81*, 5929.

[83]For some examples where additivity fails, see Fischer, A.; Vaughan, J.; Wright, G.J. *J. Chem. Soc. B* ***1967***, 368; Coombes, R.G.; Crout, D.H.G.; Hoggett, J.G.; Moodie, R.B.; Schofield, K. *J. Chem. Soc. B* ***1970***, 347; Richards, K.E.; Wilkinson, A.L.; Wright, G.J. *Aust. J. Chem.* ***1972***, *25*, 2369; Cook, R.S.; Phillips, R.; Ridd, J.H. *J. Chem. Soc. Perkin Trans. 2* ***1974***, 1166. For a theoretical treatment of why additivity fails, see Godfrey, M. *J. Chem. Soc. B* ***1971***, 1545.

there should be 35% 5 substitution and 65% 4 substitution, but acetylation gave 79% 5 substitution and 21% of the 4 isomer. The treatment is thrown off by steric effects, such as those mentioned earlier (p. 673), by-products arising from ipso attack (p. 671) and by resonance interaction *between* groups (e.g., **29**), which must make the results deviate from simple additivity of the effects of the groups.

Another approach that avoids the problem created by having competing leaving groups present in the same substrate is the use of substrates that contain only one leaving group. This is most easily accomplished by the use of a leaving group other than hydrogen. By this means overall rate ratios can be measured for specific positions.[84] Results obtained in this way[85] give a reactivity order quite consistent with that for hydrogen as leaving group.

A quantitative scale of reactivity for aromatic substrates (fused, heterocyclic, and substituted rings) has been devised, based on the hard–soft acid–base concept (p. 375).[86] From molecular-orbital theory, a quantity called *activation hardness* can be calculated for each position of an aromatic ring. The smaller the activation hardness, the faster the attachment at that position; hence the treatment predicts the most likely orientations for incoming groups.

A Quantitative Treatment of Reactivity of the Electrophile: The Selectivity Relationship

Not all electrophiles are equally powerful. The nitronium ion attacks not only benzene but also aromatic rings that contain a strongly deactivating group. On the other hand, diazonium ions couple only with rings containing a powerful activating group. Attempts have been made to correlate the influence of substituents with the power of the attacking group. The most obvious way to do this is with the Hammett equation (p. 392):

$$\log \frac{k}{k_0} = \rho\,\sigma$$

For aromatic substitution,[87] k_0 is divided by 6 and, for meta substitution, k is divided by 2, so that comparisons are made for only one position (consequently, k/k_0 for, say, the methyl group at a para position is identical to the partial rate factor p_f^{Me}). It was soon found that, while this approach worked fairly well for electron-withdrawing groups, it failed for those that are electron donating. However, if the equation is modified by the insertion of the Brown σ^+ values instead of the Hammett σ values (because a positive charge develops during the transition state), more satisfactory correlations can be made, even for electron-donating groups (see Table 9.4

[84]For a review of aryl-silicon and Related cleavages, see Eaborn, C. *J. Organomet. Chem.* ***1975***, *100*, 43.
[85]See, for example, Deans, F.B.; Eaborn, C. *J. Chem. Soc.* ***1959***, 2299; Eaborn, C.; Jackson, P.M. *J. Chem. Soc. B* **1969**, 21.
[86]Zhou, Z.; Parr, R.G. *J. Am. Chem. Soc.* ***1990***, *112*, 5720.
[87]See Exner, O.; Böhm, S. *J. Org. Chem.* ***2002***, *67*, 6320.

TABLE 11.3. Relative Rates and Product Distributions in Some Electrophilic Substitutions on Toluene and Benzene[89]

Reaction	Relative Rate	Product Distribution, %	
	$k_{toluene}/k_{benzene}$	m	p
Bromination	605	0.3	66.8
Chlorination	350	0.5	39.7
Benzoylation	110	1.5	89.3
Nitration	23	2.8	33.9
Mercuration	7.9	9.5	69.5
Isopropylation	1.8	25.9	46.2

for a list of σ^+ values).[88] Groups with a negative value of σ_p^+ or σ_m^+ are activating for that position; groups with a positive value are deactivating. The ρ values correspond to the susceptibility of the reaction to stabilization or destabilization by the Z group and to the reactivity of the electrophile. The ρ values vary not only with the electrophile, but also with conditions. A large negative value of ρ means an electrophile of relatively low reactivity. Of course, this approach is completely useless for ortho substitution, since the Hammett equation does not apply there.

A modification of the Hammett approach, suggested by Brown, called the *selectivity relationship*,[89] is based on the principle that reactivity of a species varies inversely with selectivity. Table 11.3 shows how electrophiles can be arranged in order of selectivity as measured by two indexes: (*1*) their selectivity in attacking toluene rather than benzene, and (*2*) their selectivity between the meta and para positions in toluene.[90] As the table shows, an electrophile more selective in one respect is also more selective in the other. In many cases, electrophiles known to be more stable (hence less reactive) than others show a higher selectivity, as would be expected. For example, the *tert*-butyl cation is more stable and more selective than the isopropyl (p. 236), and Br_2 is more selective than Br^+. However, deviations from the relationship are known.[91] Selectivity depends not only on the nature of the electrophile but also on the temperature. As expected, it normally decreases with increasing temperature.

Brown assumed that a good measurement of selectivity was the ratio of the para and meta partial rate factors in toluene. He defined the selectivity S_f of a reaction as

$$S_f = \log \frac{p_f^{Me}}{m_f^{Me}}$$

[88]For a discussion of the limitations of the Hammett equation approach, see Koptyug, V.A.; Salakhutdinov, N.F.; Detsina, A.N. *J. Org. Chem. USSR* ***1984***, *20*, 1039.

[89]Stock, L.M.; Brown, H.C. *Adv. Phys. Org. Chem.* ***1963***, *1*, 35.

[90]Stock, L.M.; Brown, H.C. *Adv. Phys. Org. Chem.* ***1963***, *1*, 35, see p. 45.

[91]At least some of these may arise from migration of groups already on the ring; see Olah, G.A.; Olah, J.A.; Ohyama, T. *J. Am. Chem. Soc.* ***1984***, *106*, 5284.

That is, the more reactive an attacking species, the less preference it has for the para position compared to the meta. If we combine the Hammett–Brown $\sigma^+\rho$ relationship with the linearity between log S_f and log p_f^{Me} and between log S_f and log m_f^{Me}, it is possible to derive the following expressions:

$$\log p_f^{Me} = \frac{\sigma_p^+}{\sigma_p^+ - \sigma_m} S_f$$

$$\log m_f^{Me} = \frac{\sigma_m^+}{\sigma_p^+ - \sigma_m^+} S_f$$

S_f is related to ρ by

$$S_f = \rho(\sigma_p^+ - \sigma_m^+)$$

The general validity of these equations is supported by a great deal of experimental data on aromatic substitution reactions of toluene. Examples of values for some reactions obtained from these equations are given in Table 11.4.[92] For other substituents, the treatment works well with groups that, like methyl, are not very polarizable. For more polarizable groups the correlations are sometimes satisfactory and sometimes not, probably because each electrophile in the transition state makes a different demand on the electrons of the substituent group.

Not only are there substrates for which the treatment is poor, but it also fails with very powerful electrophiles; this is why it is necessary to postulate the encounter complex mentioned on p. 664. For example, relative rates of nitration of *p*-xylene, 1,2,4-trimethylbenzene, and 1,2,3,5-tetramethylbenzene were 1.0, 3.7, and 6.4,[93] though the extra methyl groups should enhance the rates much more (*p*-xylene itself reacted 295 times faster than benzene). The explanation is that with powerful electrophiles the reaction rate is so rapid (reaction taking place at virtually every

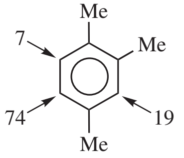
TABLE 11.4. Values of m_f^{Me}, p_f^{Me}, S_f, and ρ for Three Reactions of Toluene[92]

Reaction	m_f^{Me}	p_f^{Me}	S_f	ρ
$PhMe + EtBr \xrightarrow[\text{benzene, 25°C}]{GaBr_3}$	1.56	6.02	0.587	−2.66
$PhMe + HNO_3 \xrightarrow[\text{45°C}]{\text{90\% HOAc}}$	2.5	58	1.366	−6.04
$PhMe + BR_2 \xrightarrow[\text{25°C}]{\text{85\% HOAc}}$	5.5	2420	2.644	−11.40

[92]Stock, L.M.; Brown, H.C. *J. Am. Chem. Soc.* ***1959***, *81*, 3323. Stock, L.M.; Brown, H.C. *Adv. Phys. Org. Chem.* ***1963***, *1*, 35 presents many tables of these kinds of data. See also, DeHaan, F.P.; Chan, W.H.; Chang, J.; Ferrara, D.M.; Wainschel, L.A. *J. Org. Chem.* ***1986***, *51*, 1591, and other papers in this series.
[93]Olah, G.A.; Lin, H.C. *J. Am. Chem. Soc.* ***1974***, *96*, 2892.

encounter[94] between an electrophile and substrate molecule)[95] that the presence of additional activating groups can no longer increase the rate.[96]

Given this behavior (little selectivity in distinguishing between different substrate molecules), the selectivity relationship would predict that positional selectivity should also be very small. However, it is not. For example, under conditions where nitration of *p*-xylene and 1,2,4-trimethylbenzene takes place at about equal rates, there was no corresponding lack of selectivity at positions *within* the latter.[97] Though



Relative rate ratios

steric effects are about the same at both positions, >10 times as much 5-nitro product was formed as 6-nitro product. It is clear that the selectivity relationship has broken down and it becomes necessary to explain why such an extremely rapid reaction should occur with positional selectivity. The explanation offered is that the rate-determining step is formation of an encounter complex (**12**, p. 664).[98] Since the position of attachment is not determined in the rate-determining step, the 5:6 ratio is not related to the reaction rate. Essentially the same idea was suggested earlier[99] and for the same reason (failure of the selectivity relationship in some cases), but the earlier explanation specifically pictured the complex as a π complex, and we have seen (p. 664) that there is evidence against this.

One interesting proposal[100] is that the encounter pair is a radical pair $\overline{\mathrm{NO_2{\bullet}ArH{\bullet}^{+}}}$ formed by an electron transfer (SET), which would explain why the electrophile, once in the encounter complex, can acquire the selectivity that the free NO_2^+ lacked (it is not proposed that a radical pair is present in all aromatic substitutions; only in those that do not obey the selectivity relationship). The radical

[94]See Coombes, R.G.; Moodie, R.B.; Schofield, K. *J. Chem. Soc. B* ***1968***, 800; Moodie, R.B.; Schofield, K.; Thomas, P.N. *J. Chem. Soc. Perkin Trans. 2* ***1978***, 318.

[95]For a review of diffusion control in electrophilic aromatic substitution, see Ridd, J.H. *Adv. Phys. Org. Chem.* ***1978***, *16*, 1.

[96]Coombes, R.G.; Moodie, R.B.; Schofield, K. *J. Chem. Soc. B* ***1968***, 800; Hoggett, J.G.; Moodie, R.B.; Schofield, K. *J. Chem. Soc. B* ***1969***, 1; Manglik, A.K.; Moodie, R.B.; Schofield, K.; Dedeoglu, E.; Dutly, A.; Rys, P. *J. Chem. Soc. Perkin Trans. 2* ***1981***, 1358.

[97]Barnett, J.W.; Moodie, R.B.; Schofield, K.; Taylor, P.G.; Weston, J.B. *J. Chem. Soc. Perkin Trans. 2* ***1979***, 747.

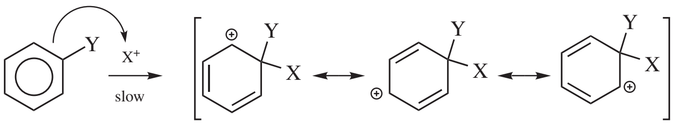
[98]For kinetic evidence in favor of encounter complexes, see Sheats, G.F.; Strachan, A.N. *Can. J. Chem.* ***1978***, *56*, 1280. For evidence for such complexes in the gas phase, see Attinà, M.; Cacace, F.; de Petris, G. *Angew. Chem. Int. Ed.* ***1987***, *26*, 1177.

[99]Olah, G.A. *Acc. Chem. Res.* ***1971***, *4*, 240.

[100]Perrin, C.L. *J. Am. Chem. Soc.* ***1977***, *99*, 5516.

pair subsequently collapses to the arenium ion. There is evidence[101] both for and against this proposal.[102]

The Effect of the Leaving Group



30

In the vast majority of aromatic electrophilic substitutions, the leaving group is H^+ as indicated above, and very little work has been done on the relative electrofugal ability of other leaving groups. However, the following orders of leaving-group ability have been suggested:[103] (*1*) for leaving groups that depart without assistance (S_N1 process with respect to the leaving group), NO_2^+[104] $< i\text{Pr}^+ \sim SO_3 < t\text{-Bu}^+ \sim ArN_2^+ < ArCHOH^+ < NO^+ < CO_2$; (*2*) for leaving groups that depart with assistance from an outside nucleophile (S_N2 process), $Me^+ < Cl^+ < Br^+ < D^+ \sim RCO^+ < H^+ \sim I^+ < Me_3Si^+$. We can use this kind of list to help predict which group, X or Y, will cleave from an arenium ion **30** (see **1**, where Y = H) once it has been formed, and so obtain an idea of which electrophilic substitutions are feasible. However, a potential leaving group can also affect a reaction in another way: by influencing the rate at which attack of the original electrophile leads to attachment directly at the ipso position. Partial rate factors for electrophilic attack at a position substituted by a group other than hydrogen are called ipso partial rate factors (i_f^X).[53] Such factors for the nitration of *p*-haloanisoles are 0.18, 0.08, and 0.06, for *p*-iodo, *p*-bromo-, and *p*-chloroanisole, respectively.[105] This means, for example, that attack at the electrophile in this case leads to attachment at the 4 position of 4-iodoanisole 0.18 times as fast as a single position of benzene. Note that this is far slower than attachment at the 4 position resulting from attack of anisole itself so that the presence of the iodo group greatly slows the reaction at that position. A similar experiment on *p*-cresol showed that ipso

[101]For evidence in favor of the proposal, see Reents, Jr., W.D.; Freiser, B.S. *J. Am. Chem. Soc.* ***1980***, *102*, 271; Morkovnik, A.S.; Dobaeva, N.M.; Panov, V.B.; Okhlobystin, O.Yu. *Doklad. Chem.* ***1980***, *251*, 116; Sankararaman, S.; Haney, W.A.; Kochi, J.K. *J. Am. Chem. Soc.* ***1987***, *109*, 5235; Keumi, T.; Hamanaka, K.; Hasegawa, K.; Minamide, N.; Inoue, Y.; Kitajima, H. *Chem. Lett.* ***1988***, 1285; Johnston, J.F.; Ridd, J.H.; Sandall, J.P.B. *J. Chem. Soc., Chem. Commun.* ***1989***, 244. For evidence against it, see Barnes, C.E.; Myhre, P.C. *J. Am. Chem. Soc.* ***1978***, *100*, 975; Eberson, L.; Radner, F. *Acc. Chem. Res.* ***1987***, *20*, 53; Baciocchi, E.; Mandolini, L. *Tetrahedron* ***1987***, *43*, 4035.

[102]For a review, see Morkovnik, A.S. *Russ. Chem. Rev.* ***1988***, *57*, 144.

[103]Perrin, C.L. *J. Org. Chem.* ***1971***, *36*, 420.

[104]For examples where NO_2^+ is a leaving group (in a migration), see Bullen, J.V.; Ridd, J.H.; Sabek, O. *J. Chem. Soc. Perkin Trans. 2* ***1990***, 1681, and other papers in this series.

[105]Perrin, C.L.; Skinner, G.A. *J. Am.Chem. Soc.* ***1971***, *93*, 3389. See also, Fischer, P.B.; Zollinger, H. *Helv. Chim. Acta* ***1972***, *55*, 2139.

attack at the methyl position was 6.8 times slower than attack of phenol leading to attachment at the para position.[106] Thus, in these cases, both an iodo and a methyl group deactivate the ipso position.[107]

REACTIONS

The reactions in this chapter are classified according to leaving group. Hydrogen replacements are treated first, then rearrangements in which the attacking entity is first cleaved from another part of the molecule (hydrogen is also the leaving group in these cases), and finally replacements of other leaving groups.

Hydrogen as the Leaving Group in Simple Substitution Reactions

A. Hydrogen as the Electrophile

11-1 Hydrogen Exchange

Deuterio-de-hydrogenation or Deuteriation

$$ArH + D^+ \rightleftharpoons ArD + H^+$$

Aromatic compounds can exchange hydrogens when treated with acids. The reaction is used chiefly to study mechanistic questions[108] (including substituent effects), but can also be useful to deuterate (add ^{2}H) or tritiate (add ^{3}H) aromatic rings selectively. The usual directive effects apply and, for example, phenol treated with D_2O gives slow exchange on heating, with only ortho and para hydrogens being exchanged.[109] Strong acids, of course, exchange faster with aromatic substrates, and this exchange must be taken into account when studying the mechanism of any aromatic substitution catalyzed by acids. There is a great deal of evidence that exchange takes place by the ordinary arenium ion mechanism. Among the evidence are the orientation effects noted above and the finding that the reaction is general acid catalyzed, which means that a proton is transferred in the slow step[110] (p. 373). Furthermore, many examples have been reported of stable solutions of arenium ions formed by attack of a proton on an aromatic ring.[4] Simple aromatic compounds can be extensively deuterated in a convenient fashion by

[106]Tee, O.; Iyengar, N.R.; Bennett, J.M. *J. Org. Chem.* ***1986***, *51*, 2585.

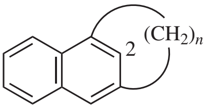
[107]For other work on ipso reactivity, see Baciocchi, E.; Illuminati, G. *J. Am. Chem. Soc.* ***1967***, *89*, 4017; Berwin, H.J. *J. Chem. Soc., Chem. Commun.* ***1972***, 237; Galley, M.W.; Hahn, R.C. *J. Am. Chem. Soc.* ***1974***, *96*, 4337; Clemens, A.H.; Hartshorn, M.P.; Richards, K.E.; Wright, G.J. *Aust. J. Chem.* ***1977***, *30*, 103, 113.

[108]For a review, see Taylor, R., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 194–277.

[109]Small, P.A.; Wolfenden, J.H. *J. Chem. Soc.* ***1936***, 1811.

[110]For example, see Challis, B.C.; Long, F.A. *J. Am. Chem. Soc.* ***1963***, *85*, 2524; Batts, B.D.; Gold, V. *J. Chem. Soc.* ***1964***, 4284; Kresge, A.J.; Chiang, Y.; Sato, Y. *J. Am. Chem. Soc.* ***1967***, *89*, 4418; Gruen, L.C.; Long, F.A. *J. Am. Chem. Soc.* ***1967***, *89*, 1287; Butler, A.B.; Hendry, J.B. *J. Chem. Soc. B* ***1970***, 852.

treatment with D_2O and BF_3.[111] It has been shown that tritium exchange takes place readily at the 2 position of **31**, despite the fact that this position is hindered by the bridge. The rates were not very different from the comparison compound 1,3-dimethylnaphthalene.[112]



n=7, 8, 10

31

Hydrogen exchange can also be effected with strong bases,[113] such as NH_2-. In these cases, the slow step is the proton transfer:

$$\text{ArH} + \text{B} \longrightarrow \text{Ar}^- + \text{BH}^+$$

so the S_E1 mechanism and not the usual arenium ion mechanism is operating.[114] Aromatic rings can also be deuterated by treatment with D_2O and a rhodium(III) chloride[115] or platinum[116] catalyst or with C_6D_6 and an alkylaluminum dichloride catalyst,[117] though rearrangements may take place during the latter procedure. Tritium (^3H, abbreviated T) can be introduced by treatment with T_2O and an alkylaluminum dichloride catalyst.[117] Tritiation at specific sites (e.g., >90% para in toluene) has been achieved with T_2 gas and a microporous aluminophosphate catalyst.[118]

B. Nitrogen Electrophiles

11-2 Nitration or Nitro-de-hydrogenation

$$\text{ArH} + \text{HNO}_3 \xrightarrow{\text{H}_2\text{SO}_4} \text{ArNO}_2$$

[111]Larsen, J.W.; Chang, L.W. *J. Org. Chem.* ***1978***, *43*, 3602.

[112]Laws, A.P.; Neary, A.P.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 1033.

[113]For a review of base-catalyzed hydrogen exchange on heterocycles, see Elvidge, J.A.; Jones, J.R.; O'Brien, C.; Evans, E.A.; Sheppard, H.C. *Adv. Heterocycl. Chem.* ***1974***, *16*, 1.

[114]Shatenshtein, A.I. *Tetrahedron* ***1962***, *18*, 95.

[115]Lockley, W.J.S. *Tetrahedron Lett.* ***1982***, *23*, 3819; *J. Chem. Res. (S)* ***1985***, 178.

[116]See, for example, Leitch, L.C. *Can. J. Chem.* ***1954***, *32*, 813; Fraser, R.R.; Renaud, R.N. *J. Am. Chem. Soc.* ***1966***, *88*, 4365; Fischer, G.; Puza, M. *Synthesis* ***1973***, 218; Blake, M.R.; Garnett, J.L.; Gregor, I.K.; Hannan, W.; Hoa, K.; Long, M.A. *J. Chem. Soc., Chem. Commun.* ***1975***, 930. See also, Parshall, G.W. *Acc. Chem. Res.* ***1975***, *8*, 113.

[117]Long, M.A.; Garnett, J.L.; West, J.C. *Tetrahedron Lett.* ***1978***, 4171.

[118]Garnett, J.L.; Kennedy, E.M.; Long, M.A.; Than, C.; Watson, A.J. *J. Chem. Soc., Chem. Commun.* ***1988***, 763.

Most aromatic compounds, whether of high or low reactivity, can be nitrated, because a wide variety of nitrating agents is available.[119] For benzene, the simple alkylbenzenes, and less reactive compounds, the most common reagent is a mixture of concentrated nitric and sulfuric acids,[120] but for active substrates, the reaction can be carried out with nitric acid alone,[121] or in water, acetic acid, acetic anhydride, or chloroform.[122] Nitric acid in acetic anhydride/trifluoroacetic anhydride on zeolite H-β was used to convert toluene to 2,4-dinitrotoluene,[123] and $AcONO_2$ on clay converted ethylbenzene to ortho–para nitro ethylbenzene.[124] In fact, these milder conditions are necessary for active compounds, such as amines, phenols, and pyrroles, since reaction with mixed nitric and sulfuric acids would oxidize these substrates. With active substrates, such as amines and phenols, nitration can be accomplished by nitrosation under oxidizing conditions with a mixture of dilute nitrous and nitric acids.[125] A mixture of $NO_2/O_2/Fe(acac)_3$ can be used for active compounds,[126] as can $NaNO_2$ with trichloroisocyanuric acid on wet silica gel,[127] or N_2O_4 and silica acetate.[128] Trimethoxybenzenes were nitrated easily with ceric ammonium nitrate on silica gel,[129] and mesitylene was nitrated in an

[119]For a discussion of a unified mechansim, see Esteves, P.M.; de M. Carneiro, J.W.; Cardoso, S.P.; Barbosa, A.G.H.; Laali, K.K.; Rasul, G.; Prakash, G.K.S.; Olah, G.A. *J. Am. Chem. Soc.* ***2003***, *125*, 4836. For monographs, see Olah, G.A.; Malhotra, R.; Narang, S.C. *Nitration: Methods and Mechanisms*, VCH, NY, ***1989***; Schofield, K. *Aromatic Nitration*; Cambridge University Press, Cambridge, ***1980***; Hoggett, J.H.; Moodie, R.B.; Penton, J.R.; Schofield, K. *Nitraton and aromatic Reactivity*, Cambridge University Press, Cambridge, ***1971***. For reviews, see Weaver, W.M., in Feuer, H. *Chemistry of the Nitro and Nitroso Groups*, pt. 2, Wiley, NY, ***1970***, pp. 1–48; de la Mare, P.B.D.; Ridd, J.H. *Aromatic Substitution Nitration and Halogenation*, Academic Press, NY, ***1959***, pp. 48–93. See also, Ref. 1. For a review of side reactions, see Suzuki, H. *Synthesis* ***1977***, 217. Also see, Bosch, E.; Kochi, J.K. *J. Org. Chem.* ***1994***, *59*, 3314; Olah, G.A.; Wang, Q.; Li, X.; Bucsi, I. *Synthesis* ***1992***, 1085; Olah, G.A.; Reddy, V.P.; Prakash, G.K.S. *Synthesis* ***1992***, 1087.

[120]For the use of sulfuric acid/nitric acid on silica, see Smith, A.C.; Narvaez, L.D.; Akins, B.G.; Langford, M.M.; Gary, T.; Geisler, V.J.; Khan, F.A. *Synth. Commun.* ***1999***, *29*, 4187. For a reaction with guanidine–nitric acid with sulfric acid, see Ramana, M.M.V.; Malik, S.S.; Parihar, J.A. *Tetrahedron Lett.* ***2004***, *45*, 8681.

[121]For a reaction with nitric acid and a lanthanum salt, see Parac-Vogt, T.N.; Binnesmans, K. *Tetrahedron Lett.* ***2004***, *45*, 3137.

[122]Used with $(NH_4)_2SO_4$•$NiSO_4$•6 H_2O: Tasneem, Ali, M.M.; Rajanna, K.C.; Saiparakash, P.K. *Synth. Commun.* ***2001***, *31*, 1123.

[123]Smith, K.; Gibbons, T.; Millar, R.W.; Claridge, R.P. *J. Chem. Soc., Perkin Trans. 1*, ***2000***, 2753.

[124]Rodrigues, J.A.R.; Filho, A.P.O.; Moran, P.J.S. *Synth. Commun.* ***1999***, *29*, 2169.

[125]For discussions of the mechanism in this case, see Giffney, J.C.; Ridd, J.H. *J. Chem. Soc. Perkin Trans. 2* ***1979***, 618; Bazanova, G.V.; Stotskii, A.A. *J. Org. Chem. USSR* ***1980***, *16*, 2070, 2075; Ross, D.S.; Moran, K.D.; Malhotra, R. *J. Org. Chem.* ***1983***, *48*, 2118; Dix, L.R.; Moodie, R.B. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 1097; Leis, J.R.; Peña, M.E.; Ridd, J.H. *Can. J. Chem.* ***1989***, *67*, 1677. For a review, see Ridd, J.H. *Chem. Soc. Rev.* ***1991***, *20*, 149.

[126]Suzuki, H.; Yonezawa, S.; Nonoyama, N.; Mori, T. *J. Chem. Soc. Perkin Trans. 1* ***1996***, 2385.

[127]Zolfigol, M.A.; Madrakian, E.; Ghaemi, E. *Synlett* ***2003***, 2222.

[128]Iranpoor, N.; Firouzabadi, H.; Heydari, R. *Synth. Commun.* ***2003***, *33*, 703.

[129]Khadilkar, B.M.; Madyar, V.R. *Synth. Commun.* ***1999***, *29*, 1195.

ionic liquid using nitric acid–acetic anhydride.[130] Phenol can be nitrated in an ionic liquid.[131]

If anhydrous conditions are required, nitration can be effected with N_2O_5[132] in CCl_4 in the presence of P_2O_5, which removes the water formed in the reaction.[133] These reagents can also be used with proton or Lewis acid catalysts. Representative nitrating agents are $NaNO_2$ and trifluoroacetic acid,[134] N_2O_4 (which gives good yields with polycyclic hydrocarbons[135]), N_2O_4/O_2 and a catalytic amount of zeolite Hβ,[136] $Yb(OTf)_3$,[137] and nitronium salts,[138] such as $NO_2^+BF_4^-$, $NO_2^+PF_6^-$, and $NO_2^+CF_3SO_3^-$.[139] A mixture of NO_2 and ozone has also been used.[140] Clays, such as clay-supported cupric nitrate (Claycop),[141,142] or Montmorillonite KSF—$Bi(NO_3)$[143] can be used to nitrate aromatic rings. Nitration of styrene poses a problem since addition occurs to the C=C unit to give a 1-nitroethyl aryl.[144] Heterocycles, such as pyridine, are nitrated with N_2O_5 and SO_2.[145] Deactivated aromatic rings, as in acetophenone, were nitrated with N_2O_5 and $Fe(acac)_2$.[146]

[130]In bmpy NTf_2, 1-butyl-4-methylpyridinium triflimide: Lancaster, N.L.; Llopis-Mestre, V. *Chem. Commun.* ***2003***, 2812.

[131]In bbim BF_4, 1,3-dibutylimidazoliiuum tetrafluoroborate: Rajogopal, R.; Srinivasan, K.V. *Synth. Commun.* ***2004***, *34*, 961.

[132]For a review of N_2O_5, see Fischer, J.W. in Feuer, H.; Nielsen, A.T. *Nitro Compounds, Recent Advances in synthesis and Chemistry*; VCH, NY, ***1990***, pp. 267–365.

[133]For another method, see Olah, G.A.; Krishnamurthy, V.V.; Narang, S.C. *J. Org. Chem.* ***1982***, *47*, 596.

[134]Uemura, S.; Toshimitsu, A.; Okano, M. *J. Chem. Soc. Perkin Trans. 1* ***1978***, 1076. For a reaction with $NaNO_2$ and wet silica, see Zolfigol, M.A.; Ghaemi, E.; Madrakian, E. *Synth. Commun.* ***2000***, *30*, 1689; Zolfigol, M.A.; Bagherzadeh, M.; Madrakian, E.; Gaemi, E.; Taqian-Nasab, A. *J. Chem. Res. (S)* ***2001***, 140.

[135]Radner, F. *Acta Chem. Scand. Ser. B* ***1983***, *37*, 65.

[136]Smith, K.; Almeer, S.; Black, S.J. *Chem. Commun.* ***2000***, 1571. See also, Smith, K.; Musson, A.; DeBoos, G.A. *J. Org. Chem.* ***1998***, *63*, 8448.

[137]Barrett, A.G.M.; Braddock, D.C.; Ducray, R.; McKinnell, R.M.; Waller, F.J. *Synlett* ***2000***, 57.

[138]Olah, G.A.; Kuhn, S.J. *J. Am. Chem. Soc.* ***1962***, *84*, 3684. These have also been used together with crown ethers: Masci, B. *J. Org. Chem.* ***1985***, *50*, 4081; Iranpoor, N.; Firouzabadi, H.; Heydari, R. *Synth. Commun.* ***1999***, *29*, 3295. For a review of nitronium salts in organic chemistry, see Guk,Yu. V.; Ilyushin, M.A.; Golod, E.L.; Gidaspov, B.V. *Russ. Chem. Rev.* ***1983***, *52*, 284.

[139]This salt gives a very high yield of products at low temperatures, see Coon, C.L.; Blucher, W.G.; Hill, M.E. *J. Org. Chem.* ***1973***, *38*, 4243; Effenberger, F.; Geke, J. *Synthesis* ***1975***, 40.

[140]Nose, M.; Suzuki, H.; Suzuki, H. *J. Org. Chem.* ***2001***, *66*, 4356; Peng, X.; Suzuki, H. *Org. Lett.* ***2001***, *3*, 3431; Suzuki, H.; Tomaru, J.-i.; Murashima, T. *J. Chem. Soc. Perkin Trans. 1* ***1994***, 2413; Suzuki, H.; Tatsumi, A.; Ishibashi, T.; Mori, T. *J. Chem. Soc. Perkin Trans. 1* ***1995***, 339.

[141]For reviews of clay-supported nitrates, see Cornélis, A.; Laszlo, P. *Synthesis* ***1985***, 909; Laszlo, P. *Acc. Chem. Res.* ***1986***, 121; Laszlo, P.; Cornélis, A. *Aldrichimica Acta* ***1988***, *21*, 97.

[142]Cornélis, A.; Delaude, L.; Gerstmans, A.; Laszlo, P. *Tetrahedron Lett.* ***1988***, *29*, 5657. See also, Smith, K.; Fry, K.; Butters, M.; Nay, B. *Tetrahedron Lett.* ***1989***, *30*, 5333; Cornélis, A.; Laszlo, P.; Pennetreau, P. *Bull. Soc. Chim. Belg.*, ***1984***, *93*, 961; Poirier, J.; Vottero, C. *Tetrahedron* ***1989***, *45*, 1415. For a method of nitrating phenols in the ortho position, see Pervez, H.; Onyiriuka, S.O.; Rees, L.; Rooney, J.R.; Suckling, C.J. *Tetrahedron* ***1988***, *44*, 4555.

[143]Samajdar, S.; Becker, F.F.; Banik, B.K. *Tetrahedron Lett.* ***2000***, *41*, 8017.

[144]Lewis, R.J.; Moodie, R.B. *J. Chem. Soc. Perkin Trans. 2* ***1997***, 563.

[145]Arnestad, B.; Bakke, J.M.; Hegbom, I.; Ranes, E. *Acta Chem. Scand. B* ***1996***, *50*, 556.

[146]Bak, R.R.; Smallridge, A.J. *Tetrahedron Lett.* ***2001***, *42*, 6767.

An alternative route for the nitration of activated aromatic compounds, such as anisole, used a nitrate ester ($RONO_2$) with triflic acid in an ionic liquid for ortho-selective nitration.[147] Nitration in alkaline media can be accomplished with esters of nitric acid, such as ethyl nitrate ($EtONO_2$).

When anilines are nitrated under strong acid conditions, meta orientation is generally observed, because the species undergoing nitration is actually the conjugate acid of the amine. If the conditions are less acidic, the free amine is nitrated and the orientation is ortho–para. Although the free base may be present in much smaller amounts than the conjugate acid, it is far more susceptible to aromatic substitution (see also p. 668). Because of these factors and because they are vulnerable to oxidation by nitric acid, primary aromatic amines are often protected before nitration by treatment with acetyl chloride (**16-72**) or acetic anhydride (**16-73**). Nitration of the resulting acetanilide derivative avoids all these problems. There is evidence that when the reaction takes place on the free amine, it is the nitrogen that is attacked to give an *N*-nitro compound $Ar{-}NH{-}NO_2$ which rapidly undergoes rearrangement (see **11-28**) to give the product.[148]

Since the nitro group is deactivating, it is usually easy to stop the reaction after one group has entered the ring, but a second and a third group can be introduced if desired, especially when an activating group is also present. Even *m*-dinitrobenzene can be nitrated if vigorous conditions are applied. This has been accomplished with $NO_2^+BF_4^-$ in FSO_3H at 150°C.[149]

With most of the reagents mentioned, the attacking species is the nitronium ion NO_2^+. Among the ways in which this ion is formed are

1. In concentrated sulfuric acid, by an acid–base reaction in which nitric acid is the base:

$$HNO_3 + 2\,H_2SO_4 \rightleftharpoons NO_2^+ + H_3O^+ + 2\,HSO_4^-$$

This ionization is essentially complete.

2. In concentrated nitric acid alone,[150] by a similar acid–base reaction in which one molecule of nitric acid is the acid and another the base:

$$2\,HNO_3 \rightleftharpoons NO_2^+ + NO_3^- + H_2O$$

This equilibrium lies to the left (~4% ionization), but enough NO_2^+ is formed for nitration to occur.

[147]In emim OTf, 1-ethyl-3-methylimidazolium triflate: Laali, K.K.; Gettwert, V.J. *J. Org. Chem.* ***2001***, *66*, 35.

[148]Ridd, J.H.; Scriven, E.F.V. *J. Chem. Soc., Chem. Commun.* ***1972***, 641. See also, Helsby, P.; Ridd, J.H. *J. Chem. Soc. Perkin Trans. 2* ***1983***, 1191.

[149]Olah, G.A.; Lin, H.C. *Synthesis* ***1974***, 444.

[150]See Belson, D.J.; Strachan, A.N. *J. Chem. Soc. Perkin Trans. 2* ***1989***, 15.

3. The equilibrium just mentioned occurs to a small extent even in organic solvents.
4. With N_2O_5 in CCl_4, there is spontaneous dissociation:

$$N_2O_5 \rightleftharpoons NO_2^+ + NO_3^-$$

but in this case there is evidence that some nitration also takes place with undissociated N_2O_5 as the electrophile.
5. When nitronium salts are used, NO_2^+ is of course present to begin with. Esters and acyl halides of nitric acid ionize to form NO_2^+. Nitrocyclohexadienones are converted to NO_2^+ and the corresponding phenol.[132]

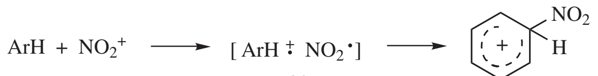
There is a great deal of evidence that NO_2^+ is present in most nitration reactions and that it is the attacking entity,[151] for example,

1. Nitric acid has a peak in the Raman spectrum. When nitric acid is dissolved in concentrated sulfuric acid, the peak disappears and two new peaks appear, one at 1400 cm^{-1} attributable to NO_2^+ and one at 1050 cm^{-1} due to HSO_4-.[152]
2. On addition of nitric acid, the freezing point of sulfuric acid is lowered about four times the amount expected if no ionization has taken place.[153] This means that the addition of one molecule of nitric acid results in the production of four particles, which is strong evidence for the ionization reaction between nitric and sulfuric acids given above.
3. The fact that nitronium salts in which nitronium ion is known to be present (by X-ray studies) nitrate aromatic compounds shows that this ion does attack the ring.
4. The rate of the reaction with most reagents is proportional to the concentration of NO_2^+, not to that of other species.[154] When the reagent produces this ion in small amounts, the attack is slow and only active substrates can be nitrated. In concentrated and aqueous mineral acids, the kinetics are second order: first order each in aromatic substrate and in nitric acid (unless pure nitric acid is used in which case there are pseudo-first-order kinetics). But in organic solvents such as nitromethane, acetic acid, and CCl_4, the kinetics are first order in nitric acid alone and zero order in aromatic substrate, because the rate-determining step is formation of NO_2^+ and the substrate does not take part in this.

[151]For an exhaustive study of this reaction, see Hughes, E.D.; Ingold, C.K.in a series of several papers with several different co-workers, see *J. Chem. Soc.* ***1950***, 2400.
[152]Ingold, C.K.; Millen, D.J.; Poole, H.G. *J. Chem. Soc.* ***1950***, 2576.
[153]Gillespie, R.J.; Graham, J.; Hughes, E.D.; Ingold, C.K.; Peeling, E.R.A. *J. Chem. Soc.* ***1950***, 2504.
[154]This is not always strictly true. See Ross, D.S.; Kuhlmann, K.F.; Malhotra, R. *J. Am. Chem. Soc.* ***1983***, *105*, 4299.

An interesting route to nitrobenzene begins with bromobenzene. Reaction with butyllithium gives phenyllithium, which reacts with an excess of N_2O_4 to give nitrobenzene.[155]

In a few cases, depending on the substrate and solvent, there is evidence that the arenium ion is not formed directly, but via the intermediacy of a radical pair (see p. 682) such as **32**.[156]

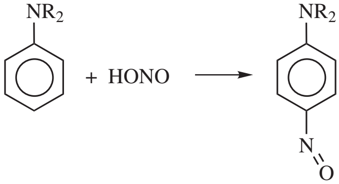


32

Arylboronic acids have been shown to react with ammonium nitrate and trifluoroacetic acid to give the corresponding nitrobenzene.[157]

OS **I**, 372, 396, 408 (see also OS **53**, 129); **II**, 254, 434, 438, 447, 449, 459, 466; **III**, 337, 644, 653, 658, 661, 837; **IV**, 42, 364, 654, 711, 722, 735; **V**, 346, 480, 829, 1029, 1067.

11-3 Nitrosation or Nitroso-de-hydrogenation



Ring nitrosation[158] with nitrous acid is normally carried out only with active substrates, such as amines and phenols. However, primary aromatic amines give diazonium ions (**13-19**) when treated with nitrous acid,[159] and secondary amines tend to give *N*-nitroso rather than *C*-nitroso compounds (**12-50**); hence this reaction is normally limited to phenols and tertiary aromatic amines. Nevertheless, secondary aromatic amines can be *C*-nitrosated in two ways. The *N*-nitroso compound first obtained can be isomerized to a *C*-nitroso compound (**11-29**), or it can be treated with another equivalent of nitrous acid to give an *N,C*-dinitroso compound. Also, a successful nitrosation of anisole has been reported, where the solvent was $CF_3COOH–CH_2Cl_2$.[160]

[155] Tani, K.; Lukin, K.; Eaton, P.E. *J. Am. Chem. Soc.* ***1997***, *119*, 1476.

[156] For a review of radical processes in aromatic nitration, see Ridd, J.H. *Chem. Soc. Rev.* ***1991***, *20*, 149. For a review of aromatic substitutions involving radical cations, see Kochi, J.K. *Adv. Free Radical Chem. (Greenwich, Conn.)* ***1990***, *1*, 53.

[157] Salzbrunn, S.; Simon, J.; Prakash, G.K.S.; Petasis, N.A.; Olah, G.A. *Synlett* ***2000***, 1485; Prakash, G.K.S.; Panja, C.; Mathew, T.; Surampudi, V.; Petasis, N.A.; Olah, G.A. *Org. Lett.* ***2004***, *6*, 2205.

[158] For a review, see Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, ***1988***, pp. 58–76. Also see Atherton, J.H.; Moodie, R.B.; Noble, D.R.; O'Sullivan, B. *J. Chem. Soc. Perkin Trans. 2* ***1997***, 663.

[159] For examples of formation of *C*-nitroso compounds from primary and secondary amines, see Hoefnagel, M.A.; Wepster, B.M. *Recl. Trav. Chim. Pays-Bas* ***1989***, *108*, 97.

[160] Radner, F.; Wall, A.; Loncar, M. *Acta Chem. Scand.* ***1990***, *44*, 152.

Much less work has been done on the mechanism of this reaction than on **11-2**.[161] In some cases, the attacking entity is NO^+, but in others it is apparently NOCl, NOBr, N_2O_3, and so on, in each of which there is a carrier of NO^+. Both NOCl and NOBr are formed during the normal process of making nitrous acid (the treatment of sodium nitrite with HCl or HBr). Nitrosation requires active substrates because NO^+ is much less reactive than NO_2^+. Kinetic studies have shown that NO^+ is at least 10^{14} times less reactive than NO_2^+.[162] A consequence of the relatively high stability of NO^+ is that this species is easily cleaved from the arenium ion, so that k_{-1} competes with k_2 (p. 660) and isotope effects are found.[163] With phenols, there is evidence that nitrosation may first take place at the OH group, after which the nitrite ester thus formed rearranges to the C-nitroso product.[164] Tertiary aromatic amines substituted in the ortho position generally do not react with HONO, probably because the ortho substituent prevents planarity of the dialkylamino group, without which the ring is no longer activated. This is an example of steric inhibition of resonance (p. 48).

OS **I**, 214, 411, 511; **II**, 223; **IV**, 247.

11-4 Diazonium Coupling

Arylazo-de-hydrogenation

$$ArH + Ar'N_2^+ \longrightarrow Ar{-}N{=}N{-}Ar'$$

Aromatic diazonium ions normally couple only with active substrates, such as amines and phenols.[165] Many of the products of this reaction are used as dyes (*azo dyes*).[166] Presumably because of the size of the attacking species, substitution is mostly para to the activating group, unless that position is already occupied, in which case ortho substitution takes place. The pH of the solution is important both for phenols and amines. For amines, the solutions may be mildly acidic or neutral. The fact that amines give ortho and para products shows that even in mildly acidic solution they react in their un-ionized form. If the acidity is too high, the reaction does not occur, because the concentration of free amine becomes too small. Phenols must be coupled in slightly alkaline solution where they are converted to the more reactive phenoxide ions, because phenols themselves are not active enough for the

[161]For a review of nitrosation mechanisms at C and other atoms, see Williams, D.L.H. *Adv. Phys. Org. Chem.* ***1983***, *19*, 381. See Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, ***1988***, pp. 58–76; Atherton, J.H.; Moodie, R.B.; Noble, D.R.; O'Sullivan, B. *J. Chem. Soc. Perkin Trans. 2* ***1997***, 663.

[162]Challis, B.C.; Higgins, R.J.; Lawson, A.J. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 1831; Challis, B.C.; Higgins, R.J. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 2365.

[163]Challis, B.C.; Higgins, R.J. *J. Chem. Soc. Perkin Trans. 2* ***1973***, 1597.

[164]Gosney, A.P.; Page, M.I. *J. Chem. Soc. Perkin Trans. 2* ***1980***, 1783.

[165]For reviews, see Szele, I.; Zollinger, H. *Top. Curr. Chem.* ***1983***, *112*, 1; Hegarty, A.F., in Patai's. *The Chemistry of Diazonium and Diazo Groups*, pt. 2, Wiley, NY, ***1978***, pp. 545–551.

[166]For reviews of azo dyes, see Zollinger, H. *Color Chemistry*, VCH, NY, ***1987***, pp. 85–148; Gordon, P.F.; Gregory, P. *Organic Chemistry in Colour*, Springer, NY, ***1983***, pp. 95–162.

reaction. However, neither phenols nor amines react in moderately alkaline solution, because the diazonium ion is converted to a diazo hydroxide Ar—N=N—OH. Primary and secondary amines face competition from attack at the nitrogen.[167] However, the resulting *N*-azo compounds (aryl triazenes) can be isomerized to *C*-azo compounds (**11-30**). In at least some cases, even when the *C*-azo compound is isolated, it is the result of initial *N*-azo compound formation followed by isomerization. It is therefore possible to synthesize the *C*-azo compound directly in one laboratory step.[168] Acylated amines and phenolic ethers and esters are ordinarily not active enough for this reaction, though it is sometimes possible to couple them (as well as such polyalkylated benzenes as mesitylene and pentamethylbenzene) to diazonium ions containing electron-withdrawing groups in the para position, since such groups increase the concentration of the positive charge and thus the electrophilicity of the ArN_2^+. Some coupling reactions which are otherwise very slow (in cases where the coupling site is crowded) are catalyzed by pyridine for reasons discussed on p. 661. Phase transfer catalysis has also been used.[169]

Coupling of a few aliphatic diazonium compounds to aromatic rings has been reported. All the examples reported so far involve cyclopropanediazonium ions and bridgehead diazonium ions, in which loss of N_2 would lead to very unstable carbocations.[170] Azobenzenes have been prepared by Pd-catalyzed coupling of aryl hydrazides with aryl halides, followed by direct oxidation.[171]

The mechanism of Z/E isomerization in Ar-N=NAr systems has been studied.[172]

OS **I**, 49, 374; **II**, 35, 39, 145.

11-5 Direct Introduction of the Diazonium Group

Diazoniation or Diazonio-de-hydrogenation

$$\mathrm{ArH} \xrightarrow[\mathrm{HX}]{2\,\mathrm{HONO}} \mathrm{ArN_2^+X^-}$$

Diazonium salts can be prepared directly by replacement of an aromatic hydrogen without the necessity of going through the amino group.[173] The reaction is essentially limited to active substrates (amines and phenols), since otherwise poor yields are obtained. Since the reagents and the substrate are the same as in reaction **11-3**, the first species formed is the nitroso compound. In the presence of excess nitrous acid, this is converted to the diazonium ion.[174] The reagent

[167]See Penton, J.R.; Zollinger, H. *Helv. Chim. Acta* ***1981***, *64*, 1717, 1728.

[168]Kelly, R.P.; Penton, J.R.; Zollinger, H. *Helv. Chim. Acta* ***1982***, *65*, 122.

[169]Hashida, Y.; Kubota, K.; Sekiguchi, S. *Bull. Chem. Soc. Jpn.* ***1988***, *61*, 905.

[170]See Szele, I.; Zollinger, H. *Top. Curr. Chem.* ***1983***, *112*, 1, see pp. 3–6.

[171]Lim, Y.-K.; Lee, K.-S.; Cho, C.-G. *Org. Lett.* ***2003***, *5*, 979.

[172]Asano, T.; Furuta, H.; Hofmann, H.-J.; Cimiraglia, R.; Tsuno, Y.; Fujio, M. *J. Org. Chem.* ***1993***, *58*, 4418.

[173]Tedder, J.M. *J. Chem. Soc.* ***1957***, 4003.

[174]Tedder, J.M.; Theaker, G. *Tetrahedron* ***1959***, *5*, 288; Kamalova, F.R.; Nazarova, N.E.; Solodova, K.V. ; Yaskova, M.S. *J. Org. Chem. USSR* ***1988***, *24*, 1004.

(azidochloromethylene)dimethylammonium chloride [$Me_2N{=}C(Cl)N_3\ Cl^-$] can also introduce the diazonium group directly into a phenol.[175] A synthesis of solid aryldiazonium chlorides is now available.[176]

11-6 Amination or Amino-de-hydrogenation[177]

$$ArH + HN_3 \xrightarrow{AlCl_3} ArNH_2$$

Aromatic compounds can be converted to primary aromatic amines, in 10–65% yields, by treatment with hydrazoic acid HN_3 in the presence of $AlCl_3$ or H_2SO_4.[178] Higher yields (>90%) have been reported with trimethylsilyl azide (Me_3SiN_3) and triflic acid F_3CSO_2OH.[179] Treatment of an aromatic compound with tetramethylhydrazonium iodide and then ammonium also give the aryl amine.[180] Tertiary amines have been prepared in ~50–90% yields by treatment of aromatic hydrocarbons with *N*-chlorodialkylamines; by heating in 96% sulfuric acid; or with $AlCl_3$ or $FeCl_3$ in nitroalkane solvents; or by irradiation.[181] Treatment of an aryl halide with an amine and a palladium catalyst leads to the aniline derivative.[182]

Tertiary (and to a lesser extent, secondary) aromatic amines can also be prepared in moderate to high yields by amination with an *N*-chlorodialkylamine (or an *N*-chloroalkylamine) and a metallic-ion catalyst (e.g., Fe^{2+}, Ti^{3+}, Cu^+, Cr^{2+}) in the presence of sulfuric acid.[183] The attacking species in this case is the aminium radical ion $R_2NH\bullet$ formed by[184]

$$R_2\overset{\oplus}{N}HCl \quad + \quad M^+ \longrightarrow R_2\overset{\oplus}{N}H\bullet \quad + \quad M^{2+} \quad + \quad Cl^-$$

Because attack is by a positive species (even though it is a free radical), orientation is similar to that in other electrophilic substitutions (e.g., phenol and acetanilide give ortho and para substitution, mostly para). When an alkyl group is present, attack at the benzylic position competes with ring substitution. Aromatic rings containing only meta-directing groups do not give the reaction at all. Fused ring systems react well.[185]

[175]Kokel, B.; Viehe, H.G. *Angew. Chem. Int. Ed.* ***1980***, *19*, 716.

[176]Mohamed, S.K.; Gomaa, M.A.-M.; El-Din, A..M.N. *J. Chem. Res. (S)* ***1997***, 166.

[177]For a review, see Kovacic, P., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 1493–1506.

[178]Kovacic, P.; Russell, R.L.; Bennett, R.P. *J. Am. Chem. Soc.* ***1964***, *86*, 1588.

[179]Olah, G.A.; Ernst, T.D. *J. Org. Chem.* ***1989***, *54*, 1203.

[180]Rozhkov, V.V.; Shevelev, S.A.; Chervin, I.T.; Mitchel, A.R.; Schmidt, R.D. *J. Org. Chem.* ***2003***, *68*, 2498.

[181]Bock, H.; Kompa, K. *Angew. Chem. Int. Ed.* ***1965***, *4*, 783; *Chem. Ber.* ***1966***, *99*, 1347, 1357, 1361.

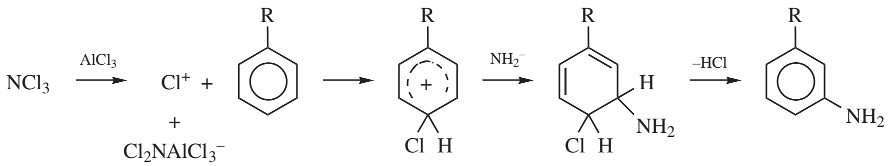
[182]Guram, A.S.; Rennels, R.A.; Buchwald, S.L. *Angew. Chem. Int. Ed. Engl.* ***1995***, *34*, 1348.

[183]For reviews, see Minisci, F. *Top. Curr. Chem.* ***1976***, *62*, 1, see pp. 6–16, *Synthesis* ***1973***, 1, see pp. 2–12, Sosnovsky, G.; Rawlinson, D.J. *Adv. Free-Radical Chem.* ***1972***, *4*, 203, see pp. 213–238.

[184]For a review of aminium radical ions, see Chow, Y.L. *React. Intermed. (Plenum)* ***1980***, *1*, 151.

[185]The reaction has been extended to the formation of primary aromatic amines, but the scope is narrow: Citterio, A.; Gentile, A.; Minisci, F.; Navarrini, V.; Serravalle, M.; Ventura, S. *J. Org. Chem.* ***1984***, *49*, 4479.

Unusual orientation has been reported for amination with haloamines and with NCl_3 in the presence of $AlCl_3$. For example, toluene gave predominately meta amination.[186] It has been suggested that initial attack in this case is by Cl^+ and that a nitrogen nucleophile (whose structure is not known, but is represented here as NH_2^- for simplicity) adds to the resulting arenium ion, so that the initial reaction is addition to a carbon–carbon double bond followed by elimination of HCl from **33**.[187]



33

According to this suggestion, the electrophilic attack is at the para position (or the ortho, which leads to the same product) and the meta orientation of the amino group arises indirectly. This mechanism is called the *σ-substitution mechanism.*

Diphenylliodonium salts react with amines in the presence of a copper catalyst. Diphenyliodonium tetrafluoroborate, $Ph_2I^+BF_4^-$, reacts with indole in DMF at 150°C with a $Cu(OAc)_2$ catalyst, for example, to give *N*-phenylindole.[188]

Aromatic compounds that do not contain meta-directing groups can be converted to diarylamines by treatment with aryl azides in the presence of phenol at −60°C: $ArH + Ar'N_3 \rightarrow ArNHAr'$.[189] Diarylamines are also obtained by the reaction of *N*-arylhydroxylamines with aromatic compounds (benzene, toluene, anisole) in the presence of F_3CCOOH: $ArH + Ar'NHOH \rightarrow ArNHAr'$.[190]

Direct *amidation* can be carried out if an aromatic compound is heated with a hydroxamic acid (**34**) in polyphosphoric acid, but the scope is essentially limited to phenolic ethers.[191] The reaction of an aromatic compound with aniline, Bu_4NF and $KMnO_4$ led to the diarylamine.[192] The formation of hydroindole derivatives was accomplished by reaction of a *N*-carbamoyl phenylethylamine derivative with phenyliodine (III) diacetate, followed by Bu_4NF.[193] Direct amidation via ipso substitution by nitrogen was accomplished when a *N*-methoxy arylethylamide (**35**) was

[186]See Strand, J.W.; Kovacic, P. *J. Am. Chem. Soc.* ***1973***, *95*, 2977, and references cited therein.

[187]Kovacic, P.; Levisky, J.A. *J. Am. Chem. Soc.* ***1966***, *88*, 1000.

[188]Zhou, T.; Chen, Z.-C. *Synth. Commun.* ***2002***, *32*, 903.

[189]Nakamura, K.; Ohno, A.; Oka, S. *Synthesis* ***1974***, 882. See also, Takeuchi, H.; Takano, K. *J. Chem. Soc. Perkin Trans. 1* ***1986***, 611.

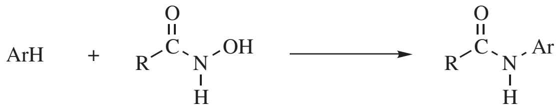
[190]Shudo, K.; Ohta, T.; Okamoto, T. *J. Am. Chem. Soc.* ***1981***, *103*, 645.

[191]Wassmundt, F.W.; Padegimas, S.J. *J. Am. Chem. Soc.* ***1967***, *89*, 7131; March, J.; Engenito Jr., J.S. *J. Org. Chem.* ***1981***, *46*, 4304. Also see, Cablewski, T.; Gurr, P.A.; Rander, K.D.; Strauss, C.R. *J. Org. Chem.* ***1994***, *59*, 5814.

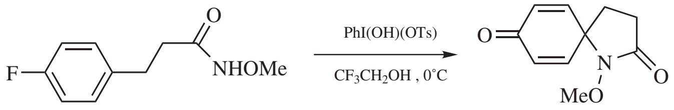
[192]Huertas, I.; Gallardo, I.; Marquet, J. *Tetrahedron Lett.* ***2001***, *42*, 3439.

[193]Pouységu, L.; Avellan, A.-V.; Quideau, S. *J. Org. Chem.* ***2002***, *67*, 3425.

treated with [hydroxyl(tosyloxy)iodo]benzene (HTIB) in 2,2,2-trifluoroethanol, giving a *N*-methoxy spirocylcic amide, **36**.[194]



34



35 **36**

Aromatic compounds add to DEAD (diethyl azodicarboxylate), in the presence of $InCl_3$–SiO_2 and microwave irradiation, to give the *N*-aryldiamino compound [ArN(CO_2Et)–NHCO_2Et].[195]

An interesting variation in the alkylation reaction used five equivalents of aluminum chloride in a reaction of *N*-methyl-*N*-phenylhydrazine and benzene to give *N*-methyl-4-phenylaniline.[196]

Also see **13-5**, **13-16**.

C. Sulfur Electrophiles

11-7 Sulfonation or Sulfo-de-hydrogenation

$$ArH + H_2SO_4 \longrightarrow ArSO_2OH$$

The sulfonation reaction is very broad in scope and many aromatic hydrocarbons (including fused ring systems), aryl halides, ethers, carboxylic acids, amines,[197] acylated amines, ketones, nitro compounds, and sulfonic acids have been sulfonated.[198] Phenols can also be successfully sulfonated, but attack at oxygen may compete.[199] Sulfonation is often accomplished with concentrated sulfuric acid, but it can also be done with fuming sulfuric acid, SO_3, $ClSO_2OH$, $ClSO_2NMe_2$/In(OTf)$_3$,[200] or other reagents.[201] As with nitration (**11-2**), reagents of a wide variety of activity are available to suit both highly active and highly inactive substrates. Since this is a reversible reaction (see **11-38**), it may be necessary to drive the reaction to completion.

[194]Miyazawa, E.; Sakamoto, T.; Kikugawa, Y. *J. Org. Chem.* ***2003***, *68*, 5429.

[195]Yadav, J.S.; Subba Reddy, B.V.; Kumar, G.M.; Madan, C. *Synlett* ***2001***, 1781.

[196]Ohwada, A.; Nara, S.; Sakamoto, T.; Kikugawa, Y. *J. Chem. Soc, Perkin Trans. 1* ***2001***, 3064.

[197]See Khelevin, R.N. *J. Org. Chem. USSR* ***1987***, *23*, 1709; ***1988***, *24*, 535, and references cited therein.

[198]For reviews, see Nelson, K.L. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 1355–1392; Gilbert, E.E. *Sulfonation and Related Reactions*, Wiley, NY, ***1965***, pp. 62–83, 87–124.

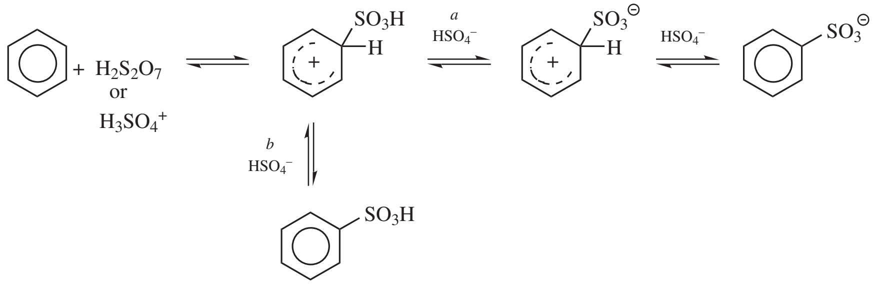
[199]See, for example, de Wit, P.; Woldhuis, A.F.; Cerfontain, H. *Recl. Trav. Chim. Pays-Bas* ***1988***, *107*, 668.

[200]Frost, C.G.; Hartley, J.P.; Griffin, D. *Synlett* ***2002***, 1928.

[201]For a reaction using silica sulfuric acid, see Hajipour, A.R.; Mirjalili, B.B.F.; Zarei, A.; Khazdooz, L.; Ruoho, A.E. *Tetrahedron Lett.* ***2004***, *45*, 6607.

However, at low temperatures the reverse reaction is very slow and the forward reaction is practically irreversible.[202] Sulfur trioxide reacts much more rapidly than sulfuric acid with benzene it is nearly instantaneous. Sulfones are often side products. When sulfonation is carried out on a benzene ring containing four or five alkyl and/or halogen groups, rearrangements usually occur (see **11-36**).

A great deal of work has been done on the mechanism,[203] chiefly by Cerfontain and co-workers. Mechanistic study is made difficult by the complicated nature of the solutions. Indications are that the electrophile varies with the reagent, though SO_3 is involved in all cases, either free or combined with a carrier. In aqueous H_2SO_4 solutions, the electrophile is thought to be $H_3SO_4^+$ (or a combination of H_2SO_4 and H_3O^+) at concentrations below ~ 80–85% H_2SO_4, and $H_2S_2O_7$ (or a combination of H_2SO_4 and SO_3) at concentrations higher than this[204] (the change-over point varies with the substrate[205]). Evidence for a change in electrophile is that in the dilute and in the concentrated solutions the rate of the reaction was proportional to the activity of $H_3SO_4^+$ and $H_2S_2O_7$, respectively. Further evidence is that with toluene as substrate the two types of solution gave very different ortho/para ratios. The mechanism is essentially the same for both electrophiles and may be shown as:[204]



The other product of the first step is HSO_4^- or H_2O from $H_2S_2O_7$ or $H_3SO_4^+$, respectively. Path *a* is the principal route, except at very high H_2SO_4 concentrations, when path *b* becomes important. With $H_3SO_4^+$ the first step is rate determining under all conditions, but with $H_2S_2O_7$ the first step is the slow step only up to ~ 96% H_2SO_4, when a subsequent proton transfer becomes partially rate determining.[206] The $H_2S_2O_7$ is more reactive than $H_3SO_4^+$. In fuming sulfuric acid (H_2SO_4 containing excess SO_3), the electrophile is thought to be $H_3S_2O_7^+$ (protonated $H_2S_2O_7$) up to

[202]Spryskov, A.A. *J. Gen. Chem. USSR* ***1960***, *30*, 2433.

[203]For a monograph, see Cerfontain, H. *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*, Wiley, NY, ***1968***. For reviews, see Cerfontain, H. *Recl. Trav. Chim. Pays-Bas* ***1985***, *104*, 153; Cerfontain, H.; Kort, C.W.F. *Int. J. Sulfur Chem. C* ***1971***, *6*, 123; Taylor, R., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 56–77.

[204]Cerfontain, H.; Lambrechts, H.J.A.; Schaasberg-Nienhuis, Z.R.H.; Coombes, R.G.; Hadjigeorgiou, P.; Tucker, G.P. *J. Chem. Soc. Perkin Trans. 2* ***1985***, 659, and references cited therein.

[205]See, for example, Kaandorp, A.W.; Cerfontain, H. *Recl. Trav. Chim. Pays-Bas* ***1969***, *88*, 725.

[206]Kort, C.W.F.; Cerfontain, H. *Recl. Trav. Chim. Pays-Bas* ***1967***, *86*, 865.

~104% H_2SO_4 and $H_2S_4O_13$ ($H_2SO_4 + 3SO_3$) beyond this concentration.[207] Finally, when pure SO_3 is the reagent in aprotic solvents, SO_3 itself is the actual electrophile.[208] Free SO_3 is the most reactive of all these species, so that attack here is generally fast and a subsequent step is usually rate determining, at least in some solvents.

OS **II**, 42, 97, 482, 539; **III**, 288, 824; **IV**, 364; **VI**, 976.

11-8 Halosulfonation or Halosulfo-de-hydrogenation

$$ArH + ClSO_2OH \longrightarrow ArSO_2Cl$$

Aromatic sulfonyl chlorides can be prepared directly, by treatment of aromatic rings with chlorosulfuric acid.[209] Since sulfonic acids can also be prepared by the same reagent (**11-7**), it is likely that they are intermediates, being converted to the halides by excess chlorosulfuric acid.[210] The reaction has also been effected with bromo- and fluorosulfuric acids. Sulfinyl chlorides (ArSOCl) have been prepared by the reaction of thionyl chloride and an aromatic compound on Montmorillonite K10 clay.[211]

OS **I**, 8, 85.

11-9 Sulfonylation

Alkylsulfonylation or **Alkylsulfo-de-hydrogenation**

$$ArH + SOCl_2 \xrightarrow{TfOH} ArSOAr$$

$$ArH + Ar'SO_2Cl \xrightarrow{AlCl_3} ArSO_2Ar'$$

Diaryl sulfoxides can be prepared by the reaction of aromatic compounds with thionyl chloride and triflic acid.[212] Diaryl sulfones have also been prepared using thionyl chloride with the ionic liquid [bmim]Cl•$AlCl_3$.[213] Diaryl sulfones can be formed by treatment of aromatic compounds with aryl sulfonyl chlorides and a Friedel–Crafts catalyst[214] This reaction is analogous to Friedel–Crafts acylation with carboxylic acid halides (**11-17**). In a better procedure, the aromatic compound

[207]Koeberg-Telder, A.; Cerfontain, H. *J. Chem. Soc. Perkin Trans. 2* ***1973***, 633.

[208]Lammertsma, K.; Cerfontain, H. *J. Chem. Soc. Perkin Trans. 2* ***1980***, 28, and references cited therein.

[209]For a review, see Gilbert, E.E. *Sulfonaton and Related Reactions*, Wiley, NY, ***1965***, pp. 84–87.

[210]For a discussion of the mechanism with this reagent, see van Albada, M.P.; Cerfontain, H. *J. Chem. Soc. Perkin Trans. 2* ***1977***, 1548, 1557.

[211]Karade, N.N.; Kate, S.S.; Adude, R.N. *Synlett* ***2001***, 1573.

[212]Olah G.A.; Marinez, E.R.; Prakash, G.K.S. *Synlett* ***1999***, 1397.

[213]In [bmim]Cl•$AlCl_3$, 1-butyl-3-methylimidazolium chloroaluminate: Mohile, S.S.; Potdar, M.K.; Salunkhe, M.M. *Tetrahedron Lett.* ***2003***, *44*, 1255.

[214]For reviews, see Taylor, R., in Bamford, C.H.; Tipper, C.F.H *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 77–83; Jensen, F.R.; Goldman, G. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 1319–1347. For a solid-state reaction using Fe^{3+}-Montmorillonite, see Choudary, B.M.; Chowdari, N.S.; Kantam, M.L. *J. Chem. Soc., Perkin Trans. 1*, ***2000***, 2689.

is treated with an aryl sulfonic acid and P_2O_5 in polyphosphoric acid.[215] Still another method uses an arylsulfonic trifluoromethanesulfonic anhydride $ArSO_2OSO_2CF_3$ (generated *in situ* from $ArSO_2Br$ and CF_3SO_3Ag) without a catalyst.[216] Indium *tris*(triflate)[217] and indium trichloride[218] give sulfonation with sulfonyl chlorides, and indium bromide was used in indoles.[219] A ferric chloride catalyzed reaction with microwave irradiation has also been reported,[220] as has the use of zinc metal with microwave irradiation.[221]

The reaction can be extended to the preparation of alkyl aryl sulfones by the use of a sulfonyl fluoride.[222]

Direct formation of diaryl sulfones from benzenesulfonic acid and benzene was accomplished using Nafion-H.[223]

OS **X**, 147.

D. Halogen Electrophiles

11-10 Halogenation[224]

Halo-de-hydrogenation

$$ArH + Br_2 \xrightarrow{\text{catalyst}} ArBr$$

1. *Chlorine and Bromine*. Aromatic compounds can be brominated or chlorinated by treatment with bromine or chlorine in the presence of a catalyst. For amines and phenols the reaction is so rapid that it is carried out with a dilute solution of Br_2 or Cl_2 in water at room temperature, or with aqueous HBr in DMSO.[225] Even so, with amines it is not possible to stop the reaction before all the available ortho and para positions are substituted, because the initially formed haloamines are weaker bases than the original amines and are less

[215]Graybill, B.M. *J. Org. Chem.* ***1967***, *32*, 2931; Sipe, Jr., H.J.; Clary, D.W.; White, S.B. *Synthesis* ***1984***, 283. See also, Ueda, M.; Uchiyama, K.; Kano, T. *Synthesis* ***1984***, 323.
[216]Effenberger, F.; Huthmacher, K. *Chem. Ber.* ***1976***, *109*, 2315. For similar methods, see Hancock, R.A.; Tyobeka, T.E.; Weigel, H. *J. Chem. Res. (S)* ***1980***, 270; Ono, M.; Nakamura, Y.; Sato, S.; Itoh, I. *Chem. Lett.* ***1988***, 395.
[217]Frost, C.G.; Hartley, J.P.; Whittle, A.J. *Synlett* ***2001***, 830.
[218]Garzya, V.; Forbes, I.T.; Lauru, S.; Maragni, P. *Tetahedron Lett.* ***2004***, *45*, 1499.
[219]Yadav, J.S.; Reddy, B.V.S.; Krishna, A.D.; Swamy, T. *Tetahedron Lett.* ***2003***, *44*, 6055.
[220]Marquié, J.; Laporterie, A.; Dubac, J.; Roques, N.; Desmurs, J.-R. *J. Org. Chem.* ***2001***, *66*, 421.
[221]Bandgar, B.P.; Kasture, S.P. *Synth. Commun.* ***2001***, *31*, 1065.
[222]Hyatt, J.A.; White, A.W. *Synthesis* ***1984***, 214.
[223]Olah, G.A.; Mathew, T.; Prakash, G.K.S. *Chem. Commun.* ***2001***, 1696.
[224]For a monograph, see de la Mare, P.B.D. *Electrophilic Halogenation*, Cambridge University Press, Cambridge, ***1976***. For reviews, see Buehler, C.A.; Pearson, D.E. *Survey of Organic Synthesis*, Wiley, NY, ***1970***, pp. 392–404; Braendlin, H.P.; McBee, E.T., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 1517–1593. For a review of the halogenation of heterocyclic compounds, see Eisch, J.J. *Adv. Heterocycl. Chem.* ***1966***, *7*, 1. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 619–628.
[225]Srivastava, S.K.; Chauhan, P.M.S.; Bhaduri, A.P. *Chem. Commun.* ***1996***, 2679.

likely to be protonated by the liberated HX.[226] For this reason, primary amines are often converted to the corresponding anilides if monosubstitution is desired. With phenols it is possible to stop after one group has entered.[227] The rapid room-temperature reaction with amines and phenols is often used as a test for these compounds.

For less activated aromatic rings, iron was commonly used at one time for halogenation, but the real catalyst was shown not to be the iron itself, but rather the ferric bromide or ferric chloride formed in small amounts from the reaction between iron and the reagent. Indeed, ferric chloride and other Lewis acids are typically directly used as catalysts, as is iodine. For active substrates, including amines, phenols, naphthalene, and polyalkylbenzenes,[228] such as mesitylene and isodurene, no catalyst is needed. Many Lewis acids can be used, including thallium(III) acetate, which promotes bromination with high regioselectivity para to an ortho–para-directing group.[229] A mixture of $Mn(OAc)_3$ and acetyl chloride, with ultrasound, chlorinates anisole with high selectivity.[230] Bromination on NaY zeolite occurs with high para selectivity.[231]

Other acids can be used to promote chlorination or bromination. *N*-Bromosuccinimide and HBF_4 can be used to brominate phenols with high *para*-selectivity,[232] as can pyridinium bromide perbromide,[233] and NBS in acetic acid with ultrasound is effective.[234] The use of NBS with a catalytic amount of HCl has also been reported.[235] Both NCS and NBS with aqueous BF_3 gave the respective chloride or bromide.[236] Note that NBS in an ionic liquid[237] gave the brominated aromatic. Bromine on silica gel gave good yields of the brominated aromatic compound.[238] HBr with hydrogen peroxide

[226]Monobromination (para) of aromatic amines has been achieved with tetrabutylammonium tribromide: Berthelot, J.; Guette, C.; Desbène, P.; Basselier, J.; Chaquin, P.; Masure, D. *Can. J. Chem.* ***1989***, *67*, 2061. For another procedure, see Onaka, M.; Izumi, Y. *Chem. Lett.* ***1984***, 2007.

[227]For a review of the halogenation of phenols, see Brittain, J.M.; de la Mare, P.B.D., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement D*, pt. 1, Wiley, NY, ***1983***, pp. 522–532.

[228]For a review of aromatic substitution on polyalkylbenzenes, see Baciocchi, E.; Illuminati, G. *Prog. Phys. Org. Chem.* ***1967***, *5*, 1.

[229]McKillop, A.; Bromley, D.; Taylor, E.C. *J. Org. Chem.* ***1972***, *37*, 88.

[230]Prokes, I.; Toma, S.; Luche, J.-L. *J. Chem. Res. (S)* ***1996***, 164.

[231]See Smith, K.; Bahzad, D. *Chem. Commun.* ***1996***, 467; Smith, K.; Musson, A.; DeBoos, G.A. *J. Org. Chem.* ***1998***, *63*, 8448. Also see, Paul, V.; Sudalai, A.; Daniel, T.; Srinivasan, K.V. *Tetrahedron Lett.* ***1994***, *35*, 7055.

[232]Oberhauser, T. *J. Org. Chem.* ***1997***, *62*, 4504.

[233]Reeves, W.P.; Lu, C.V.; Schulmeier, B.; Jonas, L.; Hatlevik, O. *Synth. Commun.* ***1998***, *28*, 499; Reeves, W.P.; King II, R.M. *Synth. Commun.* ***1993***, *23*, 855. Also see, Bisarya, S.C.; Rao, R. *Synth. Commun.* ***1993***, *23*, 779.

[234]Paul, V.; Sudalai, A.; Daniel, T.; Srinivasan, K.V. *Synth. Commun.* ***1995***, *25*, 2401.

[235]Andersh, B.; Murphy, D.L.; Olson, R.J. *Synth. Commun.* ***2000***, *30*, 2091.

[236]Prakash, G.K.S.; Mathew, T.; Hoole, D.; Esteves, P.M.; Wang, Q.; Rasul, G.; Olah, G.A. *J. Am. Chem. Soc.* ***2004***, *126*, 15770.

[237]In bbim BF_4, 1,3-di-*n*-butylimidazolium tetrafluoroborate: Rajagopal, R.; Jarikote, D.V.; Lahoti, R.J.; Daniel, T.; Srinivasan, K.V. *Tetrahedron Lett.* ***2003***, *44*, 1815.

[238]Ghiaci, M.; Asghari, J. *Bull. Chem. Soc. Jpn.* ***2001***, *74*, 1151.

converted aniline to 2,4,6-tribromoaniline.[239] Majetich and co-workers reported the use of HBr/DMSO for the remarkably selective bromination of aniline.[240] *para*-Bromination of aniline was reported by mixing aniline with the ionic liquid, bmim Br_3.[241] Similarly, hmim Br_3[242] without another reagent is a brominating agent.

Other reagents have been used for chlorination and bromination, among them HOCl,[243] HOBr, and *N*-chloro and *N*-bromo amides (especially NBS and tetraalkylammonium polyhalides[244]). In all but the last of these cases, the reaction is catalyzed by the addition of acids. Sulfuryl chloride (SO_2Cl_2) in acetic acid effective chlorinates anisole derivatives,[245] and LiBr with ceric ammonium nitrate in acetonitrile brominates.[246] Acetyl chloride with a catalytic amount of ceric ammonium nitrate also converted aromatic compounds to the corresponding chlorinated derivative.[247] A mixture of KCl and Oxone® as chlorinated activated aromatic compounds.[248] Oxone® and KBr gave good para bromination of anisole.[249] Dibromoisocyanuric acid in H_2SO_4 is a very good brominating agent[250] for substrates with strongly deactivating substituents.[251] If the substrate contains alkyl groups, side-chain halogenation (**14-1**) is possible with most of the reagents mentioned, including chlorine and bromine. Since side-chain halogenation is catalyzed by light, the reactions should be run in the absence of light wherever possible. Both NCS in isopropanol[252] and *tert*-butyl hypochlorite[253] chlorinate aniline derivatives, and $KBr/NaBO_3{\bullet}4\ H_2O$ has been used for the bromination of aniline derivatives.[254] Anisole was brominated with para selectivity using HBr, in the presence of *tert*-butyl hydroperoxide and hydrogen peroxide.[255] Potassium bromide (KBr) with a zeolite (HZSM-5), acetic acid and 30% hydrogen peroxide was used to brominate both anisole and aniline derivatives.[256] Conversion of aniline to the *N*-$SnMe_3$ derivative allowed

[239]Vyas, P.V.; Bhatt, A.K.; Ramachandraiah, G.; Bedekar, A.V. *Tetrahedron Lett.* ***2003***, *44*, 4085.

[240]Majetich, G.; Hicks, R.; Reister, S. *J. Org. Chem.* ***1997***, *62*, 4321.

[241]1-Butyl-3-methylimidazolium tribromide: Lei, Z.-G.; Chen, Z.-C.; Hu, Y.;. Zheng, Q.-G. *Synthesis* ***2004***, 2809.

[242]In hmim, *N*-methylimidazolium: See Chiappe, C.; Leandri, E.; Pieraccini, D. *Chem. Commun.* ***2004***, 2536.

[243]For the use of calcium hypochlorite, see Nwaukwa, S.O.; Keehn, P.M. *Synth. Commun.* ***1989***, *19*, 799.

[244]See Kajigaeshi, S.; Moriwaki, M.; Tanaka, T.; Fujisaki, S.; Kakinami, T.; Okamoto, T. *J. Chem. Soc. Perkin Trans. 1* ***1990***, 897, and other papers in this series.

[245]Yu, G.; Mason, H.J.; Wu, X.; Endo, M.; Douglas, J.; Macor, J.E. *Tetrahedron Lett.* ***2001***, *42*, 3247.

[246]Roy, S.C.; Guin, C.; Rana, K.K.; Maiti, G. *Tetrahedron Lett.* ***2001***, *42*, 6941.

[247]Roy, S.C.; Rana, K.K.; Guin, C.; Banerjee, B. *Synlett* ***2003***, 221.

[248]Narender, N.; Srinivasu, P.; Kulkarni, S.J.; Raghavan, K.V. *Synth. Commun.* ***2002***, *32*, 279.

[249]Tamhankar, B.V.; Desai, U.V.; Mane, R.B.; Wadgaonkar, P.P.; Bedekar, A.V. *Synth. Commun.* ***2001***, *31*, 2021.

[250]Nitrobenzene is pentabrominated in 1 min with this reagent in 15% oleum at room temperature.

[251]Gottardi, W. *Monatsh. Chem.* ***1968***, *99*, 815; ***1969***, *100*, 42.

[252]Zanka, A.; Kubota, A. *Synlett* ***1999***, 1984.

[253]Lengyel, I.; Cesare, V.; Stephani, R. *Synth. Commun.* ***1998***, *28*, 1891.

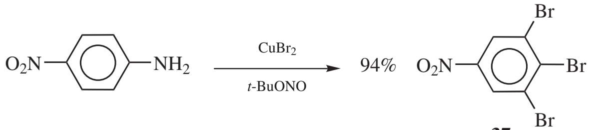
[254]Roche, D.; Prasad, K.; Repic, O.; Blacklock, T.J. *Tetrahedron Lett.* ***2000***, *41*, 2083.

[255]Barhate, N.B.; Gajare, A.S.; Wakharkar, R.D.; Bedekar, A.V. *Tetrahedron* ***1999***, *55*, 11127.

[256]Narender, N.; Srinivasu, P.; Kulkarni, S.J.; Raghavan, K.V. *Synth. Commun.* ***2000***, *30*, 3669.

in situ bromination with bromine, with high para selectivity after conversion to the free amine with aqueous KF.[257] Pyridinium bromochromate converted phenolic derivatives to brominated phenols.[258]

Chlorine is a more active reagent than bromine. Phenols can be brominated exclusively in the ortho position (disubstitution of phenol gives 2,6-dibromophenol) by treatment with Br_2 at about $-70°C$, in the presence of *tert*-butylamine or triethylenediamine to precipitate out the liberated HBr.[259] Predominant ortho chlorination[260] of phenols has been achieved with chlorinated cyclohexadienes,[261] while para chlorination of phenols, phenolic ethers, and amines can be accomplished with *N*-chloroamines[262] and with *N*-chlorodimethylsulfonium chloride ($Me_2S^+Cl\,Cl^-$).[263] The last method is also successful for bromination when *N*-bromodimethylsufonium bromide is used. On the other hand, certain alkylated phenols can be brominated in the meta positions with Br_2 in the superacid solution SbF_5—HF.[264] It is likely that the meta orientation is the result of conversion by the super acid of the OH group to the OH_2^+ group, which should be meta directing because of its positive charge. Bromination and the Sandmeyer reaction (**14-20**) can be carried out in one laboratory step to give **37** by treatment of an aromatic primary amine with $CuBr_2$ and *tert*-butyl nitrite, for example[265]



37

With deactivated aromatic derivatives, such as nitrobenzene, BrF_3 and Br_2 is an effective reagent, gives the *meta*-brominated product.[266] Tetrabutylammonium bromide and P_2O_5 at 100°C has been used to convert 2-hydroxypyridine derivatives to the corresponding 2-bromopyridine.[267] Bromination at C-6 of 2-aminopyridine was accomplished with NBS.[268] An alternative route

[257]Smith, M.B.; Guo, L.; Okeyo, S.; Stenzel, J.; Yanella, J.; La Chapelle, E. *Org. Lett.* ***2002***, *4*, 2321.

[258]Patwari, S.B.; Baseer, M.A.; Vibhute, Y.B.; Bhusare, S.R. *Tetrahedron Lett.* ***2003***, *44*, 4893.

[259]Pearson, D.E.; Wysong, R.D.; Breder, C.V. *J. Org. Chem.* ***1967***, *32*, 2358.

[260]For other methods of regioselective chlorination or bromination, see Kodomari, M.; Takahashi, S.; Yoshitomi, S. *Chem. Lett.* ***1987***, 1901; Kamigata, N.; Satoh, T.; Yoshida, M.; Matsuyama, H.; Kameyama, M. *Bull. Chem. Soc. Jpn.* ***1988***, *61*, 2226; de la Vega, F.; Sasson, Y. *J. Chem. Soc., Chem. Commun.* ***1989***, 653.

[261]Lemaire, M.; Guy, A.; Guette, J. *Bull. Soc. Chim. Fr.* ***1985***, 477.

[262]Lindsay Smith, J.R.; McKeer, L.C.; Taylor, J.M. *J. Chem. Soc. Perkin Trans. 2* ***1989***, 1529, 1537. See also, Minisci, F.; Vismara, E.; Fontana, F.; Platone, E.; Faraci, G. *J. Chem. Soc. Perkin Trans. 2* ***1989***, 123.

[263]Olah, G.A.; Ohannesian, L.; Arvanaghi, M. *Synthesis* ***1986***, 868.

[264]Jacquesy, J.; Jouannetaud, M.; Makani, S. *J. Chem. Soc., Chem. Commun.* ***1980***, 110.

[265]Doyle, M.P.; Van Lente, M.A.; Mowat, R.; Fobare, W.F. *J. Org. Chem.* ***1980***, *45*, 2570.

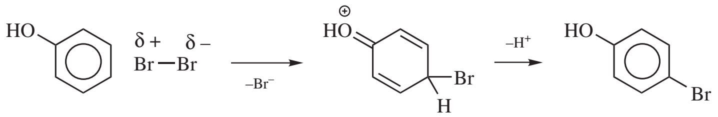
[266]Rozen, S.; Lerman, O. *J. Org. Chem.* ***1993***, *58*, 239.

[267]Kato, Y.; Okada, S.; Tomimoto, K.; Mase, T. *Tetrahedron Lett.* ***2001***, *42*, 4849.

[268]Cañibano, V.; Rodríguez, J.F.; Santos, M.; Sanz-Tejedor, A.; Carreño, M.C.; González, G.; García-Ruano, J.L. *Synthesis* ***2001***, 2175.

reacted pyridine *N*-oxide was $POCl_3$ and triethylamine to give 2-chloropyridine.[269] Pyridinium dichlorobromate with $FeCl_3$ brominates benzene.[270]

For reactions in the absence of a catalyst, the attacking entity is simply Br_2 or Cl_2 that has been polarized by the ring.[271]



38

Evidence for molecular chlorine or bromine as the attacking species in these cases is that acids, bases, and other ions, especially chloride ion, accelerate the rate about equally, though if chlorine dissociated into Cl^+ and Cl^-, the addition of chloride should decrease the rate and the addition of acids should increase it. Intermediate **38** has been detected spectrally in the aqueous bromination of phenol.[272]

When a Lewis acid catalyst is used with chlorine or bromine, the attacking entity may be Cl^+ or Br^+, formed by $FeCl_3 + Br_2 \rightarrow FeCl_3Br^- + Br^+$, or it may be Cl_2 or Br_2, polarized by the catalyst. With other reagents, the attacking entity in brominations may be Br^+ or a species, such as H_2OBr^+ (the conjugate acid of HOBr), in which H_2O is a carrier of Br^+.[273] With HOCl in water the electrophile may be Cl_2O, Cl_2, or H_2OCl^+; in acetic acid it is generally AcOCl. All these species are more reactive than HOCl itself.[274] It is extremely doubtful that Cl^+ is a significant electrophile in chlorinations by HOCl.[274] It has been demonstrated in the reaction between *N*-methylaniline and calcium hypochlorite that the chlorine attacking entity attacks the *nitrogen* to give *N*-chloro-*N*-methylaniline, which rearranges (as in **11-31**) to give a mixture of ring-chlorinated *N*-methylanilines in which the ortho isomer predominates.[275] In addition to hypohalous acids and metal hypohalites, organic hypohalites are reactive. An example is *tert*-butylhypobromite (*t*-BuOBr), which brominated toluene in the presence of zeolite HNaX.[276]

[269]Jung, J.-C.; Jung, Y.-J.; Park, O.-S. *Synth. Commun.* ***2001***, *31*, 2507.

[270]Muathen, H.A. *Synthesis* ***2002***, 169.

[271]For reviews of the mechanism of halogenation, see de la Mare, P.B.D., *Electrophilic Halogenation*, Cambridge University Press, Cambridge, ***1976***; de la Mare, P.B.D.; Swedlund, B.E., in Patai. S. *The Chemistry of the Carbon–Halogen Bond*, pt. 1, Wiley, NY, ***1973***; pp. 490–536; Taylor, R., in Bamford, C.H.; Tipper, C.F.H *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 83–139. See also, Schubert, W.M.; Dial, J.L. *J. Am. Chem. Soc.* ***1975***, *97*, 3877; Keefer, R.M.; Andrews, L.J. *J. Am. Chem. Soc.* ***1977***, *99*, 5693; Tee, O.S.; Paventi, M.; Bennett, J.M. *J. Am. Chem. Soc.* ***1989***, *111*, 2233.

[272]Tee, O.S.; Iyengar, N.R.; Paventi, M. *J. Org. Chem.* ***1983***, *48*, 759. See also, Tee, O.S.; Iyengar, N.R. *Can. J. Chem.* ***1990***, *68*, 1769.

[273]For discussions, see Gilow, H.M.; Ridd, J.H. *J. Chem. Soc. Perkin Trans. 2* ***1973***, 1321; Rao, T.S.; Mali, S.I.; Dangat, V.T. *Tetrahedron* ***1978***, *34*, 205.

[274]Swain, C.G.; Crist, D.R. *J. Am. Chem. Soc.* ***1972***, *94*, 3195.

[275]Gassman, P.G.; Campbell, G.A. *J. Am. Chem. Soc.* ***1972***, *94*, 3891; Paul, D.F.; Haberfield, P. *J. Org. Chem.* ***1976***, *41*, 3170.

[276]Smith, K.; El-Hiti, G.A.; Hammond, M.E.W.; Bahzad, D.; Li, Z.; Siquet, C. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 2745.

When chlorination or bromination is carried out at high temperatures (e.g., 300–400°C), ortho–para-directing groups direct meta and vice versa.[277] A different mechanism operates here, which is not completely understood. It is also possible for bromination to take place by the S_E1 mechanism, for example, in the *t*-BuOK-catalyzed bromination of 1,3,5-tribromobenzene.[278]

Furan and thiophene are known to polymerize in the presence of strong acid, both Brønsted–Lowry and Lewis. For such highly reactive heteroaromatic systems, alternative halogenating reagents are commonly used. Furan was converted to 2-bromofuran with a bromine•dioxane complex, for example, at <0°C.[279] 3-Butylthiophene reacted with NBS/acetic acid to give 2-bromo-3-butylthiophene.[280] *N*-Methylpyrrole reacted with NBS and a catalytic amount of PBr_3, at $-78°C \rightarrow -10°C$, to give *N*-methyl-3-bromopyrrole.[281]

2. *Iodine*. Iodine is the least reactive of the halogens in aromatic substitution.[282] Except for active substrates, an oxidizing agent must normally be present to oxidize I_2 to a better electrophile.[283] Examples of such oxidizing agents are HNO_3, HIO_3, SO_3, MnO_2,[284] hypervalent iodine compounds, such as $PhI(OTf)_2$,[285] $NaIO_4$,[286] peroxyacetic acid, H_2O_2[287] peroxydisulfates,[288] and ammonium iodide with Oxone®.[289] The ICl is a better iodinating agent than iodine itself.[290] Among other reagents used have been IF (prepared directly from the elements),[291] and benzyltrialkylammonium dichloroiodate (which iodinates phenols, aromatic amines, and *N*-acylated aromatic amines,[292] as well

[277]For a review of this type of reaction, see Kooyman, E.C. *Pure. Appl. Chem.* ***1963***, *7*, 193.

[278]Mach, M.H.; Bunnett, J.F. *J. Am. Chem. Soc.* ***1974***, *96*, 936.

[279]See Baciocchi, E.; Clementi, S.; Sebastiani, G.V. *J. Chem. Soc., Chem. Commun.* ***1975***, 875.

[280]Hoffmann, K.J.; Carlsen, P.H.J. *Synth. Commun.* ***1999***, *29*, 1607.

[281]Dvornikova, E.; Kamieňska-Trela, K. *Synlett* ***2002***, 1152.

[282]For reviews of I_2 as an electrophilic reagent, see Pizey, J.S., in Pizey, J.S. *Synthetic Reagents*, Vol. 3, Wiley, NY, ***1977***, pp. 227–276. For a review of aromatic iodination, see Merkushev, E.B. *Synthesis* ***1988***, 923.

[283]Butler, A.R. *J. Chem. Educ.* ***1971***, *48*, 508.

[284]Luliski, P.; Skulski, L. *Bull. Chem. Soc. Jpn.* ***1999***, *72*, 115.

[285]D'Auria, M.; Mauriello, G. *Tetrahedron Lett.* ***1995***, *36*, 4883; Togo, H.; Abe, S.; Nogami, G.; Yokoyama, M. *Bull. Chem. Soc. Jpn.* ***1999***, *72*, 2351; Panunzi, B.; Rotiroti, L.; Tingoli, M. *Tetrahedron Lett.* ***2003***, *44*, 8753.

[286]Luliński, P.; Skulski, L. *Bull. Chem. Soc. Jpn.* ***2000***, *73*, 951.

[287]For a discussion, see Makhon'kov, D.I.; Cheprakov, A.V.; Beletskaya, I.P. *J. Org. Chem. USSR* ***1989***, *24*, 2029. See Iskra, J.; Stavber, S.; Zupan, M. *Synthesis* ***2004***, 1869.

[288]Tajik, H.; Esmaeili, A.A.; Mohammadpoor-Baltork, I.; Ershadi, A.; Tajmehri, H. *Synth. Commun.* ***2003***, *33*, 1319.

[289]Mohan, K.V.V.K.; Narender, N.; Kulkarni, S.J. *Tetrahedron Lett.* ***2004***, *45*, 8015.

[290]For a review of ICl, see McCleland, C.W., in Pizey, J.S. *Synthetic Reagents*, Vol. 5, Wiley, NY, ***1983***, pp. 85–164. For a reaction using ICl, ZnO and an iron catalyst, see Mukaiyama, T.; Kitagawa, H.; Matsuo, J.-i. *Tetrahedron Lett.* ***2000***, *41*, 9383.

[291]Rozen, S.; Zamir, D. *J. Org. Chem.* ***1990***, *55*, 3552.

[292]See Kajigaeshi, S.; Kakinami, T.; Watanabe, F.; Okamoto, T. *Bull. Chem. Soc. Jpn.* ***1989***, *62*, 1349, and references cited therein. For a reaction of anisole with $Me_4N\ ICl_2$ to give *p*-iodoanisole exclusively, see Hajipour, A.R.; Arbabian, M.; Ruoho, A.E. *J. Org. Chem.* ***2002***, *67*, 8622.

as unprotected aniline derivatives[293]). Iodination can also be accomplished by treatment of the substrate with NCI and sulfuric acid,[294] NIS and trifluoroacetic acid,[295] KI/KIO_3 in aqueous methanol,[296] I_2 in the presence of copper salts,[297] Al_2O_3,[298] and NaI with an iron catalyst.[299] Sodium periodate and iodine was used to iodinate β-carbolines.[300] Sodium iodide in liquid NO_2 can be used to iodinate aniline derivatives.[301] A solvent-free iodination was accomplished using $NaICl_2$ and an *N*-bromoammonium salt.[302] Another solvent-free iodination used I_2 with $Bi(NO_3)_3$ on silica gel.[303] Iodine with Selectfluor also leads to iodination of aromatic compounds.[304]

The actual attacking species is less clear than with bromine or chlorine. Iodine itself is too unreactive, except for active species, such as phenols, where there is good evidence that I_2 is the attacking entity.[305] There is evidence that AcOI may be the attacking entity when peroxyacetic acid is the oxidizing agent,[306] and I_3^+ when SO_3 or HIO_3 is the oxidizing agent.[307] The I^+ ion has been implicated in several procedures.[308] For an indirect method for accomplishing aromatic iodination, see **12-31**.

Note that conversion of aniline derivatives to the corresponding para aryllithium, followed by reaction with $B(OMe)_3$ and then bromine at −78°C gave *p*-bromoaniline.[309]

3. *Fluorine*. Direct fluorination of aromatic rings with F_2 is not feasible at room temperature, because of the extreme reactivity of F_2.[310] It has been accomplished at low temperatures (e.g., −70 to −20°C, depending on the

[293]Kosynkin, D.V.; Tour, J.M. *Org. Lett.* ***2001***, *3*, 991.

[294]Chaikovskii, V.K.; Shorokhodov, V.I.; Filimonov, V.D. *Russ. J. Org. Chem.* ***2001***, *37*, 1503.

[295]Castanet, A.-S.; Colobert, F.; Broutin, P.-E. *Tetrahedron Lett.* ***2002***, *43*, 5047.

[296]Adimurthy, S.; Ramachandraiah, G.; Ghosh, P.K.; Bedekar, A.V. *Tetrahedron Lett.* ***2003***, *44*, 5099.

[297]Baird Jr., W.C.; Surridge, J.H. *J. Org. Chem.* ***1970***, *35*, 3436; Horiuchi, C.A.; Satoh, J.Y. *Bull. Chem. Soc. Jpn.* ***1984***, *57*, 2691; Makhon'kov, D.I.; Cheprakov, A.V.; Rodkin, M.A.; Beletskaya, I.P. *J. Org. Chem. USSR* ***1986***, *22*, 1003.

[298]Pagni, R.M.; Kabalka, G.W.; Boothe, R.; Gaetano, K.; Stewart, L.J.; Conaway, R.; Dial, C.; Gray, D.; Larson, S.; Luidhart, T. *J. Org. Chem.* ***1988***, *53*, 4477.

[299]Firouzabadi, H.; Iranpoor, N.; Shiri, M. *Tetrahedron Lett.* ***2003***, *44*, 8781.

[300]Bonesi, S.M.; Erra-Balsells, R. *J. Heterocyclic Chem.* ***2001***, *38*, 77.

[301]Suzuki, H.; Nonoyama, N. *Tetrahedron Lett.* ***1998***, *39*, 4533.

[302]Hajipour, A.R.; Ruoho, A.E. *Org. Prep. Proceed. Int.* ***2002***, *34*, 647.

[303]Alexander, V.M.; Khandekar, A.C.; Samant, S.D. *Synlett* ***2003***, 1895.

[304]Stavber, S.; Kralj, P.; Zupan, M. *Synlett* ***2002***, 598.

[305]Grovenstein, Jr., E.; Aprahamian, N.S.; Bryan, C.J.; Gnanapragasam, N.S.; Kilby, D.C.; McKelvey Jr., J.M.; Sullivan, R.J. *J. Am. Chem. Soc.* ***1973***, *95*, 4261.

[306]Ogata, Y.; Urasaki, I. *J. Chem. Soc. C* ***1970***, 1689.

[307]Arotsky, J.; Butler, R.; Darby, A.C. *J. Chem. Soc. C* ***1970***, 1480.

[308]Galli, C. *J. Org. Chem.* ***1991***, *56*, 3238.

[309]Zhao, J.; Jia, X.; Zhai, H. *Tetrahedron Lett.* ***2003***, *44*, 9371.

[310]For a monograph on fluorinating agents, see German, L.; Zemskov, S. *New Fluorinating Agents in Organic Synthesis*, Springer, NY, ***1989***. For reviews of F_2 in organic synthesis see Purrington, S.T.; Kagen, B.S.; Patrick, T.B. *Chem. Rev.* ***1986***, *86*, 997; Grakauskas, V. *Intra-Sci. Chem. Rep.* ***1971***, *5*, 85. For a review of fluoroaromatic compounds, see Hewitt, C.D.; Silvester, M.J. *Aldrichimica Acta* ***1988***, *21*, 3.

substrate),[311] but the reaction is not yet of preparative significance. Fluorination has also been reported with acetyl hypofluorite CH_3COOF (generated from F_2 and sodium acetate),[312] with XeF_2,[313] and with an *N*-fluoroperfluoroalkyl sulfonamide, for example $(CF_3SO_2)_2NF$.[314] Pyridine has been converted to 2-fluoropyridine with $F_2/I_2/NEt_3$ in 1,1,2-trichloro-1,2,2-trifluoroethane.[315] However, none of these methods seems likely to displace the Schiemann reaction (**13-23**; heating diazonium tetrafluoroborates) as the most common method for introducing fluorine into aromatic rings.

The overall effectiveness of reagents in aromatic substitution is $Cl_2 > BrCl > Br_2 > ICl > I_2$.

OS **I**, 111, 121, 123, 128, 207, 323; **II**, 95, 97, 100, 173, 196, 343, 347, 349, 357, 592; **III**, 132, 134, 138, 262, 267, 575, 796; **IV**, 114, 166, 256, 545, 547, 872, 947; **V**, 117, 147, 206, 346; **VI**, 181, 700; **VIII**, 167; **IX**, 121, 356. Also see, OS **II**, 128.

E. Carbon Electrophiles

In the reactions in this section, a new carbon–carbon bond is formed. With respect to the aromatic ring, they are electrophilic substitutions, because a positive species attacks the ring. We treat them in this manner because it is customary. However, with respect to the electrophile, most of these reactions are nucleophilic substitutions, and what was said in Chapter 10 is pertinent to them.

11-11 Friedel–Crafts Alkylation

Alkylation or **Alkyl-de-hydrogenation**

$$ArH + RCl \xrightarrow{AlCl_3} ArCl$$

The alkylation of aromatic rings, called *Friedel–Crafts alkylation*, is a reaction of very broad scope.[316] The most important reagents are alkyl halides, alkenes, and

[311]Grakauskas, V. *J. Org. Chem.* ***1970***, *35*, 723; Cacace, F.; Giacomello, P.; Wolf, A.P. *J. Am. Chem. Soc.* ***1980***, *102*, 3511; Stavber, S.; Zupan, M. *J. Org. Chem.* ***1983***, *48*, 2223. See also, Purrington, S.T.; Woodard, D.L. *J. Org. Chem.* ***1991***, *56*, 142.

[312]See Hebel, D.; Lerman, O.; Rozen, S. *Bull. Soc. Chim. Fr.* ***1986***, 861; Visser, G.W.M.; Bakker, C.N.M.; van Halteren, B.W.; Herscheid, J.D.M.; Brinkman, G.A.; Hoekstra, A. *J. Org. Chem.* ***1986***, *51*, 1886.

[313]Shaw, M.J.; Hyman, H.H.; Filler, R. ***1970***, *92*, 6498; *J. Org. Chem.* ***1971***, *36*, 2917; Mackenzie, D.R.; Fajer, J. *J. Am. Chem. Soc.* ***1970***, *92*, 4994; Filler, R. *Isr. J. Chem.* ***1978***, *17*, 71.

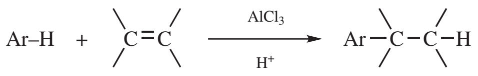
[314]Singh, S.; DesMarteau, D.D.; Zuberi, S.S.; Witz, M.; Huang, H. *J. Am. Chem. Soc.* ***1987***, *109*, 7194.

[315]Chambers, R.D.; Parsons, M.; Sandford, G.; Skinner, C.J.; Atherton, M.J.; Moilliet, J.S. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 803.

[316]For a monograph, see Roberts, R.M.; Khalaf, A.A. *Friedel–Crafts Alkylation Chemistry*, Marcel Dekker, NY, ***1984***. For a treatise on Friedel–Crafts reactions in general, see Olah, G.A. *Friedel–Crafts and Related Reactions*, Wiley, NY, ***1963–1965***. Volume 1 covers general aspects, such as catalyst activity, intermediate complexes, and so on. Volume 2 covers alkylation and related reactions. In this volume, the various reagents are treated by the indicated authors as follows: alkenes and alkanes, Patinkin, S.H.; Friedman, B.S. pp. 1–288; dienes and substituted alkenes, Koncos, R.; Friedman, B.S. pp. 289–412; alkynes, Franzen, V. pp. 413–416; alkyl halides, Drahowzal, F.A. pp. 417–475; alcohols and ethers, Schriesheim, A. pp. 477–595; sulfonates and inorganic esters, Drahowzal, F.A. pp. 641–658. For a monograph in which five chapters of the above treatise are reprinted and more recent material added, see Olah, G.A. *Friedel–Crafts Chemistry*, Wiley, NY, ***1973***.

alcohols, but other types of reagent have also been employed.[316] Tertiary halides are particularly good substrates since they form relatively stable tertiary carbocations. *tert*-Butyl chloride reacts with phenetole in the presence of a $ReBr(CO)_5$ catalyst, for example, to give the 4-*tert*-butyl isomer as the major product.[317] When alkyl halides are used, the reactivity order is F > Cl > Br > I.[318] This trend can be seen in reactions of dihalo compounds, such as $FCH_2CH_2CH_2Cl$, which react with benzene to give $PhCH_2CH_2CH_2Cl$[319] when the catalyst is BCl_3. By the use of this catalyst, it is therefore possible to place a haloalkyl group on a ring (see also, **11-14**).[320] Di- and trihalides, when all the halogens are the same, usually react with more than one molecule of an aromatic compound; it is usually not possible to stop the reaction earlier.[321] Thus, benzene with CH_2Cl_2 gives not $PhCH_2Cl$, but Ph_2CH_2; benzene with $CHCl_3$ gives Ph_3CH. With CCl_4, however, the reaction stops when only three rings have been substituted to give Ph_3CCl. Functionalized alkyl halides, such as $ClCH(SEt)CO_2Et$, undergo Friedel–Crafts alkylation.[322] Interestingly, benzyl chloride was converted to diphenylmethane in benzene at 130°C with 10 atm of CO,[323] and also with a $LiB(C_6F_5)_4$ catalyst.[324]

Alkenes are especially good alkylating agents, generally proceeding by formation of an intermediate carbocation that reacts with the electron rich aromatic ring, and the final product (**39**) incorporates a H and Ar from ArH to a C=C double bond. Many variations are possible. This reaction has been accomplished in an ionic liquid, using $Sc(OTf)_3$ as the catalyst.[325] Intramolecular versions lead to polycyclic aromatic compounds.[326] Benzene reacted with 1,2,3,6-tetrahydropyridine in the presence of trifluoromethanesulfonic acid to give 4-phenylpiperidine.[327]



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[317]Nishiyama, Y.; Kakushou, F.; Sonoda, N. *Bull. Chem. Soc. Jpn.* ***2000***, *73*, 2779.

[318]For example, see Calloway, N.O. *J. Am. Chem. Soc.* ***1937***, *59*, 1474; Brown, H.C.; Jungk, H. *J. Am. Chem. Soc.* ***1955***, *77*, 5584.

[319]Olah, G.A.; Kuhn, S.J. *J. Org. Chem.* ***1964***, *29*, 2317.

[320]For a review of selectivity in this reaction, see Olah, G.A., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 1, Wiley, NY, ***1963***, pp. 881–905. This review also covers the case of alkylation versus acylation.

[321]It has proven possible in some cases. Thus, arenes ArH have been converted to $ArCCl_3$ with CCl_4 and excess $AlCl_3$: Raabe, D.; Hörhold, H. *J. Prakt. Chem.* ***1987***, *329*, 1131; Belen'kii, L.I.; Brokhovetsky, D.B.; Krayushkin, M.M. *Chem. Scr.*, ***1989***, *29*, 81.

[322]For the reaction of anisole using a $Yb(OTf)_3$ catalyst, see Sinha, S.; Mandal, B.; Chandrasekaran, S. *Tetrahedron Lett.* ***2000***, *41*, 9109.

[323]Ogoshi, S.; Nakashima, H.; Shimonaka, K.; Kurosawa, H. *J. Am. Chem. Soc.* ***2001***, *123*, 8626.

[324]Mukaiyama, T.; Nakano, M.; Kikuchi, W.; Matsuo, J.-i. *Chem. Lett.* ***2000***, 1010.

[325]In emim SbF_6, 1-ethyl-3-mthylimidazolium: Song, C.E.; Shim, W.H.; Roh, E.J.; Choi, J.H. *Chem. Commun.* ***2000***, 1695.

[326]For a $RuCl_3$/AgOTf catalyzed version, see Youn, S.W.; Pastine, S.J.; Sames, D. *Org. Lett.* ***2004***, *6*, 581.

[327]Klumpp, D.A.; Beauchamp, P.S.; Sanchez Jr., G.V.; Aguirre, S.; de Leon, S. *Tetrahedron Lett.* ***2001***, *42*, 5821.

When 4-methoxyphenol reacted with isobutylene (electrolysis with 3 *M* $LiClO_4$ in nitromethane and acetic acid, initial reaction with the phenolic oxygen generated an ether moiety and the resulting carbocation was attacked by the aromatic ring to form a benzofuran.[328] Acetylene reacts with 2 mol of aromatic compound to give 1,1-diarylethanes, and phenylacetylene reacted to give 1,1-diarylethenes with a $Sc(OTf)_3$ catalyst.[329] Variations are possible here as well. Phenol reacted with trimethylsilylethyne, in the presence of $SnCl_4$ and 50% BuLi, at 105°C, to give the 2-vinyl phenolic derivative.[330] A palladium-catalyzed reaction of ethyl propiolate and *p*-xylene, with trifluoroacetic acid, gave the 3-arylalkenyl ester.[331] A ruthenium catalyzed intramolecular reaction with a pendant alkyne unit led to a dihydronapthalene derivative.[332]

Alcohols are more active than alkyl halides, but if a Lewis acid catalyst is used more catalyst is required, since the catalyst complexes with the OH group. However, proton acids, such as H_2SO_4, are often used to catalyze alkylation with alcohols. An intramolecular cyclization was reported from an allylic alcohol, using P_2O_5, to give indene derivatives.[333] When carboxylic esters are the reagents, there is competition between alkylation and acylation (**11-17**). This competition can often be controlled by choice of catalyst, and alkylation is usually favored, but carboxylic esters are not often employed in Friedel–Crafts reactions. Other alkylating agents are ethers, thiols, sulfates, sulfonates, alkyl nitro compounds,[334] and even alkanes and cycloalkanes, under conditions where these are converted to carbocations. Notable here are ethylene oxide, which puts the CH_2CH_2OH group onto the ring,[335] and cyclopropyl[336] units. For all types of reagent the reactivity order is allylic $\sim$ benzylic $>$ tertiary $>$ secondary $>$ primary.

[328]Chiba, K.; Fukuda, M.; Kim, S.; Kitano, Y.; Toda, M. *J. Org. Chem.* ***1999***, *64*, 7654. For a variation using a seleno ether to form a fused six-membered ring, see Abe, H.; Koshiba, N.; Yamasaki, A.; Harayama, T. *Heterocycles* ***1999***, *51* 2301. See also, Shen, Y.; Atobe, M.; Fuchigami, T. *Org. Lett.* ***2004***, *6*, 2441.

[329]Tsuchimoto, T.; Maeda, T.; Shirakawa, E.; Kawakami, Y. *Chem. Commun.* ***2000***, 1573.

[330]Kobayasshi, K.; Yamaguchi, M. *Org. Lett.* ***2001***, *3*, 241.

[331]Jia, C.; Lu, W.; Oyamada, J.; Kitamura, T.; Katsuda, K.; Irie, M.; Fujiwara, Y. *J. Am. Chem. Soc.* ***2000***, *122*, 7252.

[332]Chatani, N.; Inoue, H.; Ikeda, T.; Murai, S. *J. Org. Chem.* ***2000***, *65*, 4913. For a $GaCl_3$ catalyzed version, see Inoue, H.; Chatani, N.; Murai, S. *J. Org. Chem.* ***2002***, *67*, 1414. For a mercuric salt catalyst, see Nishizawa, M.; Takao, H.; Yadav, V.K.; Imagawa, H.; Sugihara, T. *Org. Lett.* ***2003***, *5*, 4563. For a BF_3 catalyzed version that generates allenes, see Ishikawa, T.; Manabe, S.; Aikawa, T.; Kudo, T.; Saito, S. *Org. Lett.* ***2004***, *6*, 2361. See also, Fillion, E.; Carson, R.J.; Trépanier, V.E.; Goll, J.M.; Remorova, A.A. *J. Am. Chem. Soc.* ***2004***, *126*, 15354.

[333]Basavaiah, D.; Bakthadoss, M.; Reddy, G.J. *Synthesis* ***2001***, 919. For a variation involving a propargylic alcohols with a ruthenium catalyst and ammonium tetrafluoroborate, see Nishibayashi, Y.; Joshikawa, M.; Inada, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* ***2002***, *124*, 11846.

[334]Bonvino, V.; Casini, G.; Ferappi, M.; Cingolani, G.M.; Pietroni, B.R. *Tetrahedron* ***1981***, *37*, 615.

[335]Taylor, S.K.; Dickinson, M.G.; May, S.A.; Pickering, D.A.; Sadek, P.C. *Synthesis* ***1998***, 1133. See also, Brandänge, S.; Bäckvall, J.-E.; Leijonmarck, H. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 2051.

[336]Patra, P.K.; Patro, B.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* ***1993***, *34*, 3951.

Regardless of which reagent is used, a catalyst is nearly always required.[337] Aluminum chloride and boron trifluoride are the most common, but many other Lewis acids have been used, and also proton acids, such as HF and H_2SO_4.[338] For active halides a trace of a less active catalyst, such as $ZnCl_2$, may be enough. For an unreactive halide, such as chloromethane, a more powerful catalyst, such as $AlCl_3$, is needed, and in larger amounts. In some cases, especially with alkenes, a Lewis acid catalyst causes reaction only if a small amount of proton-donating cocatalyst is present. Catalysts have been arranged in the following order of overall reactivity: $AlBr_3 > AlCl_3 > GaCl_3 > FeCl_3 > SbCl_5$[339]$> ZrCl_4, SnCl_4 > BCl_3, BF_3, SbCl_3$;[340] but the reactivity order in each case depends on the substrate, reagent, and conditions.

Alkyl mesylates undergo alkylation reaction with benzene rings in the presence of $Sc(OTf)_3$.[341] Allylic acetates undergo alkylation with $Mo(CO)_6$[342] and allylic chlorides react in the presence of $ZnCl_2/SiO_2$.[343] Montmorillonite clay (K10) is an effective medium for alkylation reactions.[344] Nafion-H, a super acidic perfluorinated resin sulfonic acid, is a very good catalyst for gas phase alkylations with alkyl halides, alcohols,[345] or alkenes.[346]

Friedel–Crafts alkylation is unusual among the principal aromatic substitutions in that the entering group is activating (the product is more reactive than the starting aromatic substrate), and di- and polyalkylation are frequently observed. However, the activating effect of simple alkyl groups (e.g., ethyl, isopropyl) is only ~1.5–3 times as fast as benzene for Friedel–Crafts alkylations,[347] so it is often possible to obtain high yields of monoalkyl product.[348] Actually, the fact that di- and polyalkyl derivatives are frequently obtained is not due to the small difference in reactivity, but to the circumstance that alkylbenzenes are preferentially soluble in the catalyst layer, where the reaction actually takes place.[349] This factor can be removed by the use of a suitable solvent, by high temperatures, or by high–speed stirring.

[337]There are a few exceptions. Certain alkyl and vinylic triflates alkylate aromatic rings without a catalyst, see Gramstad, T.; Haszeldine, R.N. *J. Chem. Soc.* ***1957***, 4069; Olah, G.A.; Nishimura, J. *J. Am. Chem. Soc.* ***1974***, *96*, 2214; Stang, P.J.; Anderson, A.G. *J. Am. Chem. Soc.* ***1978***, *100*, 1520.

[338]For a review of catalysts and solvents in Friedel–Crafts reactions, see Olah, G.A., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 1, Wiley, NY, ***1963***, pp. 201–366, 853–881.

[339]For a review of $SbCl_5$ as a Friedel–Crafts catalyst, see Yakobson, G.G.; Furin, G.G. *Synthesis* ***1980***, 345.

[340]Russell, G.A. *J. Am. Chem. Soc.* ***1959***, *81*, 4834.

[341]Kotsuki, H.; Oshisi, T.; Inoue, M.; Kojima, T. *Synthesis* ***1999***, 603; Singh, R.P.; Kamble, R.M.; Chandra, K.L.; Saravanani, P.; Singh, V.K. *Tetrahedron* ***2001***, *57*, 241.

[342]Shimizu, I.; Sakamoto, T.; Kawaragi, S.; Maruyama, Y.; Yamamoto, A. *Chem. Lett.* ***1997***, 137.

[343]Kodomari, M.; Nawa, S.; Miyoshi, T. *J. Chem. Soc. Chem.Commun.* ***1995***, 1895.

[344]Sieskind, O.; Albrecht, P. *Tetrahedron Lett.* ***1993***, *34*, 1197.

[345]Aleksiuk, O.; Biali, S.E. *Tetrahedron Lett.* ***1993***, *34*, 4857.

[346]For a review of Nafion-H in organic synthesis, see Olah, G.A.; Iyer, P.S.; Prakash, G.K.S. *Synthesis* ***1986***, 513.

[347]Condon, F.E. *J. Am. Chem. Soc.* ***1948***, *70*, 2265; Olah, G.A.; Kuhn, S.J.; Flood, S.H. *J. Am. Chem. Soc.* ***1962***, *84*, 1688.

[348]See Davister, M.; Laszlo, P. *Tetrahedron Lett.* ***1993***, *34*, 533 for examples of paradoxical selectivity in Friedel–Crafts alkylation.

[349]Francis, A.W. *Chem. Rev.* ***1948***, *43*, 257.

It is important to note that the OH, OR, NH_2, and so on groups do not facilitate the reaction, since most Lewis acid catalysts coordinate with these basic groups. Although phenols give the usual Friedel–Crafts reactions, orienting ortho and para, the reaction is very poor for aniline derivatives. However, amines can undergo the reaction if alkenes are used as reagents and aluminum anilides as catalysts.[350] In this method, the catalyst is prepared by treating the amine to be alkylated with $\frac{1}{3}$ equivalent of $AlCl_3$. A similar reaction can be performed with phenols, though here the catalyst is $Al(OAr)_3$.[351] Primary aromatic amines (and phenols) can be methylated regioselectively in the ortho position by an indirect method (see **11-23**). For an indirect method for regioselective ortho methylation of phenols (see p. 1247).

Naphthalene and other fused ring compounds are so reactive that they react with the catalyst, and therefore tend to give poor yields in Friedel–Crafts alkylation. Heterocyclic rings are also tend to be poor substrates for the reaction. Although some furans and thiophenes have been alkylated, polymerization is quite common, and a true alkylation of a pyridine or a quinoline has never been described.[352] *N*-Methylpyrrole reacted with the C=C unit of methacrolein in the presence of a chiral catalyst (a chiral Friedel–Crafts catalyst) to give the 2-alkylated pyrrole, with good enantioselectivity.[353] Alkylation at C-5 of 2-trimethylsilylfuran was accomplished using the carbocation $[(p\text{-MeOC}_6H_4)_2CH^+ \text{ OTf}]$ and Proton Sponge (see p. 386).[354] Although mechanistically different, an intramolecular cyclization of an *N*-allylic pyrrole was accomplished using a rhodium catalyst with 100 atm of CO/H_2.[355] Note that alkylation of pyridine and other nitrogen heterocycles can be accomplished by a free radical[356] (**14-19**) and by a nucleophilic method (**13-17**). A variation generates an electrophilic species on the aromatic substrate. The reaction of isoquinoline with $ClCO_2Ph$ and AgOTf, followed by reaction with an allylic silane, led to a 2-allylic dihydroisoquinoline.[357]

In most cases, meta-directing groups make the ring too inactive for alkylation. Nitrobenzene cannot be alkylated, and there are only a few reports of successful Friedel–Crafts alkylations when electron-withdrawing groups are present.[358] This is not because the attacking species is not powerful enough; indeed we have

[350]For a review, see Stroh, R.; Ebersberger, J.; Haberland, H.; Hahn, W. *Newer Methods Prep. Org. Chem.* ***1963***, *2*, 227. This article also appeared in *Angew. Chem.* ***1957***, *69*, 124.

[351]Koshchii, V.A.; Kozlikovskii, Ya.B.; Matyusha, A.A. *J. Org. Chem. USSR* ***1988***, *24*, 1358; Laan, J.A.M.; Giesen, F.L.L.; Ward, J.P. *Chem. Ind. (London)* ***1989***, 354. For a review, see Stroh, R.; Seydel, R.; Hahn, W. *Newer Methods Prep. Org. Chem.* ***1963***, *2*, 337. This article also appeared in *Angew. Chem.* ***1957***, *69*, 669.

[352]Drahowzal, F.A., in Olah, G.A., *Friedel–Crafts and Related Reactions*, Vol. 2, Wiley, NY, ***1964***, p. 433.

[353]Paras, N.A.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2001***, *123*, 4370.

[354]Herrlich, M.; Hampel, N.; Mayr, H. *Org. Lett.* ***2001***, *3*, 1629.

[355]Settambalo, R.; Caiazzo, A.; Lazzaroni, R. *Tetraehdron Lett.* ***2001***, *42*, 4045.

[356]For a silyl-mediated reaction with 2-bromopyridine and 2 equivalents of AIBN, see Núñez, A.; Sánchez, A.; Burgos, C.; Alvarez-Builla, J. *Tetrahedron* ***2004***, *60*, 6217.

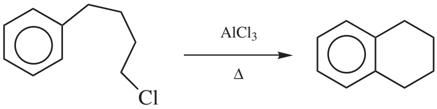
[357]Yamaguchi, R.; Nakayasu, T.; Hatano, B.; Nagura, T.; Kozima, S.; Fujita, K.-i. *Tetrahedron* ***2001***, *57*, 109.

[358]Campbell Jr., B.N.; Spaeth, E.C. *J. Am. Chem. Soc.* ***1959***, *81*, 5933; Yoneda, N.; Fukuhara, T.; Takahashi, Y.; Suzuki, A. *Chem. Lett.* ***1979***, 1003; Shen, Y.; Liu, H.; Chen,Y. *J. Org. Chem.* ***1990***, *55*, 3961.

seen (p. 681) that alkyl cations are among the most powerful of electrophiles. The difficulty is caused by the fact that, with inactive substrates, degradation and polymerization of the electrophile occurs before it can attack the ring. However, if an activating and a deactivating group are both present on a ring, Friedel–Crafts alkylation can be accomplished.[359] Aromatic nitro compounds can be methylated by a nucleophilic mechanism (**13-17**).

The intermediate for Friedel–Crafts alkylation is a carbocation, and rearrangement to a more stable cation can be quite facile. Therefore, rearrangement of the alkyl substrate occurs frequently and is an important synthetic limitation of Friedel–Crafts alkylation. For example, benzene treated with *n*-propyl bromide gives mostly isopropylbenzene (cumene) and much less *n*-propylbenzene. Rearrangement is usually in the order primary → secondary → tertiary and usually occurs by migration of the smaller group on the adjacent carbon. Therefore, in the absence of special electronic or resonance influences on the migrating group (such as phenyl), H migrates before methyl, which migrates before ethyl, and so on (see discussion of rearrangement mechanisms in Chapter 18). It is therefore not usually possible to put a primary alkyl group (other than methyl[360] and ethyl) onto an aromatic ring by Friedel–Crafts alkylation. Because of these rearrangements, *n*-alkylbenzenes are often prepared by *acylation* (**11-17**), followed by reduction (**19-61**).

An important use of the Friedel–Crafts alkylation reaction is to effect ring closure.[361] The most common method is to heat with aluminum chloride an aromatic compound having a halogen, hydroxy, or alkene group in the proper position, as, for example, in the preparation of tetralin, **40**.



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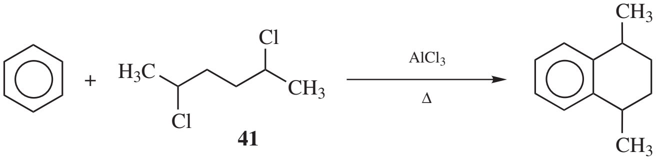
Another way of effecting ring closure through Friedel–Crafts alkylation is to use a reagent containing two groups, such as **41**.



41

These reactions are most successful for the preparation of six-membered rings,[362] though five- and Seven-membered rings have also been closed in this

[359]Olah, G.A. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 1, Wiley, NY, ***1963***, p. 34.

[360]For methylation using a specialized aluminum reagent, with a nickel catalyst, see Gelman, D.; Schumann, H.; Blum, J. *Tetrahedron Lett.* ***2000***, *41*, 7555.

[361]For a review, see Barclay, L.R.C., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 2, Wiley, NY, ***1964***, pp. 785–977.

[362]See Khalaf, A.A.; Roberts, R.M. *J. Org. Chem.* ***1966***, *31*, 89.

manner. For other Friedel–Crafts ring-closure reactions, see **11-15**, **11-13**, and **11-17**. An interesting variation in this reaction showed that *N*-acyl aniline derivatives, upon treatment with $Et_2P(=O)H$ in water and a water soluble initiator (V-501) led to an intramolecular alkylation reaction to give an amide.[363]

As mentioned above, the electrophile in Friedel–Crafts alkylation is a carbocation, at least in most cases.[364] This is in accord with the knowledge that carbocations rearrange in the direction primary → secondary → tertiary (see Chapter 18). In each case the cation is formed from the attacking reagent and the catalyst. For the three most important types of reagent these reactions are

From alkyl halides: $RCl + AlCl_3 \longrightarrow R^+ + AlCl_4^-$

From alcohols[365] and Lewis acids: $ROH + AlCl_3 \longrightarrow ROAlCl_2 \longrightarrow R^+ + {}^-OAlCl_2$

From alcohols and proton acids: $ROH + H^+ \longrightarrow ROH_2^+ \longrightarrow R^+ + H_2O$

From alkenes (a supply of protons is usually required): $>C{=}C< + H^+ \longrightarrow H{-}\overset{|}{C}{-}C^{\oplus}$

There is direct evidence, from ir and nmr spectra, that the *tert*-butyl cation is quantitatively formed when *tert*-butyl chloride reacts with $AlCl_3$ in anhydrous liquid HCl.[366] In the case of alkenes, Markovnikov's rule (p. 1019) is followed. Carbocation formation is particularly easy from some reagents, because of the stability of the cations. Triphenylmethyl chloride[367] and 1-chloroadamantane[368] alkylate activated aromatic rings (e.g., phenols, amines) with no catalyst or solvent. Ions as stable as this are less reactive than other carbocations and often attack only active substrates. The tropylium ion, for example, alkylates anisole, but not benzene.[369] It was noted on p. 476 that relatively stable vinylic cations can be generated from certain vinylic compounds. These have been used to introduce vinylic groups into aryl substrates.[370] Lewis acids, such as BF_3[371] or $AlEt_3$,[372] can also be used to alkylation of aromatic rings with alkene units.

[363]Khan, T.A.; Tripoli, R.; Crawford, J.T.; Martin, C.G. Murphy, J.A. *Org. Lett.* ***2003***, *5*, 2971.

[364]For a discussion of the mechanism, see Taylor, R. *Electrophilic Aromatic Substitution*, *Electrophilic Aromatic Substitution*, Wiley, NY, ***1990***, pp. 188–213.

[365]See Bijoy, P.; Subba Rao, G.S.R. *Tetrahedron Lett.* ***1994***, *35*, 3341 for a double Friedle–Crafts alkylation involving a diol.

[366]Kalchschmid, F.; Mayer, E. *Angew. Chem. Int. Ed.* ***1976***, *15*, 773.

[367]See, for example, Hart, H.; Cassis, F.A. *J. Am. Chem. Soc.* ***1954***, *76*, 1634; Hickinbottom, W.J. *J. Chem. Soc.* ***1934***, 1700; Chuchani, G.; Zabicky, J. *J. Chem. Soc. C* ***1966***, 297.

[368]Takaku, M.; Taniguchi, M.; Inamoto, Y. *Synth. Commun.* ***1971***, *1*, 141.

[369]Bryce-Smith, D.; Perkins, N.A. *J. Chem. Soc.* ***1962***, 5295.

[370]Kitamura, T.; Kobayashi, S.; Taniguchi, H.; Rappoport, Z. *J. Org. Chem.* ***1982***, *47*, 5503.

[371]Majetich, G.; Liu, S.; Siesel, D. *Tetrahedron Lett.* ***1995***, *36*, 4749; Majetich, G.; Zhang, Y.; Feltman, T.L.; Belfoure, V. *Tetrahedron Lett.* ***1993***, *34*, 441; Majetich, G.; Zhang, Y.; Feltman, T.L.; Duncan Jr., S. *Tetrahedron Lett.* ***1993***, *34*, 445.

[372]Majetich, G.; Zhang, Y.; Liu, S. *Tetrahedron Lett.* ***1994***, *35*, 4887.

There is considerable evidence that many Friedel–Crafts alkylations, especially with primary reagents, do not go through a completely free carbocation. The ion may exist as a tight ion pair with, say, $AlCl_4^-$ as the counterion or as a complex. Among the evidence is that methylation of toluene by methyl bromide and methyl iodide gave different ortho/para/meta ratios,[373] although we would expect the same ratios if the same species attacked in each case. Other evidence is that, in some cases, the reaction kinetics are third order; first order each in aromatic substrate, attacking reagent, and catalyst.[374] In these instances a mechanism in which the carbocation is slowly formed and then rapidly attacked by the aromatic ring is ruled out since, in such a mechanism, the substrate would not appear in the rate expression. Since it is known that free carbocations, once formed, are rapidly attacked by the ring (acting as a nucleophile), there are no free carbocations here. Another possibility (with alkyl halides) is that some alkylations take place by an S_N2 mechanism (with respect to the halide), in which case no carbocations would be involved at all. However, a completely S_N2 mechanism requires inversion of configuration. Most investigations of Friedel–Crafts stereochemistry, even where an S_N2 mechanism might most be expected, have resulted in total racemization, or at best a few percent inversion. A few exceptions have been found,[375] most notably where the reagent was optically active propylene oxide, in which case 100% inversion was reported.[376]

Rearrangement is possible even with a non-carbocation mechanism. The rearrangement could occur *before* the attack on the ring takes place. It has been shown that treatment of $CH_3{}^{14}CH_2Br$ with $AlBr_3$ in the absence of any aromatic compound gave a mixture of the starting material and $^{14}CH_3CH_2Br$.[377] Similar results were obtained with $PhCH_2{}^{14}CH_2Br$, in which case the rearrangement was so fast that the rate could be measured only below −70°C.[378] Rearrangement could also occur *after* formation of the product, since alkylation is reversible (see **11-33**).[379]

See **14-17** and **14-19** for free-radical alkylation.

A variation of this reaction involves acylation of a β-keto ester, followed by Friedel–Crafts cyclization of the ketone moiety. The product is a coumarin **43**, in what is known as the *Pechmann condensation.*[380] Isolation of esters, such as **42**, is not

[373]Brown, H.C.; Jungk, H. *J. Am. Chem. Soc.* ***1956***, *78*, 2182.

[374]For examples see Choi, S.U.; Brown, H.C. *J. Am. Chem. Soc.* ***1963***, *85*, 2596.

[375]Some instances of retention of configuration have been reported; a neighboring-group mechanism is likely in these cases: see Masuda, S.; Nakajima, T.; Suga, S. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 1089; Effenberger, F.; Weber, T. *Angew. Chem. Int. Ed.* ***1987***, *26*, 142.

[376]Nakajima, T.; Suga, S.; Sugita, T.; Ichikawa, K. *Tetrahedron* ***1969***, *25*, 1807. For cases of almost complete inversion, with acyclic reagents, see Piccolo, O.; Azzena, U.; Melloni, G.; Delogu, G.; Valoti, E. *J. Org. Chem.* ***1991***, *56*, 183.

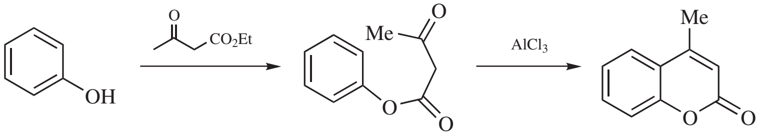
[377]Adema, E.H.; Sixma, F.L.J. *Recl. Trav. Chim. Pays-Bas* ***1962***, *81*, 323, 336.

[378]For a review of the use of isotopic labeling to study Friedel–Crafts reactions, see Roberts, R.M.; Gibson, T.L. *Isot. Org. Chem.* ***1980***, *5*, 103.

[379]For an example, see Lee, C.C.; Hamblin, M.C.; Uthe, J.F. *Can. J. Chem.* ***1964***, *42*, 1771.

[380] von Pechmann, H.; Duisberg, C. *Berchti* ***1883***, *16*, 2119; Sethna, S.; Shah, N.M. *Chem. Rev.* ***1945***, *36*, 1 (see p 10); Sethna, S.; Phadke, R. *Org. React.* ***1953***, *7*, 1.

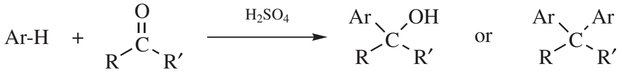
always necessary, and protonic acids can be used rather than Lewis acids. The Pechmann condensation is facilitated by the presence of hydroxyl (OH), dimethylamino (NMe_2) and alkyl groups meta to the hydroxyl of the phenol.[381] The reaction has been accomplished using microwave irradiation on graphite/ Montmorillonite K10.[382] Pechmann condensation in an ionic liquid using ethyl acetate has also been reported.[383]



42 43

OS **I**, 95, 548; **II**, 151, 229, 232, 236, 248; **III**, 343, 347, 504, 842; **IV**, 47, 520, 620, 665, 702, 898, 960; **V**, 130, 654; **VI**, 109, 744.

11-12 Hydroxyalkylation or Hydroxyalkyl-de-hydrogenation



When an aldehyde, ketone, or other carbonyl-containing substrate is treated with a protonic or Lewis acid, an oxygen-stabilized cation is generated. In the presence of an aromatic ring, Friedel–Crafts type alkylation occurs. The condensation of aromatic rings with aldehydes or ketones is called *hydroxyalkylation*.[384] The reaction can be used to prepare alcohols,[385] though more often the alcohol initially produced reacts with another molecule of aromatic compound (**11-11**) to give diarylation. For this the reaction is quite useful, an example being the preparation of DDT, **44**:

44

The diarylation reaction is especially common with phenols (the diaryl product here is called a bisphenol). The reaction is normally carried out in alkaline solution on

[381]Shah, M.M.; Shah, R.C. *Ber.* ***1938***, *71*, 2075; Miyano, M.; Dorn, C.R. *J. Org. Chem.* ***1972***, *37*, 259.

[382]Frère, S.; Thiéry, V.; Besson, T. *Tetrahedron Lett.* ***2001***, *42*, 2791.

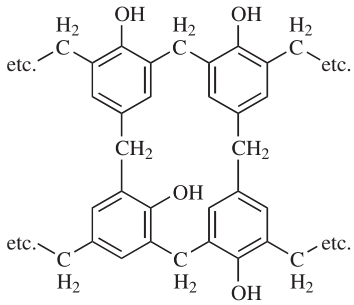
[383]In [bmim]Cl·$2AlCl_3$, 1-butyl-3-methylimidazolium chloroaluminate: Potdar, M.K.; Mohile, S.S.; Salunkhe, M.M. *Tetrahedron Lett.* ***2001***, *42*, 9285.

[384]For a review, see Hofmann, J.E.; Schriesheim, A., in Olah, G.A., *Friedel–Crafts and Related Reactions*, Vol. 2, Wiley, NY, ***1963***, pp. 597–640.

[385]See, for example, Casiraghi, G.; Casnati, G.; Puglia, G.; Sartori, G. *Synthesis* ***1980***, 124.

the phenolate ion.[386] Another variation involved Friedel–Crafts coupling of an aldehyde to an activated aromatic compound (an aniline derivative) to give diaryl carbinols that exhibited atropisomerism (see 146).[387] When the reaction was done with a chiral aluminum complex, modest enantioselectivity was observed.

The hydroxymethylation of phenols with formaldehyde is called the *Lederer–Manasse reaction*. This reaction must be carefully controlled,[388] since it is possible for the para and both ortho positions to be substituted and for each of these to be rearylated, so that a polymeric structure **45** is produced. However, such polymers, which are of the Bakelite type (phenol–formaldehyde resins, **45**), are of considerable commercial importance.



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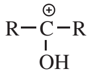
The attacking species is the carbocation,



formed from the aldehyde or ketone and the acid catalyst, except when the reaction is carried out in basic solution.

When an aromatic ring is treated with diethyl oxomalonate, $(EtOOC)_2C{=}O$, the product is an arylmalonic acid derivative $ArC(OH)(COOEt)_2$, which can be converted to an arylmalonic acid, $ArCH(COOEt)_2$.[389] This is therefore a way of applying the malonic ester synthesis (**10-67**) to an aryl group (see also, **13-14**). Of course, the opposite mechanism applies here: The aryl species is the nucleophile.

Two methods, both involving boron-containing reagents, have been devised for the regioselective ortho hydroxymethylation of phenols or aromatic amines.[390]

OS **III**, 326; **V**, 422; **VI**, 471, 856; **VIII**, 75, 77, 80. Also see, OS **I**, 214.

[386]For a review, see Schnell, H.; Krimm, H. *Angew. Chem. Int. Ed.* ***1963***, *2*, 373.

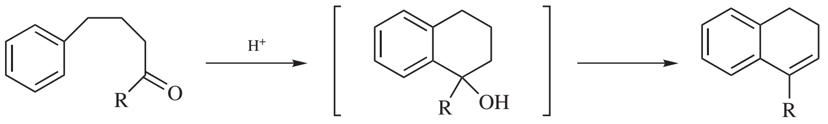
[387]Gothelf, A.S.; Hansen, T.; Jørgensen, K.A. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 854.

[388]See, for example, Casiraghi, G.; Casnati, G.; Pochini, A.; Puglia, G.; Ungaro, R.; Sartori, G. *Synthesis* ***1981***, 143.

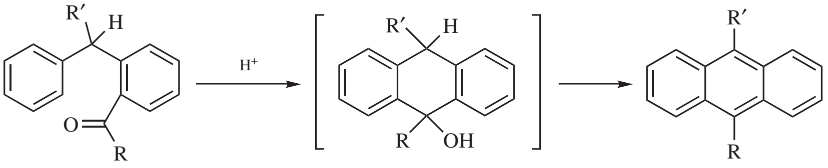
[389]Ghosh, S.; Pardo, S.N.; Salomon, R.G. *J. Org. Chem.* ***1982***, *47*, 4692.

[390]Sugasawa, T.; Toyoda, T.; Adachi, M.; Sasakura, K. *J. Am. Chem. Soc.* ***1978***, *100*, 4842; Nagata, W.; Okada, K.; Aoki, T. *Synthesis* ***1979***, 365.

11-13 Cyclodehydration of Carbonyl-Containing Compounds



As described in the previous section (**11-12**), the reaction of carbonyl-containing functional groups with protonic or Lewis acids lead to oxygen-stabilized carbocations. When generated in the presence of an aromatic ring, Friedel–Crafts alkylation occurs to give an alcohol or an alkene, if dehydration occurs under the reaction conditions. When an aromatic compound contains an aldehyde or ketone function in a position suitable for closing a suitably sized ring, treatment with acid results in cyclodehydration. The reaction is a special case of **11-12**, but in this case dehydration almost always takes place to give a double bond conjugated with the aromatic ring.[391] The method is very general and is widely used to close both carbocyclic and heterocyclic rings.[392] Polyphosphoric acid is a common reagent, but other acids have also been used. In a variation known as the *Bradsher reaction*,[393] diarylmethanes containing a carbonyl group in the ortho position can be cyclized to anthracene derivatives, **46**. In this case, 1,4-dehydration takes place, at least formally.



46

An intramolecular cyclization of an aryl ether to the carbonyl of a pendant aryl ketone, on clay with microwave irradiation, led to a benzofuran via Friedel–Crafts cyclization and elimination of water.[394]

The carbonyl unit involved in the cyclization process is not restricted to aldehydes and ketones. The carbonyl of acid derivatives, such as amides can also be utilized. One of the more important cyclodehydration reactions is applied to the formation of heterocyclic systems via cyclization of β-aryl amides, in what is called the *Bischler–Napieralski reaction*.[395] In this reaction amides of the type **47** are

[391]For examples where the hydroxy compound was the principal product (with R = CF_3), see Fung, S.; Abraham, N.A.; Bellini, F.; Sestanj, K. *Can. J. Chem.* ***1983***, *61*, 368; Bonnet-Delpon, D.; Charpentier-Morize, M.; Jacquot, R. *J. Org. Chem.* ***1988***, *53*, 759.

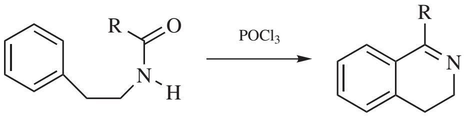
[392]For a review, see Bradsher, C.K. *Chem. Rev.* ***1987***, *87*, 1277.

[393]For examples, see Bradsher, C.K. *J. Am. Chem. Soc.* ***1940***, *62*, 486; Saraf, S.D.; Vingiello, F.A. *Synthesis* ***1970***, 655; Bradsher, C.K. Chem. Rev. ***1987***, *87*, 1277, see pp. 1287–1294.

[394]Meshram, H.M.; Sekhar, K.C.; Ganesh, Y.S.S.; Yadav, J.S. *Synlett* ***2000***, 1273.

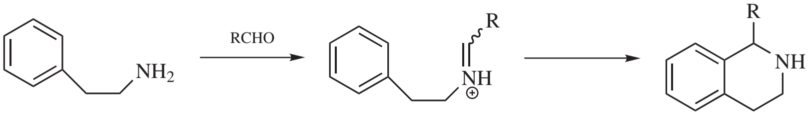
[395]For a review of the mechanism, see Fodor, G.; Nagubandi, S. *Tetrahedron* ***1980***, *36*, 1279.

cyclized with phosphorous oxychloride or other reagents, including polyphosphoric acid, sulfuric acid or phosphorus pentoxide, to give a dihydroisoquinoline, **48**. The Bischler–Napieralski reaction has been done in ionic liquids using $POCl_3$.[396] The reaction has also been done using solid-phase (see p. 416) techniques.[397]



47 **48**

If the starting compound contains a hydroxyl group in the α position, an additional dehydration takes place and the product is an isoquinoline.[398] Higher yields can be obtained if the amide is treated with PCl_5 to give an imino chloride $ArCH_2CH_2N{=}CR{-}Cl$, which is isolated and then cyclized by heating.[399] In this latter case, a nitrilium ion $ArCH_2CH_2{}^{\oplus}N{\equiv}CR$ is an intermediate.



49

Another useful variation is the *Pictet–Spengler isoquinoline synthesis*, also known as the *Pictet–Spengler reaction*.[400] The reactive intermediate is an iminium ion **49** rather than an oxygen-stabilized cation, but attack at the electrophilic carbon of the C=N unit (see **16-31**) leads to an isoquinoline derivative. When a β-arylamine reacts with an aldehyde, the product is an iminium salt, which cyclizes with an aromatic ring to complete the reaction and generate a tetrahydroisoquinoline.[401] A variety of aldehydes can be used, and substitution on the aromatic ring leads to many derivatives. When the reaction is done in the presence of a chiral thiourea catalyst, good enantioselectivity was observed.[402]

Another variation in this basic procedure leads to tetrahydroisoquinolines. When phenethylamine was treated with *N*-hydroxymethylbenzotriazole and then $AlCl_3$ in chloroform, cyclization occurred, and reduction with sodium borohydride gave the 1,2,3,4-tetrahydro-*N*-methylisoquinoline.[403]

[396]The reaction was done in bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Judeh, Z.M.A.; Ching, C.B.; Bu, J.; McCluskey, A. *Tetrahedron Lett.* ***2002***, *43*, 5089.
[397]Chern, M.-S.; Li, W.R. *Tetrahedron Lett.* ***2004***, *45*, 8323.
[398]Wang, X.-j.; Tan, J.; Grozinger, K. *Tetrahedron Lett.* ***1998***, *39*, 6609.
[399]Fodor, G.; Gal, G.; Phillips, B.A. *Angew. Chem. Int. Ed.* ***1972***, *11*, 919.
[400] Pictet, A.; Spengler, T. *Ber.* ***1911***, *44*, 2030; Cox, E.D.; Cook, J.M. *Chem. Rev.* ***1995***, *95*, 1797. See also Whaley, W.M.; Govindachari, T.R. *Org. React.* ***1951***, *6*, 74.
[401]Ong, H.H.; May, E.L. *J. Heterocyclic Chem.* ***1971***, *8*, 1007.
[402]Taylor, M.S.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2004***, *126*, 10558.
[403]Locher, C.; Peerzada, N. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 179.

OS **I**, 360, 478; **II**, 62, 194; **III**, 281, 300, 329, 568, 580, 581; **IV**, 590; **V**, 550; **VI**, 1. Also see, OS **I**, 54.

11-14 Haloalkylation or Haloalkyl-de-hydrogenation

$$ArH + HCHO + HCl \xrightarrow{ZnCl_2} ArCH_2Cl$$

When certain aromatic compounds are treated with formaldehyde and HCl, the CH_2Cl group is introduced into the ring in a reaction called *chloromethylation*. The reaction has also been carried out with other aldehydes and with HBr and HI. The more general term *haloalkylation* covers these cases.[404] The reaction is successful for benzene, and alkyl-, alkoxy-, and halobenzenes. It is greatly hindered by meta-directing groups, which reduce yields or completely prevent the reactions. Amines and phenols are too reactive and usually give polymers unless deactivating groups are also present, but phenolic ethers and esters successfully undergo the reaction. Compounds of lesser reactivity can often be chloromethylated with chloromethyl methyl ether ($ClCH_2OMe$), or methoxyacetyl chloride $MeOCH_2COCl$.[405] Zinc chloride is the most common catalyst, but other Friedel–Crafts catalysts are also employed. As with reaction **11-12** and for the same reason, an important side product is the diaryl compound Ar_2CH_2 (from formaldehyde).

Apparently, the initial step involves reaction of the aromatic compound with the aldehyde to form the hydroxyalkyl compound, exactly as in **11-12**, and then the HCl converts this to the chloroalkyl compound.[406] The acceleration of the reaction by $ZnCl_2$ has been attributed[407] to the raising of the acidity of the medium, causing an increase in the concentration of $HOCH_2^+$ ions.

OS **III**, 195, 197, 468, 557; **IV**, 980.

11-15 Friedel–Crafts Arylation: The Scholl Reaction

De-hydrogen-coupling

$$2\,ArH \xrightarrow[H^+]{AlCl_3} Ar\text{—}Ar + H_2$$

The coupling of two aromatic molecules by treatment with a Lewis acid and a proton acid is called the *Scholl reaction*.[408] Yields are low and the synthesis is seldom useful. High temperatures and strong-acid catalysts are required, and the reaction fails for substrates that are destroyed by these conditions. Because the reaction

[404]For reviews, see Belen'kii, L.I.; Vol'kenshtein, Yu.B.; Karmanova, I.B. *Russ. Chem. Rev.* ***1977***, *46*, 891; Olah, G.A.; Tolgyesi, W.S., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 2, Wiley, NY, ***1963***, pp. 659–784.

[405]McKillop, A.; Madjdabadi, F.A.; Long, D.A. *Tetrahedron Lett.* ***1983***, *24*, 1933.

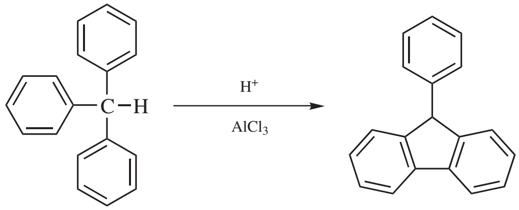
[406]Ziegler, E.; Hontschik, I.; Milowiz, L. *Monatsh. Chem.* ***1948***, *79*, 142; Ogata, Y.; Okano, M. *J. Am. Chem. Soc.* ***1956***, *78*, 5423. See also, Olah, G.A.; Yu, S.H. *J. Am. Chem. Soc.* ***1975***, *97*, 2293.

[407]Lyushin, M.M.; Mekhtiev, S.D.; Guseinova, S.N. *J. Org. Chem. USSR* ***1970***, *6*, 1445.

[408]For reviews, see Kovacic, P.; Jones, M.B. *Chem. Rev.* ***1987***, *87*, 357; Balaban, A.T.; Nenitzescu, C.D., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 2, Wiley, NY, ***1964***, pp. 979–1047.

becomes important with large fused-ring systems, ordinary Friedel–Crafts reactions (**11-11**) on these systems are rare. For example, naphthalene gives binaphthyl under Friedel–Crafts conditions. Yields can be increased by the addition of a salt, such as $CuCl_2$ or $FeCl_3$, which acts as an oxidant.[409] Rhodium catalysts have also been used.[410]

Intramolecular Scholl reactions, such as formation of **50** from triphenylmethane,



50

are much more successful than the intermolecular reaction. The mechanism is not clear, but it may involve attack by a proton to give an arenium ion of the type **12** (p. 662), which would be the electrophile that attacks the other ring.[411] Sometimes arylations have been accomplished by treating aromatic substrates with particularly active aryl halides, especially fluorides. For free-radical arylations, see reactions **12-15**, **13-26**, **13-27**, **13-10**, **14-17**, and **14-18**.

OS **IV**, 482; **X**, 359. Also see, OS **V**, 102, 952.

11-16 Arylation of Aromatic Compounds By Metalated Aryls

$$\text{Ar-M} \xrightarrow{\text{Ar}'\text{-H}} \text{Ar—Ar}'$$

Many metalated aryl compounds are known to couple with aromatic compounds. Aniline derivatives react with $ArPb(OAc)_3$, for example, to give the 2-arylaniline.[412] Phenolic anions also react to form biaryls, with modest enantioselectivity in the presence of brucine.[413]

Phenylboronates [$ArB(OR)_2$] react with electron-deficient aromatic compounds, such as acetophenone, to give the biaryl.[414] Arylboronates also react with π-allyl palladium complexes to form the alkylated aromatic compound.[415]

[409]Kovacic, P.; Koch, Jr., F.W. *J. Org. Chem.* ***1965***, *30*, 3176; Kovacic, P.; Wu, C. *J. Org. Chem.* ***1961***, *26*, 759, 762. For examples with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 77–84; Sartori, G.; Maggi, R.; Bigi, F.; Grandi, M. *J. Org. Chem.* ***1993***, *58*, 7271

[410]Barrett, A.G.M.; Itoh, T.; Wallace, E.M. *Tetrahedron Lett.* ***1993***, *34*, 2233.

[411]For a discussion, see Clowes, G.A. *J. Chem. Soc., C* ***1968***, 2519.

[412]Saito, S.; Kano, T.; Ohyabu, Y.; Yamamoto, H. *Synlett* ***2000***, 1676.

[413]Kano, T.; Ohyabu, Y.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* ***2002***, *124*, 5365.

[414]Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* ***2003***, *125*, 1698.

[415]Ortar, G. *Tetrahedron Lett.* ***2003***, *44*, 4311.

11-17 Friedel–Crafts Acylation

Acylation or Acyl-de-hydrogenation

$$ArH + RCOCl \xrightarrow{AlCl_3} ArCOR$$

The most important method for the preparation of aryl ketones is known as *Friedel–Crafts acylation*.[416] The reaction is of wide scope. Reagents other than acyl halides can be used,[417] including carboxylic acids,[418] anhydrides, and ketenes. Oxalyl chloride has been used to give diaryl 1,2-diketones.[419] Carboxylic esters usually give alkylation as the predominant product (see **11-11**).[420] *N*-Carbamoyl β-lactams reacted with naphthalene in the presence of trifluoromethanesulfonic acid to give the keto-amide.[421]

The alkyl group (R in RCOCl) may be aryl as well as alkyl. The major disadvantages of Friedel–Crafts alkylation, polyalkylation, and rearrangement of the intermediate carbocation, are not a problem in Friedel–Crafts acylation. Rearrangement of the alkyl group (R in RCOCl) is never found because the intermediate is an acylium ion (an acyl cation, $RC{\equiv}O^+$, see below). Because the RCO group is deactivating, the reaction stops cleanly after one group is introduced. All four acyl halides can be used, though chlorides are most commonly employed. The order of activity is usually, but not always, I > Br > Cl > F.[422] Catalysts are Lewis acids,[423] similar to those in reaction **11-11**, but in acylation a little > than 1 equivalent of catalyst is required per mole of reagent, because the first mole coordinates

[416]For reviews of Friedel–Crafts acylation, see Olah, G.A. *Friedel–Crafts and Related Reactions*, Wiley, NY, ***1963–1964***, as follows: Vol. 1, Olah, G.A. pp. 91–115; Vol. 3, Gore, P.H. pp. 1–381; Peto, A.G. pp. 535–910; Sethna, S. pp. 911–1002; Jensen, F.R.; Goldman, G. pp. 1003–1032. For another review, see Gore, P.H. *Chem. Ind. (London)* ***1974***, 727.

[417]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1423–1426.

[418]Ranu, B.C.; Ghosh, K.; Jana, U. *J. Org. Chem.* ***1996***, *61*, 9546; Kawamura, M.; Cui, D.-M.; Hayashi, T.; Shimada, S. *Tetrahedron Lett.* ***2003***, *44*, 7715. For an example of acylation by heating with octanoic acid, without a catalyst, see Kaur, J.; Kozhevnikov, I.V. *Chem.Commun.* ***2002***, 2508.

[419]Mohr, B.; Enkelmann, V.; Wegner, G. *J. Org. Chem.* ***1994***, *59*, 635; Taber, D.F.; Sethuraman, M.R. *J. Org. Chem.* ***2000***, *65*, 254.

[420]For a reaction involving the Friedel–Crafts acylation using an ester, see Hwang, J.P.; Prakash, G.K.S.; Olah, G.A. *Tetrahedron* ***2000***, *56*, 7199.

[421]Anderson, K.W.; Tepe, J. *Org. Lett.* ***2002***, *4*, 459.

[422]Yamase, Y. *Bull. Chem. Soc. Jpn.* ***1961***, *34*, 480; Corriu, R. *Bull. Soc. Chim. Fr.* ***1965***, 821.

[423]The usual Lewis acids can be used, as described in **11–11**, and ferric chloride, iodine, zinc chloride, and iron are probably the most common catalysts. For a review, see Pearson, D.E.; Buehler, C.A. *Synthesis* ***1972***, 533. Recently employed catalysts include, **$Ga(ONf)_3$**, where Nf = nonafluorobutanesulfonate: Matsu, J.-i.; Odashima, K.; Kobayashi, S. *Synlett* ***2000***, 403. **$In(OTf)_3$** with $LiClO_4$: Chapman, C.J.; Frost, C.G.; Hartley, J.P.; Whittle, A.J. *Tetrahedron Lett.* ***2001***, *42*, 773. **$InCl_3$**: Choudhary, V.R.; Jana, S.K.; Patil, N.S. *Tetrahedron Lett.* ***2002***, *43*, 1105. **$Sc(OTf)_3$**: Kawada, A.; Mitamura, S.; Matsuo, J-i.; Tsuchiya, T.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* ***2000***, *73*, 2325. **$Yb[C(SO_2C_4F_4)_3]_3$**: Barrett, A.G.M.; Bouloc, N.; Braddock, D.C.; Chadwick, D.; Henderson, D.A. *Synlett* ***2002***, 1653. **$BiOCl_3$**: Répichet, S.; Le Roux, C.; Roques, N.; Dubac, J. *Tetrahedron Lett.* ***2003***, *44*, 2037. **ZnO**: Sarvari, M.H.; Sharghi, H. *J. Org. Chem.* ***2004***, *69*, 6953.

with the oxygen of the reagent [as in $R(Cl)C{=}O^{+}\ {}^{-}AlCl_3$].[424] A reusable catalyst [$Ln(OTf)_3$—$LiClO_4$] has been developed as well.[425] HY-Zeolite has also been used to facilitate the reaction with acetic anhydride.[426] A platinum catalyst was used with acetic anhydride,[427] $TiCl_4$ with acetyl chloride[428] or acetyl chloride and zinc powder with microwave irradiation.[429] Friedel–Crafts acylation using a carboxylic acid with a catalyst called Envirocat-EPIC (an acid-treated clay-based material was reported.[430] Friedel–Crafts acylation was reported in an ionic liquid.[431] An interesting acylation reaction was reported that coupled trichlorophenylmethane to benzene, giving benzophenone in the presence of the ionic liquid $AlCl_3$-*n*-BPC.[432] Acylation has been accomplished in carbon disulfide.[433]

Proton acids can be used as catalysts when the reagent is a carboxylic acid. The mixed carboxylic sulfonic anhydrides $RCOOSO_2CF_3$ are extremely reactive acylating agents and can smoothly acylate benzene without a catalyst.[434] With active substrates (e.g., aryl ethers, fused-ring systems, thiophenes), Friedel–Crafts acylation can be carried out with very small amounts of catalyst, often just a trace, or even sometimes with no catalyst at all.

The reaction is quite successful for many types of substrate, including fused ring systems, which give poor results in **11-11**. Compounds containing ortho–para-directing groups, including alkyl, hydroxy, alkoxy, halogen, and acetamido groups, are easily acylated and give mainly or exclusively the para products, because of the relatively large size of the acyl group. However, aromatic amines give poor results. With amines and phenols there may be competition from *N*- or *O*-acylation; however, *O*-acylated phenols can be converted to *C*-acylated phenols by the Fries rearrangement (**11-27**). Friedel–Crafts acylation is usually prevented by meta-directing groups. Indeed, nitrobenzene is often used as a solvent for the reaction. Many heterocyclic systems, including furans, thiophenes, pyrans, and pyrroles[435]

[424]The crystal structures of several of these complexes have been reported: Rasmussen, S.E.; Broch, N.C. *Acta Chem. Scand.* ***1966***, *20*, 1351; Chevrier, B.; Le Carpentier, J.; Weiss, R. *J. Am. Chem. Soc.* ***1972***, *94*, 5718. For a review of these complexes, see Chevrier, B.; Weiss, R. *Angew. Chem. Int. Ed.* ***1974***, *13*, 1.

[425]Kawada, A.; Mitamura, S.; Kobayashi, S. *Chem. Commun.* ***1996***, 183. See Kawada, A.; Mitamura, S.; Kobayashi, S. *SynLett*, ***1994***, 545 for the use of $Sc(OTf)_3$ with acetic anhydride and Hachiya, I.; Moriwaki, M.; Kobayashi, S. *Tetrahedron Lett.* ***1995***, *36*, 409 for the use of $Hf(OTf)_4$.

[426]Sreekumar, R.; Padmukumar, R. *Synth. Commun.* ***1997***, *27*, 777. See Paul, V.; Sudalai, A.; Daniel, T.; Srinivasan, K.V. *Tetrahedron Lett.* ***1994***, *35*, 2601 for the use of an acidic zeolite.

[427]Fürstner, A.; Voigtländer, D.; Schrader, W.; Giebel, D.; Reetz, M.T. *Org. Lett.* ***2001***, *3*, 417.

[428]Bensari, A.; Zaveri, N.T. *Synthesis* ***2003***, 267.

[429]Paul, S.; Nanda, P.; Gupta, R.; Loupy, A. *Synthesis* ***2003***, 2877.

[430]Bandgari, B.P.; Sadavarte, V.S. *Synth. Commun.* ***1999***, *29*, 2587.

[431]The reaction was catalyzed by Br_2O_3 in bmim NTf_2, 1-butyl-3-methylimidazolium triflimide: Gmouth, S.; Yang, H.; Vaultier, M. *Org. Lett.* ***2003***, *5*, 2219.

[432]This catalyst is *n*-butylpyridinium chloroaluminate, see Rebeiro, G.L.; Khadilkar, B.M. *Synth. Commun.* ***2000***, *30*, 1605.

[433]Georgakilas, V.; Perdikomatis, G.P.; Triantafyllou, A.S.; Siskos, M.G.; Zarkadis, A.K. *Tetrahedron* ***2002***, *58*, 2441.

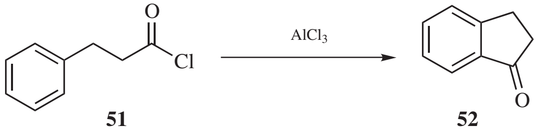
[434]Effenberger, F.; Sohn, E.; Epple, G. *Chem. Ber.* ***1983***, *116*, 1195. See also, Keumi, T.; Yoshimura, K.; Shimada, M.; Kitajima, H. *Bull. Chem. Soc. Jpn.* ***1988***, *44*, 455.

[435]Yadav, J.S.; Reddy, B.V.S.; Kondaji, G.; Rao, R.S.; Kumar, S.P. *Tetrahedron Lett.* ***2002***, *43*, 8133.

but not pyridines or quinolines, can be acylated in good yield. Initial reaction of indole with Et_2AlCl[436] or $SnCl_4$,[437] followed by acetyl chloride leads to 3-acetylindole. By comparison, the reaction of *N*-acetylindole with acetic anhydride and $AlCl_3$ gave *N*,6-diacetylindole.[438] Acetylation at C-3 was also accomplished with acetyl chloride in the ionic liquid emimcl-$AlCl_3$.[439] Gore, in Ref. 417 (pp. 36–100; with tables, pp. 105–321), presents an extensive summary of the substrates to which this reaction has been applied. Pyridines and quinolines can be also be acylated by a free-radical mechanism (reaction **14-19**).

When a mixed-anhydride RCOOCOR′ is the reagent, two products are possible: ArCOR and ArCOR′. Which product predominates depends on two factors. If R contains electron-withdrawing groups, then ArCOR′ is chiefly formed, but if this factor is approximately constant in R and R′, the ketone with the larger R group predominantly forms.[440] This means that *formylations* of the ring do not occur with mixed anhydrides of formic acid HCOOCOR.

An important use of the Friedel–Crafts acylation is to effect ring closure.[441] This can be done if an acyl halide, anhydride, or carboxylic acid[442] group is in the proper position. An example is the conversion of **51** to **52**.



51 **52**

The reaction is used mostly to close six-membered rings, but has also been done for five- and seven-membered rings, which close less readily. Even larger rings can be closed by high-dilution techniques.[443] Tricyclic and larger systems are often made by using substrates containing one of the acyl groups on a ring. Many fused-ring systems are made in this manner. If the bridging group is CO, the product is a quinone.[444] One of the most common catalysts for intramolecular Friedel–Crafts

[436] Okauchi, T.; Itonaga, M.; Minami, T.; Owa, T.; Kitoh, K.; Yoshino, H. *Org. Lett.* ***2000***, *2*, 1485; Zhang, Z; Yang, Z.; Wong, H.; Zhu, J.; Meanwell, N.A.; Kadow, J.F.; Wang, T. *J. Org. Chem.* ***2002***, *67*, 6226.

[437] Ottoni, O.; de V.F. Neder, A.; Dias, A.K.B.; Cruz, R.P.A.; Aquino, L.B. *Org. Lett.* ***2001***, *3*, 1005.

[438] Cruz, R.P.A.; Ottoni, O.; Abella, C.A.M.; Aquino, L.B. *Tetrahedron Lett.* ***2001***, *42*, 1467. 3-Methylindole was converted to 2-acetyl-3-methylindole with acetyl chloride and zinc(II) chloride: see Pal, M.; Dakarapu, R.; Padakanti, S. *J. Org. Chem.* ***2004***, *69*, 2913.

[439] The ionic liquid emimcl-$AlCl_3$ is 1-ethyl-3-methylimidazolium chloroaluminate, see Yeung, K.-S.; Farkas, M.E.; Qiu, Z.; Yang, Z. *Tetrahedron lett.* ***2002***, *43*, 5793.

[440] Edwards, Jr., W.R.; Sibelle, E.C. *J. Org. Chem.* ***1963***, *28*, 674.

[441] For a review, see Sethna, S., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 911–1002;. For examples with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1427–1431.

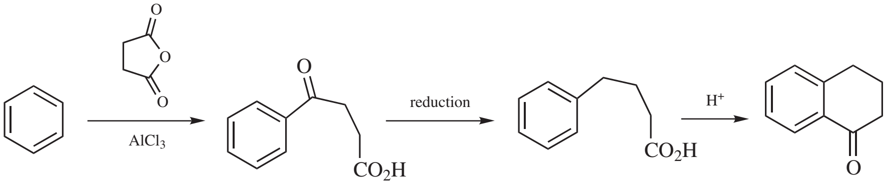
[442] For an example using $Tb(OTf)_3$, see Cui, D.-M.; Zhang, C.; Kawamura, M.; Shimada, S. *Tetrahedron Lett.* ***2004***, *45*, 1741.

[443] For example, see Schubert, W.M.; Sweeney, W.A.; Latourette, H.K. *J. Am. Chem. Soc.* ***1954***, *76*, 5462.

[444] For discussions, see Naruta, Y.; Maruyama, K., in Patai, S.; Rappoport, Z. *The Chemistry of the Quinonoid Compounds*, Vol. 2, pt. 1, Wiley, NY, ***1988***, pp. 325–332; Thomson, R.H., in Patai, S. *The Chemistry of the Quinonoid Compounds*, Vol. 1, pt. 1, Wiley, NY, ***1974***; pp. 136–139.

acylation is polyphosphoric acid[445] (because of its high potency), but $AlCl_3$, H_2SO_4, and other Lewis and proton acids are also used, though acylations with acyl halides are not generally catalyzed by proton acids.

Friedel–Crafts acylation can be carried out with cyclic anhydrides,[446] in which case the product contains a carboxyl group in the side chain (**53**). When succinic anhydride is used, the product is $ArCOCH_2CH_2COOH$. This can be reduced (**19-61**) to $ArCH_2CH_2CH_2COOH$, which can then be cyclized by an internal Friedel–Crafts acylation to give **54**. The total process is called the *Haworth reaction*:[447]

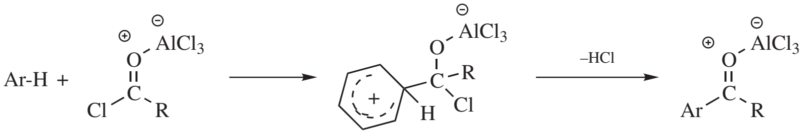


53 **54**

The mechanism of Friedel–Crafts acylation is not completely understood,[448] but at least two mechanisms probably operate, depending on conditions.[449] In most cases the attacking species is the acyl cation, either free or as an ion pair, formed by[450]

$$RCOCl + AlCl_3 \longrightarrow RCO^+ + AlCl_4^-$$

If R is tertiary, RCO^+ may lose CO to give R^+, so that the alkyl arene ArR is often a side product or even the main product. This kind of cleavage is much more likely with relatively unreactive substrates, where the acylium ion has time to break down. For example, pivaloyl chloride Me_3CCOCl gives the normal acyl product with anisole, but the alkyl product Me_3CPh with benzene. In the other mechanism, an acyl cation is not involved, but the 1:1 complex (**55**) attacks directly.[451]



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[445]For a review of polyphosphoric acid, see Rowlands, D.A., in Pizey, J.S. *Synthetic Reagents*, Vol. 6, Wiley, NY, ***1985***, pp. 156–414.

[446]For a review see Peto, A.G., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, p. 535.

[447]See Agranat, I.; Shih, Y. *J. Chem. Educ.* ***1976***, *53*, 488.

[448]See Effenberger, F.; Eberhard, J.K.; Maier, A.H. *J. Am. Chem. Soc.* ***1996***, *118*, 12572 for first evidence of the reacting electrophile.

[449]For a review of the mechanism, see Taylor, R. *Electrophilic Aromatic Substitution*, Wiley, NY, ***1990***, pp. 222–237.

[450]After 2 min, exchange between PhCOCl and $Al(^{36}Cl)_3$ is complete: Oulevey, G.; Susz, P.B. *Helv. Chim. Acta* ***1964***, *47*, 1828.

[451]For example, see Corriu, R.; Dore, M.; Thomassin, R. *Tetrahedron* ***1971***, *27*, 5601, 5819; Tan, L.K.; Brownstein, S. *J. Org. Chem.* ***1983***, *48*, 302.

Free-ion attack is more likely for sterically hindered R.[452] The ion CH_3CO^+ has been detected (by IR spectroscopy) in the liquid complex between acetyl chloride and aluminum chloride, and in polar solvents, such as nitrobenzene; but in nonpolar solvents, such as chloroform, only the complex and not the free ion is present.[453] In any event, 1 equivalent of catalyst certainly remains complexed to the product at the end of the reaction. When the reaction is performed with $RCO^+SbF_6^-$, no catalyst is required and the free ion[454] (or ion pair) is undoubtedly the attacking entity.[455] The use of $LiClO_4$ on the metal triflate-catalyzed Friedel–Crafts acylation of methoxy-naphthalene derivatives has been examined, and the presence of the lithium salt leads to acylation in the ring containing the methoxy unit, whereas reaction occurs in the other ring in the absence of lithium salts.[456] Note that lithium perchlorate forms a complex with acetic anhydride, which can be used for the Friedel–Crafts acetylation of activated aromatic compounds.[457]

OS **I**, 109, 353, 476, 517; **II**, 3, 8, 15, 81, 156, 169, 304, 520, 569; **III**, 6, 14, 23, 53, 109, 183, 248, 272, 593, 637, 761, 798; **IV**, 8, 34, 88, 898, 900; **V**, 111; **VI**, 34, 618, 625 **X**, 125.

Reaction **11-18** is a direct formylation of the ring.[458] Reaction **11-17** has not been used for formylation, since neither formic anhydride nor formyl chloride is stable at ordinary temperatures. Formyl chloride has been shown to be stable in chloroform solution for 1 h at −60°C,[459] but it is not useful for formylating aromatic rings under these conditions. Formic anhydride has been prepared in solution, but has not been isolated.[460] Mixed anhydrides of formic and other acids are known[461] and can be used to formylate amines (see **16-73**) and alcohols, but no formylation takes place when they are applied to aromatic rings. See **13-17** for a nucleophilic method for the formylation of aromatic rings.

A related reaction involves a biaryl, where one ring is a phenol. Treatment with BCl_3 and an $AlCl_3$ catalyst, followed by reaction with CO and $Pd(OAc)_2$, led to

[452]Yamase, Y. *Bull. Chem. Soc. Jpn.* ***1961***, *34*, 484; Gore, P.H. *Bull. Chem. Soc. Jpn.* ***1962***, *35*, 1627; Satchell, D.P.N. *J. Chem. Soc.* ***1961***, 5404.

[453]Cook, D. *Can. J. Chem.* ***1959***, *37*, 48; Cassimatis, D.; Bonnin, J.P.; Theophanides, T. *Can. J. Chem.* ***1970***, *48*, 3860.

[454]Crystal structures of solid RCO^+ $SbF_6{}^-$ salts have been reported: Boer, F.P. *J. Am. Chem. Soc.* ***1968***, *90*, 6706; Chevrier, B.; Le Carpentier, J.; Weiss, R. *Acta Crystallogr., Sect. B*, ***1972***, *28*, 2673; *J. Am. Chem. Soc.* ***1972***, *94*, 5718.

[455]Olah, G.A.; Lin, H.C.; Germain, A. *Synthesis* ***1974***, 895. For a review of acylium salts in organic synthesis, see Al-Talib, M.; Tashtoush, H. *Org. Prep. Proced. Int.* ***1990***, *22*, 1.

[456]Kobayashi, S.; Komoto, I. *Tetrahedron* ***2000***, *56*, 6463.

[457]Bartoli, G.; Bosco, M.; Marcantoni, E.; Massaccesi, M.; Rinalde, S.; Sambri, L. *Tetrahedron Lett.* ***2002***. *43*, 6331.

[458]For a review, see Olah, G.A.; Kuhn, S.J. Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 1153–1256. For a review of formylating agents, see Olah, G.A.; Ohannesian, L.; Arvanaghi, M. *Chem. Rev.* ***1987***, *87*, 671. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1423–1426.

[459]Staab, H.A.; Datta, A.P. *Angew. Chem. Int. Ed.* ***1964***, *3*, 132.

[460]Olah, G.A.; Vankar, Y.D.; Arvanaghi, M.; Sommer, J. *Angew. Chem. Int. Ed.* ***1979***, *18*, 614; Schijf, R.; Scheeren, J.W.; van Es, A.; Stevens, W. *Recl. Trav. Chim. Pays-Bas* ***1965***, *84*, 594.

[461]Stevens, W.; van Es, A. *Recl. Trav. Chim. Pays-Bas* ***1964***, *83*, 863.

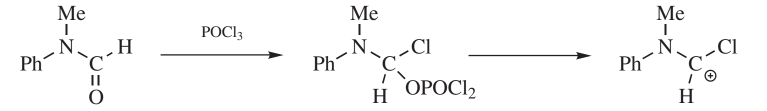
carbonylation and acylation to give the corresponding lactone.[462] Carbonylation of aromatic compounds can lead to aryl ketones. Heating an aromatic compound with $Ru(CO)_{12}$, ethylene and 20 atm of CO gave the corresponding aryl ethyl ketone.[463]

11-18 Formylation

Formylation or Formyl-de-hydrogenation

$$\text{Ar-H} \longrightarrow \text{Ar-CHO}$$

The reaction with disubstituted formamides R_2N—CHO and phosphorus oxychloride, called the *Vilsmeier* or the *Vilsmeier–Haack reaction*,[464] is the most common method for the formylation of aromatic rings.[465] However, it is applicable only to active substrates, such as amines and phenols. An intramolecular version is also known.[466] Aromatic hydrocarbons and heterocycles can also be formylated, but only if they are much more active than benzene (e.g., azulenes, ferrocenes). Although *N*-phenyl-*N*-methylformamide is a common reagent, other arylalkyl amides and dialkyl amides are also used.[467] Phosgene ($COCl_2$) has been used in place of $POCl_3$. The reaction has also been carried out with other amides to give ketones (actually an example of **11-17**), but not often. The attacking species[468] is **56**,[469] and the mechanism is probably that shown to give **57**, which is unstable and easily hydrolyzes to the product. Either formation of **56** or the reaction of **56** with the substrate can be rate determining, depending on the reactivity of the substrate.[470]



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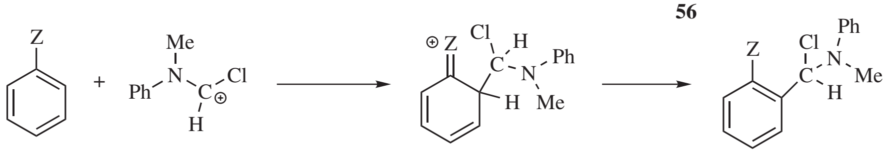

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[462]Zhou, Q.J.; Worm, K.; Dolle, R.E. *J.Org. Chem.* ***2004***, *69*, 5147.

[463]Ie, Y.; Chatani, N.; Ogo, T.; Marshall, D.R.; Fukuyama, T.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* ***2000***, *65*, 1475.

[464]See Blaser, D.; Calmes, M.; Daunis, J.; Natt, F.; Tardy-Delassus, A.; Jacquier, R. *Org. Prep. Proceed. Int.* ***1993***, *25*, 338 for improvements in this reaction.

[465]For a review, see Jutz, C. *Adv. Org. Chem.* ***1976***, *9*, pt. 1, 225.

[466]Meth-Cohn, O.; Goon, S. *J. Chem. Soc. Perkin Trans. 1* ***1997***, 85.

[467]For a review of dimethylformamide, see Pizey, J.S. *Synthetic Reagents*, Vol. 1, Wiley, NY, ***1974***, pp. 1–99.

[468]For a review of such species, see Kantlehner, W. *Adv. Org. Chem.* ***1979***, *9*, pt. 2, 5.

[469]See Arnold, Z.; Holy, A. *Collect. Czech. Chem. Commun.* ***1962***, *27*, 2886; Fritz, H.; Oehl, R. *Liebigs Ann. Chem.* ***1971***, *749*, 159; Jugie, G.; Smith, J.A.S.; Martin, G.J. *J. Chem. Soc. Perkin Trans. 2* ***1975***, 925.

[470]Alunni, S.; Linda, P.; Marino, G.; Santini, S.; Savelli, G. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 2070.

When $(CF_3SO_2)_2O$ was used instead of $POCl_3$, the reaction was extended to some less-active compounds, including naphthalene and phenanthrene.[471]

In a related reaction, paraformaldehyde can be used, with $MgCl_2$—NEt_3, to convert phenol to phenol 2-carboxaldehyde.[472] Another variation treated acetanilide with $POCl_3$—DMF and generated 2-chloroquinoline-3-carboxaldehyde.[473] Used in conjunction with conjugated hydroxylamines, a tandem Vilsmeier–Beckman reaction (see **18-17** for the Beckman rearrangement) leads to pyridines (2-chloro-3-carboxaldehyde).[474] A chain-extension variation has been reported in which an aryl alkyl ketone is treated with $POCl_3$/DMF on silica with microwave irradiation to give a conjugated aldehyde, ArC(=O)R → ArC(Cl)=CHCHO.[475]

OS **I**, 217; **III**, 98, **IV**, 331, 539, 831, 915.

$$ArH + Zn(CN)_2 \xrightarrow{HCl} ArCH{=}NH_2^+\,Cl^- \xrightarrow{H_2O} ArCHO$$

Formylation with $Zn(CN)_2$ and HCl is called the *Gatterman reaction*.[476] It can be applied to alkylbenzenes, phenols and their ethers, and many heterocyclic compounds. However, it cannot be applied to aromatic amines. In the original version of this reaction the substrate was treated with HCN, HCl, and $ZnCl_2$, but the use of $Zn(CN)_2$ and HCl (HCN and $ZnCl_2$ are generated *in situ*) makes the reaction more convenient to carry out and yields are not diminished. The mechanism of the Gatterman reaction has not been investigated very much, but it is known that an initially formed but not isolated nitrogen-containing product is hydrolyzed to aldehyde. This product is presumed to be $ArCH{=}NH_2^+Cl^-$, as shown. When benzene was treated with NaCN under superacid conditions (F_3CSO_2OH—SbF_5, see p. 236), a good yield of product was obtained, leading to the conclusion that the electrophile in this case was $^+C(H){=}N^+H_2$.[477] The Gatterman reaction may be regarded as a special case of **11-24**.

Another method, formylation with CO and HCl in the presence of $AlCl_3$ and CuCl[478] (the *Gatterman–Koch reaction*), is limited to benzene and alkylbenzenes.[479]

[471]Martínez, A.G.; Alvarez, R.M.; Barcina, J.O.; Cerero, S. de la M.; Vilar, E.T.; Fraile, A.G.; Hanack, M.; Subramanian, L.R. *J. Chem. Soc., Chem. Commun.* ***1990***, 1571.

[472]Hofsløkken, N.U.; Skattebøl, L. *Acta Chem. Scand.* ***1999***, *53*, 258.

[473]Ali, M.M.; Tasneem, Rajanna, K.C.; Prakash, P.K.S. *Synlett* ***2001***, 251. For another variation to generate 4-chloro-2-phenyl-*N*-formyldihydroquinoline derivatives, see Akila, S.; Selvi, S.; Balasubramanian, K. *Tetrahedron* ***2001***, *57*, 3465.

[474]Amaresh, R.R.; Perumal, P.T. *Synth. Commun.* ***2000***, *30*, 2269.

[475]Paul, S.; Gupta, M.; Gupta, R. *Synlett* ***2000***, 1115.

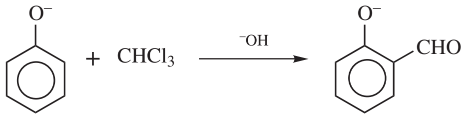
[476]For a review, see Truce, W.E. *Org. React.* ***1957***, *9*, 37. See Tanaka, M.; Fujiwara, M.; Ando, H. *J. Org. Chem.* ***1995***, *60*, 2106 for rate studies.

[477]Yato, M.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* ***1991***, *113*, 691.

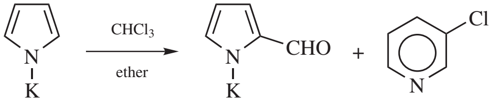
[478]The CuCl is not always necessary: see Toniolo, L.; Graziani, M. *J. Organomet. Chem.* ***1980***, *194*, 221.

[479]For a review, see Crounse, N.N. *Org. React.* ***1949***, *5*, 290.

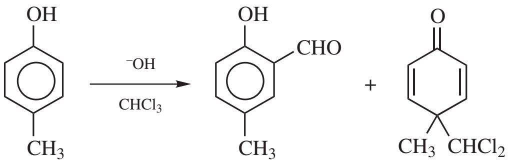
OS **II**, 583; **III**, 549.



In the *Reimer–Tiemann reaction*, aromatic rings are formylated by reaction with chloroform and hydroxide ion.[480] The method is useful only for phenols and certain heterocyclic compounds such as pyrroles and indoles. Unlike the previous formylation methods (**11-18**), this one is conducted in basic solution. Yields are generally low, seldom rising above 50%.[481] The incoming group is directed ortho, unless both ortho positions are filled, in which case the attack is para.[482] Certain substrates have been shown to give abnormal products instead of or in addition to the normal ones. For example, **58** and **60** gave, respectively, **59** and **61** as well as the normal aldehyde products. From the nature of the reagents and



58 **59**



60 **61**

from the kind of abnormal products obtained, it is clear that the reactive entity in this reaction is dichlorocarbene CCl_2.[483] This is known to be produced by treatment of chloroform with bases (p. 521); it is an electrophilic reagent and is known to give ring expansion of aromatic rings (see **15-64**), accounting for products like **58**. The mechanism of the normal reaction is thus something like this.[484]

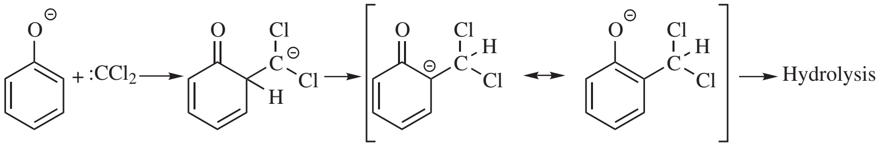
[480]For a review, see Wynberg, H.; Meijer, E.W. *Org. React.* ***1982***, *28*, 1.

[481]For improved procedures, see Thoer, A.; Denis, G.; Delmas, M.; Gaset, A. *Synth. Commun.* ***1988***, *18*, 2095; Cochran, J.C.; Melville, M.G. *Synth. Commun.* ***1990***, *20*, 609.

[482]Increased para selectivity has been achieved by the use of polyethylene glycol: Neumann, R.; Sasson, Y. *Synthesis* ***1986***, 569.

[483]For a review of carbene methods for introducing formyl and acyl groups into organic molecules see Kulinkovich, O.G. *Russ. Chem. Rev.* ***1989***, *58*, 711.

[484]Robinson, E.A. *J. Chem. Soc.* ***1961***, 1663; Hine, J.; van der Veen, J.M. *J. Am. Chem. Soc.* ***1959***, *81*, 6446. See also, Langlois, B.R. *Tetrahedron Lett.* ***1991***, *32*, 3691.



The formation of **61** in the case of **60** can be explained by attack of some of the CCl_2 ipso to the CH_3 group. Since this position does not contain a hydrogen, normal proton loss cannot take place and the reaction ends when the CCl_2^- moiety acquires a proton.

A method closely related to the Reimer–Tiemann reaction is the *Duff reaction*, in which hexamethylenetetramine $(CH_2)_6N_4$ is used instead of chloroform. This reaction can be applied only to phenols and amines; ortho substitution is generally observed and yields are low. A mechanism[485] has been proposed that involves initial aminoalkylation (**11-22**) to give $ArCH_2NH_2$, followed by dehydrogenation to ArCH=NH and hydrolysis of this to the aldehyde product. When $(CH_2)_6N_4$ is used in conjunction with F_3CCOOH, the reaction can be applied to simple alkylbenzenes; yields are much higher and a high degree of regioselectively para substitution is found.[486] In this case too an imine seems to be an intermediate.

OS **III**, 463; **IV**, 866

$$ArH + Cl_2CHOMe \xrightarrow{AlCl_3} ArCHO$$

Besides **11-18**, several other formylation methods are known.[487] In one of these, dichloromethyl methyl ether formylates aromatic rings with Friedel–Crafts catalysts.[488] The ArCHClOMe compound is probably an intermediate. Orthoformates have also been used.[489] In another method, aromatic rings are formylated with formyl fluoride HCOF and BF_3.[490] Unlike formyl chloride, formyl fluoride is stable enough for this purpose. This reaction was successful for benzene, alkylbenzenes, PhCl, PhBr, and naphthalene. Phenols can be regioselectively formylated in the ortho position in high yields by treatment with 2 equivalents of paraformaldehyde in aprotic solvents in the presence of $SnCl_4$ and a tertiary amine.[491] Phenols have also been formylated indirectly by conversion to the aryllithium reagent followed by treatment with *N*-formyl piperidine.[492] See also the indirect method mentioned at **11-23**.

[485]Ogata, Y.; Kawasaki, A.; Sugiura, F. *Tetrahedron* ***1968***, *24*, 5001.

[486]Smith, W.E. *J. Org. Chem.* ***1972***, *37*, 3972.

[487]For methods other than those described here, see Smith, R.A.J.; Manas, A.R.B. *Synthesis* ***1984***, 166; Olah, G.A.; Laali, K.; Farooq, O. *J. Org. Chem.* ***1985***, *50*, 1483; Nishino, H.; Tsunoda, K.; Kurosawa, K. *Bull. Chem. Soc. Jpn.* ***1989***, *62*, 545.

[488]Rieche, A.; Gross, H.; Höft, E. *Chem. Ber.* ***1960***, *93*, 88; Lewin, A.H.; Parker, S.R.; Fleming, N.B.; Carroll, F.I. *Org. Prep. Proceed. Int.* ***1978***, *10*, 201.

[489]Gross, H.; Rieche, A.; Matthey, G. *Chem. Ber.* ***1963***, *96*, 308.

[490]Olah, G.A.; Kuhn, S.J. *J. Am. Chem. Soc.* ***1960***, *82*, 2380.

[491]Casiraghi, G.; Casnati, G.; Puglia, G.; Sartori, G.; Terenghi, G. *J. Chem. Soc. Perkin Trans. 1* ***1980***, 1862.

[492]Hardcastle, I.R.; Quayle, P.; Ward, E.L.M. *Tetrahedron Lett.* ***1994***, *35*, 1747.

OS **V**, 49; **VII**, 162.

Reactions **11-19** and **11-20** are direct carboxylations[493] of aromatic rings.[494]

11-19 Carboxylation With Carbonyl Halides

Carboxylation or **Carboxy-de-hydrogenation**

$$ArH + COCl_2 \xrightarrow{AlCl_3} ArCOOH$$

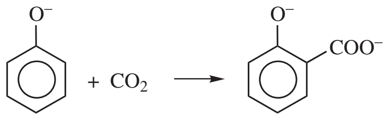
Phosgene, in the presence of Friedel–Crafts catalysts, can carboxylate the ring. This process is analogous to **11-17**, but the ArCOCl initially produced hydrolyzes to the carboxylic acid. However, in most cases the reaction does not take this course, but instead the ArCOCl attacks another ring to give a ketone ArCOAr. A number of other reagents have been used to get around this difficulty, among them oxalyl chloride, urea hydrochloride, chloral Cl_3CCHO,[495] carbamoyl chloride H_2NCOCl, and *N*,*N*-diethylcarbamoyl chloride.[496] With carbamoyl chloride the reaction is called the *Gatterman amide synthesis* and the product is an amide. Among compounds carboxylated by one or another of these reagents are benzene, alkylbenzenes, and fused ring systems.[497]

Although mechanistically different, other methods are available to convert aromatic compounds to aromatic carboxylic acids. The palladium-catalyzed reaction of aromatic compounds and formic acid leads to benzoic acid derivatives.[498] Diphenyliodonium tetrafluoroborate, $Ph_2I^+BF_4^-$ reacts with CO and In in DMF, with a palladium catalyst, to give benzophenone.[499]

OS **V**, 706; **VII**, 420.

11-20 Carboxylation With Carbon Dioxide: The Kolbe–Schmitt Reaction

Carboxylation or **Carboxy-de-hydrogenation**



[493]For other carboxylation methods, one of which leads to the anhydride, see Sakakibara, T.; Odaira, M. *J. Org. Chem.* ***1976***, *41*, 2049; Fujiwara, Y.; Kawata, I.; Kawauchi, T.; Taniguchi, H. *J. Chem. Soc., Chem. Commun.* ***1982***, 132.

[494]For a review, see Olah, G.A.; Olah, J.A., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 1257–1273.

[495]Menegheli, P.; Rezende, M.C.; Zucco, C. *Synth. Commun.* ***1987***, *17*, 457.

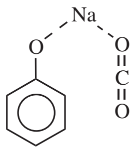
[496]Naumov, Yu.A.; Isakova, A.P.; Kost, A.N.; Zakharov, V.P.; Zvolinskii, V.P.; Moiseikina, N.F.; Nikeryasova, S.V. *J. Org. Chem. USSR* ***1975***, *11*, 362.

[497]For the use of phosgene to carboxylate phenols, see Sartori, G.; Casnati, G.; Bigi, F.; Bonini, G. *Synthesis* ***1988***, 763.

[498]Shibahara, F.; Kinoshita, S.; Nozaki, K. *Org. Lett.* ***2004***, *6*, 2437.

[499]Zhou, T.; Chen, Z.-C. *Synth. Commun.* ***2002***, *32*, 3431.

Sodium phenoxides can be carboxylated, mostly in the ortho position, by carbon dioxide (the *Kolbe–Schmitt reaction*). The mechanism is not clearly understood, but apparently some kind of a complex is formed between the reactants,[500] making the carbon of the CO_2 more positive and putting it in a good



position to attack the ring. Potassium phenoxide, which is less likely to form such a complex,[501] is chiefly attacked in the para position.[502] Carbon tetrachloride can be used instead of CO_2 under Reimer–Tiemann (**11-18**) conditions.

Sodium or potassium phenoxide can be carboxylated regioselectively in the para position in high yield by treatment with sodium or potassium carbonate and carbon monoxide.[503] ^{14}C Labeling showed that it is the carbonate carbon that appears in the *p*-hydroxybenzoic acid product.[504] The CO is converted to sodium or potassium formate. Carbon monoxide has also been used to carboxylate aromatic rings with palladium compounds as catalysts.[505] In addition, a palladium-catalyzed reaction has been used directly to prepare acyl fluorides ArH → ArCOF.[506]

An enzymatic carboxylation was reported, in supercritical CO_2 (see p. $$$), in which exposure of pyrrole to *Bacillus megaterium* PYR2910 and $KHCO_3$ gave the potassium salt of pyrrole-2-carboxylic acid.[507]

OS **II**, 557.

11-21 Amidation

N-**Alkylcarbamoyl-de-hydrogenation**

$$\text{ArH} + \text{RNCO} \xrightarrow{\text{AlCl}_3} \text{ArCONHR}$$

[500]Hales J.L.; Jones, J.I.; Lindsey, A.S. *J. Chem. Soc.* ***1954***, 3145.

[501]There is evidence that, in the complex formed from potassium salts, the bonding is between the aromatic compound and the carbon atom of CO_2: Hirao, I.; Kito, T. *Bull. Chem. Soc. Jpn.* ***1973***, *46*, 3470.

[502]Actually, the reaction seems to be more complicated than this. At least part of the potassium *p*-hydroxybenzoate that forms comes from a rearrangement of initially formed potassium salicylate. Sodium salicylate does not rearrange. See Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 344–348. See also, Ota, K. *Bull. Chem. Soc. Jpn.* ***1974***, *47*, 2343.

[503]Yasuhara, Y.; Nogi, T. *J. Org. Chem.* ***1968***, *33*, 4512, *Chem. Ind. (London)* ***1969***, 77.

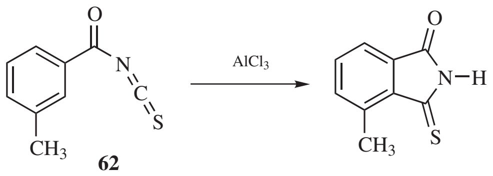
[504]Yasuhara, Y.; Nogi, T.; Saishō *Bull. Chem. Soc. Jpn.* ***1969***, *42*, 2070.

[505]See Sakakibara, T.; Odaira, Y. *J. Org. Chem.* ***1976***, *41*, 2049; Jintoku, T.; Taniguchi, H.; Fujiwara, Y. *Chem. Lett.* ***1987***, 1159; Ugo, R.; Chiesa, A. *J. Chem. Soc. Perkin Trans. 1* ***1987***, 2625.

[506]Sakakura, T.; Chaisupakitsin, M.; Hayashi, T.; Tanaka, M. *J. Organomet. Chem.* ***1987***, *334*, 205.

[507]Matsuda, T.; Ohashi, Y.; Harada, T.; Yanagihara, R.; Nagasawa, T.; Nakamura, K. *Chem. Commun.* ***2001***, 2194.

N-Substituted amides can be prepared by direct attack of isocyanates on aromatic rings.[508] The R group may be alkyl or aryl, but if the latter, dimers and trimers are also obtained. Isothiocyanates similarly give thioamides.[509] The reaction has been carried out intramolecularly both with aralkyl isothiocyanates and acyl isothiocyanates.[510] In the latter case, the product is easily hydrolyzable to a dicarboxylic acid; this is a way



of putting a carboxyl group on a ring ortho to one already there (**62** is prepared by treatment of the acyl halide with lead thiocyanate). The reaction gives better yields with substrates of the type $ArCH_2CONCS$, where six-membered rings are formed.

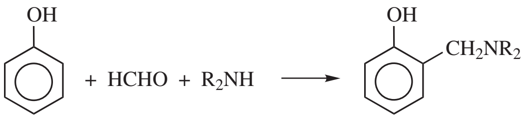
There are interesting transition metal-catalyzed-reactions that lead to aryl amides. The use of $POCl_3$ and DMF, with a palladium catalyst, converts aryl iodides to benzamides.[511] A palladium-catalyzed reaction of aryl halides and formamide leads to benzamide derivatives.[512] Carbonylation is another method that generates amides. When an aryl iodide was treated with a secondary amine and $Mo(CO)_6$, in the presence of 3 equivalents of DBU, 10% $Pd(OAc)_2$, with microwave irradiation at 100°C, the corresponding benzamide was obtained.[513]

OS **V**, 1051; **VI**, 465.

Reactions **11-12–11-23** involve the introduction of a CH_2Z group, where Z is halogen, hydroxyl, amino, or alkylthio. They are all Friedel–Crafts reactions of aldehydes and ketones and, with respect to the carbonyl compound, additions to the C=O double bond. They follow mechanisms discussed in Chapter 16.

11-22 Aminoalkylation and Amidoalkylation

Dialkylaminoalkylation or **Dialkylamino-de-hydrogenation**



[508]Effenberger, F.; Gleiter, R.; Heider, L.; Niess, R. *Chem. Ber.* ***1968***, *101*, 502; Piccolo, O.; Filippini, L.; Tinucci, L.; Valoti, E.; Citterio, A. *Tetrahedron* ***1986***, *42*, 885.

[509]Jagodziński, T. *Synthesis* ***1988***, 717.

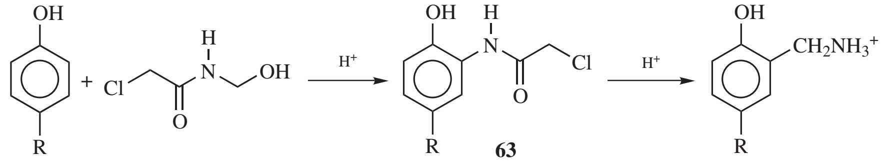
[510]Smith, P.A.S.; Kan, R.O. *J. Org. Chem.* ***1964***, *29*, 2261.

[511]Hosoi, K.; Nozaki, K.; Hiyama, T. *Org. Lett.* ***2002***, *4*, 2849.

[512]Schnyder, A.; Beller, M.; Mehltretter, G.; Nsenda, T.; Studer, M.; Indolese, A.F. *J. Org. Chem.* ***2001***, *66*, 4311. See also, Schnyder, A.; Indolese, A.F. *J. Org. Chem.* ***2002***, *67*, 594.

[513]Wannberg, J.; Larhed, M. *J. Org. Chem.* ***2003***, *68*, 5750.

Phenols, secondary and tertiary aromatic amines,[514] pyrroles, and indoles can be aminomethylated by treatment with formaldehyde and a secondary amine. Other aldehydes have sometimes been employed. Aminoalkylation is a special case of the Mannich reaction (**16-19**). When phenols and other activated aromatic compounds are treated with *N*-hydroxymethylchloroacetamide, *amidomethylation* takes place[515] to

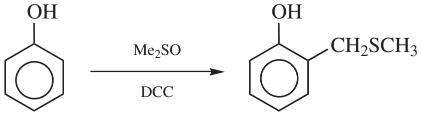


give **63**, which is often hydrolyzed *in situ* to the aminoalkylated product. Other *N*-hydroxyalkyl and *N*-chlorinated compounds have also been used.[374]

OS **I**, 381; **IV**, 626; **V**, 434; **VI**, 965; **VII**, 162.

11-23 Thioalkylation

Alkylthioalkylation or **Alkylthioalkyl-de-hydrogenation**



A methylthiomethyl group can be inserted into the ortho position of phenols by heating with dimethyl sulfoxide and dicyclohexylcarbodiimide (DCC).[516] Other reagents can be used instead of DCC, among them $SOCl_2$,[517] and acetic anhydride.[518] Alternatively, the phenol can be treated with dimethyl sulfide and *N*-chlorosuccinimide, followed by triethylamine.[519] The reaction can be applied to amines (to give *o*-$NH_2C_6H_4CH_2SMe$) by treatment with *t*-BuOCl, Me_2S, and NaOMe in CH_2Cl_2.[520] Aromatic hydrocarbons have been thioalkylated with ethyl α-(chloromethylthio)-acetate $ClCH_2SCH_2COOEt$ (to give $ArCH_2SCH_2CO$-OEt)[521] and with methyl methylsulfinylmethyl sulfide $MeSCH_2SOMe$ or methylthiomethyl *p*-tolyl sulfone $MeSCH_2$-$SO_2C_6H_4Me$ (to give $ArCH_2SMe$),[522] in each case with a Lewis acid catalyst.

OS **VI**, 581, 601.

[514]Miocque, M.; Vierfond, J. *Bull. Soc. Chim. Fr.* ***1970***, 1896, 1901, 1907.

[515]For a review, see Zaugg, H.E. *Synthesis* ***1984***, 85.

[516]Burdon, M.G.; Moffatt, J.G. *J. Am. Chem. Soc.* ***1966***, *88*, 5855, ***1967***, *89*, 4725; Olofson, R.A.; Marino, J.P. *Tetrahedron* ***1971***, *27*, 4195.

[517]Sato, K.; Inoue, S.; Ozawa, K.; Tazaki, M. *J. Chem. Soc. Perkin Trans. 1* ***1984***, 2715.

[518]Hayashi, Y.; Oda, R. *J. Org. Chem.* ***1967***, *32*, 457; Pettit, G.H.; Brown, T.H. *Can. J. Chem.* ***1967***, *45*, 1306; Claus, P. *Monatsh. Chem.* ***1968***, *99*, 1034.

[519]Gassman, P.G.; Amick, D.R. *J. Am. Chem. Soc.* ***1978***, *100*, 7611.

[520]Gassman, P.G.; Gruetzmacher, G. *J. Am. Chem. Soc.* ***1973***, *95*, 588; Gassman, P.G.; van Bergen, T.J. *J. Am. Chem. Soc.* ***1973***, *95*, 590, 591.

[521]Tamura, Y.; Tsugoshi, T.; Annoura, H.; Ishibashi, H. *Synthesis* ***1984***, 326.

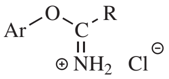
[522]Torisawa, Y.; Satoh, A.; Ikegami, S. *Tetrahedron Lett. 1988, 29*, 1729.

11-24 Acylation with Nitriles: The Hoesch Reaction

Acylation or **Acyl-de-hydrogenation**

$$ArH + RCN \xrightarrow[ZnCl_2]{HCl} ArCOR$$

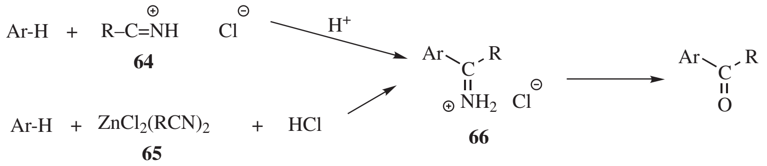
Friedel–Crafts acylation with nitriles and HCl is called the *Hoesch* or the *Houben–Hoesch reaction*.[523] In most cases, a Lewis acid is necessary; zinc chloride is the most common. The reaction is generally useful only with phenols, phenolic ethers, and some reactive heterocyclic compounds such as pyrrole, but it can be extended to aromatic amines by the use of BCl_3.[524] Acylation in the case of aniline derivatives is regioselectively ortho. Monohydric phenols, however, generally do not give ketones[525] but are attacked at the oxygen to



An imino ester

produce imino esters. Many nitriles have been used. Even aryl nitriles give good yields if they are first treated with HCl and $ZnCl_2$ and then the substrate added at 0°C.[526] In fact, this procedure increases yields with any nitrile. If thiocyanates RSCN are used, thiol esters ArCOSR can be obtained. The Gatterman reaction (**11-18**) is a special case of the Hoesch synthesis.

The reaction mechanism is complex and not completely settled.[527] The first stage consists of an attack on the substrate by a species containing the nitrile and HCl (and the Lewis acid, if present) to give an imine salt (**66**). Among the possible attacking species are **64** and **65**. In the second stage, the salts are hydrolyzed to the products, first the iminium salt, and then the ketone. Ketones can also be obtained by treating phenols or phenolic ethers with a nitrile in the presence of F_3CSO_2OH.[528] The mechanism in this case is different.



OS **II**, 522.

[523]For a review, see Ruske, W., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 383–497.

[524]Sugasawa, T.; Toyoda, T.; Adachi, M.; Sasakura, K. *J. Am. Chem. Soc.* ***1978***, *100*, 4842; Sugasawa, T.; Adachi, M.; Sasakura, K.; Kitagawa, A. *J. Org. Chem.* ***1979***, *44*, 578.

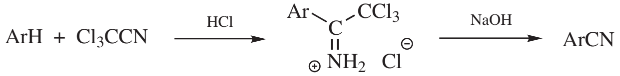
[525]For an exception, see Toyoda, T.; Sasakura, K.; Sugasawa, T. *J. Org. Chem.* ***1981***, *46*, 189.

[526]Zil'berman, E.N.; Rybakova, N.A. *J. Gen. Chem. USSR* ***1960***, *30*, 1972.

[527]For discussions, see Ruske, W., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, p. 383; Jeffery, E.A.; Satchell, D.P.N. *J. Chem. Soc. B* ***1966***, 579.

[528]Amer, M.I.; Booth, B.L.; Noori, G.F.M.; Proença, M.F.J.R.P. *J. Chem. Soc. Perkin Trans. 1* ***1983***, 1075.

11-25 Cyanation or Cyano-de-hydrogenation



Aromatic hydrocarbons (including benzene), phenols, and phenolic ethers can be cyanated with trichloroacetonitrile, BrCN, or mercury fulminate Hg(ONC)$_2$.[529] In the case of Cl_3CCN, the actual attacking entity is probably $Cl_3C{-}\overset{\oplus}{C}{=}NH$, formed by addition of a proton to the cyano nitrogen. Secondary aromatic amines ArNHR, as well as phenols, can be cyanated in the ortho position with Cl_3CCN and BCl_3.[530]

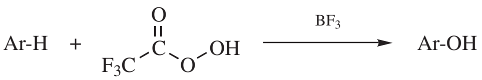
It is noted that aryl triflates are converted to the aryl nitrile by treatment with $Zn(CN)_2$ and a palladium catalyst.[531]

OS **III**, 293.

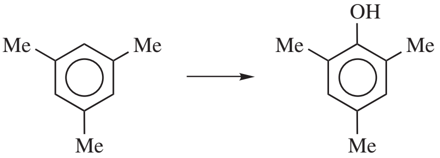
F. Oxygen Electrophiles

Oxygen electrophiles are very uncommon, since oxygen does not bear a positive charge very well. However, there is one reaction that can be mentioned.

11-26 Hydroxylation or Hydroxy-de-hydrogenation



There have been only a few reports of direct hydroxylation[532] by an electrophilic process (see, however, **14-5**).[533] In general, poor results are obtained, partly because the introduction of an OH group activates the ring to further attack. Quinone formation is common. However, alkyl-substituted benzenes, such as mesitylene or durene can be hydroxylated in good yield with trifluoroperacetic acid and boron trifluoride.[534] In the case of mesitylene, the product (**67**) is not subject to further attack.



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[529]Olah, G.A., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 1, Wiley, NY, ***1963***, pp. 119–120.

[530]Adachi, M.; Sugasawa, T. *Synth. Commun.* ***1990***, *20*, 71.

[531]Kubota, H.; Rice, K.C. *Tetrahedron Lett.* ***1998***, *39*, 2907.

[532]For a list of hydroxylation reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 977–978.

[533]For reviews of electrophilic hydroxylation, see Jacquesy, J.; Gesson, J.; Jouannetaud, M. *Rev. Chem. Intermed.* ***1988***, *9*, 1, see pp. 5–10; Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Academic Press, NY, ***1985***, pp. 173–176, 347–350.

[534]Hart, H.; Buehler, C.A. *J. Org. Chem.* ***1964***, *29*, 2397. See also, Hart, H. *Acc. Chem. Res.* ***1971***, *4*, 337.

In a related procedure, even benzene and substituted benzenes (e.g., PhMe, PhCl, xylenes) can be converted to phenols in good yields with sodium perborate–F_3CSO_2OH.[535] Aromatic amines, *N*-acyl amines, and phenols were hydroxylated with H_2O_2 in SbF_5—HF.[536] Pyridine and quinoline were converted to their 2-acetoxy derivatives in high yields with acetyl hypofluorite AcOF at −75°C.[537]

Another hydroxylation reaction is the *Elbs reaction*.[538] In this method phenols can be oxidized to *p*-diphenols with $K_2S_2O_8$ in alkaline solution.[539] Primary, secondary, or tertiary aromatic amines give predominant or exclusive ortho substitution unless both ortho positions are blocked, in which case para substitution is found. The reaction with amines is called the *Boyland–Sims oxidation*. Yields are low with either phenols or amines, generally <50%. The mechanisms are not clear,[540] but for the Boyland–Sims oxidation there is evidence that the $S_2O_8{}^{2-}$ ion attacks at the ipso position, and then a migration follows.[541]

Electrolysis of benzene, in the presence of trifluoroacetic acid and triethylamine, leads to a 73% yield of phenol.[542]

G. Metal Electrophiles

Reactions in which a metal replaces the hydrogen of an aromatic ring are considered along with their aliphatic counterparts in Chapter 12 (**12-22** and **12-23**).

HYDROGEN AS THE LEAVING GROUP IN REARRANGEMENT REACTIONS

In these reactions, a group is detached from a *side chain* and then attacks the ring, but in other aspects they resemble the reactions already treated in this chapter.[543] Since a group moves from one position to another in a molecule, these are rearrangements. In all these reactions, the question arises as to whether the group that cleaves from a given molecule attacks the same molecule or another one, that is is the reaction intramolecular or intermolecular? For intermolecular reactions the mechanism is the same as ordinary aromatic substitution, but for intramolecular

[535]Prakash, G.K.S.; Krass, N.; Wang, Q.; Olah, G.A. *Synlett* ***1991***, 39.

[536]Berrier, C.; Carreyre, H.; Jacquesy, J.; Joannetaud, M. *New J. Chem.* ***1990***, *14*, 283, and cited references.

[537]Rozen, S.; Hebel, D.; Zamir, D. *J. Am. Chem. Soc.* ***1987***, *109*, 3789.

[538]For a review of the Elbs and Boyland–Sims reactions, see Behrman, E.J. *Org. React.* ***1988***, *35*, 421.

[539]For a method for the ortho hydroxylation of phenols, see Capdevielle, P.; Maumy, M. *Tetrahedron Lett.* ***1982***, *23*, 1573, 1577.

[540]Behrman, E.J. *J. Am. Chem. Soc.* ***1967***, *89*, 2424; Ogata, Y.; Akada, T. *Tetrahedron* ***1970***, *26*, 5945; Walling, C.; Camaioni, D.M.; Kim, S.S. *J. Am. Chem. Soc.* ***1978***, *100*, 4814.

[541]Srinivasan, C.; Perumal, S.; Arumugam, N. *J. Chem. Soc. Perkin Trans. 2* ***1985***, 1855.

[542]Fujimoto, K.; Tokuda, Y.; Maekawa, H.; Matsubara, Y.; Mizuno, T.; Nishiguchi, I. *Tetrahedron* ***1996***, *52*, 3889; Fujimoto, K.; Maekawa, H.; Tokuda, Y.; Matsubara, Y.; Mizuno, T.; Nishiguchi, I. *SynLett*, ***1995***, 661.

[543]For a monograph, see Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***. For reviews, see Williams, D.L.H.; Buncel, I.M. *Isot. Org. Chem.* ***1980***, *5*, 147; Williams, D.L.H., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 433–486.

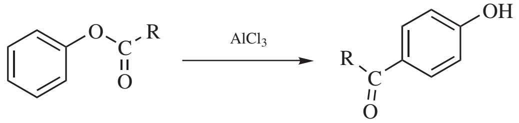
cases the migrating group could never be completely free, or else it would be able to attack another molecule. Since the migrating species in intramolecular rearrangements is thus likely to remain near the atom from which it cleaved, it has been suggested that intramolecular reactions are more likely to lead to ortho products than are the intermolecular type. This characteristic has been used, among others, to help decide whether a given rearrangement is inter- or intramolecular, though there is evidence that at least in some cases, an intermolecular mechanism can still result in a high degree of ortho migration.[544]

The Claisen (**18-33**) and benzidine (**18-36**) rearrangements, which superficially resemble those in this section, have different mechanisms and are treated in Chapter 18.

A. Groups Cleaving from Oxygen

11-27 The Fries Rearrangement

1/*C*-Hydro,5/*O*-acyl-interchange[545]



Phenolic esters can be rearranged by heating with Friedel–Crafts catalysts in a synthetically useful reaction known as the *Fries rearrangement*.[546] Both *o*- and *p*-acylphenols can be produced, and it is often possible to select conditions so that either one predominates. The ortho/para ratio is dependent on the temperature, solvent, and amount of catalyst used. Exceptions are known, but low temperatures generally favor the para product and high temperatures the ortho product. The R group may be aliphatic or aromatic. Any meta-directing substituent on the ring interferes with the reactions, as might be expected for a Friedel–Crafts process. In the case of aryl benzoates treated with F_3CSO_2OH, the Fries rearrangement was shown to be reversible and an equilibrium was established.[547] Transition-metal-catalyzed Fries rearrangements have been reported.[548]

[544]See Dawson, I.M.; Hart, L.S.; Littler, J.S. *J. Chem. Soc. Perkin Trans. 2* ***1985***, 1601.

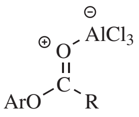
[545]This is the name for the para migration. For the ortho migration, the name is 1/*C*-hydro,3/*O*-acyl-interchange.

[546]For reviews, see Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 72–82, 365–368; Gerecs, A., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 499–533. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, p. 1310.

[547]Effenberger, F.; Gutmann, R. *Chem. Ber.* ***1982***, *115*, 1089.

[548]With **Sc(OTf)$_3$**, see Kobayashi, S.; Moriwaki, M.; Hachiya, I. *Tetrahedron Lett.* ***1996***, *37*, 4183; with $ZrCl_4$ see Harrowven, D.C.; Dainty, R.F. *Tetrahedron Lett.* ***1996***, *37*, 7659; with **Hf(OTf)$_4$** see Kobayashi, S.; Moriwaki, M.; Hachiya, I. *Tetrahedron Lett.* ***1996***, *37*, 2053. Also see Kobayashi, S.; Moriwaki, M.; Hachiya, I. *J. Chem. Soc., Chem. Commun.* ***1995***, 1527.

The exact mechanism has still not been completely worked out.[549] Opinions have been expressed that it is completely intermolecular,[550] completely intramolecular,[551] and partially inter- and intramolecular.[552] One way to decide between inter- and intramolecular processes is to run the reaction of the phenolic ester in the presence of another aromatic compound, say, toluene. If some of the toluene is acylated, the reaction must be, at least in part, intermolecular. If the toluene is not acylated, the presumption is that the reaction is intramolecular, though this is not certain, for it may be that the toluene is not attacked because it is less active than the other. A number of such experiments (called *crossover experiments*) have been carried out; sometimes crossover products have been found and sometimes not. As in **11-17**, an initial complex (**68**) is formed between the substrate and the catalyst, so that a catalyst/substrate molar ratio of at least 1:1 is required. In the presence of aluminum chloride, the Fries rearrangement can be induced with microwave irradiation.[553] Simply heating phenyl acetate with microwave irradiation gives the Fries rearrangement.[554] The Fries rearrangement has been carried out in ionic melts.[555]



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The Fries rearrangement can also be carried out with UV light, in the absence of a catalyst.[556] This reaction, called the *photo-Fries rearrangement*,[557] is predominantly an intramolecular free-radical process. Both ortho and para migration are observed.[558] Unlike the Lewis acid-catalyzed Fries rearrangement, the photo-Fries reaction can be accomplished, though often in low yields, when meta-directing groups are on the ring. The available evidence strongly suggests the following

[549]For the mechanism in polyphosphoric acid, see Sharghi, H.; Eshghi, H. *Bull. Chem. Soc. Jpn.* ***1993***, *66*, 135.

[550]Martin, R.; Gavard, J.; Delfly, M.; Demerseman, P.; Tromelin, A. *Bull. Soc. Chim. Fr.* ***1986***, 659 and cited references.

[551]Ogata, Y.; Tabuchi, H. *Tetrahedron* ***1964***, *20*, 1661.

[552]Munavilli, S. *Chem. Ind. (London)* ***1972***, 293; Warshawsky, A.; Kalir, R.; Patchornik, A. *J. Am. Chem. Soc.* ***1978***, *100*, 4544; Dawson, I.M.; Hart, L.S.; Littler, J.S. *J. Chem. Soc. Perkin Trans. 2* ***1985***, 1601.

[553]Khadilkar, B.M.; Madyar, V.R. *Synth. Commun.* ***1999***, *29*, 1195.

[554]Paul, S.; Gupta, M. *Synthesis* ***2004***, 1789.

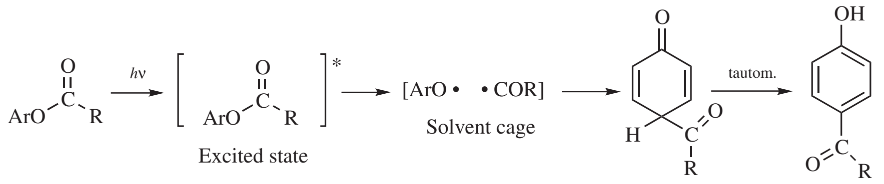
[555]Harjani, J.R.; Nara, S.J.; Salunkhe, M.M. *Tetrahedron Lett.* ***2001***, *42*, 1979.

[556]Kobsa, H. *J. Org. Chem.* ***1962***, *27*, 2293; Anderson, J.C.; Reese, C.B. *J. Chem. Soc.* ***1963***, 1781; Finnegan, R.A.; Matice, J.J. *Tetrahedron* ***1965***, *21*, 1015.

[557]For reviews, see Belluš, D. *Adv. Photochem.* ***1971***, *8*, 109; Belluš, D.; Hrdlovič, P. *Chem. Rev.* ***1967***, *67*, 599; Stenberg, V.I. *Org. Photochem.* ***1967***, *1*, 127. See Cui, C.; Wang, X.; Weiss, R.G. *J. Org. Chem.* ***1996***, *61*, 1962.

[558]The migration can be made almost entirely ortho by cyclodextrin encapsulation (see p. 129): Syamala, M.S.; Rao, B.N.; Ramamurthy, V. *Tetrahedron* ***1988***, *44*, 7234. See also, Veglia, A.V.; Sanchez, A.M.; de Rossi, R.H. *J. Org. Chem.* ***1990***, *55*, 4083.

mechanism involving formation of the excited state ester followed by dissociation to a radical pair[559] for the photo-Fries rearrangement[560] (illustrated for para attack).



The phenol ArOH is always a side product, resulting from some ArO• that leaks from the solvent cage and abstracts a hydrogen atom from a neighboring molecule. When the reaction was performed on phenyl acetate in the gas phase, where there are no solvent molecules to form a cage (but in the presence of isobutane as a source of abstractable hydrogens), phenol was the chief product and virtually no *o*- or *p*-hydroxyacetophenone was found.[561] Other evidence[562] for the mechanism is that CIDNP has been observed during the course of the reaction[563] and that the ArO•radical has been detected by flash photolysis[564] and by nanosecond time-resolved Raman spectroscopy.[565]

Treatment of *O*-arylsulfonate esters with $AlCl_3$—$ZnCl_2$, on silica with microwave irradiation, leads to 2-sulfonyl phenols in a thia-Fries rearrangement.[566] A similar reaction was reported with *O*-arylsulfonamides.[567]

OS **II**, 543; **III**, 280, 282.

B. Groups Cleaving from Nitrogen[568]

It has been shown that $PhNH_2D$ rearranges to *o*- and *p*-deuterioaniline.[569] The migration of OH, formally similar to reactions **11-28–11-32**, is a nucleophilic substitution and is treated in Chapter 13 (**13-32**).

[559]Proposed by Kobsa, H. *J. Org. Chem.* ***1962***, *27*, 2293.

[560]It has been suggested that a second mechanism, involving a four-center transition state, is also possible: Bellus, D.; Schaffner, K.; Hoigné, J. *Helv. Chim. Acta* ***1968***, *51*, 1980; Sander, M.R.; Hedaya, E.; Trecker, D.J. *J. Am. Chem. Soc.* ***1968***, *90*, 7249; Belluš, D. *Adv. Photochem.* ***1971***, *8*, 109.

[561]Meyer, J.W.; Hammond, G.S. *J. Am. Chem. Soc.* ***1972***, *94*, 2219.

[562]For evidence from isotope effect studies, see Shine, H.J.; Subotkowski, W. *J. Org. Chem.* ***1987***, *52*, 3815.

[563]Adam, W.; Arce de Sanabia, J.; Fischer, H. *J. Org. Chem.* ***1973***, *38*, 2571; Adam, W. *J. Chem. Soc., Chem. Commun.* ***1974***, 289.

[564]Kalmus, C.E.; Hercules D.M. *J. Am. Chem. Soc.* ***1974***, *96*, 449.

[565]Beck, S.M.; Brus, L.E. *J. Am. Chem. Soc.* ***1982***, *104*, 1805.

[566]Moghaddam, F.M.; Dakamin, M.G. *Tetrahedron Lett.* ***2000***, *41*, 3479.

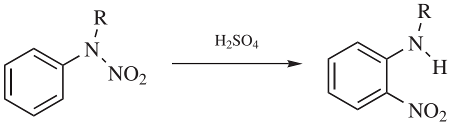
[567]Benson, G.A.; Maughan, P.J.; Shelly, D.P.; Spillane, W.J. *Tetrahedron Lett.* ***2001***, *42*, 8729.

[568]For a review, see Stevens, T.S.; Watts, W.E. *Selected Molecular Rearrangements*, Van Nostrand-Reinhold, Princeton, NJ ***1973***, pp. 192–199.

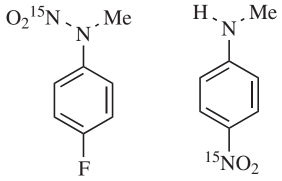
[569]Okazaki, N.; Okumura, A. *Bull. Chem. Soc. Jpn.* ***1961***, *34*, 989.

11-28 Migration of the Nitro Group

1/*C*-Hydro,3/*N*-nitro-interchange



N-Nitro aromatic amines rearrange on treatment with acids to *o*- and *p*-nitroamines with the ortho compounds predominating.[570] Aside from this indication of an intramolecular process, there is also the fact that virtually no meta isomer is produced in this reaction,[571] although direct nitration of an aromatic amine generally gives a fair amount of meta product. Thus a mechanism in which NO_2^+ is dissociated from the ring, and then attacks another molecule must be ruled out. Further results indicating an intramolecular process include the observation that rearrangement of several substrates in the presence of $K^{15}NO_3$ gave products containing no ^{15}N,[572] and that rearrangement of a mixture of $PhNH^{15}NO_2$ and unlabeled *p*-$MeC_6H_4NHNO_2$ gave 2-nitro-4-methylaniline containing no ^{15}N.[573] On the other hand, rearrangement of **69** in the presence of



69 **70**

unlabeled $PhNMeNO_2$ gave labeled **70**, which did not arise by displacement of F.[574] The R group may be hydrogen or alkyl. Two principal mechanisms have been suggested, one involving cyclic attack by the oxygen of the nitro group at the ortho position before the group cleaves,[575] and the other involving a cleavage into a

[570]For reviews, see Williams, D.L.H., in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 1, Wiley, NY, ***1982***, pp. 127–153; White, W.N. *Mech. Mol. Migr.* ***1971***, *3*, 109–143; Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 235–249.

[571]Hughes, E.D.; Jones, G.T. *J. Chem. Soc.* ***1950***, 2678.

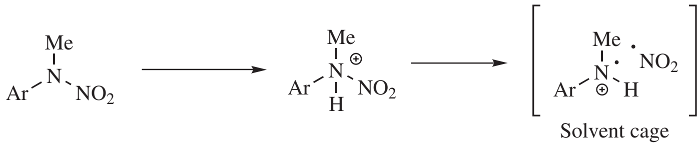
[572]Brownstein, S.; Bunton, C.A.; Hughes, E.D. *J. Chem. Soc.* ***1958***, 4354; Banthorpe, D.V.; Thomas, J.A.; Williams, D.L.H. *J. Chem. Soc.* ***1965***, 6135.

[573]Geller, B.A.; Dubrova, L.N. *J. Gen. Chem. USSR* ***1960***, *30*, 2627.

[574]White, W.N.; Golden, J.T. *J. Org. Chem.* ***1970***, *35*, 2759.

[575]Banthorpe, D.V.; Thomas, J.A. *J. Chem. Soc.* ***1965***, 7149, 7158. Also see, Brownstein, S.; Bunton, C.A.; Hughes, E.D. *J. Chem. Soc.* ***1958***, 4354; Banthorpe, D.V.; Thomas, J.A.; Williams, D.L.H. *J. Chem. Soc.* ***1965***, 6135.

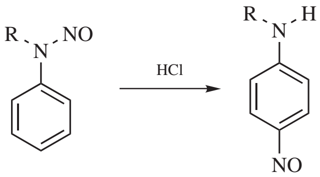
radical and a radical ion held together in a solvent cage.[576] Among the evidence for the latter view[577] are



the effects of substituents on the rate of the reaction,[578] ^{15}N and ^{14}C kinetic isotope effects that show non-concertedness,[579] and the fact that both *N*-methylaniline and nitrous acid are produced in sizable and comparable amounts in addition to the normal products *o*- and *p*-nitro-*N*-methylaniline.[580] These side products are formed when the radicals escape from the solvent cage.

11-29 Migration of the Nitroso Group: The Fischer–Hepp Rearrangement

1/*C*-Hydro-5/*N*-nitroso-interchange



The migration of a nitroso group, formally similar to **11-28**, is important because *p*-nitroso secondary aromatic amines cannot generally be prepared by direct *C*-nitrosation of secondary aromatic amines (see **12-50**). The reaction, known as the *Fischer–Hepp rearrangement*,[581] is brought about by treatment of *N*-nitroso secondary aromatic amines with HCl. Other acids give poor or no results. In benzene systems the para product is usually formed exclusively.[582] The mechanism of the rearrangement is not completely understood. The fact that the reaction takes place in a large excess of urea[583] shows that it is intramolecular[584] since, if NO^+, NOCl,

[576]White, W.N.; White, H.S.; Fentiman, A. *J. Org. Chem.* ***1976***, *41*, 3166.

[577]For additional evidence, see White, W.N.; Klink, J.R. *J. Org. Chem.* ***1977***, *42*, 166; Ridd, J.H.; Sandall, J.P.B. *J. Chem. Soc., Chem. Commun.* ***1982***, 261.

[578]White, W.N.; Klink, J.R. *J. Org. Chem.* ***1970***, *35*, 965.

[579]Shine, H.J.; Zygmunt, J.; Brownawell, M.L.; San Filippo, Jr., J. *J. Am. Chem. Soc.* ***1984***, *106*, 3610.

[580]White, W.N.; White, H.S. *J. Org. Chem.* ***1970***, *35*, 1803.

[581]For reviews, see Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, ***1988***, pp. 113–128; Williams, D.L.H., in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 1, Wiley, NY, ***1982***, Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 231–235.

[582]For a report of formation of 15% ortho product in the case of *N,N*-diaryl-*N*-nitroso amides, see Titova, S.P.; Arinich, A.K.; Gorelik, M.V. *J. Org. Chem. USSR* ***1986***, *22*, 1407.

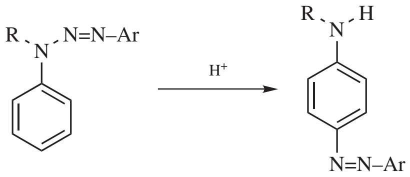
[583]Aslapovskaya, T.I.; Belyaev, E.Yu.; Kumarev, V.P.; Porai-Koshits, B.A. *Org. React. USSR* ***1968***, *5*, 189; Morgan, T.D.B.; Williams, D.L.H. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 74.

[584]See also, Belyaev, E.Yu.; Nikulicheva, T.I. *Org. React. USSR* ***1971***, *7*, 165; Williams, D.L.H. *Tetrahedron* ***1975***, *31*, 1343; *J. Chem. Soc. Perkin Trans. 2* ***1982***, 801.

or some similar species were free in the solution, it would be captured by the urea, preventing the rearrangement.

11-30 Migration of an Arylazo Group

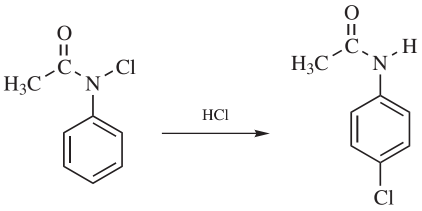
1/*C*-Hydro-5/*N*-arylazo-interchange



Rearrangement of aryl triazenes can be used to prepare azo derivatives of primary and secondary aromatic amines.[585] These are first diazotized at the amino group (see **11-4**) to give triazenes, which are then rearranged by treatment with acid. The rearrangement always gives the para isomer, unless that position is occupied.

11-31 Migration of Halogen: The Orton Rearrangement

1/*C*-Hydro-5/*N*-halo-interchange



Migration of a halogen from a nitrogen side chain to the ring by treatment with HCl is called the *Orton rearrangement*.[586] The main product is the para isomer, though some ortho product may also be formed. The reaction has been carried out with *N*-chloro- and *N*-bromoamines and less often with *N*-iodo compounds. The amine must be acylated, except that $PhNCl_2$ gives 2,4-dichloroaniline. The reaction is usually performed in water or acetic acid. There is considerable evidence (cross-halogenation, labeling, etc.) that this is an intermolecular process.[587] First, the HCl reacts with the starting material to give $ArNHCOCH_3$ and Cl_2; then the chlorine halogenates the ring as in **11-10**. Among the evidence is that chlorine has been isolated from the reaction mixture. The Orton rearrangement can also

[585]For a review, see Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 212–221.

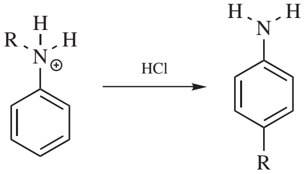
[586]For reviews, see Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 221–230, 362–364: Bieron, J.F.; Dinan, F.J., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 263–269.

[587]The reaction has been found to be intramolecular in aprotic solvents: Golding, P.D.; Reddy, S.; Scott, J.M.W.; White, V.A.; Winter, J.G. *Can. J. Chem.* ***1981***, *59*, 839.

be brought about photochemically[588] and by heating in the presence of benzoyl peroxide.[589] These are free-radical processes.

11-32 Migration of an Alkyl Group[590]

1/*C*-Hydro-5/*N*-alkyl-interchange



When HCl salts of arylalkylamines are heated at ~200–300°C, migration occurs in what is called the *Hofmann–Martius reaction.* It is an intermolecular reaction, since crossing is found. For example, methylanilinium bromide gave not only the normal products *o*- and *p*-toluidine but also aniline and di- and trimethylanilines.[591] As would be expected for an intermolecular process, there is isomerization when R is primary.

With primary R, the reaction probably goes through the alkyl halide formed initially in an S_N2 reaction:

$$R\overset{\oplus}{N}H_2Ar + Cl^- \longrightarrow RCl + ArNH_2$$

Evidence for this view is that alkyl halides have been isolated from the reaction mixture and that Br^-, Cl^-, and I^- gave different ortho/para ratios, which indicates that the halogen is involved in the reaction.[591] Further evidence is that the alkyl halides isolated are not rearranged (as would be expected if they are formed by an S_N2 mechanism), even though the alkyl groups in the ring are rearranged. Once the alkyl halide is formed, it reacts with the substrate by a normal Friedel–Crafts alkylation process (**11-11**), accounting for the rearrangement. When R is secondary or tertiary, carbocations may be directly formed so that the reaction does not go through the alkyl halides.[592]

It is also possible to carry out the reaction by heating the amine (not the salt) at a temperature between 200 and 350°C with a metal halide, such as $CoCl_2$, $CdCl_2$, or $ZnCl_2$. When this is done, the reaction is called the *Reilly–Hickinbottom rearrangement*. Primary R groups larger than ethyl give both rearranged and unrearranged products.[593] The reaction is not generally useful for secondary and tertiary R groups, which are usually cleaved to alkenes under these conditions.

[588]For example, see Hodges, F.W. *J. Chem. Soc.* ***1933***, 240.

[589]For example, Ayad, K.N.; Beard, C.; Garwood, R.F.; Hickinbottom, W.J. *J. Chem. Soc.* ***1957***, 2981; Coulson, J.; Williams, G.H.; Johnston, K.M. *J. Chem. Soc. B* ***1967***, 174.

[590]For reviews, see Grillot, G.F. *Mech. Mol. Migr.* ***1971***, *3* 237; Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 249–257.

[591]Ogata, Y.; Tabuchi, H.; Yoshida, K. *Tetrahedron* ***1964***, *20*, 2717.

[592]Hart, H.; Kosak, J.R. *J. Org. Chem.* ***1962***, *27*, 116.

[593]For example, see Birchal, J.M.; Clark, M.T.; Goldwhite, H.; Thorpe, D.H. *J. Chem. Soc. Perkin Trans. 1* ***1972***, 2579.

When acylated arylamines are photolyzed, migration of an acyl group takes place[594] in a process that resembles the photo-Fries reaction (**11-27**).

OTHER LEAVING GROUPS

Three types of reactions are considered in this section.

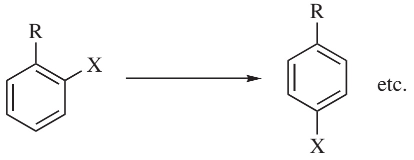
1. Reactions in which hydrogen replaces another leaving group:

$$\mathrm{ArX} + \mathrm{H}^+ \longrightarrow \mathrm{ArH}$$

2. Reactions in which an electrophile other than hydrogen replaces another leaving group:

$$\mathrm{ArX} + \mathrm{Y}^+ \longrightarrow \mathrm{ArY}$$

3. Reactions in which a group (other than hydrogen) migrates from one position in a ring to another. Such migrations can be either inter- or intramolecular:



The three types are not treated separately, but reactions are classified by leaving group.

A. Carbon Leaving Groups

11-33 Reversal of Friedel–Crafts Alkylation

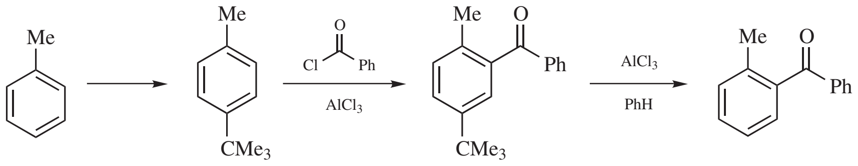
Hydro-de-alkylation or **Dealkylation**

$$\mathrm{ArR} + \mathrm{H}^+ \xrightarrow{\mathrm{AlCl_3}} \mathrm{ArH}$$

Alkyl groups can be cleaved from aromatic rings by treatment with proton and/or Lewis acids. Tertiary R groups are the most easily cleaved; because this is true, the *tert*-butyl group is occasionally introduced into a ring, used to direct another

[594]For examples see Elad, D.; Rao, D.V.; Stenberg, V.I. *J. Org. Chem.* ***1965***, *30*, 3252; Shizuka, H.; Tanaka, I. *Bull. Chem. Soc. Jpn.* ***1968***, *41*, 2343; ***1969***, *42*, 909; Fischer, M. *Tetrahedron Lett.* ***1968***, 4295; Hageman, H.J. *Recl. Trav. Chim. Pays-Bas* ***1972***, *91*, 1447; Chênevert, R.; Plante, R. *Can. J. Chem.* ***1983***, *61*, 1092; Abdel-Malik, M.M.; de Mayo, P. *Can. J. Chem.* ***1984***, *62*, 1275; Nassetta, M.; de Rossi, R.H.; Cosa, J.J. *Can. J. Chem.* ***1988***, *66*, 2794.

group, and then removed.[595] For example, 4-*tert*-butyltoluene (**71**) reacted with benzoyl chloride and $AlCl_3$ to give the acylated product, and subsequent treatment with $AlCl_3$ led to loss of the *tert*-butyl group to give **72**.[596]



71 **72**

Secondary R groups are harder to cleave, and primary R harder still. Because of this reaction, care must be taken when using Friedel–Crafts catalysts (Lewis or proton acids) on aromatic compounds containing alkyl groups. True cleavage, in which the R becomes an alkene, occurs only at high temperatures, >400°C.[597] At ordinary temperatures, the R group attacks another ring, so that the bulk of the product may be dealkylated, but there is a residue of heavily alkylated material. The isomerization reaction, in which a group migrates from one position in a ring to another or to a different ring, is therefore more important than true cleavage. In these reactions, the meta isomer is generally the most favored product among the dialkylbenzenes; and the 1,3,5 product the most favored among the trialkylbenzenes, because they have the highest thermodynamic stabilities. Alkyl migrations can be inter- or intramolecular, depending on the conditions and on the R group. The following experiments can be cited: Ethylbenzene treated with HF and BF_3 gave, almost completely, benzene and diethylbenzenes[598] (entirely intermolecular); propylbenzene labeled in the β position gave benzene, propylbenzene, and di- and tripropylbenzenes, but the propylbenzene recovered was partly labeled in the a position and not at all in the γ position[599] (both intra- and intermolecular); *o*-xylene treated with HBr and $AlBr_3$ gave a mixture of *o*- and *m*-, but no *p*-xylene, while *p*-xylene gave *p*- and *m*-, but no *o*-xylene, and no trimethyl compounds could be isolated in these experiments[600] (exclusively intramolecular rearrangement). Apparently, methyl groups migrate only intramolecularly, while other groups may follow either path.[601]

[595]For reviews of such reactions, where the blocking group is *tert*-butyl, benzyl, or a halogen, see Tashiro, M. *Synthesis* ***1979***, 921; Tashiro, M.; Fukata, G. *Org. Prep. Proced. Int.* ***1976***, *8*, 51.

[596]Hofman, P.S.; Reiding, D.J.; Nauta, W.T. *Recl. Trav. Chim. Pays-Bas* ***1960***, *79*, 790.

[597]Olah, G.A., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 1, Wiley, NY, ***1963***, pp. 36–38.

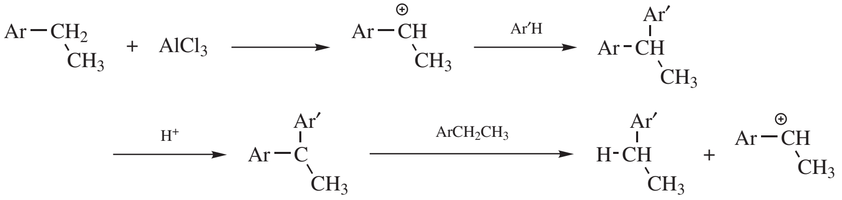
[598]McCaulay, D.A.; Lien, A.P. *J. Am. Chem. Soc.* ***1953***, *75*, 2407. For similar results, see Roberts, R.M.; Roengsumran, S. *J. Org. Chem.* ***1981***, *46*, 3689; Bakoss, H.J.; Roberts, R.M.G.; Sadri, A.R. *J. Org. Chem.* ***1982***, *47*, 4053.

[599]Roberts, R.M.G.; Douglass, J.E. *J. Org. Chem.* ***1963***, *28*, 1225.

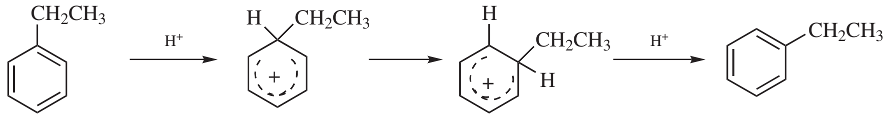
[600]Brown, H.C.; Jungk, H. *J. Am. Chem. Soc.* ***1955***, *77*, 5579; Allen, R.H.; Yats, L.D. *J. Am. Chem. Soc.* ***1959***, *81*, 5289.

[601]Allen, R.H. *J. Am. Chem. Soc.* ***1960***, *82*, 4856.

The mechanism[602] of intermolecular rearrangement can involve free alkyl cations, but there is much evidence to show that this is not necessarily the case. For example, many of them occur without rearrangement within the alkyl group. The following mechanism has been proposed for intermolecular rearrangement without the involvement of carbocations that are separated from the ring.[603]



Evidence for this mechanism is that optically active $PhCHDCH_3$ labeled in the ring with ^{14}C and treated with $GaBr_3$ in the presence of benzene gave ethylbenzene containing no deuterium and two deuterium atoms and that the rate of loss of radioactivity was about equal to the rate of loss of optical activity.[603] The mechanism of intramolecular rearrangement is not very clear. 1,2-shifts of this kind have been proposed:[604]



There is evidence from ^{14}C labeling that intramolecular migration occurs only through 1,2-shifts.[605] Any 1,3 or 1,4 migration takes place by a series of two or more 1,2-shifts.

Phenyl groups have also been found to migrate. Thus *o*-terphenyl, heated with $AlCl_3$—H_2O, gave a mixture containing 7% *o*-, 70% *m*-, and 23% *p*-terphenyl.[606] Alkyl groups have also been replaced by groups other than hydrogen (e.g., nitro groups).

Unlike alkylation, *Friedel–Crafts acylation* has been generally considered to be irreversible, but a number of instances of electrofugal acyl groups have been reported,[607] especially where there are two ortho substituents, for example the

[602]For a review of the mechanism of this and closely related reactions, see Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 1–55.

[603]Streitwieser, Jr., A.; Reif, L. *J. Am. Chem. Soc.* ***1964***, *86*, 1988.

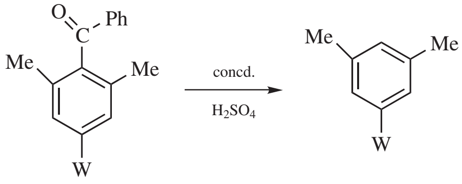
[604]Olah, G.A.; Meyer, M.W.; Overchuk, N.A. *J. Org. Chem.* ***1964***, *29*, 2313.

[605]See, for example, Steinberg, H.; Sixma, F.L.J. *Recl. Trav. Chim. Pays-Bas* ***1962***, *81*, 185; Koptyug, V.A.; Isaev, I.S.; Vorozhtsov, Jr., N.N. *Doklad. Akad. Nauk SSSR*, ***1963***, *149*, 100.

[606]Olah, G.A.; Meyer, M.W. *J. Org. Chem.* ***1962***, *27*, 3682.

[607]For some other examples see Agranat, I.; Bentor, Y.; Shih, Y. *J. Am. Chem. Soc.* ***1977***, *99*, 7068; Bokova, A.I.; Buchina, I.K. *J. Org. Chem. USSR* ***1984***, *20*, 1199; Benedikt, G.M.; Traynor, L. *Tetrahedron Lett.* ***1987***, *28*, 763; Gore, P.H.; Moonga, B.S.; Short, E.L. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 485; Keumi, T.; Morita, T.; Ozawa, Y.; Kitajima, H. *Bull. Chem. Soc. Jpn.* ***1989***, *62*, 599; Giordano, C.; Villa, M.; Annunziata, R. *Synth. Commun.* ***1990***, *20*, 383.

hydro-de-benzoylation of **73**.[608]



73

W = Me, Cl, OH, and so on

OS **V**, 332. Also see OS **III**, 282, 653; **V**, 598.

11-34 Decarbonylation of Aromatic Aldehydes

Hydro-de-formylation or **Deformylation**

$$\text{ArCHO} \xrightarrow{H_2SO_4} \text{ArH} + \text{CO}$$

The decarbonylation of aromatic aldehydes with sulfuric acid[609] is the reverse of the *Gatterman–Koch reaction* (**11-18**). It has been carried out with trialkyl- and trialkoxybenzaldehydes. The reaction takes place by the ordinary arenium ion mechanism: the attacking species is H^+ and the leaving group is HCO^+, which can lose a proton to give CO or combine with OH^- from the water solvent to give formic acid.[610] Aromatic aldehydes have also been decarbonylated with basic catalysts.[611] When basic catalysts are used, the mechanism is probably similar to the S_E1 process of **11-35** (see also **14-32**).

11-35 Decarboxylation of Aromatic Acids

Hydro-de-carboxylation or **Decarboxylation**

$$\text{ArCOOH} \xrightarrow[\text{quinoline}]{\text{Cu}} \text{ArH} + CO_2$$

The decarboxylation of aromatic acids is most often carried out by heating with copper and quinoline. However, two other methods can be used with certain substrates. In one method the salt of the acid ($ArCOO^-$) is heated, and in the other the carboxylic acid is heated with a strong acid, often sulfuric. The latter method is accelerated by the presence of electron-donating groups in ortho and para positions

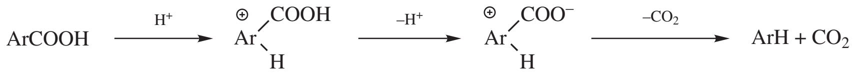
[608] Al-Ka'bi, J.; Farooqi, J.A.; Gore, P.H.; Moonga, B.S.; Waters, D.N. *J. Chem. Res. (S)* ***1989***, 80.

[609] For reviews of the mechanism, see Taylor, R. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 316–323; Schubert, W.M.; Kintner, R.R., in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 695–760.

[610] Burkett, H.; Schubert, W.M.; Schultz, F.; Murphy, R.B.; Talbott, R. *J. Am. Chem. Soc.* ***1959***, *81*, 3923.

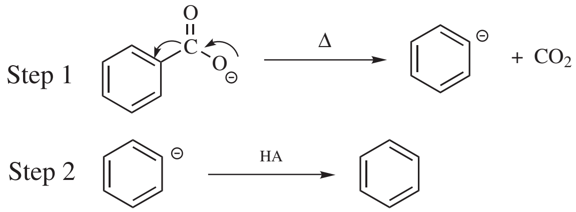
[611] Bunnett, J.F.; Miles J.H.; Nahabedian, K.V. *J. Am. Chem. Soc.* ***1961***, *83*, 2512; Forbes, E.J.; Gregory, M.J. *J. Chem. Soc. B* ***1968***, 205.

and by the steric effect of groups in the ortho positions; in benzene systems it is generally limited to substrates that contain such groups. In this method, decarboxylation takes place by the arenium ion mechanism,[612] with



H^+ as the electrophile and CO_2 as the leaving group.[613] Evidently, the order of electrofugal ability is $CO_2 > H^+ > COOH^+$, so that it is necessary, at least in most cases, for the COOH to lose a proton before it can cleave.

When carboxylate *ions* are decarboxylated, the mechanism is entirely different, being of the S_E1 type. Evidence for this mechanism is that the reaction is first order and that electron-withdrawing groups, which would stabilize a carbanion, facilitate the reaction.[614]



Despite its synthetic importance, the mechanism of the copper–quinoline method has been studied very little, but it has been shown that the actual catalyst is cuprous ion.[615] In fact, the reaction proceeds much faster if the acid is heated in quinoline with cuprous oxide instead of copper, provided that atmospheric oxygen is rigorously excluded. A mechanism has been suggested in which it is the cuprous salt of the acid that actually undergoes the decarboxylation.[615] It has been shown that cuprous salts of aromatic acids are easily decarboxylated by heating in quinoline[616] and that arylcopper compounds are intermediates that can be isolated in some cases.[617] Metallic silver has been used in place of copper, with higher yields.[618]

[612]For a review, see Taylor, R., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 303–316. For a review of isotope effect studies of this reaction, see Willi, A.V. *Isot. Org. Chem.* ***1977***, *3*, 257.

[613]See, for example, Los, J.M.; Rekker, R.F.; Tonsbeeck, C.H.T. *Recl. Trav. Chim. Pays-Bas* ***1967***, *86*, 622; Huang, H.H.; Long, F.A. *J. Am. Chem. Soc.* ***1969***, *91*, 2872; Willi, A.V.; Cho, M.H.; Won, C.M. *Helv. Chim. Acta* ***1970***, *53*, 663.

[614]See, for example, Segura, P.; Bunnett, J.F.; Villanova, L. *J. Org. Chem.* ***1985***, *50*, 1041.

[615]Cohen, T.; Schambach, R.A. *J. Am. Chem. Soc.* ***1970***, *92*, 3189. See also, Aalten, H.L.; van Koten, G.; Tromp, J.; Stam, C.H.; Goubitz, K.; Mak, A.N.S. *Recl. Trav. Chim. Pays-Bas* ***1989***, *108*, 295.

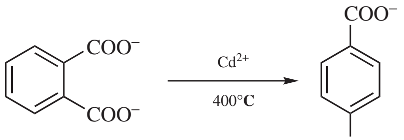
[616]Cairncross, A.; Roland, J.R.; Henderson, R.M.; Sheppard, W.A. *J. Am. Chem. Soc.* ***1970***, *92*, 3187; Cohen, T.; Berninger, R.W.; Wood, J.T. *J. Org. Chem.* ***1978***, *43*, 37.

[617]For example, see Ibne-Rasa, K.M. *J. Am. Chem. Soc.* ***1962***, *84*, 4962; Tedder, J.M.; Theaker, G. *J. Chem. Soc.* ***1959***, 257.

[618]Chodowska-Palicka, J.; Nilsson, M. *Acta Chem. Scand.* ***1970***, *24*, 3353.

In certain cases, the carboxyl group can be replaced by electrophiles other than hydrogen, for example NO,[618] I,[619] Br,[620] or Hg.[621]

Rearrangements are also known to take place. For example, when the phthalate ion is heated with a catalytic amount of cadmium, the terphthalate ion (**74**) is produced:[622]



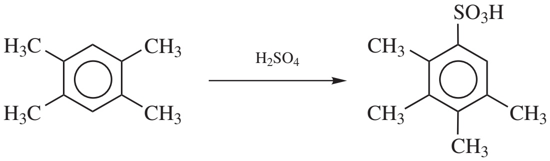
Phthalate ion **74**

In a similar process, potassium benzoate heated with cadmium salts disproportionates to benzene and **74**. The term *Henkel reaction* (named for the company that patented the process) is used for these rearrangements.[623] An S_E1 mechanism has been suggested.[624] The terphthalate is the main product because it crystallizes from the reaction mixture, driving the equilibrium in that direction.[625]

For aliphatic decarboxylation, see **12-40**.

OS **I**, 274, 455, 541; **II**, 100, 214, 217, 341; **III**, 267, 272, 471, 637; **IV**, 590, 628; **V**, 635, 813, 982, 985. Also see, OS **I**, 56.

11-36 The Jacobsen Reaction



When polyalkyl- or polyhalobenzenes are treated with sulfuric acid, the ring is sulfonated, but rearrangement also takes place. The reaction, known as the *Jacobsen reaction*, is limited to benzene rings that have at least four substituents, which can be any combination of alkyl and halogen groups, where the alkyl groups can be

[619]Singh, R.; Just, G. *Synth. Commun.* ***1988***, *18*, 1327.

[620]For example, see Grovenstein, Jr., E.; Ropp, G.A. *J. Am. Chem. Soc.* ***1956***, *78*, 2560.

[621]For a review, see Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, ***1985***, pp. 101–105.

[622]Raecke, B. *Angew. Chem.* ***1958***, *70*, 1; Riedel, O.; Kienitz, H. *Angew. Chem.* ***1960***, *72*, 738; McNelis, E. *J. Org. Chem.* ***1965***, *30*, 1209; Ogata, Y.; Nakajima, K. *Tetrahedron* ***1965***, *21*, 2393; Ratusky, J.; Sorm, F. *Chem. Ind. (London)*, ***1966***, 1798.

[623]For a review, see Ratusky, J., in Patai, S. *The Chemistry of Acid Derivatives*, pt. 1, Wiley, NY, ***1979***, pp. 915–944.

[624]See Ratusky, J. *Collect. Czech. Chem. Commun.* ***1973***, *38*, 74, 87, and references cited therein.

[625]Ratusky, J. *Collect. Czech. Chem. Commun.* ***1968***, *33*, 2346.

ethyl or methyl and the halogen iodo, chloro, or bromo. When isopropyl or *tert*-butyl groups are on the ring, these groups are cleaved to give alkenes. Since a sulfo group can later be removed (**11-38**), the Jacobsen reaction can be used as a means of rearranging polyalkylbenzenes. The rearrangement always brings the alkyl or halo groups closer together than they were originally. Side products in the case illustrated above are pentamethylbenzenesulfonic acid, 2,4,5-trimethylbenzenesulfonic acid, and so on, indicating an intermolecular process, at least partially.

The mechanism of the Jacobsen reaction is not established,[626] but there is evidence, at least for polymethylbenzenes, that the rearrangement is intermolecular, and that the species to which the methyl group migrates is a polymethylbenzene, not a sulfonic acid. Sulfonation takes place after the migration.[627] It has been shown by labeling that ethyl groups migrate without internal rearrangement.[628]

Isomerization of alkyl groups in substituted biphenyls has been observed[629] when the medium is a superacid (see p. 236).

B. Oxygen Leaving Groups

11-37 Deoxygenation

$$\text{ArOR} \longrightarrow \text{ArH}$$

In a few cases, it is possible to remove an oxygen substituent directly from the aromatic ring. Treatment of an aryl mesylate (ArOMs) with a nickel catalyst in DMF, for example, leads to the deoxygenated product, Ar—H.[630]

C. Sulfur Leaving Groups

11-38 Desulfonation or Hydro-de-sulfonation

$$\text{ArSO}_3\text{H} \xrightarrow[\text{dil. H}_2\text{SO}_4]{135-200^\circ\text{C}} \text{ArH} + \text{H}_2\text{SO}_4$$

The cleavage of sulfo groups from aromatic rings is the reverse of **11-7**.[631] By the principle of microscopic reversibility, the mechanism is also the reverse.[632] Dilute H_2SO_4 is generally used, as the reversibility of sulfonation decreases with

[626]For discussions, see Suzuki, H. *Bull. Chem. Soc. Jpn.* ***1963***, *36*, 1642; Koeberg-Telder, A.; Cerfontain, H. *J. Chem. Soc. Perkin Trans. 2* ***1977***, 717; Cerfontain, H. *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*, Wiley, NY, ***1968***, pp. 214–226; Taylor, R., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 22–32, 48–55.

[627]Koeberg-Telder, A.; Cerfontain, H. *Recl. Trav. Chim. Pays-Bas* ***1987***, *106*, 85; Cerfontain, H.; Koeberg-Telder, A. *Can. J. Chem.* ***1988***, *66*, 162.

[628]Marvell, E.N.; Webb, D. *J. Org. Chem.* ***1962***, *27*, 4408.

[629]Sherman, S. C.; Iretskii, A. V.; White, M. G.; Gumienny, C.; Tolbert, L. M.; Schiraldi, D. A. *J. Org. Chem.* ***2002***, *67*, 2034.

[630]Sasaki, K.; Kubo, T.; Sakai, M.; Kuroda, Y. *Chem. Lett*, ***1997***, 617.

[631]For reviews, see Cerfontain, H. *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*, Wiley, NY, ***1968***, pp. 185–214; Taylor, R., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 349–355; Gilbert, E.E. *Sulfonation and Related Reactions*, Wiley,NY, ***1965***, pp. 427–442. See also, Krylov, E.N. *J. Org. Chem. USSR* ***1988***, *24*, 709.

[632]For a discussion, see Kozlov, V.A.; Bagrovskaya, N.A. *J. Org. Chem. USSR* ***1989***, *25*, 1152.

increasing H_2SO_4 concentration. The reaction permits the sulfo group to be used as a blocking group to direct meta and then to be removed. The sulfo group has also been replaced by nitro and halogen groups. Sulfo groups have also been removed from the ring by heating with an alkaline solution of Raney nickel.[633] In another catalytic process, aromatic sulfonyl bromides or chlorides are converted to aryl bromides or chlorides, respectively, on heating with chlorotris(triphenylphosphine) rhodium(I).[634] This reaction is similar to the decarbonylation of aromatic acyl halides mentioned in **14-32**.

$$ArSO_2Br \xrightarrow{RhCl(PPh_3)_3} ArBr$$

OS **I**, 388; **II**, 97; **III**, 262; **IV**, 364. Also see OS **I**, 519; **II**, 128; **V**, 1070.

D. Halogen Leaving groups

11-39 Dehalogenation or Hydro-de-halogenation

$$ArX \xrightarrow{AlCl_3} ArH$$

Aryl halides can be dehalogenated by Friedel–Crafts catalysts. Iodine is the most easily cleaved. Dechlorination is seldom performed and defluorination apparently never. The reaction is most successful when a reducing agent, say, Br^- or I^- is present to combine with the I^+ or Br^+ coming off.[635] Except for deiodination, the reaction is seldom used for preparative purposes. Migration of halogen is also found,[636] both intramolecular[637] and intermolecular.[638] The mechanism is probably the reverse of that of **11-10**.[639] Debromination of aromatic rings having two attached amino groups was accomplished by refluxing in aniline containing acetic acid/HBr.[640]

Rearrangement of polyhalobenzenes can also be catalyzed by very strong bases; for example 1,2,4-tribromobenzene is converted to 1,3,5-tribromobenzene by treatment with PhNHK.[641] This reaction, which involves aryl carbanion intermediates (S_E1 mechanism), has been called the *halogen dance*.[642]

[633]Feigl, F. *Angew. Chem.* ***1961***, *73*, 113.

[634]Blum, J.; Scharf, G. *J. Org. Chem.* ***1970***, *35*, 1895.

[635]Pettit, G.R.; Piatak, D.M. *J. Org. Chem.* ***1960***, *25*, 721.

[636]Olah, G.A.; Tolgyesi, W.S.; Dear, R.E.A. *J. Org. Chem.* ***1962***, *27*, 3441, 3449, 3455; De Valois, P.J.; Van Albada, M.P.; Veenland, J.U. *Tetrahedron* ***1968***, *24*, 1835; Olah, G.A.; Meidar, D.; Olah, J.A. *Nouv. J. Chim.*, ***1979***, *3*, 275.

[637]Koptyug, V.A.; Isaev, I.S.; Gershtein, N.A.; Berezovskii, G.A. *J. Gen. Chem. USSR* ***1964***, *34*, 3830; Erykalov, Yu.G.; Becker, H.; Belokurova, A.P. *J. Org. Chem. USSR* ***1968***, *4*, 2054; Jacquesy, J.; Jouannetaud, M. *Tetrahedron Lett.* ***1982***, *23*, 1673.

[638]Augustijn, G.J.P.; Kooyman, E.C.; Louw, R. *Recl. Trav. Chim. Pays-Bas* ***1963***, *82*, 965.

[639]Choguill, H.S.; Ridd, J.H. *J. Chem. Soc.* ***1961***, 822; Shine, H.J. *Aromatic Rearrangements, Elsevier, NY,* ***1967***, p. 1; Ref. 636.

[640]Choi, H.; Chi, D.Y. *J. Am. Chem. Soc.* ***2001***, *123*, 9202.

[641]Moyer, Jr., C.E.; Bunnett, J.F. *J. Am. Chem. Soc.* ***1963***, *85*, 1891.

[642]Bunnett, J.F. *Acc. Chem. Res.* ***1972***, *5*, 139; Mach, M.H.; Bunnett, J.F. *J. Org. Chem.* ***1980***, *45*, 4660; Sauter, F.; Fröhlich, H.; Kalt, W. *Synthesis* ***1989***, 771.

Removal of halogen from aromatic rings can also be accomplished by various reducing agents, among them Bu_3SnH,[643] catalytic hydrogenolysis,[644] catalytic transfer hydrogenolysis,[645] $Fe(CO)_5$,[646] Na–Hg in liquid NH_3,[647] $LiAlH_4$,[648] $LiAlH_4$ and a $NbCl_5$ catalyst,[649] $NaBH_4$ and a catalyst,[650] Ni/C with $Me_2NH{\bullet}BH_3$,[651] NaH,[652] HCOOH[653] or aqueous $HCOO^-$[654] with Pd/C, and Raney nickel in alkaline solution,[655] the last method being effective for fluorine, as well as for the other halogens. Carbon monoxide, with potassium tetracarbonylhydridoferrate $KHFe(CO)_4$ as a catalyst, specifically reduces aryl iodides.[656] Polymethylhydrosiloxane (PHMS) and KF, with a palladium catalyst, also reduces aryl iodides.[657] Not all these reagents operate by electrophilic substitution mechanisms. Some are nucleophilic substitutions and some are free-radical processes. Photochemical[658] and electrochemical[659] reduction are also known. Halogen can also be removed from aromatic rings indirectly by conversion to Grignard reagents (**12-38**) followed by hydrolysis (**11-41**).

OS **III**, 132, 475, 519; **V**, 149, 346, 998; **VI**, 82, 821.

11-40 Formation of Organometallic Compounds

$$ArBr + M \longrightarrow ArM$$
$$ArBr + RM \longrightarrow ArM + RBr$$

[643]Maitra, U.; Sarma, K.D. *Tetrahedron Lett.* ***1994***, *35*, 7861.

[644]For example, see Subba Rao, Y.V.; Mukkanti, K.; Choudary, B.M. *J. Organomet. Chem.* ***1989***, *367*, C29. See also, Sajiki, H.; Kume, A.; Hattori, K.; Hirota, K. *Tetrahedron Lett.* ***2002***, *43*, 7247.

[645]Anwer, M.K.; Spatola, A.F. *Tetrahedron Lett.* ***1985***, *26*, 1381.

[646]Brunet, J.-J.; El Zaizi, A. *Bull. Soc. Chim. Fr.* ***1996***, *133*, 75.

[647]Austin, E.; Alonso, R.A.; Rossi, R.A. *J. Chem. Res. (S)* ***1990***, 190.

[648]Karabatsos, G.J.; Shone, R.L. *J. Org. Chem.* ***1968***, *33*, 619; Brown, H.C.; Chung, S.; Chung, F. *Tetrahedron Lett.* ***1979***, 2473. Evidence for a free-radical mechanism has been found in this reaction; see Chung, F.; Filmore, K.L. *J. Chem. Soc., Chem. Commun.* ***1983***, 358; Beckwith, A.L.J.; Goh, S.H. *J. Chem. Soc., Chem. Commun.* ***1983***, 905. See also, Beckwith, A.L.J.; Goh, S.H. *J. Chem. Soc., Chem. Commun.* ***1983***, 907; Han, B.H.; Baudjouk, P. *Tetrahedron Lett.* ***1982***, *23*, 1643.

[649]Fuchibe, K.; Akiyama, T. *Synlett* ***2004***, 1282.

[650]Egli, R.A. *Helv. Chim. Acta* ***1968***, *51*, 2090; Lin, S.; Roth, J.A. *J. Org. Chem.* ***1979***, *44*, 309; Narisada, M.; Horibe, I.; Watanabe, F.; Takeda, K. *J. Org. Chem.* ***1989***, *54*, 5308.

[651]Lipshutz, B.H.; Tomioka, T.; Sato, K. *Synlett* ***2001***, 970; Lipshutz, B.H.; Tomioka, T.; Pfeiffer, S.S. *Tetrahedron Lett.* ***2001***, *42*, 7737.

[652]Nelson, R.B.; Gribble, G.W. *J. Org. Chem.* ***1974***, *39*, 1425.

[653]Barren, J.P.; Baghel, S.S.; McCloskey, P.J. *Synth. Commun.* ***1993***, *23*, 1601.

[654]Arcadi, A.; Cerichelli, G.; Chiarini, M.; Vico, R.; Zorzan, D. *Eur. J. Org. Chem.* ***2004***, 3404.

[655]Buu-Hoï, N.P.; Xuong, N.D.; van Bac, N. *Bull. Soc. Chim. Fr.* ***1963***, 2442; de Koning, A.J. *Org. Prep. Proced. Int.* ***1975***, *7*, 31.

[656]Brunet, J.; Taillefer, M. *J. Organomet. Chem.* ***1988***, *348*, C5.

[657]Maleczka, Jr., R.E.; Rahaim, Jr., R.J.; Teixeira, R.R. *Tetrahedron Lett.* ***2002***, *43*, 7087.

[658]See, for example, Pinhey, J.T.; Rigby, R.D.G. *Tetrahedron Lett.* ***1969***, 1267, 1271; Barltrop, J.A.; Bradbury, D. *J. Am. Chem. Soc.* ***1973***, *95*, 5085.

[659]See Fry, A.J. *Synthetic Organic Electrochemistry*, 2nd ed., Wiley, NY, ***1989***, pp. 142–143. Also see, Bhuvaneswari, N.; Venkatachalam, C.S.; Balasubramanian, K.K. *Tetrahedron Lett.* ***1992***, *33*, 1499.

These reactions are considered along with their aliphatic counterparts at reactions **12-38** and **12-39**.

E. Metal Leaving Groups

11-41 Hydrolysis of Organometallic Compounds

Hydro-de-metallation or **Demetallation**

$$\text{ArM} + \text{H}^+ \longrightarrow \text{ArH} + \text{M}^+$$

Organometallic compounds can be hydrolyzed by acid treatment. For active metals, such as Mg, Li, and so on water is sufficiently acidic. The most important example of this reaction is hydrolysis of Grignard reagents, but M may be many other metals or metalloids. Examples are SiR_3, HgR, Na, and $B(OH)_2$. Since aryl Grignard and aryllithium compounds are fairly easy to prepare, they are often used to prepare salts of weak acids, such as alkynes.

$$\text{PhMgBr} + \text{H–C}{\equiv}\text{C–H} \longrightarrow \text{H–C}{\equiv}\text{C:}^- \ {}^+\text{MgBr} + \text{PhH}$$

Where the bond between the metal and the ring is covalent, the usual arenium ion mechanism operates.[660] Where the bonding is essentially ionic, this is a simple acid–base reaction. For the aliphatic counterpart of this reaction, see reaction **12-24**.

Other reactions of aryl organometallic compounds are treated with their aliphatic analog: reactions **12-25–12-27** and **12-30–12-37**.

[660]For a discussion of the mechanism, see Taylor, R., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 278–303, 324–349.

CHAPTER 12

Aliphatic, Alkenyl, and Alkynyl Substitution, Electrophilic and Organometallic

In Chapter 11, it was pointed out that the most important leaving groups in electrophilic substitution are those that can best exist with an outer shell that is deficient in a pair of electrons. For aromatic systems, the most common leaving group is the proton. The proton is also a leaving group in aliphatic systems, but the reactivity depends on the acidity. Protons in saturated alkanes are very unreactive, but electrophilic substitutions are often easily carried out at more acidic positions, for example, α to a carbonyl group, or at an alkynyl position (RC≡CH). Since metallic ions are easily able to bear positive charges, we might expect that organometallic compounds would be especially susceptible to electrophilic substitution, and this is indeed the case.[1] Another important type of electrophilic substitution, known as *anionic cleavage*, involves the breaking of C–C bonds; in these reactions there are carbon leaving groups (**12-40–12-46**). A number of electrophilic substitutions at a nitrogen atom are treated at the end of the chapter.

Since a carbanion is what remains when a positive species is removed from a carbon atom, the subject of carbanion structure and stability (Chapter 5) is inevitably related to the material in this chapter. So is the subject of very weak acids and very strong bases (Chapter 8), because the weakest acids are those in which the hydrogen is bonded to carbon.

[1]For books on the preparation and reactions of organometallic compounds, see Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, 5 vols., Wiley, NY, ***1984–1990***; Haiduc, I.; Zuckerman, J.J. *Basic Organometallic Chemistry*, Walter de Gruyter, NY, ***1985***; Negishi, E. *Organometallics in Organic Synthesis*, Wiley, NY, ***1980***; Aylett, B.J. *Organometallic Compounds*, 4th ed., Vol. 1, pt. 2, Chapman and Hall, NY, ***1979***; Coates, G.E.; Green, M.L.H.; Wade, K. *Organometallic Compounds*, 3rd ed., 2 vols., Methuen, London, ***1967–1968***; Eisch, J.J. *The Chemistry of Organometallic Compounds*, Macmillan, NY, ***1967***. For reviews, see Maslowsky, Jr., E. *Chem. Soc. Rev.* ***1980***, *9*, 25, and in Tsutsui, M. *Characterization of Organometallic Compounds*, Wiley, NY, ***1969–1971***, the articles by Cartledge, F.K.; Gilman, H. pt. 1, pp. 1–33, and by Reichle, W.T. pt. 2, pp. 653–826.

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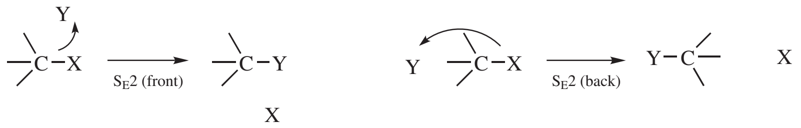
MECHANISMS

For aliphatic electrophilic substitution, we can distinguish at least four possible major mechanisms,[2] which we call S_E1, S_E2 (front), S_E2 (back), and S_Ei. The S_E1 is unimolecular; the other three are bimolecular. It is noted that the term "S_EAr" has been proposed to represent electrophilic aromatic substitution, so that the term "S_E2" refers exclusively to electrophilic substitutions where a steric course is possible.[3] To describe the steric course of an aliphatic substitution reaction, the suffixes "ret" and "inv" were proposed, referring to retention and inversion of configuration, respectively.

BIMOLECULAR MECHANISMS. S_E2 AND S_Ei

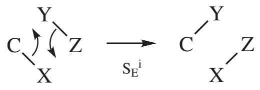
The bimolecular mechanisms for electrophilic aliphatic substitution are analogous to the S_N2 mechanism in that the new bond forms as the old one breaks. However, in the S_N2 mechanism the incoming group brings with it a pair of electrons, and this orbital can overlap with the central carbon only to the extent that the leaving group takes away its electrons; otherwise the carbon would have more than eight electrons at once in its outer shell. Since electron clouds repel, this means also that the incoming group attacks backside, at a position 180° from the leaving group, resulting in inversion of configuration. When the nucleophilic species attacks (donates electrons to) an electrophile, which brings to the substrate only a vacant orbital, predicting the direction the attack is not as straightforward. We can imagine two main possibilities: delivery of the electrophile to the front, which we call S_E2 (front), and delivery of the electrophile to the rear, which we call S_E2 (back). The possibilities can be pictured (charges not shown):



Both the S_E2 (front) and S_E2 (back) mechanisms are designated D_EA_E in the IUPAC system. With substrates in which we can distinguish the possibility, the former

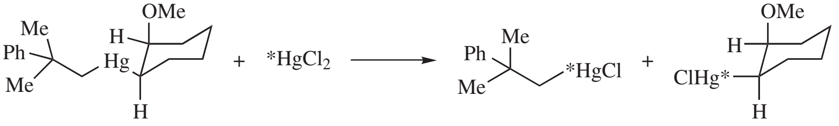
[2]For monographs, see Abraham, M.H. *Comprehensive Chemical Kinetics*, Bamford, C.H.; Tipper, C.F.H. Eds., Vol. 12, Elsevier, NY, ***1973***; Jensen, F.R.; Rickborn, B. *Electrophilic Substitution of Organomercurials*, McGraw-Hill, NY, ***1968***; Reutov, O.A.; Beletskaya, I.P. *Reaction Mechanisms of Organometallic Compounds*, North-Holland Publishing Company, Amsterdam, The Netherlands, ***1968***. For reviews, see Abraham, M.H.; Grellier, P.L., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 2, Wiley, NY, pp. 25–149; Beletskaya, I.P. *Sov. Sci. Rev. Sect. B* ***1979***, *1*, 119; Reutov, O.A. *Pure Appl. Chem.* ***1978***, *50*, 717; ***1968***, *17*, 79; *Tetrahedron* ***1978***, *34*, 2827; *J. Organomet. Chem.* ***1975***, *100*, 219; *Russ. Chem. Rev.* ***1967***, *36*, 163; *Fortschr. Chem. Forsch.* ***1967***, *8*, 61; Matteson, D.S. *Organomet. Chem. Rev. Sect. A* ***1969***, *4*, 263; Dessy, R.E.; Kitching, W. *Adv. Organomet. Chem.* ***1966***, *4*, 267.
[3]Gawley, R.E. *Tetrahedron Lett.* ***1999***, *40*, 4297.

mechanism should result in retention of configuration and the latter in inversion. The reaction of allylsilanes with adamantyl chloride and $TiCl_4$, for example, gives primarily the antiproduct via a S_E2' reaction.[4] When the electrophile reacts from the front, there is a third possibility. A portion of the electrophile may assist in the removal of the leaving group, forming a bond with it at the same time that the new C–Y bond is formed:



This mechanism, which we call the S_Ei mechanism[5] (IUPAC designation: *cyclo*-$D_EA_ED_nA_n$), also results in retention of configuration.[6] Plainly, where a second-order mechanism involves this kind of internal assistance, backside attack is impossible.

It is evident that these three mechanisms are not easy to distinguish. All three give second-order kinetics, and two result in retention of configuration.[7] In fact, although much work has been done on this question, there are few cases in which we can unequivocally say that one of these three and not another is actually



1 **2**

taking place. Clearly, a study of the stereochemistry can distinguish between S_E2 (back) on the one hand and S_E2 (front) or S_Ei on the other. Many such investigations have been made. In the overwhelming majority of second-order electrophilic substitutions, the result has been retention of configuration or some other indication of frontside attack, indicating an S_E2 (front) or S_Ei mechanism. For example, when *cis*-**1** was treated with labeled mercuric chloride, the **2** produced was 100% cis. The bond between the mercury and the ring must have been broken (as well as the other Hg–C bond), since each of the products contained about half of the labeled mercury.[8] Another indication of frontside attack is that second-order

[4]Buckle, M.J.C.; Fleming, I.; Gil, S. *Tetrahedron Lett.* ***1992***, *33*, 4479.

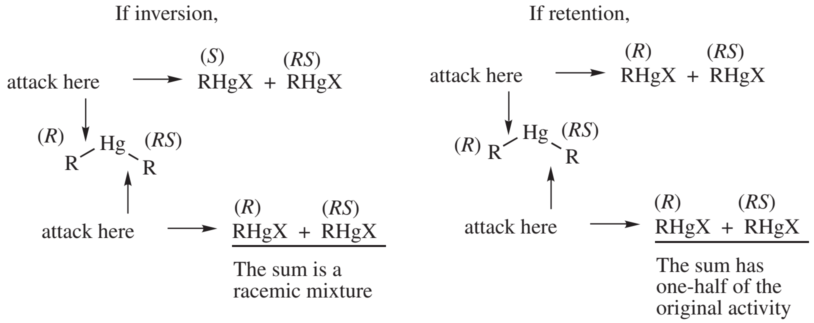
[5]The names for these mechanisms vary throughout the literature. For example, the S_Ei mechanism has also been called the S_F2, the S_E2 (closed), and the S_E2 (cyclic) mechanism. The original designations, S_E1, S_E2, and so on, were devised by the Hughes–Ingold school.

[6]It has been contended that the S_Ei mechanism violates the principle of conservation of orbital symmetry (p. 1208), and that the S_E2 (back) mechanism partially violates it: Slack, D.A.; Baird, M.C. *J. Am. Chem. Soc.* ***1976***, *98*, 5539.

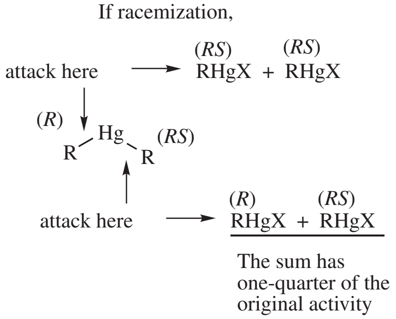
[7]For a review of the stereochemistry of reactions in which a carbon-transition-metal σ bond is formed or broken, see Flood, T.C. *Top. Stereochem.* ***1981***, *12*, 37. See also Jensen, F.R.; Davis, D.D. *J. Am. Chem. Soc.* ***1971***, *93*, 4048.

[8]Winstein, S.; Traylor, T.G.; Garner, C.S. *J. Am. Chem. Soc.* ***1955***, *77*, 3741.

electrophilic substitutions proceed very easily at *bridgehead* carbons (see p. 429).[9] Still another indication is the behavior of neopentyl as a substrate. S_N2 reactions at neopentyl are extremely slow (p. 479), because attack from the rear is blocked and the transition state for the reaction lies very high in energy. The fact that neopentyl systems undergo electrophilic substitution only slightly more slowly than ethyl[10] is further evidence for frontside attack. One final elegant experiment may be noted.



The compound di-*sec*-butylmercury was prepared with one *sec*-butyl group optically active and the other racemic.[11] This was accomplished by treatment of optically active *sec*-butylmercuric bromide with racemic *sec*-butylmagnesium bromide. The di-*sec*-butyl compound was then treated with mercuric bromide to give 2 eqiuivalents of *sec*-butylmercuric bromide. The steric course of the reaction could then be predicted by the following analysis, assuming that the bonds between the mercury and each carbon have a 50% chance of breaking. The original activity referred to is the activity of the optically active *sec*-butylmercuric bromide used to make the dialkyl compound. The actual result was that, under several different sets of conditions, the product had one-half of the original activity, demonstrating retention of configuration.



[9]Winstein, S.; Traylor, T.G. *J. Am. Chem. Soc.* ***1956***, *78*, 2597; Schöllkopf, U. *Angew. Chem.* ***1960***, *72*, 147. For a discussion, see Fort Jr., R.C.; Schleyer, P.v.R. *Adv. Alicyclic Chem.* ***1966***, *1*, 283, pp. 353–370.
[10]Hughes, E.D.; Volger, H.C. *J. Chem. Soc.* ***1961***, 2359.
[11]Jensen, F.R. *J. Am. Chem. Soc.* ***1960***, *82*, 2469; Ingold, C.K. *Helv. Chim. Acta* ***1964***, *47*, 1191.

However, inversion of configuration has been found in certain cases, demonstrating that the S_E2 (back) mechanism can take place. For example, the reaction of optically active *sec*-butyltrineopentyltin with bromine (**12-40**) gives inverted *sec*-butyl bromide.[12] A number of other organometallic compounds have also been shown to give inversion when treated with halogens,[13] although others do not.[14] So far, no inversion has been found with an organomercury substrate. It may be that still other examples of backside

$$sec\text{-BuSnR}_3 \quad + \quad Br_2 \longrightarrow sec\text{-BuBr} \qquad R = \text{neopentyl}$$

attack exist,[15] but have escaped detection because of the difficulty in preparing compounds with a configurationally stable carbon–metal bond. Compounds that are chiral because of a stereogenic carbon at which a carbon–metal bond is located[16] are often difficult to resolve and once resolved are often easily racemized. The resolution has been accomplished most often with organomercury compounds,[17] and most stereochemical investigations have therefore been made with these substrates. Only a few optically active Grignard reagents have been prepared[18] (i.e., in which the only stereogenic center is the carbon bonded to the magnesium). Because of this, the steric course of electrophilic substitutions at the C–Mg bond has not often been determined. However, in one such case, the reaction of both the exo and endo isomers of the 2-norbornyl Grignard reagent with $HgBr_2$ (to give 2-norbornylmercuric bromide) has been shown to proceed with retention of configuration.[19] It is likely that inversion takes place only when steric hindrance

[12]Jensen, F.R.; Davis, D.D. *J. Am. Chem. Soc.* ***1971***, *93*, 4048. For a review of the stereochemistry of S_E2 reactions with organotin substrates, see Fukuto, J.M.; Jensen, F.R. *Acc. Chem. Res.* ***1983***, *16*, 177.

[13]For example, See Applequist, D.E.; Chmurny, G.N. *J. Am. Chem. Soc.* ***1967***, *89*, 875; Glaze, W.H.; Selman, C.M.; Ball Jr., A.L.; Bray, L.E. *J. Org. Chem.* ***1969***, *34*, 641; Brown, H.C.; Lane, C.F. *Chem. Commun.* ***1971***, 521; Jensen, F.R.; Madan, V.; Buchanan, D.H. *J. Am. Chem. Soc.* ***1971***, *93*, 5283; Espenson, J.H.; Williams, D.A. *J. Am. Chem. Soc.* ***1974***, *96*, 1008; Bock, P.L.; Boschetto, D.J.; Rasmussen, J.R.; Demers, J.P.; Whitesides, G.M. *J. Am. Chem. Soc.* ***1974***, *96*, 2814; Magnuso, R.H.; Halpern, J.; Levitin, I.Ya.; Vol'pin, M.E. *J. Chem. Soc. Chem. Commun.* ***1978***, 44.

[14]See, for example, Rahm, A.; Pereyre, M. *J. Am. Chem. Soc.* ***1977***, *99*, 1672; McGahey, L.F.; Jensen, F.R. *J. Am. Chem. Soc.* ***1979***, *101*, 4397. Electrophilic bromination of certain organotin compounds was found to proceed with inversion favored for equatorial and retention for axial C–Sn bonds: Olszowy, H.A.; Kitching, W. *Organometallics* ***1984***, *3*, 1676. For a similar result, see Rahm, A.; Grimeau, J.; Pereyre, M. *J. Organomet. Chem.* ***1985***, *286*, 305.

[15]Cases of inversion involving replacement of a metal by a metal have been reported. See Tada, M.; Ogawa, H. *Tetrahedron Lett.* ***1973***, 2639; Fritz, H.L.; Espenson, J.H.; Williams, D.A.; Molander, G.A. *J. Am. Chem. Soc.* ***1974***, *96*, 2378; Gielen, M.; Fosty, R. *Bull. Soc. Chim. Belg.* ***1974***, *83*, 333; Bergbreiter, D.E.; Rainville, D.P. *J. Organomet. Chem.* ***1976***, *121*, 19.

[16]For a monograph, see Sokolov, V.I. *Chirality and Optical Activity in Organometallic Compounds*, Gordon and Breach, NY, ***1990***.

[17]Organomercury compounds were first resolved by three groups: Jensen, F.R.; Whipple, L.D.; Wedegaertner, D.K.; Landgrebe, J.A. *J. Am. Chem. Soc.* ***1959***, *81*, 1262; Charman, H.B.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1959***, 2523, 2530; Reutov, O.A.; Uglova, E.V. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1959***, 735.

[18]This was done first by Walborsky, H.M.; Young, A.E. *J. Am. Chem. Soc.* ***1964***, *86*, 3288.

[19]Jensen, F.R.; Nakamaye, K.L. *J. Am. Chem. Soc.* ***1966***, *88*, 3437.

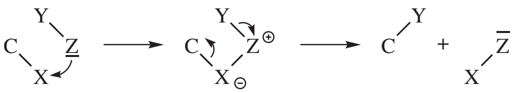
prevents reaction on the frontside and when the electrophile does not carry a Z group (p. 754).

The S_E2 (back) mechanism can therefore be identified in certain cases (if inversion of configuration is found), but it is plain that stereochemical investigations cannot distinguish between the S_E2 (front) and the S_Ei mechanisms and that, in the many cases where configurationally stable substrates cannot be prepared, such investigations are of no help at all in distinguishing among all three of the second-order mechanisms. Unfortunately, there are not many other methods that lead to unequivocal conclusions. One method that has been used in an attempt to distinguish between the S_Ei mechanism on the one hand and the S_E2 pathways on the other involves the study of salt effects on the rate. It may be recalled (p. 501) that reactions in which neutral starting molecules acquire charges in the transition state are aided by an increasing concentration of added ions. Thus the S_Ei mechanism would be less influenced by salt effects than would either of the S_E2 mechanisms. On this basis, Abraham and co-workers[20] concluded that the reactions $R_4Sn + HgX_2 \rightarrow RHgX + R_3SnX$ ($X = Cl$ or I) take place by S_E2 and not by S_Ei mechanisms. Similar investigations involve changes in solvent polarity (see also, p. 765).[21] In the case of the reaction

$$sec\text{-BuSnR}_2\text{R}' + \text{Br}_2 \longrightarrow sec\text{-BuBr}$$

(where $R = R' = i$Pr and $R = i$Pr, $R' =$ neopentyl), the use of polar solvents gave predominant inversion, while nonpolar solvents gave predominant retention.[22]

On the basis of evidence from reactivity studies, it has been suggested[23] that a variation of the S_Ei mechanism is possible in which the group Z becomes attached to X before the latter becomes detached:



This process has been called the S_EC[22] or S_E2 (co-ord)[24] mechanism (IUPAC designation $A_n + cyclo\text{-}D_EA_ED_n$).

It has been shown that in certain cases (e.g., $Me_4Sn + I_2$) the reactants in an S_E2 reaction, when mixed, give rise to an immediate charge-transfer spectrum (p. 115), showing that an electron donor–acceptor (EDA) complex has been formed.[25] In these cases it is likely that the EDA complex is an intermediate in the reaction.

[20] Abraham, M.H.; Johnston, G.F. *J. Chem. Soc. A*, ***1970***, 188.

[21] See, for example, Abraham, M.H.; Dorrell, F.J. *J. Chem. Soc. Perkin Trans. 2* ***1973***, 444.

[22] Fukuto, J.M.; Newman, D.A.; Jensen, F.R. *Organometallics* ***1987***, *6*, 415.

[23] Abraham, M.H.; Hill, J.A. *J. Organomet. Chem.* ***1967***, *7*, 11.

[24] Abraham, M.H. *Comprehensive Chemical Kinetics*, Bamford, C.H.; Tipper, C.F.H. Eds., Vol. 12, Elsevier, NY, ***1973***, p. 15.

[25] Fukuzumi, S.; Kochi, J.K. *J. Am. Chem. Soc.* ***1980***, *102*, 2141, 7290.

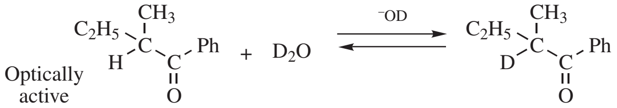
THE S_E1 MECHANISM

The S_E1 mechanism is analogous to the S_N1. It involves two steps: a slow ionization and a fast combination.

$$\text{Step 1} \quad R\text{—}X \xrightarrow{\text{slow}} R^- + X^+$$

$$\text{Step 2} \quad R^- + Y^+ \longrightarrow R\text{—}Y$$

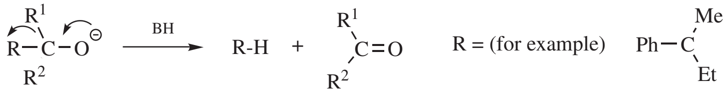
The IUPAC designation is $D_E + A_E$. First-order kinetics are predicted and many such examples have been found. Other evidence for the S_E1 mechanism was obtained in a study of base-catalyzed tautomerization. In the reaction



the rate of deuterium exchange was the same as the rate of racemization[26] and there was an isotope effect.[27]

The S_N1 reactions do not proceed at strained bridgehead carbons (e.g., in [2.2.1] bicyclic systems, p. 435) because planar carbocations cannot form at these carbons. However, carbanions not stabilized by resonance are probably not planar, and S_E1 reactions readily occur with this type of substrate. Indeed, the question of carbanion structure is intimately tied into the problem of the stereochemistry of the S_E1 reaction. If a carbanion is planar, racemization should occur. If it is pyramidal and *can hold its structure*, the result should be retention of configuration. On the other hand, even a pyramidal carbanion will give racemization if it cannot hold its structure, that is, if there is pyramidal inversion as with amines (p. 142). Unfortunately, the only carbanions that can be studied easily are those stabilized by resonance, which makes them planar, as expected (p. 258). For simple alkyl carbanions, the main approach to determining structure has been to study the stereochemistry of S_E1 reactions rather than the other way around. Racemization is almost always observed, but whether this is caused by planar carbanions or by oscillating pyramidal carbanions is not known. In either, case racemization occurs whenever a carbanion is completely free or is symmetrically solvated.

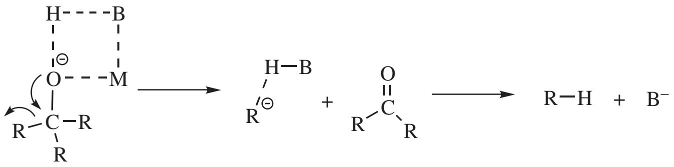
However, even planar carbanions need not give racemization. Cram found that retention and even inversion can occur in the alkoxide (see **3**) cleavage reaction (**12-41**):



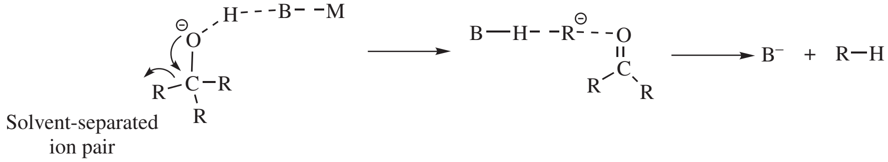
3

[26]Hsu, S.K.; Ingold, C.K.; Wilson, C.L. *J. Chem. Soc.* ***1938***, 78.
[27]Wilson, C.L. *J. Chem. Soc.* ***1936***, 1550.

which is a first-order S_E1 reaction involving resonance-stabilized planar carbanions (here designated R^-).[28] By changing the solvent Cram was able to produce products ranging from 99% retention to 60% inversion and including complete racemization. These results are explained by a carbanion that is not completely free but is solvated. In nondissociating, nonpolar solvents, such as benzene or dioxane, the alkoxide ion exists as an ion pair, solvated by the solvent BH:

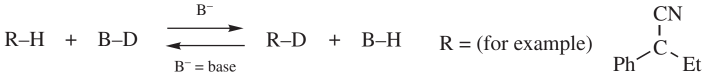


In the course of the cleavage, the proton of the solvent moves in to solvate the newly forming carbanion. As is easily seen, this solvation is asymmetrical since the solvent molecule is already on the front side of the carbanion. When the carbanion actually bonds with the proton, the result is retention of the original configuration. In protic solvents, such as diethylene glycol, a good deal of inversion is found. In these solvents, the *leaving group* solvates the carbanion, so the solvent can solvate it only from the opposite side:



When C–H bond formation occurs, the result is inversion. Racemization results in polar aprotic solvents, such as DMSO. In these solvents, the carbanions are relatively long lived (because the solvent has no proton to donate) and symmetrically solvated.

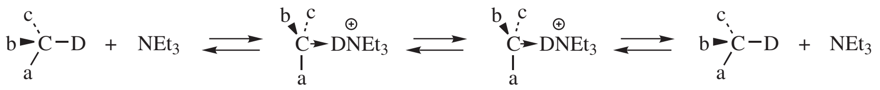
Similar behavior was found for carbanions generated by base-catalyzed hydrogen exchange (reaction **12-1**):[29]



[28]See Cram, D.J.; Langemann, A.; Allinger, J.; Kopecky, K.R. *J. Am. Chem. Soc.* ***1959***, *81*, 5740; Hoffman, T.D.; Cram, D.J. *J. Am. Chem. Soc.* ***1969***, *91*, 1009. For a discussion, see Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, ***1965***, pp. 138–158.

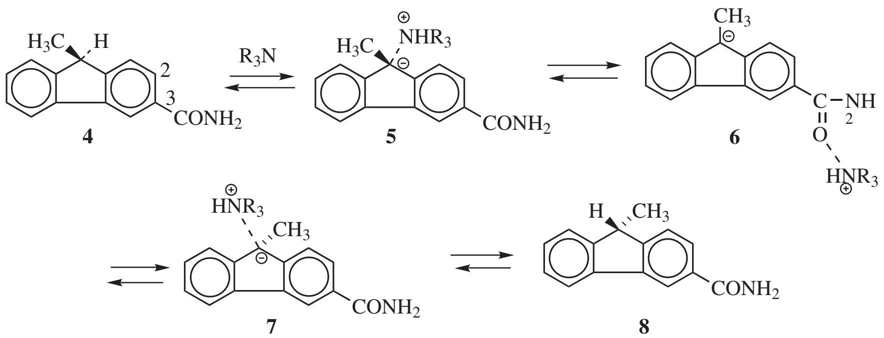
[29]See Roitman, J.N.; Cram, D.J. *J. Am. Chem. Soc.* ***1971***, *93*, 2225, 2231 and references cited therein; Cram, J.M.; Cram, D.J. *Intra-Sci. Chem. Rep.* ***1973***, *7(3)*, 1. For a discussion, see Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, ***1965***, pp. 85–105.

In this case, information was obtained from measurement of the ratio of k_e (rate constant for isotopic exchange) to k_a (rate constant for racemization). A k_e/k_a ratio substantially >1 means retention of configuration, since many individual isotopic exchanges are not producing a change in configuration. A k_e/k_a ratio of ~1 indicates racemization and a ratio of $\frac{1}{2}$ corresponds to inversion (see p. 430). All three types of steric behavior were found, depending on R, the base, and the solvent. As with the alkoxide cleavage reaction, retention was generally found in solvents of low dielectric constant, racemization in polar aprotic solvents, and inversion in protic solvents. However, in the proton-exchange reactions, a fourth type of behavior was encountered. In aprotic solvents, with aprotic bases like tertiary amines, the k_e/k_a ratio was found to be *less* than 0.5, indicating that racemization took place *faster* than isotopic exchange (this process is known as *isoracemization*). Under these conditions, the conjugate acid of the amine remains associated with the carbanion as an ion pair. Occasionally, the ion pair dissociates long enough for the carbanion to turn over and recapture the proton:



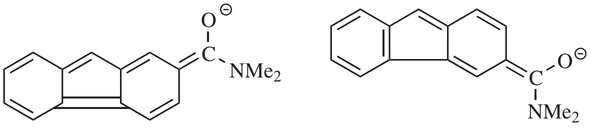
Thus, inversion (and hence racemization, which is produced by repeated acts of inversion) occurs without exchange. A single act of inversion without exchange is called *isoinversion*.

The isoinversion process can take place by a pathway in which a positive species migrates in a stepwise fashion around a molecule from one nucleophilic position to another. For example, in the exchange reaction of 3-carboxamido-9-methylfluorene (**4**) with Pr_3N in *t*-BuOH, it has been proposed that the amine removes



a proton from the 9 position of **4** and conducts the proton out to the C=O oxygen (**6**), around the molecule, and back to C-9 on the opposite face of the anion. Collapse of **7** gives the inverted product **8**. Of course, **6** could also go back to **4**, but a molecule that undergoes the total process **4** → **5** → **6** → **7** → **8** has experienced an inversion without an exchange. Evidence for this pathway, called the *conducted*

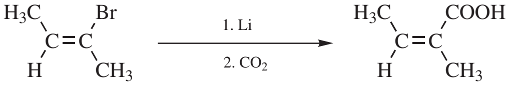
tour mechanism,[30] is that the 12-carboxamido isomer of **4** does not give isoracemization. In this case, the negative charge on the oxygen atom in the anion corresponding to **6** is less, because a canonical form in which oxygen acquires a full negative charge (**9**) results in disruption of the aromatic sextet in both



9 **10**

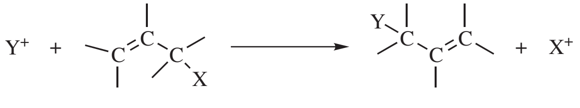
benzene rings (cf. **10** where one benzene ring is intact). Whether the isoracemization process takes place by the conducted tour mechanism or a simple nonstructured contact ion-pair mechanism depends on the nature of the substrate (e.g., a proper functional group is necessary for the conducted tour mechanism) and of the base.[31]

It is known that vinylic carbanions *can* maintain configuration, so that S_E1 mechanisms should produce retention there. This has been found to be the case. For example, *trans*-2-bromo-2-butene was converted to 64–74% angelic acid:[32]



Only ~5% of the cis isomer, tiglic acid, was produced. In addition, certain carbanions in which the negative charge is stabilized by *d*-orbital overlap can maintain configuration (p. 258) and S_E1 reactions involving them proceed with retention of configuration.

Electrophilic Substitution Accompanied by Double-Bond Shifts



11 **12**

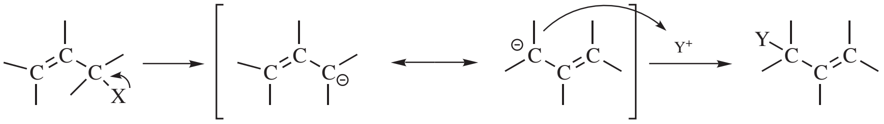
When electrophilic substitution is carried out at an allylic substrate, the product may be rearranged (**11** → **12**). This type of process is analogous to the nucleophilic

[30] Cram, D.J.; Ford, W.T.; Gosser, L. *J. Am. Chem. Soc.* ***1968***, *90*, 2598; Ford, W.T.; Cram, D.J. *J. Am. Chem. Soc.* ***1968***, *90*, 2606, 2612. See also Wong, S.M.; Fischer, H.P.; Cram, D.J. *J. Am. Chem. Soc.* ***1971***, *93*, 2235; Buchholz, S.; Harms, K.; Massa, W.; Boche, G. *Angew. Chem. Int. Ed.* ***1989***, *28*, 73.

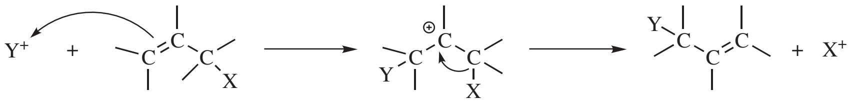
[31] Almy, J.; Hoffman, D.H.; Chu, K.C.; Cram, D.J. *J. Am. Chem. Soc.* ***1973***, *95*, 1185.

[32] Dreiding, A.S.; Pratt, R.J. *J. Am. Chem. Soc.* ***1954***, *76*, 1902. See also Walborsky, H.M.; Turner, L.M. *J. Am. Chem. Soc.* ***1972***, *94*, 2273.

allylic rearrangements discussed in Chapter 10 (p. 468). There are two principal pathways. The first of these is analogous to the S_E1 mechanism in that the leaving group is first removed, giving a resonance-stabilized allylic carbanion, which then attacks the electrophile.

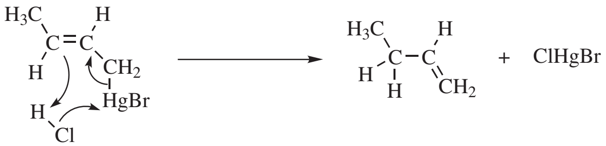


In the other pathway, the Y group is first attacked by the π-bond, giving a carbocation, which then loses X with formation of the alkene unit.

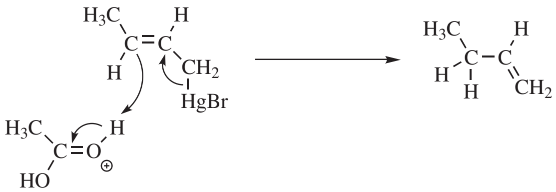


These mechanisms are more fully discussed under reaction **12-2**.

Most electrophilic allylic rearrangements involve loss of hydrogen, but they have also been observed with metallic leaving groups.[33] Sleezer, Winstein, and Young found that crotylmercuric bromide reacted with HCl ~10^7 times faster than *n*-butylmercuric bromide and the product was >99% 1-butene.[34] These facts point to an S_Ei' mechanism (IUPAC designation *cyclo*-1/3/$D_EA_ED_nA_n$):



The reaction of the same compound with acetic acid-perchloric acid seems to proceed by an S_E2' mechanism (IUPAC designation 1/3/D_EA_E):[34]



[33]For a review of reactions of allylic organometallic compounds, see Courtois, G.; Miginiac, L. *J. Organomet. Chem.* ***1974***, *69*, 1.

[34]Sleezer, P.D.; Winstein, S.; Young, W.G. *J. Am. Chem. Soc.* ***1963***, *85*, 1890. See also, Cunningham, I.M.; Overton, K.H. *J. Chem. Soc. Perkin Trans. 1* ***1975***, 2140; Kashin, A.N.; Bakunin, V.N.; Khutoryanskii, V.A.; Beletskaya, I.P.; Reutov, O.A. *J. Org. Chem. USSR* ***1979***, *15*, 12; *J. Organomet. Chem.* ***1979***, *171*, 309.

The geometry of electrophilic allylic rearrangement has not been studied very much (cf. the nucleophilic case, p. 471), but in most cases the rearrangement takes place with anti stereoselectivity,[35] although syn stereoselectivity has also been demonstrated.[36] In one case, use of the electrophile H^+ and the leaving group $SnMe_3$ gave both syn and anti stereoselectivity, depending on whether the substrate was cis or trans.[37]

Other Mechanisms

Addition–elimination (**12-16**) and cyclic mechanisms (**12-40**) are also known.

Much less work has been done on electrophilic aliphatic substitution mechanisms than on nucleophilic substitutions, and the exact mechanisms of many of the reactions in this chapter are in doubt. For many of them, not enough work has been done to permit us to decide which of the mechanisms described in this chapter is operating, if indeed any is. There may be other electrophilic substitution mechanisms, and some of the reactions in this chapter may not even be electrophilic substitutions at all.

REACTIVITY

Only a small amount of work has been done in this area, compared to the vast amount done for aliphatic nucleophilic substitution and aromatic electrophilic substitution. Only a few conclusions, most of them sketchy or tentative, can be drawn.[38]

1. *Effect of Substrate*. For S_E1 reactions electron-donating groups decrease rates and electron-withdrawing groups increase them. This is as would be expected from a reaction in which the rate-determining step is analogous to the cleavage of a proton from an acid. For the S_E2 (back) mechanism, Jensen and Davis[12] showed that the reactivity of alkyl groups is similar to that for the S_N2 mechanism (i.e., Me > Et > Pr > *i*Pr > neopentyl), as would be expected, since both involve backside attack and both are equally affected by steric hindrance. In fact, this pattern of reactivity can be regarded as evidence for the occurrence of the S_E2 (back) mechanism in cases where

[35]Hayashi, T.; Ito, H.; Kumada, M. *Tetrahedron Lett.* ***1982***, *23*, 4605; Wetter, H.; Scherer, P. *Helv. Chim. Acta* ***1983***, *66*, 118; Wickham, G.; Kitching, W. *J. Org. Chem.* ***1983***, *48*, 612; Fleming, I.; Kindon, N.D.; Sarkar, A.K. *Tetrahedron Lett.* ***1987***, *28*, 5921; Hayashi, T.; Matsumoto, Y.; Ito, Y. *Chem. Lett.* ***1987***, 2037, *Organometallics* ***1987***, *6*, 885; Matassa, V.G.; Jenkins, P.R.; Kümin, A.; Damm, L.; Schreiber, J.; Felix, D.; Zass, E.; Eschenmoser, A. *Isr. J. Chem.* ***1989***, *29*, 321.

[36]Wetter, H.; Scherer, P.; Schweizer, W.B. *Helv. Chim. Acta* ***1979***, *62*, 1985; Young, D.; Kitching, W. *J. Org. Chem.* ***1983***, *48*, 614; *Tetrahedron Lett.* ***1983***, *24*, 5793.

[37]Kashin, A.N.; Bakunin, V.N.; Beletskaya, I.P.; Reutov, O.A. *J. Org. Chem. USSR* ***1982***, *18*, 1973. See also, Wickham, G.; Young, D.; Kitching, W. *Organometallics* ***1988***, *7*, 1187.

[38]For a discussion, see Abraham, M.H. *Comprehensive Chemical Kinetics*, Bamford, C.H.; Tipper, C.F.H., Eds., Vol. 12; Elsevier, NY, ***1973***, pp. 211–241.

TABLE 12.1. Relative Rates of the Reaction of RHgBr with Br_2 and Br^- [41]

R	Relative Rate	R	Relative Rate
Me	1	Et	10.8
Et	10.8	*i*Bu	1.24
*i*Pr	780	Neopentyl	0.173
t-Bu	3370		

stereochemical investigation is not feasible.[39] For S_E2 reactions that proceed with retention, several studies have been made with varying results, depending on the reaction.[40] One such study, which examined the reaction $RHgBr + Br_2 \rightarrow RBr$ catalyzed by Br^-, gave the results shown in Table 12.1.[41] As can be seen, a branching increased the rates, while β branching decreased them. Sayre and Jensen attributed the decreased rates to steric hindrance, although attack here was definitely frontside, and the increased rates to the electron-donating effect of the alkyl groups, which stabilized the electron-deficient transition state.[42] Of course, steric hindrance should also be present with the a branched groups, so these workers concluded that if it were not, the rates would be even greater. The Br electrophile is a rather large one and it is likely that smaller steric effects are present with smaller electrophiles. The rates of certain second-order substitutions of organotin compounds have been found to increase with increasing electron withdrawal by substituents. This behavior has been ascribed[43] to an S_E2 mechanism involving ion pairs, analogous to Sneen's ion-pair mechanism for nucleophilic substitution (p. 441). Solvolysis of 2-bromo-1,1,1-trifluoro-2-(*p*-methoxyphenyl)ethane in water proceeds via a free carbocation intermediate, but ion pairing influences the reaction in the presence of bromide ion.[44]

2. *Effect of Leaving Group.* For both S_E1 and second-order mechanisms, the more polar the C–X bond, the easier it is for the electrofuge to cleave. For metallic leaving groups in which the metal has a valence >1, the nature of the other group or groups attached to the metal thus has an effect on the reaction.

[39]Another method involves measurement of the susceptibility of the rate to increased pressure: See Isaacs, N.S.; Javaid, K. *Tetrahedron Lett.* ***1977***, 3073; Isaacs, N.S.; Laila, A.H. *Tetrahedron Lett.* ***1984***, *25*, 2407.

[40]For some of these, see Abraham, M.H.; Grellier, P.L. *J. Chem. Soc. Perkin Trans. 2* ***1973***, 1132; Dessy, R.E.; Reynolds, G.F.; Kim, J. *J. Am. Chem. Soc.* ***1959***, *81*, 2683; Minato, H.; Ware, J.C.; Traylor, T.G. *J. Am. Chem. Soc.* ***1963***, *85*, 3024; Boué, S.; Gielen, M.; Nasielski, J. *J. Organomet. Chem.* ***1967***, *9*, 443; Abraham, M.H.; Broadhurst, A.T.; Clark, I.D.; Koenigsberger, R.U.; Dadjour, D.F. *J. Organomet. Chem.* ***1981***, *209*, 37.

[41]Sayre, L.M.; Jensen, F.R. *J. Am. Chem. Soc.* ***1979***, *101*, 6001.

[42]A similar conclusion, that steric and electronic effects are both present, was reached for a different system by Nugent, W.A.; Kochi, J.K. *J. Am. Chem. Soc.* ***1976***, *98*, 5979.

[43]Reutov, O.A. *J. Organomet. Chem.* ***1983***, *250*, 145. See also, Butin, K.P.; Magdesieva, T.V. *J. Organomet. Chem.* ***1985***, *292*, 47; Beletskaya, I.P. *Sov. Sci. Rev. Sect. B* ***1979***, *1*, 119.

[44]Richard, J.P. *J. Org. Chem.* ***1992***, *57*, 625.

For example, consider a series of organomercurials RHgW. Because a more electronegative W decreases the polarity of the C–Hg bond and furthermore results in a less stable HgW^+, the electrofugal ability of HgW decreases with increasing electronegativity of W. Thus, HgR′ (from RHgR′) is a better leaving group than HgCl (from RHgCl). Also in accord with this is the leaving-group order Hg-*t*-Bu > Hg-*i*Pr > HgEt > HgMe, reported for acetolysis of R_2Hg,[42] since the more highly branched alkyl groups better help to spread the positive charge. It might be expected that, when metals are the leaving groups, S_E1 mechanisms would be favored, while with carbon leaving groups, second-order mechanisms would be found. However, the results so far reported have been just about the reverse of this. For carbon leaving groups the mechanism is usually S_E1, while for metallic leaving groups the mechanism is almost always S_E2 or S_Ei. A number of reports of S_E1 reactions with metallic leaving groups have appeared,[45] but the mechanism is not easy to prove and many of these reports have been challenged.[46] Reutov and co-workers[45] have expressed the view that in such reactions a nucleophile (which may be the solvent) must assist in the removal of the electrofuge and refer to such processes as $S_E1(N)$ reactions.

3. *Effect of Solvent.*[47] In addition to the solvent effects on certain S_E1 reactions, mentioned earlier (p. 758), solvents can influence the mechanism that is preferred. As with nucleophilic substitution (p. 501), an increase in solvent polarity increases the possibility of an ionizing mechanism, in this case S_E1, in comparison with the second-order mechanisms, which do not involve ions. As previously mentioned (p. 758), the solvent can also exert an influence between the S_E2 (front or back) and S_Ei mechanisms in that the rates of S_E2 mechanisms should be increased by an increase in solvent polarity, while S_Ei mechanisms are much less affected.

REACTIONS

The reactions in this chapter are arranged in order of leaving group: hydrogen, metals, halogen, and carbon. Electrophilic substitutions at a nitrogen atom are treated last.

Hydrogen as Leaving Group

A. Hydrogen as the Electrophile

[45]For discussions, see Reutov, O.A. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1980***, *29*, 1461; Beletskaya, I.P.; Butin, K.P.; Reutov, O.A. *Organomet. Chem. Rev. Sect. A* ***1971***, *7*, 51. See also, Deacon, G.B.; Smith, R.N.M. *J. Org. Chem. USSR* ***1982***, *18*, 1584; Dembech, P.; Eaborn, C.; Seconi, G. *J. Chem. Soc. Chem. Commun.* ***1985***, 1289.

[46]For a discussion, see Kitching, W. *Rev. Pure Appl. Chem.* ***1969***, *19*, 1.

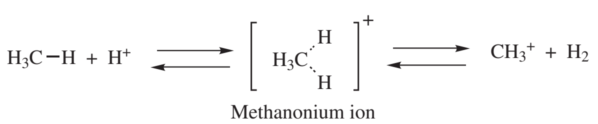
[47]For a discussion of solvent effects on organotin alkyl exchange reactions, see Petrosyan, V.S. *J. Organomet. Chem.* ***1983***, *250*, 157.

12-1 Hydrogen Exchange

Deuterio-de-hydrogenation or **Deuteriation**

$$R{-}H + D^+ \rightleftharpoons R{-}D + H^+$$

Hydrogen exchange can be accomplished by treatment with acids or bases. As with **11-1**, the exchange reaction is mostly used to study mechanistic questions, such as relative acidities, but it can be used synthetically to prepare deuterated or tritiated molecules. When ordinary strong acids, such as H_2SO_4 are used, only fairly acidic protons *n* carbon exchange, for example, acetylenic and allylic. However, primary, secondary, and tertiary hydrogens of alkanes can be exchanged by treatment with superacids (p. 236).[48] The order of hydrogen reactivity is tertiary > secondary > primary. Where C–C bonds are present, they may be cleaved also (**12-47**). The mechanism of the exchange (illustrated for methane) has been formulated as involving attack of H^+ on the C–H bond to give the pentavalent methanonium ion that loses H_2 to give a tervalent



carbocation.[49] The methanonium ion $CH_5{}^+$ has a three-center, two-electron bond.[50] It is not known whether the methanonium ion is a transition state or a true intermediate, but an ion $CH_5{}^+$ has been detected in the mass spectrum.[51] The IR spectrum of the ethanonium ion $C_2H_7{}^+$ has been measured in the gas phase.[52] Note that the two electrons in the three-center, two-electron bond can move in three directions, in accord with the threefold symmetry of such a structure. The electrons can move to unite the two hydrogens, leaving the $CH_3{}^+$ free (the forward reaction), or they can unite the CH_3 with either of the two hydrogens, leaving the other hydrogen as a free H^+ ion (the reverse reaction). Actually, the methyl cation is not stable under these conditions. It can go back to CH_4 by the route shown (leading to H^+ exchange) or it can react with additional CH_4 molecules (**12-20**) to eventually yield the *tert*-butyl cation, which is stable in these superacid solutions. Hydride ion can also be removed from alkanes (producing tervalent carbocations) by treatment with pure SbF_5 in the absence of any source of H^+.[53] Complete or almost complete perdeuteriation of cyclic alkenes has been achieved by treatment with dilute DCl/D_2O in sealed Pyrex tubes at 165–280°C.[54]

[48]For reviews, see Olah, G.A.; Prakash, G.K.S.; Sommer, J. *Superacids*, Wiley, NY, ***1985***, pp. 244–249; Olah, G.A. *Angew. Chem. Int. Ed.* ***1973***, *12*, 173; Brouwer, D.M.; Hogeveen, H. *Prog. Phys. Org. Chem.* ***1972***, *9*, 179, 180–203.

[49]The mechanism may not be this simple in all cases. For discussions, see McMurry, J.E.; Lectka, T. *J. Am. Chem. Soc.* ***1990***, *112*, 869; Culmann, J.; Sommer, J. *J. Am. Chem. Soc.* ***1990***, *112*, 4057.

[50]For a monograph on this type of species, see Olah, G.A.; Prakash, G.K.S.; Williams, R.E.; Field, L.D.; Wade, K. *Hypercarbon Chemistry*; Wiley, NY, ***1987***.

[51]See, for example, Sefcik, M.D.; Henis, J.M.S.; Gaspar, P.P. *J. Chem. Phys.* ***1974***, *61*, 4321.

[52]Yeh, L.I.; Pric, J.M.; Lee, Y.T. *J. Am. Chem. Soc.* ***1989***, *111*, 5597.

[53]Lukas, J.; Kramer, P.A.; Kouwenhoven, A.P. *Recl. Trav. Chim. Pays-Bas* ***1973***, *92*, 44.

[54]Werstiuk, N.H.; Timmins, G. *Can. J. Chem.* ***1985***, *63*, 530; ***1986***, *64*, 1564.

Exchange with bases involves an S_E1 mechanism.

$$\text{Step 1} \quad RH + B^- \longrightarrow R^- + BH$$

$$\text{Step 2} \quad R^- + BD \longrightarrow RD + B^-$$

Of course, such exchange is most successful for relatively acidic protons, such as those a to a carbonyl group, but even weakly acidic protons can exchange with bases if the bases are strong enough (see p. 251).

Alkanes and cycloalkanes, of both low and high molecular weight, can be fully perdeuterated treatment with D_2 gas and a catalyst, such as Rh, Pt, or Pd.[55]

OS **VI**, 432.

12-2 Migration of Double Bonds

3/Hydro-de-hydrogenation

$$C_5H_{11}\text{—}CH_2\text{—}CH{=}CH_2 \xrightarrow[Me_2SO]{KNH_2} C_5H_{11}\text{—}CH{=}CH\text{—}CH_3$$

The double bonds of many unsaturated compounds are shifted[56] on treatment with strong bases.[57] In many cases, equilibrium mixtures are obtained and the thermodynamically most stable isomer predominates.[58] Thus, if the new double bond can be in conjugation with one already present or with an aromatic ring, the migration favors the conjugated compound.[59] If the choice is between an exocyclic and an endocyclic double bond (particularly with six-membered rings), it generally chooses the latter. In the absence of considerations like these, Zaitsev's rule (p. 1497) applies and the double bond goes to the carbon with the fewest hydrogens. All these considerations lead us to predict that terminal alkenes can be isomerized to internal ones, nonconjugated alkenes to conjugated, exo six-membered-ring alkenes to endo, and so on, and not the other way around. This is indeed usually the case.

[55]See, for example, Atkinson, J.G.; Luke, M.O.; Stuart, R.S. *Can. J. Chem.* ***1967***, *45*, 1511.

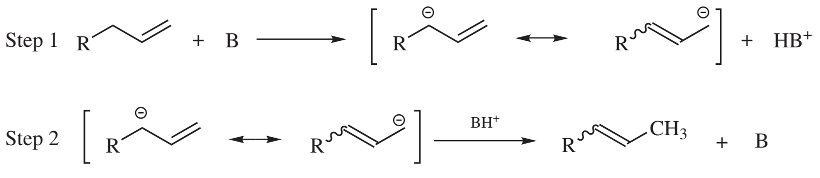
[56]For a list of methods used to shift double and triple bonds, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 220–226, 567–568.

[57]For reviews of double-bond migrations, see Pines, H.; Stalick, W.M. *Base-Catalyzed Reactions of Hydrocarbons and Related Compounds*, Academic Press, NY, ***1977***, pp. 25–123; DeWolfe, R.H., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 437–449; Yanovskaya, L.A.; Shakhidayatov, Kh. *Russ. Chem. Rev.* ***1970***, *39*, 859; Hubert, A.J.; Reimlinger, H. *Synthesis* ***1969***, 97; ***1970***, 405; Mackenzie, K., in *The Chemistry of Alkenes*, Vol. 1, Patai, S. pp. 416–436, vol. 2, Zabicky, J. pp. 132–148; Wiley, NY, 1964, ***1970***; Broaddus, C.D. *Acc. Chem. Res.* ***1968***, *1*, 231; Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, ***1965***, pp. 175–210.

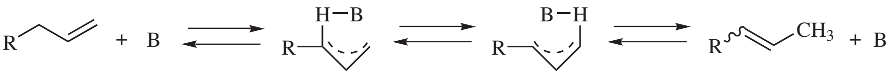
[58]For lists of which double bonds are more stable in conversions of $XCH_2CH{=}CHY$ to $XCH{=}CHCH_2Y$, see Hine, J.; Skoglund, M.J. *J. Org. Chem.* ***1982***, *47*, 4766. See also, Hine, J.; Linden, S. *J. Org. Chem.* ***1983***, *48*, 584.

[59]For a review of conversions of β,γ enones to α,β enones, see Pollack, R.M.; Bounds, P.L.; Bevins, C.L., in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 1, Wiley, NY, ***1989***, pp. 559–597.

This reaction, for which the term *prototropic rearrangement* is sometimes used, is an example of electrophilic substitution with accompanying allylic rearrangement. The mechanism involves abstraction by a base to give a resonance-stabilized carbanion, which then combines with a proton at the position that will give the more stable alkene:[60]



This mechanism is exactly analogous to the allylic-rearrangement mechanism for nucleophilic substitution (p. 468). UV spectra of allylbenzene and 1-propenylbenzene in solutions containing NH_2^- are identical, which shows that the same carbanion is present in both cases, as required by this mechanism.[61] The acid BH^+ protonates the position that will give the more stable product, although the ratio of the two possible products can vary with the identity of BH^+.[62] It has been shown that base-catalyzed double-bond shifts are partially intramolecular, at least in some cases.[63] The intramolecular nature has been ascribed to a *conducted tour mechanism* (p. 761) in which the base leads the proton from one carbanionic site to the other (**13** → **14**).[64]



13 **14**

Triple bonds can also migrate in the presence of bases,[65] but through the allene intermediate:[66]

$$R{-}CH_2{-}C{\equiv}CH \rightleftharpoons R{-}CH{=}C{=}CH_2 \rightleftharpoons R{-}C{\equiv}C{-}CH_3$$

[60]See, for example, Hassan, M.; Nour, A.R.O.A.; Satti, A.M.; Kirollos, K.S. *Int. J. Chem. Kinet.* ***1982***, *14*, 351; Pollack, R.M.; Mack, J.P.G.; Eldin, S. *J. Am. Chem. Soc.* ***1987***, *109*, 5048.

[61]Rabinovich, E.A.; Astaf'ev, I.V.; Shatenshtein, A.I. *J. Gen. Chem. USSR* ***1962***, *32*, 746.

[62]Hünig, S.; Klaunzer, N.; Schlund, R. *Angew. Chem. Int. Ed.* ***1987***, *26*, 1281.

[63]See, for example, Cram, D.J.; Uyeda, R.T. *J. Am. Chem. Soc.* ***1964***, *86*, 5466; Bank, S.; Rowe, Jr., C.A.; Schriesheim, A. *J. Am. Chem. Soc.* ***1963***, *85*, 2115; Doering, W. von E.; Gaspar, P.P. *J. Am. Chem. Soc.* ***1963***, *85*, 3043; Ohlsson, L.; Wold, S.; Bergson, G. *Ark. Kemi.*, ***1968***, *29*, 351.

[64]Almy, J.; Cram, D.J. *J. Am. Chem. Soc.* ***1969***, *91*, 4459; Hussénius, A.; Matsson, O.; Bergson, G. *J. Chem. Soc. Perkin Trans. 2* ***1989***, 851.

[65]For reviews, see Pines, H.; Stalick, W.M. *Base-Catalyzed Reactions of Hydrocarbons and Related Compounds*, Academic Press, NY, ***1977***, pp. 124–204; Théron F.; Verny, M.; Vessière, R. in Patai, S. *The Chemistry of Carbon–Carbon Triple Bond*, pt. 1, Wiley, NY, ***1978***, pp. 381–445; Bushby, R.J. *Q. Rev. Chem. Soc.* ***1970***, *24*, 585; Iwai, I. *Mech. Mol. Migr.* ***1969***, *2*, 73; Wotiz, J.H., in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 365–424; Vartanyan, S.A.; Babanyan, Sh.O. *Russ. Chem. Rev.* ***1967***, *36*, 670.

[66]For a review of rearrangements involving allenes, see Huntsman, W.D., in Patai, S. *The Chemistry of Ketenes, Allenes, and Related Compounds*, pt. 2; Wiley, NY, ***1980***, pp. 521–667.

In general, strong bases, for example, $NaNH_2$, convert internal alkynes to terminal alkynes (a particularly good base for this purpose is potassium 3-aminopropylamide $NH_2CH_2CH_2CH_2NHK$[67]), because the equilibrium is shifted by formation of the acetylid ion. With weaker bases such as NaOH (which are not strong enough to remove the acetylenic proton), the internal alkynes are favored because of their greater thermodynamic stability. In some cases the reaction can be stopped at the allene stage.[68] The reaction then becomes a method for the preparation of allenes.[69] The reaction of propargylic alcohols with tosylhydrazine, PPh_3, and DEAD also generates allenes.[70]

Double-bond rearrangements can also take place on treatment with acids. Both proton and Lewis[71] acids can be used. The mechanism in the case of proton acids is the reverse of the previous one; first a proton is gained, giving a carbocation, and then another is lost:

$$\text{Step 1} \qquad CH_3{-}CH_2{-}CH{=}CH_2 \ + \ H^+ \longrightarrow CH_3{-}CH_2{-}\overset{\oplus}{C}H{-}CH_3$$

$$\text{Step 2} \qquad CH_3{-}CH_2{-}\overset{\oplus}{C}H{-}CH_3 \longrightarrow CH_3{-}CH{=}CH{-}CH_3 \ + \ H^+$$

As in the case of the base-catalyzed reaction, the thermodynamically most stable alkene is the one predominantly formed. However, the acid-catalyzed reaction is much less synthetically useful because carbocations give rise to many side products. If the substrate has several possible locations for a double bond, mixtures of all possible isomers are usually obtained. Isomerization of 1-decene, for example, gives a mixture that contains not only 1-decene and *cis*- and *trans*-2-decene, but also the cis and trans isomers of 3-, 4-, and 5-decene as well as branched alkenes resulting from rearrangement of carbocations. It is true that the most stable alkenes predominate, but many of them have stabilities that are close together. Acid-catalyzed migration of triple bonds (with allene intermediates) can be accomplished if very strong acids (e.g., $HF{-}PF_5$) are used.[72] If the mechanism is the same as that for double bonds, vinyl cations are intermediates.

Double-bond isomerization can also take place in other ways. Nucleophilic allylic rearrangements were discussed in Chapter 10 (p. 468). Electrocyclic and sigmatropic rearrangements are treated at **18-27–18-35**. Double-bond migrations have also been accomplished photochemically,[73] and by means of metallic ion (most

[67]Brown, C.A.; Yamashita, A. *J. Am. Chem. Soc.* ***1975***, *97*, 891; Macaulay, S.R. *J. Org. Chem.* ***1980***, *45*, 734; Abrams, S.R. *Can. J. Chem.* ***1984***, *62*, 1333.

[68]For an example, see Oku, M.; Arai, S.; Katayama, K.; Shioiri, T. *Synlett* ***2000***, 493.

[69]See Enomoto, M.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* ***1986***, *27*, 4599; Cunico, R.F.; Zaporowski, L.F.; Rogers, M. *J. Org. Chem.* ***1999***, *64*, 9307.

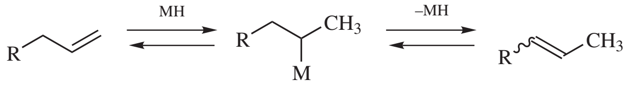
[70]Myers, A.G.; Zheng, B. *J. Am. Chem. Soc.* ***1996***, *118*, 4492. See Moghaddam, F.M.; Emami, R. *Synth. Commun.* ***1997***, *27*, 4073 for the formation of alkoxy allenes from propargyl ethers.

[71]For an example of a Lewis acid catalyzed rearrangement, see Cameron G.S.; Stimson, V.R. *Aust. J. Chem.* ***1977***, *30*, 923.

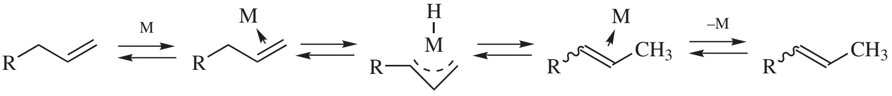
[72]Barry, B.J.; Beale, W.J.; Carr, M.D.; Hei, S.; Reid, I. *J. Chem. Soc. Chem. Commun.* ***1973***, 177.

[73]Schönberg, A. *Preparative Organic Photochemistry*, Springer, NY, ***1968***, pp. 22–24.

often complex ions containing Pt, Rh, or Ru) or metal carbonyl catalysts.[74] In the latter case, there are at least two possible mechanisms. One of these, which requires external hydrogen, is called the *metal hydride addition–elimination mechanism*:



The other mechanism, called the *π-allyl complex mechanism*, does not require external hydrogen and proceeds by hydrogen abstraction to form the η^3-π-allyl complex **15** (see p. 117 and **10-60**).



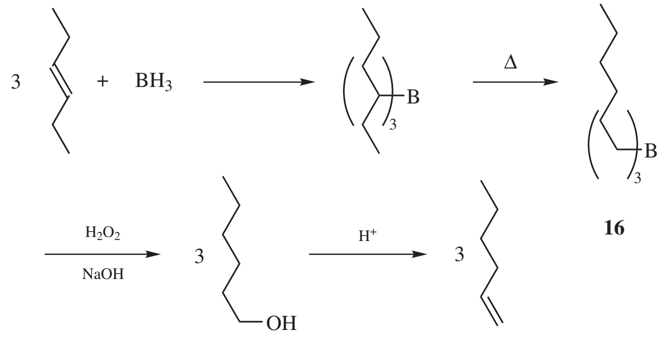
15

Another difference between the two mechanisms is that the former involves 1,2- and the latter 1,3-shifts. The isomerization of 1-butene by rhodium(I) is an example of a reaction that takes place by the metal hydride mechanism,[75] while an example of the π-allyl complex mechanism is found in the $Fe_3(CO)_{12}$-catalyzed isomerization of 3-ethyl-1-pentene.[76] A palladium catalyst was used to convert alkynones $RCOC{\equiv}CCH_2CH_2R'$ to 2,4-alkadien-1-ones, $RCOCH{=}CHCH{=}CHCHR'$.[77] The reaction of an en-yne with $HSiCl_3$ and a palladium catalyst generated an allene with moderate enantioselectivity (see p 148 for chiral allenes).[78]

The metal catalysis method has been used for the preparation of simple enols, by isomerization of allylic alcohols, for example,[79] these enols are stable enough for isolation (see p. 231), but slowly tautomerize to the aldehyde or ketone, with half-lives ranging from 40 to 50 min to several days.[79]

[74]For reviews, see Rodriguez, J.; Brun, P.; Waegell, B. *Bull. Soc. Chim. Fr.* ***1989***, 799–823; Jardine, F.R., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 4, Wiley, NY, pp. 733–818, 736–740; Otsuka, S.; Tani, K., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 5, Academic Press, NY, ***1985***, pp. 171–191 (enantioselective); Colquhoun, H.M.; Holton, J.; Thompson, D.J.; Twigg, M.V. *New Pathways for Organic Synthesis*, Plenum, NY, ***1984***, pp. 173–193; Khan, M.M.T.; Martell, A.E. *Homogeneous Catalysis by Metal Complexes*, Academic Press, NY, ***1974***, pp. 9–37; Heck, R.F. *Organotransition Metal Chemistry*, Academic Press, NY, ***1974***, pp. 76–82; Jira, R.; Freiesleben, W. *Organomet. React.* ***1972***, *3*, 1, 133–149; Biellmann, J.F.; Hemmer, H.; Levisalles, J., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 2, Wiley, NY, pp. 224–230; Bird, C.W. *Transition Metal Intermediates in Organic Synthesis*, Academic Press, NY, ***1967***, pp. 69–87; Davies, N.R. *Rev. Pure Appl. Chem.* ***1967***, *17*, 83; Orchin, M. *Adv. Catal.* ***1966***, *16*, 1.
[75]Cramer, R. *J. Am. Chem. Soc.* ***1966***, *88*, 2272.
[76]Casey, C.P.; Cyr, C.R. *J. Am. Chem. Soc.* ***1973***, *95*, 2248.
[77]Trost, B.M.; Schmidt, T. *J. Am. Chem. Soc.* ***1988***, *110*, 2301.
[78]Han, J.W.; Tokunaga, N.; Hayashi, T. *J. Am. Chem. Soc.* ***2001***, *123*, 12915.
[79]Bergens, S.H.; Bosnich, B. *J. Am. Chem. Soc.* ***1991***, *113*, 958.

No matter which of the electrophilic methods of double-bond shifting is employed, the thermodynamically most stable alkene is usually formed in the largest amount in most cases, although a few anomalies are known. However, an indirect method of double-bond isomerization us known, leading to migration in the other direction. This involves conversion of the alkene to a borane (**15-16**), rearrangement of the borane (**18-11**), oxidation and hydrolysis of the newly formed borane to the alcohol **17** (see **12-31**), and dehydration of the alcohol (**17-1**) to the alkene. The reaction is driven by the fact that with heating the addition of borane is reversible, and the equilibrium favors formation of the less sterically hindered borane, which is **16** in this case.



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17

Since the migration reaction is always toward the end of a chain, terminal alkenes can be produced from internal ones, so the migration is often opposite to that with the other methods. Alternatively, the rearranged borane can be converted directly to the alkene by heating with an alkene of molecular weight higher than that of the product (**17-15**). Photochemical isomerization can also lead to the thermodynamically less stable isomer.[80]

If a hydroxy group is present in the chain, *it* may lose a proton, so that a ketone is the product, for example,[81]

$$R_2C{=}CHCH_2CH_2CHOHCH_3 \xrightarrow[\text{acid}]{\text{polyphosphoric}} R_2CHCH_2CH_2CH_2COCH_3$$

Similarly, α-hydroxy triple-bond compounds have given α,β-unsaturated ketones.[82]

[80]For example, see Kropp, P.J.; Krauss, H.J. *J. Am. Chem. Soc.* ***1967***, *89*, 5199; Reardon, Jr., E.J.; Krauss, H. *J. Am. Chem. Soc.* ***1971***, *93*, 5593; Duhaime, R.M.; Lombardo, D.A.; Skinner, I.A.; Weedon, A.C. *J. Org. Chem.* ***1985***, *50*, 873.

[81]Colonge, J.; Brunie, J. *Bull. Soc. Chim. Fr.* ***1963***, 1799. For an example with basic catalysis, see Hoffmann, H.M.R.; Köver, A.; Pauluth, D. *J. Chem. Soc. Chem. Commun.* ***1985***, 812. For an example with a ruthenium complex catalyst, see Trost, B.M.; Kulawiec, R.J. *Tetrahedron Lett.* ***1991***, *32*, 3039.

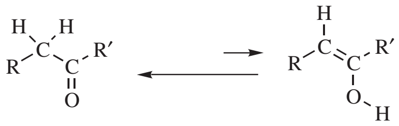
[82]For example, see Chabardes, P. *Tetrahedron Lett.* ***1988***, *29*, 6253.

See **15-1** for related reactions in which double bonds migrate or isomerize.

OS **II**, 140; **III**, 207; **IV**, 189, 192, 195, 234, 398, 683; **VI**, 68, 87, 815, 925; **VII**, 249; **VIII**, 146, 196, 251, 396, 553; **X**, 156, 165; **81**, 147

12-3 Keto–Enol Tautomerization

3/*O*-Hydro-de-hydrogenation



The tautomeric equilibrium between enols and ketones or aldehydes (keto–enol tautomerism) is a form of prototropy,[83] but is not normally a preparative reaction. For some ketones, however, both forms can be prepared (see p. 101 for a discussion of this and other aspects of tautomerism). Keto–enol tautomerism occurs in systems containing one or more carbonyl groups linked to sp^3 carbons bearing one or more hydrogen atoms. The keto tautomer is generally more stable than the enol tautomer for neutral systems, and for most ketones and aldehydes only the keto form is detectable under ordinary conditions. The availability of additional intramolecular stabilization through hydrogen bonding or complete electron delocalization (as in phenol), may cause the enol tautomer to be favored.

Keto–enol tautomerism cannot take place without at least a trace of acid or base,[84] since the acidic or basic center or both in the tautomeric substance is too weak.[85] In this equilibrium, the heteroatom is the basic site the proton is the acidic site. For tautomerism in general (see p 98),[86] the presence of an acid or a base is not necessary to initiate the isomerization since each tautomeric substance possesses amphiprotic properties.[85] Keto-enol tautomerism is therefore the exception.

[83]Patai, S. *The Chemistry of the Carbonyl Group*, Wiley, London, ***1966***; Rappoport, Z. *The Chemistry of Enols*, Wiley, NY, ***1990***; Kresge, A.J. *Chem. Soc. Rev.* ***1996***, *25*, 275; Karelson, M.; Maran, U.; Katritzky, A.R. *Tetrahedron* ***1996***, *52*, 11325; Rappoport, Z.; Frey, J.; Sigalov, M.; Rochlin, E. *Pure Appl. Chem.* ***1997***, *69*, 1933; Fontana, A.; De Maria, P.; Siani, G.; Pierini, M.; Cerritelli, S.; Ballini, R. *Eur. J. Org. Chem.* ***2000***, 1641; Iglesias, E. *Curr. Org. Chem.* ***2004***, *8*, 1.

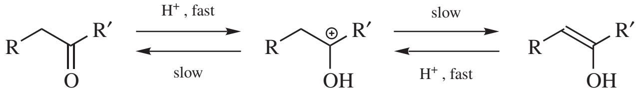
[84]Bell, R.P. *Acid–Base Catalysis*, Oxford University Press, Oxford, ***1941***; Jones, J.R. *The Ionisation of Carbon Acids*, Academic Press, London, ***1973***; Pederson, K.J. *J. Phys. Chem.* ***1934***, *38*, 581; Lienhard, G.E.; Wang, T. C. *J. Am. Chem. Soc.* ***1969***, *91*, 1146; Toullec, J. *Adv. Phys. Org. Chem.* ***1982***, *18*, 1. See also, Chiang, Y.; Kresge, A.J.; Santaballa, J.A.; Wirz, J. *J. Am. Chem. Soc.* ***1988***, *110*, 5506.

[85]Raczynska, E. D.; Kosinska, W.; Osmialowski, B.; Gawinecki, R. *Chem. Rev.* ***2005***, *105*, 3561.

[86]See Patai, S. *The Chemistry of the Carbonyl Group*, Wiley, London, ***1966***; Rappoport, Z. *The Chemistry of Enols*, Wiley, NY, ***1990***; Patai, S. *The Chemistry of the Thiol Group*, Wiley, London, ***1974***; Zabicky, J. *The Chemistry of Amides*, Wiley, London, ***1970***; Boyer, J. H. *The Chemistry of the Nitro and Nitroso Groups*, Interscience Publishers, NY, ***1969***; Patai, S. *The Chemistry of Amino, Nitroso, Nitro Compounds and their Derivatives*, Wiley, NY, ***1982***; Patai, S. *The Chemistry of Amino, Nitroso, Nitro and Related Groups, Supplement F2*,Wiley, Chichester, ***1996***; Cook, A. G. *Enamines*, 2nd ed., Marcel Dekker, NY, ***1998***.

Polar protic solvents, such as water or alcohol, may participate in the proton transfer by forming a cyclic or a linear complex with the tautomers.[87] Whether the complex formed is cyclic or linear depends on the conformation and configuration of the tautomers. In a strongly polar aprotic solvent and in the presence of an acid or a base, the tautomeric molecule may lose or gain a proton and form the corresponding mesomeric anion or cation, which, in turn, may gain or lose a proton, respectively, and yield a new tautomeric form.[88] The structural features of the carbonyl compound influences the equilibrium.[89] There is a rate acceleration when $LiN(SiMe_3)_2$–NEt_3 is used.[90] It has been shown that ring strain plays no significant role on the rate of base-catalyzed enolization.[91] Differing conjugative stabilization by CH-π orbital overlap does not directly influence stereoselectivity, and steric effects are generally not large enough to cause the several kcal/mol energy difference seen between transition structures unless there is exceptional crowding.[92] It is noted that sterically stabilized enols are known,[93] including arylacetaldehydes.[94] Torsional strain involving vicinal bonds does contribute significantly to stereoselectivity in enolate formation.[92]

The acid and base catalyzed mechanisms are identical to those in **12-2**.[95]
Acid-catalyzed



[87]Lledós, A.; Bertran, J. *Tetrahedron Lett.* ***1981***, *22*, 775; Zielinski, T.J.; Poirier, R.A.; Peterson, M.R.; Csizmadia, I.G. *J. Comput. Chem.* ***1983***, *4*, 419; Yamabe, T.; Yamashita, K.; Kaminoyama, M.; Koizumi, M.; Tachibana, A.; Fukui, K. *J. Phys. Chem.* ***1984***, *88*, 1459; Chen, Y.; Gai, F.; Petrich, J.W. *J. Am. Chem. Soc.* ***1993***, *115*, 10158; Herbich, J.; Dobkowski, J.; Thummel, R.P.; Hegde, V.; Waluk, J. *J. Phys. Chem. A* ***1997***, *101*, 5839; Gorb, L.; Leszczynski, J. *J. Am. Chem. Soc.* ***1998***, *120*, 5024; Guo, J. X.; Ho, J. J. *J. Phys. Chem. A* ***1999***, *103*, 6433.

[88]Watson, H.B. *Trans. Faraday Soc.* ***1941***, *37*, 713; Kabachnik, M.I. *Dokl. Akad. Nauk SSSR* ***1952***, *83*, 407; Perez Ossorio, R.; Hughes, E.D. *J. Chem. Soc.* ***1952***, 426; Briegleb, G.; Strohmeier, W. *Angew. Chem.* ***1952***, *64*, 409; Baddar, F.G.; Iskander, Z. *J. Chem. Soc.* ***1954***, 203.

[89]Hegarty, A.F.; Dowling, J.P.; Eustace, S.J.; McGarraghy, M. *J. Am. Chem. Soc.* ***1998***, *120*, 2290.

[90]Zhao, P.; Collum, D.B. *J. Am. Chem. Soc.* ***2003***, *125*, 4008.

[91]Cantlin, R.J.; Drake, J.; Nagorski, R.W. *Org. Lett.* ***2002***, *4*, 2433.

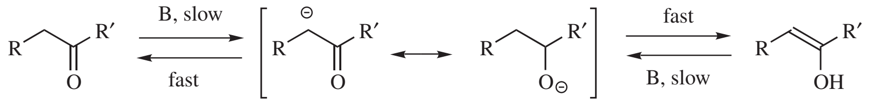
[92]Behnam, S.M.; Behnam, S.E.; Ando, K.; Green, N.S.; Houk, K.N. *J. Org. Chem.* ***2000***, *65*, 8970.

[93]Miller, A.R. *J. Org. Chem.*, ***1976***, *41*, 3599.

[94]Fuson, R.C.; Southwick, P.L.; Rowland, Jr., S.P. *J. Am. Chem. Soc.* ***1944***, *66*, 1109; Fuson, R.C.; Tan, T.-L. *J. Am. Chem. Soc.* ***1948***, *70*, 602.

[95]For reviews of the mechanism, see Keeffe, J.R.; Kresge, A.J., in Rappoport, Z. *The Chemistry of Enols*, Wiley, NY, ***1990***, pp. 399–480; Toullec, J. *Adv. Phys. Org. Chem.* ***1982***, *18*, 1; Lamaty, G. *Isot. Org. Chem.* ***1976***, *2*, 33. For discussions, see Ingold, C.K. *Structure and Mechanism in Organic Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, ***1969***, pp. 794–837; Bell, R.P. *The Proton in Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, ***1973***, pp. 171–181; Bruice, P.Y.; Bruice, T.C. *J. Am. Chem. Soc.* ***1976***, *98*, 844; Shelly, K.P.; Venimadhavan, S.; Nagarajan, K.; Stewart, R. *Can. J. Chem.* ***1989***, *67*, 1274. For a review of stereoelectronic control in this mechanism, see Pollack, R.M. *Tetrahedron* ***1989***, *45*, 4913.

Base-catalyzed[96]



18

For each catalyst, the mechanism for one direction is the exact reverse of the other, by the principle of microscopic reversibility.[97] As expected from mechanisms in which the C–H bond is broken in the rate-determining step, substrates of the type RCD_2COR show deuterium isotope effects (of ~5) in both the basic-[98] and the acid[99]-catalyzed processes. The keto–enol/enolate anion equilibrium has been studied in terms of the influence of β-oxygen[100] or β-nitrogen[101] substituents.

Although the conversion of an aldehyde or a ketone to its enol tautomer is not generally a preparative procedure, the reactions do have their preparative aspects. If a full equivalent of base per equivalent of ketone is used, the enolate ion (**18**) is formed and can be isolated[102] (see, e.g., the alkylation reaction in **10-68**).[103] When enol ethers or esters are hydrolyzed, the enols initially formed immediately tautomerize to the aldehydes or ketones. In addition, the overall processes (forward plus reverse reactions) are often used for equilibration purposes. When an optically active compound in which the chirality is due to an stereogenic carbon α to a carbonyl group (as in **19**) is treated with acid or base, racemization results.[104]

[96]Another mechanism for base-catalyzed enolization has been reported when the base is a tertiary amine: See Bruice, P.Y. *J. Am. Chem. Soc.* ***1983***, *105*, 4982; ***1989***, *111*, 962; ***1990***, *112*, 7361.

[97]It has been proposed that the acid-catalyzed ketonization of simple enols is concerted; that is, both of the processes shown in the equation take place simultaneously. This would mean that in these cases the forward reaction is also concerted. For evidence in favor of this proposal, see Capon, B.; Siddhanta, A.K.; Zucco, C. *J. Org. Chem.* ***1985***, *50*, 3580. For evidence against it, see Chiang, Y.; Hojatti, M.; Keeffe, J.R.; Kresge, A.J.; Schepp, N.P.; Wirz, J. ***1987***, *109*, 4000 and references cited therein.

[98]Riley, T.; Long, F.A. *J. Am. Chem. Soc.* ***1962***, *84*, 522; Xie, L.; Saunders, Jr., W.H. *J. Am. Chem. Soc.* ***1991***, *113*, 3123.

[99]Swain, C.G.; Stivers, E.C.; Reuwer Jr., J.F.; Schaad, L.J. *J. Am. Chem. Soc.* ***1958***, *80*, 5885; Lienhard, G.E.; Wang, T. *J. Am. Chem. Soc.* ***1969***, *91*, 1146. See also Toullec, J.; Dubois, J.E. *J. Am. Chem. Soc.* ***1974***, *96*, 3524.

[100]Chiang, Y.; Kresge, A.J.; Meng, Q.; More, O'Farrall, R.A.; Zhu, Y. *J. Am. Chem. Soc.* ***2001***, *123*, 11562.

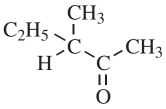
[101]Chiang, Y.; Griesbeck, A. G.; Heckroth, H.; Hellrung, B.; Kresge, A. J.; Meng, Q.; O'Donoghue, A. C.; Richard, J. P.; Wirz, J. *J. Am. Chem. Soc.* ***2001***, *123*, 8979.

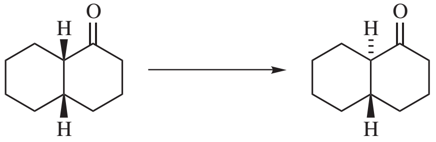
[102]For nmr studies of the Li enolate of acetaldehyde in solution, see Wen, J.Q.; Grutzner, J.B. *J. Org. Chem.* ***1986***, *51*, 4220.

[103]For a review of the preparation and uses of enolates, see d'Angelo, J. *Tetrahedron* ***1976***, *32*, 2979. For a discussion of solid state enolate chemistry, see Fruchart, J.-S.; Lippens, G.; Kuhn, C.; Gran-Masse, H.; Melnyk, O. *J. Org. Chem.* ***2002***, *67*, 526.

[104]For an exception, see Guthrie, R.D.; Nicolas, E.C. *J. Am. Chem. Soc.* ***1981***, *103*, 4637.

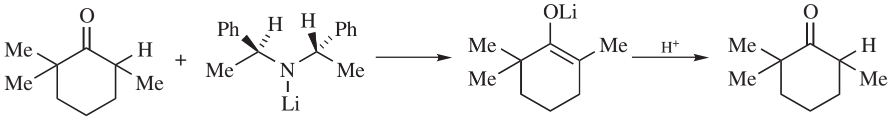
If there is another





19 *cis*-Decalone *trans*-Decalone

stereogenic center in the molecule, the less stable epimer can be converted to the more stable one in this manner, and this is often done. For example, *cis*-decalone can be equilibrated to the trans isomer. Isotopic exchange can also be accomplished at the a position of an aldehyde or ketone in a similar manner. The role of additives, such as $ZnCl_2$ on the stereogenic enolization reactions using chiral cases has been discussed.[105] Enantioselective enolate anion protonation reactions have been studied.[106] For the acid-catalyzed process, exchange or equilibration is accomplished only if the carbonyl compound is completely converted to the enol and then back, but in the base-catalyzed process exchange or equilibration can take place if only the first step (conversion to the enolate ion) takes place. The difference is usually academic. In cyclic compounds, cis- to trans-isomerization can occur via the enol.[107]



20 Racemic **21** **22** **20** Optically active

In the case of the ketone **20**, a racemic mixture was converted to an optically active mixture (optical yield 46%) by treatment with the chiral base **21**.[108] This happened because **21** reacted with one enantiomer of **20** faster than with the other (an example of kinetic resolution). The enolate **22** must remain coordinated with the chiral amine, and it is the amine that reprotonate **22**, not an added proton donor.

Enolizable hydrogens can be replaced by deuterium (and ^{16}O by ^{18}O) by passage of a sample through a deuterated (or ^{18}O-containing) gas-chromatography column.[109]

[105]Coggins, P.; Gaur, S.; Simpkins, N.S. *Tetrahedron Lett.* ***1995***, *36*, 1545.

[106]Vedejs, E.; Kruger, A.W.; Suna, E. *J. Org. Chem.* ***1999***, *64*, 7863.

[107]Dechoux, L.; Doris, E. *Tetrahedron Lett.* ***1994***, *35*, 2017.

[108]Eleveld, M.B.; Hogeveen, H. *Tetrahedron Lett.* ***1986***, *27*, 631. See also, Shirai, R.; Tanaka, M.; Koga, K. *J. Am. Chem. Soc.* ***1986***, *108*, 543; Cain, C.M.; Cousins, R.P.C.; Coumbarides, G.; Simpkins, N.S. *Tetrahedron* ***1990***, *46*, 523.

[109]Senn, M.; Richter, W.J.; Burlingame, A.L. *J. Am. Chem. Soc.* ***1965***, *87*, 680; Richter, W.J.; Senn, M.; Burlingame, A.L. *Tetrahedron Lett.* ***1965***, 1235.

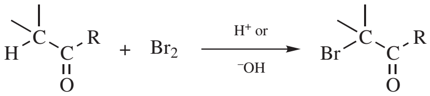
There are many enol-keto interconversions and acidification reactions of enolate ions to the keto forms listed in *Organic Syntheses*. No attempt is made to list them here.

B. Halogen Electrophiles

Halogenation of unactivated hydrocarbons is discussed in **14-1**.

12-4 Halogenation of Aldehydes and Ketones

Halogenation or **Halo-de-hydrogenation**



Aldehydes and ketones can be halogenated in the a position with bromine, chlorine, or iodine.[110] The reaction is not successful with fluorine.[111] Sulfuryl chloride,[112] $NaClO_2/Mn(acac)_3$,[113] $Me_3SiCl–Me_2SO$,[114] $Me_3SiCl–MnO_2$,[115] and cupric chloride[116] have been used as reagents for chlorination, and *N*-bromosuccinimide (see **14-3**),[117] *t*-BuBr–DMSO,[118] Me_3SiBr–DMSO,[119] tetrabutylammonium tribromide,[120] and bromine • dioxane on silica with microwave irradiation[121] for bromination. Bromination of methyl ketones was done using PhI(OH)OTs with microwave irradiation, followed by treatment with $MgBr_2$ and microwave irradiation.[122] α-Chloro aldehydes are formed with Cl_2 and a catalytic amount of tetraethylammonium chloride.[123] Chlorination of aldehydes with good enantioselectivity was

[110]For a review, see House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 459–478. For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp.709–719. For a monograph, see De Kimpe, N.; Verhé, R. *The Chemistry of a Haloketones*, *α-Haloaldehydes, and α-Haloimines,* Wiley, NY, 1988.

[111]For a review of the preparation of α-fluoro carbonyl compounds, see Rozen, S.; Filler, R. *Tetrahedron* ***1985***, *41*, 1111. For a monograph, see German, L.; Zemskov, S. *New Fluorinating Agents in Organic Chemistry*, Springer, NY, ***1989***.

[112]For a review of sulfuryl chloride, see Tabushi, I.; Kitaguchi, H. in Pizey, J.S. *Synthetic Reagents*, Vol. 4; Wiley, NY, ***1981***, pp. 336–396.

[113]Yakabe, S.; Hirano, M.; Morimoto, T. *Synth. Commun.* ***1998***, *28*, 131.

[114]Bellesia, F.; Ghelfi, F.; Grandi, R.; Pagnoni, U.M. *J. Chem. Res. (S)* ***1986***, 426; Fraser, R.R.; Kong, F. *Synth. Commun.* ***1988***, *18*, 1071.

[115]Bellesia, F.; Ghelfi, F.; Pagnoni, U.M.; Pinetti, A. *J. Chem. Res. (S)* ***1990***, 188.

[116]For a review, see Nigh, W.G., in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B, Academic Press, NY, ***1973***, pp. 67–81. Cupric chloride has been used to chlorinate α,β-unsaturated aldehydes and ketones in the γ position: Dietl, H.K.; Normark, J.R.; Payne, D.A.; Thweatt, J.G.; Young, D.A. *Tetrahedron Lett.* ***1973***, 1719.

[117]For an example, see Tanemura, K.; Suzuki, T.; Nishida, Y.; Satsumabayashi, K.; Horaguchi, T. *Chem. Commun.* ***2004***, 470.

[118]Armani, E.; Dossena, A.; Marchelli, R.; Casnati, G. *Tetrahedron* ***1984***, *40*, 2035.

[119]Bellesia, F.; Ghelfi, F.; Grandi, R.; Pagnoni, U.M. *J. Chem. Res. (S)* ***1986***, 428.

[120]Kajigaeshi, S.; Kakinami, T.; Okamoto, T.; Fujisaki, S. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 1159.

[121]Paul, S.; Gupta, V.; Gupta, R.; Loupy, A. *Tetrahedron Lett.* ***2003***, *44*, 439.

[122]Lee, J.C.; Park, J.Y.; Yoon, S.Y.; Bae, Y.H.; Lee, S.J. *Tetrahedron Lett.* ***2004***, *45*, 191.

[123]Bellesia, F.; DeBuyck, L.; Ghelfi, F.; Pagnoni, U.M.; Parson, A.F.; Pinetti, A. *Synthesis* ***2003***, 2173.

reported using a chlorinated quinone and L-proline, with the reaction proceeding via the chiral enamine.[124] Iodination has been accomplished with I_2–$HgCl_2$,[125] with I_2-cerium(IV) ammonium nitrate,[126] and with iodine using 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate), known as Selectfluor F–TEDA–BF_4, in methanol.[127] Treatment of a ketone with (hydroxy-*p*-nitrobenzene-sulfonyloxy)benzene followed by SmI_2 give the α-iodo ketone.[128] Methyl ketones react with *N*-iodosuccinimide (NIS) and tosic acid with microwave irradiation without solvent to give the α-iodo ketone.[129] Several methods have been reported for the preparation of α-fluoro aldehydes and ketones.[130] Another Selectfluor, 1-Fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) has been used for the monofluorination of ketones,[131] as has a mixture of KI–KIO_3–H_2SO_4.[132] Active compounds, such as β-keto esters and β-diketones, have been fluorinated with an *N*-fluoro-*N*-alkylsulfonamide[133] (this can result in enantioselective fluorination, if an optically active *N*-fluorosulfonamide is used[134]), with F_2/N_2–HCOOH,[135] with NF_3O/Bu_4NOH,[136] and with acetyl hypofluorite.[137] The last reagent also fluorinates simple ketones in the form of their lithium enolates.[138]

For unsymmetrical ketones, the preferred position of halogenation is usually the more substituted: a CH group, then a CH_2 group, and then CH_3;[139] however, mixtures are frequent. With aldehydes the aldehydic hydrogen is sometimes replaced (see **14-4**). It is also possible to prepare di- and polyhalides. When basic catalysts are used, one a position of a ketone is completely halogenated before the other is

[124]Brochu, M.P.; Brown, S.P.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2004***, *126*, 4108. For this chlorination using a chiral pyrrolidine derivative with NCS, see Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jorgensen, K.A. *J. Am. Chem. Soc.* ***2004***, *126*, 4790. See Wack, H.; Taggi, A.E.; Hafez, A.M.; Drury III, W. J.; Lectka, T. *J. Am. Chem. Soc.* ***2001***, *123*, 1531; Hafez, A.M.; Taggi, A.E.; Wack, H.; Esterbrook III, J.; Lectka, T. *Org. Lett.* ***2001***, *3*, 2049.

[125]Barluenga, J.; Martinez-Gallo, J.M.; Najera, C.; Yus, M. *Synthesis* ***1986***, 678.

[126]Horiuchi, C.A.; Kiji, S. *Bull. Chem. Soc. Jpn.* ***1997***, *70*, 421. For another reagent, see Sket, B.; Zupet, P.; Zupan, M.; Dolenc, D. *Bull. Chem. Soc. Jpn.* ***1989***, *62*, 3406.

[127]Jereb, M.; Stavber, S.; Zupan, M. *Tetrahedron* ***2003***, *59*, 5935.

[128]Lee, J.C.; Jin, Y.S. *Synth. Commun.* ***1999***, *29*, 2769.

[129]Lee, J.C.; Bae, Y.H. *Synlett* ***2003***, 507.

[130]Davis, F.A.; Kasu, P.V.N. *Org. Prep. Proceed. Int.* ***1999***, *31*, 125.

[131]Stavber, S.; Zupan, M. *Tetrahedron Lett.* ***1996***, *37*, 3591.

[132]Okamoto, T.; Kakinami, T.; Nishimura, T.; Hermawan, I.; Kajigaeshi, S. *Bull. Chem. Soc. Jpn.* ***1992***, *65*, 1731.

[133]Barnette, W.E. *J. Am. Chem. Soc.* ***1984***, *106*, 452; Ma, J.-A. For an example using a chiral copper catalyst for asymmetric induction, see Cahard, D. *Tetrahedron Asymm* ***2004***, *15*, 1007.

[134]Differding, E.; Lang, R.W. *Tetrahedron* ***1988***, *29*, 6087.

[135]Chambers, R.D.; Greenhall, M.P.; Hutchinson, J. *J. Chem. Soc. Chem. Commun.* ***1995***, 21.

[136]Gupta, O.D.; Shreeve, J.M. *Tetrahedron Lett.* ***2003***, *44*, 2799.

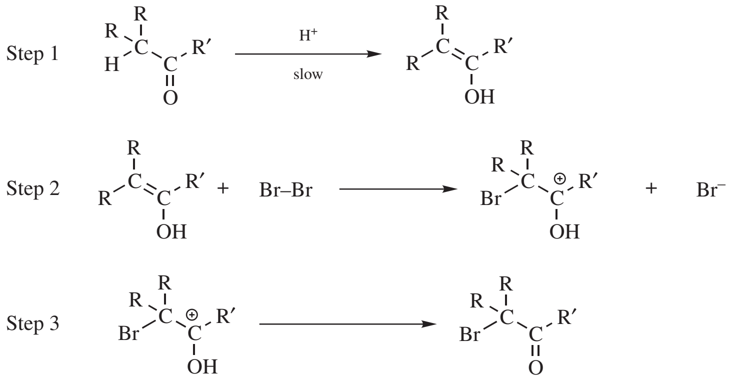
[137]Lerman, O.; Rozen, S. *J. Org. Chem.* ***1983***, *48*, 724. See also Purrington, S.T.; Jones, W.A. *J. Org. Chem.* ***1983***, *48*, 761.

[138]Rozen, S.; Brand, M. *Synthesis* ***1985***, 665. For another reagent, see Davis, F.A.; Han, W. *Tetrahedron Lett.* ***1991***, *32*, 1631.

[139]For chlorination this is reversed if the solvent is methanol: Gallucci, R.R.; Going, R. *J. Org. Chem.* ***1981***, *46*, 2532.

attacked, and the reaction cannot be stopped until all the hydrogens of the first carbon have been replaced (see below). If one of the groups is methyl, the haloform reaction (**12-44**) takes place. With acid catalysts, it is easy to stop the reaction after only one halogen has entered, although a second halogen can be introduced by the use of excess reagent. In chlorination the second halogen generally appears on the same side as the first,[140] while in bromination the α,α'-dibromo product is found.[141] Actually, with both halogens it is the α,α-dihalo ketone that is formed first, but in the case of bromination this compound isomerizes under the reaction conditions to the α,α' isomer.[140] α,α'-Dichloro ketones are formed by reaction of a methyl ketone with an excess of $CuCl_2$ and LiCl in DMF[142] or with HCl and H_2O_2 in methanol.[143] Aryl methyl ketones can be dibrominated ($ArCOCH_3 \rightarrow ArCOCHBr_2$) in high yields with benzyltrimethylammonium tribromide.[144] Active methylene compounds are chlorinated with NCS and $Mg(ClO_4)_2$.[145] Similar chlorination in the presence of a chiral copper catalyst led to α-chlorination with modest enantioselectivity.[146]

It is not the aldehyde or ketone itself that is halogenated, but the corresponding enol or enolate ion. The purpose of the catalyst is to provide a small amount of enol or enolate. The reaction is often done without addition of acid or base, but traces of acid or base are always present, and these are enough to catalyze formation of the enol or enolate. With acid catalysis the mechanism is



[140]Rappe, C. *Ark. Kemi* ***1965***, *24*, 321. But see also Teo, K.E.; Warnhoff, E.W. *J. Am. Chem. Soc.* ***1973***, *95*, 2728.

[141]Rappe, C.; Schotte, L. *Acta Chem. Scand.* ***1962***, *16*, 2060; Rappe, C. *Ark. Kemi* ***1964***, *21*, 503; Garbisch, Jr., E.W. *J. Org. Chem.* ***1965***, *30*, 2109.

[142]Nobrega, J.A.; Gonalves, S.M.C.; Reppe, C. *Synth. Commun.* ***2002***, *32*, 3711.

[143]Terent'ev, A.O.; Khodykin, S.V.; Troitskii, N.A.; Ogibin, Y.N.; Nikishin, G.I. *Synthesis* ***2004***, 2845.

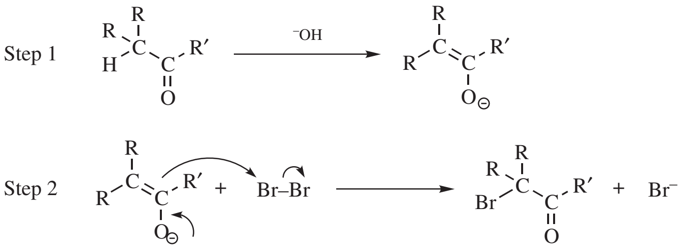
[144]Kajigaeshi, S.; Kakinami, T.; Tokiyama, H.; Hirakawa, T.; Okamoto, T. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 2667.

[145]Yang, D.; Yan, Y.-L.; Lui, B. *J. Org. Chem.* ***2002***, *67*, 7429.

[146]Marigo, M.; Kumaragurubaran, N.; Jørgensen, K.A. *Chem. Eur. J.* ***2004***, *10*, 2133.

The first step, as we have already seen (**12-3**), actually consists of two steps. The second step is very similar to the first step in electrophilic addition to double bonds (p. 999). There is a great deal of evidence for this mechanism: (*1*) the rate is first order in substrate; (*2*) bromine does not appear in the rate expression at all,[147] a fact consistent with a rate-determining first step;[148] (*3*) the reaction rate is the same for bromination, chlorination, and iodination under the same conditions;[149] (*4*) the reaction shows an isotope effect; and (*5*) the rate of the step 2–step 3 sequence has been independently measured (by starting with the enol) and found to be very fast.[150]

With basic catalysts the mechanism may be the same as that given above (since bases also catalyze formation of the enol), or the reaction may go directly through the enolate ion without formation of the enol:



It is difficult to distinguish the two possibilities. It was mentioned above that in the base-catalyzed reaction, if the substrate has two or three a halogens on the same side of the C=O group, it is not possible to stop the reaction after just one halogen atom has entered. The reason is that the electron-withdrawing field effect of the first halogen increases the acidity of the remaining hydrogens, that is, a CHX group is more acidic than a CH_2 group, so that initially formed halo ketone is converted to enolate ion (and hence halogenated) more rapidly than the original substrate. Other halogenating agents can be used in this reaction. Reaction of a lithium enolate anion with tosyl chloride gave the corresponding α-chloro ketone.[151] When an aldehyde was treated with a catalytic amount of 2,5-lutidine to generate the enolate anion, reaction with 35% HCl in dichloromethane gave the α,α-dichloroaldehyde.[152]

[147]When the halogenating species is at low concentration or has a low reactivity, it can appear in the rate expression. The reaction becomes first order in the halogenating species. See, for example, Tapuhi, E.; Jencks, W.P. *J. Am. Chem. Soc.* ***1982***, *104*, 5758. For a case in which the reaction is first order in bromine, even at relatively high Br_2 contentration, see Pinkus, A.G.; Gopalan, R. *J. Am. Chem. Soc.* ***1984***, *106*, 2630. For a study of the kinetics of iodination, see Pinkus, A.G.; Gopalan, R. *Tetrahedron* ***1986***, *42*, 3411.

[148]Under some conditions it is possible for step 2 to be rate-determining: Deno, N.C.; Fishbein, R. *J. Am. Chem. Soc.* ***1973***, *95*, 7445.

[149]Bell, R.P.; Yates, K. *J. Chem. Soc.* ***1962***, 1927.

[150]Hochstrasser, R.; Kresge, A.J.; Schepp, N.P.; Wirz, J. *J. Am. Chem. Soc.* ***1988***, *110*, 7875.

[151]Brummond, K.M.; Gesenberg, K.D. *Tetrahedron Lett.* ***1999***, *40*, 2231.

[152]Bellesia, F.; DeBuyck, L.; Ghelfi, F.; Libertini, E.; Pagnoni, U.M.; Roncaglia, F. *Tetrahedron* ***2000***, *56*, 7507.

Regioselectivity in the halogenation of unsymmetrical ketones can be attained by treatment of the appropriate enol borinate of the ketone with *N*-bromo- or *N*-chlorosuccinimide.[153] The desired halo

ketone is formed in high yield. Another method for achieving the same result involves bromination of the appropriate lithium enolate at a low temperature[154] (see p. 630 for the regioselective formation of enolate ions). In a similar process, α-halo aldehydes have been prepared in good yield by treatment of silyl enol ethers $R_2C{=}CHOSiMe_3$ with Br_2 or Cl_2,[155] with sulfuryl chloride SO_2Cl_2;[156] or with I_2 and silver acetate.[157] Other chlorinating agents can be used with a variety of silyl enol ethers to generate α-chloroketones with good enantioselectivity, including $ZrCl_4$ in conjunction with an α,α-dichloromalonate ester.[158] Silyl enol ethers can also be fluorinated, with XeF_2[159] or with 5% F_2 in N_2 at –78°C in $FCCl_3$.[160] Enol acetates have been regioselectively iodinated with I_2 and either thallium(I) acetate[161] or copper(II) acetate.[162]

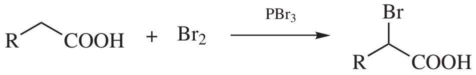
α,β-Unsaturated ketones can be converted to α-halo-α,β-unsaturated ketones by treatment with phenylselenium bromide or chloride,[163] and to α-halo-β,γ-unsaturated ketones by two-phase treatment with HOCl.[164] Conjugated ketones were converted to the α-bromo conjugated ketone (a vinyl bromide) using the Dess–Martin periodinane (see p. 1723) and tetraethylammonium bromide.[165]

OS **I**, 127; **II**, 87, 88, 244, 480; **III**, 188, 343, 538; **IV**, 110, 162, 590; **V**, 514; **VI**, 175, 193, 368, 401, 512, 520, 711, 991; **VII**, 271; **VIII**, 286. See also, OS **VI**, 1033; **VIII**, 192.

[153]Hooz, J.; Bridson, J.N. *Can. J. Chem.* ***1972***, *50*, 2387.
[154]Stotter, P.L.; Hill, K.A. *J. Org. Chem.* ***1973***, *38*, 2576.
[155]Reuss, R.H.; Hassner, A. *J. Org. Chem.* ***1974***, *39*, 1785; Blanco, L.; Amice, P.; Conia, J.M. *Synthesis* ***1976***, 194.
[156]Olah, G.A.; Ohannesian, L.; Arvanaghi, M.; Prakash, G.K.S. *J. Org. Chem.* ***1984***, *49*, 2032.
[157]Rubottom, G.M.; Mott, R.C. *J. Org. Chem.* ***1979***, *44*, 1731.
[158]Zhang, Y.; Shibatomi, K.; Yamamoto, H. *J. Am. Chem. Soc.* ***2004***, *126*, 15038.
[159]Tsushima, T.; Kawada, K.; Tsuji, T. *Tetrahedron Lett.* ***1982***, *23*, 1165.
[160]Purrington, S.T.; Bumgardner, C.L.; Lazaridis, N.V.; Singh, P. *J. Org. Chem.* ***1987***, *52*, 4307.
[161]Cambie, R.C.; Hayward, R.C.; Jurlina, J.L.; Rutledge, P.S.; Woodgate, P.D. *J. Chem. Soc. Perkin Trans. 1* ***1978***, 126.
[162]Horiuchi, C.A.; Satoh, J.Y. *Synthesis* ***1981***, 312.
[163]Ley, S.V.; Whittle, A.J. *Tetrahedron Lett.* ***1981***, *22*, 3301.
[164]Hegde, S.G.; Wolinsky, J. *Tetrahedron Lett.* ***1981***, *22*, 5019.
[165]Fache, F.; Piva, O. *Synlett* ***2002***, 2035.

12-5 Halogenation of Carboxylic Acids and Acyl Halides

Halogenation or **Halo-de-hydrogenation**



Using a phosphorus halide as catalyst, the α hydrogens of carboxylic acids can be replaced by bromine or chlorine.[166] The reaction, known as the *Hell–Volhard–Zelinskii reaction*, is not applicable to iodine or fluorine. When there are two α hydrogens, one or both may be replaced, although it is often hard to stop with just one. The reaction actually takes place on the acyl halide formed from the carboxylic acid and the catalyst. The acids alone are inactive, except for those with relatively high enol content, such as malonic acid. Less than one full mole of catalyst (per mole of substrate) is required, because of the exchange reaction between carboxylic acids and acyl halides (see **16-79**). Each molecule of acid is α halogenated while it is in the acyl halide stage. The halogen from the catalyst does not enter the α position. For example, the use of Cl_2 and PBr_3 results in α chlorination, not bromination. As expected from the foregoing, acyl halides undergo a halogenation without a catalyst. An enantioselective α-halogenation was reported yielding via an alkaloid catalyzed reaction of acyl halides with perhaloquinone-derived reagents to give to chiral α-haloesters.[167] So do anhydrides and many compounds that enolize easily (e.g., malonic ester and aliphatic nitro compounds). The mechanism is usually regarded as proceeding through the enol as in **12-4**.[168] If chlorosulfuric acid $ClSO_2OH$ is used as a catalyst, carboxylic acids can be α-iodinated,[169] as well as chlorinated or brominated.[170] *N*-Bromosuccinimide in a mixture of sulfuric acid–trifluoroacetic acid can mono-brominate simple carboxylic acids.[171]

A number of other methods exist for the a halogenation of carboxylic acids or their derivatives.[172] Under electrolytic conditions with NaCl, malonates are converted to 2-chloro malonates.[173] Acyl halides can be a brominated or chlorinated by use of *N*-bromo- or *N*-chlorosuccinimide and HBr or HCl.[174] The latter is an ionic, not a free-radical halogenation (see **14-3**). Direct iodination of carboxylic acids has been achieved with I_2–Cu(II) acetate in HOAc.[175] Acyl chlorides can

[166]For a review, see Harwood, H.J. *Chem. Rev.* ***1962***, *62*, 99, pp. 102-103.

[167]Wack, H.; Taggi, A.E.; Hafez, A.M.; Drury III, W.J.; Lectka, T. *J. Am. Chem. Soc.* ***2001***, *123*, 1531. See also, France, S.; Wack, H.; Taggi, A.E.; Hafez, A.M.; Wagerle, Ty.R.; Shah, M.H.; Dusich, C.L.; Lectka, T. *J. Am. Chem. Soc.* ***2004***, *126*, 4245.

[168]See, however, Kwart, H.; Scalzi, F.V. *J. Am. Chem. Soc.* ***1964***, *86*, 5496.

[169]Ogata, Y.; Watanabe, S. *J. Org. Chem.* ***1979***, *44*, 2768; ***1980***, *45*, 2831.

[170]Ogata, Y.; Adachi, K. *J. Org. Chem.* ***1982***, *47*, 1182.

[171]Zhang, L.H.; Duan, J.; Xu, Y.; Dolbier, Jr., W.R. *Tetrahedron Lett.* ***1998***, *39*, 9621.

[172]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 730–738.

[173]Okimoto, M.; Takahashi, Y. *Synthesis* ***2002***, 2215.

[174]Harpp, D.N.; Bao, L.Q.; Black, C.J.; Gleason, J.G.; Smith, R.A. *J. Org. Chem.* ***1975***, *40*, 3420.

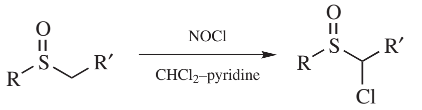
[175]Horiuchi, C.A.; Satoh, J.Y. *Chem. Lett.* ***1984***, 1509.

be a iodinated with I_2 and a trace of HI.[176] Carboxylic esters can be a halogenated by conversion to their enolate ions with lithium *N*-isopropylcyclohexylamide in THF and treatment of this solution at −78° with I_2[176] or with a carbon tetrahalide.[177] Carboxylic acids, esters, and amides have been α-fluorinated at −78°C with F_2 diluted in N_2.[178] Amides have been α-iodinated using iodine and s-collidine.[179]

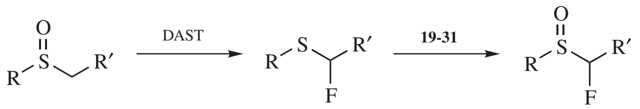
OS **I**, 115, 245; **II**, 74, 93; **III**, 347, 381, 495, 523, 623, 705, 848; **IV**, 254, 348, 398, 608, 616; **V**, 255; **VI**, 90, 190, 403; **IX**, 526. Also see, OS **IV**, 877; **VI**, 427.

12-6 Halogenation of Sulfoxides and Sulfones

Halogenation or **Halo-de-hydrogenation**



Sulfoxides can be chlorinated in the α position[180] by treatment with Cl_2[181] or *N*-chlorosuccinimide,[182] in the presence of pyridine. These methods involve basic conditions. The reaction can also be accomplished in the absence of base with SO_2Cl_2 in CH_2Cl_2,[183] or with $TsNCl_2$.[184] The bromination of sulfoxides with bromine[185] and with NBS-bromine[186] have also been reported. Sulfones have been chlorinated by treatment of their conjugate bases $RSO_2C^{\ominus}$ HR′ with various reagents, among them SO_2Cl_2, CCl_4,[187] *N*-chlorosuccinimide,[188] and hexachloroethane.[189] The α fluorination of sulfoxides has been accomplished in a two-step procedure. Treatment with diethylaminosulfur trifluoride Et_2NSF_3 (DAST) produces an



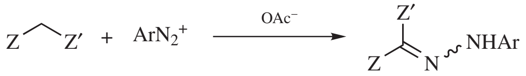
[176]Rathke, M.W.; Lindert, A. *Tetrahedron Lett.* ***1971***, 3995.
[177]Arnold, R.T.; Kulenovic, S.T. *J. Org. Chem.* ***1978***, *43*, 3687.
[178]Purrington, S.T.; Woodard, D.L. *J. Org. Chem.* ***1990***, *55*, 3423.
[179]Kitagawa, O.; Hanano, T.; Hirata, T.; Inoue, T.; Taguchi, T. *Tetrahedron Lett.* ***1992***, *33*, 1299.
[180]For a review, see Venier, C.G.; Barager III, H.J. *Org. Prep. Proced. Int.* ***1974***, *6*, 77, pp. 81–84.
[181]Tsuchihashi, G.; Iriuchijima, S. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 2271.
[182]Ogura, K.; Imaizumi, J.; Iida, H.; Tsuchihashi, G. *Chem. Lett.* ***1980***, 1587.
[183]Tin, K.; Durst, T. *Tetrahedron Lett.* ***1970***, 4643.
[184]Kim, Y.H.; Lim, S.C.; Kim, H.R.; Yoon, D.C. *Chem. Lett.* ***1990***, 79.
[185]Cinquini, M.; Colonna, S. *J. Chem. Soc. Perkin Trans. 1* 1972, 1883. See also, Cinquini, M.; Colonna, S. *Synthesis* **1972**, 259.
[186]Iriuchijima, S.; Tsuchihashi, G. *Synthesis* ***1970***, 588.
[187]Regis, R.R.; Doweyko, A.M. *Tetrahedron Lett.* ***1982***, *23*, 2539.
[188]Paquette, L.A.; Houser, R.W. *J. Org. Chem.* ***1971***, *36*, 1015.
[189]Kattenberg, J.; de Waard, E.R.; Huisman, H.O. *Tetrahedron* ***1973***, *29*, 4149; ***1974***, *30*, 463.

α-fluoro thioether, usually in high yield. Oxidation of this compound with *m*-chloroperoxybenzoic acid gives the sulfoxide.[190]

C. Nitrogen Electrophiles

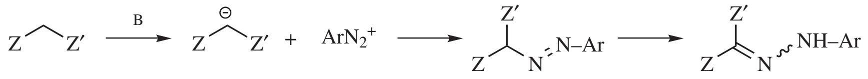
12-7 Aliphatic Diazonium Coupling

Arylhydrazono-de-dihydro-bisubstitution



If a C–H bond is acidic enough, it couples with diazonium salts in the presence of a base, most often aqueous sodium acetate.[191] The reaction is commonly carried out on compounds of the form Z–CH_2–Z′, where Z and Z′ are as defined on p. 1358, for example, β-keto esters, β-keto amides, malonic ester.

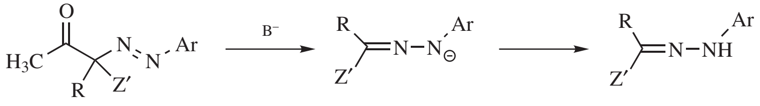
The mechanism is probably of the simple S_E1 type:



23

Aliphatic azo compounds in which the carbon containing the azo group is attached to a hydrogen are unstable and tautomerize to the isomeric hydrazones (**23**), which are therefore the products of the reaction.

When the reaction is carried out on a compound of the form Z–CHR–Z′, so that the azo compound does not have a hydrogen that can undergo tautomerism, if at least one Z is acyl or carboxyl, this group usually cleaves:

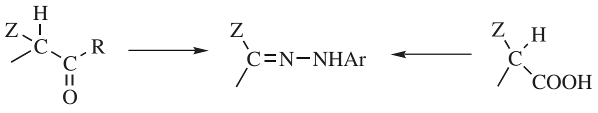


24

so the product in this case is also the hydrazone, and not the azo compound. In fact, compounds of the type **24** are seldom isolable from the reaction, although this has been accomplished.[192] The cleavage step shown is an example of **12-43** and, when a carboxyl group cleaves, of **12-40**. The overall process in this case is called the *Japp–Klingemann reaction*[193] and involves conversion of a ketone (**25**) or a

[190]McCarthy, J.R.; Pee, N.P.; LeTourneau, M.E.; Inbasekaran, M. *J. Am. Chem. Soc.* ***1985***, *107*, 735. See also, Umemoto, T.; Tomizawa, G. *Bull. Chem. Soc. Jpn.* ***1986***, *59*, 3625.
[191]For a review, see Parmerter, S.M. *Org. React.* ***1959***, *10*, 1.
[192]See, for example, Yao, H.C.; Resnick, P. *J. Am. Chem. Soc.* ***1962***, *84*, 3514.
[193]For a review, see Phillips, R.R. *Org. React.* ***1959***, *10*, 143.

carboxylic acid (**26**)



25 **26** **27**

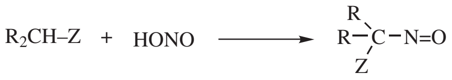
to a hydrazone (**27**). When an acyl and a carboxyl group are both present, the leaving group order has been reported to be MeCO > COOH > PhCO.[194] When there is no acyl or carboxyl group present, the aliphatic azo compound is stable.

OS **III**, 660; **IV**, 633.

12-8 Nitrosation at a Carbon Bearing an Active Hydrogen

Hydroxyimino-de-dihydro-bisubstitution

Nitrosation or **Nitroso-de-hydrogenation**



Carbons adjacent to a Z group (as defined on p. 622) can be nitrosated with nitrous acid or alkyl nitrites.[195] The initial product is the *C*-nitroso compound, but these are stable only when there is no hydrogen that can undergo tautomerism. When there is, the product is the more stable oxime. The situation is analogous to that with azo compounds and hydrazones (**12-7**). The mechanism is similar to that in **12-7**:[196] $R{-}H \rightarrow R^- + {}^+N{=}O \rightarrow R{-}N{=}O$. The attacking species is either NO^+ or a carrier of it. When the substrate is a simple ketone, the mechanism goes through the enol (as in halogenation **12-4**):

Evidence is that the reaction, in the presence of X^- (Br^-, Cl^-, or SCN^-), was first order in ketone and in H^+, but zero order in HNO_2 and X^-.[197] Furthermore, the rate of the nitrosation was about the same as that for enolization of the same ketones. The species NOX is formed by $HONO + X^- + H^+ \rightarrow HOX + H_2O$. In

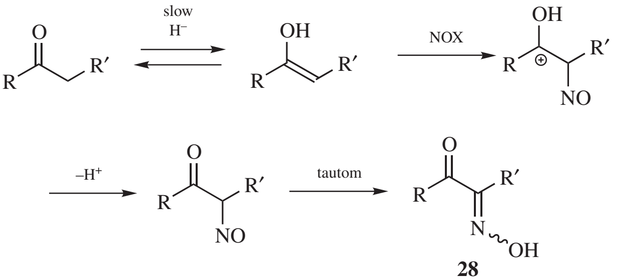
[194]Neplyuev, V.M.; Bazarova, I.M.; Lozinskii, M.O. *J. Org. Chem. USSR* ***1989***, *25*, 2011. This paper also includes a sequence of leaving group ability for other Z groups.

[195]For a review, see Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, ***1988***, pp. 1–45.

[196]For a review, see Williams, D.L.H. *Adv. Phys. Org. Chem.* ***1983***, *19*, 381. See also Williams, D.L.H. *Nitrosation*, Cambridge Univ. Press, Cambridge, ***1988***.

[197]Leis, J.R.; Peña, M.E.; Williams, D.L.H.; Mawson, S.D. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 157.

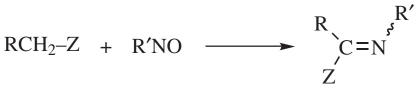
the cases of $F_3CCOCH_2COCF_3$ and malononitrile the nitrosation went entirely through the enolate ion rather than the enol.[198]



28

As in the Japp–Klingemann reaction, when Z is an acyl or carboxyl group (in the case of R_2CH–Z), it can be cleaved. Since oximes and nitroso compounds can be reduced to primary amines, this reaction often provides a route to amino acids. As in the case of **12-4**, the silyl enol ether of a ketone can be used instead of the ketone itself.[199] Good yields of α-oximinoketones (**28**) can be obtained by treating ketones with *tert*-butyl thionitrate.[200]

Imines can be prepared in a similar manner by treatment of an active hydrogen compound with a nitroso compound:



Alkanes can be nitrosated photochemically, by treatment with NOCl and UV light.[201] For nitration at an activated carbon, see **12-9**. Trialkyltin enol ethers ($C{=}C{-}O{-}SnR_3$) react with PhNO to give α-(N-hydroxylamino)ketones.[202]

OS **II**, 202, 204, 223, 363; **III**, 191, 513; **V**, 32, 373; **VI**, 199, 840. Also see, OS **V**, 650.

12-9 Nitration of Alkanes

Nitration or **Nitro-de-hydrogenation**

$$RH \quad + \quad HNO_3 \xrightarrow{400^\circ C} RNO_2$$

[198]Iglesias, E.; Williams, D.L.H. *J. Chem. Soc. Perkin Trans. 2* ***1989***, 343; Crookes, M.J.; Roy, P.; Williams, D.L.H. *J. Chem. Soc. Perkin Trans. 2* ***1989***, 1015. See also Graham, A.; Williams, D.L.H. *J. Chem. Soc. Chem. Commun.* ***1991***, 407.

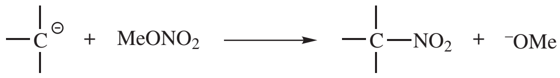
[199]Rasmussen, J.K.; Hassner, A. *J. Org. Chem.* ***1974***, *39*, 2558.

[200]Kim, Y.H.; Park, Y.J.; Kim, K. *Tetrahedron Lett.* ***1989***, *30*, 2833.

[201]For a review, see Pape, M. *Fortschr. Chem. Forsch.* ***1967***, *7*, 559.

[202]Momiyama, N.; Yamamoto, H. *Org. Lett.* ***2002***, *4*, 3579.

Nitration of alkanes[203] can be carried out in the gas phase at ~400°C or in the liquid phase. The reaction is not practical for the production of pure products for any alkane except methane. For other alkanes, not only does the reaction produce mixtures of the mono-, di-, and polynitrated alkanes at every combination of positions, but extensive chain cleavage occurs.[204] A free-radical mechanism is involved.[205]



Activated positions (e.g., ZCH_2Z' compounds) can be nitrated by fuming nitric acid in acetic acid, by acetyl nitrate and an acid catalyst,[206] or by alkyl nitrates under alkaline conditions.[207] In the latter case, it is the carbanionic form of the substrate that is actually nitrated. What is isolated under these alkaline conditions is the conjugate base of the nitro compound. Yields are not high. Of course, the mechanism in this case is not of the free-radical type, but is electrophilic substitution with respect to the carbon (similar to the mechanisms of **12-7** and **12-8**). Positions activated by only one electron-withdrawing group, for example, a positions of simple ketones, nitriles, sulfones, or *N*,*N*-dialkyl amides, can be nitrated with alkyl nitrates if a very strong base, for example, *t*-BuOK or $NaNH_2$, is present to convert the substrate to the carbanionic form.[208]

Electrophilic nitration of alkanes has been performed with nitronium salts, for example, $NO_2^+\ PF_6^-$ and with HNO_3–H_2SO_4 mixtures, but mixtures of nitration and cleavage products are obtained and yields are generally low.[209] The reaction of alkanes with nitric acid and *N*-hydroxysuccinimide (NHS), however, gave moderate-to-good yields of the corresponding nitroalkane.[210] Similar nitration was accomplished with NO_2, NHS and air.[211]

Aliphatic nitro compounds can be a nitrated [$R_2C^{\ominus}NO_2 \rightarrow R_2C(NO_2)_2$] by treatment of their conjugate bases $RCNO_2$ with $NO_2^-$and $K_3Fe(CN)_6$.[212]

[203]For reviews, see Olah, G.A.; Malhotra, R.; Narang, S.C. *Nitration*, VCH, NY, ***1989***, pp. 219–295; Ogata, Y. in Trahanovsky, W.S. *Oxidation in Organic Chemisry*, part C, Academic Press, NY, ***1978***, pp. 295–342; Ballod, A.P.; Shtern, V.Ya. *Russ. Chem. Rev.* ***1976***, *45*, 721.

[204]For a discussion of the mechanism of this cleavage, see Matasa, C.; Hass, H.B. *Can. J. Chem.* ***1971***, *49*, 1284.

[205]Titov, A.I. *Tetrahedron* ***1963***, *19*, 557.

[206]Sifniades, S. *J. Org. Chem.* ***1975***, *40*, 3562.

[207]For a review, see Larson, H.O., in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, Vol. 1, Wiley, NY, ***1969***, pp. 310–316.

[208]For examples, see Truce, W.E.; Christensen, L.W. *Tetrahedron* ***1969***, *25*, 181; Pfeffer, P.E.; Silbert, L.S. *Tetrahedron Lett.* ***1970***, 699; Feuer, H.; Spinicelli, L.F. *J. Org. Chem.* ***1976***, *41*, 2981; Feuer, H.; Van Buren II, W.D.; Grutzner, J.B. *J. Org. Chem.* ***1978***, *43*, 4676.

[209]Olah, G.A.; Lin, H.C. *J. Am. Chem. Soc.* ***1973***, *93*, 1259. See also, Bach, R.D.; Holubka, J.W.; Badger, R.C.; Rajan, S. *J. Am. Chem. Soc.* ***1979***, *101*, 4416.

[210]Isozaki, S.; Nishiwaki, Y.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* ***2001***, 1352.

[211]Sakaguchi, S.; Nishiwaki, Y.; Kitamura, T.; Ishii, Y. *Angew. Chem. Int. Ed.* ***2001***, *40*, 222; Nishiwaki, Y.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* ***2002***, *67*, 5663.

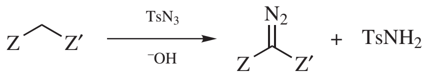
[212]Matacz, Z.; Piotrowska, H.; Urbanski, T. *Pol. J. Chem.* ***1979***, *53*, 187; Kornblum, N.; Singh, H.K.; Kelly, W.J. *J. Org. Chem.* ***1983***, *48*, 332; Garver, L.C.; Grakauskas, V.; Baum, K. *J. Org. Chem.* ***1985***, *50*, 1699.

A novel reaction converted a vinyl methyl moiety to a vinyl nitro. The reaction of MeCH=C(Ph)CN with NO_x and iodine gave O_2NCH=C(Ph)CN.[213]

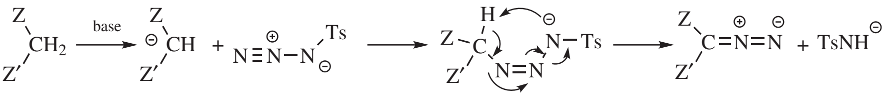
OS **I**, 390; **II**, 440, 512.

12-10 Direct Formation of Diazo Compounds

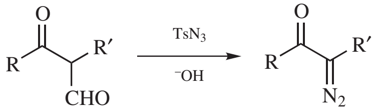
Diazo-de-dihydro-bisubstitution



Compounds containing a CH_2 bonded to two Z groups (active methylene compounds, with Z as defined on p. 622) can be converted to diazo compounds on treatment with tosyl azide in the presence of a base.[214] The use of phase-transfer catalysis increases the convenience of the method.[215] *p*-Dodecylbenzenesulfonyl azide,[216] methanesulfonyl azide,[217] and *p*-acetamidobenzenesulfonyl azide[218] also give the reaction. The reaction, which is called the *diazo-transfer reaction*, can also be applied to other reactive positions (e.g., the 5 position of cyclopentadiene).[219] The mechanism is probably as follows:



A diazo group can be introduced adjacent to a single carbonyl group indirectly by first converting the ketone to an α-formyl ketone (**16-85**) and then treating it with tosyl azide. As in the similar cases of



12-7 and **12-8**, the formyl group is cleaved during the reaction.[220]

OS **V**, 179; **VI**, 389, 414.

[213]Navarro-Ocaña, A.; Barzana, E.; López-González, D.; Jiménez-Estrada, M. *Org. Prep. Proceed. Int.* ***1999***, *31*, 117.

[214]For reviews, see Regitz, M.; Maas, G. *Diazo Compounds*, Academic Press, NY, ***1986***, pp. 326–435; Regitz, M. *Synthesis* ***1972***, 351; *Angew. Chem. Int. Ed.* ***1967***, *6*, 733; *Newer Methods Prep. Org. Chem.* ***1971***, *6*, 81. See also, Hünig, S. *Angew. Chem. Int. Ed.* ***1968***, *7*, 335; Koskinen, A.M.P.; Muñoz, L. *J. Chem. Soc. Chem. Commun.* ***1990***, 652.

[215]Ledon, H. *Synthesis* ***1974***, 347, *Org. Synth.* ***VI***, 414. For another convenient method, see Ghosh, S.; Datta, I. *Synth. Commun.* ***1991***, *21*, 191.

[216]Hazen, G.G.; Weinstock, L.M.; Connell, R.; Bollinger, F.W. *Synth. Commun.* ***1981***, *11*, 947.

[217]Taber, D.F.; Ruckle Jr., R.E.; Hennessy, M.J. *J. Org. Chem.* ***1986***, *51*, 4077.

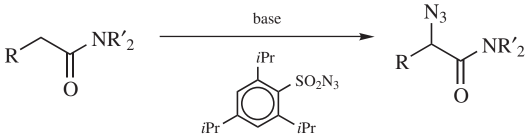
[218]Baum, J.S.; Shook, D.A.; Davies, H.M.L.; Smith, H.D. *Synth. Commun.* ***1987***, *17*, 1709.

[219]Doering, W. von E.; DePuy, C.H. *J. Am. Chem. Soc.* ***1953***, *75*, 5955.

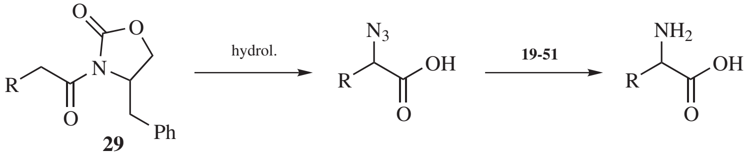
[220]For a similar approach, see Danheiser, R.L.; Miller, R.F.; Brisbois, R.G.; Park, S.Z. *J. Org. Chem.* ***1990***, *55*, 1959.

12-11 Conversion of Amides to α-Azido Amides

Azidation or **Azido-de-hydrogenation**



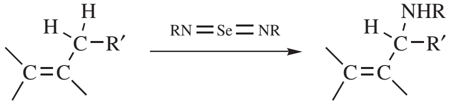
In reaction **12-10**, treatment of Z–CH_2–Z′ with tosyl azide gave the α-diazo compound via diazo transfer. When this reaction is performed on a compound with a single Z group such as an amide, formation of the azide becomes a competing process via the enolate anion.[221] Factors favoring azide formation rather than diazo transfer include K^+ as the enolate counterion rather than Na^+ or Li^+ and the use of 2,4,6-triisopropylbenzenesulfonyl azide rather than TsN_3. When the reaction was applied to amides with a chiral R', such as the oxazolidinone derivative **29**, it was highly stereoselective, and the product could be converted to an optically active amino acid.[221]



29

12-12 Direct Amination at an Activated Position

Alkyamino-de-hydrogenation, and so on



R = *t*-Bu, Ts

Alkenes can be aminated[222] in the allylic position by treatment with solutions of imido selenium compounds R–N=Se=N–R.[223] The reaction, which is similar to the allylic oxidation of alkenes with SeO_2 (see **19-14**), has been performed with R = *t*-Bu and R = Ts. The imido sulfur compound TsN=S=NTs has also been used,[224] as well

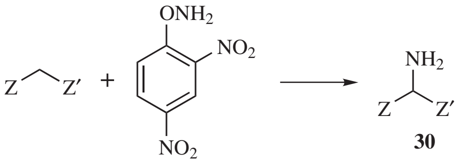
[221]Evans, D.A.; Britton, T.C. *J. Am. Chem. Soc.* ***1987***, *109*, 6881, and references cited therein.

[222]For a review of direct aminations, see Sheradsky, T., in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 1, Wiley, NY, ***1982***, pp. 395–416.

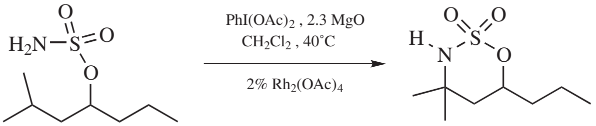
[223]Sharpless, K.B.; Hori, T.; Truesdale, L.K.; Dietrich, C.O. *J. Am. Chem. Soc.* ***1976***, *98*, 269. For another method, see Kresze, G.; Münsterer, H. *J. Org. Chem.* ***1983***, *48*, 3561. For a review, see Cheikh, R.B.; Chaabouni, R.; Laurent, A.; Mison, P.; Nafti, A. *Synthesis* ***1983***, 685, pp. 691–696.

[224]Sharpless, K.B.; Hori, T. *J. Org. Chem.* ***1979***, *41*, 176; Singer, S.P.; Sharpless, K.B. *J. Org. Chem.* ***1978***, *43*, 1448. For other reagents, see Mahy, J.P.; Bedi, G.; Battioni, P.; Mansuy, D. *Tetrahedron Lett.* ***1988***, *29*, 1927; Tsushima, S.; Yamada, Y.; Onami, T.; Oshima, K.; Chaney, M.O.; Jones, N.D.; Swartzendruber, J.K. *Bull. Chem. Soc. Jpn.* ***1989***, *62*, 1167.

as $PhNHOH–FeCl_2/FeCl_3$.[225] Benzylic positions can be aminated with *t*-BuOO-CONHTs in the presence of a catalytic amount of $Cu(OTf)_2$.[226] In another reaction, compounds containing an active hydrogen can be converted to primary amines (**30**) in moderate yields by treatment with *O*-(2,4-dinitrophenyl)hydroxylamine.[227]



30



31 **32**

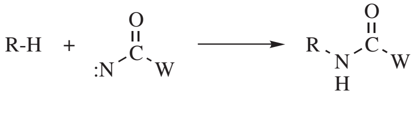
Tertiary alkyl hydrogen can be replaced in some cases via C–H nitrogen insertion. The reaction of sulfamate ester **31** with $PhI(OAc)_2$, MgO and a dinuclear Rh carboxylate catalyst, for example, generated oxathiazinane **32**.[228] This transformation is a formal oxidation, and primary carbamates have been similarly converted to oxazolidin-2-ones.[229]

In an indirect amination process, acyl halides are converted to amino acids.[230] Reaction of the acyl halide with a chiral oxazolidinone leads to a chiral amide, which reacts with the N=N unit of a dialkyl azodicarboxylate[$R^2O_2C–N=N–CO_2R'$]. Hydrolysis and catalytic hydrogenation leads to an amino acid with good enantioselectivity.[226]

See also, **10-39**.

12-13 Insertion by Nitrenes

***CH*-[Acylimino]-insertion**, and so on



[225]Srivastava, R.S.; Nicholas, K.M. *Tetrahedron Lett.* ***1994***, *35*, 8739.

[226]Kohmura, Y.; Kawasaki, K.; Katsuki, T. *Synlett*, ***1997***, 1456.

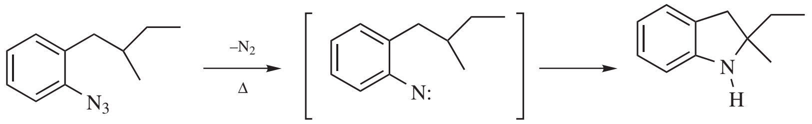
[227]Sheradsky, T.; Salemnick, G.; Nir, Z. *Tetrahedron* ***1972***, *28*, 3833; Radhakrishna, A.; Loudon, G.M.; Miller, M.J. *J. Org. Chem.* ***1979***, *44*, 4836.

[228]Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* ***2001***, *123*, 6935.

[229]Espino, C.G.; Du Bois, J. *Angew. Chem. Int. Ed.* ***2001***, *40*, 598.

[230]Trimble, L.A.; Vederas, J.C. *J. Am. Chem. Soc.* ***1986***, *108*, 6397; Evans, D.A.; Britton, T.C.; Dorow, R.L.; Dellaria, J.F. *Tetrahedron* ***1988***, *44*, 5525; Gennari, C.; Colombo, L.; Bertolini, G. *J. Am. Chem. Soc.* ***1986***, *108*, 6394; Oppolzer, W.; Moretti, R. *Helv. Chim. Acta* ***1986***, *69*, 1923; *Tetrahedron* ***1988***, *44*, 5541; Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron* ***1988***, *44*, 5523.

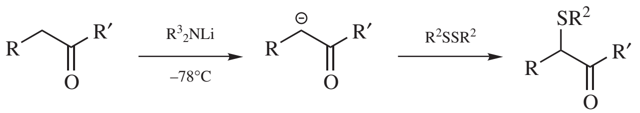
Carbonylnitrenes: NCOW (W = R′, Ar, or OR′) are very reactive species (p. 293) and insert into the C–H bonds of alkanes to give amides (W = R′ or Ar) or carbamates (W = OR′).[231] The nitrenes are generated as discussed on p. 293. The order of reactivity among alkane C–H bonds is tertiary > secondary > primary.[232] Indications are that in general it is only singlet and not triplet nitrenes that insert.[233] Retention of configuration is found at a chiral carbon.[234] The mechanism is presumably similar to the simple one-step mechanism for insertion of carbenes (**12-21**). Other nitrenes [e.g., cyanonitrene (NCN)[235] and arylnitrenes (NAr)[236]] can also insert into C–H bonds, but alkylnitrenes usually undergo rearrangement before they can react with the alkane. *N*-Carbamoyl nitrenes undergo insertion reactions that often lead to mixtures of products, but exceptions are known,[237] chiefly in cyclizations.[238] For example, heating of 2-(2-methylbutyl)phenyl azide gave ~60% 2-ethyl-2-methylindoline.[234] Enantioselective nitrene insertion reactions are known.[239]



D. Sulfur Electrophiles

12-14 Sulfenylation, Sulfonation, and Selenylation of Ketones and Carboxylic Esters

Alkylthio-de-hydrogenation, and so on



[231]For a review, see Lwowski, W., in Lwowski, W. *Nitrenes*, Wiley, NY, ***1970***, pp. 199–207.

[232]For example, see Maslak, P. *J. Am. Chem. Soc.* ***1989***, *111*, 8201. Nitrenes are much more selective (and less reactive) in this reaction than carbenes (**12-17**). For a discussion, see Alewood, P.F.; Kazmaier, P.M.; Rauk, A. *J. Am. Chem. Soc.* ***1973***, *95*, 5466.

[233]For example, see Simson, J.M.; Lwowski, W. *J. Am. Chem. Soc.* ***1969***, *91*, 5107; Inagaki, M.; Shingaki, T.; Nagai, T. *Chem. Lett.* ***1981***, 1419.

[234]Smolinsky, G.; Feuer, B.I. *J. Am. Chem. Soc.* ***1964***, *86*, 3085.

[235]For a review of cyanonitrenes, see Anastassiou, A.G.; Shepelavy, J.N.; Simmons, H.E.; Marsh, F.D., in Lwowski, W. *Nitrenes*, Wiley, NY, ***1970***, pp. 305–344.

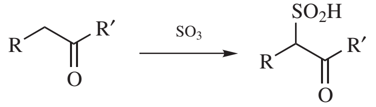
[236]For a review of arylnitrenes, see Scriven, E.F.V. *Azides and Nitrenes*, Academic Press, NY, ***1984***, pp. 95–204.

[237]For a synthetically useful noncyclization example, see Meinwald, J.; Aue, D.H. *Tetrahedron Lett.* ***1967***, 2317.

[238]For a list of examples, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1148–1149.

[239]For a review, see Müller, P.; Fruit, C. *Chem. Rev.* ***2003***, *103*, 2905.

Sulfonation or **Sulfo-de-hydrogenation**



Ketones, carboxylic esters (including lactones),[240] and amides (including lactams)[241] can be sulfenylated[242] in the α position by conversion to the enolate ion with a base, such as lithium *N*-isopropylcyclohexylamide and subsequent treatment with a disulfide.[243] The reaction, shown above for ketones, involves nucleophilic substitution at sulfur. Analogously, α-phenylseleno ketones RCH(SePh)COR′ and α-phenylseleno esters RCH(SePh)COOR′ can be prepared[244] by treatment of the corresponding enolate anions with PhSeBr,[245] PhSeSePh,[246] or benzeneseleninic anhydride PhSe(O)OSe(O)Ph.[247] Another method for the introduction of a phenylseleno group into the α position of a ketone involves simple treatment of an ethyl acetate solution of the ketone with PhSeCl (but not PhSeBr) at room temperature.[248] This procedure is also successful for aldehydes, but not for carboxylic esters. *N*-Phenylselenophthalimide has been used to convert ketones[249] and aldehydes[250] to the α- PhSe derivative. In another method that avoids the use of PhSeX reagents, a ketone enolate is treated with selenium to give an R′COCHRSe– ion, which is treated with MeI, producing the α-methylseleno ketone R′COCHRSeMe.[251] This method has also been applied to carboxylic esters.

[240]Trost, B.M.; Salzmann, T.N. *J. Am. Chem. Soc.* ***1973***, *95*, 6840; Seebach, D.; Teschner, M. *Tetrahedron Lett.* ***1973***, 5113. For discussions, see Trost, B.M. *Pure Appl. Chem.* ***1975***, *43*, 563, pp. 572–578; Caine, D., in Augustine, R.L. *Carbon–Carbon Bond Formation*, Vol. 1, Marcel Dekker, NY, ***1979***, pp. 278–282.

[241]Zoretic, P.A.; Soja, P. *J. Org. Chem.* ***1976***, *41*, 3587; Gassman, P.G.; Balchunis, R.J. *J. Org. Chem.* ***1977***, *42*, 3236.

[242]For a discussion of the synthesis of sulfenates, see Sandrinelli, F.; Fontaine, G.; Perrio, S.; Beslin, P. *J. Org. Chem.* ***2004***, *69*, 6916.

[243]For another reagent, see Scholz, D. *Synthesis* ***1983***, 944.

[244]For reviews of selenylations, see Back, T.G., in Liotta, D.C. *Organoselenium Chemistry*, Wiley, NY, ***1987***, pp. 1–125; Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*, Pergamon, Elmsford, NY, ***1986***, pp. 95–98.

[245]Reich, H.J.; Reich, I.J.; Renga, J.M. *J. Am. Chem. Soc.* ***1973***, *95*, 5813; Clive, D.L.J. *J. Chem. Soc. Chem. Commun.* ***1973***, 695; Brocksom, T.J.; Petragnani, N.; Rodrigues, R. *J. Org. Chem.* ***1974***, *39*, 2114; Schwartz, J.; Hayasi, Y. *Tetrahedron Lett.* ***1980***, *21*, 1497. See also Liotta, D. *Acc. Chem. Res.* ***1984***, *17*, 28.

[246]Grieco, P.A.; Miyashita, M. *J. Org. Chem.* ***1974***, *39*, 120. α-Phenylselenation can also be accomplished with PhSeSePh, SeO_2, and an acid catalyst: Miyoshi, N.; Yamamoto, T.; Kambe, N.; Murai, S.; Sonoda, N. *Tetrahedron Lett.* ***1982***, *23*, 4813.

[247]Barton, D.H.R.; Morzycki, J.W.; Motherwell, W.B.; Ley, S.V. *J. Chem. Soc. Chem. Commun.* ***1981***, 1044.

[248]Sharpless, K.B.; Lauer, R.F.; Teranishi, A.Y. *J. Am. Chem. Soc.* ***1973***, *95*, 6137.

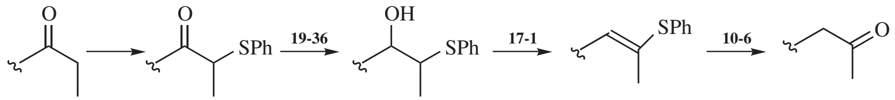
[249]Cossy, J.; Furet, N. *Tetrahedron Lett.* ***1993***, *34*, 7755.

[250]Wang, W.; Wang, K.; Li, H. *Org. Lett.* ***2004***, *6*, 2817.

[251]Saindane, M.; Barnum, C.; Ensley, H.; Balakrishnan, P. *Tetrahedron Lett.* ***1981***, *22*, 3043; Liotta, D. *Acc. Chem. Res.* ***1984***, *17*, 28.

Silyl enol ethers are converted to α-thioalkyl and α-thioaryl ketones via a sulfenylation method, driven by aromatization of an added quinone mono-*O*,*S*-acetal in the presence of Me_3SiOTf.[252]

The α-seleno and α-sulfenyl carbonyl compounds prepared by this reaction can be converted to α,β-unsaturated carbonyl compounds (**17-12**). The sulfenylation reaction has also been used[253] as a key step in a sequence for moving the position of a carbonyl group to an adjacent carbon.[254]



OS VI, 23, 109; 68, 8.

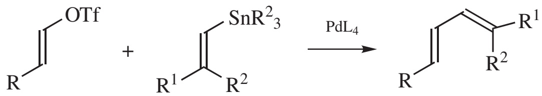
Aldehydes, ketones, and carboxylic acids containing α hydrogens can be sulfonated with sulfur trioxide.[255] The mechanism is presumably similar to that of **12-4**. Sulfonation has also been accomplished at vinylic hydrogen.

OS **VI**, 23, 109; **VIII**, 550. OS **IV**, 846, 862.

E. Carbon Reagents

12-15 Arylation and Alkylation of Alkenes

Alkylation or **Alkyl-de-oxysulfonation (de-halogenation)**, **Arylation** or **Aryl-de-oxysulfonation (de-halogenation)**, and so on



Vinyl triflates ($C{=}C\text{-}OSO_2CF_3$) react with vinyl tin derivatives in the presence of palladium catalysts to form dienes, in what is known as the *Stille coupling*.[256] Vinyl triflates can be prepared from the enolate by reaction with *N*-phenyl triflimide.[257] Vinyltin compounds are generally prepared by the reaction of an alkyne with an trialkyltin halide (see **15-17** and **15-21**).[258] Still cross-coupling reactions are quite important.[259] Stille reactions are compatible with many functional groups,

[252]Matsugi, M.; Murata, K.; Gotanda, K.; Nambu, H.; Anilkumar, G.; Matsumoto, K.; Kita, Y. *J. Org. Chem.*, ***2001***, *66*, 2434.

[253]Trost, B.M.; Hiroi, K.; Kurozumi, S. *J. Am. Chem. Soc.* ***1975***, *97*, 438.

[254]There are numerous other ways of achieving this conversion. For reviews, see Morris, D.G. *Chem. Soc. Rev.* ***1982***, *11*, 397; Kane, V.V.; Singh, V.; Martin, A.; Doyle, D.L. *Tetrahedron* ***1983***, *39*, 345.

[255]For a review, see Gilbert, E.E. *Sulfonation and Related Reactions*, Wiley, NY, ***1965***, pp. 33–61.

[256]Scott, W.J.; Crisp, G.T.; Stille, J.K. *J. Am. Chem. Soc.* ***1984***, *106*, 4630. See Roth, G.P.; Farina, V.; Liebeskind, L.S.; Peña-Cabrera, E. *Tetrahedron Lett.* ***1995***, *36*, 2191 for an optimized version of this reaction.

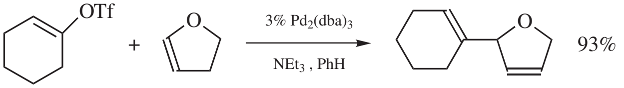
[257]McMurry, J.E.; Scott, W.J. *Tetrahedron Lett.* ***1983***, *24*, 979.

[258]For an example, see Maleczka Jr., R.E.; Lavis, J.M.; Clark, D.H.; Gallagher, W.P. *Org. Lett.* ***2000***, *2*, 3655.

[259]Stille, J.K. *Angew. Chem. Int. Ed.* ***1986***, *25*, 508; Stille, J.K.; Groh, B.L. *J. Am. Chem. Soc.* ***1987***, *109*, 813; Farina, V.; Krishnamurthy, V.; Scott, W.J. *Org. React.* ***1997***, *50*, 1.

proceed with a retention of geometry of the C=C units, and are usually regiospecific with respect to the newly formed C–C σ-bond. Vinyl halides can be used,[260] and allenic tin compounds have been used.[261] Intamolecualr reactions are possible.[262] Stille coupling has been done using microwave irradiation,[263] in fluorous solvents,[264] and in supercritical carbon dioxide (see p. 415).[265] One-pot hydrostannylation/Stille coupling has been reported using catalytic amounts of tin with alkyne substrates reacting with vinyl halides.[266]

This reaction is highly stereoselective. Cine substitution is known with this reaction, and its mechanism has been studied.[267] Using $ArSnCl_3$ derivatives, Stille coupling can be done in aq. KOH.[268] A related reaction couples reagents with C=C–I^+Ph reagents, in the presence of a palladium catalyst.[269] Aryl halides[270] and heteroaryl halides[271] can be coupled to vinyltin reagents[272] using a palladium catalyst. Vinylation of heteroaryl triflates[273] also possible. Vinyl halides can be coupled to alkenes to form dienes.[274] The reaction of dihydrofurans with vinyl triflates and a palladium catalyst leads to a nonconjugated diene, **33**.[275] This example illustrates that the product is formed by an elimination step, as with the Heck reaction (**13-10**), and double bond migration can occur resulting in allylic rearrangement.



33

[260]Johnson, C.R.; Adams, J.P.; Braun, M.P.; Senanayake, C.B.W. *Tetrahedron Lett.* ***1992***, *33*, 919.

[261]Badone, D.; Cardamone, R.; Guzzi, U. *Tetrahedron Lett.* ***1994***, *35*, 5477.

[262]Segorbe, M.M.; Adrio, J.; Carretero, J.C. *Tetrahedron Lett.* ***2000***, *41*, 1983.

[263]Larhed, M.; Hoshino, M.; Hadida, S.; Curran, D.P.; Hallberg, A. *J. Org. Chem.* ***1997***, *62*, 5583; Olofsson, K.; Kim, S.-Y.; Larhed, M.; Curran, D.P.; Hallberg, A. *J. Org. Chem.* ***1999***, *64*, 4539.

[264]Olofsson, K.; Kim, S.-Y.; Larhed, M.; Curran, D.P.; Hallberg, A. *J. Org. Chem.* ***1999***, *64*, 4539; Hoshino, M.; Degenkolb, P.; Curran, D.P. *J. Org. Chem.* ***1997***, *62*, 8341; Curran, D.P.; Hadida, S. *J. Am. Chem. Soc.* ***1996***, *118*, 2531.

[265]Jessop, P. G.; Ikariya, T.; Noyori, R. *Chem. Rev.* ***1999***, *99*, 475.

[266]Maleczka Jr., R.E.; Gallagher, W.P.; Terstiege, I. *J. Am. Chem. Soc.* ***2000***, *122*, 384; Gallagher, W.P.; Terstiege, I.; Maleczka Jr., R.E. *J. Am. Chem. Soc.* ***2001***, *123*, 3194.

[267]Farina, V.; Hossain, M.A. *Tetrahedron Lett.* ***1996***, *37*, 6997.

[268]Rai, R.; Aubrecht, K.B.; Collum, D.B. *Tetrahedron Lett.* ***1995***, *36*, 3111.

[269]Moriarty, R.M.; Epa, W.R. *Tetrahedron Lett.* ***1992***, *33*, 4095.

[270]Corriu, R.J.P.; Geng, B.; Moreau, J.J.E. *J. Org. Chem.* ***1993***, *58*, 1443; Levin, J.I. *Tetrahedron Lett.* ***1993***, *34*, 6211; Littke, A.F.; Fu, G.C. *Angew. Chem. Int. Ed.* ***1999***, *38*, 2411.

[271]Barchín, B.M.; Valenciano, J.; Cuadro, A.M.; Builla-Alvarez, J.; Vaquero, J.J. *Org. Lett.* ***1999***, *1*, 545; Clapham, B.; Sutherland, A.J. *J. Org. Chem.* ***2001***, *66*, 9033.

[272]For a coupling reaction using a butenolide-vinyltin reagent, see Rousset, S.; Abarbri, M.; Thibonnet, J.; Duchêne, A.; Parrain, J.-L. *Org. Lett.* ***1999***, *1*, 701. For a vinyltin reagent with a nitrogen substituent (a tinylated enamide), see Minière, S.; Cintrat, J.-C. *J. Org. Chem.* ***2001***, *66*, 7385.

[273]Bernabé, P.; Rutjes, P.J.T.; Hiemstra, H.; Speckamp, W.N. *Tetrahedron Lett.* ***1996***, *37*, 3561; Schaus, J.V.; Panek, J.S. *Org. Lett.* ***2000***, *2*, 469.

[274]Voigt, K.; Schick, U.; Meyer, F.E.; de Meijere, A. *Synlett* ***1994***, 189.

[275]Gilbertson, S.R.; Fu, Z.; Xie, D. *Tetrahedron Lett.* ***2001***, *42*, 365.

The accepted mechanism for the Stille reaction involves a catalytic cycle[276] in which an oxidative addition[277] and a reductive elimination step[278] are fast, relative to Sn/Pd transmetallation (the rate-determining step).[279] It appears that the more coordinatively unsaturated species, probably with a coordinated solvent molecule, is involved in the electrophilic substitution at tin. Another mechanism has been proposed, in which oxidative addition of the vinyl triflate to the ligated palladium gives a *cis*-palladium complex that isomerizes rapidly to *trans*-palladium complex, which then reacts with the organotin compound following a S_E2 (cyclic) mechanism, with release of a ligand.[280] This pathway gives a bridged intermediate, and subsequent elimination of $XSnBu_3$ yields a three-coordinate species cis-palladium complex, which readily gives the coupling product.[280]

Cyclopropylboronic acids (**12-28**) couple with vinylic halides[281] or vinyl triflates[282] to give vinylcyclopropanes, using a palladium catalyst. Vinyl borates (**12-28**) were coupled to vinyl triflates using a palladium catalyst.[283] In a variation, phenylboronic acid reacted with a symmetrical internal alkyne and a nickel catalyst to give a conjugated diene bearing a phenyl group.[284] Stille coupling to enols has been reported.[285] A variation of this latter reaction coupled vinyl triflates to vinyl ethers, without a palladium catalyst, but using microwave irradiation.[286] The

[276]Stanforth, S.P. *Tetrahedron* ***1998***, *54*, 263; Farina, V.; Roth, G.P. *Adv. Metalorg. Chem.* ***1996***, *5*, 1; Curran, D.P.; Hoshino, M. *J. Org. Chem.* ***1996***, *61*, 6480; Mateo, C.; Cárdenas, D.J.; Fernández-Rivas, C.; Echavarren, A.M. *Chem. Eur. J.* ***1996***, *2*, 1596; Roth, G.P.; Farina, V.; Liebeskind, L.S.; Peña-Cabrera, E. *Tetrahedron Lett.* ***1995***, *36*, 2191; Mitchell, T.N. *Synthesis* ***1992***, 803; Scott, W.J.; Stille, J.K. *J. Am. Chem. Soc.* ***1986***, *108*, 3033; Stille, J.K. *Angew. Chem., Int. Ed.* ***1986***, *25*, 508; Beletskaya, I.P. *J. Organomet. Chem.* ***1983***, *250*, 551; Farina, V., in, Abel, E. W., Stone, F. G. A., Wilkinson, G. *Comprehensive Organometallic Chemistry II*, Vol. 12, Pergamon, Oxford, U.K., ***1995***, Chapter 3.4.; Brown, J.M.; Cooley, N.A. *Chem. Rev.* ***1988***, *88*, 1031.

[277]Amatore, C.; Jutand, A.; Suarez, A. *J. Am. Chem. Soc.* ***1993***, *115*, 9531; Amatore, C.; Pflüger, F. *Organometallics* ***1990***, *9*, 2276, and references cited therein.

[278]Ozawa, F.; Fujimori, M.; Yamamoto, T.; Yamamoto, A. *Organometallics* ***1986***, *5*, 2144; Tatsumi, K.; Hoffmann, R.; Yamamoto, A.; Stille, J.K. *Bull. Chem. Soc. Jpn.* ***1981***, *54*, 1857; Ozawa, F.; Ito, T.; Nakamura, Y.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* ***1981***, *54*, 1868; Moravsikiy, A.; Stille, J.K. *J. Am. Chem. Soc.* ***1981***, *103*, 4182; Loar, M.K.; Stille, J.K. *J. Am. Chem. Soc.* ***1981***, *103*, 4174; Ozawa, F.; Ito, T.; Yamamoto, A. *J. Am. Chem. Soc.* ***1980***, *102*, 6457; Gillie, A.; Stille, J.K. *J. Am. Chem. Soc.* ***1980***, *102*, 4933; Komiya, S.; Albright, T.A.; Hoffmann, R.; Kochi, J.K. *J. Am. Chem. Soc.* ***1976***, *98*, 7255.

[279]Labadie, J.W.; Stille, J.K. *J. Am. Chem. Soc.* ***1983***, *105*, 6129; Eaborn, C.; Odell, K.J.; Pidcock, A. *J. Chem. Soc., Dalton Trans.* ***1978***, 357; Eaborn, C.; Odell, K.J.; Pidcock, A. *J. Chem. Soc., Dalton Trans.* ***1979***, 758; Deacon, G.B.; Gatehouse, B.M.; Nelson-Reed, K.T. *J. Organomet. Chem.* ***1989***, *359*, 267.

[280]Casado, A.L.; Espinet, P.; Gallego, A.M. *J. Am. Chem. Soc.* ***2000***, *122*, 11771; Casado, A.L.; Espinet, P. *J. Am. Chem. Soc.* ***1998***, *120*, 8978.

[281]Zhou, S.-m.; Deng, M.-z. *Tetrahedron Lett.* ***2000***, *41*, 3951.

[282]Yao, M.-L.; Deng, M.-Z. *J. Org. Chem.* ***2000***, *65*, 5034; Yao, M.-L.; Deng, M.-Z. *Tetrahedron Lett.* ***2000***, *41*, 9083.

[283]Occhiato, E.G.; Trabocchi, A.; Guarna, A. *J. Org. Chem.* ***2001***, *66*, 2459.

[284]Shirakawa, E.; Takahashi, G.; Tsuchimoto, T.; Kawakami, Y. *Chem. Commun.* ***2001***, 2688.

[285]See Fu, X.; Zhang, S.; Yin, J.; McAllister, T.L.; Jiang, S.A.; Tann, C.-H.; Thiruvengadam, T.K.; Zhang, F. *Tetrahedron Lett.* ***2002***, *43*, 573.

[286]Vallin, K.S.A.; Larhed, M.; Johansson, K.; Hallberg, A. *J. Org. Chem.* ***2000***, *65*, 4537.

coupling of vinyl silanes to give the symmetrically conjugated diene using CuCl and air was reported.[287] Vinyl zinc halides were coupled to 1-halo enol ether to give a conjugated diene bearing a vinyl ether unit, using a palladium catalyst.[288] Tertiary propargyl alcohols (R-C=C-CMe_2OH) are coupled to conjugated alkenes in a Heck-like process using a palladium catalyst and oxygen to give the conjugated ene-yne.[289]

Coupling is not restricted to two vinyl units or an aryl with a vinyl. 1-Lithioalkynes were coupled to vinyl tellurium compounds (C=C–TeBu) using a nickel catalyst[290] or a palladium catalyst[291] to give a conjugated en-yne. 2-Alkynes (R-C=C-Me) react with $HgCl_2$, *n*-butyllithium, and $ZnBr_2$, sequentially, and then with vinyl iodides and a palladium catalyst to give the nonconjugated en-yne.[292] Alkynyl groups can be coupled to vinyl groups to give ene-ynes, via reaction of silver alkynes (Ag-C=C-R) with vinyl triflates and a palladium catalyst.[293] In the presence of CuI and a palladium catalyst, vinyl triflates[294] or vinyl halides[295] couple to terminal alkynes. Alkynyl zinc reagents (R-C=C-ZnBr) can be coupled to vinyl halides with a palladium catalyst to give the conjugate ene-yne.[296]

Alkyl groups can be coupled to a vinyl unit to give substituted alkenes. The reaction of vinyl iodides and EtZnBr, with a palladium catalyst, gave the ethylated alkene (C=C–Et).[297] A similar coupling reaction was observed with RZnI reagents and vinyl nitro compounds (C=C–NO_2), which gave the alkyne (C=C–R) with microwave irradiation.[298] Aliphatic alkyl bromides reacted with vinyltin compounds to give the alkylated alkene using a palladium catalyst.[299] Allylic tosylates were coupled to conjugated alkenes to give a non-conjugated diene using a palladium catalyst.[300] An internal coupling reaction was reported in which an alkenyl enamide (**34**) reacted with Ag_3PO_4 and a chiral palladium catalyst to give **35** enantioselectively.[301]

[287]Nishihara, Y.; Ikegashira, K.; Toriyama, F.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* ***2000***, *73*, 985.

[288]Su, M.; Kang, Y.; Yu, W.; Hua, Z.; Jin, Z. *Org. Lett.* ***2002***, *4*, 691.

[289]Nishimura, T.; Araki, H.; Maeda, Y.; Uemura, S. *Org. Lett.* ***2003***, *5*, 2997.

[290]Raminelli, C.; Gargalak, Jr., J.; Silveira, C.C.; Comasseto, J.V. *Tetrahedron Lett.* ***2004***, *45*, 4927; Silveira, C.C.; Braga, A.L.; Vieira, A.S.; Zeni, G. *J. Org. Chem.* ***2003***, *68*, 662.

[291]Zeni, G.; Comasseto, J.V. *Tetrahedron Lett.* ***1999***, *40*, 4619.

[292]Ma, S.; Zhang, A.; Yu, Y.; Xia, W. *J. Org. Chem.* ***2000***, *65*, 2287.

[293]Dillinger, S.; Bertus, P.; Pale, P. *Org. Lett.* ***2001***, *3*, 1661. See Halbes, U.; Bertus, P.; Pale, P. *Tetrahedron Lett.* ***2001***, *42*, 8641; Bertus, P.; Halbes, U.; Pale, P. *Eur. J. Org. Chem.* ***2001***, 4391.

[294]Braga, A.L.; Emmerich, D.J.; Silveira, C.C.; Martins, T.L.C.; Rodrigues, O.E.D. *Synlett* ***2001***, 369.

[295]Lee, J.-H.; Park, J.-S.; Cho, C.-G. *Org. Lett.* ***2002***, *4*, 1171. For an example using another copper catalyst, see Bates, C.G.; Saejueng, P.; Venkataraman, D. *Org. Lett.* ***2004***, *6*, 1441.

[296]Negishi, E.; Qian, M.; Zeng, F.; Anastasia, L.; Babinski, D. *Org. Lett.* ***2003***, *5*, 1597.

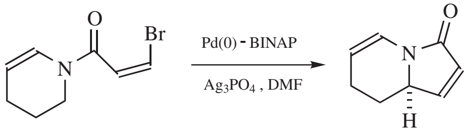
[297]Abarbri, M.; Parrain, J.-L.; Kitamura, M.; Noyori, R.; Duchêne, A. *J. Org. Chem.* ***2000***, *65*,7475.

[298]Hu, Y.; Yu, J.; Yang, S.; Wang, J.-X.; Yin, Y. *Synth. Commun.* ***1999***, *29*, 1157.

[299]Menzel, K.; Fu, G.C. *J. Am. Chem. Soc.* ***2003***, *125*, 3718.

[300]Tsukada, N.; Sato, T.; Inoue, Y. *Chem. Commun.* ***2003***, 2404.

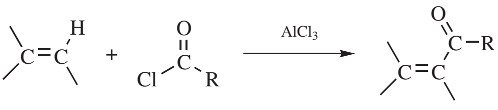
[301]Kiewel, K.; Tallant, M.; Sulikowski, G.A. *Tetrahedron Lett.* ***2001***, *42*, 6621.



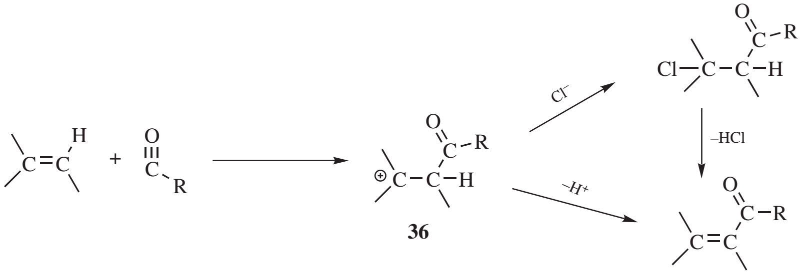
34 **35**

12-16 Acylation at an Aliphatic Carbon

Acylation or **Acyl-de-hydrogenation**



Alkenes can be acylated with an acyl halide and a Lewis acid catalyst in what is essentially a Friedel–Crafts reaction at an aliphatic carbon.[302] The product can arise by two paths. The initial attack is by the π-bond of the alkene unit on the acyl cation (RCO^+; or on the acyl halide free or complexed; see **11-17**) to give a carbocation, **36**.



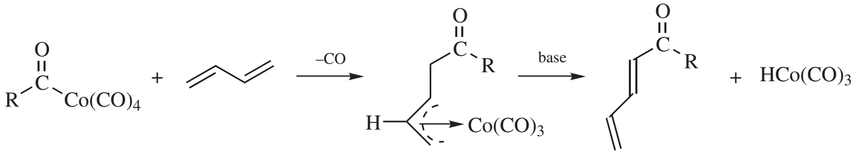
36

Ion **36** can either lose a proton or combine with chloride ion. If it loses a proton, the product is an unsaturated ketone; the mechanism is similar to the tetrahedral mechanism of Chapter 10, but with the charges reversed. If it combines with chloride, the product is a β-halo ketone, which can be isolated, so that the result is addition to the double bond (see **15-47**). On the other hand, the β-halo ketone may, under the conditions of the reaction, lose HCl to give the unsaturated ketone, this time by an addition–elimination mechanism. In the case of unsymmetrical alkenes, the more stable alkene is formed (the more highly substituted and/or conjugated alkene, following Markovnikov's rule, see p. 1019). Anhydrides and carboxylic acids (the latter with a proton acid such as anhydrous HF, H_2SO_4, or polyphosphoric acid as a catalyst) are sometimes used instead of acyl halides. With some sub-

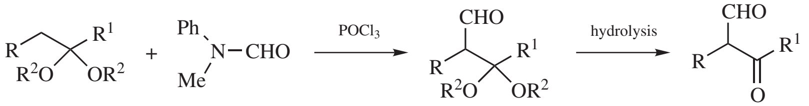
[302]For reviews, see Groves, E.E. *Chem. Soc. Rev.* ***1972***, *1*, 73; Satchell, D.P.N.; Satchell, R.S., in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 259–266, 270–273; Nenitzescu, C.D.; Balaban, A.T., in Olah A, G.A. *Friedel-Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 1033–1152.

strates and catalysts double-bond migrations are occasionally encountered so that, for example, when 1-methylcyclohexene was acylated with acetic anhydride and zinc chloride, the major product was 6-acetyl-1-methylcyclohexene.[303]

Conjugated dienes can be acylated by treatment with acyl- or alkylcobalt tetracarbonyls, followed by base-catalyzed cleavage of the resulting π-allyl carbonyl derivatives[304] (π-allyl metal complexes were discussed on p. 117. The reaction is very general. With unsymmetrical dienes, the acyl group generally substitutes most readily at a cis double bond, next at a terminal alkenyl group, and least readily at a trans double bond. The most useful bases are strongly basic, hindered amines, such as dicyclohexylethylamine. The use of an alkylcobalt tetracarbonyl $RCo(CO)_4$ gives the same product as that shown above. Acylation of vinylic ethers has been accomplished with aromatic acyl chlorides, a base, and a palladium catalyst: $ROCH{=}CH_2 \rightarrow ROCH{=}CHCOAr$.[305]



Formylation of alkenes can be accomplished with *N*-disubstituted formamides and $POCl_3$.[306] This is an aliphatic Vilsmeier reaction (see **11-18**). Vilsmeier formylation can also be performed on the α position of acetals and ketals, so that hydrolysis of the products gives keto aldehydes or dialdehydes:[307] A variation of this reaction heated a 1,1-dibromoalkene with a secondary amine in aq. DMF to give the corresponding amide.[308]



Acetylation of acetals or ketals can be accomplished with acetic anhydride and BF_3-etherate.[309] The mechanism with acetals or ketals also involves attack at an

[303]Deno, N.C.; Chafetz, H. *J. Am. Chem. Soc.* ***1952***, *74*, 3940. For other examples, see Beak, P.; Berger, K.R. *J. Am. Chem. Soc.* ***1980***, *102*, 3848; Dubois, J.E.; Saumtally, I.; Lion, C. *Bull. Soc. Chim. Fr.* ***1984***, II-133; Grignon-Dubois, M.; Cazaux, M. *Bull. Soc. Chim. Fr.* ***1986***, 332.

[304]For a review, see Heck, R.F., in Wender, I.; Pino, P. *Organic Syntheses via Metal Carbonyls*, Vol. 1, Wiley, NY, ***1968***, pp. 388–397.

[305]Andersson, C.; Hallberg, A. *J. Org. Chem.* ***1988***, *53*, 4257.

[306]For reviews, see Burn, D. *Chem. Ind. (London)* ***1973***, 870; Satchell, D.P.N.; Satchell, R.S., in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 281–282.

[307]Youssefyeh, R.D. *Tetrahedron Lett.* ***1964***, 2161.

[308]Shen, W.; Kunzer, A. *Org. Lett.* ***2002***, *4*, 1315.

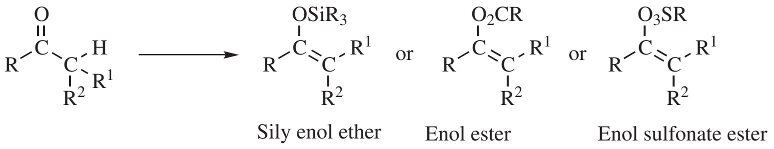
[309]Youssefyeh, R.D. *J. Am. Chem. Soc.* ***1963***, *85*, 3901.

alkenyl carbon, since enol ethers are intermediates.[309] Ketones can be formylated in the α position by treatment with CO and a strong base.[310]

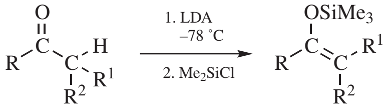
OS **IV**, 555, 560; **VI**, 744. Also see OS **VI**, 28.

12-17 Conversion Of Enolates to Silyl Enol Ethers, Silyl Enol Esters, and Silyl Enol Sulfonate Esters

3/*O*-Trimethylsilyl-de-hydrogenation



Silyl enol ethers,[311] important reagents with a number of synthetic uses (see, e.g., **10-68**, **12-4**, **15-24**, **15-64**, **16-36**), can be prepared by base treatment of a ketone (converting it to its enolate anion) followed by addition of a trialkylchlorosilane. Other silylating agents have also been used.[312] Both strong bases, e.g., lithium diisopropylamide (LDA), and weaker bases (e.g. Et_3N) have been used for this purpose.



In some cases, the base and the silylating agent can be present at the same time.[313] Enolates prepared in other ways (e.g., as shown on p. 603) also give the reaction.[314] The reaction can be applied to aldehydes by the use of the base KH in 1,2-dimethoxyethane.[315] A particularly mild method for conversion of ketones

[310]See, for example, van der Zeeuw, A.J.; Gersmann, H.R. *Recl. Trav. Chim. Pays-Bas* ***1965***, *84*, 1535.

[311]For reviews of these compounds, see Poirier, J. *Org. Prep. Proced. Int.* ***1988***, *20*, 319; Brownbridge, P. *Synthesis* ***1983***, 1, 85; Rasmussen, J.K. *Synthesis* ***1977***, 91. For monographs on silicon reagents in organic synthesis, see Colvin, E.W. *Silicon Reagents in Organic Synthesis*, Academic Press, NY, ***1988***. For reviews, see Colvin, E.W., in Hartley, C.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 4, Wiley, NY, pp. 539–621; Ager, D.J. *Chem. Soc. Rev.* ***1982***, *11*, 493; Colvin, E.W. *Chem. Soc. Rev.* ***1978***, *7*, 15, pp. 43–50.

[312]For a review of silylating agents, see Mizhiritskii, M.D.; Yuzhelevskii, Yu.A. *Russ. Chem. Rev.* ***1987***, *56*, 355. For a list, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1488–1491.

[313]Corey, E.J.; Gross, A.W. *Tetrahedron Lett.* ***1984***, *25*, 495. See Lipshutz, B.H.; Wood, M.R.; Lindsley, C.W. *Tetrahedron Lett.* ***1995***, *36*, 4385 for a discussion of the role of Me_3SiCl in deprotonations with $LiNR_2$.

[314]See Cahiez, G.; Figadère, B.; Cléry, P. *Tetrahedron Lett.* ***1994***, *35*, 6295.

[315]Ladjama, D.; Riehl, J.J. *Synthesis* ***1979***, 504. This base has also been used for ketones: See Orban, J.; Turner, J.V.; Twitchin, B. *Tetrahedron Lett.* ***1984***, *25*, 5099.

or aldehydes to silyl enol ethers uses Me_3SiI and the base hexamethyldisilazane, $(Me_3Si)_2NH$.[316] Cyclic ketones can be converted to silyl enol ethers in the presence of acyclic ketones, by treatment with Me_3SiBr, tetraphenylstibonium bromide, Ph_4SbBr, and an aziridine.[317] bis(Trimethylsilyl)acetamide is an effective reagent for the conversion of ketones to the silyl enol ether, typically giving the thermodynamic product (see below).[318] Silyl enol ethers have also been prepared by the direct reaction of a ketone and a silane (R_3SiH) with a platinum complex catalyst.[319]

Unsymmetrical ketones can give the more substituted (thermodynamic) silyl enol ether or the less substituted (kinetic) product, depending on the use of thermodynamic conditions (protic solvents, e.g., ethanol, water, or ammonia; a base generating a conjugate acid stronger than the starting ketone; more ionic counterions, e.g., K or Na; higher temperatures and longer reaction times) or kinetic conditions (aprotic solvents, such as ether or THF; a base generating a conjugate acid weaker than the starting ketone; more covalent counterions, e.g., Li; lower temperatures and relatively short reaction times). Other reaction conditions have been developed to control or influence the relative amounts of kinetic or thermodynamic silyl enol ether. Magnesium diisopropyl amide has been used to prepare kinetic silyl enol ethers in virtual quantitative yield.[320] Reaction with Me_3SiCl/KI in DMF gives primarily the thermodynamic silyl enol ether.[321] The reaction of an unsymmetrical ketone with Mg and TMSCl in DMF gives a roughly 2:1 mixture of thermodynamic: kinetic silyl enol ether.[322]

An interesting synthesis of silyl enol ethers involves chain extension of an aldehyde. Aldehydes are converted to the silyl enol ether of a ketone upon reaction with lithium (trimethylsilyl)diazomethane and then a dirhodium catalyst.[323] Initial reaction of lithium(trimethylsilyl)diazomethane [LTMSD, prepared *in situ* by reaction of butyllithium with (trimethylsilyl)diazomethane] to the aldehyde (e.g., **37**) gave the alkoxide addition product. Protonation, and then capture by a transition-metal catalyst, and a 1,2-hydride migration gave the silyl enol ether, **38**.

[316]Miller, R.D.; McKean, D.R. *Synthesis* ***1979***, 730; *Synth. Commun.* ***1982***, *12*, 319. See also, Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron* ***1987***, *43*, 2075, 2089; Ahmad, S.; Khan, M.A.; Iqbal, J. *Synth. Commun.* ***1988***, *18*, 1679.

[317]Fujiwara, M.; Baba, A.; Matsuda, H. *Chem. Lett.* ***1989***, 1247.

[318]Smietana, M.; Mioskowski, C. *Org. Lett.* ***2001***, *3*, 1037. See also, Tanabe, Y.; Misaki, T.; Kurihara, M.; Iida, A.; Nishii, Y. *Chem. Commun.* ***2002***, 1628.

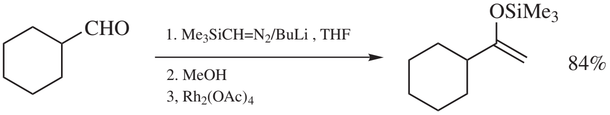
[319]Ozawa, F.; Yamamoto, S.; Kayagishi, S.; Hiraoka, M.; Ideda, S.;Minami, T.; Ito, S.; Yoshifuji, M. *Chem. Lett.* ***2001***, 972. For the conversion of a conjugated ketone to a silyl enol ether with R_3SiH and a triarylborane catalyst, see Blackwell, J.M.; Morrison, D.J.; Piers, W.E. *Tetahedron* ***2002***, *58*, 8247. For the conversion of a conjugated ketone to a silyl enol ether with R_3SiH and a rhodium catalyst, see Mori, A.; Kato, T. *Synlett* ***2002***, 1167.

[320]Lessène, G.; Tripoli, R.; Cazeau, P.; Biran, C.; Bordeau, M. *Tetrahedron Lett.* ***1999***, *40*, 4037.

[321]Lin, J.-M.; Liu, B.-S. *Synth. Commun.* ***1997***, *27*, 739.

[322]Patonay, T.; Hajdu, C.; Jekö, J.; Lévai, A.; Micskei, K.; Zucchi, C. *Tetrahedron Lett.* ***1999***, *40*, 1373.

[323]Aggarwal, V. K.; Sheldon, C. G.; Macdonald, G. J.; Martin, W. P. *J. Am. Chem. Soc.* ***2002***, *124*, 10300.



37 38

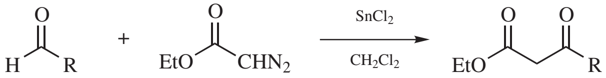
Enol acetates are generally prepared by the reaction of an enolate anion with a suitable acylating reagent.[324] Enolate anions react with acyl halides and with anhydrides to give the acylated product. Both *C*-acylation and *O*-acylation are possible, but in general *O*-acylation predominates.[325] Note that the extent of *O*- versus *C*-acylation is very dependent on the local environment and electronic effects within the enolate anion.[326] Silyl sulfonate esters can be prepared by similar methods, using sulfonic acid anhydrides rather than carboxylic anhydrides. A polymer-supported triflating agent was used to prepare silyl enol triflate from ketones, in the presence of diisopropylethylamine.[327]

When a silyl enol ether is the trimethylsilyl derivative (Me_3Si–O-C=C), treatment with methyllithium will regenerate the lithium enolate anion and the volatile trimethylsilane (Me_3SiH).[328] The enolate anion can be used in the usual reactions. In a similar reaction, a trimethylsilyl enol ether was treated with Cp_2Zr (from Cp_2ZrCl_2/2 BuLi/THF/–78°C), and subsequent quenching with D_2O led to incorporation of deuterium at the vinyl carbon (C=C–D).[329]

OS **VI**, 327, 445; **VII**, 282, 312, 424, 512; **VIII**, 1, 286, 460; **IX**, 573. See also OS **VII**, 66, 266. For the conversion of ketones to vinylic triflates,[330] see OS **VIII**, 97, 126.

12-18 Conversion of Aldehydes to β-Keto Esters or Ketones

Alkoxycarbonylalkylation or **Alkoxycarbonylalkyl-de-hydrogenation**



β-Keto esters have been prepared in moderate to high yields by treatment of aldehydes with diethyl diazoacetate in the presence of a catalytic amount of a Lewis acid, such as $SnCl_2$, BF_3, or $GeCl_2$.[331] The reaction was successful for both aliphatic and aromatic aldehydes, but the former react more rapidly than the latter, and the

[324]For the synthesis of enol acetates, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, 1484–1485.

[325]See Krapcho, A.P.; Diamanti, J.; Cayen, C.; Bingham, R. *Org. Synth. Coll. Vol. V* ***1973***, 198.

[326]For example, see Honda, T.; Namiki, H.; Kudoh, M.; Watanabe, N.; Nagase, H.; Mizutani, H. *Tetrahedron Lett.* ***2000***, *41*, 5927.

[327]Wentworth, A.D.; Wentworth, Jr., P.; Mansoor, U.F.; Janda, K.D. *Org. Lett.* ***2000***, *2*, 477.

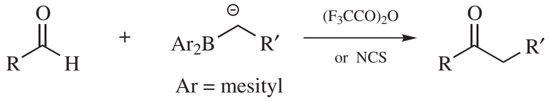
[328]House, H.O.; Czuba, L.J.; Gall, M.; Olmstead, H.D. *J. Org. Chem.* ***1969***, *34*, 2324.

[329]Ganchegui, B.; Bertus, P.; Szymoniak, J. *Synlett* ***2001***, 123.

[330]Comins, D.L.; Dehghani, A. *Tetrahedron Lett.* ***1992***, *33*, 6299.

[331]Holmquist, C.R.; Roskamp, E.J. *J. Org. Chem.* ***1989***, *54*, 3258.

difference is great enough to allow selective reactivity. In a similar process, aldehydes react with certain carbanions stabilized by boron, in the presence of $(F_3CCO)_2O$ or NCS, to give ketones.[332]

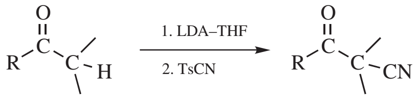


Ketones can be prepared from aryl aldehydes (ArCHO) by treatment with a rhodium complex $(Ph_3P)_2Rh(CO)Ar'$, whereby the Ar group is transferred to the aldehyde, producing the ketone, Ar–CO–Ar′.[333] In a rhodium catalyzed reaction, aryl aldehydes (ArCHO) react with Me_3SnAr' to give the diaryl ketone Ar–CO–Ar′.[334]

12-19 Cyanation or Cyano-de-hydrogenation

There are several reactions in which a C–H unit is replaced by C–CN. In virtually all cases, the hydrogen being replaced is on a carbon α to a heteroatom or functional group. There are several examples.

Introduction of a cyano group α to the carbonyl group of a ketone can be accomplished by prior formation of the enolate anion with LDA in THF and addition of this solution to *p*-TsCN at −78°C.[335] The products are formed in moderate to high yields but the reaction is not applicable to methyl ketones. Treatment of $TMSCH_2N(Me)C{=}Nt$-Bu with *sec*-butyllithium and $R_2C{=}O$, followed by iodomethane and NaOMe leads to the nitrile, R_2CH–CN.[336]



Cyanation has been shown to occur α to a nitrogen, specifically in *N,N*-dimethylaniline derivatives. Treatment with a catalytic amount of $RuCl_3$ in the presence of oxygen and NaCN leads to the corresponding cyanomethylamine.[337]

[332]Pelter, A.; Smith, K.; Elgendy, S.; Rowlands, M. *Tetrahedron Lett.* ***1989***, *30*, 5643.
[333]Krug, C.; Hartwig, J. F *J. Am. Chem. Soc.* ***2002***, *124*, 1674.
[334]Pucheault, M.; Darses, S.; Genet, J.-P. *J. Am. Chem. Soc.* ***2004***, *126*, 15356.
[335]Kahne, D.; Collum, D.B. *Tetrahedron Lett.* ***1981***, *22*, 5011.
[336]Santiago, B.; Meyers, A.I. *Tetrahedron Lett.* ***1993***, *34*, 5839.
[337]Murahashi, S.-I.; Komiya, N.; Terai, H.; Nakae, T. *J. Am. Chem. Soc.* ***2003***, *125*, 15312; North, M. *Angew. Chem. Int. Ed.* ***2004***, *43*, 4126.

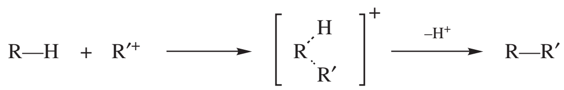
In a different kind of reaction, nitro compounds are α-cyanated by treatment with ^{-}CN and $K_3Fe(CN)_6$.[338] The mechanism probably involves ion radicals. In still another reaction, secondary amines are converted to α-cyanoamines by treatment with phenylseleninic anhydride and NaCN or Me_3SiCN.[339] The compound Me_3SiCN has also been used in a reaction that cyanates benzylic positions.[340]

12-20 Alkylation of Alkanes

Alkylation or **Alkyl-de-hydrogenation**

$$RH + R'^{+} \longrightarrow R{-}R' + H^{+}$$

Alkanes can be alkylated by treatment with solutions of stable carbocations[341] (p. 235), but the availability of such carbocations is limited and mixtures are usually obtained. In a typical experiment, the treatment of propane with isopropyl fluoroantimonate (Me_2C^{+} SbF_6–) gave 26% 2,3-dimethylbutane, 28% 2-methylpentane, 14% 3-methylpentane, and 32% *n*-hexane, as well as some butanes, pentanes (formed by **12-47**), and higher alkanes. Mixtures arise in part because intermolecular hydrogen exchange ($RH + R'^{+}$ $R^{+} + R'H$) is much faster than alkylation, so that alkylation products are also derived from the new alkanes and carbocations formed in the exchange reaction. Furthermore, the carbocations present are subject to rearrangement (Chapter 18), giving rise to new carbocations. Products result from all the hydrocarbons and carbocations present in the system. As expected from their relative stabilities, secondary alkyl cations alkylate alkanes more readily than tertiary alkyl cations (the *tert*-butyl cation does not alkylate methane or ethane). Stable primary alkyl cations are not available, but alkylation has been achieved with complexes formed between CH_3F or C_2H_5F and SbF_5.[342] The mechanism of alkylation can be formulated (similar to that shown in hydrogen exchange with superacids, **12-1**) as



[338]Matacz, Z.; Piotrowska, H.; Urbanski, T. *Pol. J. Chem.* ***1979***, *53*, 187; Kornblum, N.; Singh, N.K.; Kelly, W.J. *J. Org. Chem.* ***1983***, *48*, 332.

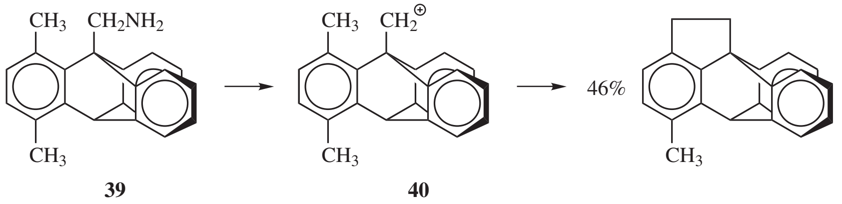
[339]Barton, D.H.R.; Billion, A.; Boivin, J. *Tetrahedron Lett.* ***1985***, *26*, 1229.

[340]Lemaire, M.; Doussot, J.; Guy, A. *Chem. Lett.* ***1988***, 1581. See also, Hayashi, Y.; Mukaiyama, T. *Chem. Lett.* ***1987***, 1811.

[341]Olah, G.A.; Mo, Y.K.; Olah, J.A. *J. Am. Chem. Soc.* ***1973***, *95*, 4939. For reviews, see Olah, G.A.; Farooq, O.; Prakash, G.K.S., in Hill, C.L. *Activation and Functionalization of Alkanes*, Wiley, NY, ***1989***, pp. 27–78; Ref. 48. For a review of the thermodynamic behavior of alkanes in superacid media, see Fabre, P.; Devynck, J.; Trémillon, B. *Chem. Rev.* ***1982***, *82*, 591. See also, Olah, G.A.; Prakash, G.K.S.; Williams, R.E.; Field, L.D.; Wade, K. *Hypercarbon Chemistry*, Wiley, NY, ***1987***.

[342]Olah, G.A.; DeMember, J.R.; Shen, J. *J. Am. Chem. Soc.* ***1973***, *95*, 4952. See also, Sommer, J.; Muller, M.; Laali, K. *Nouv. J. Chem.* ***1982***, *6*, 3.

It is by means of successive reactions of this sort that simple alkanes like methane and ethane give *tert*-butyl cations in superacid solutions (p. 236).[343]



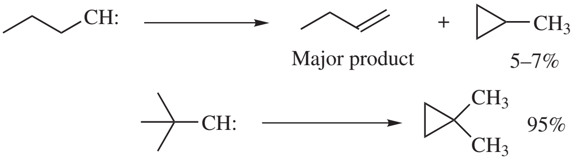
Intramolecular insertion has been reported. The positively charged carbon of the carbocation **40**, generated from the diazonium salt of the triptycene compound **39**, reacted with the CH_3 group in close proximity with it.[344]

12-21 Insertion by Carbenes

***CH*-Methylene-insertion**

$$RH + :CH_2 \longrightarrow RCH_3$$

The highly reactive species methylene ($:CH_2$) inserts into C–H bonds,[345] both aliphatic and aromatic,[346] although with aromatic compounds subsequent ring expansion is also possible (see **15-64**). This is effectively a homologation reaction.[347] The methylene insertion reaction has limited utility because of its nonselectivity (see p. 284). The insertion reaction of carbenes has been used for synthetic purposes.[348] The carbenes can be generated in any of the ways mentioned in Chapter 5 (p. 287). Alkylcarbenes usually rearrange rather than give



[343]For example, see Hogeveen, H.; Roobeek, C.F. *Recl. Trav. Chim. Pays-Bas* ***1972***, *91*, 137.

[344]Yamamoto, G.; Ō ki, M. *Chem. Lett.* ***1987***, 1163.

[345]First reported by Meerwein, H.; Rathjen, H.; Werner, H. *Berchtt.* ***1942***, *75*, 1610. For reviews, see Bethell, D., in McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, ***1973***, pp. 92–101; Kirmse, W. *Carbene Chemistry*, 2nd ed., Academic Press, NY, ***1971***, pp. 209–266.

[346]Terao, T.; Shida, S. *Bull. Chem. Soc. Jpn.* ***1964***, *37*, 687. See also, Moss, R.A.; Fedé, J.-M.; Yan, S. *J. Am. Chem. Soc.* ***2000***, *122*, 9878.

[347]For a discussion of organozinc carbenoid homologation reactions, see Marek, I. *Tetrahedron* ***2002***, *58*, 9463.

[348]For some examples of intramolecular carbene insertions used synthetically, see Gilbert, J.C.; Giamalva, D.H.; Weerasooriya, U. *J. Org. Chem.* ***1983***, *48*, 5251; Taber, D.F.; Ruckle, Jr., R.E. *J. Am. Chem. Soc.* ***1986***, *108*, 7686; Paquette, L.A.; Kobayashi, T.; Gallucci, J.C. *J. Am. Chem. Soc.* ***1988***, *110*, 1305; Adams, J.; Poupart, M.; Grenier, L.; Schaller, C.; Ouimet, N.; Frenette, R. *Tetrahedron Lett.* ***1989***, *30*, 1749; Doyle, M.P.; Bagheri, V.; Pearson, M.M.; Edwards, J.D. *Tetrahedron Lett.* ***1989***, *30*, 7001.

insertion (p. 291), but, when this is impossible, *intramolecular* insertion[349] is found rather than intermolecular.[350] Methylene ($:CH_2$) generated by photolysis of diazomethane (CH_2N_2) in the liquid phase is indiscriminate (totally nonselective) in its reactivity (p. 288). Methylene ($:CH_2$) generated in other ways and mono-alkyl and dialkyl carbenes are less reactive and insert in the order tertiary > secondary > primary.[351] Carbene insertion with certain allylic systems can proceed with rearrangement of the double bond.[352] Carbenes have been generated in the presence of ultrasound.[353] Halocarbenes ($:CCl_2$, $:CBr_2$, etc.) insert much less readily, although a number of instances have been reported.[354] Insertion into the O–H bond of alcohols, to produce ethers, has been reported using a diazocarbonyl compound and an $In(OTf)_3$ catalyst.[355]

For the similar insertion reaction of nitrenes, see **12-13**.

The metal carbene insertion reaction, in contrast to the methylene insertion reaction, can be highly selective,[356] is very useful in synthesis,[357] and there are numerous examples, usually requiring a catalyst.[358] The catalyst typically convert a diazoalkane or diazocarbonyl compound to the metal carbene *in situ*, allowing the subsequent insertion reaction. Intermolecular reactions are known, including diazoalkane insertion reaction with a dirhodium catalyst.[359] When chiral ligands are present good enantioselectivity is observed in the insertion product.[360] Insertion at an allylic carbon of alkenes has been reported.[361] Insertion into a 2-pyrrolidinone derivative using $Me_3SiCH_2N_2$ followed by $AgCO_2Ph$ with ultrasound gave a

[349]Kirmse, W.; Doering, W. von E. *Tetrahedron* ***1960***, *11*, 266; Friedman, L.; Berger, J.G. *J. Am. Chem. Soc.* ***1961***, *83*, 492, 500. See Padwa, A.; Krumpe, K.E. *Tetrahedron* ***1992***, *48*, 5385.

[350]For a review of the intramolecular insertions of carbenes or carbenoids generated from diazocarbonyl compounds, see Burke, S.D.; Grieco, P.A. *Org. React.* ***1979***, *26*, 361.

[351]Doering, W. von E.; Knox, L.H. *J. Am. Chem. Soc.* ***1961***, *83*, 1989.

[352]Carter, D.S.; Van Vranken, D.L. *Org. Lett.* ***2000***, *2*, 1303; Kirmse, W.; Kapps, M. *Chem. Ber.* ***1968***, *101*, 994; Doyle, M.P.; Griffin, J.H.; Chinn, M.S.; van Leusen, D. *J. Org. Chem.* ***1984***, *49*, 1917; Doyle, M.P.; McKervey, M.A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, Wiley,NY, ***1998***; Meyer, O.; Cagle, P.C.; Weickhardt, K.; Vichard, D.; Gladysz, J.A. *Pure Appl. Chem.* ***1996***, *68*, 79.

[353]Bertram, A.K.; Liu, M.T.H. *J. Chem. Soc. Chem. Commun.* ***1993***, 467.

[354]For example, see Parham, W.E.; Koncos, R. *J. Am. Chem. Soc.* ***1961***, *83*, 4034; Fields, E.K. *J. Am. Chem. Soc.* ***1962***, *82*, 1744; Anderson, J.C.; Lindsay, D.G.; Reese, C.B. *J. Chem. Soc.* ***1964***, 4874; Seyferth, D.; Cheng, Y.M. *J. Am. Chem. Soc.* ***1973***, *95*, 6763; *Synthesis* ***1974***, 114; Steinbeck, K. *Tetrahedron Lett.* ***1978***, 1103; Boev, V.I. *J. Org. Chem. USSR* ***1981***, *17*, 1190.

[355]Matusamy, S.; Arulananda, S.; Babu, A.; Gunanathan, C. *Tetrahedron Lett.* ***2002*** *43*, 3133.

[356]Particularly the C–H insertion reaction, see Sulikowski, G.A.; Cha, K.L.; Sulikowski, M.M. *Tetrahedron Asymmetry*, ***1998***, *9*, 3145; Taber, D.F.; Meagley, R.P. *Tetrahedron Lett.* ***1994***, *35*, 7909.

[357]Ye, T.; McKervey, M.A. *Chem. Rev.* ***1994***, *94*, 1091.

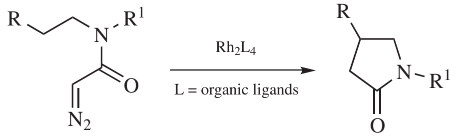
[358]Doyle, M.P. *Pure Appl. Chem.* ***1998***, *70*, 1123. See Taber, D.F.; Malcolm, S.C. *J. Org. Chem.* ***1998***, *63*, 3717 for a discussion of transition state geometry in rhodium mediated C—H insertion.

[359]Davies, H.M.; Hansen, T.; Churchill, M.R. *J. Am. Chem. Soc.* ***2000***, *122*, 3063; Davies, H.M.L.; Jin, Q.; Ren, P.; Kovalensky, A.Yu. *J. Org. Chem.* ***2002***, *67*, 4165; Davies, H.M.L.; Beckwith, R.E.J.; Antoulinakis, E.G.; Jin, Q. *J. Org. Chem.* ***2003***, *68*, 6126; Davies, H.M.L.; Jin, Q. *Org. Lett.* ***2004***, *6*, 1769. For a review, see Davies, H.M.L.; Loe, Ø. *Synthesis* ***2004***, 2595.

[360]For a review, see Davies, H.M.L.; Beckwith, R.E.J. *Chem. Rev.* ***2003***, *103*, 2861.

[361]Davies, H.M.L.; Ren, P.; Jin, Q. *Org. Lett.* ***2001***, *3*, 3587.

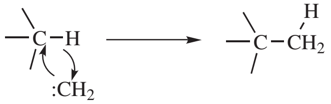
2-piperidone derivative.[362] The copper-catalyzed insertion of a diazo ester into an oxetane gives the ring-expanded tetrahydrofuran derivative.[363] Dirhodium catalyzed insertion into H–C^{sp2} bonds is also known,[364] and also H–C^{sp} bonds.[365] Insertion of diazoalkane and diazocarbonyl compounds can be catalyzed by copper compounds[366] and silver compounds[367] as well. Intramolecular insertion reactions are well known, and tolerate a variety of functional groups.[368] Intramolecular insertion at the α-carbon of a ketone by a diazoketone, using $TiCl_4$, gives a bicyclic 1,3-diketone.[369] A typical example is the insertion of the diazocarbonyl unit into the C–H bond to give the lactam.[370] Similar insertion at the α-carbon of an ether leads to cyclic ethers, with high enantioselectivity when a chiral ligand is used with a rhodium catalyst.[371] Similar insertion at the α-carbon of silyl ethers has been reported.[372] Aryl ketenes react with Me_3SiCHN_2 and then silica to give 2-indanone derivatives.[373]



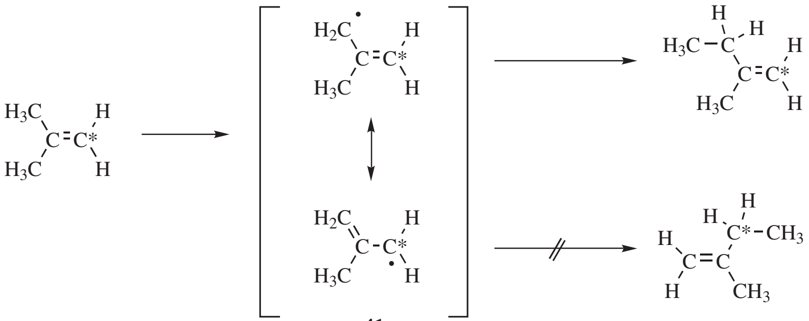
The mechanism[374] of the insertion reaction is not known with certainty, but there seem to be at least two possible pathways.

[362]Coutts, I.G.C.; Saint, R.E.; Saint, S.L.; Chambers-Asman, D.M. *Synthesis* ***2001***, 247.
[363]Lo, M.M.-C.; Fu, G.C. *Tetrahedron* ***2001***, *57*, 2621.
[364]Gibe, R.; Kerr, M.A. *J. Org. Chem.* ***2002***, *67*, 6247.
[365]Arduengo III, A.J.; Calabrese, J.C.; Davidson, F.; Dias, H.V.R.; Goerlich, J.R.; Krafczyk, R.; Marshall, W.J.; Tamm, M.; Schmutzler, R. *Helv. Chim. Acta.* ***1999***, *82*, 2348.
[366]See Caballero, A.; Díaz-Requejo, M.M.; Belderraín, T.R.; Nicasio, M.C.; Trofimenko, S.; Pérez, P. J. *J. Am. Chem. Soc.* ***2003***, *125*, 1446.
[367]Dias, H.V.R.; Browning, R.G.; Polach, S.A.; Diyabalanage, H.V.K.; Lovely, C.J. *J. Am. Chem. Soc.* ***2003***, *125*, 9270.
[368]For examples, see Marmsäter, F.P.; Murphy, G.K.; West, F.G. *J. Am. Chem. Soc.* ***2003***, *125*, 14724; Müller, P.; Polleux, P. *Helv. Chim. Acta* ***1994***, *77*, 645; Doyle, M.P.; Kalinin, A.V. *Synlett*, ***1995***, 1075; Watanabe, N.; Ohtake, Y.; Hashimoto, S.; Shiro, M.; Ikegami, S. *Tetrahedron Lett.* ***1995***, *36*, 1491; Maruoka, K.; Concepcion, A.B.; Yamamoto, H. *J. Org. Chem.* ***1994***, *59*, 4725; Spero, D.M.; Adams, J. *Tetrahedron Lett.* ***1992***, *33*, 1143.
[369]Muthusamy, S.; Babu, S.A.; Gunanathan, C. *Synth. Commun.* ***2001***, *31*, 1205.
[370]Doyle, M.P.; Protopopova, M.N.; Winchester, W.R.; Daniel, K.L. *Tetrahedron Lett.* ***1992***, *33*, 7819. See also, Wang, J.; Hou, Y.; Wu, P. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 2277; Clark, J.S.; Hodgson, P.B.; Goldsmith, M.D.; Street, L.J. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 3312. For a related reaction, see Yang, H.; Jurkauskas, V.; Mackintosh, N.; Mogren, T.; Stephenson, C.R.J.; Foster, K.; Brown, W.; Roberts, E. *Can. J. Chem.* ***2000***, *78*, 800.
[371]Davies, H.M.L.; Grazini, M.V.A.; Aouad, E. *Org. Lett.* ***2001***, *3*, 1475.
[372]Yoon, C.H.; Zaworotko, M.J.; Moulton, B.; Jung, K.W. *Org. Lett.* ***2001***, *3*, 3539.
[373]Dalton, A.M.; Zhang, Y.; Davie, C.P.; Danheiser, R.L. *Org. Lett.* ***2002***, *4*, 2465.
[374]For a discussion, see Bethell, D. *Adv. Phys. Org. Chem.* ***1969***, *7*, 153, pp. 190–194.

1. A simple one-step process involving a three-center cyclic transition state:



The most convincing evidence for this mechanism is that in the reaction between isobutene-1-^{14}C and carbene the product 2-methyl-1-butene was labeled only in the 1 position.[375] This rules out a free radical or a carbocation or carbanion intermediate. If **41** (or a corresponding ion) were an intermediate, resonance would ensure that some carbene attacked at the 1 position:



41

Not found

Other evidence is that retention of configuration, which is predicted by this mechanism, has been found in a number of instances.[376] An ylid intermediate was trapped in the reaction of :CH_2 with allyl alcohol.[377]

2. A free-radical process in which the carbene directly abstracts a hydrogen from the substrate to generate a pair of free radicals:

$$\mathrm{RH} + \mathrm{CH_2} \longrightarrow \mathrm{R}\bullet + \bullet\mathrm{CH_3}$$
$$\mathrm{R}\bullet + \bullet\mathrm{CH_3} \longrightarrow \mathrm{RCH_3}$$

One fact supporting this mechanism is that among the products obtained (beside butane and isobutane) on treatment of propane with CH_2 (generated by photolysis of diazomethane and ketene) were propene and ethane,[378] which could arise, respectively, by

$$2\ \mathrm{CH_3CH_2CH_2}\bullet \longrightarrow \mathrm{CH_3CH{=}CH_2} + \mathrm{CH_3CH_2CH_3} \quad \text{(disproportionation)}$$

[375]Doering, W. von E.; Prinzbach, H. *Tetrahedron* ***1959***, *6*, 24.

[376]See, for example, Kirmse, W.; Buschhoff, M. *Chem. Ber.* ***1969***, *102*, 1098; Seyferth, D.; Cheng, Y.M. *J. Am. Chem. Soc.* ***1971***, *93*, 4072.

[377]Sobery, W.; DeLucca, J.P. *Tetrahedron Lett.* ***1995***, *36*, 3315.

[378]Frey, H.M. *Proc. Chem. Soc.* ***1959***, 318.

and

$$CH_3CH_2CH_3 + :CH_2 \longrightarrow CH_3CH_2CH_2\bullet + \bullet CH_3$$
$$2\bullet CH_3 \longrightarrow CH_3CH_3$$

That this mechanism can take place under suitable conditions has been demonstrated by isotopic labeling[379] and by other means.[380] However, the formation of disproportionation and dimerization products does not always mean that the free-radical abstraction process takes place. In some cases, these products arise in a different manner.[381] We have seen that the product of the reaction between a carbene and a molecule may have excess energy (p. 288). Therefore it is possible for the substrate and the carbene to react by mechanism 1 (the direct-insertion process) and for the excess energy to cause the compound thus formed to cleave to free radicals. When this pathway is in operation, the free radicals are formed *after* the actual insertion reaction.

The mechanism of cyclopropylcarbene reactions has also been discussed.[382] It has been suggested[383] that singlet carbenes insert by the one-step direct-insertion process and triplets (which, being free radicals, are more likely to abstract hydrogen) by the free-radical process. In support of this suggestion is that CIDNP signals[384] (p. 269) were observed in the ethylbenzene produced from toluene and triplet CH_2, but not from the same reaction with singlet CH_2.[385] Carbenoids (e.g., compounds of the form R_2CMCl, see **12-39**) can insert into a C–H bond by a different mechanism, similar to pathway 2, but involving abstraction of a hydride ion rather than a hydrogen atom.[386]

An interesting insertion reaction involves $EtZnCH_2I$ and β-keto carbonyl compounds. The reaction of this reagent with *N,N*-dibutyl-**3**-oxobutanamide, for example, gives the methylene insertion product *N,N*-dibutyl 4-oxopentanamide.[387]

The reaction in which aldehydes are converted to methyl ketones, $RCHO + CH_2N_2 \rightarrow RCOCH_3$, while apparently similar, does not involve a free carbene intermediate. It is considered in Chapter 18 (**18-9**).

OS **VII**, 200.

[379]Halberstadt, M.L.; McNesby, J.R. *J. Chem. Phys.* ***1966***, *45*, 1666; McNesby, J.R.; Kelly, R.V. *Int. J. Chem. Kinet.*, ***1971***, *3*, 293.

[380]Ring, D.F.; Rabinovitch, B.S. *J. Am. Chem. Soc.* ***1966***, *88*, 4285; *Can J. Chem.* ***1968***, *46*, 2435.

[381]Bell, J.A. *Prog. Phys. Org. Chem.* ***1964***, *2*, 1, pp. 30–43.

[382]Cummins, J.M.; Porter, T.A.; Jones Jr., M. *J. Am. Chem. Soc.* ***1998***, *120*, 6473.

[383]Richardson, D.B.; Simmons, M.C.; Dvoretzky, I. *J. Am. Chem. Soc.* ***1961***, *83*, 1934.

[384]For a review of the use of CIDNP to study carbene mechanisms, see Roth, H.D. *Acc. Chem. Res.* ***1977***, *10*, 85.

[385]Roth, H.D. *J. Am. Chem. Soc.* ***1972***, *94*, 1761. See also Closs, G.L.; Closs, L.E. *J. Am. Chem. Soc.* ***1969***, *91*, 4549; Bethell, D.; McDonald, K. *J. Chem. Soc. Perkin Trans. 2* ***1977***, 671.

[386]See Oku, A.; Yamaura, Y.; Harada, T. *J. Org. Chem.* ***1986***, *51*, 3730; Ritter, R.H.; Cohen, T. *J. Am. Chem. Soc.* ***1986***, *108*, 3718.

[387]Hilgenkamp, R.; Zercher, C.K. *Tetrahedron* ***2001***, *57*, 8793.

F. Metal Electrophiles

12-22 Metalation With Organometallic Compounds

Metalation or **Metalo-de-hydrogenation**

$$RH + R'M \longrightarrow RM + R'M$$

Many organic compounds can be metalated by treatment with an organometallic compound.[388] Since the reaction involves a proton transfer, the equilibrium lies on the side of the weaker acid.[389] For example, fluorene reacts with butyllithium to give butane and 9-fluoryllithium. Since aromatic hydrocarbons are usually stronger acids than aliphatic ones, R is most often aryl. The most common reagent is butyllithium.[390] Normally, only active aromatic rings react with butyllithium. Benzene itself reacts very slowly and in low yield, although benzene can be metalated by butyllithium either in the presence of *t*-BuOK[391] or by *n*-butyllithium that is coordinated with various diamines.[392] Metalation of aliphatic RH is most successful when the carbanions are stabilized by resonance (allylic, benzylic, propargylic,[393] etc.) or when the negative charge is at an *sp* carbon (at triple bonds). Very good reagents for allylic metalation are trimethylsilylmethyl potassium Me_3SiCH_2K[394] and a combination of an organolithium compound with a bulky alkoxide (LICKOR superbase).[395] The former is also useful for benzylic positions. A combination of BuLi, *t*-BuOK, and tetramethylethylenediamine has been used to convert ethylene to vinylpotassium.[396] In certain cases, *gem*-dialkali metal or 1,1,1-trialkali metal compounds can be prepared.[397] Examples are the conversion of phenylacetonitrile

[388]For reviews, see Wardell, J.L., in Zuckerman,J.J. *Inorganic Reactions and Methods*, Vol. 11, VCH, NY, ***1988***, pp. 44–107; Wardell, J.L., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 4, Wiley, NY, pp. 1–157, 27–71; Narasimhan, M.S.; Mali, R.S. *Synthesis* ***1983***, 957; Biellmann, J.F.; Ducep, J. *Org. React.* ***1982***, *27*, 1; Gschwend, H.W.; Rodriguez, H.R. *Org. React.* ***1979***, *26*, 1; Mallan, J.M.; Bebb, R.L. *Chem. Rev.* ***1969***, *69*, 693.

[389]See Saá, J.M.; Martorell, G.; Frontera, A. *J. Org. Chem.* ***1996***, *61*, 5194 for a discussion of the mechanism of lithiation of aromatic species.

[390]For a review, see Durst, T., in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, Vol. 5, pt. B, Elsevier, NY, ***1984***, pp. 239–291, 265–279. For an article on the safe handling of RLi compounds, see Anderson, R. *Chem. Ind. (London)* ***1984***, 205.

[391]Schlosser, M. *J. Organomet. Chem.* ***1967***, *8*, 9. See also, Schlosser, M.; Katsoulos, G.; Takagishi, S. *Synlett*, ***1990***, 747.

[392]Eberhardt, G.G.; Butte, W.A. *J. Org. Chem.* ***1964***, *29*, 2928; Langer, Jr., A.W. *Trans. N.Y. Acad. Sci.* ***1965***, *27*, 741; Eastham, J.F.; Screttas, C.G. *J. Am. Chem. Soc.* ***1965***, *87*, 3276; Rausch, M.D.; Ciappenelli, D.J. *J. Organomet. Chem.* ***1967***, *10*, 127.

[393]For a review of directive effects in allylic and benzylic metallation, see Klein, J. *Tetrahedron* ***1983***, *39*, 2733. For a review of propargylic metallation, see Klein, J., in Patai, S. *The Chemistry of the Carbon-Carbon Triple Bond*, pt. 1, Wiley, NY, ***1978***, pp. 343–379.

[394]Hartmann, J.; Schlosser, M. *Helv. Chim. Acta* ***1976***, *59*, 453.

[395]Schlosser, M. *Pure Appl. Chem.* ***1988***, *60*, 1627. For sodium analogs, see Schlosser, M.; Hartmann, J.; Stähle, M.; Kramăr, J.; Walde, A.; Mordini, A. *Chimia*, ***1986***, *40*, 306.

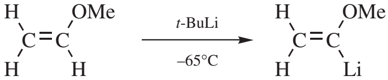
[396]Brandsma, L.; Verkruijsse, H.D.; Schade, C.; Schleyer, P.v.R. *J. Chem. Soc. Chem. Commun.* ***1986***, 260.

[397]For a review of di- and polylithium compounds, see Maercker, A.; Theis, M. *Top. Curr. Chem.* ***1987***, *138*, 1.

to 1,1-dilithiophenylacetonitrile ($PhCLi_2CN$)[398] and propyne to tetralithiopropyne ($Li_3CC{\equiv}CLi$)[399] in each case by treatment with excess butyllithium. The reaction can be used to determine relative acidities of very weak acids by allowing two R–H compounds to compete for the same R′M and to determine which proton in a molecule is the most acidic.[400]

In general, the reaction can be performed only with organometallics of active metals such as lithium, sodium, and potassium, but Grignard reagents abstract protons from a sufficiently acidic C–H bond, as in R–C≡C–H → R–C≡C–MgX. This is the best method for the preparation of alkynyl Grignard reagents.[401]

When a heteroatom, such as N, O, S,[402] or a halogen,[403] is present in a molecule containing an aromatic ring or a double bond, lithiation is usually quite regioselective.[404] The lithium usually bonds with the sp^2 carbon closest to the heteroatom, probably because the attacking species coordinates with the heteroatom.[405] Such reactions with compounds such as anisole are often called directed metalations.[406] In the case of aromatic rings this means attack at the ortho position,[407] but this is considered in **13-17**.



Ref. 408

[398]Kaiser, E.M.; Solter, L.E.; Schwartz, R.A.; Beard, R.D.; Hauser, C.R. *J. Am. Chem. Soc.* ***1971***, *93*, 4237. See also, Kowalski, C.J.; O'Dowd, M.L.; Burke, M.C.; Fields, K.W. *J. Am. Chem. Soc.* ***1980***, *102*, 5411.

[399]Priester, W.; West, R. *J. Am. Chem. Soc.* ***1976***, *98*, 8421, 8426, and references cited therein.

[400]For examples, see Broaddus, C.D.; Logan, T.J.; Flautt, T.J. *J. Org. Chem.* ***1963***, *28*, 1174; Finnegan, R.A.; McNees, R.S. *J. Org. Chem.* ***1964***, *29*, 3234; Shirley, D.A.; Hendrix, J.P. *J. Organomet. Chem.* ***1968***, *11*, 217.

[401]For a review of the synthetic applications of metallation by Grignard reagents at positions other than at triple bonds, see Blagoev, B.; Ivanov, D. *Synthesis* ***1970***, 615.

[402]For example, see Figuly, G.D.; Loop, C.K.; Martin, J.C. *J. Am. Chem. Soc.* ***1989***, *111*, 654; Block, E.; Eswarakrishnan, V.; Gernon, M.; Ofori-Okai, G.; Saha, C.; Tang, K.; Zubieta, J. *J. Am. Chem. Soc.* ***1989***, *111*, 658; Smith, K.; Lindsay, C.M.; Pritchard, G.J. *J. Am. Chem. Soc.* ***1989***, *111*, 665.

[403]Fluorine is an especially powerful ortho director in lithiation of aromatic systems: Gilday, J.P.; Negri, J.T.; Widdowson, D.A. *Tetrahedron* ***1989***, *45*, 4605.

[404]For a review of regioselective lithiation of heterocycles, see Katritzky, A.R.; Lam, J.N.; Sengupta, S. *Prog. Heterocycl. Chem.* ***1989***, *1*, 1.

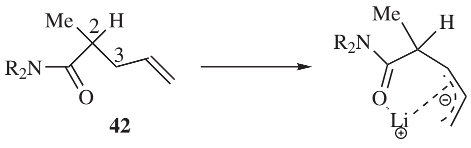
[405]For many examples with references, see Ref. 388; Beak, P.; Meyers, A.I. *Acc. Chem. Res.* ***1986***, *19*, 356; Beak, P.; Snieckus, V. *Acc. Chem. Res.* ***1982***, *15*, 306; Snieckus, V. *Bull. Soc. Chim. Fr.* ***1988***, 67; Narasimhan, N.S.; Mali, R.S. *Top. Curr. Chem.* ***1987***, *138*, 63; Reuman, M.; Meyers, A.I. *Tetrahedron* ***1985***, *41*, 837; and the papers in *Tetrahedron* ***1983***, *39*, 1955.

[406]Slocum, D.W.; Moon, R.; Thompson, J.; Coffey, D.S.; Li, J.D.; Slocum, M.G.; Siegel, A.; Gayton-Garcia, R. *Tetrahedron Lett.* ***1994***, *35*, 385; Slocum, D.W.; Coffey, D.S.; Siegel, A.; Grimes, P. *Tetrahedron Lett.* ***1994***, *35*, 389.

[407]For reviews of ortho metallation, see Snieckus, V. *Chem. Rev.* ***1990***, *90*, 879; *Pure Appl. Chem.* ***1990***, *62*, 2047. For a discussion of the mechanism, see Bauer, W.; Schleyer, P. v.R. *J. Am. Chem. Soc.* ***1989***, *111*, 7191.

[408]Baldwin, J.E.; Höfle, G.A.; Lever, Jr., O.W. *J. Am. Chem. Soc.* ***1974***, *96*, 7125.

In the case of γ,δ-unsaturated disubstituted amides (**42**),the lithium does not go to the closest position, but in this case too the regiochemistry is controlled

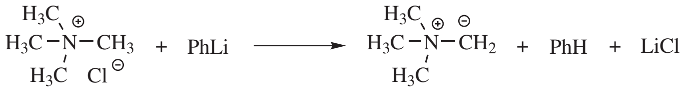


by coordination to the oxygen.[409]

The mechanism involves an attack by R′− (or a polar R′) on the *hydrogen*[410] (an acid–base reaction) Evidence is that resonance effects of substituents in R seem to make little difference. When R is aryl, OMe and CF_3 *both* direct ortho, while isopropyl directs meta and para (mostly meta).[411] These results are exactly what would be expected from pure field effects, with no contribution from resonance effects, which implies that attack occurs at the hydrogen and not at R. Other evidence for the involvement of H in the rate-determining step is that there are large isotope effects.[412] The nature of R′ also has an effect on the rate. In the reaction between triphenylmethane and R′Li, the rate decreased in the order R′ = allyl > Bu > Ph > vinyl > Me, although this order changed with changing concentration of R′Li, because of varying degrees of aggregation of the R′Li.

With respect to the reagent, this reaction is a special case of **12-24**.

A closely related reaction is formation of nitrogen ylids[414] from quaternary ammonium salts (see **17-8**):



Phosphonium salts undergo a similar reaction (see **16-44**).

OS **II**, 198; **III**, 413, 757; **IV**, 792; **V**, 751; **VI**, 436, 478, 737, 979; **VII**, 172, 334, 456, 524; **VIII**, 19, 391, 396, 606.

[409]Beak, P.; Hunter, J.E.; Jun, Y.M.; Wallin, A.P. *J. Am. Chem. Soc.* ***1987***, *109*, 5403. See also, Stork, G.; Polt, R.L.; Li, Y.; Houk, K.N. *J. Am. Chem. Soc.* ***1988***, *110*, 8360; Barluenga, J.; Foubelo, F.; Fañanas, F.J.; Yus, M. *J. Chem. Res. (S)* ***1989***, 200.

[410]Benkeser, R.A.; Trevillyan, E.A.; Hooz, J. *J. Am. Chem. Soc.* ***1962***, *84*, 4971.

[411]Bryce-Smith, D. *J. Chem. Soc.* ***1963***, 5983; Benkeser, R.A.; Hooz, J.; Liston, T.V.; Trevillyan, E.A. *J. Am. Chem. Soc.* ***1963***, *85*, 3984.

[412]Bryce-Smith, D.; Gold, V.; Satchell, D.P.N. *J. Chem. Soc.* ***1954***, 2743; Pocker, Y.; Exner, J.H. *J. Am. Chem. Soc.* ***1968***, *90*, 6764.

West, P.; Waack, R.; Purmort, J.I. *J. Am. Chem. Soc.* ***1970***, *92*, 840.

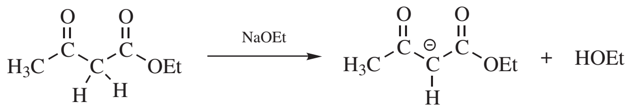
[414]Zugravescu, I.; Petrovanu, M. *Nitrogen-Ylid Chemistry*, McGraw-Hill, NY, ***1976***, pp 251–283; Kröhnke, F. *Berchtt* ***1935***, *68*, 1177; Wittig, G.; Wetterling, M. *Ann.* ***1947***, *557*, 193; Wittig, G.; Rieber, M. *Ann.* ***1949***, *562*, 177; Wittig, G.; Polster, R. *Ann.* ***1956***, *599*, 1.

12-23 Metalation With Metals and Strong Bases

Metalation or **Metalo-de-hydrogenation**

$$2\ RH + M \longrightarrow 2\ RM + H_2$$

Organic compounds can be metalated at suitably acidic positions by active metals and by strong bases.[415] The reaction has been used to study the acidities of very weak acids (see p. 250). The conversion of terminal alkynes to acetylid ions is one important application.[416] Synthetically, an important use of the method is to convert aldehydes and ketones,[417] carboxylic esters, and similar compounds to their enolate forms,[418] for example,



for use in nucleophilic substitutions (**10-67**, **10-68**, and **13-14**) and in additions to multiple bonds (**15-24** and **16-53**). It has been shown that lithiation with lithium amides can also be regioselective (see **12-22**).[419] Lithium enolates exist as aggregates in solution.[420] For very weak acids, the most common reagents for synthetic purposes are lithium amides, especially LDA, which has the structure $(i\text{Pr})_2\text{NLi}$.[421] The mechanism for this deprotonation reaction has been studied,[422] as has the rate of deprotonation.[423]

OS **I**, 70, 161, 490; **IV**, 473; **VI**, 468, 542, 611, 683, 709; **VII**, 229, 339. Conversions of ketones or esters to enolates are not listed.

[415]For a review, see Durst, T., in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, Vol. 5, pt. B, Elsevier, NY, ***1984***, pp. 239–291. For reviews with respect to lithium, see Wardell, J.L. Ref. 388; Wakefield, B.J. *Organolithium Methods*, Academic Press, NY, ***1988***, pp. 32–44.

[416]For a review, see Ziegenbein, W., in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 170–185. For an improved method, see Fisch, A.; Coisne, J.M.; Figeys, H.P. *Synthesis* ***1982***, 211.

[417]Hegarty, A.F.; Dowling, J.P.; Eustace, S.J.; McGarraghy, M. *J. Am. Chem. Soc.* ***1998***, *120*, 2290.

[418]For a review, see Caine, D. in Augustine, R.L. *Carbon–Carbon Bond Formation*, Vol. 1, Marcel Dekker, NY,***1979***, pp. 95–145, 284–291.

[419]For example, see Comins, D.L.; Killpack, M.O. *J. Org. Chem.* ***1987***, *52*, 104. See Xie, L.; Isenberger, K.M.; Held, G.; Dahl, M. *J. Org. Chem.* ***1997***, *62*, 7516 for steric versus electronic effects in kinetic enolate formation.

[420]Abu-Hasanayn, F.; Stratakis, M.; Streitwieser, A. *J. Org. Chem.* ***1995***, *60*, 4688; Jackman, L.M.; Szeverenyi, N.M. *J. Am. Chem. Soc.* ***1977***, *99*, 4954; Jackman, L.M.; Lange, B.C. *J. Am. Chem. Soc.* ***1981***, *103*, 4494; House, H.O.; Gall, M.; Olmstead, H.D. *J. Org. Chem.* ***1971***, *36*, 2361; Zook, H.D.; Kelly, W.L.; Posey, I.Y. *J. Org. Chem.* ***1968***, *33*, 3477; Stork, G.; Hudrlik, P.F. *J. Am. Chem. Soc.* ***1968***, *90*, 4464.

[421]The alkali metal hydrides, LiH, NaH, and KH, when prepared in a special way, are very rapid metallation agents: Klusener, P.A.A.; Brandsma, L.; Verkruijsse, H.D.; Schleyer, P.v.R.; Friedl, T.; Pi, R. *Angew. Chem. Int. Ed.* ***1986***, *25*, 465.

[422]Romesberg, F.E.; Collum, D.B. *J. Am. Chem. Soc.* ***1995***, *117*, 2166; Sun, X.; Kenkre, S.L.; Remenar, J.F.; Gilchrist, J.H. *J. Am. Chem. Soc.* ***1997***, *119*, 4765.

[423]Majewski, M.; Nowak, P. *Tetrahedron Lett.* ***1998***, *39*, 1661.

METALS AS LEAVING GROUPS

A. Hydrogen as the Electrophile

12-24 Replacement of Metals by Hydrogen

Hydro-de-metallation or **Demetallation**

$$RM + HA \longrightarrow RH + MA$$

Organometallic compounds, including enolate anions, react with acids in reactions in which the metal is replaced by hydrogen.[424] The R group may be aryl (see **11-41**). The reaction is often used to introduce deuterium or tritium into susceptible positions. For Grignard reagents, water is usually a strong enough acid, but stronger acids are also used. An important method for the reduction of alkyl halides consists of the process RX → RMgX → RH.

Other organometallic compounds that are hydrolyzed by water are those of sodium, potassium, lithium, zinc, and so on, the ones high in the electromotive series. Enantioselective protonation of lithium enolates[425] and cyclopropyllithium compounds[426] have been reported. When the metal is less active, stronger acids are required. For example, R_2Zn compounds react explosively with water, R_2Cd slowly, and R_2Hg not at all, although the latter can be cleaved with concentrated HCl. However, this general statement has many exceptions, some hard to explain. For example, BR_3 compounds are completely inert to water, and GaR_3 at room temperature cleave just one R group, but AlR_3 react violently with water. However, BR_3 can be converted to RH with carboxylic acids.[427] For less active metals it is often possible to cleave just one R group from a multivalent metal. For example,

$$R_2Hg + HCl \longrightarrow RH + RHgCl$$

Organometallic compounds of less active metals and metalloids (e.g., silicon,[428] antimony, and bismuth, are quite inert to water. Organomercury compounds (RHgX or R_2Hg) can be reduced to RH by H_2, $NaBH_4$, or other reducing agents.[429] The reduction with $NaBH_4$ takes place by a free-radical mechanism.[430] Alkyl–Si

[424]For reviews, see Abraham, M.H.; Grellier, P.L., in Hartley, FR.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 2, Wiley, NY, pp. 25–149, 105–136; Abraham, M.H. *Comprehensive Chemical Kinetics*, Bamford, C.H.; Tipper, C.F.H., eds., Vol. 12, Elsevier, NY, ***1973***, pp. 107–134; Jensen, F.R.; Rickborn, B. *Electrophilic Substitution of Organomercurials*, McGaw-Hill, NY, ***1968***, pp. 45–74; Schlosser, M. *Angew. Chem. Int. Ed.* ***1964***, *3*, 287, 362; *Newer Methods Prep. Org. Chem.* ***1968***, *5*, 238.

[425]Fehr, C. *Angew. Chem. Int. Ed.* ***1996***, *35*, 2567.

[426]Walborsky, H.M.; Ollman, J.; Hamdouchi, C.; Topolski, M. *Tetrahedron Lett.* ***1992***, *33*, 761.

[427]Brown, H.C.; Murray, K.J. *Tetrahedron* ***1986***, *42*, 5497; Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, pp. 242–244.

[428]For a review of hydro-de-silylation of allylic and vinylic silanes, see Fleming, I.; Dunoguès, J.; Smithers, R. *Org. React.* ***1989***, *37*, 57, see pp. 89–97, 194–243. Also see, **10-12**

[429]For a review, see Makarova, L.G. *Organomet. React.* ***1970***, *1*, 119, see pp. 251–270, 275–300.

[430]For a review of this and other free-radical reactions of organomercury compounds, see Barluenga, J.; Yus, M. *Chem. Rev.* ***1988***, *88*, 487.

bonds can be cleaved by H_2SO_4, for example, $HOOCCH_2CH_2SiMe_3 \rightarrow 2\ CH_4 + (HOOCCH_2CH_2SiMe_2)_2O$.[431]

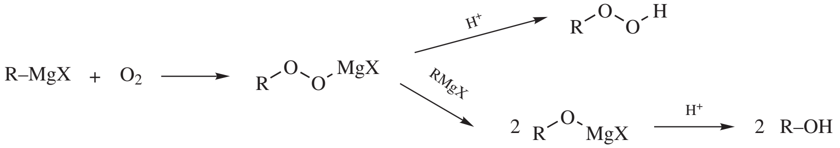
When the hydrogen of the HA is attached to carbon, this reaction is the same as **12-22**.

We do not list the many hydrolyses of sodium or potassium enolates, and so on found in *Organic Syntheses*. The hydrolysis of a Grignard reagent to give an alkane is found at OS **II**, 478; the reduction of a vinylic tin compound at OS **VIII**, 381; and the reduction of an alkynylsilane at OS **VIII**, 281.

B. Oxygen Electrophiles

12-25 The Reaction between Organometallic Reagents and Oxygen[432]

Hydroperoxy-de-metalation; Hydroxy-de-metalation



Oxygen reacts with Grignard reagents to give either hydroperoxides[433] or alcohols. The reaction can be used to convert alkyl halides to alcohols without side reactions. With aryl Grignard reagents yields are lower and only phenols are obtained, not hydroperoxides. Because of this reaction, oxygen should be excluded when Grignard reagents are prepared and used in various reactions.

Most other organometallic compounds also react with oxygen. Trialkylboranes and alkyldichloroboranes $RBCl_2$ can be conveniently converted to hydroperoxides by treatment with oxygen followed by hydrolysis.[434] Dilithiated carboxylic acids (see **10-70**) react with oxygen to give (after hydrolysis) α-hydroxy carboxylic acids.[435] There is evidence that the reaction between Grignard reagents and oxygen involves a free-radical mechanism.[436]

The 1,1-dimetallic compounds $R_2C(SnMe_3)ZnBr$ were oxidized by dry air at -10 to 0°C in the presence of Me_3SiCl to give aldehydes or ketones $R_2C{=}O$.[437]

OS **V**, 918. See also, OS **VIII**, 315.

[431]Sommer, L.H.; Marans, N.S.; Goldberg, G.M.; Rockett, J.; Pioch, R.P. *J. Am. Chem. Soc.* ***1951***, *73*, 882. See also, Abraham, M.H.; Grellier, P.L., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 2, Wiley, NY, p. 117.

[432]For a monograph, see Brilkina, T.G.; Shushunov, V.A. *Reactions of Organometallic Compounds with Oxygen and Peroxides*, CRC Press, Boca Raton, FL, ***1969***. For a review, see Wardell, J.L.; Paterson, E.S., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 2, Wiley, NY, ***1985***, pp. 219–338, see pp. 311–316.

[433]For the preparation of propargyl hydroperoxides, see Harada, T.; Kutsuwa, E. *J. Org. Chem.* ***2003***, *68*, 6716.

[434]Brown, H.C.; Midland, M.M. *Tetrahedron* ***1987***, *43*, 4059.

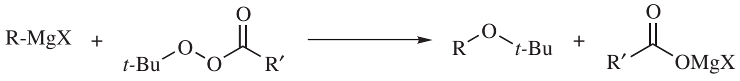
[435]Moersch, G.W.; Zwiesler, M.L. *Synthesis* ***1971***, 647; Adam, W.; Cueto, O. *J. Org. Chem.* ***1977***, *42*, 38.

[436]Davies, A.G.; Roberts, B.P. *J. Chem. Soc. B*, ***1969***, 317; Walling, C.; Cioffari, A. *J. Am. Chem. Soc.* ***1970***, *92*, 6609; Garst, J.F.; Smith, C.D.; Farrar, A.C. *J. Am. Chem. Soc.* ***1972***, *94*, 7707. For a review, see Davies, A.G. *J. Organomet. Chem.* ***1980***, *200*, 87.

[437]Knochel, P.; Xiao, C.; Yeh, M.C.P. *Tetrahedron Lett.* ***1988***, *29*, 6697.

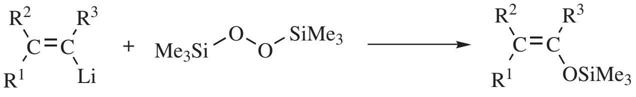
12-26 Reaction between Organometallic Reagents and Peroxides

tert-But**oxy-de-metalation**



A convenient method of preparation of *tert*-butyl ethers consists of treating Grignard reagents with *tert*-butyl acyl peroxides.[438] Both alkyl and aryl Grignard reagents can be used. The application of this reaction to Grignard reagents prepared from cyclopropyl halides permits cyclopropyl halides to be converted to *tert*-butyl ethers of cyclopropanols,[439] which can then be easily hydrolyzed to the cyclopropanols. The direct conversion of cyclopropyl halides to cyclopropanols by **10-1** is not generally feasible, because cyclopropyl halides do not generally undergo nucleophilic substitutions without ring opening.

Vinylic lithium reagents (**43**) react with silyl peroxides to give high yields of silyl enol ethers with retention of configuration.[440] Since the preparation of **43** from vinylic halides



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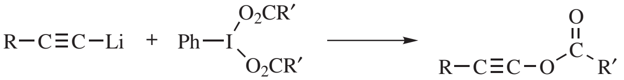
(**12-39**) also proceeds with retention, the overall procedure is a method for the stereospecific conversion of a vinylic halide to a silyl enol ether. In a related reaction, alkynyl esters can be prepared from lithium acetylides and phenyliodine(III) dicarboxylates.[441]



OS **V**, 642, 924.

12-27 Oxidation of Trialkylboranes to Borates

$$R_3B \xrightarrow[\text{NaOH}]{H_2O_2} (RO)_3B \longrightarrow 3\ ROH + B(OH)_3$$

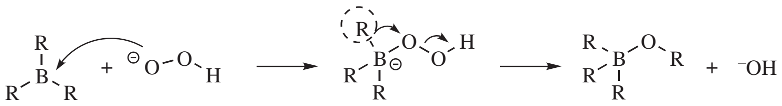
[438]Lawesson, S.; Frisell, C.; Denney, D.B.; Denney, D.Z. *Tetrahedron* ***1963***, *19*, 1229. For a monograph on the reactions of organometallic compounds with peroxides, see Brilkina, T.G.; Shushunov, V.A. *Reactions of Organometallic Compounds with Oxygen and Peroxides*, CRC Press, Boca Raton, FL, ***1969***. For a review, see Razuvaev, G.A.; Shushunov, V.A.; Dodonov, V.A.; Brilkina, T.G., in Swern, D. *Organic Peroxides*, Vol. 3, Wiley, NY, ***1972***, pp. 141–270.

[439]Longone, D.T.; Miller, A.H. *Tetrahedron Lett.* ***1967***, 4941.

[440]Davis, F.A.; Lal, G.S.; Wei, J. *Tetrahedron Lett.* ***1988***, *29*, 4269.

[441]Stang, P.J.; Boehshar, M.; Wingert, H.; Kitamura, T. *J. Am. Chem. Soc.* ***1988***, *110*, 3272.

The reaction of alkenes with borane, monoalkyl and dialkylboranes leads to a new organoborane (see **15-16**). Treatment of organoboranes with alkaline H_2O_2 oxidizes trialkylboranes to esters of boric acid.[442] This reaction does not affect double or triple bonds, aldehydes, ketones, halides, or nitriles that may be present elsewhere in the molecule. There is no rearrangement of the R group itself, and this reaction is a step in the hydroboration method of converting alkenes to alcohols (**15-16**). The mechanism has been formulated as involving initial formation of an ate complex when the hydroperoxide anion attacks the electrophilic boron atom. Subsequent rearrangement from boron to oxygen,[442] as shown, leads to the B–O–R unit.



Similar migration of the other two R groups and hydrolysis of the B–O bonds leads to the alcohol and boric acid. Retention of configuration is observed in R. Boranes can also be oxidized to borates in good yields with oxygen,[443] with sodium perborate $NaBO_3$,[444] and with trimethylamine oxide, either anhydrous[445] or in the form of the dihydrate.[446] The reaction with oxygen is free radical in nature.[447]

OS **V**, 918; **VI**, 719, 852, 919.

12-28 Preparation of Borates and Boronic Acids

$$\text{R-M} \longrightarrow \text{R-B(OH)}_2$$

$$\text{Ar-M} \longrightarrow \text{Ar-B(OH)}_2$$

$$\text{R-OH} + \text{BX}_3 \text{ or B(OH)}_3 \longrightarrow \text{B(OR)}_3$$

Alkylboronic acids and arylboronic acids, $RB(OH)_2$, and $ArB(OH)_2$, respectively, are increasingly important in organic chemistry. The palladium catalyzed coupling reaction of aryl halides and aryl triflates with arylboronic acids (the Suzuki–Miyaura

[442]For reviews, see Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Aademic Press, NY, ***1988***, pp. 244–249; Brown, H.C. *Boranes in Organic Chemistry*; Cornell University Press, Ithaca, NY, ***1972***, pp. 321–325; Matteson, D.S., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, pp. 307–409, 337–340. See also, Brown, H.C.; Snyder, C.; Subba Rao, B.C.; Zweifel, G. *Tetrahedron* ***1986***, *42*, 5505.

[443]Brown, H.C.; Midland, M.M.; Kabalka, G.W. *J. Am. Chem. Soc.* ***1971***, *93*, 1024; *Tetrahedron* ***1986***, *42*, 5523.

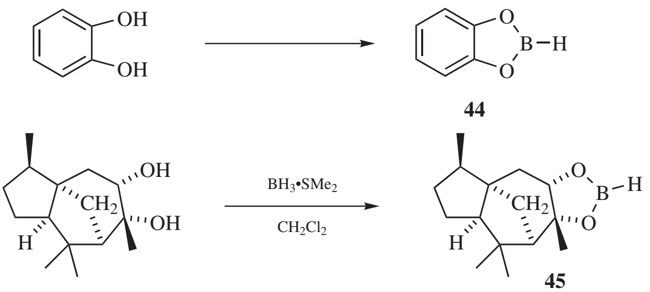
[444]Kabalka, G.W.; Shoup, T.M.; Goudgaon, N.M. *J. Org. Chem.* ***1989***, *54*, 5930.

[445]Köster, R.; Arora, S.; Binger, P. *Angew. Chem. Int. Ed.* ***1969***, *8*, 205.

[446]Kabalka, G.W.; Hedgecock, Jr., H.C. *J. Chem. Educ.* ***1975***, *52*, 745; Kabalka, G.W.; Slayden, S.W. *J. Organomet. Chem.* ***1977***, *125*, 273.

[447]Mirviss, S.B. *J. Am. Chem. Soc.* ***1961***, *83*, 3051; *J. Org. Chem.* ***1967***, *32*, 1713; Davies, A.G.; Roberts, B.P. *Chem. Commun.* ***1966***, 298; Midland, M.M.; Brown, H.C. *J. Am. Chem. Soc.* ***1971***, *93*, 1506.

reaction, **13-12**) is probably the most notable example. A simple synthesis involve the reaction of a Grignard reagent, such as phenylmagnesium bromide with an alkyl borate to give phenylboronic acid.[448] Alkylboronic acids are similarly prepared.[449] Note that boronic acids are subject to cyclic trimerization with loss of water to form boroxines. Trimethylborate, $B(OMe)_3$, can be used in place of tri-*n*-butyl borate.[450] Newer methods involve the palladium-mediated borylation of alcohols with bis(pinacolato)diboron[451] or pinacolborane,[452] but deprotection of the boronate esters can be a problem. Diolboranes, such as catecholborane **44**,[453] are prepared by the reaction of a diol with borane. Cedranediolborane (**45**, prepared from the cedrane-8,9-diol[454] by treatment with borane•dimethyl sulfide) can be coupled to aryl iodides with a palladium catalyst, and generates the free boronic acid by treatment with diethanolamine and then aqueous acid.[455] Boronate esters are often prepared as a means to purify the organoboron species, but some of these esters are hydrolytically unstable and difficult to deal with upon completion of the reaction.[456]



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Alkeneboronic esters and acids are also readily available, as in the addition of vinylmagnesium chloride[457] to trimethyl borate below −50°C, followed by hydrolysis.[458]

[448]Bean, F.R.; Johnson, J.R. *J. Am. Chem Soc.* ***1932***, *54*, 4415. For a review, see Lappert, M.F. *Chem. Rev.* ***1956***, *56*, 959.
[449]Khotinsky, E.; Melamed, M. *Chem. Ber.* ***1909***, *42*, 3090.
[450]Soloway, A.H. *J. Am. Chem. Soc.* ***1959***, *81*, 3017.
[451]Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* ***1995***, *60*, 7508.
[452]Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* ***2000***, *65*, 164; Song, Y.L. *Synlett* ***2000***, 1210.
[453]Brown, H.C.; Gupta, S.K. *J. Am. Chem. Soc.* ***1972***, *94*, 4370; Kanth, J. V. B.; Periasamy, M.; Brown, H.C. *Org. Process Res. Dev.* ***2000***, *4*, 550.
[454]Narula, A.S.; Trifilieff, E.; Bang, L.; Ourisson, G. *Tetrahedron Lett.* ***1977***, *18*, 3959; Song, Y.; Ding, Z.; Wang, Q.; Tao, F. *Synth. Commun.* ***1998***, *28*, 3757.
[455]Song, Y.-L.; Morin, C. *Synlett* ***2001***, 266.
[456]Lightfoot, A.P.; Maw, G.; Thirsk, C.; Twiddle, S.J.R.; Whiting, A. *Tetrahedron Lett.* ***2003***, *44*, 7645.
[457]Ramsden, H.E.; Leebrick, J.R.; Rosenberg, S.D.; Miller, E.H.; Walburn, J.J.; Balint, A.E.; Cserr, R. *J. Org, Chem.*, ***1957***, *22*, 1602.
[458]D.S. Matteson *J. Am. Chem. Soc.* ***1960***, 82, 4228; Matteson, D.S. *Acc. Chem. Res.* ***1970***, *3*, 186; Matteson, D.S. *Progr. Boron Chem.* ***1970***, *3*, 117.

A nonaqueous workup procedure has been reproted for the preparation of arylboronic esters [ArB(OR'$_2$)].[459] Uncontrollable polymerization or oxidation of much of the boronic acid occurred during the final stages of the isolation procedure, but could be avoided by *in situ* conversion to the dibutyl ester by adding the crude product to 1-butanol. The samarium(III)-catalyzed hydroboration of olefins with catecholborane is a good synthesis of boronate esters.[460]

Trialkyl borates (called orthoborates) can be prepared by heating the appropriate alcohol with boron trichloride in a sealed tube, but the procedure works well only for relatively simple alkyl groups.[461] Heating alcohols with boron trioxide (B_2O_3) in an autoclave at 110–170°C give the trialkyl borate.[462] Boric acid can be used for the preparation of orthoborates[463] by heating with alcohols in the presence of either hydrogen chloride or concentrated sulfuric acid. Removal of water as an azeotrope with excess alcohol improves the yield,[464] and good yields can be obtained for trialkyl borates[465] and even for triphenyl borate.[466] This method is unsuccessful for those borates whose parent alcohols do not form azeotropes with water and for the tertiary alkyl borates,[467] impure samples are usually obtained.[468]

Potassium organotrifluoroborates (RBF_3K) are readily prepared by the addition of inexpensive KHF_2 to a variety of organoboron intermediates.[469] They are monomeric, crystalline solids that are readily isolated and indefinitely stable in the air. These reagents can be used in several of the applications where boronic acids or esters are used (**13-10–13-13**).[470] Note that vinylboronic acid and even vinylboronate esters are unstable to polymerization,[471] whereas the analogous vinyltrifluoroborate is readily synthesized and completely stable.[472]

O.S. 13, 16; **81**, 134.

[459]Wong, K.-T.; Chien, Y.-Y.; Liao, Y.-L.; Lin, C.-C.; Chou, M.-Y.; Leung, M.-K. *J. Org. Chem.* ***2002***, *67*, 1041.

[460]Evans, D.A.; Muci, A.R.; Stuermer, R. *J. Org. Chem.*, ***1993***, *58*, 5307.

[461]Councler, C. *Ber.* ***1876***, *9*, 485; ***1877***, *10*, 1655; ***1878***, *11*, 1106.

[462]Schiff, H. *Ann. Suppl.* ***1867***, *6*, 158; Councler, C. *J. Prakt. Chem.* ***1871***, *16*, 371.

[463]Cohn, G. *Pharm. Zentr.* ***1911***, *62*, 479.

[464]Bannister, W.J. U.S. Patent 1,668,797 (*Chem. Abstr.* ***1928***, *22*:2172).

[465]Ballard, S.A, U.S. Patent 2,431,224 (*Chem. Abstr.* ***1948***, *42*:1960); Haider, S.Z.; Khundhar, M.H.; Siddiqulah, Md. *J. Appl. Chem.* ***1954***, *4*, 93; Scattergood, A.; Miller, W.H.; Gammon, J. *J. Am. Chem. Soc.* ***1945***, *67*, 2150; Wuyts, H.; Duquesne, A. *Bull. Soc. Chim. Belg.* ***1939***, *48*, 77.

[466]Colclough, T.; Gerrard, W.; Lappert, M.F. *J. Chem. Soc.* ***1955***, 907.

[467]Haider, S.Z.; Khundhar, M.H.; Siddiqullah, Md. *J. Appl. Chem.* ***1954***, *4*, 93; Scattergood, A., Miller, W.H.; Gammon, J. *J. Am. Chem. Soc.* ***1945***, *67*, 2150.

[468]Ahmad, T.; Khundkar, M.H. *Chem. Ind.* ***1954***, 248.

[469]Vedejs, E.; Chapman, R.W.; Fields, S.C.; Lin, S.; Schrimpf, M.R. *J. Org. Chem.* ***1995***, *60*, 3020; Vedejs, E.; Fields, S.C.; Hayashi, R.; Hitchcock, S.R.; Powell, D.R.; Schrimpf, M.R. *J. Am. Chem. Soc.* ***1999***, *121*, 2460.

[470]Molander, G.A.; Ito, T. *Org. Lett.* ***2001***, *3*, 393; Molander, G.A.; Biolatto, B. *Org. Lett.* ***2002***, *4*, 1867; Molander, G.A.; Biolatto, B. *J. Org. Chem.* ***2003***, *68*, 4302; Molander, G.A.; Katona, B.W.; Machrouhi, F. *J. Org. Chem.* ***2002***, *67*, 8416; Molander, G.A.; Yun, C.; Ribagorda, M.; Biolatto, B. *J. Org. Chem.* ***2003***, *68*, 5534; Molander, G.A.; Ribagorda, M. *J. Am. Chem. Soc.* ***2003***, *125*, 11148.

[471]Matteson, D.S. *J. Am. Chem. Soc.* ***1960***, *82*, 4228.

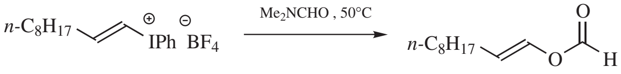
[472]Molander, G.A.; Felix, L.A. *J. Org. Chem.* ***2005***, *70*, 3950.

12-29 Oxygenation of Organometallic Reagents and Other Substrates to *O*-Esters and Related Compounds

$$R\text{–}M \longrightarrow R\text{–}OOCR'$$

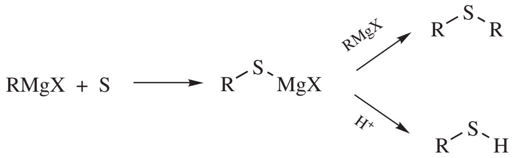
$$R\text{–}Y \longrightarrow R\text{–}OOCR'$$

In some cases, it is possible to oxygenated a nonaromatic carbon atom using various reagents, where the product is an *O*- ester rather than an alcohol. In one example, a vinyl iodonium salt was heated with DMF to product the corresponding formate ester.[473]



C. Sulfur Electrophiles

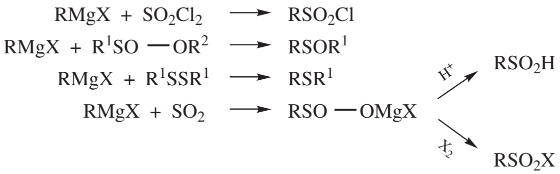
12-30 Conversion of Organometallic Reagents to Sulfur Compounds



Thio-de-dimetallo-*aggre*-substitution

Mercapto-de-metallation

Thiols and sulfides are occasionally prepared by treatment of Grignard reagents with sulfur.[474] Analogous reactions are known for selenium and tellurium compounds. Grignard reagents and other organometallic



compounds[475] react with sulfuryl chloride to give sulfonyl chlorides,[476] with esters of sulfinic acids to give (stereospecifically) sulfoxides,[477] with disulfides to give

[473]Ochiai, M.; Yamamoto, S.; Sato, K. *Chem. Commun.* ***1999***, 1363.

[474]For reviews of the reactions in this section, see Wardell, J.L.; Paterson, E.S., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 2, Wiley, NY, ***1985***, pp. 316–323; Wardell, J.L., in Patai, S. *The Chemistry of the Thiol Group*, pt. 1, Wiley, NY, ***1974***, pp. 211–215; Wakefield, B.J. *Organolithium Methods*, Academic Press, NY, ***1988***, pp. 135–142.

[475]For a discussion of conversions of organomercury compounds to sulfur-containing compounds, see Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, ***1985***, pp. 210–216.

[476]Bhattacharya, S.N.; Eaborn, C.; Walton, D.R.M. *J. Chem. Soc. C* ***1968***, 1265. For similar reactions with organolithiums, see Quast, H.; Kees, F. *Synthesis* ***1974***, 489; Hamada, T.; Yonemitsu, O. *Synthesis* ***1986***, 852.

[477]Harpp, D.N.; Vines, S.M.; Montillier, J.P.; Chan, T.H. *J. Org. Chem.* ***1976***, *41*, 3987.

sulfides,[478] and with SO_2 to give sulfinic acid salts[479] which can be hydrolyzed to sulfinic acids or treated with halogens to give sulfonyl halides.[480]

OS **III**, 771; **IV**, 667; **VI**, 533, 979.

D. Halogen Electrophiles

12-31 Halo-de-metalation

$$RMgX + I_2 \longrightarrow RI + MgIX$$

Grignard reagents react with halogens to give alkyl halides. The reaction is useful for the preparation of iodo compounds from the corresponding chloro or bromo compounds. The reaction is not useful for preparing chlorides, since the reagents RMgBr and RMgI react with Cl_2 to give mostly RBr and RI, respectively.[481]

Most organometallic compounds, both alkyl and aryl, also react with halogens to give alkyl or aryl halides.[482] The reaction can be used to convert acetylide ions to 1-haloalkynes.[483] Since acetylide ions are easily prepared from alkynes (**12-23**), this provides a means of accomplishing the conversion $RC{\equiv}CH \rightarrow RC{\equiv}CX$. Vinyliodonium tetrafluoroborates were converted to vinyl fluorides by heating.[484] Similarly, vinyl trifluoroborates were converted to the vinyl iodide with NaI and chloramine-T in aq. THF.[485] The reaction of an alkene with CuO•BF4, iodine and triethylsilane gave the 2-iodo alkane.[486]

Trialkylboranes react rapidly with I_2[487] or Br_2[488] in the presence of NaOMe in methanol, or with $FeCl_3$ or other reagents[489] to give alkyl iodides, bromides, or chlorides, respectively. Combined with the hydroboration reaction (**15-16**), this is an indirect way of adding HBr, HI, or HCl to a double bond to give products with an

[478]For a discussion, see Negishi, E. *Organometallics in Organic Synthesis*, Wiley, NY, ***1980***, pp. 243–247.

[479]For a review of the reactions of organometallic compounds with SO_2, see Kitching, W.; Fong, C.W. *Organomet. Chem. Rev. Sect. A* ***1970***, *5*, 281.

[480]Asinger, F.; Laue, P.; Fell, B.; Gubelt, C. *Chem. Ber.* ***1967***, *100*, 1696.

[481]Zakharkin, L.I.; Gavrilenko, V.V.; Paley, B.A. *J. Organomet. Chem.* ***1970***, *21*, 269.

[482]For a review, see Abraham, M.H.; Grellier, P.L., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 2, Wiley, NY, pp. 72–105. For reviews with respect to organomercury compounds, see Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, ***1985***, pp. 158–178; Makarova, L.G. *Organomet. React.* ***1970***, *1*, 119, pp. 325–348.

[483]For a review, see Delavarenne, S.Y.; Viehe, H.G., in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 665–688. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 655–656. For an improved procedure, see Brandsma, L.; Verkruijsse, H.D. *Synthesis* ***1990***, 984.

[484]Okuyama, T.; Fujita, M.; Gronheid, R.; Lodder, G. *Tetrahedron Lett.* ***2000***, *41*. 5125.

[485]Kabalka, G.W.; Mereddy, A.R. *Tetrahedron Lett.* ***2004***, *45*, 1417.

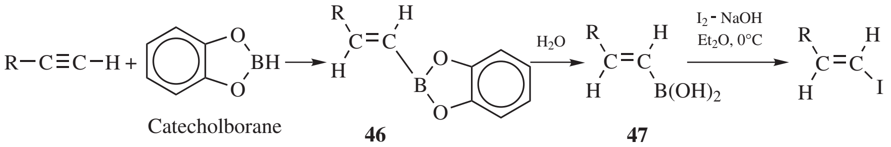
[486]Campos, P.J.; García, B.; Rodríguez, M.A. *Tetrahedron Lett.* ***2002***, *43*, 6111.

[487]Brown, H.C.; Rathke, M.W.; Rogić, M.M.; De Lue, N.R. *Tetrahedron* ***1988***, *44*, 2751.

[488]Brown, H.C.; Lane, C.F. *Tetrahedron* ***1988***, *44*, 2763; Brown, H.C.; Lane, C.F.; De Lue, N.R. *Tetrahedron* ***1988***, *44*, 2273. For another reagent, see Nelson, D.J.; Soundararajan, R. *J. Org. Chem.* ***1989***, *54*, 340.

[489]Nelson, D.J.; Soundararajan, R. *J. Org. Chem.* ***1988***, *53*, 5664. For other reagents, see Jigajinni, V.B.; Paget, W.E.; Smith, K. *J. Chem. Res. (S)* ***1981***, 376; Brown, H.C.; De Lue, N.R. *Tetrahedron* ***1988***, *44*, 2785.

anti-Markovnikov orientation (see **15-1**). Trialkylboranes can also be converted to alkyl iodides by treatment with allyl iodide and air in a free-radical process.[490] *trans*-1-Alkenylboronic acids **47**, prepared by hydroboration of terminal alkynes with catecholborane to give **46**[491] (**15-16**), followed by hydrolysis, react with I_2 in the presence of NaOH at 0°C in ethereal solvents to give trans vinylic iodides.[492] Treatment with ICl also gives the vinyl iodide.[493] This is an indirect way of accomplishing the anti-Markovnikov addition of HI to a



terminal triple bond. The reaction cannot be applied to alkenylboronic acids prepared from internal alkynes. However, alkenylboronic acids prepared from both internal and terminal alkynes react with Br_2 (2 equivalents of Br_2 must be used) followed by base to give the corresponding vinylic bromide, but in this case with *inversion* of configuration; so the product is the cis vinylic bromide.[494] Alkenylboronic acids also give vinylic bromides and iodides when treated with a mild oxidizing agent and NaBr or NaI, respectively.[495] Treatment of **47** (prepared from terminal alkynes) with Cl_2 gave vinylic chlorides with inversion.[496] Vinylic boranes can be converted to the corresponding vinylic halide by treatment with NCS or NBS.[497] Vinylic halides can also be prepared from vinylic silanes[498] and from vinylic copper reagents. The latter react with I_2 to give iodides,[499] and with NCS or NBS at −45°C to give chlorides or bromides.[500] T

For the reaction of lithium enolate anions of esters with I_2 or CX_4, see **12-5**.

The conversion of terminal alkynes to 1-iodo-1-alkynes was reported using NaI under electrochemical conditions.[501] The reaction of an aryl alkyne with $HInCl_2/BEt_3$,

[490]Suzuki, A.; Nozawa, S.; Harada, M.; Itoh, M.; Brown, H.C.; Midland, M.M. *J. Am. Chem. Soc.* ***1971***, *93*, 1508. For reviews, see Brown, H.C.; Midland, M.M. *Angew. Chem. Int. Ed.* ***1972***, *11*, 692, pp. 699–700; Brown, H.C. *Boranes in Organic Chemistry*, Cornell Univ. Press, Ithica, NY, ***1972***, pp. 442–446.
[491]For a review of this reagent, see Kabalka, G.W. *Org. Prep. Proced. Int.* ***1977***, *9*, 131.
[492]Brown, H.C.; Hamaoka, T.; Ravindran, N.; Subrahmanyam, C.; Somayaji, V.; Bhat, N.G. *J. Org. Chem.* ***1989***, *54*, 6075. See also, Kabalka, G.W.; Gooch, E.E.; Hsu, H.C. *Synth. Commun.* ***1981***, *11*, 247.
[493]Stewart, S.K.; Whiting, A. *Tetrahedron Lett.* ***1995***, *36*, 3929.
[494]Brown, H.C.; Hamaoka, T.; Ravindran, N. *J. Am. Chem. Soc.* ***1973***, *95*, 6456. See also, Brown, H.C.; Bhat, N.G. *Tetrahedron Lett.* ***1988***, *29*, 21.
[495]See Kabalka, G.W.; Sastry, K.A.R.; Knapp, F.F.; Srivastava, P.C. *Synth. Commun.* ***1983***, *13*, 1027.
[496]Kunda, S.A.; Smith, T.L.; Hylarides, M.D.; Kabalka, G.W. *Tetrahedron Lett.* ***1985***, *26*, 279.
[497]Hoshi, M.; Shirakawa, K. *Tetrahedron Lett.* ***2000***, *41*, 2595.
[498]See, for example, Chou, S.P.; Kuo, H.; Wang, C.; Tsai, C.; Sun, C. *J. Org. Chem.* ***1989***, *54*, 868.
[499]Normant, J.F.; Chaiez, G.; Chuit, C.; Villieras, J. *J. Organomet. Chem.* ***1974***, *77*, 269; *Synthesis* ***1974***, 803.
[500]Westmijze, H.; Meijer, J.; Vermeer, P. *Recl. Trav. Chim. Pays-Bas* ***1977***, *96*, 168; Levy, A.B.; Talley, P.; Dunford, J.A. *Tetrahedron Lett.* ***1977***, 3545.
[501]Nishiguchi, I.; Kanbe, O.; Itoh, K.; Maekawa, H. *Synlett* ***2000***, 89.

and then iodine leads to a *Z*-vinyl iodide with respect to the aryl group and the iodine atom.[502] 1-Bromo-1-alkynes were converted to the 1-iodo-1-alkyne with CuI.[503]

It is unlikely that a single mechanism suffices to cover all conversions of organometallic compounds to alkyl halides.[504] In a number of cases, the reaction has been shown to involve inversion of configuration (see p. 757), indicating an S_E2 (back) mechanism, while in other cases retention of configuration has been shown,[505] implicating an S_E2 (front) or S_Ei mechanism. In still other cases, complete loss of configuration as well as other evidence have demonstrated the presence of a free-radical mechanism.[505,506]

OS **I**, 125, 325, 326; **III**, 774, 813; **V**, 921; **VI**, 709; **VII**, 290; **VIII**, 586; **IX**, 573. Also see, OS **II**, 150.

E. Nitrogen Electrophiles

12-32 The Conversion of Organometallic Compounds to Amines

Amino-de-metalation

$$RLi \xrightarrow[MeLi]{CH_3ONH_2} RNH_2$$

There are several methods for conversion of alkyl- or aryllithium compounds to primary amines.[507] The two most important are treatment with hydroxylamine derivatives and with certain azides.[508] In the first of these methods, treatment of RLi with methoxyamine and MeLi in ether at −78°C gives RNH_2.[509] Grignard reagents from aliphatic halides give lower yields. The reaction can be extended to give secondary amines by the use of *N*-substituted methoxyamines (CH_3ONHR').[510] There is evidence[511] that the mechanism involves the direct displacement of OCH_3 by R

[502] Takami, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* ***2002***, *4*, 2993.

[503] Abe, H.; Suzuki, H. *Bull. Chem. Soc. Jpn.* ***1999***, *72*, 787.

[504] For reviews of the mechanisms, see Abraham, M.H.; Grellier, P.L., in Hartley, F.R.; Patai, S. *The Chemistry of the Carbon–Metal Bond*, Vol. 2, Wiley, NY, p. 72; Abraham, M.H. *Comprehensive Chemical Kinetics*, Bamford, C.H.; Tipper, C.F.H., Eds., Vol. 12; Elsevier, NY, ***1973***, pp. 135–177; Jensen, F.R.; Rickborn, B. *Electrophilic Substitution of Organomercurials*, McGraw-Hil, NY, ***1968***, pp. 75–97.

[505] For example, see Jensen, F.R.; Gale, L.H. *J. Am. Chem. Soc.* ***1960***, *82*, 148.

[506] See, for example, Beletskaya, I.P.; Reutov, O.A.; Gur'yanova, T.P. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1961***, 1483; Beletskaya, I.P.; Ermanson, A.V.; Reutov, O.A. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1965***, 218; de Ryck, P.H.; Verdonck, L.; Van der Kelen, G.P. *Bull. Soc. Chim. Belg.*, ***1985***, *94*, 621.

[507] For a review of methods for achieving the conversion RM → RNH_2, see Erdik, E.; Ay, M. *Chem. Rev.* ***1989***, *89*, 1947.

[508] For some other methods of converting organolithium or Grignard reagents to primary amines, see Alvernhe, G.; Laurent, A. *Tetrahedron Lett.* ***1972***, 1007; Hagopian, R.A.; Therien, M.J.; Murdoch, J.R. *J. Am. Chem. Soc.* ***1984***, *106*, 5753; Genet, J.P.; Mallart, S.; Greck, C.; Piveteau, E. *Tetrahedron Lett.* ***1991***, *32*, 2359.

[509] Beak, P.; Kokko, B.J. *J. Org. Chem.* ***1982***, *47*, 2822. For other hydroxylamine derivatives, see Colvin, E.W.; Kirby, G.W.; Wilson, A.C. *Tetrahedron Lett.* ***1982***, *23*, 3835; Boche, G.; Bernheim, M.; Schrott, W. *Tetrahedron Lett.* ***1982***, *23*, 5399; Boche, G.; Schrott, W. *Tetrahedron Lett.* ***1982***, *23*, 5403.

[510] Kokko, B.J.; Beak, P. *Tetrahedron Lett.* ***1983***, *24*, 561.

[511] Beak, P.; Basha, A.; Kokko, B.; Loo, D. *J. Am. Chem. Soc.* ***1986***, *108*, 6016.

on an intermediate $CH_2ONR'^-$($CH_3ONR'^-$ Li^+ + RLi → CH_3OLi + RNR'^- Li^+). The most useful azide is tosyl azide TsN_3.[512] The initial product is usually RN_3, but this is easily reducible to the amine (**19-51**). With some azides, such as azidomethyl phenyl sulfide ($PhSCH_2N_3$), the group attached to the N_3 is a poor leaving group, so the initial product is a triazene (in this case $ArNHN{=}NCH_2SPh$ from ArMgX), which can be hydrolyzed to the amine.[513]

$$R_3B \xrightarrow{NH_3-NaOCl} 2\,RNH_2 + RB(OH)_2$$

Organoboranes react with a mixture of aqueous NH_3 and NaOCl to produce primary amines.[514] It is likely that the actual reagent is chloramine (NH_2Cl). Chloramine itself,[515] hydroxylamine-*O*-sulfonic acid in diglyme,[516] and trimethylsilyl azide[517] also give the reaction. Since the boranes can be prepared by the hydroboration of alkenes (**15-16**), this is an indirect method for the addition of NH_3 to a double bond with anti-Markovnikov orientation. Secondary amines can be prepared[518] by the treatment of alkyl- or aryldichloroboranes or dialkylchloroboranes with alkyl or aryl azides.

$$RBCl_2 + R'N_3 \longrightarrow RR'NBCl_2 \xrightarrow[OH^-]{H_2O} RNHR'$$

$$R_2BCl + R'N_3 \xrightarrow[2.H_2O]{1.Et_2O} RNHR'$$

The use of an optically active R^*BCl_2 gave secondary amines of essentially 100% optical purity.[519] Aryllead triacetates, $ArPb(OAc)_3$, give secondary amines (ArNHAr′) when treated with primary aromatic amines $Ar'NH_2$ and $Cu(OAc)_2$.[520]

Secondary amines have been converted to tertiary amines by treatment with lithium dialkylcuprate reagents: R_2CuLi + NHR → RNR_2'.[521] The reaction was also used to convert primary amines to secondary, but yields were lower.[522]

[512]See, for example, Spagnolo, P.; Zanirato, P.; Gronowitz, S. *J. Org. Chem.* ***1982***, *47*, 3177; Reed, J.N.; Snieckus, V. *Tetrahedron Lett.* ***1983***, *24*, 3795. For other azides, see Hassner, A.; Munger, P.; Belinka Jr., B.A. *Tetrahedron Lett.* ***1982***, *23*, 699; Mori, S.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* ***1984***, *25*, 429.

[513]Trost, B.M.; Pearson, W.H. *J. Am. Chem. Soc.* ***1981***, *103*, 2483; ***1983***, *105*, 1054.

[514]Kabalka, G.W.; Wang, Z.; Goudgaon, N.M. *Synth. Commun.* ***1989***, *19*, 2409. For the extension of this reaction to the preparation of secondary amines, see Kabalka, G.W.; Wang, Z. *Organometallics* ***1989***, *8*, 1093; *Synth. Commun.* ***1990***, *20*, 231.

[515]Brown, H.C.; Heydkamp, W.R.; Breuer, E.; Murphy, W.S. *J. Am. Chem. Soc.* ***1964***, *86*, 3565.

[516]Brown, H.C.; Kim, K.; Srebnik, M.; Singaram, B. *Tetrahedron* ***1987***, *43*, 4071. For a method of using this reaction to prepare optically pure chiral amines, see Brown, H.C.; Kim, K.; Cole, T.E.; Singaram, B. *J. Am. Chem. Soc.* ***1986***, *106*, 6761.

[517]Kabalka, G.W.; Goudgaon, N.M.; Liang, Y. *Synth. Commun.* ***1988***, *18*, 1363.

[518]Brown, H.C.; Midland, M.M.; Levy, A.B.; Suzuki, A.; Sono, S.; Itoh, M. *Tetrahedron* ***1987***, *43*, 4079; Carboni, B.; Vaultier, M.; Courgeon, T.; Carrié, R. *Bull. Soc. Chim. Fr.* ***1989***, 844.

[519]Brown, H.C.; Salunkhe, A.M.; Singaram, B. *J. Org. Chem.* ***1991***, *56*, 1170.

[520]Barton, D.H.R.; Donnelly, D.M.X.; Finet, J.; Guiry, P.J. *Tetrahedron Lett.* ***1989***, *30*, 1377.

[521]Yamamoto, H.; Maruoka, K. *J. Org. Chem.* ***1980***, *45*, 2739.

[522]Merkushev, E.B. *Synthesis* ***1988***, 923

In the presence of a CuI catalyst, acetamide reacted with vinyl iodides to give the corresponding enamide, where the nitrogen of the amide replaced the iodine atom.[523]

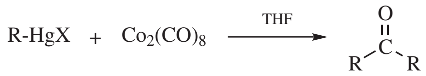
Terminal alkynes reacted with chlorodiphenylphosphine (Ph_2PCl) and a nickel catalyst to give the 1-diphenylphosphino alkyne (R-C≡C-PPh_2).[524] Alkynyl halides can be used for a similar reaction. Treatment of methyl carbamates with KHMDS and CuI, followed by two equivalents of 1-bromo phenylacetylene gave the *N*-substituted alkyne, Ph–C≡C–N(CO_2Me)R.[525]

OS **VI**, 943.

F. Carbon Electrophiles

12-33 The Conversion of Organometallic Compounds to Ketones, Aldehydes, Carboxylic Esters, or Amides

Acyl-de-metalation, and so on



Symmetrical ketones[526] can be prepared in good yields by the reaction of organomercuric halides[527] with dicobalt octacarbonyl in THF,[528] or with nickel carbonyl in DMF or certain other solvents.[529] The R group may be aryl or alkyl. However, when R is alkyl, rearrangements may intervene in the $CO_2(CO)_8$ reaction, although the $Ni(CO)_4$ reaction seems to be free from such rearrangements.[530] Divinylic ketones (useful in the Nazarov cyclization, **15-20**) have been prepared in high yields by treatment of vinylic mercuric halides with CO and a rhodium catalyst.[530] In a more general synthesis of unsymmetrical ketones, tetraalkyltin compounds (R_4Sn) are treated with a halide R′X (R′ = aryl, vinylic, benzylic), CO, and a Pd complex catalyst.[531] Similar reactions use Grignard reagents, $Fe(CO)_5$, and an alkyl halide.[532] Cyclobutanone derivatives were prepared by carbonylation (treatment with CO) of a cyclic titanium compound.[533]

Grignard reagents react with formic acid to give good yields of aldehydes. Two equivalents of RMgX are used; the first converts HCOOH to HCOO–, which reacts

[523]Jiang, L.; Job, G.E.; Klapars, A.; Buchwald, S.L. *Org. Lett.* ***2003***, *5*, 3667.

[524]Beletskaya, I.P.; Affanasiev, V.V.; Kazankova, M.A.; Efimova, I.V. *Org. Lett.* ***2003***, *5*, 4309.

[525]Dunetz, J.R.; Danheiser, R.L. *Org. Lett.* ***2003***, *5*, 4011.

[526]For reviews of the reactions in this section, and related reactions, see Narayana, C.; Periasamy, M. *Synthesis* ***1985***, 253; Gulevich, Yu.V.; Bumagin, N.A.; Beletskaya, I.P. *Russ. Chem. Rev.* ***1988***, *57*, 299.

[527]For a monograph on the synthetic uses of organomercury compounds, see Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, ***1985***. For reviews, see Larock, R.C. *Tetrahedron* ***1982***, *38*, 1713; *Angew. Chem. Int. Ed.* ***1978***, *17*, 27.

[528]Seyferth, D.; Spohn, R.J. *J. Am. Chem. Soc.* ***1969***, *91*, 3037.

[529]Ryu, I.; Ryang, M.; Rhee, I.; Omura, H.; Murai, S.; Sonoda, N. *Synth. Commun.* ***1984***, *14*, 1175 and references cited therein. For another method, see Hatanaka, Y.; Hiyama, T. *Chem. Lett.* ***1989***, 2049.

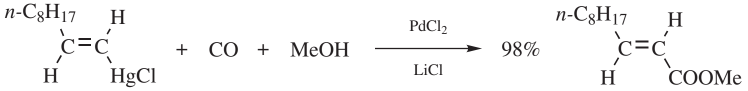
[530]Larock, R.C.; Hershberger, S.S. *J. Org. Chem.* ***1980***, *45*, 3840.

[531]Tanaka, M. *Tetrahedron Lett.* ***1979***, 2601.

[532]Yamashita, M.; Suemitsu, R. *Tetrahedron Lett.* ***1978***, 761. See also, Vitale, A.A.; Doctorovich, F.; Nudelman, N.S. *J. Organomet. Chem.* ***1987***, *332*, 9.

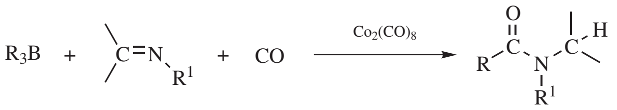
[533]Carter, C.A.G.; Greidanus, G.; Chen, J.-x.; Stryker, J.M. *J. Am. Chem. Soc.* ***2001***, *123*, 8872.

with the second equivalent to give RCHO.[534] Alkyllithium reagents and Grignard reagents react with CO to give symmetrical ketones.[535] An interesting variation reacts CO_2 with an organolithium, which is then treated with a different organolithium reagent to give the unsymmetrical ketone.[536] α,β-Unsaturated aldehydes can be prepared by treatment of vinylic silanes with dichloromethyl methyl ether and $TiCl_4$ at −90°C.[537] α,β-Unsaturated esters can be prepared by treating boronic esters **27** with CO, $PdCl_2$, and NaOAc in MeOH.[538] The synthesis of α,β-unsaturated esters has also been accomplished by treatment of vinylic mercuric chlorides with CO at atmospheric pressure and a Pd catalyst in an alcohol as solvent, for example,[539]



Alkyl and aryl Grignard reagents can be converted to carboxylic esters with $Fe(CO)_5$ instead of CO.[540]

Amides have been prepared by the treatment of trialkyl or triarylboranes with CO and an imine, in the presence of catalytic amounts of cobalt carbonyl:[541]



In another method for the conversion RM → RCONR, Grignard reagents, and organolithium compounds are treated with a formamide ($HCONR_2'$) to give the intermediate $RCH(OM)NR_2'$, which is not isolated, but treated with PhCHO or Ph_2CO to give the product $RCONR_2'$.[542]

Direct conversion of a hydrocarbon to an aldehyde (R–H → R–CHO) was reported by treatment of the hydrocarbon with $GaCl_3$ and CO.[543]

See also, reactions **10-76**, **15-32**, and **18-23–18-24**.

OS **VIII**, 97.

[534]Sato, F.; Oguro, K.; Watanabe, H.; Sato, M. *Tetrahedron Lett.* ***1980***, *21*, 2869. For another method of converting RMgX to RCHO, see Meyers, A.I.; Comins, D.L. *Tetrahedron Lett.* ***1978***, 5179; Comins, D.L.; Meyers, A.I. *Synthesis* ***1978***, 403; Amaratunga, W.; Fréchet, J.M.J. *Tetrahedron Lett.* ***1983***, *24*, 1143.

[535]Ryang, M.; Sawa, Y.; Hasimoto, T.; Tsutsumi, S. *Bull. Chem. Soc. Jpn.* ***1964***, *37*, 1704; Trzupek, L.S.; Newirth, T.L.; Kelly, E.G.; Sbarbati, N.E.; Whitesides, G.M. *J. Am. Chem. Soc.* ***1973***, *95*, 8118.

[536]Zadel, G.; Breitmaier, E. *Angew. Chem. Int. Ed.* ***1992***, *31*, 1035.

[537]Yamamoto, K.; Yohitake, J.; Qui, N.T.; Tsuji, J. *Chem. Lett.* ***1978***, 859.

[538]Miyaura, N.; Suzuki, A. *Chem. Lett.* ***1981***, 879. See also Yamashina, N.; Hyuga, S.; Hara, S.; Suzuki, A. *Tetrahedron Lett.* ***1989***, *30*, 6555.

[539]Larock, R.C. *J. Org. Chem.* ***1975***, *40*, 3237.

[540]Yamashita, M.; Suemitsu, R. *Tetrahedron Lett.* ***1978***, 1477.

[541]Alper, H.; Amaratunga, S. *J. Org. Chem.* ***1982***, *47*, 3593.

[542]Screttas, C.G.; Steele, B.R. *J. Org. Chem.* ***1988***, *53*, 5151.

[543]Oshita, M.; Chatani, N. *Org. Lett.* ***2004***, *6*, 4323.

12-34 Cyano-de-metalation

$$\text{R-M} + \text{CuCN} \longrightarrow \text{R-CN}$$

Vinylic copper reagents react with ClCN to give vinyl cyanides, although BrCN and ICN give the vinylic halide instead.[544] Vinylic cyanides have also been prepared by the reaction between vinylic lithium compounds and phenyl cyanate (PhOCN).[545] Alkyl nitriles (RCN) have been prepared, in varying yields, by treatment of sodium trialkylcyanoborates with NaCN and lead tetraacetate.[546] Vinyl bromides reacted with KCN, in the presence of a nickel complex and zinc metal to give the vinyl nitrile.[547] Vinyl triflates react with LiCN, in the presence of a palladium catalyst, to give the vinyl nitrile.[548]

For other electrophilic substitutions of the type RM → RC, which are discussed under nucleophilic substitutions in Chapter 10. See also, **16-81–16-85** and **16-99**.

OS IX, 548

G. Metal Electrophiles

12-35 Transmetallation With a Metal

Metalo-de-metalation

$$\text{RM} + \text{M}' \rightleftharpoons \text{RM}' + \text{M}$$

Many organometallic compounds are best prepared by this reaction, which involves replacement of a metal in an organometallic compound by another metal. The RM' compound can be successfully prepared only when M' is above M in the electromotive series, unless some other way is found to shift the equilibrium. That is, RM is usually an unreactive compound and M' is a metal more active than M. Most often, RM is R_2Hg, since mercury alkyls[527] are easy to prepare and mercury is far down in the electromotive series.[549] Alkyls of Li, Na, K, Be, Mg, Al, Ga, Zn, Cd, Te, Sn, and so on have been prepared this way. An important advantage of this method over **12-38** is that it ensures that the organometallic compound will be prepared free of any possible halide. This method can be used for the isolation of solid sodium and potassium alkyls.[550] If the metals lie too close together in the series, it may not be possible to shift the equilibrium. For example, alkylbismuth compounds cannot be prepared in this way from alkylmercury compounds.

OS V, 1116.

[544]Westmijze, H.; Vermeer, P. *Synthesis* ***1977***, 784.

[545]Murray, R.E.; Zweifel, G. *Synthesis* ***1980***, 150.

[546]Masuda, Y.; Hoshi, M.; Yamada, T.; Arase, A. *J. Chem. Soc. Chem. Commun.* ***1984***, 398.

[547]Sakakibara, Y.; Enami, H.; Ogawa, H.; Fujimoto, S.; Kato, H.; Kunitake, K.; Sasaki, K.; Sakai, M. *Bull. Chem. Soc. Jpn.* ***1995***, *68*, 3137.

[548]Piers, E.; Fleming, F.F. *Can. J. Chem.* ***1993***, *71*, 1867.

[549]For a review of the reaction when M is Hg, see Makarova, L.G. *Organomet. React.* ***1970***, *1*, 119, pp. 190–226. For a review where M' is Li, see Wardell, J.L., in Zuckerman, J.J. *Inorganic Reactions and Methods*, Vol. 11, VCH, NY, ***1988***, pp. 31–44.

[550]BuNa and BuK have also been prepared by exchange of BuLi with *t*-BuONa or *t*-AmOK: Pi, R.; Bauer, W.; Brix, B.; Schade, C.; Schleyer, P.v.R. *J. Organomet. Chem.* ***1986***, *306*, C1.

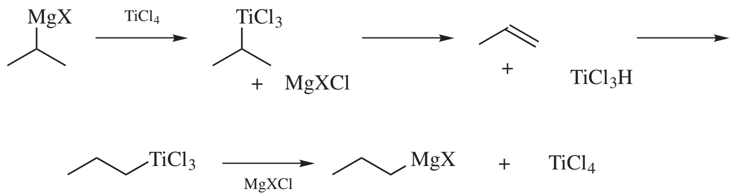
12-36 Transmetallation With a Metal Halide

Metalo-de-metalation

$$RM + M'X \rightleftharpoons RM' + MX$$

In contrast to **12-35**, the reaction between an organometallic compound and a metal *halide* is successful only when M' is *below* M in the electromotive series.[551] The two reactions considered together therefore constitute a powerful tool for preparing all kinds of organometallic compounds. In this reaction, the most common substrates are Grignard reagents and organolithium compounds.[552]

The MgX of Grignard reagents[553] can migrate to terminal positions in the presence of small amounts of $TiCl_4$.[554] The proposed mechanism consists of metal exchange (**12-36**), elimination–addition, and metal exchange:



The addition step is similar to **15-16** or **15-17** and follows Markovnikov's rule, so the positive titanium goes to the terminal carbon.

Among others, alkyls of Be, Zn,[555] Cd, Hg, Al, Sn, Pb, Co, Pt, and Au have been prepared by treatment of Grignard reagents with the appropriate halide.[556] The reaction has been used to prepare alkyls of almost all nontransition metals and even of some transition metals. Alkyls of metalloids and of nonmetals, including

[551]For reviews of the mechanism, see Abraham, M.H.; Grellier, P.L. in Hartley, F.R.; Patai, S. *The Chemistry of the Carbon–Metal Bond*, Vol. 2, Wiley, NY, pp. 25–149; Abraham, M.H. *Comprehensive Chemical Kinetics*, Bamford, C.H.; Tipper, C.F.H., Eds., Vol. 12; Elsevier, NY, ***1973***, pp. 39–106; Jensen, F.R.; Rickborn, B. *Electrophilic Substituton of Organomercurials*, McGraw-Hill, NY, ***1968***, pp. 100–192. Also see Schlosser, M. *Angew. Chem. Int. Ed.* ***1964***, *3*, 287, 362; *Newer Methods Prep. Org. Chem.* ***1968***, *5*, 238.

[552]For monographs on organolithium compounds, see Wakefield, B.J. *Organolithium Methods*, Academic Press, NY, ***1988***; Wakefield, B.J. *The Chemistry of Organolithium Compounds*, Pergamon: Elmsford, NY, ***1974***.

[553]For reviews of rearrangements in organomagnesium chemistry, see Hill, E.A. *Adv. Organomet. Chem.* ***1977***, *16*, 131; *J. Organomet. Chem.* ***1975***, *91*, 123.

[554]Cooper, G.D.; Finkbeiner, H.L. *J. Org. Chem.* ***1962***, *27*, 1493; Fell, B.; Asinger, F.; Sulzbach, R.A. *Chem. Ber.* ***1970***, *103*, 3830. See also, Ashby, E.C.; Ainslie, R.D. *J. Organomet. Chem.* ***1983***, *250*, 1.

[555]For a review of the use of activated zinc, see Erdik, E. *Tetrahedron* ***1987***, *43*, 2203.

[556]For a review, see Noltes, J.G. *Bull. Soc. Chim. Fr.* ***1972***, 2151.

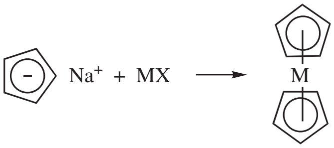
Si, B,[557] Ge, P, As, Sb, and Bi, can also be prepared in this manner.[558] Except for alkali-metal alkyls and Grignard reagents, the reaction between RM and M′X is the most common method for the preparation of organometallic compounds.[559]

Lithium dialkylcopper reagents can be prepared by mixing 2 equivalents of RLi with 1 equivalent of a cuprous halide in ether at low temperatures:[560]

$$2\ RLi + CuX \longrightarrow R_2CuLi + LiX$$

Another way is to dissolve an alkylcopper compound in an alkyllithium solution. Higher order cuprates can also be prepared, as well as "non-ate" copper reagents.[561]

Metallocenes (**48**, see p. 66) are usually made by this method:



48

Among others, metallocenes of Sc, Ti, V, Cr, Mn, Fe, Co, and Ni have been prepared in this manner.[562]

Metal nitrates are sometimes used instead of halides.

In a related reaction sulfurated boranes (R_2B–$SSiR'_2$) react with Grignard reagents, such as methylmagneisum bromide to give the B-alkyl borane (e.g., R_2B–Me) upon heating *in vacuo*.[563]

OS **I**, 231, 550; **III**, 601; **IV**, 258, 473, 881; **V**, 211, 496, 727, 918, 1001; **VI**, 776, 875, 1033; **VII**, 236, 290, 524; **VIII**, 23, 57, 268, 474, 586, 606, 609. Also see, OS **IV**, 476

[557]For a method of preparing organoboranes from RMgX and BF_3, where the RMgX is present only *in situ*, see Brown, H.C.; Racherla, U.S. *Tetrahedron Lett.* ***1985***, *26*, 4311.

[558]For reviews as applied to Si, B, and P, see Wakefield, B.J. *Organolithium Methods*, Academic Press, NY, ***1988***, pp. 149–158; Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*; Prentice-Hall: Englewood Cliffs, NJ, ***1954***, pp. 1306–1345.

[559]For a review with respect to Al, see Mole, T. *Organomet. React.* ***1970***, *1*, 1, pp. 31–43; to Hg, see Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, ***1985***, pp. 9–26; Makarova, L.G. *Organomet. React.* ***1970***, *1*, 119, pp. 129–178, 227–240; to Cu, Ag, or Au, see van Koten, G., in Zuckerman, J.J. *Inorganic Reactions and Methods*, Vol. 11, VCH, NY, ***1988***, pp. 219–232; to Zn, Cd, or Hg, see Wardell, J.L. in Zuckerman, J.J. *Inorganic Reactions and Methods*, Vol. 11, VCH, NY, ***1988***, pp. 248–270.

[560]House, H.O.; Chu, C.; Wilkins, J.M.; Umen, M.J. *J. Org. Chem.* ***1975***, *40*, 1460. But see also, Lipshutz, B.H.; Whitney, S.; Kozlowski, J.A.; Breneman, C.M. *Tetrahedron Lett.* ***1986***, *27*, 4273; Bertz, S.H.; Dabbagh, G. *Tetrahedron* ***1989***, *45*, 425.

[561]Stack, D.E.; Klein, W.R.; Rieke, R.D. *Tetrahedron Lett.* ***1993***, *34*, 3063.

[562]For reviews of the preparation of metallocenes, see Bublitz, D.E.; Rinehart, Jr., K.L. *Org. React.* ***1969***, *17*, 1; Birmingham, J.M. *Adv. Organomet. Chem.* ***1965***, *2*, 365, p. 375.

[563]Soderquist, J.A.; DePomar, J.C.J. *Tetrahedron Lett.* ***2000***, *41*, 3537.

12-37 Transmetalation With an Organometallic Compound

Metalo-de-metalation

$$\text{RM} + \text{R}'\text{M}' \rightleftharpoons \text{RM}' + \text{R}'\text{M}$$

This type of metallic exchange is used much less often than **12-35** and **12-36**. It is an equilibrium reaction and is useful only if the equilibrium lies in the desired direction. Usually the goal is to prepare a lithium compound that is not prepared easily in other ways,[564] for example, a vinylic or an allylic lithium, most commonly from an organotin substrate. Examples are the preparation of vinyllithium from phenyllithium and tetravinyltin and the formation of α-dialkylamino organolithium compounds from the corresponding organotin compounds[565]

$$\text{RR}'\text{NCH}_2\text{SnBu}_3 + \text{BuLi} \xrightarrow{0^\circ\text{C}} \text{RR}'\text{NCH}_2\text{Li} + \text{Bu}_4\text{Sn}$$

The reaction has also been used to prepare 1,3-dilithiopropanes[566] and 1,1-dilithiomethylenecyclohexane[567] from the corresponding mercury compounds. In general, the equilibrium lies in the direction in which the more electropositive metal is bonded to that alkyl or aryl group that is the more stable carbanion (p. 250). The reaction proceeds with retention of configuration;[568] an S_Ei mechanism is likely.[569]

"Higher order" cuprates[570] (see **10-58**) have been produced by this reaction starting with a vinylic tin compound:[571]

$$\text{RSnR}'_3 + \text{Me}_2\text{Cu(CN)Li}_2 \longrightarrow \text{RCuMe(CN)Li}_2 + \text{MeSnR}'_{3-} \qquad \text{R} = \text{a vinylic group}$$

[564] For reviews, see Wardell, J.L. in Hartley, F.R; Patai, S. *The Chemistry of the Carbon-Metal Bond*, Vol. 4, Wiley, NY, pp. 1–157, see pp. 81–89; Kauffmann, T. *Top. Curr. Chem.* ***1980***, *92*, 109, p. 130.

[565] Peterson, D.J.; Ward, J.F. *J. Organomet. Chem.* ***1974***, *66*, 209; Pearson, W.H.; Lindbeck, A.C. *J. Org. Chem.* ***1989***, *54*, 5651.

[566] Seetz, J.W.F.L.; Schat, G.; Akkerman, O.S.; Bickelhaupt, F. *J. Am. Chem. Soc.* ***1982***, *104*, 6848.

[567] Maercker, A.; Dujardin, R. *Angew. Chem. Int. Ed.* ***1984***, *23*, 224.

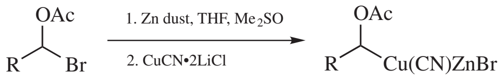
[568] Seyferth, D.; Vaughan, L.G. *J. Am. Chem. Soc.* ***1964***, *86*, 883; Sawyer, J.S.; Kucerovy, A.; Macdonald, T.L.; McGarvey, G.J. *J. Am. Chem. Soc.* ***1988***, *110*, 842.

[569] Dessy, R.E.; Kaplan, F.; Coe, G.R.; Salinger, R.M. *J. Am. Chem. Soc.* ***1963***, *85*, 1191.

[570] For reviews of these and other "higher order" organocuprates, see Lipshutz, B.H.; Wilhelm, R.S.; Kozlowski, J.A. *Tetrahedron* ***1984***, *40*, 5005; Lipshutz, B.H. *Synthesis* ***1987***, 325; *Synlett*, ***1990***, 119. See also, Bertz, S.H. *J. Am. Chem. Soc.* ***1990***, *112*, 4031; Lipshutz, B.H.; Sharma, S.; Ellsworth, E.L. *J. Am. Chem. Soc.* ***1990***, *112*, 4032.

[571] Behling, J.R.; Babiak, K.A.; Ng, J.S.; Campbell, A.L.; Moretti, R.; Koerner, M.; Lipshutz, B.H. *J. Am. Chem. Soc.* ***1988***, *110*, 2641.

These compounds are not isolated, but used directly *in situ* for conjugate addition reactions (**15-25**). Another method for the preparation of such reagents (but with Zn instead of Li) allows them to be made from α-acetoxy halides:[572]



OS **V**, 452; **VI**, 815; **VIII**, 97.

HALOGEN AS LEAVING GROUP

The reduction of alkyl halides can proceed by an electrophilic substitution mechanism, but it is considered in Chapter 19 (**19-53**).

12-38 Metalo-de-halogenation

$$\text{RX} + \text{M} \longrightarrow \text{RM}$$

Alkyl halides react directly with certain metals to give organometallic compounds.[573] The most common metal is magnesium, and of course this is by far the most common method for the preparation of Grignard reagents.[574] The order of halide activity is I > Br > Cl. The reaction can be applied to many alkyl halides primary, secondary, and tertiary and to aryl halides, although aryl *chlorides* require the use of THF or another higher boiling solvent instead of the usual ether, or special entrainment methods.[575] Aryl iodides and bromides can be treated in the usual manner. Allylic Grignard reagents can also be prepared in the usual manner (or in THF),[576] although in the presence of excess halide these may give Wurtz-type coupling products (see **10-56**).[577] Like aryl chlorides, vinylic halides require higher boiling solvents (see OS **IV**, 258). A good procedure for benzylic and allylic halides is to use magnesium anthracene (prepared from Mg and anthracene in THF)[578]

[572]Chou, T.; Knochel, P. *J. Org. Chem.* ***1990***, *55*, 4791.

[573]For reviews, see Massey, A.G.; Humphries, R.E. *Aldrichimica Acta* ***1989***, *22*, 31; Negishi, E. *Organometallics in Organic Synthesis*, Wiley, NY, ***1980***, pp. 30–37; Rochow, E.G. *J. Chem. Educ.* ***1966***, *43*, 58.

[574]For reviews, see Raston, C.L.; Salem, G., in Hartley, F.R.; Patai, S. *The Chemistry of the Carbon–Metal Bond*, Vol. 4, Wiley, NY, pp. 159–306, 162–175; Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Monmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 5–91.

[575]Pearson, D.E.; Cowan, D.; Beckler, J.D. *J. Org. Chem.* ***1959***, *24*, 504.

[576]For a review of allyl and crotyl Grignard reagents, see Benkeser, R.A. *Synthesis* ***1971***, 347.

[577]For a method of reducing coupling in the formation of allylic Grignard reagents, see Oppolzer, W.; Schneider, P. *Tetrahedron Lett.* ***1984***, *25*, 3305.

[578]Freeman, P.K.; Hutchinson, L.L. *J. Org. Chem.* ***1983***, *48*, 879; Bogdanović, B.; Janke, N.; Kinzelmann, H. *Chem. Ber.* ***1990***, *123*, 1507, and other papers in this series.

instead of ordinary magnesium,[579] although activated magnesium turnings have also been used.[580] Alkynyl Grignard reagents are not generally prepared by this method at all. For these, **12-22** is used. Grignard reagents can also be formed from an alkyl halide and 1,2-dibromoethane with iodine as an initiator.[581]

Dihalides[582] can be converted to Grignard reagents if the halogens are different and are at least three carbons apart. If the halogens are the same, it is possible to obtain dimagnesium compounds (e.g., $BrMg(CH_2)_4MgBr$).[583] 1,2-Dihalides give elimination[584] instead of Grignard reagent formation (**17-22**), and the reaction is seldom successful with 1,1-dihalides, although the preparation of *gem*-disubstituted compounds, such as $CH_2(MgBr)_2$, has been accomplished with these substrates.[585] α-halo Grignard reagents and α-halolithium reagents can be prepared by the method given in **12-39**.[586] Alkylmagnesium fluorides can be prepared by refluxing alkyl fluorides with Mg in the presence of appropriate catalysts (e.g., I_2 or EtBr) in THF for several days.[587] Nitrogen-containing Grignard reagents have been prepared.[588]

The presence of other functional groups in the halide usually affects the preparation of the Grignard reagent. Groups that contain active hydrogen (defined as any hydrogen that will react with a Grignard reagent), such as OH, NH_2, and COOH, can be present in the molecule, but only if they are converted to the salt form (O^-, NH^-, COO^-, respectively). Groups that react with Grignard reagents, such as C=O, C≡N, NO_2, COOR, inhibit Grignard formation entirely. In general, the only functional groups that may be present in the halide molecule without any interference at all are double and triple bonds (except terminal triple bonds) and OR and NR_2 groups. However, β-halo ethers generally give β elimination when treated with

[579]Gallagher, M.J.; Harvey, S.; Raston, C.L.; Sue, R.E. *J. Chem. Soc. Chem. Commun.* ***1988***, 289.

[580]Baker, K.V.; Brown, J.M.; Hughes, N.; Skarnulis, A.J.; Sexton, A. *J. Org. Chem.* ***1991***, *56*, 698. For a review of the use of activated magnesium, see Lai, Y. *Synthesis* ***1981***, 585.

[581]Li, J.; Liao, X.; Liu, H.; Xie, Q.; Liu, Z.; He, X. *Synth. Commun.* ***1999***, *29*, 1037.

[582]For reviews of the preparation of Grignard reagents from dihalides, see Raston, C.L.; Salem, G. in Hartley, F.R.; Patai, S. *The Chemistry of the Carbon–Metal Bond*, Vol. 4, Wiley, NY, pp. 187–193; Heaney, H. *Organomet. Chem. Rev.* ***1966***, *1*, 27. For a review of di-Grignard reagents, see Bickelhaupt, F. *Angew. Chem. Int. Ed.* ***1987***, *26*, 990.

[583]For example, see Denise, B.; Ducom, J.; Fauvarque, J. *Bull. Soc. Chim. Fr.* ***1972***, 990; Seetz, J.W.F.L.; Hartog, F.A.; Böhm, H.P.; Blomberg, C.; Akkerman, O.S.; Bickelhaupt, F. *Tetrahedron Lett.* ***1982***, *23*, 1497.

[584]For formation of 1,2-dilithio compounds and 1,2-di-Grignard reagents, but not by this method, see van Eikkema Hommes, N.J.R.; Bickelhaupt, F.; Klumpp, G.W. *Recl. Trav. Chim. Pays-Bas* ***1988***, *107*, 393; *Angew. Chem. Int. Ed.* ***1988***, *27*, 1083.

[585]For example, see Bertini, F.; Grasselli, P.; Zubiani, G.; Cainelli, G. *Tetrahedron* ***1970***, *26*, 1281; Bruin, J.W.; Schat, G.; Akkerman, O.S.; Bickelhaupt, F. *J. Organomet. Chem.* ***1985***, *288*, 13. For the synthesis of *gem*-dilithio and 1,1,1-trilithio compounds, see Baran, Jr., J.R.; Lagow, R. *J. Am. Chem. Soc.* ***1990***, *112*, 9415.

[586]For a review of compounds containing both carbon–halogen and carbon-metal bonds, see Chivers, T. *Organomet. Chem. Rev. Sect. A* ***1970***, *6*, 1.

[587]Yu, S.H.; Ashby, E.C. *J. Org. Chem.* ***1971***, *36*, 2123.

[588]Sugimoto, O.; Yamada, S.; Tanji, K. *J. Org. Chem.* ***2003***, *68*, 2054.

magnesium (see **17-24**), and Grignard reagents from α-halo ethers[589] can only be formed in THF or dimethoxymethane at a low temperature, for example,[590]

$$EtOCH_2Cl + Mg \xrightarrow[-30°C]{THF\ or\ CH_2(OMe)_2} EtOCH_2MgCl$$

because such reagents immediately undergo a elimination (see **12-39**) at room temperature in ether solution.

Because Grignard reagents react with water (**12-24**) and with oxygen (**12-25**), it is generally best to prepare them in an anhydrous nitrogen atmosphere. Grignard reagents are generally neither isolated nor stored; solutions of Grignard reagents are used directly for the required synthesis. Grignard reagents can also be prepared in benzene or toluene, if a tertiary amine is added to complex with the RMgX.[591] This method eliminates the need for an ether solvent. With certain primary alkyl halides it is even possible to prepare alkylmagnesium compounds in hydrocarbon solvents in the absence of an organic base.[592] It is also possible to obtain Grignard reagents in powdered form, by complexing them with the chelating agent tris(3,6-dioxaheptyl)amine, $N(CH_2CH_2OCH_2CH_2OCH_3)_3$.[593]

Next to the formation of Grignard reagents, the most important application of this reaction is the conversion of alkyl and aryl halides to organolithium compounds,[594] but it has also been carried out with many other metals (e.g., Na, Be, Zn, Hg, As, Sb, and Sn). With sodium, the Wurtz reaction (**10-56**) is an important side reaction. In some cases where the reaction between a halide and a metal is too slow, an alloy of the metal with potassium or sodium can be used instead. The most important example is the preparation of tetraethyl lead from ethyl bromide and a Pb–Na alloy.

The efficiency of the reaction can often be improved by use of the metal in its powdered[595] or vapor[596] form. These techniques have permitted the preparation of some organometallic compounds that cannot be prepared by the standard

[589]For a review of organometallic compounds containing a hetero atom (N, O, P, S, or Si), see Peterson, D.J. *Organomet. Chem. Rev. Sect. A* ***1972***, *7*, 295.

[590]For example, see Normant, H.; Castro, B. *C. R. Acad. Sci.* ***1963***, *257*, 2115; ***1964***, *259*, 830; Castro, B. *Bull. Soc. Chim. Fr.* ***1967***, 1533, 1540, 1547; Taeger, E.; Kahlert, E.; Walter, H. *J. Prakt. Chem.* ***1965***, *[4] 28*, 13.

[591]Ashby, E.C.; Reed, R. *J. Org. Chem.* ***1966***, *31*, 971; Gitlitz, M.H.; Considine, W.J. *J. Organomet. Chem.* ***1970***, *23*, 291.

[592]Smith Jr., W.N. *J. Organomet. Chem.* ***1974***, *64*, 25.

[593]Boudin, A.; Cerveau, G.; Chuit, C.; Corriu, R.J.P.; Reye, C. *Tetrahedron* ***1989***, *45*, 171.

[594]For reviews, see Wakefield, B.J. *Organolithium Methods*, Academic Press, NY, ***1988***, pp. 21–32; Wardell, J.L., in Hartley, F.R.; Patai, S. Vol. 4, pp. 1–157, 5–27; Newcomb, M.E., in Zuckerman, J.J. *Inorganic Reactions and Methods*, Vol. 11, VCH, NY, ***1988***, pp. 3–14.

[595]For a review, see Rieke, R.D. *Science* ***1989***, *246*, 1260.

[596]For reviews, see Klabunde, K.J. *React. Intermed.* (*Plenum*) ***1980***, *1*, 37; *Acc. Chem. Res.*; ***1975***, *8*, 393; Skell, P.S. Havel, J.J.; McGlinchey, M.J. *Acc. Chem. Res.* ***1973***, *6*, 97; Timms, P.L. *Adv. Inorg. Radiochem.* ***1972***, *14*, 121.

procedures. Among the metals produced in an activated form are Mg,[597] Ca,[598] Zn,[599] Al, Sn, Cd,[600] Ni, Fe, Ti, Cu,[601] Pd, and Pt.[602]

The mechanism of Grignard reagent formation involves free radicals,[603] and there is much evidence for this, from CIDNP[604] (p. 269) and from stereochemical, rate, and product studies.[605] Further evidence is that free radicals have been trapped,[606] and that experiments that studied the intrinsic reactivity of MeBr on a magnesium single-crystal surface showed that Grignard reagent formation does not take place by a single-step insertion mechanism.[607] The following SET mechanism has been proposed:[604]

$$R{-}X + \overline{Mg} \longrightarrow R{-}X^{\bullet -} + Mg_s^{\bullet +}$$
$$R{-}X^{\bullet -} \longrightarrow R^{\bullet} + X^{-}$$
$$X^{-} + Mg_s^{\bullet +} \longrightarrow XMg_s^{\bullet}$$
$$R^{\bullet} + XMg_s^{\bullet} \longrightarrow RMgX$$

Other evidence has been offered to support a SET-initiated radical process for the second step of this mechanism.[608] The species $R{-}X^{\bullet -}$ and $Mg^{\bullet +}$ are radical ions.[609] The subscript "s" is meant to indicate that the species so marked are bound to the surface of the magnesium. It is known that this is a surface reaction.[610] It has been suggested that some of the $R^{\bullet}$ radicals diffuse from the magnesium surface into the solution and then return to the surface to react with the $XMg^{\bullet}$. There is evidence

[597]Ebert, G.W.; Rieke, R.D. *J. Org. Chem.* ***1988***, *53*, 4482. See also, Baker, K.V.; Brown, J.M.; Hughes, N.; Skarnulis, A.J.; Sexton, A. *J. Org. Chem.* ***1991***, *56*, 698.

[598]Wu, T.; Xiong, H.; Rieke, R.D. *J. Org. Chem.* ***1990***, *55*, 5045.

[599]Rieke, R.D.; Li, P.T.; Burns, T.P.; Uhm, S.T. *J. Org. Chem.* ***1981***, *46*, 4323. See also, Grondin, J.; Sebban, M.; Vottero, G.P.; Blancou, H.; Commeyras, A. *J. Organomet. Chem.* ***1989***, *362*, 237; Berk, S.C.; Yeh, M.C.P.; Jeong, N.; Knochel, P. *Organometallics* ***1990***, *9*, 3053; Zhu, L.; Wehmeyer, R.M.; Rieke, R.D. *J. Org. Chem.* ***1991***, *56*, 1445.

[600]Burkhardt, E.R.; Rieke, R.D. *J. Org. Chem.* ***1985***, *50*, 416.

[601]Stack, D.E.; Dawson, B.T.; Rieke, R.D. *J. Am. Chem. Soc.* ***1991***, *113*, 4672, and references cited therein.

[602]For reviews, see Lai, Y. *Synthesis* ***1981***, 585; Rieke, R.D. *Acc. Chem. Res.* ***1977***, *10*, 301; *Top. Curr. Chem.* ***1975***, *59*, 1.

[603]For a review, see Blomberg, C. *Bull. Soc. Chim. Fr.* ***1972***, 2143.

[604]Bodewitz, H.W.H.J.; Blomberg, C.; Bickelhaupt, F. *Tetrahedron Lett.* ***1975***, 2003; *Tetrahedron* ***1975***, *31*, 1053. See also, Lawler, R.G.; Livant, P. *J. Am. Chem. Soc.* ***1976***, *98*, 3710; Schaart, B.J.; Blomberg, C.; Akkerman, O.S.; Bickelhaupt, F. *Can. J. Chem.* ***1980***, *58*, 932.

[605]See, for example, Walborsky, H.M.; Aronoff, M.S. *J. Organomet. Chem.* ***1973***, *51*, 31; Czernecki, S.; Georgoulis, C.; Gross, B.; Prevost, C. *Bull. Soc. Chim. Fr.* ***1968***, 3720; Rogers, H.R.; Hill, C.L.; Fujiwara, Y.; Rogers, R.J.; Mitchell, H.L.; Whitesides, G.M. *J. Am. Chem. Soc.* ***1980***, *102*, 217; Barber, J.J.; Whitesides, G.M. *J. Am. Chem. Soc.* ***1980***, *102*, 239.

[606]Root, K.S.; Hill, C.L.; Lawrence, L.M.; Whitesides, G.M. *J. Am. Chem. Soc.* ***1989***, *111*, 5405.

[607]Nuzzo, R.G.; Dubois, L.H. *J. Am. Chem. Soc.* ***1986***, *108*, 2881.

[608]Hoffmann, R. W.; Brönstrup, M.; Müller, M. *Org. Lett.* ***2003***, *5*, 313.

[609]For additional evidence for this mechanism, see Vogler, E.A.; Stein, R.L.; Hayes, J.M. *J. Am. Chem. Soc.* ***1978***, *100*, 3163; Sergeev, G.B.; Zagorsky, V.V.; Badaev, F.Z. *J. Organomet. Chem.* ***1983***, *243*, 123. However, there is evidence that the mechanism may be more complicated: de Souza-Barboza, J.C.; Luche, J.; Pétrier, C. *Tetrahedron Lett.* ***1987***, *28*, 2013.

[610]Walborsky, H.M.; Topolski, M. *J. Am. Chem. Soc.* ***1992***, *114*, 3455; Walborsky, H.M.; Zimmermann, C. *J. Am. Chem. Soc.* ***1992***, *114*, 4996; Walborsky, H.M. *Accts. Chem. Res.* ***1990***, *23*, 286.

both for[611] and against[612] this suggestion. Another proposal is that the fourth step is not the one shown here, but that the R• is reduced by Mg^+ to the carbanion R^-, which combines with MgX^+ to give RMgX.[613]

There are too many preparations of Grignard reagents in *Organic Syntheses* for us to list here. Chiral Grignard reagents are rare, since they are configurationally unstable in most cases. However, a few chiral Grignard reagents are known.[614] Use of the reaction to prepare other organometallic compounds can be found in OS **I**, 228; **II**, 184, 517, 607; **III**, 413, 757; **VI**, 240; **VII**, 346; **VIII**, 505. The preparation of unsolvated butylmagnesium bromide is described at OS **V**, 1141. The preparation of highly reactive (powdered) magnesium is given at OS **VI**, 845.

12-39 Replacement of a Halogen by a Metal from an Organometallic Compound

Metalo-de-halogenation

$$RX + R'M \longrightarrow RM + R'X$$

The exchange reaction between halides and organometallic compounds occurs most readily when M is lithium and X is bromide or iodide,[615] although it has been shown to occur with magnesium.[616] The R' group is usually, although not always, alkyl, and often butyl; R is usually aromatic.[617] Alkyl halides are generally not reactive enough, while allylic and benzylic halides usually give Wurtz coupling. Of course, the R that becomes bonded to the halogen is the one for which RH is the weaker acid. Despite the preponderance of reactions with bromides and iodides, it is noted that the reaction of 1-fluorooctane with 4–10 equivalents of lithium powder and 2–4 equivalents of DTBB (4,4′-di-*tert*-butylbiphenyl) in THP at 0°C for 5 min, was shown to give a solution of the corresponding 1-octyllithium.[618] Vinylic halides react with retention of configuration.[619] The

[611]Garst, J.F.; Deutch, J.E.; Whitesides, G.M. *J. Am. Chem. Soc.* ***1986***, *108*, 2490; Ashby, E.C.; Oswald, J. *J. Org. Chem.* ***1988***, *53*, 6068; Garst, J.F. *Acc. Chem. Res.* ***1991***, *24*, 95; Garst, J.F.; Ungváry, F.; Batlaw, R.; Lawrence, K.E. *J. Am. Chem. Soc.* ***1991***, *113*, 5392.

[612]Walborsky, H.M.; Rachon, J. *J. Am. Chem. Soc.* ***1989***, *111*, 1896; Rachon, J.; Walborsky, H.M. *Tetrahedron Lett.* ***1989***, *30*, 7345; Walborsky, H.M. *Acc. Chem. Res.* ***1990***, *23*, 286.

[613]de Boer, H.J.R.; Akkerman, O.S.; Bickelhaupt, F. *Angew. Chem. Int. Ed.* ***1988***, *27*, 687.

[614]See Hölzer, B.; Hoffmann, R.W. *Chem. Commun.* ***2003***, 732; Walborsky, H.M.; Impastato, F.J.; Young, A.E. *J. Am. Chem. Soc.* ***1964***, *86*, 3283; Tanaka, M.; Ogata, I. *Bull. Chem. Soc. Jpn.* ***1975***, *48*, 1094; Schumann, H.; Wassermann, B.C.; Hahn, F.E. *Organometallics* ***1992***, *11*, 2803; Dakternieks, D.; Dunn, K.; Henry, D.J.; Schiesser, C.H.; Tiekink, E.R. *Organometallics* ***1999***, *18*, 3342.

[615]For reviews, see Wardell, J.L., in Zuckerman, J.J. *Inorganic Reactions and Methods*, Vol. 11, VCH, NY, ***1988***, pp. 107–129; Parham, W.E.; Bradsher, C.K. *Acc. Chem. Res.* ***1982***, *15*, 300.

[616]See, for example, Zakharkin, L.I.; Okhlobystin, O.Yu.; Bilevitch, K.A. *J. Organomet. Chem.* ***1964***, *2*, 309; Tamborski, C.; Moore, G.J. *J. Organomet. Chem.* ***1971***, *26*, 153.

[617]For the preparation of primary alkyllithiums by this reaction, see Bailey, W.F.; Punzalan, E.R. *J. Org. Chem.* ***1990***, *55*, 5404; Negishi, E.; Swanson, D.R.; Rousset, C.J. *J. Org. Chem.* ***1990***, *55*, 5406.

[618]Yus, M.; Herrera, R.P.; Guijarro, A. *Tetrahedron Lett.*, ***2003***, *44*, 5025.

[619]For examples of exchange where R = vinylic, see Neumann, H.; Seebach, D. *Chem. Ber.* ***1978***, *111*, 2785; Miller, R.B.; McGarvey, G. *Synth. Commun.* ***1979***, *9*, 831; Sugita, T.; Sakabe, Y.; Sasahara, T.; Tsukuda, M.; Ichikawa, K. *Bull. Chem. Soc. Jpn.* ***1984***, *57*, 2319.

reaction can be used to prepare α-halo organolithium and α-halo organomagnesium compounds,[620] for example,[621]

$$CCl_4 + BuLi \xrightarrow[-105^\circ C]{THF} Cl_3C\text{—}Li$$

Such compounds can also be prepared by hydrogen–metal exchange, for example,[622]

$$Br_3CH + i\text{PrMgCl} \xrightarrow[-95^\circ C]{THF-HMPA} Br_3C\text{—}MgCl + C_3H_8$$

This is an example of **12-22**. However, these α-halo organometallic compounds are stable (and configurationally stable as well[623]) only at low temperatures (ca. -100°C) and only in THF or mixtures of THF and other solvents (e.g., HMPA). At ordinary temperatures they lose MX (α elimination) to give carbenes (which then react further) or carbenoid reactions. The α-chloro-α-magnesio sulfones $ArSO_2CH(Cl)MgBr$ are exceptions, being stable in solution at room temperature and even under reflux.[624] Compounds in which a halogen and a transition metal are on the same carbon can be more stable than the ones with lithium.[625]

There is evidence that the mechanism[626] of the reaction of alkyllithium compounds with alkyl and aryl iodides involves free radicals.[627]

$$RX + R'M \rightleftarrows \underset{\text{Solvent cage}}{[R\bullet, X, M, R'\bullet]} \rightleftarrows RM + R'X$$

Among the evidence is the fact that coupling and disproportionation products are obtained from R• and R′• and the observation of CIDNP.[627,628] However, in the degenerate exchange between PhI and PhLi the ate complex Ph_2I^- Li^+ has been

[620]For reviews of such compounds, see Siegel, H. *Top. Curr. Chem.* ***1982***, *106*, 55; Negishi, E. *Organometallics in Organic Synthesis*, Wiley, NY, ***1980***, pp. 136–151; Köbrich, G. *Angew. Chem. Int. Ed.* ***1972***, *11*, 473; ***1967***, *6*, 41; *Bull. Soc. Chim. Fr.* ***1969***, 2712; Villieras, J. *Organomet. Chem. Rev. Sect. A* ***1971***, *7*, 81. For related reviews, see Krief, A. *Tetrahedron* ***1980***, *36*, 2531; Normant, H. *J. Organomet. Chem.* ***1975***, *100*, 189; Zhil'tsov, S.F.; Druzhkov, O.N. *Russ. Chem. Rev.* ***1971***, *40*, 126.

[621]Hoeg, D.F.; Lusk, D.I.; Crumbliss, A.L. *J. Am. Chem. Soc.* ***1965***, *87*, 4147. See also, Villieras, J.; Tarhouni, R.; Kirschleger, B.; Rambaud, M. *Bull. Soc. Chim. Fr.* ***1985***, 825.

[622]Villieras, J. *Bull. Soc. Chim. Fr.* ***1967***, 1520.

[623]Schmidt, A.; Köbrich, G.; Hoffmann, R.W. *Chem. Ber.* ***1991***, *124*, 1253; Hoffmann, R.W.; Bewersdorf, M. *Chem. Ber.* ***1991***, *124*, 1259.

[624]Stetter, H.; Steinbeck, K. *Liebigs Ann. Chem.* ***1972***, *766*, 89.

[625]Kauffmann, T.; Fobker, R.; Wensing, M. *Angew. Chem. Int. Ed.* ***1988***, *27*, 943.

[626]For reviews of the mechanism, see Bailey, W.F.; Patricia, J.J. *J. Organomet. Chem.* ***1988***, *352*, 1; Beletskaya, I.P.; Artamkina, G.A.; Reutov, O.A. *Russ. Chem. Rev.* ***1976***, *45*, 330.

[627]Ward, H.R.; Lawler, R.G.; Cooper, R.A. *J. Am. Chem. Soc.* ***1969***, *91*, 746; Lepley, A.R.; Landau, R.L. *J. Am. Chem. Soc.* ***1969***, *91*, 748; Ashby, E.C.; Pham, T.N. *J. Org. Chem.* ***1987***, *52*, 1291. See also, Bailey, W.F.; Patricia, J.J.; Nurmi, T.T.; Wang, W. *Tetrahedron Lett.* ***1986***, *27*, 1861.

[628]Ward, H.R.; Lawler, R.G.; Loken, H.Y. *J. Am. Chem. Soc.* ***1968***, *90*, 7359.

shown to be an intermediate,[629] and there is other evidence that radicals are not involved in all instances of this reaction.[630]

In a completely different kind of process, alkyl halides can be converted to certain organometallic compounds by treatment with organometalate ions, for example,

$$RX + R'_3SnLi \longrightarrow RSnR'_3 + LiX$$

Most of the evidence is in accord with a free-radical mechanism involving electron transfer, although an S_N2 mechanism can compete under some conditions.[631]

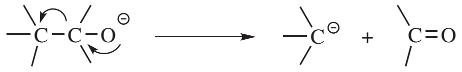
OS **VI**, 82; **VII**, 271, 326, 495; **VIII**, 430. See also, OS **VII**, 512; **VIII**, 479.

CARBON LEAVING GROUPS

In these reactions (**12-40–12-48**), a carbon–carbon bond cleaves. We regard as the substrate the side that retains the electron pair; hence the reactions are considered electrophilic substitutions. The incoming group is hydrogen in all but one (**12-42**) of the cases. The reactions in groups A and B are sometimes called *anionic cleavages*,[632] although they do not always occur by mechanisms involving free carbanions (S_E1). When they do, the reactions are facilitated by increasing stability of the carbanion.

A. Carbonyl-Forming Cleavages

These reactions follow the pattern



The leaving group is stabilized because the electron deficiency at its carbon is satisfied by a pair of electrons from the oxygen. With respect to the leaving group the reaction is elimination to form a C=O bond. Retrograde aldol reactions (**16-34**) and cleavage of cyanohydrins (**16-52**) belong to this classification but are treated in Chapter 16 under their more important reverse reactions. Other eliminations to form C=O bonds are discussed in Chapter 17 (**17-32**).

12-40 Decarboxylation of Aliphatic Acids

Hydro-de-carboxylation

$$RCOOH \longrightarrow RH + CO_2$$

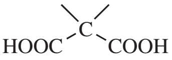
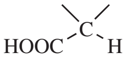
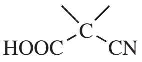
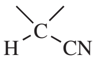
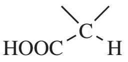
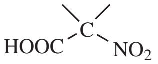
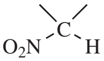
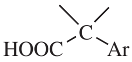
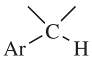
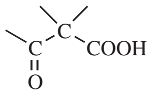
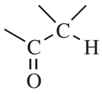
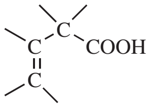
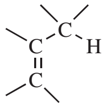
[629]See Farnham, W.B.; Calabrese, J.C. *J. Am. Chem. Soc.* ***1986***, *108*, 2449; Reich, H.J.; Green, D.P.; Phillips, N.H. *J. Am. Chem. Soc.* ***1989***, *111*, 3444.

[630]Rogers, H.R.; Houk, J. *J. Am. Chem. Soc.* ***1982***, *104*, 522; Beak, P.; Allen, D.J.; Lee, W.K. *J. Am. Chem. Soc.* ***1990***, *112*, 1629.

[631]See San Filippo, Jr., J.; Silbermann, J. *J. Am. Chem. Soc.* ***1982***, *104*, 2831; Ashby, E.C.; Su, W.; Pham, T.N. *Organometallics* ***1985***, *4*, 1493; Alnajjar, M.S.; Kuivila, H.G. *J. Am. Chem. Soc.* ***1985***, *107*, 416.

[632]For a review, see Artamkina, G.A.; Beletskaya, I.P. *Russ. Chem. Rev.* ***1987***, *56*, 983.

TABLE 12.2. Some Acids that Undergo Decarboxylation Fairly Readily[a]

	Acid Type	Decarboxylation Product
Malonic		
α-Cyano		 or 
α-Nitro		
α-Aryl		
α,α,α-Trihalo	X_3C——COOH	X_3C–H
β-Keto		
β,γ-Unsaturated		

[a]Others are described in the text.

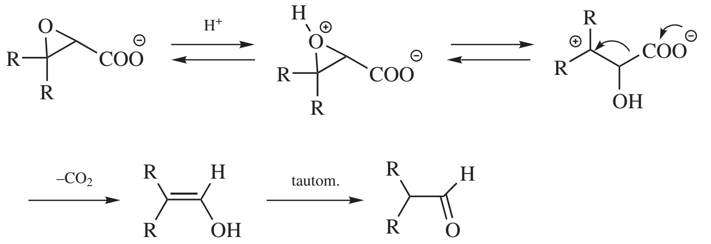
Many carboxylic acids can be successfully decarboxylated, either as the free acid or in the salt form, but not simple fatty acids.[633] An exception is acetic acid, which as the acetate, heated with base, gives good yields of methane. Malonic acid derivatives are the most common substrates for decarboxylation, giving the corresponding monocarboxylic acid. Decarboxylation of 2-substituted malonic acids has been reported using microwave irradiation.[634] Aliphatic acids that do undergo successful decarboxylation have certain functional groups or double or triple bonds in the α or β position. Some of these are shown in Table 12.2. For decarboxylation of aromatic acids, see **11-35**. Decarboxylation of an α-cyano acid can give a nitrile or a carboxylic acid, since the cyano group may or may not be hydrolyzed in the course of the reaction. In addition to the compounds listed in Table 12.2, decarboxylation can also be carried out on α,β-unsaturated and α,β-acetylenic acids. α,β-Unsaturated acids can also be decarboxylated[635] with copper

[633]March, J. *J. Chem. Educ.* ***1963***, *40*, 212.

[634]Zara, C.L.; Jin, T.; Giguere, R.J. *Synth. Commun.* ***2000***, *30*, 2099.

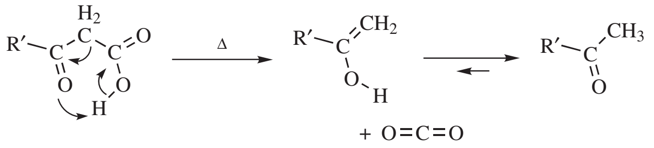
[635]For an example involving the conversion of C=C-COOH to C=C-Br with LiBr and ceric ammonium nitrate in aqueous acetonitrile, see Roy, S.C.; Guin, C.; Maiti, G. *Tetrahedron Lett.* ***2001***, *42*, 9253.

and quinoline in a manner similar to that discussed in **11-35**. Glycidic acids give aldehydes on decarboxylation. The following mechanism has been suggested:[636]



The direct product is an enol that tautomerizes to the aldehyde.[637] This is the usual last step in the Darzens reaction (**16-40**).

Decarboxylations can be regarded as reversals of the addition of carbanions to carbon dioxide (**16-82**), but free carbanions are not always involved.[638] When the carboxylate *ion* is decarboxylated, the mechanism can be either S_E1 or S_E2. In the case of the S_E1 mechanism, the reaction is of course aided by the presence of electron-withdrawing groups, which stabilize the carbanion.[639] Decarboxylations of carboxylate ions can be accelerated by the addition of a suitable crown ether, which in effect removes the metallic ion.[640] The reaction without the metallic ion has also been performed in the gas phase.[641] But some acids can also be decarboxylated directly and, in most of these cases, there is a cyclic, six-center mechanism:



Here too there is an enol that tautomerizes to the product. The mechanism is illustrated for the case of β-keto acids,[642] but it is likely that malonic acids, α-cyano acids, α-nitro acids, and β,γ-unsaturated acids[643] behave similarly,

[636]Singh, S.P.; Kagan, J. *J. Org. Chem.* ***1970***, *35*, 2203.

[637]Shiner, Jr., V.J.; Martin, B. *J. Am. Chem. Soc.* ***1962***, *84*, 4824.

[638]For reviews of the mechanism, see Richardson, W.H.; O'Neal, H.E., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 5, Elsevier, NY, ***1972***, pp. 447–482; Clark, L.W., in Patai, S. *The Chemistry of Carboxylic Acids and Esters*; Wiley, NY, ***1969***, pp. 589–622. For a review of carbon isotope effect studies, see Dunn, G.E. *Isot. Org. Chem.* ***1977***, *3*, 1.

[639]See, for example, Oae, S.; Tagaki, W.; Uneyama, K.; Minamida, I. *Tetrahedron* ***1968***, *24*, 5283; Buncel, E.; Venkatachalam, T.K.; Menon, B.C. *J. Org. Chem.* ***1984***, *49*, 413.

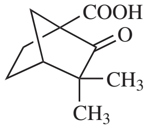
[640]Hunter, D.H.; Patel, V.; Perry, R.A. *Can. J. Chem.* ***1980***, *58*, 2271, and references cited therein.

[641]Graul, S.T.; Squires, R.R. *J. Am. Chem. Soc.* ***1988***, *110*, 607.

[642]For a review of the mechanism of the decarboxylation of β-keto acids, see Jencks, W.P. *Catalysis in Chemistry and Enzmology*; McGraw-Hill, NY, ***1969***, pp. 116–120.

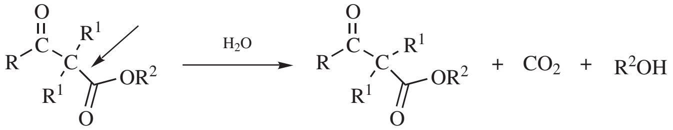
[643]Bigley, D.B.; Clarke, M.J. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 1, and references cited therein. For a review, see Smith, G.G.; Kelly, F.W. *Prog. Phys. Org. Chem.* ***1971***, *8*, 75, pp. 150–153.

since similar six-membered transition states can be written for them. Some α,β-unsaturated acids are also decarboxylated by this mechanism by isomerizing to the β,γ-isomers before they



49

actually decarboxylate.[644] Evidence is that **49** and similar bicyclic β-keto acids resist decarboxylation.[645] In such compounds, the six-membered cyclic transition state cannot form for steric reasons, and if it could, formation of the intermediate enol would violate Bredt's rule (p. 229).[646] Some carboxylic acids that cannot form a six-membered transition state can still be decarboxylated, and these presumably react through an S_E1 or S_E2 mechanism.[647] Further evidence for the cyclic mechanism is that the reaction rate varies very little with a change from a nonpolar to a polar solvent (even from benzene to water[648]), and is not subject to acid catalysis.[649] The rate of decarboxylation of a β,γ-unsaturated acid was increased $\sim 10^5$–10^6 times by introduction of a β-methoxy group, indicating that the cyclic transition state has dipolar character.[650]



β-Keto acids[651] are easily decarboxylated, but such acids are usually prepared from β-keto esters, and the esters are easily decarboxylated themselves on hydrolysis without isolation of the acids.[652] This decarboxylation of β-keto esters

[644]Bigley, D.B. *J. Chem. Soc.* ***1964***, 3897.

[645]Wasserman, H.H., in Newman *Steric Effects in Organic Chemistry*, Wiley, NY, ***1956***, p. 352. See also, Buchanan, G.L.; Kean, N.B.; Taylor, R. *Tetrahedron* ***1975***, *31*, 1583.

[646]Sterically hindered β-keto acids decarboxylate more slowly: Meier, H.; Wengenroth, H.; Lauer, W.; Krause, V. *Tetrahedron Lett.* ***1989***, *30*, 5253.

[647]For example, see Ferris, J.P.; Miller, N.C. *J. Am. Chem. Soc.* ***1966***, *88*, 3522.

[648]Westheimer, F.H.; Jones, W.A. *J. Am. Chem. Soc.* ***1941***, *63*, 3283; Swain, C.G.; Bader, R.F.W.; Esteve Jr., R.M.; Griffin, R.N. *J. Am. Chem. Soc.* ***1961***, *83*, 1951.

[649]Pedersen, K.J. *Acta Chem. Scand.* ***1961***, *15*, 1718; Noyce, D.S.; Metesich, M.A. *J. Org. Chem.* ***1967***, *32*, 3243.

[650]Bigley, D.B.; Al-Borno, A. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 15.

[651]For a review of β-keto acids, see Oshry, L.; Rosenfeld, S.M. *Org. Prep. Proced. Int.* ***1982***, *14*, 249.

[652]For a list examples, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1542–1543. For an example of decarboxylation of the β-keto ester with Cp2TiCl2 and *i*-PrMgBr, followed by treatment with 2*N* HCl, see Yu, Y.; Zhang, Y. *Synth. Commun.* ***1999***, *29*, 243.

involving cleavage on the carboxyl side of the substituted methylene group (arrow) is carried out under acidic, neutral, or slightly basic conditions to yield a ketone. When strongly basic conditions are used, cleavage occurs on the other side of the CR_2 group (**12-43**). β-Keto esters can be decarbalkoxylated without passing through the free-acid stage by treatment with boric anhydride (B_2O_3) at 150°C.[653] The alkyl portion of the ester (R') is converted to an alkene or, if it lacks a β hydrogen, to an ether R'OR'. Another method for the decarbalkoxylation of β-keto esters, malonic esters, and α-cyano esters consists of heating the substrate in wet DMSO containing NaCl, Na_3PO_4, or some other simple salt.[654] In this method too, the free acid is probably not an intermediate, but here the alkyl portion of the substrate is converted to the corresponding alcohol. Ordinary carboxylic acids, containing no activating groups, can be decarboxylated by conversion to esters of *N*-hydroxypyridine-2-thione and treatment of these with Bu_3SnH.[655] A free-radical mechanism is likely. α-Amino acids have been decarboxylated by treatment with a catalytic amount of 2-cyclohexenone.[656] Amino acids are decarboxylated by sequential treatment with NBS at pH 5 followed by $NaBH_4$ and $NiCl_2$.[657] Certain decarboxylations can also be accomplished photochemically.[658] See also, the decarbonylation of acyl halides, mentioned in **14-32**. In some cases, decarboxylations can give organometallic compounds: $RCOOM \rightarrow RM + CO_2$.[659]

Some of the decarboxylations listed in *Organic Syntheses* are performed with concomitant ester or nitrile hydrolysis and others are simple decarboxylations.

With ester or nitrile hydrolysis: OS **I**, 290, 451, 523; **II**, 200, 391; **III**, 281, 286, 313, 326, 510, 513, 591; **IV**, 55, 93, 176, 441, 664, 708, 790, 804; **V**, 76, 288, 572, 687, 989; **VI**, 615, 781, 873, 932; **VII**, 50, 210, 319; **VIII**, 263.

Simple decarboxylations: OS **I**, 351, 401, 440, 473, 475; **II**, 21, 61, 93, 229, 302, 333, 368, 416, 474, 512, 523; **III**, 213, 425, 495, 705, 733, 783; **IV**, 234, 254, 278, 337, 555, 560, 597, 630, 731, 857; **V**, 251, 585; **VI**, 271, 965; **VII**, 249, 359; **VIII**, 235, 444, 536; **75**, 195. Also see, OS **IV**, 633.

[653]Lalancette, J.M.; Lachance, A. *Tetrahedron Lett.* ***1970***, 3903.

[654]For a review of the synthetic applications of this method, see Krapcho, A.P. *Synthesis* ***1982***, 805, 893. For other methods, see Aneja, R.; Hollis, W.M.; Davies, A.P.; Eaton, G. *Tetrahedron Lett.* ***1983***, *24*, 4641; Brown, R.T.; Jones, M.F. *J. Chem. Res. (S)* ***1984***, 332; Dehmlow, E.V.; Kunesch, E. *Synthesis* ***1985***, 320; Taber, D.F.; Amedio, Jr., J.C.; Gulino, F. *J. Org. Chem.* ***1989***, *54*, 3474.

[655]Barton, D.H.R.; Crich, D.; Motherwell, W.B. *Tetrahedron* ***1985***, *41*, 3901; Della, E.W.; Tsanaktsidis, J. *Aust. J. Chem.* ***1987***, *39*, 2061. For another method of more limited scope, see Maier, W.F.; Roth, W.; Thies, I.; Schleyer, P.v.R. *Chem. Ber.* ***1982***, *115*, 808.

[656]Hashimoto, M.; Eda, Y.; Osanai, Y.; Iwai, T.; Aoki, S. *Chem. Lett.* ***1986***, 893.

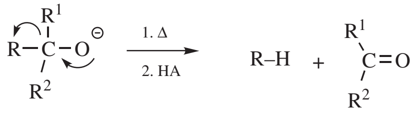
[657]Laval, G.; Golding, B.T. *Synlett* ***2003***, 542.

[658]See Davidson, R.S.; Steiner, P.R. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 1357; Kraeutler, B.; Bard, A.J. *J. Am. Chem. Soc.* ***1978***, *100*, 5985; Hasebe, M.; Tsuchiya, T. *Tetrahedron Lett. 1987, 28*, 6207; Okada, K.; Okubo, K.; Oda, M. *Tetrahedron Lett. 1989, 30*, 6733.

[659]For reviews, see Deacon, G.B. *Organomet. Chem. Rev. A* ***1970***, 355; Deacon, G.B.; Faulks, S.J.; Pain, G.N. *Adv. Organomet. Chem.* ***1986***, *25*, 237.

12-41 Cleavage of Alkoxides

Hydro-de-(α-oxidoalkyl)-substitution



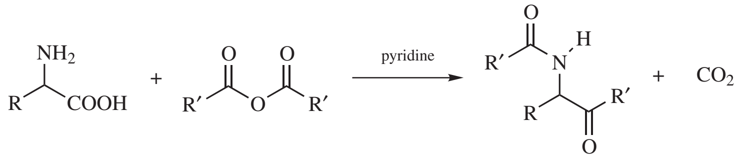
Alkoxides of tertiary alcohols can be cleaved in a reaction that is essentially the reverse of addition of carbanions to ketones (**16-24**).[660] The reaction is unsuccessful when the R groups are simple unbranched alkyl groups, for example, the alkoxide of triethylcarbinol. Cleavage is accomplished with branched alkoxides, such as the alkoxides of diisopropylneopentylcarbinol or tri-*tert*-butylcarbinol.[661] Allylic,[662] benzylic,[663] and aryl groups also cleave; for example, the alkoxide of triphenylcarbinol gives benzene and benzophenone. Studies in the gas phase show that the cleavage is a simple one, giving the carbanion and ketone directly in one step.[664] However, with some substrates in solution, substantial amounts of dimer R–R have been found, indicating a radical pathway.[665] Hindered alcohols (not the alkoxides) also lose one R group by cleavage, also by a radical pathway.[666]

The reaction has been used for extensive mechanistic studies (see p. 758).

OS **VI**, 268.

12-42 Replacement of a Carboxyl Group by an Acyl Group

Acyl-de-carboxylation



[660]Zook, H.D.; March, J.; Smith, D.F. *J. Am. Chem. Soc.* ***1959***, *81*, 1617; Barbot, F.; Miginiac, P. *J. Organomet. Chem.* ***1977***, *132*, 445; Benkeser, R.A.; Siklosi, M.P.; Mozdzen, E.C. *J. Am. Chem. Soc.* ***1978***, *100*, 2134.

[661]Arnett, E.M.; Small, L.E.; McIver Jr., R.T.; Miller, J.S. *J. Org. Chem.* ***1978***, *43*, 815. See also Lomas, J.S.; Dubois, J.E. *J. Org. Chem.* ***1984***, *49*, 2067.

[662]See Snowden, R.L.; Linder, S.M.; Muller, B.L.; Schulte-Elte, K.H. *Helv. Chim. Acta* ***1987***, *70*, 1858, 1879.

[663]Partington, S.M.; Watt, C.I.F. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 983.

[664]Tumas, W.; Foster, R.F.; Brauman, J.I. *J. Am. Chem. Soc.* ***1988***, *110*, 2714; Ibrahim, S.; Watt, C.I.F.; Wilson, J.M.; Moore, C. *J. Chem. Soc. Chem. Commun.* ***1989***, 161.

[665]Paquette, L.A.; Gilday, J.P.; Maynard, G.D. *J. Org. Chem.* ***1989***, *54*, 5044; Paquette, L.A.; Maynard, G.D. *J. Org. Chem.* ***1989***, *54*, 5054.

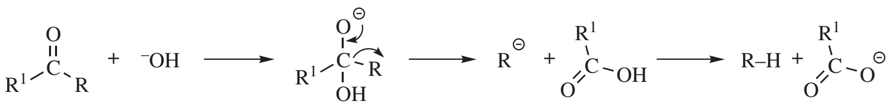
[666]See Lomas, J.S.; Fain, D.; Briand, S. *J. Org. Chem.* ***1990***, *55*, 1052, and references cited therein.

When an α-amino acid is treated with an anhydride in the presence of pyridine, the carboxyl group is replaced by an acyl group and the NH_2 becomes acylated. This is called the *Dakin–West reaction*.[667] The mechanism involves formation of an oxazolone.[668] The reaction sometimes takes place on carboxylic acids even when an a amino group is not present. A number of *N*-substituted amino acids, RCH(NHR′)COOH, give the corresponding *N*-alkylated products.

OS **IV**, 5; **V**, 27.

B. Acyl Cleavages

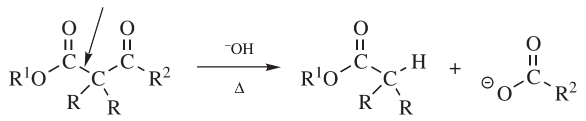
In these reactions (**12-43–12-46**), a carbonyl group is attacked by a hydroxide ion (or amide ion), giving an intermediate that undergoes cleavage to a carboxylic acid (or an amide). With respect to the leaving group, this is nucleophilic substitution at a carbonyl group and the mechanism is the tetrahedral one discussed in Chapter 10.



With respect to R this is of course electrophilic substitution. The mechanism is usually S_E1.

12-43 Basic Cleavage of β-Keto Esters and β-Diketones

Hydro-de-acylation

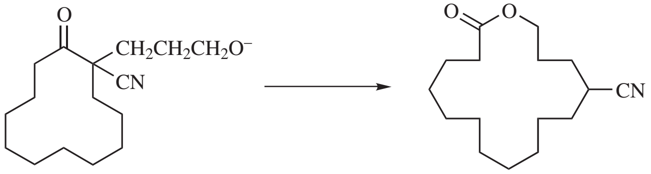


When β-keto esters are treated with concentrated base, cleavage occurs, but is on the keto side of the CR_2 group (arrow) in contrast to the acid cleavage mentioned on page 838. The products are a carboxylic ester and the salt of an acid. However, the utility of the reaction is somewhat limited by the fact that decarboxylation is a side reaction, even under basic conditions. β-Diketones behave similarly to give a ketone and the salt of a carboxylic acid. With both β-keto esters and β-diketones, $^-$OEt can be used instead of $^-$OH, in which case the ethyl esters of the corresponding acids are obtained instead of the salts. In the case of β-keto esters, this is the reverse of Claisen condensation (**16-85**). The similar cleavage of cyclic α-cyano

[667]For a review, see Buchanan, G.L. *Chem. Soc. Rev.* ***1988***, *17*, 91.

[668]Allinger, N.L.; Wang, G.L.; Dewhurst, B.B. *J. Org. Chem.* ***1974***, *39*, 1730.

ketones, in an intramolecular fashion, has been used to effect a synthesis of macrocyclic lactones such as **50**.[669]

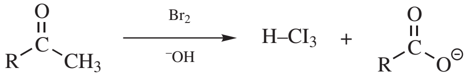


50

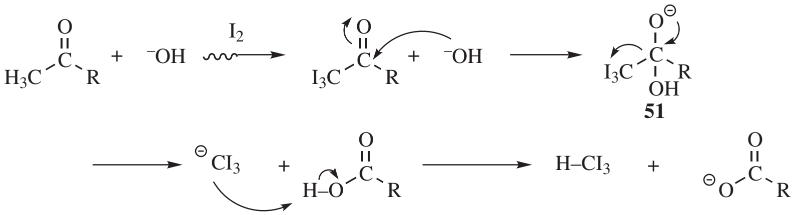
Activated F^- (from KF and a crown ether) has been used as the base to cleave an α-cyano ketone.[670]

OS **II**, 266, 531; **III**, 379; **IV**, 415, 957; **V**, 179, 187, 277, 533, 747, 767.

12-44 Haloform Reaction



In the *haloform reaction*, methyl ketones (and the only methyl aldehyde, acetaldehyde) are cleaved with halogen and a base.[671] The halogen can be bromine, chlorine, or iodine. What takes place is actually a combination of two reactions. The first is an example of **12-4**, in which, under the basic conditions employed, the methyl group is trihalogenated. Then the resulting trihalo ketone is attacked by hydroxide ion to give tetrahedral intermediate **51**.[672] The X_3C^- group is a sufficiently good leaving group (not HX_2C^- or H_2XC^-) that a carboxylic acid is formed, with quickly reacts with the carbanion to give the final products. Primary or secondary methylcarbinols also give the reaction, because they are oxidized to the carbonyl compounds under the conditions employed.



[669]Milenkov, B.; Hesse, M. *Helv. Chim. Acta* ***1987***, *70*, 308. For a similar preparation of lactams, see Wälchli, R.; Bienz, S.; Hesse, M. *Helv. Chim. Acta* ***1985***, *68*, 484.

[670]Beletskaya, I.P.; Gulyukina, N.S.; Borodkin, V.S.; Solov'yanov, A.A.; Reutov, O.A. *Doklad. Chem.* ***1984***, *276*, 202. See also, Mignani, G.; Morel, D.; Grass, F. *Tetrahedron Lett.* ***1987***, *28*, 5505.

[671]For a review of this and related reactions, see Chakrabartty, S.K., in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. C, Academic Press, NY, ***1978***, pp. 343–370.

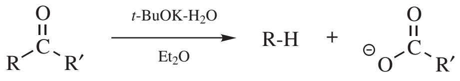
[672]For a complete kinetic analysis of the chlorination of acetone, see Guthrie, J.P.; Cossar, J. *Can. J. Chem.* ***1986***, *64*, 1250. For a discussion of the mechanism of the cleavage step, see Zucco, C.; Lima, C.F.; Rezende, M.C.; Vianna, J.F.; Nome, F. *J. Org. Chem.* ***1987***, *52*, 5356.

As with **12-4**, the rate-determining step is the preliminary enolization of the methyl ketone.[673] A side reaction is α halogenation of the non-methyl R group. Sometimes these groups are also cleaved.[674] The reaction cannot be applied to F_2, but ketones of the form $RCOCF_3$ (R = alkyl or aryl) give fluoroform and $RCOO^-$ when treated with base.[675] Rate constants for cleavage of X_3CCOPh (X = F, Cl, Br) were found to be in the ratio $1 : 5.3 \times 10^{10} : 2.2 \times 10^{13}$, showing that an F_3C^- group cleaves much more slowly than the others.[676] The haloform reaction is often used as a test for methylcarbinols and methyl ketones. Iodine is most often used as the test reagent, since iodoform (HCI_3) is an easily identifiable yellow solid. The reaction is also frequently used for synthetic purposes. Methyl ketones $RCOCH_3$ can be converted directly to methyl esters $RCOOCH_3$ by an electrochemical reaction.[677] Trifluoromethyl ketones have been converted to ethyl esters via treatment with NaH in aqueous DMF followed by reaction with bromoethane.[678]

OS **I**, 526; **II**, 428; **III**, 302; **IV**, 345; **V**, 8. Also see, OS **VI**, 618.

12-45 Cleavage of Nonenolizable Ketones

Hydro-de-acylation



Ordinary ketones are generally much more difficult to cleave than trihalo ketones or β-diketones, because the carbanion intermediates in these cases are more stable than simple carbanions. However, nonenolizable ketones can be cleaved by treatment with a 10:3 mixture of *t*-BuOK–H_2O in an aprotic solvent, such as ether, DMSO, 1,2-dimethoxyethane (glyme), [679] or with solid *t*-BuOK in the absence of a solvent.[680] When the reaction is applied to monosubstituted diaryl ketones, that aryl group preferentially cleaves that comes off as the more stable carbanion, except that aryl groups substituted in the ortho position are more readily cleaved than otherwise because of the steric effect (relief of strain).[680,681] In certain cases, cyclic ketones can be cleaved by base treatment, even if they are enolizable.[682]

OS **VI**, 625. See also, OS **VII**, 297.

[673]Pocker, Y. *Chem. Ind.* (*London*) ***1959***, 1383.

[674]Levine, R.; Stephens, J.R. *J. Am. Chem. Soc.* ***1950***, *72*, 1642.

[675]See Hudlicky, M. *Chemistry of Organic Fluorine Compounds*, 2nd ed.; Ellis Horwood: Chichester, ***1976***, pp. 276–278.

[676]Guthrie, J.P.; Cossar, J. *Can. J. Chem.* ***1990***, *68*, 1640.

[677]Nikishin, G.I.; Elinson, M.N.; Makhova, I.V. *Tetrahedron* ***1991***, *47*, 895.

[678]Delgado, A.; Clardy, J. *Tetrahedron Lett.* ***1992***, *33*, 2789.

[679]Swan, G.A. *J. Chem. Soc.* ***1948***, 1408; Gassman, P.G.; Lumb, J.T.; Zalar, F.V. *J. Am. Chem. Soc.* ***1967***, *89*, 946.

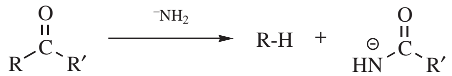
[680]March, J.; Plankl, W. *J. Chem. Soc. Perkin Trans. 1* ***1977***, 460.

[681]Davies, D.G.; Derenberg, M.; Hodge, P. *J. Chem. Soc. C* ***1971***, 455.

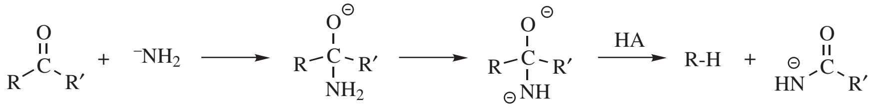
[682]For example, see Swaminathan, S.; Newman, M.S. *Tetrahedron* ***1958***, *2*, 88; Hoffman, T.D.; Cram, D.J. *J. Am. Chem. Soc.* ***1969***, *91*, 1009.

12-46 The Haller–Bauer Reaction

Hydro-de-acylation



Cleavage of ketones with sodium amide is called the *Haller–Bauer reaction*.[683] As with **12-45**, which is exactly analogous, the reaction is usually applied only to nonenolizable ketones, most often to ketones of the form $ArCOCR_3$, where the products R_3CCONH_2 are not easily attainable by other methods. However, many other ketones have been used, although benzophenone is virtually unaffected. It has been shown that the configuration of optically active alkyl groups (R) is retained.[684] The NH_2 loses its proton from the tetrahedral intermediate **52** before the R group is cleaved.[685]



52

An extension of this cleavage process involves the reaction of α-nitro ketones ($O{=}C\text{-}CHRNO_2$) with a primary amine, neat, to give the corresponding amide ($O{=}C\text{-}NHR'$).[686]

OS **V**, 384, 1074.

C. Other Cleavages

12-47 The Cleavage of Alkanes

Hydro-de-*tert*-butylation, and so on

$$(CH_3)_4C \xrightarrow{FSO_3H\text{-}SbF_5} CH_4 + (CH_3)_3C^+$$

The C–C bonds of alkanes can be cleaved by treatment with superacids[48] (p. 236). For example, neopentane in $FSO_3H–SbF_5$ can cleave to give methane and the *tert*-butyl cation. The C–H cleavage (see **12-1**) is a competing reaction and, for example, neopentane can give H_2 and the *tert*-pentyl cation (formed by rearrangement of the initially formed neopentyl cation) by this pathway. In general, the order of reactivity is tertiary C–H $>$ C–C $>$ secondary C–H $\gg$ primary C–H,

[683]For a review, see Gilday, J.P.; Paquette, L.A. *Org. Prep. Proced. Int.* ***1990***, *22*, 167. For an improved procedure, see Kaiser, E.M.; Warner, C.D. *Synthesis* ***1975***, 395.

[684]Impastato, F.J.; Walborsky, H.M. *J. Am. Chem. Soc.* ***1962***, *84*, 4838; Paquette, L.A.; Gilday, J.P. *J. Org. Chem.* ***1988***, *53*, 4972; Paquette, L.A.; Ra, C.S. *J. Org. Chem.* ***1988***, *53*, 4978.

[685]Bunnett, J.F.; Hrutfiord, B.F. *J. Org. Chem.* ***1962***, *27*, 4152.

[686]Ballini, R.; Bosica, G.; Fiorini, D. *Tetrahedron* ***2003***, *59*, 1143.

although steric factors cause a shift in favor of C–C cleavage in such a hindered compound as tri-*tert*-butylmethane. The mechanism is similar to that shown in **12-1** and **12-20** and involves attack by H^+ on the C–C bond to give a pentavalent cation.

Catalytic hydrogenation seldom breaks unactivated C–C bonds (i.e., $R{-}R' + H_2 \rightarrow RH + R'H$), but methyl and ethyl groups have been cleaved from substituted adamantanes by hydrogenation with a Ni–Al_2O_3 catalyst at about 250°C.[687] Certain C–C bonds have been cleaved by alkali metals.[688]

The C–C bond of 2-allyl-2-arylmalonate derivatives was cleaved, with loss of the allylic group to give the 2-arylmalonate, by treatment with a nickel catalyst.[689]

12-48 Decyanation or Hydro-de-cyanation

$$\text{RCN} \xrightarrow{\text{Na-NH}_3 \text{ or Na-Fe(acac)}_3} \text{RH}$$

The cyano group of alkyl nitriles can be removed[690] by treatment with metallic sodium, either in liquid ammonia,[691] or together with tris(acetylacetonato)iron(III) [$Fe(acac)_3$][692] or, with lower yields, titanocene. The two procedures are complementary. Although both can be used to decyanate many kinds of nitriles, the Na–NH_3 method gives high yields with R groups, such as trityl, benzyl, phenyl, and tertiary alkyl, but lower yields (~35–50%) when R = primary or secondary alkyl. On the other hand, primary and secondary alkyl nitriles are decyanated in high yields by the Na–$Fe(acac)_3$ procedure. Sodium in liquid ammonia is known to be a source of solvated electrons, and the reaction may proceed through the free radical R• that would then be reduced to the carbanion R^-, which by abstraction of a proton from the solvent, would give RH. The mechanism with $Fe(acac)_3$ is presumably different. Another procedure,[693] which is successful for R = primary, secondary, or tertiary, involves the use of potassium metal and the crown ether dicyclohexano-18-crown-6 in toluene.[694]

[687]Grubmüller, P.; Schleyer, P.v.R.; McKervey, M.A. *Tetrahedron Lett.* ***1979***, 181.

[688]For examples and references, see Grovenstein, Jr., E.; Bhatti, A.M.; Quest, D.E.; Sengupta, D.; VanDerveer, D. *J. Am. Chem. Soc.* ***1983***, *105*, 6290.

[689]Nečas, D.; Turský, M.; Kotora, M. *J. Am. Chem. Soc.* ***2004***, *126*, 10222.

[690]For a list of procedures, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, p. 75.

[691]Büchner, W.; Dufaux, R. *Helv. Chim. Acta* ***1966***, *49*, 1145; Arapakos, P.G.; Scott, M.K.; Huber, Jr., F.E. *J. Am. Chem. Soc.* ***1969***, *91*, 2059; Birch, A.J.; Hutchinson, E.G. *J. Chem. Soc. Perkin Trans. 1* ***1972***, 1546; Yamada, S.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* ***1976***, 61.

[692]Van Tamelen, E.E.; Rudler, H.; Bjorklund, C. *J. Am. Chem. Soc.* ***1971***, *93*, 7113.

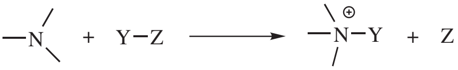
[693]For other procedures, see Cuvigny, T.; Larcheveque, M.; Normant, H. *Bull. Soc. Chim. Fr.* ***1973***, 1174; Berkoff, C.E.; Rivard, D.E.; Kirkpatrick, D.; Ives, J.L. *Synth. Commun.* ***1980***, *10*, 939; Savoia, D.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.* ***1980***, *45*, 3227; Ozawa, F.; Iri, K.; Yamamoto, A. *Chem. Lett.* ***1982***, 1707.

[694]Ohsawa, T.; Kobayashi, T.; Mizuguchi, Y.; Saitoh, T.; Oishi, T. *Tetrahedron Lett.* ***1985***, *26*, 6103.

α-Amino and α-amido nitriles RCH(CN)NR'$_2$ and RCH(CN)NHCOR' can be decyanated in high yield by treatment with $NaBH_4$.[695]

ELECTROPHILIC SUBSTITUTION AT NITROGEN

In most of the reactions in this section, an electrophile bonds with the unshared pair of a nitrogen atom. The electrophile may be a free positive ion or a positive species attached to a carrier that breaks off in the course of the attack or shortly after:



53

Further reaction of **53** depends on the nature of Y and of the other groups attached to the nitrogen.

12-49 The Conversion of Hydrazines to Azides

Hydrazine–azide transformation

$$RNHNH_2 + HONO \longrightarrow R{-}\overset{\oplus}{N}{=}\overset{\ominus}{N}{=}N$$

Monosubstituted hydrazines treated with nitrous acid give azides in a reaction exactly analogous to the formation of aliphatic diazo compounds mentioned in **13-19**. Among other reagents used for this conversion have been N_2O_4[696] and nitrosyl tetrafluoroborate ($NOBF_4$).[697]

OS **III**, 710; **IV**, 819; **V**, 157.

12-50 *N*-Nitrosation

***N*-Nitroso-de-hydrogenation**

$$R_2NH + HONO \longrightarrow R_2N{-}NO$$

When secondary amines are treated with nitrous acid (typically formed from sodium nitrite and a mineral acid),[698] *N*-nitroso compounds (also called

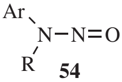
[695]Yamada, S.; Akimoto, H. *Tetrahedron Lett.* ***1969***, 3105; Fabre, C.; Hadj Ali Salem, M.; Welvart, Z. *Bull. Soc. Chim. Fr.* ***1975***, 178. See also Ogura, K.; Shimamura, Y.; Fujita, M. *J. Org. Chem.* ***1991***, *56*, 2920.

[696]Kim, Y.H.; Kim, K.; Shim, S.B. *Tetrahedron Lett.* ***1986***, *27*, 4749.

[697]Pozsgay, V.; Jennings, H.J. *Tetrahedron Lett.* ***1987***, *28*, 5091.

[698]From $NaNO_2$/oxalic acid: Zolfigol, M.A. *Synth. Commun.* ***1999***, *29*, 905. From $NaNO_2$ on wet silica: Zolfigol, M.A.; Ghaemi, E.; Madrikian, E.; Kiany-Burazjani, *M. Synth. Commun.* ***2000***, *30*, 2057.

nitrosamines) are formed.[699] The reaction can be accomplished with dialkyl-, diaryl-, or alkylarylamines, and even with mono-*N*-substituted amides: RCONHR' + HONO $\rightarrow$ RCON(NO)R'.[700] Tertiary amines have also been *N*-nitrosated, but in these cases one group cleaves, so that the product is the nitroso derivative of a secondary amine.[701] The group that cleaves appears as an aldehyde or ketone. Other reagents have also been used, for example, NOCl, which is useful for amines or amides that are not soluble in an acidic aqueous solution or where the *N*-nitroso compounds are highly reactive. *N*-Nitroso compounds can be prepared in basic solution by treatment of secondary amines with gaseous N_2O_3, N_2O_4,[702] or alkyl nitrites,[703] and, in aqueous or organic solvents, by treatment with $BrCH_2NO_2$.[704] Secondary amines are converted to the *N*-nitroso compound with H_5IO_6 on wet silica.[705]



54

The mechanism of nitrosation is essentially the same as in **13-19** up to the point where **54** is formed. Since this species cannot lose a proton, it is stable and the reaction ends there. The attacking entity can be any of those mentioned in **13-19**. The following has been suggested as the mechanism for the reaction with tertiary amines:[706]

[699]For reviews, see Williams, D.L.H. Williams, D.L.H. *Nitrosation*; Cambridge University Press, Cambridge, ***1988***, pp. 95–109; Kostyukovskii, Ya.L.; Melamed, D.B. *Russ. Chem. Rev.* ***1988***, *57*, 350; Saavedra, J.E. *Org. Prep. Proced. Int.* ***1987***, *19*, 83; Williams, D.L.H. *Adv. Phys. Org. Chem.* ***1983***, *19*, 381; Challis, B.C.; Challis, J.A. in Patai, S.; Rappoport, Z. *The Chemistry of the Functional Groups Supplement F*, pt. 2, Wiley, NY, ***1982***, pp. 1151–1223; Ridd, J.H. *Q. Rev. Chem. Soc.* ***1961***, *15*, 418. For a review of the chemistry of aliphatic *N*-nitroso compounds, including methods of synthesis see Fridman, A.L.; Mukhametshin, F.M.; Novikov, S.S. *Russ. Chem. Rev.* ***1971***, *40*, 34. For a discussion of encapsulated reagents used for nitrosation, see Zyranov, G.V.; Rudkevich, D.M. *Org. Lett.* ***2003***, *5*, 1253.

[700]For a discussion of the mechanism with amides, see Castro, A.; Iglesias, E.; Leis, J.R.; Peña, M.E.; Tato, J.V. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 1725.

[701]Hein, G.E. *J. Chem. Educ.* ***1963***, *40*, 181. See also, Verardo, G.; Giumanini, A.G.; Strazzolini, P. *Tetrahedron* ***1990***, *46*, 4303.

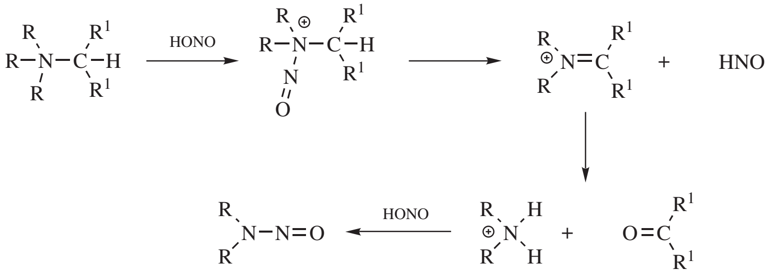
[702]Challis, B.C.; Kyrtopoulos, S.A. *J. Chem. Soc. Perkin Trans. 1* ***1979***, 299.

[703]Casado, J.; Castro, A.; Lorenzo, F.M.; Meijide, F. *Monatsh. Chem.* ***1986***, *117*, 335.

[704]Challis, B.C.; Yousaf, T.I. *J. Chem. Soc. Chem. Commun.* ***1990***, 1598.

[705]Zolfigol, M.A.; Choghamarani, A.G.; Shivini, F.; Keypour, H.; Salehzadeh, S. *Synth. Commun.* ***2001***, *31*, 359. Also with $KHSO_5$ on wet silica, see Zolfigol, M.A.; Bagherzadeh, M.; Choghamarani, A.G.; Keypour, H.; Salehzadeh, S. *Synth. Commun.* ***2001***, *31*, 1161.

[706]Smith, P.A.S.; Loeppky, R.N. *J. Am. Chem. Soc.* ***1967***, *89*, 1147; Smith, P.A.S.; Pars, H.G. *J. Org. Chem.* ***1959***, *24*, 1324; Gowenlock, B.G.; Hutchison, R.J.; Little, J.; Pfab, J. *J. Chem. Soc. Perkin Trans. 2* ***1979***, 1110. See also, Loeppky, R.N.; Outram, J.R.; Tomasik, W.; Faulconer, J.M. *Tetrahedron Lett.* ***1983***, *24*, 4271.



The evidence for this mechanism includes the facts that nitrous oxide is a product (formed by 2 HNO → $H_2O + N_2O$) and that quinuclidine, where the nitrogen is at a bridgehead, and therefore cannot give elimination, does not react. Tertiary amines have also been converted to nitrosamines with nitric acid in Ac_2O[707] and with N_2O_4.[708]

Amines and amides can be *N*-nitrated[709] with nitric acid,[710] or NO_2^+,[711] and aromatic amines can be converted to triazenes with diazonium salts. Aliphatic primary amines can also be converted to triazenes if the diazonium salts contain electron-withdrawing groups.[712] C-Nitrosation is discussed at **11-3** and **12-8**.

OS **I**, 177, 399, 417; **II**, 163, 211, 290, 460, 461, 462, 464 (also see **V**, 842); **III**, 106, 244; **IV**, 718, 780, 943; **V**, 336, 650, 797, 839, 962; **VI**, 542, 981. Also see, OS **III**, 711.

12-51 Conversion of Nitroso Compounds to Azoxy Compounds

In a reaction similar to **13-24**, azoxy compounds can be prepared by the condensation of a nitroso compound with a hydroxylamine.[713] The position of the oxygen in the final product is determined by the nature of the R groups, not by which R groups came from which starting compound. Both R and R' can be alkyl or aryl, but when two different aryl groups are involved, mixtures of azoxy compounds

[707]Boyer, J.H.; Pillai, T.P.; Ramakrishnan, V.T. *Synthesis* ***1985***, 677.

[708]Boyer, J.H.; Kumar, G.; Pillai, T.P. *J. Chem. Soc. Perkin Trans. 1* ***1986***, 1751.

[709]For other reagents, see Mayants, A.G.; Pyreseva, K.G.; Gordeichuk, S.S. *J. Org. Chem. USSR* ***1986***, *22*, 1900; Bottaro, J.C.; Schmitt, R.J.; Bedford, C.D. *J. Org. Chem.* ***1987***, *52*, 2292; Suri, S.C.; Chapman, R.D. *Synthesis* ***1988***, 743; Carvalho, E.; Iley, J.; Norberto, F.; Rosa, E. *J. Chem. Res. (S)* ***1989***, 260.

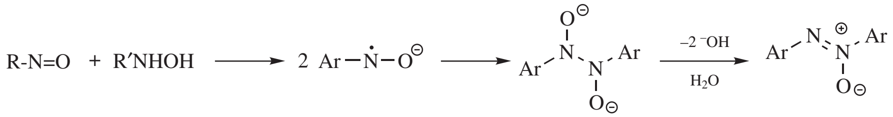
[710]Cherednichenko, L.V.; Dmitrieva, L.G.; Kuznetsov, L.L.; Gidaspov, B.V. *J. Org. Chem. USSR* ***1976***, *12*, 2101, 2105.

[711]Ilyushin, M.A.; Golod, E.L.; Gidaspov, B.V. *J. Org. Chem. USSR* ***1977***, *13*, 8; Andreev, S.A.; Lededev, B.A.; Tselinskii, I.V. *J. Org. Chem. USSR* ***1980***, *16*, 1166, 1170, 1175, 1179.

[712]For a review of alkyl traizenes, see Vaughan, K.; Stevens, M.F.G. *Chem. Soc. Rev.* ***1978***, *7*, 377.

[713]Boyer, J.H., in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, pt. 1, Wiley, NY, ***1969***, pp. 278–283.

(ArNONAr, ArNONAr′, and Ar′NONAr′) are obtained[714] and the unsymmetrical product (ArNONAr′) is likely to be formed in the smallest amount. This behavior is probably caused by an equilibration between the starting compounds prior to the actual reaction (ArNO + Ar′NHOH → Ar′NO + ArNHOH).[715] The mechanism[716] has been investigated in the presence of base. Under these conditions both reactants are converted to radical anions, which couple:



These radical anions have been detected by esr.[717] This mechanism is consistent with the following result: when nitrosobenzene and phenylhydroxylamine are coupled, ^{18}O and ^{15}N labeling show that the two nitrogens and the two oxygens become equivalent.[718] Unsymmetrical azoxy compounds can be prepared[719] by combination of a nitroso compound with an *N,N*-dibromoamine. Symmetrical and unsymmetrical azo and azoxy compounds are produced when aromatic nitro compounds react with aryliminodimagnesium reagents $ArN(MgBr)_2$.[720]

12-52 *N*-Halogenation

N-Halo-de-hydrogenation

$$RNH_2 + NaOCl \longrightarrow RNHCl$$

Treatment with sodium hypochlorite or hypobromite converts primary amines into *N*-halo- or *N,N*-dihaloamines. Secondary amines can be converted to *N*-halo secondary amines. Similar reactions can be carried out on unsubstituted and *N*-substituted amides and on sulfonamides. With unsubstituted amides the *N*-halogen product is seldom isolated but usually rearranges (see **18-13**); however, *N*-halo-*N*-alkyl amides and *N*-halo imides are quite stable. The important reagents NBS and NCS are made in this manner. *N*-Halogenation has also been accomplished with other

[714]See, for example, Ogata, Y.; Tsuchida, M.; Takagi, Y. *J. Am. Chem. Soc.* ***1957***, *79*, 3397.

[715]Knight, G.T.; Saville, B. *J. Chem. Soc. Perkin Trans. 2* ***1973***, 1550.

[716]For discussions of the mechanism in the absence of base, see Darchen, A.; Moinet, C. *Bull. Soc. Chim. Fr.* ***1976***, 812; Becker, A.R.; Sternson, L.A. *J. Org. Chem.* ***1980***, *45*, 1708. See also, Pizzolatti, M.G.; Yunes, R.A. *J. Chem. Soc. Perkin Trans. 1* ***1990***, 759.

[717]Russell, G.A.; Geels, E.J.; Smentowski, F.J.; Chang, K.; Reynolds, J.; Kaupp, G. *J. Am. Chem. Soc.* ***1967***, *89*, 3821.

[718]Shemyakin, M.M.; Maimind, V.I.; Vaichunaite, B.K. *Izv. Akad. Nauk SSSR, Ser. Khim.* ***1957***, 1260; Oae, S.; Fukumoto, T.; Yamagami, M. *Bull. Chem. Soc. Jpn.* ***1963***, *36*, 728.

[719]Zawalski, R.C.; Kovacic, P. *J. Org. Chem.* ***1979***, *44*, 2130. For another method, see Moriarty, R.M.; Hopkins, T.E.; Prakash, I.; Vaid, B.K.; Vaid, R.K. *Synth. Commun.* ***1990***, *20*, 2353.

[720]O kubo, M.; Matsuo, K.; Yamauchi, A. *Bull. Chem. Soc. Jpn.* ***1989***, *62*, 915, and other papers in this series.

reagents (e.g., sodium bromite $NaBrO_2$),[721] benzyltrimethylammonium tribromide ($PhCH_2NMe_3^+$ Br_3-),[722] NaCl with Oxone®,[723] and *N*-chlorosuccinimide.[724] The mechanisms of these reactions[725] involve attack by a positive halogen and are probably similar to those of **13-19** and **12-50**.[726] *N*-Fluorination can be accomplished by direct treatment of amines[727] or amides[728] with F_2. Fluorination of *N*-alkyl-*N*-fluoro amides (RRN(F)COR') results in cleavage to *N,N*-difluoroamines (RNF_2).[728,729] Trichloroisocyanuric acid converts primary amines to the *N,N*-dichloroamine.[730]

OS **III**, 159; **IV**, 104, 157; **V**, 208, 663, 909; **VI**, 968; **VII**, 223; **VIII**, 167, 427.

12-53 The Reaction of Amines With Carbon Monoxide or Carbon Dioxide

N-**Formylation** or *N*-**Formyl-de-hydrogenation**, and so on

Three types of product can be obtained from the reaction of amines with carbon monoxide, depending on the catalyst. (*1*) Both primary and secondary amines react with CO in the presence of various catalysts [e.g., $Cu(CN)_2$, $Me_3N–H_2Se$, rhodium or ruthenium complexes] to give *N*-substituted and *N,N*-disubstituted formamides, respectively.[731] Primary aromatic amines react with ammonium formate to give the formamide.[732] Tertiary amines react with CO and a palladium catalyst to give an amide.[733] (*2*) Symmetrically substituted ureas can be prepared by treatment of a primary amine (or ammonia) with CO[734] in the presence of selenium[735] or

[721]Kajigaeshi, S.; Nakagawa, T.; Fujisaki, S. *Chem. Lett.* ***1984***, 2045.

[722]Kajigaeshi, S.; Murakawa, K.; Asano, K.; Fujisaki, S.; Kakinami, T. *J. Chem. Soc. Perkin Trans. 1* ***1989***, 1702.

[723]Curini, M.; Epifano, F.; Marcotullio, M.C.; Rosati, O.; Tsadjout, A. *Synlett* ***2000***, 813.

[724]See Deno, N.C.; Fishbein, R.; Wyckoff, J.C. *J. Am. Chem. Soc.* ***1971***, *93*, 2065; Guillemin, J.; Denis, J.N. *Synthesis* ***1985***, 1131.

[725]For a study of the mechanism, see Matte, D.; Solastiouk, B.; Merlin, A.; Deglise, X. *Can. J. Chem.* ***1989***, *67*, 786.

[726]For studies of reactivity in this reaction, see Thomm, E.W.C.W.; Wayman, M. *Can. J. Chem.* ***1969***, *47*, 3289; Higuchi, T.; Hussain, A.; Pitman, I.H. *J. Chem. Soc. B*, ***1969***, 626.

[727]Sharts, C.M. *J. Org. Chem.* ***1968***, *33*, 1008.

[728]Grakauskas, V.; Baum, K. *J. Org. Chem.* ***1969***, *34*, 2840; ***1970***, *35*, 1545.

[729]See Barton, D.H.R.; Hesse, R.H.; Klose, T.R.; Pechet, M.M. *J. Chem. Soc. Chem. Commun.* ***1975***, 97.

[730]DeLuca, L.; Giacomelli, G. *Synlett* ***2004***, 2180.

[731]See Saegusa, T.; Kobayashi, S.; Hirota, K.; Ito, Y. *Bull. Chem. Soc. Jpn.* ***1969***, *42*, 2610; Nefedov, B.K.; Sergeeva, N.S.; Éidus, Ya.T. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1973***, *22*, 784; Yoshida, Y.; Asano, S.; Inoue, S. *Chem. Lett.* ***1984***, 1073; Bitsi, G.; Jenner, G. *J. Organomet. Chem.* ***1987***, *330*, 429.

[732]Reddy, P.G.; Kumar,. D.K.; Baskaran, S. *Tetrahedron Lett.* ***2000***, *41*, 9149.

[733]Murahashi, S.-I.; Imada, Y.; Nishimura, K. *Tetrahedron*, ***1994***, *50*, 453.

[734]For a synthesis involving a palladium catalyst, see Gabriele, B.; Salerno, G.; Mancuso, R.; Costa, M. *J. Org. Chem.* ***2004***, *69*, 4741.

[735]Sonoda, N.; Yasuhara, T.; Kondo, K.; Ikeda, T.; Tsutsumi, S. *J. Am. Chem. Soc.* ***1971***, *93*, 6344.

sulfur.[736] R can be alkyl or aryl. The same thing can be done with secondary amines, by using $Pd(OAc)_2$–I_2–K_2CO_3.[737] Primary aromatic amines react with β-keto esters and a Mo–ZrO_2 catalyst to give the symmetrical urea.[738] Treatment of a secondary amine with nitrobenzene, selenium, and carbon monoxide leads to the unsymmetrical urea.[739] (*3*) When $PdCl_2$ is the catalyst, primary amines yield isocyanates.[740] Isocyanates can also be obtained by treatment of CO with azides: $RN_3 + CO \rightarrow RNCO$,[741] or with an aromatic nitroso or nitro compound and a rhodium complex catalyst.[742] Primary amines react with di-*tert*-butyltricarbonate to give the isocyanate.[743] Lactams are converted to the corresponding *N*-chloro lactam with $Ca(OCl)_2$ with moist alumina in dichloromethane.[744]

A fourth type of product, a carbamate RNHCOOR', can be obtained from primary or secondary amines, if these are treated with CO, O_2, and an alcohol R'OH in the presence of a catalyst.[745] Primary amines react with dimethyl carbonate in supercritical CO_2 (see p. 414) to give a carbamate.[746] Carbamates can also be obtained from nitroso compounds, by treatment with CO, R'OH, $Pd(OAc)_2$, and $Cu(OAc)_2$,[747] and from nitro compounds.[748] When allylic amines ($R_2C{=}CHRCHRNR'_2$) are treated with CO and a palladium–phosphine catalyst, the CO inserts to produce the β,γ-unsaturated amides ($R_2C{=}CHRCHRCONR'_2$) in good yields.[749] Ring-expanded lactams are obtained from cyclic amines via a similar reaction[750] (see also, **16-22**). Silyloxy carbamates ($RNHCO_2SiR'_3$) can be prepared by the reaction of a primary amine with carbon dioxide and triethylamine, followed by reaction with triisopropylsilyl triflate and tetrabutylammonium fluoride.[751]

Carbon dioxide reacts with amines ($ArNH_2$) and alkyl halides, under electrolysis conditions, to give the corresponding carbamate ($ArNHCO_2Et$).[752] Secondary

[736]Franz, R.A.; Applegath, F.; Morriss, F.V.; Baiocchi, F.; Bolze, C. *J. Org. Chem.* ***1961***, *26*, 3309.
[737]Pri-Bar, I.; Alper, H. *Can. J. Chem.* ***1990***, *68*, 1544.
[738]Reddy, B.M.; Reddy, V.R. *Synth. Commun.* ***1999***, *29*, 2789.
[739]Yang, Y.; Lu, S. *Tetrahedron Lett.* ***1999***, *40*, 4845.
[740]Stern, E.W.; Spector, M.L. *J. Org. Chem.* ***1966***, *31*, 596.
[741]Bennett, R.P.; Hardy, W.B. *J. Am. Chem. Soc.* ***1968***, *90*, 3295.
[742]Unverferth, K.; Rüger, C.; Schwetlick, K. *J. Prakt. Chem.* ***1977***, *319*, 841; Unverferth, K.; Tietz, H.; Schwetlick, K. *J. Prakt. Chem.* ***1985***, *327*, 932. See also, Braunstein, P.; Bender, R.; Kervennal, J. *Organometallics* ***1982***, *1*, 1236; Kunin, A.J.; Noirot, M.D.; Gladfelter, W.L. *J. Am. Chem. Soc.* ***1989***, *111*, 2739.
[743]Peerlings, H.W.I.; Meijer, E.W. *Tetrahedron Lett.* ***1999***, *40*, 1021.
[744]Larionov, O.V.; Kozhushkov, S.I.; de Meijere, A. *Synthesis* ***2003***, 1916.
[745]Fukuoka, S.; Chono, M.; Kohno, M. *J. Org. Chem.* ***1984***, *49*, 1458; *J. Chem. Soc. Chem. Commun.* ***1984***, 399; Feroci, M.; Inesi, A.; Rossi, L. *Tetrahedron Lett.* ***2000***, *41*, 963.
[746]Selva, M.; Tundo, P.; Perosa, A. *Tetrahedron Lett.* ***2002***, *43*, 1217.
[747]Alper, H.; Vasapollo, G. *Tetrahedron Lett.* ***1987***, *28*, 6411.
[748]Cenini, S.; Crotti, C.; Pizzotti, M.; Porta, F. *J. Org. Chem.* ***1988***, *53*, 1243; Reddy, N.P.; Masdeu, A.M.; El Ali, B.; Alper, H. *J. Chem. Soc. Chem. Commun.* ***1994***, 863.
[749]Murahashi, S.; Imada, Y.; Nishimura, K. *J. Chem. Soc. Chem. Commun.* **1988**, 1578.
[750]Wang, M.D.; Alper, H. *J. Am. Chem. Soc.* ***1992***, *114*, 7018.
[751]Lipshutz, B.H.; Papa, P.; Keith, J.M. *J. Org. Chem.* ***1999***, *64, 3* 792.
[752]Casadei, M.A.; Inesi, A.; Moracci, F.M.; Rossi, L. *Chem. Commun.* ***1996***, 2575; Feroci, M.; Casadei, M.A.; Orsini, M.; Palombi, L.; Inesi, A. *J. Org. Chem.* ***2003***, *68*, 1548.

amines react with all halides and an onium salt in supercritical CO_2 (see p. 414) to give the carbamate.[753] *N*-phenylthioamines react with CO and a palladium catalyst to give a thiocarbamate ($ArSCO_2NR'_2$).[754] Urea derivatives were obtained from amines, CO_2, and an antimony catalyst.[755]

Aziridines can be converted to cyclic carbamates (oxazolidinones) by heating with carbon dioxide and a chromium–salen catalyst.[756] The reaction of aziridines with LiI, and then CO_2 also generates oxazolidinones.[757]

[753]Yoshida, M.; Hara, N.; Okuyama, S. *Chem. Commun.* ***2000***, 151.

[754]Kuniyasu, H.; Hiraike, H.; Morita, M.; Tanaka, A.; Sugoh, K.; Kurosawa, H. *J. Org. Chem.* ***1999***, *64*, 7305.

[755]Nomura, R.; Hasegawa, Y.; Ishimoto, M.; Toyosaki, T.; Matsuda, H. *J. Org. Chem.* ***1992***, *57*, 7339.

[756]Miller, A.W.; Nguyen, S.T. *Org. Lett.* ***2004***, *6*, 2301.

[757]Hancock, M.T.; Pinhas, A.R. *Tetrahedron Lett.* ***2003***, *44*, 5457.

CHAPTER 13

Aromatic Substitution, Nucleophilic and Organometallic

On p. 481, it was pointed out that nucleophilic substitutions proceed so slowly at an aromatic carbon that the reactions of Chapter 10 are not feasible for aromatic substrates. There are, however, exceptions to this statement, and it is these exceptions that form the subject of this chapter.[1] Reactions that *are* successful at an aromatic substrate are largely of four kinds: (*1*) reactions activated by electron-withdrawing groups ortho and para to the leaving group; (*2*) reactions catalyzed by very strong bases and proceeding through aryne intermediates; (*3*) reactions initiated by electron donors; and (*4*) reactions in which the nitrogen of a diazonium salt is replaced by a nucleophile. It is noted that solvent effects can be important.[2] Also, not all the reactions discussed in this chapter fit into these categories, and certain transition-metal catalyzed coupling reaction are included because they involve replacement of a leaving group on an aromatic ring.

MECHANISMS

There are four principal mechanisms for aromatic nucleophilic substitution.[3] Each of the four is similar to one of the aliphatic nucleophilic substitution mechanisms discussed in Chapter 10.

[1]For a review of aromatic nucleophilic substitution, see Zoltewicz, J.A. *Top. Curr. Chem.* ***1975***, *59*, 33.
[2]Acevedo, O.; Jorgensen, W.L. *Org. Lett.* ***2004***, *6*, 2881.
[3]For a monograph on aromatic nucleophilic substitution mechanisms, see Miller, J. *Aromatic Nucleophilic Substitution*, Elsevier, NY, ***1968***. For reviews, see Bernasconi, C.F. *Chimia* ***1980***, *34*, 1; *Acc. Chem. Res.* ***1978***, *11*, 147; Bunnett, J.F. *J. Chem. Educ.* ***1974***, *51*, 312; Ross, S.D., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13; Elsevier, NY, ***1972***, pp. 407–431; Buck, P. *Angew. Chem, Int. Ed.* ***1969***, *8*, 120; Buncel, E.; Norris, A.R.; Russell, K.E. *Q. Rev. Chem. Soc.* ***1968***, *22*, 123; Bunnett, J.F. *Tetrahedron* ***1993***, *49*, 4477; Zoltewicz, J.A. *Top. Curr. Chem.* ***1975***, *59*, 33.

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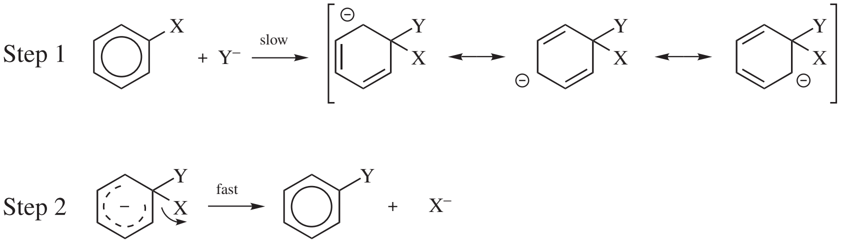
The S_NAr Mechanism[4]

By far the most important mechanism for nucleophilic aromatic substitution consists of two steps, attack of the nucleophilic species at the ipso carbon of the aromatic ring (the carbon bearing the leaving group in this case), followed by elimination of the leaving group and regeneration of the aromatic ring.



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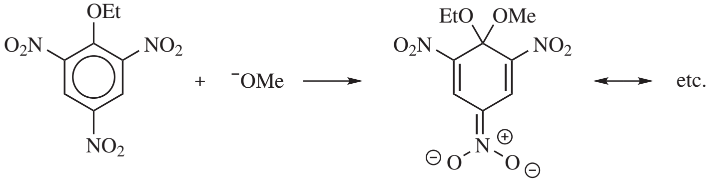
The first step is usually, but not always, rate determining. It can be seen that this mechanism greatly resembles the tetrahedral mechanism discussed in Chapter 16 and, in another way, the arenium ion mechanism of electrophilic aromatic substitution discussed in Chapter 11. In all three cases, the attacking species forms a bond with the substrate, giving an intermediate, such as **1**, and then the leaving group departs. We refer to this mechanism as the S_NAr mechanism.[5] The IUPAC designation is $A_N + D_N$ (the same as for the tetrahedral mechanism; compare the designation $A_E + D_E$ for the arenium ion mechanism). This mechanism is generally found where activating groups are present on the ring (see p. 864).

There is a great deal of evidence for the mechanism; we shall discuss only some of it.[3] Probably the most convincing evidence was the isolation, as long ago as 1902, of the intermediate **2** in the reaction between 2,4,6-trinitrophenetole and methoxide ion.[6] Intermediates of this type are stable salts, called *Meisenheimer* or *Meisenheimer–Jackson salts*,[7] and many more have been isolated.[8] The structures

[4]High pressure S_NAr reactions are known. see Barrett, I.C.; Kerr, M.A. *Tetrahedron Lett.* ***1999***, *40*, 2439.
[5]The mechanism has also been called by other names, including the S_N2Ar, the addition–elimination, and the intermediate complex mechanism. See Wu, Z.; Glaser, R. *J. Am. Chem. Soc.* ***2004***, *126*, 10632. See also, Terrier, F.; Mokhtari, M.; Goumont, T.; Hallé, J.-C.; Buncel, E. *Org. Biomol. Chem.* ***2003***, *1*, 1757.
[6]Meisenheimer, J. *Liebigs Ann. Chem.* ***1902***, *323*, 205. Similar salts were isolated even earlier by Jackson, C.L.; see Jackson, C.L.; Gazzolo, F.H. *Am. Chem. J.* ***1900***, *23*, 376; Jackson, C.L.; Earle, R.B. *Am. Chem. J.*, ***1903***, *29*, 89.
[7]Nucleophilic aromatic substitution for heteroatom nucleophiles through electrochemical oxidation of intermediate σ-complexes (Meisenheimer complexes) in simple nitroaromatic compounds has been reported, see Gallardo, I.; Guirado, G.; Marquet, J. *J. Org. Chem.* ***2002***, *67*, 2548.
[8]For a monograph on Meisenheimer salts and on this mechanism, see Buncel, E.; Crampton, M.R.; Strauss, M.J.; Terrier, F. *Electron Deficient Aromatic- and Heteroaromatic-Base Interactions*, Elsevier, NY, ***1984***. For reviews of structural and other studies, see Illuminati, G.; Stegel, F. *Adv. Heterocycl. Chem.* ***1983***, *34*, 305; Artamkina, G. A.; Egorov, M.P.; Beletskaya, I.P. *Chem. Rev.* ***1982***, *82*, 427; Terrier, F. *Chem. Rev.* ***1982***, *82*, 77; Strauss, M.J. *Chem. Rev.* ***1970***, *70*, 667; *Acc. Chem. Res.* ***1974***, *7*, 181; Hall, T.N.; Poranski, Jr., C.F., in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, pt. 2; Wiley, NY, ***1970***, pp. 329–384; Crampton, M.R. *Adv. Phys. Org. Chem.* ***1969***, *7*, 211; Foster R.; Fyfe, C.A. *Rev. Pure Appl. Chem.* ***1966***, *16*, 61.

of several of these intermediates



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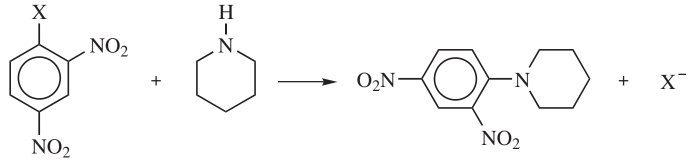
have been proved by NMR[9] and by X-ray crystallography.[10] Further evidence comes from studies of the effect of the leaving group on the reaction. If the mechanism were similar to either the S_N1 or S_N2 mechanisms described in Chapter 10, the Ar–X bond would be broken in the rate-determining step. In the S_NAr mechanism, this bond is not broken until after the rate-determining step (i.e. if step 1 is rate determining). There is some evidence that electron transfer may be operative during this process.[11] We would predict from this that if the S_NAr mechanism is operating, a change in leaving group should not have much effect on the reaction rate. In the reaction of dinitro compound **3** with piperidine,



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when X was Cl, Br, I, SOPh, SO_2Ph, or *p*-nitrophenoxy, the rates differed only by a factor of ~5.[12] This behavior would not be expected in a reaction in which the Ar–X bond is broken in the rate-determining step. We do not expect the rates to be *identical*, because the nature of X affects the rate at which Y attacks. An increase in the electronegativity of X causes a decrease in the electron density at the site of attack, resulting in a faster attack by a nucleophile. Thus, in the reaction just mentioned, when X = F, the relative rate was 3300 (compared with I = 1). The very fact that fluoro is the best leaving group among the halogens in most aromatic nucleophilic substitutions is good evidence that the mechanism is different from the S_N1

[9]First done by Crampton, M.R.; Gold, V. *J. Chem. Soc. B* ***1966***, 893. A good review of spectral studies is found, in Buncel, E.; Crampton, M.R.; Strauss, M.J.; Terrier, F. *Electron Deficient Aromatic- and Heteroaromatic-Base Interactions*, Elsevier, NY, ***1984***, pp. 15–133.

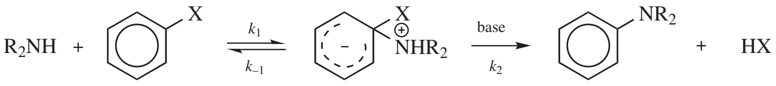
[10]Destro, R.; Gramaccioli, C.M.; Simonetta, M. *Acta Crystallogr.* ***1968***, *24*, 1369; Ueda, H.; Sakabe, M.; Tanaka, J.; Furusaki, A. *Bull. Chem. Soc. Jpn.* ***1968***, *41*, 2866; Messmer, G.G.; Palenik, G.J. *Chem. Commun.* ***1969***, 470.

[11]Grossi, L. *Tetrahedron Lett.* ***1992***, *33*, 5645.

[12]Bunnett, J.F.; Garbisch Jr., E.W.; Pruitt, K.M. *J. Am. Chem. Soc.* ***1957***, *79*, 385. See Gandler, J.R.; Setiarahardjo, I.U.; Tufon, C.; Chen, C. *J. Org. Chem.* ***1992***, *57*, 4169 for a more recent example.

and the S_N2 mechanisms, where fluoro is by far the poorest leaving group of the halogens. This is an example of the element effect (p. 475).

The pattern of base catalysis of reactions with amine nucleophiles provides additional evidence. These reactions are catalyzed by bases only when a relatively poor leaving group (e.g., OR) is present (not Cl or Br) and only when relatively bulky amines are nucleophiles.[13] Bases could not catalyze step 1, but if amines are nucleophiles, bases can catalyze step 2. Base catalysis is found precisely in those cases where the amine moiety cleaves easily but X does not, so that k_{-1} is large and step 2 is rate determining. This is evidence for the S_NAr mechanism because it implies two steps. Furthermore, in cases where bases *are* catalysts, they catalyze only at



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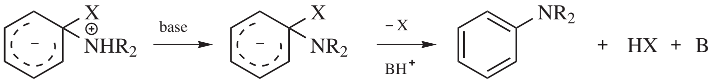
low base concentrations: a plot of the rate against the base concentration shows that small increments of base rapidly increase the rate until a certain concentration of base is reached, after which further base addition no longer greatly affects the rate. This behavior, based on a partitioning effect (see p. 660), is also evidence for the S_NAr mechanism. At low base concentration, each increment of base, by increasing the rate of step 2, increases the fraction of intermediate that goes to product rather than reverting to reactants. At high base concentration the process is virtually complete: there is very little reversion to reactants and the rate becomes dependent on step 1. Just how bases catalyze step 2 has been investigated. For protic solvents two proposals have been presented. One is that step 2 consists of two steps: rate-determining deprotonation of **4** followed by rapid loss of X,



4

and that bases catalyze the reaction by increasing the rate of the deprotonation step.[14] According to the other proposal, loss of X assisted by BH^+ is rate determining.[15] Two mechanisms, both based on kinetic evidence, have been proposed for aprotic solvents, such as benzene. In both proposals the ordinary S_NAr mechanism

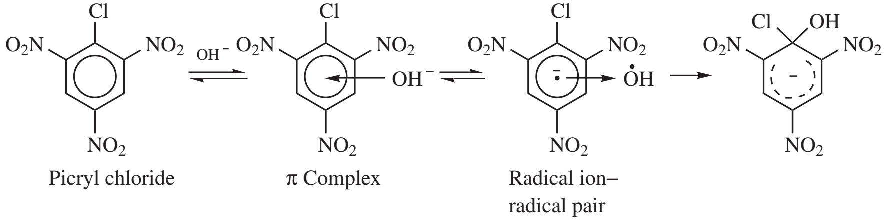
[13]Kirby, A.J.; Jencks, W.P. *J. Am. Chem. Soc.* ***1965***, *87*, 3217; Bunnett, J.F.; Bernasconi, C.F. *J. Org. Chem.* ***1970***, *35*, 70; Bernasconi, C.F.; Schmid, P. *J. Org. Chem.* ***1967***, *32*, 2953; Bernasconi, C.F.; Zollinger, H. *Helv. Chim. Acta* ***1966***, *49*, 103; ***1967***, *50*, 1; Pietra, F.; Vitali, D. *J. Chem. Soc. B* ***1968***, 1200; Chiacchiera, S.M.; Singh, J.O.; Anunziata, J.D.; Silber, J.J. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 987.

[14]Bernasconi, C.F.; de Rossi, R.H.; Schmid, P. *J. Am. Chem. Soc.* ***1977***, *99*, 4090, and references cited therein.

[15]Bunnett, J.F.; Sekiguchi, S.; Smith, L.A. *J. Am. Chem. Soc.* ***1981***, *103*, 4865, and references cited therein.

operates, but in one the attacking species involves two molecules of the amine (the *dimer mechanism*),[16] while in the other there is a cyclic transition state.[17] Further evidence for the S_NAr mechanism has been obtained from $^{18}O/^{16}O$ and $^{15}N/^{14}N$ isotope effects.[18]

Step 1 of the S_NAr mechanism has been studied for the reaction between picryl chloride (as well as other substrates) and ^{-}OH ions (**13-1**), and spectral evidence has been reported[19] for two intermediates, one a π complex (p. 662), and the other a radical ion–radical pair:



As with the tetrahedral mechanism at an acyl carbon, nucleophilic catalysis (p. 1259) has been demonstrated with an aryl substrate, in certain cases.[20] There is also evidence of an interaction of anions with the π-cloud of aromatic compounds.[21]

The S_N1 Mechanism

For aryl halides and sulfonates, even active ones, a unimolecular S_N1 mechanism (IUPAC: $D_N + A_N$) is very rare; it has only been observed for aryl triflates in which both ortho positions contain bulky groups (*tert*-butyl or SiR_3).[22] It is in reactions with diazonium salts[23] that this mechanism is important:[24]

[16]For a review of this mechanism, see Nudelman, N.S. *J. Phys. Org. Chem.* ***1989***, *2*, 1. See also Nudelman, N.S.; Montserrat, J.M. *J. Chem. Soc. Perkin Trans. 2* ***1990***, 1073.

[17]Banjoko, O.; Bayeroju, I.A. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 1853; Jain, A.K.; Gupta, V.K.; Kumar, A. *J. Chem. Soc. Perkin Trans. 2* ***1990***, 11.

[18]Hart, C.R.; Bourns, A.N. *Tetrahedron Lett.* ***1966***, 2995; Ayrey, G.; Wylie, W.A. *J. Chem. Soc. B* ***1970***, 738.

[19]Bacaloglu, R.; Blaskó, A.; Bunton, C.A.; Dorwin, E.; Ortega, F.; Zucco, C. *J. Am. Chem. Soc.* ***1991***, *113*, 238, and references cited therein. For earlier reports, based on kinetic data, of complexes with amine nucleophiles, see Forlani, L. *J. Chem. Res. (S)* ***1984***, 260; Hayami, J.; Otani, S.; Yamaguchi, F.; Nishikawa, Y. *Chem. Lett.* ***1987***, 739; Crampton, M.R.; Davis, A.B.; Greenhalgh, C.; Stevens, J.A. *J. Chem. Soc. Perkin Trans. 2* ***1989***, 675.

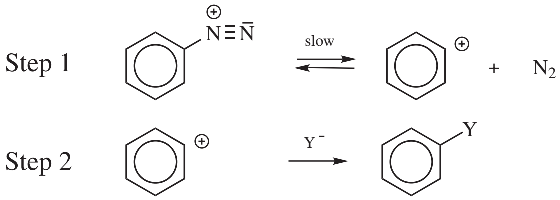
[20]See Muscio, Jr., O.J.; Rutherford, D.R. *J. Org. Chem.* ***1987***, *52*, 5194.

[21]Quiñonero, D.; Garau, C.; Rotger, C.; Frontera, A.; Ballester, P.; Costa, A.; Deyà. P.M. *Angew. Chem. Int. Ed.* ***2002***, *41*, 3389, and references cited therein.

[22]Himeshima, Y.; Kobayashi, H.; Sonoda, T. *J. Am. Chem. Soc.* ***1985***, *107*, 5286.

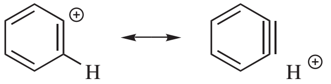
[23]See Glaser, R.; Horan, C.J.; Nelson, E.D.; Hall, M.K. *J. Org. Chem.* ***1992***, *57*, 215 for the influence of neighboring group interactions on the electronic structure of diazonium ions.

[24]Aryl iodonium salts Ar_2I^+ also undergo substitutions by this mechanism (and by a free-radical mechanism).



Among the evidence for the S_N1 mechanism[25] with aryl cations as intermediates,[26,27] is the following:[28]

1. The reaction rate is first order in diazonium salt and independent of the concentration of Y.
2. When high concentrations of halide salts are added, the product is an aryl halide but the rate is independent of the concentration of the added salts.
3. The effects of ring substituents on the rate are consistent with a unimolecular rate-determining cleavage.[29]
4. When reactions were run with substrate deuterated in the ortho position, isotope effects of ~1.22 were obtained.[30] It is difficult to account for such high secondary isotope effects in any other way except that an incipient phenyl cation is stabilized by hyperconjugation,[31] which is reduced when hydrogen is replaced by deuterium.



5. That the first step is reversible cleavage[32] was demonstrated by the observation that when $\mathrm{Ar}^{15}\overset{\mathrm{H}}{\mathrm{N}}{\equiv}\mathrm{N}$ was the reaction species, recorvered starting

[25]For additional evidence, see Lorand, J.P. *Tetrahedron Lett.* ***1989***, *30*, 7337.

[26]For a review of aryl cations, see Ambroz, H.B.; Kemp, T.J. *Chem. Soc. Rev.* ***1979***, *8*, 353.

[27]For a monograph, see Stang, P.J.; Rappoport, Z.; Hanack, M.; Subramanian, L.R. *Vinyl Cations*, Academic Press, NY, 1979. For reviews of aryl and/or vinyl cations, see Hanack, M. *Pure Appl. Chem.* ***1984***, *56*, 1819, *Angew. Chem. Int. Ed.* ***1978***, *17*, 333; *Acc. Chem. Res.* ***1976***, *9*, 364; Rappoport, Z. *Reactiv. Intermed. (Plenum)* ***1983***, *3*, 427; Ambroz, H.B.; Kemp, T.J. *Chem. Soc. Rev.* ***1979***, *8*, 353; Modena, G.; Tonellato, U. *Adv. Phys. Org. Chem.* ***1971***, *9*, 185; Stang, P.J. *Prog. Org. Chem.* ***1973***, *10*, 205. See also, Charton, M. *Mol. Struct. Energ.* ***1987***, *4*, 271. For a computational study, see Glaser, R.; Horan, C.J.; Lewis, M.; Zollinger, H. *J. Org. Chem.* ***1999***, *64*, 902.

[28]For a review, see Zollinger, H. *Angew. Chem, Int. Ed.* ***1978***, *17*, 141. For discussions, see Swain, C.G.; Sheats, J.E.; Harbison, K.G. *J. Am. Chem. Soc.* ***1975***, *97*, 783, 796; Burri, P.; Wahl, Jr., G.H.; Zollinger, H. *Helv. Chim. Acta* ***1974***, *57*, 2099; Richey Jr., H.G.; Richey, J.M., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, pp. 922–931; Zollinger, H. *Azo and Diazo Chemistry*, Wiley, NY, ***1961***, pp. 138–142; Miller, J. *Aromatic Nucleophilic Substitution*, Elsevier, NY, ***1968***, pp. 29–40.

[29]Lewis, E.S.; Miller, E.B. *J. Am. Chem. Soc.* ***1953***, *75*, 429.

[30]Swain, C.G.; Sheats, J.E.; Gorenstein, D.G.; Harbison, K.G. *J. Am. Chem. Soc.* ***1975***, *97*, 791.

[31]See Apeloig, Y.; Arad, D. *J. Am. Chem. Soc.* ***1985***, *107*, 5285.

[32]For discussions, see Williams, D.L.H.; Buncel, E. *Isot. Org. Chem.* Vol. 5, Elsevier, Amsterdam, The Netherlands, ***1980***, 147, 212; Zollinger, H. *Pure Appl. Chem.* ***1983***, *55*, 401.

material contained not only $Ar^{15}\overset{H}{N}{\equiv}N$, but also $Ar\overset{H}{N}{\equiv}{}^{15}N$.[33,34] This could arise only If the nitrogen breaks away from the ring and then returns. Additional evidence was obtained by treating $Ph\overset{H}{N}{\equiv}{}^{15}N$ with unlabeled N_2 at various pressures. At 300 atm, the recovered product had lost ~3% of the labeled nitrogen, indicating that PhN_2^+ was exchanging with atmospheric N_2.[34]

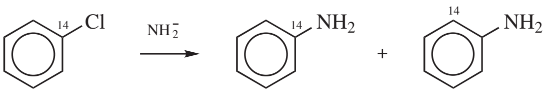
There is kinetic and other evidence[35] that step 1 is more complicated and involves two steps, both reversible:

$$ArN_2^+ \rightleftharpoons \underset{\mathbf{5}}{[Ar^+ \ N_2]} \rightleftharpoons Ar^+ + N_2$$

Intermediate **5**, which is probably some kind of a tight ion–molecule pair, has been trapped with carbon monoxide.[36]

The Benzyne Mechanism[37]

Some aromatic nucleophilic substitutions are clearly different in character from those that occur by the S_NAr mechanism (or the S_N1 mechanism). These substitutions occur on aryl halides that have no activating groups; bases are required that are stronger than those normally used; and most interesting of all, the incoming group does not always take the position vacated by the leaving group. That the latter statement is true was elegantly demonstrated by the reaction of 1-^{14}C-chlorobenzene with potassium amide:



The product consisted of almost equal amounts of aniline labeled in the 1 position and in the 2 position.[38]

[33]Lewis, E.S.; Kotcher, P.G. *Tetrahedron* ***1969***, *25*, 4873; Lewis, E.S.; Holliday, R.E. *J. Am. Chem. Soc.* ***1969***, *91*, 426; Tröndlin, F.; Medina, R.; Rüchardt, C. *Chem. Ber.* ***1979***, *112*, 1835.

[34]Bergstrom, R.G.; Landell, R.G.M.; Wahl Jr., G.H.; Zollinger, H. *J. Am. Chem. Soc.* ***1976***, *98*, 3301.

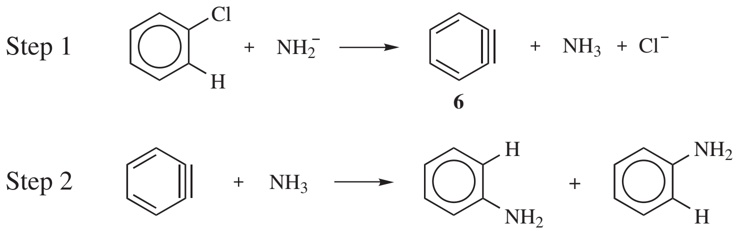
[35]Szele, I.; Zollinger, H. *Helv. Chim. Acta* ***1981***, *64*, 2728.

[36]Ravenscroft, M.D.; Skrabal, P.; Weiss, B.; Zollinger, H. *Helv. Chim. Acta* ***1988***, *71*, 515.

[37]For a monograph, see Hoffmann, R.W. *Dehydrobenzene and Cycloalkynes*, Academic Press, NY, ***1967***. For reviews, see Gilchrist, T.L., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C* pt. 1, Wiley, NY, ***1983***, pp. 383–419; Bryce, M.R.; Vernon, J.M. *Adv. Heterocycl. Chem.* ***1981***, *28*, 183; Levin R.H. *React. Intermed.* (*Wiley*) ***1985***, *3*, 1; ***1981***, *2*, 1; ***1978***, *1*, 1; Nefedov, O.M.; D'yachenko, A.I.; Prokof'ev, A.K. *Russ. Chem. Rev.* ***1977***, *46*, 941; Fields, E.K., in McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, ***1973***, pp. 449–508; Heaney, H. *Fortschr. Chem. Forsch.* ***1970***, *16*, 35; *Essays Chem.* ***1970***, *1*, 95; Hoffmann, R.W., in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 1063–1148; Fields, E.K.; Meyerson, S. *Adv. Phys. Org. Chem.* ***1968***, *6*, 1; Witting, G. *Angew. Chem. Int. Ed.* ***1965***, *4*, 731.

[38]Roberts, J.D.; Semenow, D.A.; Simmons, H.E.; Carlsmith, L.A. *J. Am. Chem. Soc.* ***1965***, *78*, 601.

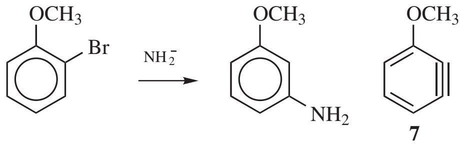
A mechanism that can explain all these facts involves elimination followed by addition. In step 1, a suitable base removes the ortho hydrogen, with subsequent (or concomitant) loss of the chlorine (leaving group) to



6

generate symmetrical intermediate **6**[39] is called benzyne (see below).[40] In step 2, benzyne is attacked by the NH_3 at either of two positions, which explains why about half of the aniline produced from the radioactive chlorobenzene was labeled at the 2 position. The fact that the 1 and 2 positions were not labeled equally is the result of a small isotope effect. Other evidence for this mechanism is the following:

1. If the aryl halide contains two ortho substituents, the reaction should not be able to occur. This is indeed the case.[36]
2. It had been known many years earlier that aromatic nucleophilic substitution occasionally results in substitution at a different position. This is called *cine substitution*[41] and can be illustrated by the conversion of *o*-bromoanisole to *m*-aminoanisole.[42] In this particular case, only the meta isomer is



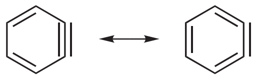
7

formed. The reason a 1:1 mixture is not formed is that the intermediate **7** is not symmetrical and the methoxy group directs the incoming group meta, but not ortho (see p. 867). However, not all cine substitutions proceed by this kind of mechanism (see **13-30**).
3. The fact that the order of halide reactivity is Br > I > Cl > F (when the reaction is performed with KNH_2 in liquid NH_3) shows that the S_NAr mechanism is not operating here.[38]

[39]For a discussion of the structure of *m*- and *p*-benzynes, see Hess, Jr., B.A. *Eur. J. Org. Chem.* ***2001***, 2185.
[40]For other methods to generate benzyne, see Kitamura, T.; Meng, Z.; Fujiwara, Y. *Tetrahedron Lett.* ***2000***, *41*, 6611, and references cited therein; Kawabata, H.; Nishino, T.; Nishiyama, Y.; Sonoda, N. *Tetrahedron Lett.* ***2002***, *43*, 4911, and references cited therein.
[41]For a review, see Suwiń ski, J.; wierczek, K. *Tetrahedron* ***2001***, *57*, 1639.
[42]This example is from Gilman, H.; Avakian, S. *J. Am. Chem. Soc.* ***1945***, *67*, 349. For a table of many such examples, see Bunnett, J.F.; Zahler, R.E. *Chem. Rev.* ***1951***, *49*, 273, p. 385.

In the conversion of the substrate to **7**, either proton removal or subsequent loss of halide ion can be rate determining. In fact, the unusual leaving-group order just mentioned (Br > I > Cl) stems from a change in the rate-determining step. When the leaving group is Br or I, proton removal is rate-determining and the rate order for this step is F > Cl > Br > I. When Cl or F is the leaving group, cleavage of the C–X bond is rate determining and the order for this step is I > Br > Cl > F. Confirmation of the latter order was found in a direct competitive study. *meta*-Dihalobenzenes in which the two halogens are different were treated with $^{-}NH_2$.[43] In such compounds, the most acidic hydrogen is the one between the two halogens; when it leaves, the remaining anion can lose either halogen. Therefore, a study of which halogen is preferentially lost provides a direct measure of leaving-group ability. The order was found to be I > Br > Cl.[43,44]

Species, such as **6** and **7**, are called *benzynes* (sometimes *dehydrobenzenes*), or more generally, *arynes*,[45] and the mechanism is known as the *benzyne mechanism*. Benzynes are very reactive. Neither benzyne nor any other aryne has yet been isolated under ordinary conditions,[46] but benzyne has been isolated in an argon matrix at 8 K,[47] where its IR spectrum could be observed. In addition, benzynes can be trapped; for example, they undergo the Diels–Alder reaction (see **15-60**). Note that the extra pair of electrons does not affect the



A **B**

aromaticity. However, evaluation by a series of aromaticity indicators, including magnetic susceptibility anisotropies and exaltations, nucleus-independent chemical shifts (NICS), and aromatic stabilization energies, and valence-bond Pauling resonance energies point to the *o*-benzyne > *m*-benzyne > *p*-benzyne aromaticity order.[48] The relative order with respect to benzene depends on the aromaticity criterion.[48] The aromtic sextet from the aromatic precursor functions as a closed ring, and the two additional electrons are merely located in a π orbital that covers only two carbons. Benzynes do not have a formal triple bond, since two canonical forms (**A** and **B**) contribute to the hybrid. The IR spectrum, mentioned above, indicates that **A** contributes more than **B**. Not only benzene rings, but other aromatic

[43]Bunnett, J.F.; Kearley, Jr., F.J. *J. Org. Chem.* ***1971***, *36*, 184.

[44]For a discussion of the diminished reactivity of ortho-substituted bromides, see Kalendra, D.M.; Sickles, B.R. *J. Org. Chem.* ***2003***, *68*, 1594.

[45]For the use of arynes in organic synthesis see Pellissier, H.; Santelli, M. *Tetrahedron* ***2003***, *59*, 701.

[46]For the measurement of aryne lifetimes in solution, see Gaviña, F.; Luis, S.V.; Costero, A.M.; Gil, P. *Tetrahedron* ***1986***, *42*, 155.

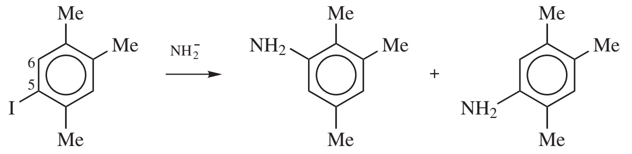
[47]Chapman, O.L.; Mattes, K.; McIntosh, C.L.; Pacansky, J.; Calder, G.V.; Orr, G. *J. Am. Chem. Soc.* ***1973***, *95*, 6134. For the ir spectrum of pyridyne trapped in a matrix, see Nam, H.; Leroi, G.E. *J. Am. Chem. Soc.* ***1988***, *110*, 4096. For spectra of transient arynes, see Berry, R.S.; Spokes, G.N.; Stiles, M. *J. Am. Chem. Soc.* ***1962***, *84*, 3570; Brown, R.D.; Godfrey, P.D.; Rodler, M. *J. Am. Chem. Soc.* ***1986***, *108*, 1296.

[48]DeProft, F.; Schleyer, P.v.R.; van Lenthe, J.H.; Stahl, F.; Geerlings, P. *Chem. Eur. J.* ***2002***, *8*, 3402.

rings[49] and even nonaromatic rings (p. 475) can react through this kind of intermediate. Of course, the non-aromatic rings do have a formal triple bond. When a benzyne unit is fused to a small ring, strain induced regioselectivity observed in its reactions.[50]

The $S_{RN}1$ Mechanism

When 5-iodo-1,2,4-trimethylbenzene **7** was treated with KNH_2 in NH_3, **8** and **10** were formed in the ratio 0.63:1. From what we have already seen, the presence of an unactivated substrate, a strong base, and the occurrence of cine substitution along with normal substitution would be strong indications of a benzyne mechanism. Yet if that were so, the 6-iodo isomer of **8** should have given **9** and **10** in the same ratio (because the same aryne intermediate would be formed in both cases), but in this case the ratio of **9–10** was 5.9:1 (the chloro and bromo analogs did give the same ratio, 1.46:1, showing that the benzyne mechanism may be taking place there).



8 **9** **10**

To explain the iodo result, it has been proposed[51] that besides the benzyne mechanism, this free-radical mechanism is also operating here:

$$\mathrm{ArI} \xrightarrow[\text{donor}]{\text{electron}} \mathrm{ArI}^{\bullet -} \longrightarrow \mathrm{Ar}^{\bullet} + \mathrm{I}^-$$

$$\mathrm{Ar}^{\bullet} + \mathrm{NH_2^-} \longrightarrow \mathrm{ArNH_2^{\bullet -}} + \mathrm{ArI} \longrightarrow \mathrm{ArNH_2} + \mathrm{ArI}^{\bullet -}$$

followed by terminations steps

This is called the $S_{RN}1$ mechanism,[52] and many other examples are known (see **13-3**, **13-4**, **13-6**, **13-14**). The IUPAC designation is $T + D_N + A_N$.[53] Note that the

[49]For reviews of *hetarynes* (benzyne intermediates in heterocyclic rings), see van der Plas, H.C.; Roeterdink, F., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 1, Wiley, NY, ***1983***, pp. 421–511; Reinecke, M.G. *React. Intermed. (Plenum)* ***1982***, *2*, 367; *Tetrahedron* ***1982***, *38*, 427; den Hertog, H.J.; van der Plas, H.C., in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 1149–1197, *Adv. Heterocycl. Chem.* ***1971***, *40*, 121; Kauffmann, T.; Wirthwein, R. *Angew. Chem, Int. Ed.* ***1971***, *10*, 20; Kauffmann, T. *Angew. Chem, Int. Ed.* ***1965***, *4*, 543; Hoffmann, R.W. *Dehydrobenzene and Cycloalkynes*, Academic Press, NY, ***1967***, pp. 275–309.

[50]Hamura, T.; Ibusuki, Y.; Sato, K.; Matsumoto, T.; Osamura, Y.; Suzuki, K. *Org. Lett.* ***2003***, *5*, 3551.

[51]Kim, J.K.; Bunnett, J.F. *J. Am. Chem. Soc.* ***1970***, *92*, 7463, 7464.

[52]For a monograph, see Rossi, R.A.; de Rossi, R.H. *Aromatic Substitution by the $S_{RN}1$ Mechanism*, American Chemical Society, Washington, 1983. For reviews, see Savéant, J. *Adv. Phys. Org. Chem.* ***1990***, *26*, 1; Russell, G.A. *Adv. Phys. Org. Chem.* ***1987***, *23*, 271; Norris, R.K. in Patai, S. Rappoport, Z. *The Chemistry of Functional Groups, Supplement D*, pt. 1, Wiley, NY, ***1983***, pp. 681–701; Chanon, M.; Tobe, M.L. *Angew. Chem, Int. Ed.* ***1982***, *21*, 1; Rossi, R.A. *Acc. Chem. Res.* ***1982***, *15*, 164; Beletskaya, I.P.; Drozd, V.N. *Russ. Chem. Rev.* ***1979***, *48*, 431; Bunnett, J.F. *Acc. Chem. Res.* ***1978***, *11*, 413; Wolfe, J.F.; Carver, D.R. *Org. Prep. Proced. Int.* ***1978***, *10*, 225. For a review of this mechanism with aliphatic substrates, see Rossi, R.A.; Pierini, A.B.; Palacios, S.M. *Adv. Free Radical Chem.* (*Greenwich, Conn.*) ***1990***, *1*, 193. For 'thermal' $S_{RN}1$ reactions, see Costentin, C.; Hapiot, P.; Médebielle, M.; Savéant, J.-M. *J. Am. Chem. Soc.* ***1999***, *121*, 4451.

[53]The symbol T is used for electron transfer.

last step of the mechanism produces $ArI^{\bullet -}$ radical ions, so the process is a chain mechanism (see p. 936).[54] An electron donor is required to initiate the reaction. In the case above it was solvated electrons from KNH_2 in NH_3. Evidence was that the addition of potassium metal (a good producer of solvated electrons in ammonia) completely suppressed the cine substitution. Further evidence for the $S_{RN}1$ mechanism was that addition of radical scavengers (which would suppress a free-radical mechanism) led to **9:10** ratios much closer to 1.46:1. Numerous other observations of $S_{RN}1$ mechanisms that were stimulated by solvated electrons and inhibited by radical scavengers have also been recorded.[55] Further evidence for the $S_{RN}1$ mechanism in the case above was that some 1,2,4-trimethylbenzene was found among the products. This could easily be formed by abstraction by $Ar^{\bullet}$ of H from the solvent NH_3. Besides initiation by solvated electrons,[56] $S_{RN}1$ reactions have been initiated photochemically,[57] electrochemically,[58] and even thermally.[59]

The $S_{RN}1$ reactions have a fairly wide scope. The efficiency of the reaction has been traced to the energy level of the radical anion of the substitution product.[60] There is no requirement for activating groups or strong bases, but in DMSO haloarenes are less reactive as the stability of the anion increases.[61] The reaction has also been done in liquid ammonia, promoted by ultrasound (p. 349),[62] and ferrous ion has been used as a catalyst.[63] Alkyl, alkoxy, aryl, and COO^- groups do not interfere, although Me_2N, O^-, and NO_2 groups do interfere. Cine substitution is not found.

Other Mechanisms

There is no clear-cut proof that a one-step S_N2 mechanism, so important at a saturated carbon, ever actually occurs with an aromatic substrate. The hypothetical aromatic S_N2 process is sometimes called the *one-stage* mechanism to distinguish it from the *two-stage* S_NAr mechanism. A "clean" example of a $S_{RN}2$ reaction has been reported, the conversion of **11** to **12** in methanol.[64] Both the $S_{RN}1$ and $S_{RN}2$ reactions have been reviewed.[65]

[54]For a discussion, see Amatore, C.; Pinson, J.; Savéant, J.; Thiébault, A. *J. Am. Chem. Soc.* ***1981***, *103*, 6930.

[55]Bunnett, J.F. *Acc. Chem. Res.* ***1978***, *11*, 413.

[56]Savéant, J.-M. *Tetrahedron* ***1994***, *50*, 10117.

[57]For reviews of photochemical aromatic nucleophilic substitutions, see Cornelisse, J.; de Gunst, G.P.; Havinga, E. *Adv. Phys. Org. Chem.* ***1975***, *11*, 225; Cornelisse, J. *Pure Appl. Chem.* ***1975***, *41*, 433; Pietra, F. *Q. Rev. Chem. Soc.* ***1969***, *23*, 504, p. 519.

[58]For a review, see Savéant, J. *Acc. Chem. Res.* ***1980***, *13*, 323. See also, Alam, N.; Amatore, C.; Combellas, C.; Thiébault, A.; Verpeaux, J.N. *J. Org. Chem.* ***1990***, *55*, 6347.

[59]Swartz, J.E.; Bunnett, J.F. *J. Org. Chem.* ***1979***, *44*, 340, and references cited therein.

[60]Galli, C.; Gentili, P.; Guarnieri, A. *Gazz. Chim. Ital.*, ***1995***, *125*, 409.

[61]Borosky, G.L.; Pierini, A.B.; Rossi, R.A. *J. Org. Chem.* ***1992***, *57*, 247.

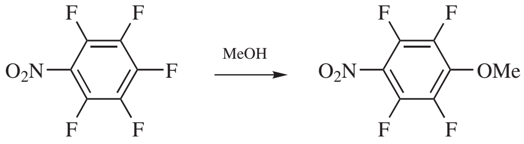
[62]Manzo, P.G.; Palacios, S.M.; Alonso, R.A. *Tetrahedron Lett.* ***1994***, *35*, 677.

[63]Galli, C.; Gentili, P.; *J. Chem. Soc. Perkin Trans. 2* ***1993***, 1135.

[64]Marquet, J.; Jiang, Z.; Gallardo, I.; Batlle, A.; Cayón, E. *Tetrahedron Lett.* ***1993***, *34*, 2801. Also see, Keegstra, M.A. *Tetrahedron* ***1992***, *48*, 2681.

[65]Rossi, R.A.; Palacios, S.M. *Tetrahedron* ***1993***, *49*, 4485.

Some of the reactions in this chapter operate by still other mechanisms, among them an addition–elimination mechanism (see **13-17**). A new mechanism has been reported in aromatic chemistry, a reductively activated 'polar' nucleophilic aromatic substitution.[66] The reaction of phenoxide with *p*-dinitrobenzene in DMF shows radical features that cannot be attributed to a radical anion, and it is not $S_{RN}2$. The new designation was proposed to account for these results.



11 **12**

REACTIVITY

The Effect of Substrate Structure

In the discussion of electrophilic aromatic substitution (Chapter 11) equal attention was paid to the effect of substrate structure on reactivity (activation or deactivation) and on orientation. The question of orientation was important because in a typical substitution there are four or five hydrogens that could serve as leaving groups. This type of question is much less important for aromatic nucleophilic substitution, since in most cases there is only one potential leaving group in a molecule. Therefore attention is largely focused on the reactivity of one molecule compared with another and not on the comparison of the reactivity of different positions within the same molecule.

S_NAr Mechanism. These substitutions are accelerated by electron-withdrawing groups, especially in positions ortho and para to the leaving group[67] and hindered by electron-attracting groups. This is, of course, opposite to the effects of these groups on electrophilic substitutions, and the reasons are similar to those discussed in Chapter 11 (p. 660). Table 13.1 contains a list of groups arranged approximately in order of activating or deactivating ability.[68] Nitrogen atoms are also strongly activating (especially to the α and γ positions) and are even more so when quaternized.[69] Both 2- and 4-chloropyridine, for example, are often used as substrates. Heteroaromatic amine *N*-oxides are readily attacked by nucleophiles in the 2 and 4 positions, but the oxygen is generally lost in these reactions.[70]

[66]Marquet, J.; Casado, F.; Cervera, M.; Espín, M.; Gallardo, I.; Mir, M.; Niat, M. *Pure Appl. Chem.* ***1995***, *67*, 703.

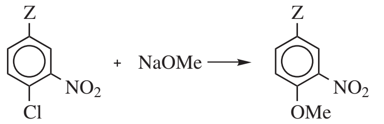
[67]The effect of meta substituents has been studied much less, but it has been reported that here too, electron-withdrawing groups increase the rate: See Nurgatin, V.V.; Sharnin, G.P.; Ginzburg, B.M. *J. Org. Chem, USSR* ***1983***, *19*, 343.

[68]For additional tables of this kind, see Miller, J. *Aromatic Nucleophilic Substitution*, Elsevier, NY, ***1968***, pp. 61–136.

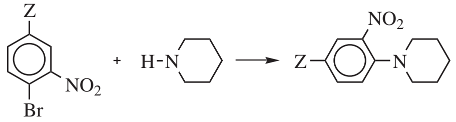
[69]Miller, J.; Parker, A.J. *Aust. J. Chem.* ***1958***, *11*, 302.

[70]Berliner, E.; Monack, L.C. *J. Am. Chem. Soc.* ***1952***, *74*, 1574.

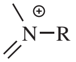
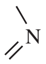
TABLE 13.1. Groups Listed in Approximate Descending Order of Activating Ability in the S_NAr Mechanism[68]



at 0°C[71] (*a*)[a]



at 25°C[72] (*a*)[a]

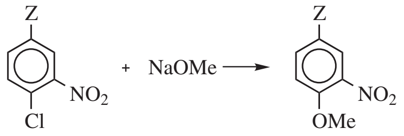
		Relative Rate of Reaction	
Comments[b]	Group Z	(*a*) H = 1[69]	(*b*) NH_2 = 1[70]
Activates halide exchange at room temperature	N_2^+		
Activates reaction with strong nucleophiles at room temperature	 (heterocyclic)		
Activate reactions with strong nucleophiles at 80–100°C	NO	5.22×10^6	
	NO_2	6.73×10^5	Very fast
	 (heterocyclic)		
With nitro also present, activate reactions with strong nucleophiles at room temperature	SO_2Me		
	NMe_3^+		
	CF_3		
	CN	3.81×10^4	
	CHO	2.02×10^4	
With nitro also present, activate reactions with strong nucleophiles at 40–60°C	COR		
	COOH		
	SO_3^-		
	Br		6.31×10^4
	Cl		4.50×10^4
	I		4.36×10^4
	COO^-		2.02×10^4
	H		8.06×10^3
	F		2.10×10^3
	CMe_3		1.37×10^3
	Me		1.17×10^3

(*continued*)

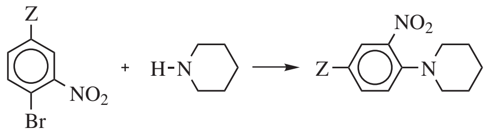
[71]For reviews of reactivity of nitrogen-containing heterocycles, see Illuminati, G. *Adv. Heterocycl. Chem.* ***1964***, *3*, 285; Shepherd, R.G.; Fedrick, J.L. *Adv. Heterocycl. Chem.* ***1965***, *4*, 145.

[72]For reviews, see Albini, A.; Pietra, S. *Heterocyclic N-Oxides*; CRC Press: Boca Raton, FL, ***1991***, pp. 142–180; Katritzky, A.R.; Lagowski, J.M. *Chemistry of the Heterocyclic N-Oxides*, Academic Press, NY, ***1971***, pp. 258–319, 550–553.

TABLE 13.1. (*Continued*)



at 0°C[71] [(a)]



at 25°C[72] [(a)]

Comments[b]	Group Z	Relative Rate of Reaction (*a*) H = 1[69]	(*b*) $NH_2 = 1$[70]
	OMe		145
	NMe_2		9.77
	OH		4.70
	NH_2		1

[a]For reaction (*a*) the rates are relative to **H**; *for (b)* they are relative to NH_2.
[b]The comments on the left column are from Ref. 73.

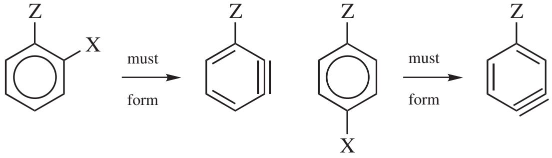
The most highly activating group, N_2^+, is seldom deliberately used to activate a reaction, but it sometimes happens that in the diazotization of a compound, such as *p*-nitroaniline or *p*-chloroaniline, the group para to the diazonium group is replaced by OH from the solvent or by X from $ArN_2^+\ X^-$, to the surprise and chagrin of the investigator, who was trying only to replace the diazonium group and to leave the para group untouched. By far, the most common activating group is the nitro group and the most common substrates are 2,4-dinitrophenyl halides and 2,4,6-trinitrophenyl halides (also called picryl halides).[74] Polyfluorobenzenes[75] (e.g., C_6F_6), also undergo aromatic nucleophilic substitution quite well.[76] Benzene rings that lack activating substituents are generally not useful substrates for the S_NAr mechanism, because the two extra electrons in **1** are in an antibonding orbital (p. 34). Activating groups, by withdrawing electron density, are able to stabilize the intermediates and the

[73]Bunnett, J.F.; Zahler, R.E. *Chem. Rev.* ***1951***, *49*, 273, p. 308.
[74]For a review of the activating effect of nitro groups, see de Boer, T.J.; Dirkx, I.P., in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, pt. 1, Wiley, NY, ***1970***, pp. 487–612.
[75]Fluorine significantly activates ortho and meta positions, and slightly deactivates (see Table 13.1) para positions: Chambers, R.D.; Seabury, N.J.; Williams, D.L.H.; Hughes, N. *J. Chem. Soc. Perkin Trans. 1* ***1988***, 255.
[76]For reviews, see Yakobson, G.G.; Vlasov, V.M. *Synthesis* ***1976***, 652; Kobrina, L.S. *Fluorine Chem. Rev.* ***1974***, *7*, 1.

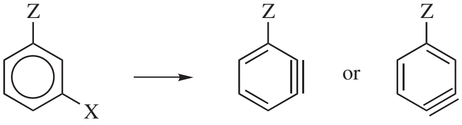
transition states leading to them. Reactions taking place by the S_NAr mechanism are also accelerated when the aromatic ring is coordinated with a transition metal.[77]

Just as electrophilic aromatic substitutions were found more or less to follow the Hammett relationship (with σ^+ instead of σ; see p. 402), so do nucleophilic substitutions, with σ^- instead of σ for electron-withdrawing groups.[78]

Benzyne Mechanism. Two factors affect the position of the incoming group, the first being the direction in which the aryne forms.[79] When there are groups ortho or para to the leaving group, there is no choice:



but when a meta group is present, the aryne can form in two different ways:



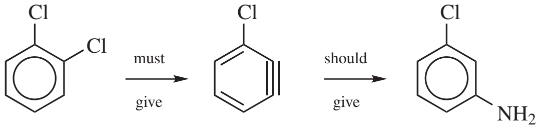
In such cases, the more acidic hydrogen is removed. Since acidity is related to the field effect of Z, it can be stated that an electron-attracting Z favors removal of the ortho hydrogen while an electron-donating Z favors removal of the para hydrogen. The second factor is that the aryne, once formed, can be attacked at two positions. The favored position for nucleophilic attack is the one that leads to the more stable carbanion intermediate, and this in turn also depends on the field effect of Z. For *-I* groups, the more stable carbanion is the one in which the negative charge is closer to the substituent. These principles are illustrated by the reaction of the three dichlorobenzenes (**13-15**) with alkali-metal

[77]For a review, see Balas, L.; Jhurry, D.; Latxague, L.; Grelier, S.; Morel, Y.; Hamdani, M.; Ardoin, N.; Astruc, D. *Bull. Soc. Chim. Fr.* ***1990***, 401. For a discussion of iron assisted nucleophilic aromatic substitution on the solid phase, see Ruhland, T.; Bang, K.S.; Andersen, K. *J. Org. Chem.* ***2002***, *67*, 5257.

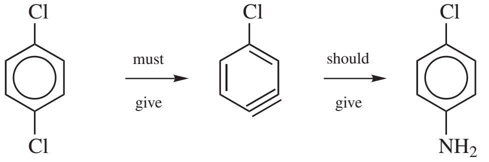
[78]For a discussion of linear free-energy relationships in this reaction, see Bartoli, G.; Todesco, P.E. *Acc. Chem. Res.* ***1977***, *10*, 125. For a list of σ^- values, see Table 9.4 on p. 404.

[79]This analysis is from Roberts, J.D.; Vaughan, C.W.; Carlsmith, L.A.; Semenow, D.A. *J. Am. Chem. Soc.* ***1956***, *78*, 611. For a discussion, see Hoffmann, R.W. *Dehydrobenzene and Cycloalkynes*, Academic Press, NY, ***1973***, pp. 134–150.

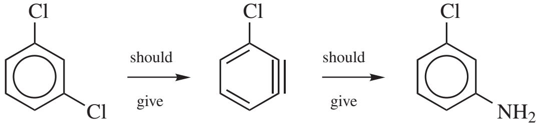
amides to give the predicted products shown.



13



14



15

In each case, the predicted product was the one chiefly formed.[80] The observation that *m*-aminoanisole is obtained, mentioned on p. 860, is also in accord with these predictions.

The Effect of the Leaving Group[81]

The common leaving groups in aliphatic nucleophilic substitution (halide, sulfate, sulfonate, NR_3^+, etc.) are also common leaving groups in aromatic nucleophilic substitutions, but the groups NO_2, OR, OAr, SO_2R,[82] and SR, which are not generally lost in aliphatic systems, *are* leaving groups when attached to aromatic rings. Surprisingly, NO_2 is a particularly good leaving group.[83] An approximate order of leaving-group ability is[84] $F > NO_2 > OTs > SOPh > Cl,\ Br,\ I > N_3 > NR_3^+ >$ OAr, OR, SR, NH_2. However, this depends greatly on the nature of the nucleophile, as illustrated by the fact that $C_6Cl_5OCH_3$ treated with NH_2^- gives mostly $C_6Cl_5NH_2$; that is, one methoxy group is replaced in preference to five chlorines.[85] As usual, OH can be a leaving group if it is converted to an inorganic ester. Among

[80]Wotiz, J.H.; Huba, F. *J. Org. Chem.* ***1959***, *24*, 595. Eighteen other reactions also gave products predicted by these principles. See also, Caubere, P.; Lalloz, L. *Bull. Soc. Chim. Fr.* ***1974***, 1983, 1989, 1996; Biehl, E.R.; Razzuk, A.; Jovanovic, M.V.; Khanapure, S.P. *J. Org. Chem.* ***1986***, *51*, 5157.
[81]For a review, see Miller, J. *Aromatic Nucleophilic Substitution*, Elsevier, NY, ***1968***, pp. 137–179.
[82]See, for example, Furukawa, N.; Ogawa, S.; Kawai, T.; Oae, S. *J. Chem. Soc. Perkin Trans. 1* ***1984***, 1839.
[83]For a review, see Beck, J.R. *Tetrahedron* ***1978***, *34*, 2057. See also, Effenberger, F.; Koch, M.; Streicher, W. *Chem. Ber.* ***1991***, *24*, 163.
[84]Loudon, J.D.; Shulman, N. *J. Chem. Soc.* ***1941***, 772; Suhr, H. *Chem. Ber.* ***1963***, *97*, 3268.
[85]Kobrina, L.S.; Yakobson, G.G. *J. Gen. Chem. USSR* ***1963***, *33*, 3238.

the halogens, fluoro is generally a much better leaving group than the other halogens, which have reactivities fairly close together. The order is usually Cl > Br > I, but not always.[86] The leaving-group order is quite different from that for the S_N1 or S_N2 mechanisms. The most likely explanation is that the first step of the S_NAr mechanism is usually rate determining, and this step is promoted by groups with strong *–I* effects. This would explain why fluoro and nitro are such good leaving groups when this mechanism is operating. Fluoro is the poorest leaving group of the halogens when the second step of the S_NAr mechanism is rate determining or when the benzyne mechanism is operating. The four halogens, as well as SPh, NMe_3^+, and $OPO(OEt)_2$, have been shown to be leaving groups in the $S_{RN}1$ mechanism.[55] The only important leaving group in the S_N1 mechanism is N_2^+.

The Effect of the Attacking Nucleophile[87]

It is not possible to construct an invariant nucleophilicity order because different substrates and different conditions lead to different orders of nucleophilicity, but an overall approximate order is $^-NH_2 > Ph_3C^- > PhNH^-$ (aryne mechanism) > $ArS^- > RO^{\neq} > R_2NH > ArO^- > {}^-OH > ArNH_2 > NH_3 > I^- > Br^- > Cl^- > H_2O > ROH$.[88] As with aliphatic nucleophilic substitution, nucleophilicity is generally dependent on base strength and nucleophilicity increases as the attacking atom moves down a column of the periodic table, but there are some surprising exceptions, for example, ^-OH, a stronger base than ArO^-, is a poorer nucleophile.[89] In a series of similar nucleophiles, such as substituted anilines, nucleophilicity *is* correlated with base strength. Oddly, the cyanide ion is not a nucleophile for aromatic systems, except for sulfonic acid salts and in the von Richter (**13-30**) and Rosenmund-von Braun (**13-8**) reactions, which are special cases.

REACTIONS

In the first part of this section, reactions are classified according to attacking species, with all leaving groups considered together, except for hydrogen and N_2^+, which are treated subsequently. Finally, a few rearrangement reactions are discussed.

[86]Reinheimer, J.D.; Taylor, R.C.; Rohrbaugh, P.E. *J. Am. Chem. Soc.* ***1961***, *83*, 835; Ross, S.D. *J. Am. Chem. Soc.* ***1959***, *81*, 2113; Bunnett, J.F.; Garbisch Jr., E.W.; Pruitt, K.M. *J. Am. Chem. Soc.* ***1957***, *79*, 385; Parker, R.E.; Read, T.O. *J. Chem. Soc.* ***1962***, 9, 3149; Litvinenko, L.M.; Shpan'ko, L.V.; Korostylev, A.P. *Doklad. Chem.* ***1982***, *266*, 309.

[87]For a review, see Miller, J. *Aromatic Nucleophilic Substitution*, Elsevier, NY, ***1968***, pp. 180–233.

[88]This list is compiled from data, in Bunnett, J.F. ; Zahler, R.E. *Chem. Rev.* ***1951***, *49*, 273, p. 340; Bunnett, J.F. *Q. Rev. Chem. Soc.* ***1958***, *12*, 1, p. 13; Sauer, J.; Huisgen, R. *Angew. Chem.* ***1960***, *72*, 294, p. 311; Bunnett, J.F. *Annu. Rev. Phys. Chem.* ***1963***, *14*, 271.

[89]For studies of nucleophilicity in the $S_{RN}1$ mechanism, see Amatore, C.; Combellas, C.; Robveille, S.; Savéant, J.; Thiébault, A. *J. Am. Chem. Soc.* ***1986***, *108*, 4754, and references cited therein.

ALL LEAVING GROUPS EXCEPT HYDROGEN AND N_2^+

A. Oxygen Nucleophiles

13-1 Hydroxylation of Aromatic Compounds

Hydroxy-de-halogenation

$$\text{ArBr} + \text{OH}^- \longrightarrow \text{ArOH}$$

Aryl halides are converted to phenols if activating groups are present or if exceedingly strenuous conditions are employed.[90] When the reaction is carried out at high temperatures, cine substitution is observed, indicating a benzyne mechanism.[91] The reaction has been done using NaOH on Montmorillonite K10 and $AgNO_3$ with microwave irradiation.[92]

A slightly related reaction involves the amino group of naphthylamines can be replaced by a hydroxyl group by treatment with aqueous bisulfite.[93] The scope is greatly limited; the amino group (which may be NH_2 or NHR) must be on a naphthalene ring, with very few exceptions. The reaction is reversible (see **13-6**), and both the forward and reverse reactions are called the *Bucherer reaction*.

$$\text{ArMgX} \xrightarrow{\text{B(OMe)}_3} \text{ArB(OMe)}_2 \xrightarrow[\text{H}_2\text{O}_2]{\text{H}^+} \text{ArOH}$$

An indirect method for conversion of an aryl halide to a phenol involves initial conversion to an organometallic, followed by oxidation to the phenol. For the conversion of aryl Grignard reagents to phenols, a good procedure is the use of trimethyl borate followed by oxidation with H_2O_2 in acetic acid[94] (see **12-31**). Phenols have been obtained from unactivated aryl halides by treatment with borane and a metal such as lithium, followed by oxidation with alkaline H_2O_2.[95] Arylboronic acids, $ArB(OH)_2$, are oxidized by aqueous hydrogen peroxide to give the corresponding phenol.[96] The reaction of an aromatic compound with a borane in the

[90]For a review of $^-$OH and $^-$OR as nucleophiles in aromatic substitution, see Fyfe, C.A., in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, ***1971***, pp. 83–124.

[91]The benzyne mechanism for this reaction is also supported by ^{14}C labeling experiments: Bottini, A.T.; Roberts, J.D. *J. Am. Chem. Soc.* ***1957***, *79*, 1458; Dalman, G.W.; Neumann, F.W. *J. Am. Chem. Soc.* ***1968***, *90*, 1601.

[92]Hashemi, M.M.; Akhbari, M. *Synth. Commun.* ***2004***, *34*, 2783.

[93]For reviews, see Seeboth, H. *Angew. Chem, Int. Ed.* ***1967***, *6*, 307; Gilbert, E.E. *Sulfonation and Related Reactions*; Wiley, NY, ***1965***, pp. 166–169.

[94]Hawthorne, M.F. *J. Org. Chem.* ***1957***, *22*, 1001. For other procedures, see Lewis, N.J.; Gabhe, S.Y. *Aust. J. Chem.* ***1978***, *31*, 2091; Hoffmann, R.W.; Ditrich, K. *Synthesis* ***1983***, 107.

[95]Pickles, G.M.; Thorpe, F.G. *J. Organomet. Chem.* ***1974***, *76*, C23.

[96]Simon, J.; Salzbrunn, S.; Prakash, G.K.S.; Petasis, N.A.; Olah, G.A. *J. Org. Chem.* ***2001***, *66*, 633.

presence of an iridium catalyst, followed by oxidation with aqueous Oxone® gave the corresponding phenol.[97] Aryllithium reagents have been converted to phenols by treatment with oxygen.[98] In a related indirect method, arylthallium bis(trifluoroacetates) (prepared by **12-23**) can be converted to phenols by treatment with lead tetraacetate followed by triphenylphosphine and then dilute NaOH.[99] Diarylthallium trifluoroacetates undergo the same reaction.[100]

OS **I**, 455; **II**, 451; **V**, 632. Also see, OS **V**, 918.

13-2 Alkali Fusion of Sulfonate Salts

Oxido-de-sulfonato-substitution

$$ArSO_3^- \xrightarrow[300\text{–}320^\circ C]{\text{NaOH fusion}} ArO^-$$

Aryl sulfonic acids can be converted, through their salts, to phenols, by alkali fusion. In spite of the extreme conditions, the reaction gives fairly good yields, except when the substrate contains other groups that are attacked by alkali at the fusion temperatures. Milder conditions can be used when the substrate contains activating groups, but the presence of deactivating groups hinders the reaction. The mechanism is obscure, but a benzyne intermediate has been ruled out by the finding that cine substitution does not occur.[101]

OS **I**, 175; **III**, 288.

13-3 Replacement by OR or OAr

Alkoxy-de-halogenation

$$ArBr + OR^- \longrightarrow ArOR$$

This reaction is similar to **13-1** and, like that one, generally requires activated substrates.[90,102] With unactivated substrates, side reactions predominate, though aryl methyl ethers have been prepared from unactivated chlorides by treatment with MeO^- in HMPA.[103] This reaction gives better yields than **13-1** and is

[97]Maleczka Jr., R.E.; Shi, F.; Holmes, D.; Smith III, M.R. *J. Am. Chem. Soc.* ***2003***, *125*, 7792.

[98]Parker, K.A.; Koziski, K.A. *J. Org. Chem.* ***1987***, *52*, 674. For other reagents, see Taddei, M.; Ricci, A. *Synthesis* ***1986***, 633; Einhorn, J.; Luche, J.; Demerseman, P. *J. Chem. Soc. Chem. Commun.* ***1988***, 1350.

[99]Taylor, E.C.; Altland, H.W.; Danforth, R.H.; McGillivray, G.; McKillop, A. *J. Am. Chem. Soc.* ***1970***, *92*, 3520.

[100]Taylor, E.C.; Altland, H.W.; McKillop, A. *J. Org. Chem.* ***1975***, *40*, 2351.

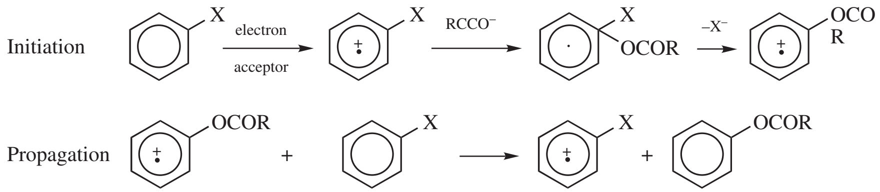
[101]Buzbee, L.R. *J. Org. Chem.* ***1966***, *31*, 3289; Oae, S.; Furukawa, N.; Kise, M.; Kawanishi, M. *Bull. Chem. Soc. Jpn.* ***1966***, *39*, 1212.

[102]See Gujadhur, R.; Venkataraman, D. *Synth. Commun.* ***2001***, *31*, 2865.

[103]Shaw, J.E.; Kunerth, D.C.; Swanson, S.B. *J. Org. Chem.* ***1976***, *41*, 732; Testaferri, L.; Tiecco, M.; Tingoli, M.; Chianelli, D.; Montanucci, M. *Tetrahedron* ***1983***, *39*, 193.

used more often. A good solvent is liquid ammonia. Aryl chlorides react with phenol and KOH with microwave irradiation to give the diaryl ether.[104] Potassium phenoxide reacts with iodobenzene in an ionic solvent at 100°C with CuCl.[105] The NaOMe reacted with *o*- and *p*-fluoronitrobenzenes ~10^9 times faster in NH_3 at −70°C than in MeOH.[106] Phase-transfer catalysis has also been used.[107] Phenols reacted with aryl fluorides with K_2CO_3/DMSO[108] or aryl chlorides with KOH,[109] with microwave irradiation, to give the diaryl ether. Aryl carbonates react with aryl oxides.[110] Phenolic compounds react with aryl fluorides in the presence of LiOH in DMF to give the diaryl ether.[111] Aryl iodides react with phenols in the presence of K_2CO_3, CuI and Raney nickel alloy.[112]

In addition to halides, leaving groups can be other OR, and so on, even OH.[113] Acid salts, $RCOO^-$, are sometimes used as nucleophiles. Good yields of aryl benzoates can be obtained by the treatment of aryl halides with cuprous benzoate in diglyme or xylene at 140–160°C.[114] Unactivated substrates have been converted to carboxylic esters in low-to-moderate yields under oxidizing conditions.[115] The following chain mechanism, called the $S_{ON}2$ mechanism,[116] has been suggested:[115]



For aroxide nucleophiles, the reaction is promoted by copper salts,[117] and when these are used, activating groups need not be present. Indeed, unactivated aryl

[104]Rebeiro, G.L.; Khadilkar, B.M. *Synth. Commun.* ***2003***, *33*, 1405.

[105]In bmim BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate: Chauhan, S.M.S.; Jain, N.; Kumar, A.; Srinivas, K.A. *Synth. Commun.* ***2003***, *33*, 3607.

[106]Kizner, T.A.; Shteingarts, V.D. *J. Org. Chem, USSR* ***1984***, *20*, 991.

[107]Artamanova, N.N.; Seregina, V.F.; Shner, V.F.; Salov, B.V.; Kokhlova, V.M.; Zhdamarova, V.N. *J. Org. Chem, USSR* ***1989***, *25*, 554.

[108]Li, F.; Wang, Q.; Ding, Z.; Tao, F. *Org. Lett.* ***2003***, *5*, 2169.

[109]Chaouchi, M.; Loupy, A.; Marque, S.; Petit, A. *Eur. J. Org. Chem.* ***2002***, 1278.

[110]Castro, E.A.; Pavez, P.; Santos, J.G. *J. Org. Chem.* ***2001***, *66*, 3129.

[111]Ankala, S.V.; Fenteany, G. *Synlett* ***2003***, 825.

[112]Xu, L.-W.; Xia, C.-G.; Li, J.-W.; Hu, X.-X. *Synlett* ***2003***, 2071.

[113]Oae, S.; Kiritani, R. *Bull. Chem. Soc. Jpn.* ***1964***, *37*, 770; ***1966***, *39*, 611.

[114]Cohen, T.; Wood, J.; Dietz Jr., A.G. *Tetrahedron Lett.* ***1974***, 3555.

[115]Jönsson, L.; Wistrand, L. *J. Org. Chem.* ***1984***, *49*, 3340.

[116]First proposed by Alder, R.W. *J. Chem. Soc. Chem. Commun.* ***1980***, 1184.

[117]For a review of copper-assisted aromatic nucleophilic substitution, see Lindley, J. *Tetrahedron* ***1984***, *40*, 1433. For other examples, see Marcoux, J.-F.; Doye, S.; Buchwald, S.L. *J. Am. Chem. Soc.* ***1997***, *119*, 10539; Ma, D.; Cai, Q. *Org. Lett.* ***2003***, *5*, 3799.

halides, such as 4-iodoanisole, were coupled to allylic alcohols using a CuI catalyst in the presence of 2% 1,10-phenanthroline and cesium carbonate.[118] This method of preparation of diaryl ethers is called the *Ullmann ether synthesis*[119] and should not be confused with the Ullmann biaryl synthesis (**13-11**). The reactivity order is typical of nucleophilic substitutions, despite the presence of the copper salts.[120] Because aryloxycopper(I) reagents ArOCu react with aryl halides to give ethers, it has been suggested that they are intermediates in the Ullmann ether synthesis.[121] Indeed, high yields of ethers can be obtained by reaction of ROCu or ArOCu with aryl halides.[122] Alcohols, via the alkoxide, displace the halogen group in aryl halides to give aryl ethers in the presence of a palladium catalyst.[123] A palladium catalyzed, intramolecular displacement of an aryl halide with a pendant alkoxide unit leads to dihydrobenzofurans.[124] Nickel catalysts have also been used.[125] The reaction has been done by heating aryl iodides and phenols in an ionic liquid.[126]

Unactivated substrates also react with phenoxide ion with electrochemical catalysis in liquid NH_3–Me_2SO, to give diaryl ethers, presumably by the $S_{RN}1$ mechanism.[127] Diaryl ethers can be prepared from activated aryl halides by treatment with a triaryl phosphate, $(ArO)_3PO$.[128]

OS **I**, 219; **II**, 445; **III**, 293, 566; **V**, 926; **VI**, 150; **X**, 418.

B. Sulfur Nucleophiles

13-4 Replacement by SH or SR

Mercapto-de-halogenation $\quad ArBr + SH^- \longrightarrow ArSH$

Alkylthio-de-halogenation $\quad ArBr + SR^- \longrightarrow ArSR$

[118]Wolter, M.; Nordmann, G.; Job, G.E.; Buchwald, S.L. *Org. Lett.* ***2002***, *4*, 973.
[119]For reviews of the Ullmann ether synthesis see Moroz, A.A.; Shvartsberg, M.S. *Russ. Chem. Rev.* ***1974***, *43*, 679; Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* ***2003***, 2428.
[120]Weingarten, H. *J. Org. Chem.* ***1964***, *29*, 977, 3624.
[121]Kawaki, T.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* ***1972***, *45*, 1499.
[122]Whitesides, G.M.; Sadowski, J.S.; Lilburn, J. *J. Am. Chem. Soc.* ***1974***, *96*, 2829.
[123]Parrish, C.A.; Buchwald, S.L. *J. Org. Chem.* ***2001***, *66*, 2498; Torraca, K.E.; Huang, X.; Parrish, C.A.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2001***, *123*, 10770.
[124]Kuwabe, S.-i.; Torraca, K.E.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2001***, *123*, 12202.
[125]Mann, G.; Hartwig, J.F. *J. Org. Chem.* ***1997***, *62*, 5413.
[126]In bmiI, 1-butyl-3-methylimidazolium iodide: Luo, Y.; Wu, J.X.; Ren, R.X. *Synlett* ***2003***, 1734.
[127]Alam, N.; Amatore, C.; Combellas, C.; Pinson, J.; Savéant, J.; Thiébault, A.; Verpeaux, J. *J. Org. Chem.* ***1988***, *53*, 1496.
[128]Ohta, A.; Iwasaki, Y.; Akita, Y. *Synthesis* ***1982***, 828. For other procedures, see Bates, R.B.; Janda, K.D. *J. Org. Chem.* ***1982***, *47*, 4374; Sammes, P.G.; Thetford, D.; Voyle, M. *J. Chem. Soc. Perkin Trans. 1* ***1988***, 3229.

Aryl thiols and thioethers can be prepared by reactions that are similar to **13-1** and **13-3**.[129] Activated aryl halides generally give good results, but side reactions are occasionally important. Some reagents give the thiol directly. 4-bromonitrobenzene reacts with Na_3SPO_3, in refluxing methanol, to give 4-nitrothiophenol.[130] Diaryl sulfides can be prepared by the use of $^-$SAr.[131] Even unactivated aryl halides react with $^-$SAr if polar aprotic solvents, for example, DMF,[132] DMSO[133] 1-methyl-2-pyrrolidinone,[134] or HMPA,[135] are used, though the mechanisms are still mostly or entirely nucleophilic substitution. 2-Iodothiophene reacts directly with thiophenol to give 2-phenylthiothiophene.[136] Unactivated aryl halides also give good yields of sulfides on treatment with ArS^- or RS^- (generated *in situ* from the corresponding thiol) in the presence of a palladium catalyst.[137] Copper catalysts have also been used.[138] Thiophenols were coupled to indoles in the presence of a vanadium catalyst.[139] Aryl iodides react with dialkyl disulfides and a nickel catalyst to give aryl alkyl sulfides.[140] Diaryl sulfides can also be prepared (in high yields) by treatment of unactivated aryl iodides with ArS^- in liquid ammonia under irradiation.[141] The mechanism in this case is probably $S_{RN}1$. The reaction (with unactivated halides) has also been carried out electrolytically, with a nickel complex catalyst.[142]

Arylboronic acids, $(ArB(OH)_2$, react with thiols and copper(II) acetate to give the corresponding alkyl aryl sulfide.[143] Arylboronic acids also react with *N*-methylthiosuccinimide, with a copper catalyst, to give the aryl methyl sulfide.[144] In the presence of a palladium catalyst, thiophenols react with diaryliodonium salts, Ar_2I^{+-} BF_4, to give the unsymmetrical diaryl sulfide.[145]

[129]For a review of sulfur nucleophiles in aromatic substitution, see Peach, M.E., in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, ***1974***, pp. 735–744.

[130]Bieniarz, C.; Cornwell, M.J. *Tetrahedron Lett.* ***1993***, *34*, 939.

[131]For generation of ArS^- with a phosphazine base and the copper-catalyzed displacement of Ar'I, see Palomo, C.; Oiarbide, M.; López, R.; Gómez-Bengoa, E. *Tetrahedron Lett.* ***2000***, *41*, 1283.

[132]Campbell, J.R. *J. Org. Chem.* ***1964***, *29*, 1830; Testaferri, L.; Tiecco, M.; Tingoli, M.; Chianelli, D.; Montanucci, M. *Synthesis* ***1983***, 751. For the extension of this to selenides, see Tiecco, M.; Testaferri, L.; Tingoli, M.; Chianelli, D.; Montanucci, M. *J. Org. Chem.* ***1983***, *48*, 4289.

[133]Bradshaw, J.S.; South, J.A.; Hales, R.H. *J. Org. Chem.* ***1972***, *37*, 2381.

[134]Caruso, A.J.; Colley, A.M.; Bryant, G.L. *J. Org. Chem.* ***1991***, *56*, 862; Shaw, J.E. *J. Org. Chem.* ***1991***, *56*, 3728.

[135]Cogolli, P.; Maiolo, F.; Testaferri, L.; Tingoli, M.; Tiecco, M. *J. Org. Chem.* ***1979***, *44*, 2642. See also Testaferri, L.; Tingoli, M.; Tiecco, M. *Tetrahedron Lett.* ***1980***, *21*, 3099; Suzuki, H.; Abe, H.; Osuka, A. *Chem. Lett.* ***1980***, 1363.

[136]Lee, S.B.; Hong, J.-I. *Tetrahedron Lett.* ***1995***, *36*, 8439.

[137]Itoh, T.; Mase, T. *Org. Lett.* ***2004***, *6*, 4587.

[138]Kwong, F.Y.; Buchwald, S.L. *Org. Lett.* ***2002***, *4*, 3517; Wu, Y.-J.; He, H. *Synlett* ***2003***, 1789; Deng, W.; Zou, Y.; Wang, Y.-F.;Liu, L.; Guo, Q.-X. *Synlett* ***2004***, 1254.

[139]Maeda, Y.; Koyabu, M.; Nishimura, T.; Uemura, S. *J. Org. Chem.* ***2004***, *69*, 7688.

[140]Tankguchi, N. *J. Org. Chem.* ***204***, *69*, 6904.

[141]Bunnett, J.F.; Creary, X. *J. Org. Chem.* ***1974***, *39*, 3173, 3611.

[142]Meyer, G.; Troupel, M. *J. Organomet. Chem.* ***1988***, *354*, 249.

[143]Herradua, P.S.; Pendola, K.A.; Guy, R.K. *Org. Lett.* ***2000,*** *2*, 2019.

[144]Savarin, C.; Srogl, J.; Liebeskind, L.S. *Org. Lett.* ***2002***, *4*, 4309.

[145]Wang, L.; Chen, Z.-C. *Synth. Commun.* ***2001***, *31*, 1227.

Other sulfur nucleophiles also react with activated aryl halides:

$$2\,ArX + S_2^{2-} \longrightarrow Ar{-}S{-}S{-}Ar \qquad ArX + SCN^- \longrightarrow ArSCN$$
$$ArX + SO_3^{2-} \longrightarrow Ar{-}SO_3^- \qquad ArX + RSO_2^- \longrightarrow Ar{-}SO_2{-}R$$

Aryl sulfones have been prepared from sulfinic acid salts, aryl iodides and CuI.[146] Formation of thiocyanates from unactivated aryl halides has been accomplished with charcoal supported copper(I) thiocyanate.[147] The copper catalyzed reaction of NaO_2SMe and aryl iodides give the aryl methyl sulfone.[148] A similar synthesis of diaryl sulfones has been reported using a palladium catalyst.[149]

An indirect method for the synthesis of aryl alkyl sulfides involves treatment of an aryl halide with butyllithium and then elemental sulfur. The resulting thiophenoxide anion reacts with an alkyl halide to give the targeted sulfide.[150]

Aryl selenides (ArSeAr and ArSeAr') can be prepared by similar methodology. Symmetrical diaryl selenides were prepared by the reaction of iodobenzene with diphenyl diselenide (PhSeSePh), in the presence of Mg and a copper catalyst.[151] Aryl halides react with tin selenides ($ArSeSnR_3$), with a copper catalyst, to give the diaryl selenide.[152]

OS **I**, 220; **III**, 86, 239, 667; **V**, 107, 474; **VI**, 558, 824. Also see, OS **V**, 977.

C. Nitrogen Nucleophiles

13-5 Replacement by NH_2, NHR, or NR_2

Amino-de-halogenation

Amido-de-halogenation

$$R_3N \;+\; Ar{-}X \xrightarrow[R\,=\,H,\ \text{alkyl (1 and 2°)}]{} R_2N{-}Ar$$

Activated aryl halides react quite well with ammonia and with primary and secondary amines to give the corresponding arylamines. Primary and secondary amines usually give better results than ammonia, with piperidine especially reactive. Picryl chloride (2,4,6-trinitrochlorobenzene) is often used to form amine derivatives. 2,4-Dinitrofluorobenzene is used to tag the amino end of a peptide or protein chain. Other leaving groups in this reaction may be NO_2,[153] N_3, OSO_2R, OR, SR, N=NAr (where Ar contains electron-withdrawing groups)[154] and even NR_2.[155]

[146]Suzuki, H.; Abe, H. *Tetrahedron Lett.* ***1995***, *36*, 6239.

[147]Clark, J.H.; Jones, C.W.; Duke, C.V.A.; Miller, J.M. *J. Chem. Soc. Chem. Commun.* ***1989***, 81. See also, Yadav, J.S.; Reddy, B.V.S.; Shubashree, S.; Sadashiv, K. *Tetrahedron Lett.* ***2004***, *45*, 2951.

[148]Baskin, J.M.; Wang, Z. *Org. Lett.* ***2002***, *4*, 4423.

[149]Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Parisi, L.M. *Org. Lett.* ***2002***, *4*, 4719; Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Parisi, L.M.; Bernini, R. *J. Org. Chem.* ***2004***, *69*, 5608.

[150]Ham, J.; Yang, I.; Kang, H. *J. Org. Chem.* ***2004***, *69*, 3236.

[151]Taniguchi, N.; Onami, T. *J. Org. Chem.* **2004**, 69, 915; Taniguchi, N.; Onami, T. *Synlett* ***2003***, 829.

[152]Beletskaya, I.P.; Sigeev, A.S.; Peregudov, A.S.; Petrovlskii, P.V. *Tetrahedron Lett.* ***2003***, *44*, 7039.

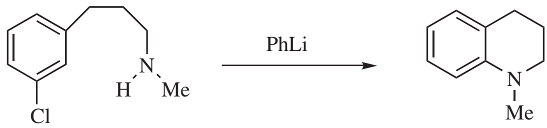
[153]For a reaction with an aryllithium reagent, see Yang, T.; Cho, B.P. *Tetrahedron Lett.* ***2003***, *44*, 7549.

[154]Kazankov, M.V.; Ginodman, L.G. *J. Org. Chem, USSR* ***1975***, *11*, 451.

[155]Sekiguchi, S.; Horie, T.; Suzuki, T. *J. Chem. Soc. Chem. Commun.* ***1988***, 698.

Aryl triflates were shown to react directly with secondary amines in *N*-methylpyrrolidine solvent using microwave irradiation.[156] Activated halides can be converted to diethylamino compounds ArX → $ArNMe_2$ by treatment with HMPA.[157] Aniline derivatives react with activated aromatic rings, in the presence of tetrabutylammonium fluoride and under photolysis conditions, to give a *N,N*-diarylamine.[158] Arylation of amines with aryl halides has also been done in ionic liquids.[159]

Unactivated aryl halides can be converted to amines by the use of $NaNH_2$, NaNHR, or $NaNR_2$.[160] Lithium dialkylamides also react with aryl halides to give the *N*-arylamine.[161] With these reagents, the benzyne mechanism generally operates, so cine substitution is often found. The reaction of an amine, an aryl halide, and potassium *tert*-butoxide generates the *N*-aryl amine.[162] *N*-Arylation was accomplished with butyllithium and a secondary amine using Ni/C-diphenylphosphinoferrocene (dppf).[163] Ring closure has been effected by this type of reaction,[164] as in the conversion of **16** to the tetrahydroquinoline.



16

Larger rings can be prepared using this approach: 8 and even 12 membered. Triarylamines have been prepared in a similar manner from ArI and Ar_2' NLi, even with unactivated ArI.[165] In the *Goldberg reaction*, an aryl bromide reacts with an acetanilide in the presence of K_2CO_3 and CuI to give an *N*-acetyldiarylamine, which can be hydrolyzed to a diarylamine: ArBr + Ar′NHAc → ArAr′NAc.[166] Aryl fluorides react in the presence of KF-alumina and 18-crown-6 in DMSO.[167] Lithium amides have been shown to react directly with aryl halides.[168] Aryl fluorides react

[156]Xu, G.; Wang, Y.-G. *Org. Lett.* ***2004***, *6*, 985.

[157]See, for example, Gupton, J.T.; Idoux, J.P.; Baker, G.; Colon, C.; Crews, A.D.; Jurss, C.D.; Rampi, R.C. *J. Org. Chem.* ***1983***, *48*, 2933.

[158]Hertas, I.; Gallardo, I.; Marquet, J. *Tetrahedron Lett.* ***2000***, *41*, 279.

[159]In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: See Yadav, J.S.; Reddy, B.V.S.; Basak, A.K.; Narsaiah, A.V. *Tetrahedron Lett.* ***2003***, *44*, 2217.

[160]For a review, see Heaney, H. *Chem Rev.* ***1962***, *62*, 81, see p. 83.

[161]Tripathy, S.; Le Blanc, R.; Durst, T. *Org. Lett.* ***1999***, *1*, 1973.

[162]Beller, M.; Breindl, C.; Riermeier, T.H.; Tillack, A. *J. Org. Chem.* ***2001***, *66*, 1403; Shi, L.; Wang, M.; Fan, C.-A.; Zhang, F.-M.; Tu, Y.-Q. *Org. Lett.* ***2003***, *5*, 3515.

[163]Tasler, S.; Lipshutz, B.H. *J. Org. Chem.* ***2003***, *68*, 1190.

[164]Huisgen, R.; König, H.; Lepley, A.R. *Chem. Ber.* ***1960***, *93*, 1496; Bunnett, J.F.; Hrutfiord, B.F. *J. Am. Chem. Soc.* ***1961***, *83*, 1691. For a review of ring closures by the benzyne mechanism, see Hoffmann, R.W. *Dehydrobenzene and Cycloalkynes*, Academic Press, NY, ***1973***, pp. 150–164.

[165]Neunhoeffer, O.; Heitmann, P. *Chem. Ber.* ***1961***, *94*, 2511.

[166]See Freeman, H.S.; Butler, J.R.; Freedman, L.D. *J. Org. Chem.* ***1978***, *43*, 4975; Renger, B. *Synthesis* ***1985***, 856.

[167]Smith III, W.J.; Sawyer, J.S. *Tetrahedron Lett.* ***1996***, *37*, 299.

[168]Kanth, J.V.B.; Periasamy, M. *J. Org. Chem.* ***1993***, *58*, 3156.

with amines in the presence of potassium carbonate/DMSO and ultrasound,[169] and aryl chlorides react on basic alumina with microwave irradiation.[170] 2-Chloronitrobenzene also reacts with aniline derivatives directly with microwave irradiation.[171] 2-Fluoropyridine reacts with R_2NBH_3Li to give the 2-aminoalkylpyridine.[172]

The reaction of amines with unactivated aryl halides requires a catalyst in most cases to initiate the reaction. There are several approaches that result in *N*-aryl amines, but recent work with aryl halides, amines, and palladium catalysts has proven quite useful.[173] Aryl halides react with amines (including aniline derivatives) in the presence of palladium catalysts to give the *N*-aryl amine.[174] Palladium catalysts have been used with aniline and or triflates[175] to give the secondary amine. Palladium catalysts have been used in conjunction with aryl halides and aliphatic amines–amide bases.[176] A considerable amount of work[177] has been done to vary the nature of the ligand and the palladium catalyst, as well as the base.[178] Aryl halides also react with aliphatic amines,[179] including cyclopropylamines,[180] and an intramolecular version of this reaction generates bicyclic amines (hydroindole derivatives).[181] Primary aliphatic amines can be converted to tertiary *N,N*-diarylalkylamines in a two-step procedure using palladium catalysts.[182] Aryl halides are

[169]Magdolen, P.; Mečiarová, M.; Toma, Š. *Tetrahedron* ***2001***, *57*, 4781.

[170]Kidwai, M.; Sapra, P.; Dave, B. *Synth. Commun.* ***2000***, *30*, 4479.

[171]Xu, Z.-B.; Lu, Y.; Guo, Z.-R. *Synlett* ***2003***, 564. See Li, W.; Yun, L.; Wang, H. *Synth. Commun.* ***2002***, *32*, 2657.

[172]Thomas, S.; Roberts, S.; Pasumansky, L.; Gamsey, S.; Singaram, B. *Org. Lett.* ***2003***, *5*, 3867.

[173]For a discussion of the mechanism of the palladium-catalyzed amination of aryl chlorides, see Alcazar-Roman, L.M.; Hartwig, J.F. *J. Am.Chem. Soc.* ***2001***, *123*, 12905.

[174]Driver, M.S.; Hartwig, J.F. *J. Am. Chem. Soc.* ***1996***, *118*, 7217; Reddy, N.P.; Tanaka, M. *Tetrahedron Lett.* ***1997***, *38*, 4807; Wolfe, J.P.; Buchwald, S.L. *J. Org. Chem.* ***1997***, *62*, 6066; Marcoux, J.-F.; Wagaw, S.; Buchwald, S.L. *J. Org. Chem.* ***1997***, *62*, 1568; Maes, B.U.W.; Loones, K.T.J.; Lemière, G.L.F.; Dommisse, R.A. *Synlett* ***2003***, 1822; Wan, Y.; Alterman, M.; Hallberg, A. *Synthesis* ***2002***, 1597.

[175]Louie, J.; Driver, M.S.; Hamann, B.C.; Hartwig, J.F. *J. Org. Chem.* ***1997***, *62*, 1268; Wolfe, J.P.; Buchwald, S.L. *J. Org. Chem.* ***1997***, *62*, 1264.

[176]Harris, M.C.; Huang, X.; Buchwald, S.L. *Org. Lett.* ***2003***, *4*, 2885.

[177]Bei, X.; Guram, A.S.; Turner, H.W.; Weinberg, W.H. *Tetrahedron Lett.* ***1999***, *40*, 1237; Guari, Y.; van Es, D.S.; Reek, J.N.H.; Kamer, P.C.J.; van Leeuwen, P.W.N.M. *Tetrahedron Lett.* ***1999***, *40*, 3789; Urgaonkar, S.; Xu, J.-H.; Verkade, J.G. *J. Org. Chem.* ***2003***, *68*, 8416; Viciu, M.S.; Kissling, R.M.; Stevens, E.D.; Nolan, S.P. *Org. Lett.* ***2002***, *4*, 2229; Gajare, A.S.; Toyota, K.; Yoshifuji, M.; Ozawa, F. *J. Org. Chem.* ***2004***, *69*, 6504; Huang, X.; Anderson, K.W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2004***, *125*, 6653; Singer, R.A.; Tom, N.J.; Frost, H.N.; Simon, W.M. *Tetrahedron Lett.* ***2004***, *45*, 4715; Smith, C.J.; Early, T.R.; Holmes, A.B.; Shute, R.E. *Chem. Commun.* ***2004***, 1976.

[178]For a study of the mechanism of the palladium catalyzed amination of aryl halides, see Singh, U.K.; Strieter, E.R.; Blackmond, D.G.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2002***, *124*, 14104. For a study of rate enhancement by the added base, see Meyers, C.; Maes, B.U.W.; Loones, K.T.J.; Bal, G.; Lemière, G.L.F.; Dommisse, R.A. *J. Org. Chem.* ***2004***, *69*, 6010.

[179]Ali, M.H.; Buchwald, S.L. *J. Org. Chem.* ***2001***, *66*, 2560; Cheng, J.; Trudell, M.L. *Org. Lett.* ***2001***, *3*, 1371; Kuwano, R.; Utsunomiya, M.; Hartwig, J.F. *J. Org. Chem.* ***2002***, *67*, 6479; Urgaonkar, S.; Nagarajan, M.; Verkade, J.G. *J. Org.Chem.* ***2003***, *68*, 452; Prashad, M.; Mak, X.Y.;Lium Y.; Repi, O. *J. Org. Chem.* ***2003***, *68*, 1163.

[180]Cui, W.; Loeppky, R.N. *Tetrahedron* ***2001***, *57*, 2953.

[181]Johnston, J.N.; Plotkin, M.A.; Viswanathan, R.; Prabhakaran, E.N. *Org. Lett.* ***2001***, *3*, 1009.

[182]Harris, M.C.; Geis, O.; Buchwald, S.L. *J. Org. Chem.* ***1999***, *64*, 6019.

converted to *N,N*-diaryl tertiary amines by reaction with *N*-alkylaniline derivatives and a palladium catalyst.[183] Beginning with a primary aromatic amine and two different aryl halides (ArBr and Ar'Cl), a triarylamine with three different aryl groups can be prepared using a palladium catalyst.[184] Polymer-bound phosphine ligands have been used in conjunction with a palladium catalyst,[185] and polymer-bound amines have been *N*-arylated with a palladium catalyst followed by treatment with trifluoroacetic acid to release the aniline derivative.[186] Palladium-catalyzed aminoalkylation of aryl halides has been reported using microwave irradiation.[187] Aryl halides (Ar–X) have also been converted to the aniline derivative (Ar–NH_2) by reaction of the halide with an imine and a palladium catalyst, followed by hydrolysis.[188] Similarly, aniline derivatives have been prepared by the reaction of aryl chlorides with silylamines (Ph_3SiNH_2) using lithium hexamethyldisilazide and a palladium catalyst.[189] Amines react with $Ph_2I^+BF_4^-$, in the presence of palladium catalysts,[190] or a CuI catalyst[191] to give the *N*-phenyl amine. These reactions have been done in ionic liquids using a palladium catalyst.[192] Arylation of the amine unit of primary enamino ketones was accomplished using a palladium catalyst.[193] Mono-arylation of a 1,2-diamine is possible.[194] Aminoalkylation of heteroaromatic rings is possible, as in the reaction of 3-bromothiophene with a primary amine and a palladium catalyst.[195] 2-Halopyridines react to give the 2-aminoalkyl pyridine.[196] Carbazole derivatives were prepared from 2-iodoaniline and 2-trimethylsilylphenol *O*-triflates, using cesium fluoride and then a palladium catalyst.[197]

Nickel catalysts have been used in the reaction of aryl halides with *N*-alkyl aniline derivatives.[198] Nickel catalyst also allow the conversion of aryl halides to *N*-arylamines via reaction with aliphatic amines.[199] An intramolecular reaction of a

[183]Wolfe, J.P.; Buchwald, S.L. *J. Org. Chem.* ***2000***, *65*, 1144; Wolfe, J.P.; Tomori, H.; Sadighi, J.P.; Yin, J.; Buchwald, S.L. *J. Org. Chem.* ***2000***, *65*, 1158.

[184]Harris, M.C.; Buchwald, S.L. *J. Org. Chem.* ***2000***, *65*, 5327.

[185]Parrish, C.A.; Buchwald, S.L. *J. Org. Chem.* ***2001***, *66*, 3820.

[186]Weigand, K.; Pelka, S. *Org. Lett.* ***2002***, *4*, 4689.

[187]Wang, T.; Magnin, D.R.; Hamann, L.G. *Org. Lett.* ***2003***, *5*, 897; Jensen, T.A.; Liang, X.; Tanner, D.; Skjaerbaek, N. *J. Org. Chem.* ***2004***, *69*, 4936.; Maes, B.U.W.; Loones, K.T.J.; Hostyn, S.; Diels, G.; Rombouts, G. *Tetrahedron* ***2004***, *60*, 11559.

[188]Wolfe, J.P.; Åhman, J.; Sadighi, J.P.; Singer, R.A.; Buchwald, S.L. *Tetrahedron Lett.* ***1997***, *38*, 6367. For a variation, see Erdik, E.; Daşkapan, T. *Tetrahedron Lett.* ***2002***, *43*, 6237.

[189]Huang, X.; Buchwald, S.L. *Org. Lett.* ***2001***, *3*, 3417.

[190]Kang, S.-K.; Lee, H.-W.; Choi, W.-K.; Hong, R.-K.; Kim, J.-S. *Synth. Commun.* ***1996***, *26*, 4219.

[191]Kang, S.-K.; Lee, S.-H.; Lee, D. *Synlett* ***2000***, 1022.

[192]In diarylimidazolium salts: Grasa, G.A.; Viciu, M.S.; Huang, J.; Nolan, S.P. *J. Org. Chem.* ***2001***, *66*, 7729.

[193]Edmondson, S.D.; Mastracchio, A.; Parmee, E.R. *Org. Lett.* ***2000***, *2*, 1109 and references cited therein.

[194]Frost, C.G.; Mendonça, P. *Tetahedron Asymmetry* ***1999***, *10*, 1831.

[195]Ogawa, K.; Radke, K.R.; Rothstein, S.D.; Rasmussen, S.C. *J. Org. Chem.* ***2001***, *66*, 9067.

[196]Junckers, T.H.M.; Maes, B.U.W.; Lemière, G.L.F.; Dommisse, R. *Tetrahedron* ***2001***, *57*, 7027; Basu, B.; Jha, S.; Mridha, N.K.; Bhuiyan, Md.M.H. *Tetrahedron Lett.* ***2002***, *43*, 7967.

[197]Liu, Z.; Larock, R.C. *Org. Lett.* ***2004***, *6*, 3739.

[198]Wolfe, J.P.; Buchwald, S.L. *J. Am. Chem. Soc.* ***1997***, *119*, 6054; Lipshutz, B.H.; Ueda, H. *Angew. Chem. Int. Ed.* ***2000***, *39*, 4492.; Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron* ***2002***, *58*, 6913.

[199]Desmarets, C.; Schneider, R.; Fort, Y. *Tetrahedron Lett.* ***2001***, *42*, 247.

pendant aminoalkyl unit with an aryl chloride moiety, catalyzed by nickel(0) gave a dihydroindole.[200] Copper catalysts allow the reaction of diarylamines and aryl halides to give the corresponding triarylamine,[201] or with aliphatic amines to give the *N*-arylamine.[202] Aniline reacts with aryl iodides an a copper catalyst and potassium *tert*-butoxide to give triphenylamine.[203] A polymer-bound copper catalyst was used in conjunction with aliphatic amines and arylboronic acids.[204] Amino alcohols react with aryl iodides and a copper catalyst to give the *N*-arylamino alcohol.[205] Treatment of alkylamines with arylboronic acids $ArB(OH)_2$ and $Cu(OAc)_2$ gave the *N*-aryl amine in 63% yield.[206] Similar reaction with arylamines, such as aniline, gave the diarylamine.[207] Arylboronic acids convert aziridines to *N*-arylaziridines,[208] and amino esters to *N*-arylated amino esters,[209] both reactions using a copper catalyst. An arylbismuth reagent reacts with aliphatic amines, in the presence of copper(II) acetate, to give an *N*-arylamine.[210] *N*-Arylation of pyrroles was accomplished by the reaction of an arylboronic acid and a copper catalyst.[211] *N*-Arylindoles[212] and *N*-arylimidazoles[213] were prepared from aryl halide using a copper catalyst. Diarylzinc reagents react with *N*-(OBz) amine derivatives, with a copper catalyst, to give the *N*-aryl amine.[214]

In a related reaction, trifluoroarylboronates react with copper(II) acetate and then an aliphatic amine to give the *N*-phenylamine.[215]

The metal catalyzed reaction with ammonia or amines likely proceeds by the S_NAr mechanism.[216] This reaction, with phase-transfer catalysis, has been used to synthesize triarylamines.[217] Copper ion catalysts (especially cuprous oxide or iodide) also permit the Gabriel synthesis (**10-41**) to be applied to aromatic substrates. Aryl bromides or iodides are refluxed with potassium phthalimide and

[200]Omar-Amrani, R.; Thomas, A.; Brenner, E.; Schneider, R.; Fort, Y. *Org. Lett.* ***2003***, *5*, 2311.

[201]Gujadhur, R.K.; Bates, C.G.; Venkataraman, D. *Org. Lett.* ***2001***, *3*, 4315.; Klapars, A.; Antilla, J.C.; Huang, X.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2001***, *123*, 7727.

[202]Kwong, F.Y.; Buchwald, S.L. *Org. Lett.* ***2003***, *5*, 793; Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* ***2003***, *5*, 2453; Okano, K.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* ***2003***, *5*, 4987; Lu, Z.; Twieg, R.J.; Huang, S.D. *Tetrahedron Lett.* ***2003***, *44*, 6289.

[203]Kelkar, A.A.; Patil, N.M.; Chaudhari, R.V. *Tetrahedron Lett.* ***2002***, *43*, 7143.

[204]Chiang, G.C.H.; Olsson, T. *Org.Lett.* ***2004***, *6*, 3079.

[205]Job, G.E.; Buchwald, S.L. *Org. Lett.* ***2002***, *4*, 3703.

[206]Lan, J.-B.; Zhang, G.-L.; Yu, X.-Q.; You, J.-S.; Chen, L.; Yan, M.; Xie, R.-G. *Synlett* ***2004***, 1095.

[207]Antilla, J.C.; Buchwald, S.L. *Org. Lett.* ***2001***, *3*, 2077.

[208]Sasaki, M.; Dalili, S.; Yudin, A.K. *J. Org. Chem.* ***2003***, *68*, 2045.

[209]Lam, P.Y.S.; Bonne, D.; Vincent, G.; Clark, C.G.; Combs, A.P. *Tetrahedron Lett.* ***2003***, *44*, 1691.

[210]Fedorov, A.Yu.; Finet, J.-P. *J. Chem. Soc. Perkin Trans. 1* ***2000***, 3775.

[211]Yu, S.; Saenz, J.; Srirangam, J.K. *J. Org. Chem.* ***2002***, *67*, 1699.

[212]Antilla, J.C.; Klapars, A.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2002***, *124*, 11684.

[213]Wu, Y.-J.; He, H.; L'Hereux, A. *Tetrahedron Lett.* ***2003***, *44*, 4217.

[214]Berman, A.M.; Johnson, J.S. *J. Am. Chem. Soc.* ***2004***, *126*, 5680.

[215]Quach, T.D.; Batey, R.A. *Org. Lett.* ***2003***, *5*, 4397.

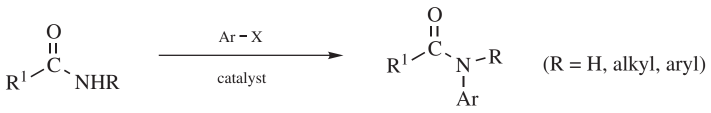
[216]For discussions of the mechanism, see Bethell, D.; Jenkins, I.L.; Quan, P.M. *J. Chem. Soc. Perkin Trans. 1* ***1985***, 1789; Tuong, T.D.; Hida, M. *J. Chem. Soc. Perkin Trans. 2* ***1974***, 676; Kondratov, S.A.; Shein, S.M. *J. Org. Chem, USSR* ***1979***, *15*, 2160; Paine, A.J. *J. Am. Chem. Soc.* ***1987***, *109*, 1496.

[217]Gauthier, S.; Fréchet, J.M.J. *Synthesis* ***1987***, 383.

Cu_2O or CuI in dimethylacetamide to give *N*-aryl phthalimides, which can be hydrolyzed to primary aryl amines.[218]

In certain cases, the $S_{RN}1$ mechanism has been found (p. 550). When the substrate is a heterocyclic aromatic nitrogen compound, still a different mechanism [the S_N(ANRORC) mechanism], involving opening and reclosing of the aromatic ring, has been shown to take place.[219]

There are a number of indirect approaches for the preparation of aryl amines. Activated aromatic compounds can be directly converted to the *N*-aryl amine with hydroxylamine in the presence of strong bases.[220] Conditions are mild and yields are high. Aryl halides can be converted to the corresponding Grignard reagent (**12-38**). Subsequent reaction of arylmagnesium halides with allyl azide ($CH_2{=}CHCH_2N_3$) followed by hydrolysis leads to the corresponding aniline derivative.[221] Aryl halides can be converted to the aryllithium via halogen–lithium exchange or hydrogen–lithium exchange (**12-38**, **12-39**). Molecular nitrogen (N_2) reacts with aryllithium compounds in the presence of compounds of such transition metals as titanium (e.g., $TiCl_4$), chromium, molybdenum, or vanadium to give (after hydrolysis) primary aromatic amines ($ArLi + N_2 +$ transition metal salts $\rightarrow ArNH_2$, after hydrolysis).[222] Primary aromatic amines $ArNH_2$ were converted to diaryl amines ArNHPh by treatment with $Ph_3Bi(OAc)_2$[223] and a copper powder catalyst.[224] Aryl Grignard reagents react with nitroaryl compounds to give, after reduction with $FeCl_3/NaBH_4$, a diaryl amine.[225]



The use of transition-metal catalysts allows aryl halides to react with the nitrogen of amides or carbamates, as well as amines, to give the corresponding *N*-aryl amide or *N*-aryl carbamate. Amides react with aryl halides in the presence of a palladium catalyst[226] or a copper catalyst.[227] *N*-Aryl lactams are prepared by the reaction of a lactam with an aryl halide in the presence of a palladium catalyst.[228]

[218]Bacon, R.G.R.; Karim, A. *J. Chem. Soc. Perkin Trans. 1* ***1973***, 272, 278; Sato, M.; Ebine, S.; Akabori, S. *Synthesis* ***1981***, 472. See also Yamamoto, T.; Kurata, Y. *Can. J. Chem.* ***1983***, *61*, 86.

[219]For reviews, see van der Plas, H.C. *Tetrahedron* ***1985***, *41*, 237; *Acc. Chem. Res.* ***1978***, *11*, 462.

[220]See Chupakhin, O.N.; Postovskii, I.Ya. *Russ. Chem. Rev.* ***1976***, *45*, 454, p. 456.

[221]Kabalka, G.W.; Li, G. *Tetrahedron Lett.* ***1997***, *38*, 5777.

[222]Vol'pin, M.E. *Pure Appl. Chem.* ***1972***, *30*, 607.

[223]For a review of arylations with bismuth reagents, see Finet, J. *Chem. Rev.* ***1989***, *89*, 1487.

[224]Dodonov, V.A.; Gushchin, A.V.; Brilkina, T.G. *Zh. Obshch. Khim.*, ***1985***, *55*, 466 [*Chem. Abstr., 103*, 22218z]; Barton, D.H.R.; Yadav-Bhatnagar, N.; Finet, J.; Khamsi, J. *Tetrahedron Lett.* ***1987***, *28*, 3111.

[225]Sapountzis, I.; Knochel, P. *J. Am.Chem. Soc.* ***2002***, *124*, 9390.

[226]Yin, J.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2002***, *124*, 6043. For an intramolecular reaction, see Yang, B.H.; Buchwald, S.L. *Org. Lett.* ***1999***, *1*, 35.

[227]Hosseinzadeh, R.; Tajbakhsh, M.; Mohadjerani, M.; Mehdinejad, H. *Synlett* ***2004***, 1517.

[228]Browning, R.G.; Badaringarayana, V.; Mahmud, H.; Lovely, C.J. *Tetrahedron* ***2004***, *60*, 359; Deng, W.; Wang, Y.-F.; Zou, Y.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett.* ***2004***, *45*, 2311; Shakespeare, W.C. *Tetrahedron Lett.* ***1999***, *40*, 2035. For the synthesis of *N*-(2-thiophene)-2-pyrrolidinone by coupling 2-iodothiophene and 2-pyrrolidinone, see Klapars, A.; Huang, X.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2002***, *124*, 7421. See also, Ferraccioli, R.; Carenzi, D.; Rombolà, O.; Catellani, M. *Org. Lett.* ***2004***, *6*, 4759.

β-Lactams also react.[229] The reaction of 2-oxazolidinones with aryl halides in the presence of a palladium catalyst gave the *N*-aryl-2-oxazolidinone.[230] Amides react with $PhSi(OMe)_3/Cu(OAc)_2/Bu_4NF$ to give the *N*-aryl amide.[231] *N*-Boc hydrazine derivatives ($BocNHNH_2$) gave the *N*-phenyl derivative $BocN(Ph)NH_2$ when reacted with iodobenzene and a catalytic amount of CuI and 10% of 1,10-phenanthroline.[232] 3-Bromothiophene was converted to the 3-amido derivative with an amide and CuI-dimethylethylenediamine,[233] and *N*-(2-thiophene)-2-pyrrolidinone was similarly prepared from 2-iodothiophene, the lactam and a copper catalyst.[234] *N*-Arylation of urea is also possible using a copper catalyst.[235] The reaction of a vinyl triflate with benzamide and a palladium catalyst gave the corresponding enamide (C=C–NHC=O).[236]

The transition-metal catalyzed couplings of primary or secondary phosphines with aryl halides or sulfonate esters to give arylphosphines is known.[237] Palladium catalyzed conversion of aryl halides to aryl phosphines using (trimethylsilyl)diphenylphosphine is known, and tolerates many functional groups (not those that are easily reducible, such as aldehydes because zinc metal[238] is often used as a coreagent), but it is mainly limited to aryl iodides.[239] Diphenylphosphine reacts with aryl iodides and a copper catalyst to give the triarylphosphine.[240] Aryl iodides also react with secondary phosphine and 5% Pd/C to give the *P*-arylphosphine.[241] Tertiary phosphines can also be used via aryl–aryl exchange, as in the reaction of an aryl triflate and triphenylphosphine and a palladium catalyst, for example, gave the arylphosphine ($ArPPh_2$).[242]

Arylsulfonic acid chlorides ($ArSO_2Cl$) have been shown to react with arylboronic acids, $Ar'B(OH)_2$, in the presence of a palladium catalyst, to give the corresponding biaryl (Ar–Ar').[243]

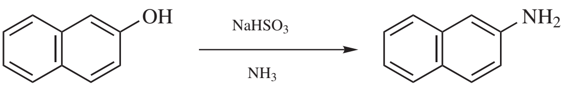
[229]For a variation of this reaction, see Klapars, A.; Parris, S.; Anderson, K.W.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2004***, *126*, 3529.
[230]Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Zappia, G. *Org. Lett.* ***2001***, *3*, 2539.
[231]Lam, P.Y.S.; Deudon, S.; Hauptman, E.; Clark, C.G. *Tetrahedron Lett.* ***2001***, *42*, 2427.
[232]Wolter, M.; Klapars, A.; Buchwald, S.L. *Org. Lett.* ***2001***, *3*, 3803.
[233]Padwa, A.; Crawford, K.R.; Rashatasakhon, P.; Rose, M. *J. Org. Chem.* ***2003***, *68*, 2609.
[234]Kang, S.-K.; Kim, D.-H.; Park, J.-N. *Synlett* ***2002***, 427.
[235]Nandakumar, M.V. *Tetrahedron Lett.* ***2004***, *45*, 1989.
[236]Wallace, D.J.; Klauber, D.J.; Chen, C.-y.; Volante, R.P. *Org. Lett.* ***2003***, *5*, 4749.
[237]Cai, D.; Payack, J.F.; Bender, D.R.; Hughes, D.L.; Verhoeven, T.R.; Reider, P.J. *J. Org. Chem.* ***1994***, *59*, 7180; Herd, O.; Heβler, A.; Machnitzki, P.; Tepper, M.; Stelzer, O. *Catalysis Today* ***1998***, *42*, 413; Gelpke, A.E.S.; Kooijman, H.; Spek, A.L.; Hiemstra, H. *Chem. Eur. J.* ***1999***, *5*, 2472; Ding, K.; Wang, Y.; Yun, H.; Liu, J.; Wu, Y.; Terada, M.; Okubo, Y.; Mikami, K. *Chem. Eur. J.* ***1999***, *5*, 1734; Vyskocil, S.; Smrcina, M.; Hanus, V.; Polasek, M.; Kocovsky, P. *J. Org. Chem.* ***1998***, *63*, 7738; Martorell, G.; Garcias, X.; Janura, M.; Saá, J.M. *J. Org. Chem.* ***1998***, *63*, 3463; Bringmann, G.; Wuzik, A.; Vedder, C.; Pfeiffer, M.; Stalke, D. *Chem. Commun.* ***1998***, 1211; Lipshutz, B.H.; Buzard, D.H.; Yun, C.S. *Tetrahedron Lett.* ***1999***, *40*, 201.
[238]Ager, D.J.; Laneman, S. *Chem. Commun.* ***1997***, 2359.
[239]Tunney, B.H.; Stille, J.K. *J. Org. Chem.* ***1987***, *52*, 748.
[240]Van Allen, D.; Venkataraman, D. *J. Org. Chem.* ***2003***, *68*, 4590.
[241]Stadler, A.; Kappe, C.O. *Org. Lett.* ***2002***, *4*, 3541.
[242]Kwong, F.Y.; Lai, C.W.; Tian, Y.; Chan, K.S. *Tetrahedron Lett.* ***2000***, *41*, 10285; Kwong, F.Y.; Lai, C.W.; Chan, K.S. *Tetrahedron Lett.* ***2002***, *43*, 3537.
[243]Dubbaka, S.R.; Vogel, P. *Org. Lett.* ***2004***, *6*, 95.

OS **I**, 544; **II**, 15, 221, 228; **III**, 53, 307, 573; **IV**, 336, 364; **V**, 816, 1067; **VII**, 15. OS **III**, 664.

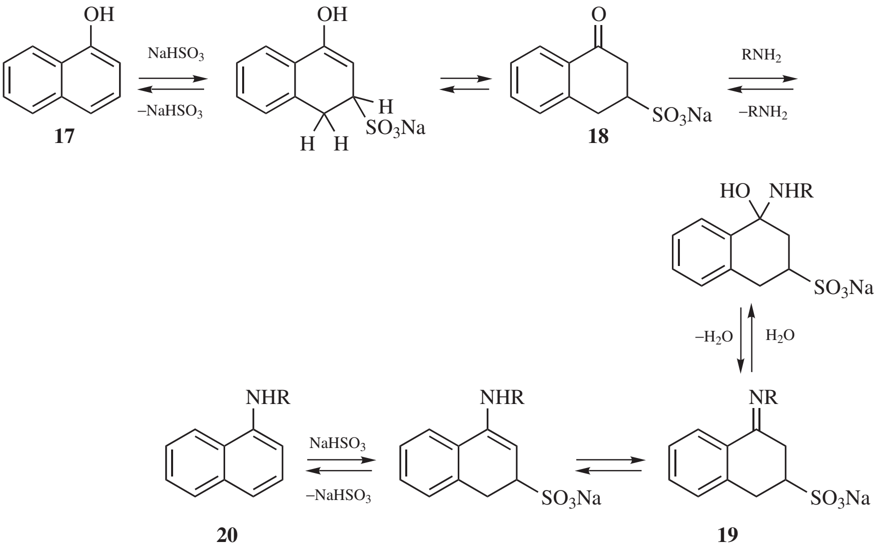
OS X, 423.

13-6 Replacement of a Hydroxy Group by an Amino Group

Amino-de-hydroxylation



The reaction of naphthols with ammonia and sodium bisulfite[81] is called the *Bucherer reaction*. Primary amines can be used instead of ammonia, in which case *N*-substituted naphthylamines are obtained. In addition, primary naphthylamines can be converted to secondary ($ArNH_2 + RNH_2 + NaSO_3 \rightarrow ArNHR$), by a transamination reaction. The mechanism of the Bucherer reaction amounts to a kind of overall addition–elimination, via **18** and **19**.[244]



The first step in either direction consists of addition of $NaHSO_3$ to one of the double bonds of the ring, which gives an enol from **17** (or enamine from **20**) that tautomerizes to the keto form **18** (or imine form, **19**). The conversion of **18** to **19** (or vice versa) is an example of **16-13** (or **16-2**). Evidence for this mechanism was the isolation of **18**[245] and the demonstration that for β-naphthol treated with ammonia and HSO_3^-, the rate of the reaction depends only on the substrate and on

[244]Rieche, A.; Seeboth, H. *Liebigs Ann. Chem.* ***1960***, *638*, 66.

[245]Rieche, A.; Seeboth, H. *Liebigs Ann. Chem.* ***1960***, *638*, 43, 57.

HSO_3^-, indicating that ammonia is not involved in the rate-determining step.[246] If the starting compound is a β-naphthol, the intermediate is a 2-keto-4-sulfonic acid compound, so the sulfur of the bisulfite in either case attacks meta to the OH or NH_2.[247]

Hydroxy groups on benzene rings can be replaced by NH_2 groups if they are first converted to aryl diethyl phosphates. Treatment of these with KNH_2 and potassium metal in liquid ammonia gives the corresponding primary aromatic amines.[248] The mechanism of the second step is $S_{RN}1$.[249]

OS **III**, 78.

D. Halogen Nucleophiles

13-7 The Introduction of Halogens

Halo-de-halogenation, and so on.

$$Ar{-}X + X'^- \rightleftharpoons Ar{-}X' + X^-$$

It is possible to replace a halogen on a ring by another halogen[250] if the ring is activated. In such cases there is an equilibrium, but it is usually possible to shift this in the desired direction by the use of an excess of added halide ion.[251] A phenolic hydroxy group can be replaced by chloro with PCl_5 or $POCl_3$, but only if activated. Unactivated phenols give phosphates when treated with $POCl_3$: 3 ArOH + $POCl_3$ → $(ArO)_3PO$. Phenols, even unactivated ones, can be converted to aryl bromides by treatment with Ph_3PBr_2[252] (see **10-47**) and to aryl chlorides by treatment with $PhPCl_4$.[253]

Halide exchange is particularly useful for putting fluorine into a ring, since there are fewer alternate ways of doing this than for the other halogens. Activated aryl chlorides give fluorides when treated with KF in DMF, DMSO, or dimethyl sulfone.[254] Reaction of aryl halides with Bu_4PF/HF is also effective for exchanging a halogen with fluorine.[255] Halide exchange can also be accomplished with copper halides. Since the leaving-group order in this case is $I > Br > Cl \gg F$ (which means that iodides cannot normally be made by this method), the S_NAr mechanism is

[246]Kozlov, V.V.; Veselovskaia, I.K. *J. Gen. Chem. USSR* ***1958***, *28*, 3359.

[247]Rieche, A.; Seeboth, H. *Liebigs Ann. Chem.* ***1960***, *638*, 76.

[248]Rossi, R.A.; Bunnett, J.F. *J. Org. Chem.* ***1972***, *37*, 3570.

[249]For another method of converting phenols to amines, see Scherrer, R.A.; Beatty, H.R. *J. Org. Chem.* ***1972***, *37*, 1681.

[250]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 671–672.

[251]Sauer, J.; Huisgen, R. *Angew. Chem.* ***1960***, *72*, 294, p. 297.

[252]Wiley, G.A.; Hershkowitz, R.L.; Rein, B.M.; Chung, B.C. *J. Am. Chem. Soc.* ***1964***, *86*, 964; Wiley, G.A.; Rein, B.M.; Hershkowitz, R.L. *Tetrahedron Lett.* ***1964***, 2509; Schaefer, J.P.; Higgins, J. *J. Org. Chem.* ***1967***, *32*, 1607.

[253]Bay, E.; Bak, D.A.; Timony, P.E.; Leone-Bay, A. *J. Org. Chem.* ***1990***, *55*, 3415.

[254]Kimura, Y.; Suzuki, H. *Tetrahedron Lett.* ***1989***, *30*, 1271. For the use of phase-transfer catalysis in this reaction, see Yoshida, Y.; Kimura, Y. *Chem. Lett.* ***1988***, 1355. For a review of the preparation of aryl fluorides by halogen exchange, see Dolby-Glover, L. *Chem. Ind.* (*London*) ***1986***, 518.

[255]Uchibori, Y.; Umeno, M.; Seto, H.; Qian, Z.; Yoshioka, H. *Synlett* ***1992***, 345.

probably not operating.[256] However, aryl iodides have been prepared from bromides, by the use of Cu supported on charcoal or Al_2O_3,[257] with an excess of NaI and a copper catalyst,[258] and by treatment with excess KI and a nickel catalyst.[259] Interestingly, aryl chlorides have been prepared from aryl iodides using 2 equivalents of $NiCl_2$ in DMF, with microwave irradiation.[260]

An indirect halogen exchange treated aryl bromides with *n*-butyllithium and the 5-(iodomethyl)-γ-butyrolactone, giving the aryl iodide and the lithium salt of 4-pentenoic acid.[261] Aryl iodides[262] and fluorides can be prepared from arylthallium bis(trifluoroacetates) (see **12-23**), indirectly achieving the conversions ArH → ArI and ArH → ArF. The bis(trifluoroacetates) react with KI to give ArI in high yields.[263] Aryllead triacetates $ArPb(OAc)_3$ can be converted to aryl fluorides by treatment with BF_3–etherate.[264] Treatment of $PhB(OH)_2$ with *N*-iodosuccinimide gives iodobenzene.[265] Arylboronic acids (**12-28**) can be converted to the corresponding aryl bromides by reaction with 1,3-dibromo-5,5-dimethylhydantoin and 5 mol % NaOMe.[266] Other aryl halides can be prepared using 1,3-dihalo-5,5-dimethylhydantoins.

OS **III**, 194, 272, 475; **V**, 142, 478; **VIII**, 57; **81**, 98.

The reduction of phenols and phenolic esters and ethers is discussed in Chapter 19 (see **19-38** and **19-35**). The reaction ArX → ArH is treated in Chapter 11 (reaction **11-39**), although, depending on reagent and conditions, it can be nucleophilic or free-radical substitution, as well as electrophilic.

E. Carbon Nucleophiles[267]

Some formations of new aryl–carbon bonds formed from aryl substrates have been considered in Chapter 10 (see **10-57**, **10-68**, **10-76**, **10-77**).

[256]Bacon, R.G.R.; Hill, H.A.O. *J. Chem. Soc.* ***1964***, 1097, 1108. See also Nefedov, V.A.; Tarygina, L.K.; Kryuchkova, L.V.; Ryabokobylko, Yu.S. *J. Org. Chem, USSR* ***1981***, *17*, 487; Suzuki, H.; Kondo, A.; Ogawa, T. *Chem. Lett.* ***1985***, 411; Liedholm, B.; Nilsson, M. *Acta Chem. Scand. Ser. B* ***1988***, *42*, 289; Clark, J.H.; Jones, C.W.; Duke, C.V.A.; Miller, J.M. *J. Chem. Res. (S)* ***1989***, 238.

[257]Clark, J.H.; Jones, C.W. *J. Chem. Soc. Chem. Commun.* ***1987***, 1409.

[258]Klapars, A.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2002***, *124*, 14844.

[259]Yang, S.H.; Li, C.S.; Cheng, C.H. *J. Org. Chem.* ***1987***, *52*, 691.

[260]Arvela, R.K.; Leadbeater, N.E. *Synlett* ***2003***, 1145.

[261]Harrowven, D.C.; Nunn, M.I.T.; Fenwick, D.R. *Tetrahedron Lett.* ***2001***, *42*, 7501.

[262]For reviews of the synthesis of aryl iodides, see Merkushev, E.B. *Synthesis* ***1988***, 923; *Russ. Chem. Rev.* ***1984***, *53*, 343.

[263]Taylor, E.C.; Kienzle, F.; McKillop, A. *Org. Synth.* ***VI***, 826; Taylor, E.C.; Katz, A.H.; Alvarado, S.I.; McKillop, A. *J. Organomet. Chem.* ***1985***, *285*, C9. For reviews, see Usyatinskii, A.Ya.; Bregadze, V.I. *Russ. Chem. Rev.* ***1988***, *57*, 1054; Uemura, S., in Hartley, F. R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, pp. 473–538. See also, Ishikawa, N.; Sekiya, A. *Bull. Chem. Soc. Jpn.* ***1974***, *47*, 1680; Taylor, E.C.; Altland, H.W.; McKillop, A. *J. Org. Chem.* ***1975***, *40*, 2351.

[264]De Meio, G.V.; Pinhey, J.T. *J. Chem. Soc. Chem. Commun.* ***1990***, 1065.

[265]Thiebes, C.; Prakash, G.K.S.; Petasis N.A.; Olah, G.A. *Synlett* ***1998***, 141.

[266]Szumigala, Jr., R.H.; Devine, P.N.; Gauthier Jr., D.R.; Volante, R.P. *J. Org. Chem.* ***2004***, *69*, 566.

[267]For a review of many of these reactions, see Artamkina, G.A.; Kovalenko, S.V.; Beletskaya, I.P.; Reutov, O.A. *Russ. Chem. Rev.* ***1990***, *59*, 750.

13-8 Cyanation of Aromatic Rings

Cyano-de-halogenation
Cyano-de-metalation

$$\text{Ar-X} \longrightarrow \text{Ar-CN}$$

The reaction between aryl halides and cuprous cyanide is called the *Rosenmund-von Braun reaction*.[268] Reactivity is in the order I > Br > Cl > F, indicating that the S_NAr mechanism does not apply.[269] Other cyanides (e.g., KCN and NaCN) do not react with aryl halides, even activated ones. This reaction has been done in ionic liquids using CuCN.[270] The reaction has also been done in water using CuCN, a phase transfer catalyst, and microwave irradiation.[271]

Aryl halides reaction with metal cyanides, often with another transition metal catalyst, to give aryl nitriles (aryl cyanides). Aryl halides react with $Zn(CN)_2$ and a palladium catalyst, for example, to give the aryl nitrile.[272] Similarly, aryl iodides react with CuCN and a palladium catalyst to give the aryl nitrile.[273] Potassium cyanide (KCN) reacts in a similar manner with a palladium catalyst.[274] Sodium cyanide has been used with a copper catalyst and 20% KI.[275] The reaction of aryl iodides and sodium cyanoborohydride/catechol, with a palladium catalyst, generates the aryl nitrile.[276] Aryl bromides react with $Ni(CN)_2$ with microwave irradiation to give ArCN.[277] In general, alkali cyanides do convert aryl halides to nitriles[278] in dipolar aprotic solvents in the presence of Pd(II) salts[279] or copper[280] or nickel[281]

[268]For a review of cyano-de-halogenation, see Ellis, G.P.; Romney-Alexander, T.M. *Chem. Rev.* ***1987***, *87*, 779.

[269]For discussions of the mechanism, see Couture, C.; Paine, A.J. *Can. J. Chem.* ***1985***, *63*, 111; Connor, J.A.; Leeming, S.W.; Price, R. *J. Chem. Soc. Perkin Trans. 1* ***1990***, 1127.

[270]In bmiI, 1-*n*-butyl-3-methylimidazolium iodide: Wu, J.X.; Beck, B.; Ren, R.X. *Tetrahedron Lett.* ***2002***, *43*, 387.

[271]Arvela, R.K.; Leadbeater, N.W.; Torenius, H.M.; Tye, H. *Org. Biomol. Chem.* ***2003***, *1*, 1119.

[272]Jin, F.; Confalone, P.N. *Tetrahedron Lett.* ***2000***, *41*, 3271; Zhang, A.; Neumeyer, J.L. *Org. Lett.* ***2003***, *5*, 201; Marcantonio, K.M.; Frey, L.F.; Liu, Y.; Chen, Y.; Strine, J.; Phenix, B.; Wallace, D.J.; Chen, C.-y. *Org. Lett.* ***2004***, *6*, 3723; Ramnauth, J.; Bhardwaj, N.; Renton, P.; Rakhit, S.; Maddaford, S.P. *Synlett* ***2003***, 2237. See Erker, T.; Nemec, S. *Synthesis* ***2004***, 23.

[273]Sakamoto, T.; Ohsawa, K. *J. Chem. Soc. Perkin Trans. 1* ***1999***, 2323.

[274]Sundermeier, M.; Zapf, A.; Beller, M.; Sans, J. *Tetrahedron Lett.* ***2001***, *42*, 6707; Yang, C.; Williams, J.M. *Org. Lett.* ***2004***, *6*, 2837 (this reaction used a catalytic amount of tributyltin chloride as well).

[275]Zanon, J.; Klapers, A.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2003***, *125*, 2890.

[276]Jiang, B.; Kan, Y.; Zhang, A. *Tetrahedron* ***2001***, *57*, 1581.

[277]Arvela, R.K.; Leadbeater, N.E. *J. Org. Chem.* ***2003***, *68*, 9122.

[278]For a list of reagents that convert aryl halides to cyanides, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1705–1709.

[279]Takagi, K.; Okamoto, T.; Sakakibara, Y.; Ohno, A.; Oka, S.; Hayama, N. *Bull. Chem. Soc. Jpn,.* ***1975***, *48*, 3298; ***1976***, *49*, 3177. See also Sekiya, A.; Ishikawa, N. *Chem. Lett.* ***1975***, 277; Takagi, K.; Sasaki, K.; Sakakibara, Y. *Bull. Chem. Soc. Jpn.* ***1991***, *64*, 1118.

[280]Connor, J.A.; Gibson, D.; Price, R. *J. Chem. Soc. Perkin Trans. 1* ***1987***, 619.

[281]Cassar, L.; Foà, M.; Montanari, F.; Marinelli, G.P. *J. Organomet. Chem.* ***1979***, *173*, 335; Sakakibara, Y.; Okuda, F.; Shimobayashi, A.; Kirino, K.; Sakai, M.; Uchino, N.; Takagi, K. *Bull. Chem. Soc. Jpn.* ***1988***, *61*, 1985.

complexes. A nickel complex also catalyzes the reaction between aryl triflates and KCN to give aryl nitriles.[282]

Arylthallium bis(trifluoroacetates) (see **12-23**) can be converted to aryl nitriles by treatment with copper(I) cyanide in acetonitrile.[283] Another procedure uses excess aqueous KCN followed by photolysis of the resulting complex ion $ArTl(CN)_3^-$ in the presence of excess KCN.[284] Alternatively, arylthallium acetates react with $Cu(CN)_2$ or CuCN to give aryl nitriles.[285] Yields from this procedure are variable, ranging from almost nothing to 90 or 100%. Aromatic ethers ArOR[286] have been photochemically converted to ArCN.

An indirect method involves the reaction of an aromatic ring with *tert*-butyllithium, particularly when there is a directing group (see **13-17**), followed by reaction with PhOCN (phenyl cyanate) to give the aryl nitrile.[287] another indirect method involve the palladium catalyzed reaction of aryl bromides with the cyanohydrin of acetone $[Me_2C(OH)CN]$ to give ArCN.[288]

OS **III**, 212, 631.

13-9 Coupling of Aryl and Alkyl Organometallic Compounds with Aryl Halides, Ethers, and Carboxylic Esters

Aryl-de-halogenation, and so on

$$\text{Ar–X} + \text{Ar}'\text{–M} \longrightarrow \text{Ar–Ar}'$$

$$\text{Ar–X} + \text{R–M} \longrightarrow \text{Ar–R}$$

A number of methods involving transition metals have been used to prepare unsymmetrical biaryls (see also, **13-11**). The uncatalyzed coupling of aryl halides and metalated aryls (particularly aryllithium reagents) is also known, including cyclization of organolithium reagents to aromatic rings.[289] Noncatalyzed coupling reactions of aryllithium reagents and haloarenes can proceed via the well-known aryne route but in some cases, a novel addition–elimination pathway is possible when substituents facilitate a chelation-driven nucleophilic substitution pathway.[290] Such noncatalyzed coupling reactions often proceed with high regioselectivity and high yield.[290] Several noncatalyzed alternative routes are available. 2-Bromopyridine reacts with pyrrolidine, at 130°C with microwave irradiation, to give 2-(2-pyrrolidino)pyridine.[291] Aryl iodides undergo homo-coupling to give the biaryl by

[282]Chambers, M.R.I.; Widdowson, D.A. *J. Chem. Soc. Perkin Trans. 1* ***1989***, 1365; Takagi, K.; Sakakibara, Y. *Chem. Lett.* ***1989***, 1957.

[283]Taylor, E.C.; Katz, A.H.; McKillop, A. *Tetrahedron Lett.* ***1984***, *25*, 5473.

[284]Taylor, E.C.; Altland, H.W.; McKillop, A. *J. Org. Chem.* ***1975***, *40*, 2351.

[285]Uemura, S.; Ikeda, Y.; Ichikawa, K. *Tetrahedron* ***1972***, *28*, 3025.

[286]Letsinger. R.L.; Colb, A.L. *J. Am. Chem. Soc.* ***1972***, *94*, 3665.

[287]Sato, N. *Tetrahedron Lett.* ***2002***, *43*, 6403.

[288]Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem. Int. Ed.* ***2003***, *42*, 1661.

[289]For a review of cyclization of organolithium reagents, see Clayden, J.; Kenworthy, M.N. *Synthesis* ***2004***, 1721.

[290]See Becht, J.-M.; Gissot, A.; Wagner, A.; Mioskowski, C. *Chem. Eur. J.* ***2003***, *9*, 3209.

[291]Narayan, S.; Seelhammer, T.; Gawley, R.E. *Tetrahedron Lett.* ***2004***, *45*, 757.

heating with triethylamine in an ionic liquid.[292] Arylsiloxanes react with aryl halides, for example, to give the biaryl derivative.[293] The reaction of $NaBPh_4$ (sodium tetraphenylborate) and a silyl dichloride (Ph_2SiCl_2) gives biphenyl.[294]

There are many catalytic methods. A homo-coupling type reaction was reported in which $PhSnBu_3$ was treated with 10% $CuCl_2$, 0.5 equivalents of iodine and heated in DMF to give biphenyl.[295] Arylsulfonyl chlorides also react with $ArSnBu_3$ with palladium and copper catalysts to give the biaryl.[296] Aryl halides undergo homo-coupling to give the biaryl with a palladium catalyst[297] or a nickel catalyst.[298] In general, aryl tin compounds couple with aryl halides.[299] An aryltin–aryl halide coupling has been done in ionic liquids.[300] Aryl iodides have been coupled to form symmetric biphenyls using $Pd(OAc)_2$[301] and self-coupling occurs with aryl triflates under electrolysis conditions with a palladium catalyst.[302] A "double-coupling" reaction involving 2-trimethysilylphenol *O*-triflate, allyltributyltin and allyl chloride, with CsF and a palladium catalyst, gave 1,2-diallylbenzene.[303] Another homo-coupling reaction of pyridyl bromides was reported using $NiBr_2$ under electrolytic conditions.[304] Thiophene derivatives,[305] pyrrole,[306] azoles,[307] quinoline,[308] and indolizine[309] have been coupled to aryl halides using a palladium catalyst.

Grignard reagents couple with aryl halides without a palladium catalyst, by the benzyne mechanism,[310] but an iron catalyzed coupling reaction was reported,[311] as

[292]In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Park, S.B.; Alper, H. *Tetrahedron Lett.* ***2004***, *45*, 5515.

[293]Mori, A.; Suguro, M. *Synlett* ***2001***, 845; Murata, M.; Shimazaki, R.; Watanabe, S.; Masuda, Y. *Synthesis* ***2001***, 2231.

[294]Sakurai, H.; Morimoto, C.; Hirao, T. *Chem. Lett.* ***2001***, 1084. See also, Powell, D.A.; Fu, G.C. *J. Am. Chem. Soc.* ***2004***, *126*, 7788.

[295]Kang, S.-K.; Baik, T.-G.; Jiao, X.H.; Lee, Y.-T. *Tetrahedron Lett.* ***1999***, ***40***, 2383.

[296]Dubbaka, S.R.; Vogel, P. *J. Am. Chem. Soc.* ***2003***, *125*, 15292.

[297]Silveira, P.B.; Lando, V.R.; Dupont, J.; Monteiro, A.L. *Tetrahedron Lett.* ***2002***, *43*, 2327; Kuroboshi, M.; Waki, Y.; Tanaka, H. *Synlett* ***2002***, 637. See also, Venkatraman, S.; Li, C.-J. *Org. Lett.* ***1999***, *1*, 1133.

[298]Leadbeater, N.E.; Resouly, S.M. *Tetrahedron Lett.* ***1999***, *40*, 4243.

[299]Wang, J.; Scott, A.I. *Tetrahedron Lett.* ***1996***, *37*, 3247; Saá, J.M.; Martorell, G.; García-Raso, A. *J. Org. Chem.* ***1992***, *57*, 678; Littke, A.F.; Schwarz, L.; Fu, G.C. *J. Am. Chem. Soc.* ***2002***, *124*, 6343; Kim, Y.M.; Yu, S. *J. Am. Chem. Soc.* ***2003***, *125*, 1696.

[300]Grasa, G.A.; Nolan, S.P. *Org. Lett.* ***2001***, *3*, 119.

[301]Penalva, V.; Hassan, J.; Lavenot, L.; Gozzi, C.; Lemaire, M. *Tetrahedron Lett.* ***1998***, *39*, 2559.

[302]Jutand, A.; Négri, S.; Mosleh, A. *J. Chem. Soc, Chem. Commun.* ***1992***, 1729.

[303]Yoshikawa, E.; Radhakrishnan, K.V.; Yamamoto, Y. *Tetrahedron Lett.* ***2000***, *41*, 729.

[304]de Franç a, K.W.R.; Navarro, M.; Léonel, É; Durandetti, M.; Nédélec, J.-Y. *J. Org. Chem.* ***2002***, *67*, 1838.

[305]Glover, B.; Harvey, K.A.; Liu, B.; Sharp, M.J.; Tymoschenko, M.F. *Org. Lett.* ***2003***, *5*, 301.

[306]With $ZnCl_2$ as an additive, see Rieth, R.D.; Mankand, N.P.; Calimano, E.; Sadighi, J.P. *Org. Lett.* ***2004***, *6*, 3981.

[307]Sezen, B.; Sames, D. *Org. Lett.* ***2003***, *5*, 3607.

[308]Quintin, J.; Franck, X.; Hocquemiller, R.; Figadère, B. *Tetrahedron Lett.* ***2002***, *43*, 3547.

[309]Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* ***2004***, *6*, 1159.

[310]Du, C.F.; Hart, H.; Ng, K.D. *J. Org. Chem.* ***1986***, *51*, 3162.

[311]Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* ***2002***, *124*, 13856.

well as a nickel-[312] and a cobalt-catalyzed reaction.[313] The coupling reaction of an excess of a Grignard reagent (RMgX) with methoxy aromatic compounds, when the aromatic ring contains multiple alkoxy groups, proceeds with replacement of the OMe group by R.[314] Aryl Grignard reagents coupled with phenyl allyl sulfone, in the presence of an iron catalyst, to give $ArCH_2CH{=}CH_2$.[315] In a similar manner, aryl sulfone coupled with aryl Grignard reagents in the presence of a nickel catalyst.[316] Arylmagnesium compounds couple to give the symmetrical biaryl in the presence of $TiCl_4$.[317] Arylmagnesium halides couple with aryl tosylates in the presence of a palladium catalyst to give unsymmetrical biaryls,[318] and to halopyridines to give the arylated pyridine.[319] Aryl Grignard reagents can be coupled to aryliodonium salts, with $ZnCl_2$ and a palladium catalyst, to give the biaryl.[320] Specialized aryl bismuth compounds have been used with a palladium catalyst to convert aryl chlorides to biaryls,[321] and specialized alkyl indium complexes have been used with a palladium catalyst to give arenes.[322] α-Lithio lactams are coupled to aryl bromides using a palladium catalyst, giving α-aryl lactams.[323]

The homo-coupling of arylzinc iodides with a palladium catalyst has been reported.[324] Vinyl halides, in the presence of an arylmagnesium halides, $ZnCl_2$ and a palladium catalyst, give the styrene compound.[325] Aryl triflates (halides) couple with ArZn(halide) reagents in the presence of a nickel catalyst.[326] Aryl triflates were coupled to triphenylbismuth using a palladium catalyst.[327] Homo-coupling of triphenylbismuth is known,[328] as well as the coupling of arylbismuth reagents to aryliodonium salts[329] and to aryltin compounds[330] with palladium chloride. Similar coupling was accomplished with aryltellurium compounds.[331] Aryl iodides undergo

[312]Dankwardt, J.W. *Angew. Chem. Int. Ed.* ***2004***, *43*, 2428; Mongin, F.; Mojovic, L.; Guillamet, B.; Trécourt, F.; Quéguiner, G. *J. Org. Chem.* ***2002***, *67*, 8991.

[313]Korn, T.J.; Cahiez, G.; Knochel, P. *Synlett* ***2003***, 1892.

[314]Kojima, T.; Ohishi, T.; Yamamoto, I.; Matsuoka, T.; Kotsuki, H. *Tetrahedron Lett.* ***2001***, *42*, 1709.

[315]Gai, Y.; Julia, M.; Verpeaux, J.-N. *Bull. Soc. Chim. Fr.* ***1996***, *133*, 805.

[316]Clayden, J.; Cooney, J.J.A.; Julia, M. *J. Chem. Soc. Perkin Trans. 1* ***1995***, 7.

[317]Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oshima, K. *Tetrahedron* ***2000***, *56*, 9601.

[318]Roy, A.H.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2003***, *125*, 8704.

[319]Bonnet, V.; Mongin, F.; Trècourt, F.; Quèguiner, G.; Knochel, P. *Tetrahedron Lett.* ***2001***, *42*, 5717.

[320]Wang, L.; Chen, Z.-C. *Synth. Commun.* ***2000***, *30*, 3607.

[321]Yamazaki, O.; Tanaka, T.; Shimada, S.; Suzuki, Y.; Tanaka, M. *Synlett* ***2004***, 1921.

[322]Shenglof, M.; Gelman, D.; Heymer, B.; Schumann, H.; Molander, G.A.; Blum, J. *Synthesis* ***2003***, 302.

[323]Cossy, J.; de Filippis, A.; Pardo, D.G. *Synlett* ***2003***, 2171.

[324]With NCS, Hossain, K.M.; Kameyama, T.; Shibata, T.; Takagi, K. *Bull. Chem. Soc. Jpn.* ***2001***, *74*, 2415. See also, Venkatraman, S.; Li, C.-J. *Tetrahedron Lett.* ***2000***, *41*, 4831; Albanese, D.; Landini, D.; Penso, M.; Petricci, S. *Synlett* ***1999***, 199.

[325]Peyrat, J.-F.; Thomas, E.; L'Hermite, N.; Alami, M.; Brion, J.-D. *Tetrahedron Lett.* ***2003***, *44*, 6703.

[326]Quesnelle, C.A.; Familoni, O.B.; Snieckus, V. *Synlett* ***1994***, 349. For the use of $NiCl_2/CrCl_2/Mn$, see Chen, C. *Synlett* ***2000***, 1491. For a reaction done with microwave irradiation, see Walla, P.; Kappe, C.O. *Chem. Commun.* ***2004***, 564.

[327]Rao, M.L.N.; Yamazaki, O.; Shimada, S.; Tanaka, T.; Suzuki, Y.; Tanaka, M. *Org. Lett.* ***2001***, *3*, 4103.

[328]Ohe, T.; Tanaka, T.; Kuroda, M.; Cho, C.S.; Ohe, K.; Uemura, S. *Bull. Chem. Soc. Jpn.* ***1999***, *72*, 1851.

[329]Kang, S.-K.; Ryu, H.-C.; Kim, J.-W. *Synth. Commun.* ***2001***, *31*, 1021.

[330]Kang, S.-K.; Ryu, H.-C.; Lee, S.-W. *Synth. Commun.* ***2001***, *31*, 1027.

[331]Kang, S.-K.; Lee, S.-W.; Kim, M.-S.; Kwon, H.S. *Synth. Commun.* ***2001***, *31*, 1721.

a homo-coupling in the presence of hydroquinone and a palladium catalyst.[332] Arylgermanium compounds are coupled with aryl iodides using tetrabutylammonium fluoride and a palladium catalyst.[333] Both alkylmanganese compounds (RMnCl)[334] and Ph_3In[335] react with aryl halides or aryl triflates to give the arene, as do arylbismuth regents with aryl triflates.[336] Aryl halides couple to vinyl acetates, with a cobalt catalyst, to give the styrene derivative.[337] Aryl halides react with cyclopentadiene and Cp_2ZrCl_2 and a palladium catalyst to give pentaphenylcyclopentadiene.[338] Aryl halides also react with phenols to form biaryls using a rhodium catalyst.[339] Diaryliodonium salts react with $PhPb(OAc)_3$ and a palladium catalyst to give the biaryl.[340] Arylsilanes can be coupled to aryl iodides using a palladium catalyst.[341] Aryl halides reacts with acrolein diethyl acetal under electrolysis conditions and a nickel catalyst to give the allyl arene ($Ar{-}CH_2CH{=}CHOEt$).[342]

Unsymmetrical binaphthyls were synthesized by photochemically stimulated reaction of naphthyl iodides with naphthoxide ions in an $S_{RN}1$ reaction.[343] Methyl chloroacetate coupled with aryl iodides under electrolysis conditions, using a nickel catalyst.[344] Unsymmetrical biaryls were prepared from two aryl iodides using a CuI catalyst and microwave irradiation.[345]

Alkylboronic acids are coupled to aryl halides using a palladium catalyst,[346] analogous to the Suzuki reaction in **13-12**. Conversely, arylboronic acids can be coupled to aliphatic halides.[347] Arylboronic acids can be coupled to allylic alcohols as well.[348] Arylboronic acids (**12-28**) were shown to react directly with benzene in the presence of $Mn(OAc)_3$.[349] Arylboronic acids also couple with alkyl halides in

[332]Hennings, D.D.; Iwama, T.; Rawal, V.H. *Org. Lett.* ***1999***, *1*, 1205.
[333]Nakamura, T.; Kinoshita, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* ***2002***, *4*, 3165.
[334]Cahiez, G.; Luart, D.; Lecomte, F. *Org. Lett.* ***2004***, *6*, 4395.
[335]Pérez, I.; Sestelo, J.P.; Sarandeses, L.A. *Org. Lett.* ***1999***, *1*, 1267; *J. Am. Chem. Soc.* ***2001***, *123*, 4155.
[336]Rao, M.L.N.; Shimada, S.; Tanaka, M. *Org. Lett.* ***1999***, *1*, 1271.
[337]Gomes, P.; Gosmini, C.; Périchon, J. *Tetrahedron* ***2003***, *59*, 2999.
[338]Dyker, G.; Heiermann, J.; Miura, M.; Inoh, J.-I.; Pivsa-Ast, S.; Satoh, T.; Nomura, M. *Chem. Eur. J.* ***2000***, *6*, 3426.
[339]Bedford, R.B.; Limmert, M.E. *J. Org. Chem.* ***2003***, *68*, 8669.
[340]Kang, S.-K.; Choi, S.-C.; Baik, T.-G. *Synth. Commun.* ***1999***, *29*, 2493.
[341]Denmark, S.E.; Wu, Z. *Org. Lett.* ***1999***, *1*, 1495; Lee, H.M.; Nolan, S.P. *Org. Lett.* ***2000***, *2*, 2053.
[342]Condon, S.; Dupré, D.; Nédélec, J.Y. *Org. Lett.* ***2003***, *5*, 4701.
[343]Beugelmans, R.; Bois-Choussy, M.; Tang, Q. *Tetrahedron Lett.* ***1988***, *29*, 1705. For other preparations of biaryls via $S_{RN}1$ processes, see Alam, N.; Amatore, C.; Combellas, C.; Thiébault, A.; Verpeaux, J.N. *Tetrahedron Lett.* ***1987***, *28*, 6171; Pierini, A.B.; Baumgartner, M.T.; Rossi, R.A. *Tetrahedron Lett.* ***1988***, *29*, 3429.
[344]Durandetti, M.; Nédélec, J.-Y.; Périchon, J. *J. Org. Chem.* ***1996***, *61*, 1748.
[345]He, H.; Wu, Y.-J. *Tetrahedron Lett.* ***2003***, *44*, 3445.
[346]Zou, G.; Reddy, Y.K.; Falck, J.R. *Tetrahedron Lett.* ***2001***, *42*, 7217; Molander, G.A.; Yun, C.-S. *Tetrahedron* ***2002***, *58*, 1465.
[347]Duan, Y.-Z.; Deng, M.-Z. *Tetrahedron Lett.* ***2003***, *44*, 3423; Bandgar, B.P.; Bettigeri, s.V.; Phopase, J. *Tetrahedron Lett.* ***2004***, *45*, 6959.
[348]Tsukamoto, H.; Sato, M.; Kondo, Y. *Chem. Commun.* ***2004***, 1200; Kayaki, Y.; Koda, T.; Ikariya, T. *Eur. J. Org. Chem.* ***2004***, 4989.
[349]Demir, A.S.; Reis, Ö; Emrullahoglu, M. *J. Org. Chem.* ***2003***, *68*, 578.

the presence of palladium(II) acetate[350] or a nickel catalyst.[351] Vinylboronic acids coupled to aryl halides to give the vinyl coupling product.[352] Vinylboronic acids have been coupled to aryldiazonium salts (**13-25**) without added base, using a palladium catalyst with an imidazolium ligand.[353]

Alkyltrifluoroborates (RBF_3K, see **12-28**) react with aryl triflates[354] or aryl halides,[355] or aryliodonium salts[356] with a palladium catalyst, to give the arene. The reaction is compatible with sensitive functionality, such as an epoxide unit.

It is possible to couple metalated alkyl compounds to aryl compounds. The lithium enolate anion of an ester was coupled to an aryl halide, for example, using a palladium catalyst.[357]

Chiral vinyl sulfoxides have been coupled to aryl iodides to give a chiral allylic aryl compounds ($C{=}C\text{-}CH_2\text{—}Ar$), in a three-step procedure with good enantioselectivity.[358]

The reaction of a cyclic zirconium–diene complex and an aryl diiodide, with CuCl, leads to highly substituted naphthalene derivatives.[359]

OS **VI**, 916; **VIII**, 430, 586; **X**, 9, 448.

13-10 Arylation and Alkylation of Alkenes

Alkylation or **Alkyl-de-hydrogenation**, and so on

$$R_2C{=}CH_2 \quad + \quad Ar\text{-}X \quad \xrightarrow{Pd(0)} \quad R_2C{=}CH\text{—}Ar$$

Arylation of alkenes can also be achieved[360] by treatment with an "arylpalladium" reagent, typical generated *in situ* from an aryl halide or other suitably functionalized aromatic compound and a palladium(0) catalyst.[361] Other methods

[350]Kirchhoff, J.H.; Netherton, M.R. Hills, I.D.; Fu, G.C. *J. Am. Chem. Soc.* ***2002***, *124*, 13662.
[351]Zhou, J.; Fu, G.C. *J. Am. Chem. Soc.* ***2004***, *126*, 1340.
[352]Collet, S.; Danion-Bougot, R.; Danion, D. *Synth. Commun.* ***2001***, *31*, 249.
[353]Andrus, M.B.; Song, C. *Org. Lett.* ***2001***, *3*, 3761; Andrus, M.B.; Song, C.; Zhang, J. *Org. Lett.* ***2002***, *4*, 2079.
[354]Molander, G.A.; Yun, C.-S.; Ribagorda, M.; Biolatto, B. *J. Org. Chem.* ***2003***, *68*, 5534.
[355]Molander, G.A.; Ribagorda, M. *J. Am. Chem. Soc.* ***2003***, *125*, 11148.
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[357]Moradi, W.A.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2001***, *123*, 7996.
[358]de la Rosa, J.C.; Díaz, N.; Carretero, J.C. *Tetrahedron Lett.* ***2000***, *41*, 4107.
[359]Zhou, X.; Li, Z.; Wang, H.; Kitamura, M.; Kanno, K.-i.; Nakajima, K.; Takahashi, T. *J. Org. Chem.* ***2004***, *69*, 4559.
[360]For reviews of this and related reactions, see Heck, R.F. *Palladium Reagents in Organic Syntheses*, Academic Press, NY, ***1985***, pp. 179–321; Ryabov, A.D. *Synthesis* ***1985***, 233; Heck, R.F. *Org. React.* ***1982***, *27*, 345; Moritani, I.; Fujiwara, Y. *Synthesis* ***1973***, 524. See Cabri, W.; Candiani, I. *Acc. Chem. Res.* ***1995***, *28*, 2.
[361]For reviews, see Heck, R.F. *Acc. Chem. Res.* ***1979***, *12*, 146; *Pure Appl. Chem.* ***1978***, *50*, 691; Kozhevnikov, I.V. *Russ. Chem. Rev.* ***1983***, *52*, 138. See also Bender, D.D.; Stakem, F.G.; Heck, R.F. *J. Org. Chem.* ***1982***, *47*, 1278; Spencer, A. *J. Organomet. Chem.* ***1983***, *258*, 101. See also, Bozell, J.J.; Vogt, C.E. *J. Am. Chem. Soc.* ***1988***, *110*, 2655; Andersson, C.; Karabelas, K.; Hallberg, A.; Andersson, C. *J. Org. Chem.* ***1985***, *50*, 3891; Merlic, C.A.; Semmelhack, M.F. *J. Organomet. Chem.* ***1990***, *391*, C23; Larock, R.C.; Johnson, P.L. *J. Chem. Soc. Chem. Commun.* ***1989***, 1368.

are available for this arylation reaction.[362] Treatment of an arylmercury compound (either Ar_2Hg or ArHgX) with $LiPdCl_3$ (ArHgX → "ArPdX") can generate the appropriate intermediate,[363] and in some cases other noble metal salts have been used. The palladium catalyzed aryl–alkene coupling reaction is known as *the Heck reaction*. The reaction works best with aryl iodides, although conditions have been developed for aryl bromides and aryl chlorides.[364] Aryldiazonium salts (**13-25**), rather than aryl halides, have also been used in the Heck reaction.[365] When 2,3,4,5,6-pentafluorobromobezene was used as a substrate, coupling occurred via the bromine, giving the pentafluorophenyl alkene.[366] Aryl halides bearing ortho-substituents also under the coupling reaction.[367] Heteroaryl halides can be used in the couple reaction.[368] Note that acetanilide derivatives reacted with conjugated esters to give the Heck product in acetic acid using a palladium catalyst.[369] Other activated aromatic compounds couple in a similar manner using palladium catalysts[370] unactivated aromatic compounds using special reaction conditions.[371]

Unlike **13-26**, the Heck reaction is not limited to activated substrates. The substrate can be a simple alkene, or it can contain a variety of functional groups, such as ester, ether,[372,373] carboxyl, phenolic, or cyano groups.[374] Coupling with vinyl ethers has been reported, C=C—OR → C=C(Ar)OR.[375] The Heck reaction can be done with heterocyclic compounds,[376] and the C—C unit of compounds, such as indene, react with aryl iodides and palladium catalyst without the need for

[362]For other methods, see Tsuji, J.; Nagashima, H. *Tetrahedron* ***1984***, *40*, 2699; Kikukawa, K.; Naritomi, M.; He, G.; Wada, F.; Matsuda, T. *J. Org. Chem.* ***1985***, *50*, 299; Chen, Q.; Yang, Z. *Tetrahedron Lett.* ***1986***, *27*, 1171; Kasahara, A.; Izumi, T.; Miyamoto, K.; Sakai, T. *Chem. Ind.* (*London*) ***1989***, 192; Miura, M.; Hashimoto, H.; Itoh, K.; Nomura, M. *Tetrahedron Lett.* ***1989***, *30*, 975.

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[364]For reviews, see Whitcombe, N.J.; Hii, K.K.; Gibson, S.E. *Tetrahedron* ***2001***, *57*, 7449; Littke, A.F.; Fu, G.C. *Angew. Chem. Int. Ed.* ***2002***, *41*, 4176.

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[369]Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* ***2002***, *124*, 1586.

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[371]Yokota, T.; Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* ***2003***, *125*, 1476.

[372]For a review pertaining to enol ethers, see Daves, Jr., G.D. *Adv. Met.- Org. Chem.* ***1991***, *2*, 59.

[373]Larhed, M.; Hallberg, A. *J. Org. Chem.* ***1996***, *61*, 9582.

[374]For a review of cases where the alkene contains an heteroatom, see Daves, Jr., G.D.; Hallberg, A. *Chem. Rev.* ***1989***, *89*, 1433.

[375]Andappan, M.M.S.; Nilsson, P.; von Schenck, H.; Larhed, M. *J. Org. Chem.* ***2004***, *69*, 5212.

[376]Pyridines: Draper, T.L.; Bailey, T.R. *Synlett* ***1995***, 157.

preparing the halide.[377] The Heck reaction has also been performed intramolecularly.[378] Asymmetric Heck reactions are known[379] and the effects of high pressure have been studied.[380]

Ethylene is the most reactive alkene. Increasing substitution lowers the reactivity. Substitution therefore takes place at the less highly substituted side of the double bond.[381] The aryl halide or aryl triflate can be coupled to dienes,[382] allenes,[383] allylic silanes,[384] allylic amines,[385] vinyl phosphonate esters,[386] and with terminal alkynes.[387] Alkylation can also be accomplished, but only if the alkyl group lacks a β-hydrogen, for example, the reaction is successful for the introduction of methyl, benzyl, and neopentyl groups.[388] However, vinylic groups, even those possessing β-hydrogens, have been successfully introduced (to give 1,3-dienes) by the reaction of the alkene with a vinylic halide in the presence of a trialkylamine and a palladium(0) catalyst.[389] Aryl iodides can be coupled to 1-methyl-1-vinyl- and 1-methyl-1-(prop-2-enyl)silacyclobutane with desilyation, using a palladium catalyst and Bu_4NF, to give the corresponding styrene derivative.[390] Indene reacts with iodobenzene with a palladium catalyst to give the phenylindene (80:20 C3/C2).[391]

Control of regiochemistry is a serious problem in the addition to unsymmetrical alkenes. Some regioselectivity can be obtained by the use of alkenes attached to an

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[383]Chang, H.-M.; Cheng, C.-H. *J. Org. Chem.* ***2000***, *65*, 1767.

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auxiliary coordinating group,[392] the use of special ligands and acrylate or styrene as substrates.[393] Steric effects are thought to control regioselectivity,[394] but electronic influences have also been proposed.[395] It has been shown that the presence of steric effects generally improve 1,2-selectivity, and that electronic effects can be used to favor 1,2- or 2,1-selectivity.[396]

Phosphine free catalysts[397] and halogen-free reactions[398] are known for the Heck reaction. Improvements on the palladium catalyst system are constantly being reported,[399] including polymer-supported catalysts.[400] The influence of the ligand has been examined.[401] Efforts have been made to produce a homogeneous catalyst for the Heck reaction.[402] The Heck reaction can be done in aq. media,[403] in perfluorinated solvents,[404] in polyethylene glycol,[405] in neat tricaprylmethylammonium

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[401]For a review, see Qadir, M.; Möchel, T.; Hii, K.K. *Tetrahedron* ***2000***, *56*, 7975. Feuerstein, M.; Doucet, H.; Santelli, M. *J. Org. Chem.* ***2001***, *66*, 5923; Yang, C.; Lee, H.M.; Nolan, S.P. *Org. Lett.* ***2001***, *3*, 1511; Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* ***2004***, *69*, 1221; Yang, D.; Chen, Y.-C.; Zhu, N.-Y. *Org. Lett.* ***2004***, *6*, 1577; Eberhard, M.R. *Org. Lett.* ***2004***, *6*, 2125; Berthiol, F.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* ***2003***, *44*, 1221; Liu, J.; Zhao, Y.; Zhou, Y.; Li, L.; Zhang, T.Y.; Zhang, H. *Org. Biomol. Chem.* ***2003***, *1*, 3227. A reaction was reported using palladium acetate in dimethylacetamide and no added ligand, see Yao, Q.; Kinney, E.P.; Yang, Z. *J. Org. Chem.* ***2003***, *68*, 7528. For a phosphine-free reaction see Consorti, C.S.; Zanini, M.L.; Leal, S.; Ebeling, G.; Dupont, J. *Org. Lett.* ***2003***, *5*, 983.

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chloride,[406] and in supercritical CO_2 (see p. 414).[407] A noncatalytic reaction was reported using supercritical water.[408] The reaction has been done on solid support,[409] including Montmorillonite clay,[410] glass beads,[411] on a reverse-phase silica support,[412] and using microwave irradiation.[413] A microwave irradiated Heck coupling was done in water using a palladium catalyst.[414] The Heck reaction has also been in ionic liquids,[415] and it is known that the nature of the halide is important in such reactions.[416]

The evidence is in accord with an addition–elimination mechanism (addition of ArPdX followed by elimination of HPdX) in most cases.[417] In the conventionally accepted reaction mechanism,[418] a four-coordinate aryl–Pd(II) intermediate is formed by oxidative addition of the aryl halide to a Pd(0) complex prior to olefin addition. This suggests that cleavage of the dimeric precursor complex, reduction of Pd^{2+}, and ligand dissociation combine to give a viable catalytic species.[419] If these processes occur on a time scale comparable to that of the catalytic reaction, nonsteady-state catalysis could occur while the active catalyst is forming, and an

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[415]In **bmim** $\mathbf{PF_6}$, 1-butyl-3-methylimidazolium hexafluorophosphate: Carmichael, A.J.; Earle, M.J.; Holbrey, J.D.; McCormac, P.B.; Seddon, K.R. *Org. Lett.* ***1999***, *1*, 997; Hagiwara, H.; Shimizu, Y.; Hoshi, T.; Suzuki, T.; Ando, M.; Ohkubo, K.; Yokoyama, C. *Tetrahedron Lett.* ***2001***, *42*, 4349. In bmim PF_6 with microwave irradiation, see Vallin, K.S.A.; Emilsson, P.; Larhed, M.; Hallberg, A. *J. Org. Chem.* ***2002***, *67*, 6243. In **bmim** $\mathbf{BF_4}$, 1-butyl-3-methylimidazolium tetrafluoroborate: Handy, S.T.; Zhang, X. *Org. Lett.* ***2001***, *3*, 233. In **bbim Br**, 1,3-di-*n*-butylimidazolium bromide, Deshmukh, R.R.; Rajagopal, R.; Srinivasan, K.V. *Chem. Commun.* ***2001***, 1544. In a **tetrabutylammonium bromide melt**, Calò, V.; Nacci, A.; Monopoli, A.; Lopez, L.; di Cosmo, A. *Tetrahedron* ***2001***, *57*, 6071. See Hagiwara, H.; Sugawara, Y.; Isobe, K.; Hoshi, T.; Suzuki, T. *Org. Lett.* ***2004***, *6*, 2325; Okubo, K.; Shirai, M.; Yokoyama, C. *Tetrahedron Lett.* ***2002***, *43*, 7115.

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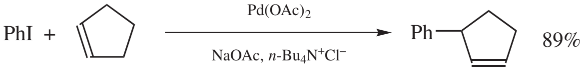
analysis of reaction kinetics under dry conditions was reported.[419] In this study, the mechanism requires a first-order dependence on olefin concentration, and anomalous kinetics may be observed when the rate-limiting step is not directly on the catalytic cycle.[419]



21

$$CH_2{=}CH{-}CH_2OH \xrightarrow{\text{"PdPdCl"}} PhCH_2CH_2CHO$$

22

The reactions are stereospecific, yielding products expected from syn addition followed by syn elimination.[420] Because the product is formed by an elimination step, with suitable substrates double bond migration can occur, resulting in allylic rearrangement (as in the reaction of cyclopentene and iodobenzene to give **21**).[421] Primary and secondary allylic alcohols (and even non-allylic unsaturated alcohols[422]) give aldehydes, such as **22** or ketones that are products of double-bond migration.[423] Similarly, dihydrofurans react with aryl triflates and a palladium catalyst that includes a chiral ligand, to give the 5-phenyl-3,4-dihydrofuran with good enantioselectivity.[424] A similar reaction was reported for an *N*-carbamoyl dihydropyrrole.[425] It has been reported that double bond isomerization can be suppressed in intramolecular Heck reactions done in supercritical CO_2 (see p. 414).[426] The mechanistic implications of asymmetric Heck reactions has been examined.[427]

There are a number of variations of this reaction, including the use of transition metal catalyst other than palladium. A silane-tethered, intramolecular Heck reaction has been reported.[428] Arylphosphonic acids, $ArP(=O)(OH)_2$, couple to aryl alkenes in the presence of a palladium catalyst.[429] Aryl halides couple with vinyl

[420]Heck, R.F. *J. Am. Chem. Soc.* ***1969***, *91*, 6707; Moritani, I.; Danno, S.; Fujiwara, Y.; Teranishi, S. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 578. See Masllorens, J.; Moreno-Mañas, M.; Pla-Quintana, A.; Plexats, R.; Roglans, A. *Synthesis* ***2002***, 1903.

[421]Larock, R.C.; Baker, B.E. *Tetrahedron Lett.* ***1988***, *29*, 905. Also see, Larock, R.C.; Gong, W.H.; Baker, B.E. *Tetrahedron Lett.* ***1989***, *30*, 2603.

[422]Larock, R.C.; Leung, W.; Stolz-Dunn, S. *Tetrahedron Lett.* ***1989***, *30*, 6629.

[423]See, for example, Melpolder, J.P.; Heck, R.F. *J. Org. Chem.* ***1976***, *41*, 265; Chalk, A.J.; Magennis, S.A. *J. Org. Chem.* ***1976***, *41*, 273, 1206.

[424]Tietze, L.F.; Thede, K.; Sannicolò, F. *Chem. Commun.* ***1999***, 1811; Hashimoto, Y.; Horie, Y.; Hayashi, M.; Saigo, K. *Tetahedron Asymmetry* ***2000***, *11*, 2205; Gilbertson, S.R.; Xie, D.; Fu, Z. *J. Org. Chem.* ***2001***, *66*, 7240; Gilbertson, S.R.; Fu, Z. *Org. Lett.* ***2001***, *3*, 161; Hennessy, A.J.; Connolly, D.J.; Malone, Y.M.; Buiry, P.J. *Tetrahedron Lett.* ***2000***, *41*, 7757.

[425]Servino, E.A.; Correia, C.R.D. *Org. Lett.* ***2000***, *2*, 3039.

[426]Shezad, N.; Clifford, A.A.; Rayner, C.M. *Tetrahedron Lett.* ***2001***, *42*, 323.

[427]Hii, K.K.; Claridge, T.D.W.; Brown, J.M.; Smith, A.; Deeth, R.J. *Helv. Chim. Acta* ***2001***, *84*, 3043.

[428]Mayasundari, A.; Young, D.G.J. *Tetrahedron Lett.* ***2001***, *42*, 203.

[429]Inoue, A.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* ***2003***, *125*, 1484.

tin reagents to form styrene derivatives in the presence of a nickel catalyst.[430] Aryl chlorides were coupled to conjugated esters using a $RuCl_3 \cdot 3\ H_2O$, in an atmosphere of O_2 and CO.[431] Alkenyl organometallic compounds have been coupled to aryl halides, including allenyltin compounds ($C{=}C{=}C\text{-}SnR_3$).[432] Divinylindium chloride, $(CH_2{=}CH)_2InCl$, reacted with an aryl iodide in aq. THF with a palladium catalyst to give the styrene derivative.[433] Trialkenylindium reagents reacted similarly with aryl halides and a palladium catalyst.[434] Arylzinc chlorides (ArZncl) were coupled to vinyl chlorides using a palladium catalyst,[435] and vinyl zinc compounds were coupled to aryl iodides.[436] Aryliodonium salts can be coupled to conjugated alkenes in a Heck-like manner using a palladium catalyst.[437] In the presence of trimethylsilylmagnesium chloride, primary alkyl halides coupled to aryl alkenes to give the substituted alkene (R′—CH=CHAr), using a cobalt catalyst.[438]

Arylboronic acids (**12-28**) have been coupled to conjugated alkenes to give the aryl–alkene coupling product using a palladium catalyst,[439] a ruthenium catalyst with copper(II) acetate,[440] or a rhodium catalyst.[441] Arylboronic acids have also been coupled to vinyl halides[442] or vinyl tosylates[443] using a palladium catalyst. Note that the reaction of an arylboronic acid and 1,2-dibromoethane, with KOH and a palladium catalyst leads to the styrene derivative.[444] vinylboronic acids have been coupled to aryl halides using a palladium catalyst.[445] Styrene derivatives have been prepared by the reaction of aryl halides and 2,4,6-trivinylcyclotriboroxane, with a palladium catalyst.[446] Conjugated esters can be coupled to benzene using a palladium acetate/benzoquinone catalyst, *tert*-butyl hydroperoxide in acetic acid–acetic anhydride, at 90°C in a sealed tube.[447] Vinyl silanes were converted to styrene derivatives upon treatment with Bu_4NF, and aryl iodide and a palladium

[430] Shirakawa, E.; Yamasaki, K.; Hiyama, T. *Synthesis* ***1998***, 1544; Chen, C.; Wilcoxen, K.; Zhu, Y.-F.; Kim, K.-i.; McCarthy, J.R. *J. Org. Chem.* ***1999***, *64*, 3476.
[431] Weissman, H.; Song, X.; Milstein, D. *J. Am. Chem. Soc.* ***2001***, *123*, 337.
[432] Huang, C.-W.; Shanmugasundarm, M.; Chang, H.-M.; Cheng, C.-H. *Tetrahedron* ***2003***, *59*, 3635.
[433] Takami, K.; Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *Org. Lett.* ***2001***, *3*, 1997.
[434] Lehmann, U.; Awasthi, S.; Minehan, T. *Org. Lett.* ***2003***, *5*, 2405.
[435] Dai, C.; Fu, G.C. *J. Am. Chem. Soc.* ***2001***, *123*, 2719.
[436] Jalil, A.A.; Kurono, N.; Tokuda, M. *Synlett* ***2001***, 1944.
[437] Xia, M.; Chen, Z.C. *Synth. Commun.* ***2000***, *30*, 1281.
[438] Ikeda, Y.; Nakamura, T.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* ***2002***, *124*, 6514.
[439] Du, X.; Suguro, M.; Hirabayashi, K.; Mori, A.; Nishikata, T.; Hagiwara, N.; Kawata, K.; Okeda, T.; Wang, H.-F.; Fugami, K.; Kosugi, M. *Org. Lett.* ***2001***, *3*, 3313; Jung, Y.C.; Mishra, R.K.; Yoon, C.H.; Jung, K.W. *Org. Lett.* ***2003***, *5*, 2231.
[440] Farrington, E.J.; Brown, J.M.; Barnard, C.F.J.; Rowsell, E. *Angew. Chem. Int. Ed.* ***2002***, *41*, 169.
[441] Lautens, M.; Roy, A.; Fukuoka, K.; Fagnou, K.; Martín-Matute, B. *J. Am. Chem. Soc.* ***2001***, *123*, 5358.
[442] Bauer, A.; Miller, M.W.; Vice, S.F.; McCombie, S.W. *Synlett* ***2001***, 254; Poondra, R.R.; Fischer, P.M.; Turner, N.J. *J. Org. Chem.* ***2004***, *69*, 6920.
[443] Wu, J.; Zhu, Q.; Wang, L.; Fathi, R.; Yang, Z. *J. Org. Chem.* ***2003***, *68*, 670.
[444] Lando, V.R.; Monteiro, A.L. *Org. Lett.* ***2003***, *5*, 2891.
[445] Peyroux, E.; Berthiol, F.; Doucet, H.; Santelli, M. *Eur. J. Org. Chem.* ***2004***, 1075.
[446] Kerins, F.; O'Shea, D. F. *J. Org. Chem.* ***2002***, *67*, 4968.
[447] Jia, C.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* ***1999***, *1*, 2097.

catalyst.[448] Arylsilanes were coupled to alkenes to give the styrene derivative using palladium acetate and an oxygen atmosphere,[449] for Bu_4NF and an iridium catalyst.[450]

In a related reaction, vinyltrifluoroborates $C{=}C\text{-}BF_3^+\ X^-$ (**12-28**), are coupled to aryl halides with a palladium catalyst to give the styrene derivative.[451]

In an unusual variation, an aryl compound bearing a tertiary alcohol substituent ($ArCMe_2OH$) reacted with aryl halides and a palladium catalyst to give the biaryl.[452] Benzoyl chloride was coupled to styrene to form PhCH=CHPh using a rhodium catalyst.[453] Benzoic acid was coupled to styrene to give the same type of product using a palladium catalyst and a diacyl peroxide.[454]

OS **VI**, 815; **VII**, 361; **81**, 42, 54, 63, 263

13-11 Homo-Coupling of Aryl Halides: The Ullmann Reaction

De-halogen-coupling

$$2\ \mathrm{ArI} \xrightarrow[\Delta]{\mathrm{Cu}} \mathrm{Ar{-}Ar}$$

The coupling of aryl halides with copper is called the *Ullmann reaction*.[455] The reaction is clearly related to **13-9**, but involves aryl copper intermediates. The reaction is of broad scope and has been used to prepare many symmetrical and unsymmetrical biaryls.[456] When a mixture of two different aryl halides is used, there are three possible products, but often only one is obtained. For example, picryl chloride and iodobenzene gave only 2,4,6-trinitrobiphenyl.[457] The best leaving group is iodo, and the reaction is most often done on aryl iodides, but bromides, chlorides, and even thiocyanates have been used.

The effects of other groups on the ring are unusual. The nitro group is strongly activating, but only in the ortho (not meta or para) position.[458] Both R and OR groups activate in all positions. Not only do OH, NH_2, NHR, and NHCOR inhibit

[448]Denmark, S.E.; Yans, S.-M. *Org. Lett.* ***2001***, *3*, 1749; Itami, K.; Nokami, T.; Yoshida, J.-I. *J. Am. Chem. Soc.* ***2001***, *123*, 5600; Hanamoto, T.; Kobayashi, T.; Kondo, M. *Synlett* ***2001***, 281; Hanamoto, T.; Kobayashi, T. *J. Org. Chem.* ***2003***, *68*, 6354. See also Taguchi, H.; Ghoroku, K.; Tadaki, M.; Tsubouchi, A.; Takeda, T. *J. Org. Chem.* ***2002***, *67*, 8450.

[449]Parrish, J.P.; Jung, Y.C.; Shin, S.I.; Jung, K.W. *J. Org. Chem.* ***2002***, *67*, 7127; Hirabayashi, K.; Ando, J.-i.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* ***2000***, *73*, 1409.

[450]Koike, T.; Du, X.; Sanada, T.; Danda, Y.; Mori, A. *Angew. Chem. Int. Ed.* ***2003***, *42*, 89.

[451]Molander, G. A.; Bernardi, C.R. *J. Org. Chem.* ***2002***, *67*, 8424.

[452]Terao, Y.; Wakui, H.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* ***2001***, *123*, 10407.

[453]Sugihara, T.; Satoh, T.; Miura, M.; Nomura, M. *Angew. Chem. Int. Ed.* ***2003***, *42*, 4672.

[454]Gooßen, L.J.; Paetzold, J.; Winkel, L. *Synlett* ***2002***, 1721.

[455]For reviews, see Fanta, P.E. *Synthesis* ***1974***, 9; Goshaev, M.; Otroshchenko, O.S.; Sadykov, A.S. *Russ. Chem. Rev.* ***1972***, *41*, 1046.

[456]For reviews of methods of aryl–aryl bond formation, see Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem, Int. Ed.* ***1990***, *29*, 977; Sainsbury, M. *Tetrahedron* ***1980***, *36*, 3327. Also see, Meyers, A.I.; Price, A. *J. Org. Chem.* ***1998***, *63*, 412.

[457]Rule, H.G.; Smith, F.R. *J. Chem. Soc.* ***1937***, 1096.

[458]Forrest, J. *J. Chem. Soc.* ***1960***, 592.

the reaction, as would be expected for aromatic nucleophilic substitution, but so do COOH (but not COOR), SO_2NH_2, and similar groups for which the reaction fails completely. These groups inhibit the coupling reaction by causing side reactions.

The mechanism is not known with certainty. It seems likely that it is basically a two-step process, similar to that of the Wurtz reaction (**10-56**), which can be represented schematically by

Step 1 ArI + Cu ⟶ ArCu

Step 2 ArCu + ArI ⟶ Ar—Ar

Organocopper compounds have been trapped by coordination with organic bases.[459] In addition, aryl copper compounds (ArCu) have been independently prepared and shown to give biaryls (Ar—Ar') when treated with aryl iodides Ar'I.[460] A similar reaction has been used for ring closure:[461]

An important alternative to the Ullmann method is the use of certain nickel complexes.[462] This method has also been used intramolecularly.[463] Aryl halides ArX can also be converted to Ar—Ar[464] by treatment with activated Ni metal,[465] with Zn and nickel complexes,[466] with aqueous alkaline sodium formate, Pd—C, and a phase-transfer catalyst,[467] and in an electrochemical process catalyzed by a nickel complex.[468]

An asymmetric Ullmann reaction has also been reported.[469]

OS **III**, 339; **V**, 1120.

[459]Lewin, A.H.; Cohen, T. *Tetrahedron Lett.* ***1965***, 4531.

[460]For examples, see Nilsson, M. *Tetrahedron Lett.* ***1966***, 675; Cairncross, A.; Sheppard, W.A. *J. Am. Chem. Soc.* ***1968***, *90*, 2186; Ullenius, C. *Acta Chem. Scand.* ***1972***, *26*, 3383; Mack, A.G.; Suschitzky, H.; Wakefield, B.J. *J. Chem. Soc. Perkin Trans. 1* ***1980***, 1682.

[461]Salfeld, J.C.; Baume, E. *Tetrahedron Lett.* ***1966***, 3365; Lothrop, W.C. *J. Am. Chem. Soc.* ***1941***, *63*, 1187.

[462]See, for example Semmelhack, M.F.; Helquist, P.M.; Jones, L.D. *J. Am. Chem. Soc.* ***1971***, *93*, 5908; Clark, F.R.S.; Norman, R.O.C.; Thomas, C.B. *J. Chem. Soc. Perkin Trans. 1* ***1975***, 121; Tsou, T.T.; Kochi, J.K. *J. Am. Chem. Soc.* ***1979***, *101*, 7547; Colon, I.; Kelsey, D.R. *J. Org. Chem.* ***1986***, *51*, 2627; Lourak, M.; Vanderesse, R.; Fort, Y.; Caubere, P. *J. Org. Chem.* ***1989***, *54*, 4840, 4844; Iyoda, M.; Otsuka, H.; Sato, K.; Nisato, N.; Oda, M. *Bull. Chem. Soc. Jpn.* ***1990***, *63*, 80. For a review of the mechanism, see Amatore, C.; Jutand, A. *Acta Chem. Scand.* ***1990***, *44*, 755.

[463]See, for example, Karimipour, M.; Semones, A.M.; Asleson, G.L.; Heldrich, F.J. *Synlett*, ***1990***, 525.

[464]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 82–84.

[465]Inaba, S.; Matsumoto, H.; Rieke, R.D. *Tetrahedron Lett.* ***1982***, *23*, 4215; Matsumoto, H.; Inaba, S.; Rieke, R.D. *J. Org. Chem.* ***1983***, *48*, 840; Chao, C.S.; Cheng, C.H.; Chang, C.T. *J. Org. Chem.* ***1983***, *48*, 4904.

[466]Takagi, K.; Hayama, N.; Sasaki, K. *Bull. Chem. Soc. Jpn.* ***1984***, *57*, 1887.

[467]Bamfield, P.; Quan, P.M. *Synthesis* ***1978***, 537.

[468]Meyer, G.; Rollin, Y.; Perichon, J. *J. Organomet. Chem.* ***1987***, *333*, 263.

[469]Nelson, T.D.; Meyers, A.I. *J. Org. Chem.* ***1994***, *59*, 2655; Nelson, T.D.; Meyers, A.I. *Tetrahedron Lett.* ***1994***, *35*, 3259.

The palladium-catalyzed coupling of aryl halides and other aryl substrates with aromatic rings containing a suitable leaving group is now well established. Other nucleophiles can be coupled to aryl halides.[470] The reaction has become so significant in organic chemistry that the transformations have been categorized as named reactions, and are discussed in Sections **13-14** and **13-15**.

13-12 Coupling of Aryl Compounds With Arylboronic acid Derivatives

Aryl-de-halogenation, and so on **Aryl-de-boronylation**, and so on

$$\text{Ar—Br} \quad + \quad \text{Ar}'\text{B(OH)}_2 \xrightarrow{\text{PdL}_4} \text{Ar—Ar}'$$

Aryl triflates react with arylboronic acids, $ArB(OH)_2$ (**12-28**),[471] or with organoboranes,[472] in the presence of a palladium catalyst,[473] to give the arene in what is called *Suzuki coupling* (or *Suzuki–Miyaura coupling*).[474] Aryl halides are commonly used, and aryl sulfonates have been used.[475] Even hindered boronic acids give good yields of the coupled product.[476] Homo-coupling of arylboronic acids has been reported.[477] Coupling of the alkynes to form a diyne (see **14-16**) can be a problem is some cases, although the aryl–alkyne coupling usually predominates.[478] Some aromatic compounds are so reactive that a catalyst may not be required. Using tetrabutylammonium bromide, phenylboronic acid was coupled to 2-bromofuran without a catalyst.[479]

[470]For a review, see Prim, D.; Campagne, J.-M.; Joseph, D.; Andrioletti, B. *Tetrahedron* ***2002***, *58*, 2041.

[471]Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* ***1981***, *11*, 513; Cheng, W.; Snieckus, V. *Tetrahedron Lett.* ***1987***, *28*, 5097; Badone, D.; Baroni, M.; Cardomone, R.; Ielmini, A.; Guzzi, U. *J. Org. Chem.* ***1997***, *62*, 7170. For a review of the synthesis and applications of heterocyclic boronic acids, see Torrell, E.; Brookes, P. *Synthesis* ***2003***, 469.

[472]Fürstner, A.; Seidel, G. *Synlett*, ***1998***, 161.

[473]For new palladium catalysts, see Wolfe, J.P.; Singer, R.A.; Yang, B.H.; Buchwald, S.L. *J. Am. Chem. Soc.* ***1999***, *121*, 9550; Bedford, R.B.; Cazin, C.S.J. *Chem. Commun.* ***2001***, 1540. For a review, see Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* ***2004***, 2419.

[474]Miyaura, N.; Suzuki, A. *Chem. Rev.* ***1995***, *95*, 2457. For a review of the Suzuki couping in synthesis see Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* ***2002***, *58*, 9633.

[475]Zim, D.; Lando, V.R.; Dupont, J.; Monteiro, A.L. *Org. Lett.* ***2001***, *3*, 3049; Zhang, W.; Chen, C.H.-T.; Lu, Y.; Nagashima, T. *Org. Lett.* ***2004***, *6*, 1473.

[476]Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* ***1992***, 207.

[477]Lei, A.; Zhang, X. *Tetrahedron Lett.* ***2002***, *43*, 2525; Parrish, J.P.; Jung, Y.C.; Floyd, R.J.; Jung, K.W. *Tetrahedron Lett.* ***2002***, *43*, 7899.

[478]See, for example, Chow, H.-F.; Wan, C.-W.; Low, K.-H.; Yeung, Y.-Y. *J. Org. Chem.* ***2001***, *66*, 1910.

[479]Bussolari, J.C.; Rehborn, D.C. *Org. Lett.* ***1999***, *1*, 965.

Different conditions (including additives and solvent) for the reaction have been reported,[480] often focusing on the palladium catalyst itself,[481] or the ligand.[482] Catalysts have been developed for deactivated aryl chlorides,[483] and nickel catalysts have been used.[484] Modifications to the basic procedure include tethering the aryl triflate[485] or the boronic acid[486] to a polymer, allowing a polymer-supported Suzuki reaction. Polymer-bound palladium complexes have also been used.[487,488] The reaction has been done neat on alumina,[489] and on alumina with microwave irradiation.[490] Suzuki coupling has also been done in ionic liquids,[491] in supercritical

[480]Littke, A.F.; Dai, C.; Fu, G.C. *J. Am. Chem. Soc.* ***2000***, *122*, 4020; Grasa, G.A.; Hillier, A.C.; Nolan, S.P. *Org. Lett.* ***2001***, *3*, 1077; Le Blond, C.R.; Andrews, A.T.; Sun, Y.; Sowa, Jr., J.R. *Org. Lett.* ***2001***, *3*, 1555; Savarin, C.; Liebeskind, L.S. *Org. Lett.* ***2001***, *3*, 2149; Liu, S.-Y.; Choi, M.J.; Fu, G.C. *Chem. Commun.* ***2001***, 2408; Li, G.-Y. *J. Org. Chem.* ***2002***, *67*, 3643; Fairlamb, I.J.S.; Kapdi, A.R.; Lee, A.F. *Org. Lett.* ***2004***, *6*, 4435; Oh, C.H.; Lim, Y.M.; You, C.H. *Tetrahedron Lett.* ***2002***, *43*, 4645; Tao, B.; Boykin, D.W. *Tetrahedron Lett.* ***2002***, *43*, 4955; Arentsen, K.; Caddick, S.; Cloke, G.N.; Herring, A.P.; Hitchcock, P.B. *Tetrahedron Lett.* ***2004***, *45*, 3511; Artok, L.; Bulat, H. *Tetrahedron Lett.* ***2004***, *45*, 3881; Arcadi, A.; Cerichelli, G.; Chiarini, M.; Correa, M.; Zorzan, D. *Eur. J. Org. Chem.* ***2003***, 4080.

[481]Pd/C has been reported as a reusable catalyst, see Sakurai, H.; Tsukuda, T.; Hirao, T. *J. Org. Chem.* ***2002***, *67*, 2721. For other recoverable or recyclable catalysts, see Nobre, S.M.; Wolke, S.I.; da Rosa, R.G.; Monteiro, A.L. *Tetrahedron Lett.* ***2004***, *45*, 6527; Blanco, B.; Mehdi, A.; Moreno-Mañas, M.; Pleixats, R.; Reyé, C. *Tetrahedron Lett.* ***2004***, *45*, 8789. A palladium catalyst was developed on nanoparticles, see Kogan V.; Aizenshtat, Z.; Popovitz-Biro, R.; Neumann, R. *Org. Lett.* ***2002***, *4*, 3529. For a colloid-metal catalyst, see Thathagar, M.B.; Beckers, J.; Rothenberg, G. *J. Am. Chem Soc.* ***2002***, *124*, 11858. Palladium (II)-sepiolite has been used, see Shimizu, K.-i.; Kan-no, T.; Kodama, T.; Hagiwara, H.; Kitayama, Y. *Tetrahedron Lett.* ***2002***, *43*, 5653. See Zhao, Y.; Zhou, Y.; Ma, D.; Liu, J.; Li, L.; Zhang, T.Y.; Zhang, H. *Org. Biomol. Chem.* ***2003***, *1*, 1643.

[482]Kataoka, N.; Shelby, Q.; Stambuli, J.P.; Hartwig, J.F. *J. Org. Chem.* ***2002***, *67*, 5553. Ligand-free catalyst systems have been developed, see Klingensmith, L.M.; Leadbeater, N.E. *Tetrahedron Lett.* ***2003***, *44*, 765; Deng, Y.; Gong, L.; Mi, A.; Li, H.; Jiang, Y. *Synthesis* ***2003***, 337. For a phosphine-free reaction, see Mino, T.; Shirae, Y.; Sakamoto, M.; Fujita, T. *Synlett* ***2003***, 882.

[483]Zapf, A.; Ehrentraut, A.; Beller, M. *Angew. Chem. Int. Ed.* ***2000***, *39*, 4153.

[484]Zim, D.; Monteiro, A.L. *Tetrahedron Lett.* ***2002***, *43*, 4009; Percec, V.; Golding, G.M.; Smidrkal, J.; Weichold, O. *J. Org. Chem.* ***2004***, *69*, 3447.

[485]Blettner, C.G.; König, W.A.; Stenzel, W.; Schotten, T. *J. Org. Chem.* ***1999***, *64*, 3885. For other reactions on solid support, see Franzén, R. *Can. J. Chem.* ***2000***, *78*, 957.

[486]Hebel, A.; Haag, R. *J. Org. Chem.* ***2002***, *67*, 9452.

[487]Inada, K.; Miyaura, N. *Tetrahedron* ***2000***, *56*, 8661, 8657; Uozumi, Y.; Nakai, Y. *Org. Lett.* ***2002***, *4*, 2997; Okamoto, K.; Akiyama, R.; Kobayashi, S. *Org. Lett.* ***2004***, *6*, 1987; Lin, C.-A.; Luo, F.-T. *Tetrahedron Lett.* ***2003***, *44*, 7565; Shieh, W.-C.; Shekhar, R.; Blacklock, T.; Tedesco, A. *Synth. Commun.* ***2002***, *32*, 1059.

[488]Wang, Y; Sauer, D.R. *Org. Lett.* ***2004***, *6*, 2793.

[489]Kabalka, G.W.; Pagni, R.M.; Hair, C.M. *Org. Lett.* ***1999***, *1*, 1423. The reaction has also been done on KF-alumina with microwave irradiation, see Basu, B.; Das, P.; Bhuiyan, Md.M.H.; Jha, S. *Tetrahedron Lett.* ***2003***, *44*, 3817.

[490]Villemin, D.; Caillot, F. *Tetrahdron Lett.* ***2001***, *42*, 639.

[491]In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate, with a nickel catalyst: Howarth, J.; James, P.; Dai, J. *Tetrahedron Lett.* ***2000***, *41*, 10319. In bbim BF_4, 1,3-di-*n*-butylimidazolium tetrafluoroborate, with ultrasound: Rajagopal, R.; Jarikote, D.V.; Srinivasan, K.V. *Chem. Commun.* ***2002***, 616. In dodecyltrihexylphosphonium chloride: McNulty, J.; Capretta, Wilson, J.; Dyck, J.; Adjabeny, G.; Robertson, A. *Chem. Commun.* ***2002***, 1986.

CO_2[492] (see p. 414), and in water with microwave irradiation[493] or in water with a palladium catalyst, air, and tetrabutylammonium fluoride.[494] A solvent free (neat) Suzuki reactions have been reported.[495] A variety of functional groups are compatible with Suzuki coupling, including $Ar_2P{=}O$,[496] CHO,[497] C=O of a ketone,[498] CO_2R,[499] cyclopropyl,[500] NO_2,[501] CN,[488] and halogen substituents.[502]

There are many structural variations of the reaction that give it enormous synthetic potential. Halogenated heteroaromatic compounds react. 2-Halopyridines react with arylboronic acids and a palladium catalyst to give 2-arylpyridines.[503] Other heterocycles have been similarly arylated.[504] 4-Pyridylboronic acids have been used.[505] The reaction of phenylboronic acid and a diallyl amide which contained a vinyl bromide, led to ring closure as well as incorporation of the phenyl group, give an *N*-tosylpyrrolidine with an exocyclic methylene unit.[506] Vinyl halides react with arylboronic acids to give alkenyl derivatives (vinyl arenes, C=C—Ar).[507] Alkylation can accompany arylation if alkyl halides are added, as in the conversion of iodobenzene to 2,6-dibutylbiphenyl.[508]

[492]Early, T.R.; Gordon, R.S.; Carroll, M.A.; Holmes, A.B.; Shute, R.E.; McConvey, I.F. *Chem. Commun.* ***2001***, 1966.

[493]Leadbeater, N.E.; Marco, M. *J. Org. Chem.* ***2003***, *68*, 888; Leadbeater, N.E.; Marco, M. *J. Org. Chem.* ***2003***, *68*, 5660; Leadbeater, N.E.; Marco, M. *Org. Lett.* ***2002***, *4*, 2973.

[494]Punna, S.; Díaz, D.D.; Finn, M.G. *Synlett* ***2004***, 2351.

[495]Nielsen, S.F.; Peters, D.; Axelsson, O. *Synth. Commun.* ***2000***, *30*, 3501; Kabalka, G.W.; Wang, L.; Pagni, R.M.; Hair, C.M.; Namboodiri, V. *Synthesis* ***2003***, 217.

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[497]Hesse, S.; Kirsch, G. *Synthesis* ***2001***, 755; Phan, N.T.S.; Brown, D.H.; Styring, P. *Tetrahedron Lett.* ***2004***, *45*, 7915.

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[500]Ma, H.-r.; Wang, X.-L.; Deng, M.-z. *Synth. Commun.* ***1999***, *29*, 2477.

[501]Tao, B.; Boykin, D.W. *J. Org. Chem.* ***2004***, *69*, 4330; Li, J.-H.; Liu, W.-J. *Org. Lett.* ***2004***, *6*, 2809; Widdowson, D.A.; Wilhelm, R. *Chem. Commun.* ***2003***, 578.

[502]Colacot, T.J.; Shea, H.A. *Org. Lett.* ***2004***, *6*, 3731; DeVasher, R.B.; Moore, L.R.; Shaughnessy, K.H. *J. Org. Chem.* ***2004***, *69*, 7919.

[503]Lohse, O.; Thevenin, P.; Waldvogel, E. *Synlett* ***1999***, 45; Gong, Y.; Pauls, H.W. *Synlett* ***2000***, 829; Navaro, O.; Kaur, H.; Mahjoor, P.; Nolan, S.P. *J. Org. Chem.* ***2004***, *69*, 3173. For a variation using hexamethyl ditin as an additive, see Zhang, N.; Thomas, L.; Wu, B. *J. Org. Chem.* ***2001***, *66*, 1500.

[504]Indole derivatives: at C2, Lane, B.S.; Sames, D. *Org. Lett.* ***2004***, *6*, 2897; Denmark, S.E.; Baird, J.D. *Org. Lett.* ***2004***, *6*, 3649. at C3, Liu, Y.; Gribble, G.W. *Tetrahedron Lett.* ***2000***, *41*, 8717. At C6, Allegretti, M.; Arcadi, A.; Marinelli, F.; Nicolini, L. *Synlett* ***2001***, 609. See also, Prieto, M.; Zurita, E.; Rosa, E.; Muñoz, L.; Lloyd-Williams, P.; Giralt, E. *J. Org. Chem.* ***2004***, *69*, 6812. Pyrimidines: Cooke, G.; de Cremiers, V.A.; Rotello, V.M.; Tarbit, B.; Vanderstraeten, P.E. *Tetrahedron* ***2001***, *57*, 2787. Furan was coupled to pyridine: Gauthier, Jr., D.R.; Szumigala Jr., R.H.; Dormer, P.G.; Armstrong III, J.D.; Volante, R.P.; Reider, P.J. *Org. Lett.* ***2002***, *4*, 375. Pyrimidines and Pyridines: Liebeskind, L.S.; Srogl, J. *Org. Lett.* ***2002***, *4*, 979; Quinolines: Wolf, C.; Lerebours, R. *J. Org. Chem.* ***2003***, *68*, 7551.

[505]Morris, G.A.; Nguyen, S.T. *Tetrahedron Lett.* ***2000***, *42*, 2093.

[506]Lee, C.-W.; Oh, K.S.; Kim, K.S. ; Ahn, K.H. *Org. Lett.* ***2000***, *2*, 1213.

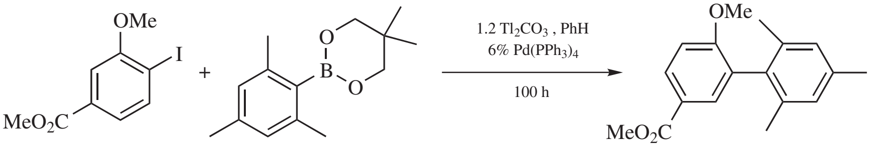
[507]Shen, W. *Synlett* ***2000***, 737.

[508]Catellani, M.; Motti, E.; Minari, M. *Chem. Commun.* ***2000*** 157. For a different approach using aryl halides having a phosphonate ester group, see Yin, J.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2000***, *122*, 12051.

Since many biaryls are chiral due to atropisomerism (see p. 147), the use of a chiral catalyst, and/or a chiral ligand can lead to enantioselectivity in the Suzuki coupling.[509]

Arylsulfonates can be coupled to aryl triflates using a palladium catalyst,[510] and arylboronic acids couple with aryl sulfonate esters.[511] Aryl boronic acids are coupled with aryl ammonium salts to give the biaryl, with a nickel catalyst.[512] Allylic acetates have been coupled to arylboronic acids using nickel bis(acetylacetonate) and diisobutylaluminum hydride.[513] Aryl halides couple with $ArB(IR'_2)$ species with a palladium catalyst.[514] Arylboronic acids couple with the phenyl group of Ph_2TeCl_2 with a palladium catalyst.[515] 3-Iodopyridine reacted with NaBPh and palladium acetate, with microwave irradiation, to give 3-phenylpyridine.[516] Tributyltinaryl compounds were coupled to the aryl group of $Ar_2I^+BF_4^-$ with a nickel catalyst.[517] Organoboranes are coupled to aryl halides with a palladium catalyst.[518] Aryl silanes can be coupled to aryl iodides using Ag_2O and a palladium catalyst,[519] and arylsiloxanes $ArSi(OR)_3$, are coupled to aryl halides with Bu_4NF and a palladium catalyst.[520]

Arylborates (**12-28**), $ArB(OR)_2$, can be used in place of the boronic acid. The coupling reaction of aryl iodide **23** with boronate **24**, for example, gave the biaryl.[521] Aryl and heteroarylboroxines (**25**) can be coupled to aryl halides using a palladium catalyst.[522]

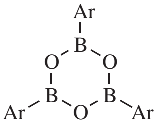


23 **24**

For a mechanistic viewpoint,[523] the Suzuki coupling proceeds via oxidative addition of areneboronic acids to give a Pd(0) species, followed by 1,2 arene migration to an electron-deficient palladium atom, eventually leading to very fast reductive

[509]Nishimura, T.; Araki, H.; Maeda, Y.; Uemura, S. *Org. Lett.* ***2003***, *5*, 2997; Navarro, O.; Kelly III, R.A.; Nolan, S.P. *J. Am. Chem. Soc.* ***2003***, *125*, 16194.
[510]Riggleman, S.; DeShong, P. *J. Org. Chem.* ***2003***, *68*, 8106.
[511]Using a nickel catalyst, Tang, Z.-Y.; Hu, Q.-S. *J. Am. Chem. Soc.* ***2004***, *126*, 3058.
[512]Blakey, S.B.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2003***, *125*, 6046.
[513]Chung, K.-G.; Miyake, Y.; Uemura, S. *J. Chem. Soc. Perkin Trans. 1* ***2000***, 15.
[514]Bumagin, N.A.; Tsarev, D.A. *Tetrahedron Lett.* ***1998***, *39*, 8155; Shen, W. *Tetrahedron Lett.* ***1997***, *38*, 5575.
[515]Kang, S.-K.; Hong, Y.-T.; Kim, D.-H.; Lee, S.-H. *J. Chem. Res.* (*S*) ***2001***, 283.
[516]Villemin, D.; Gómez-Escalonilla, M.J.; Saint-Clair, J.-F. *Tetrahedron Lett.* ***2001***, *42*, 635.
[517]Kang, S.-K.; Ryu, H.-C.; Lee, S.-W. *J. Chem. Soc. Perkin Trans. 1* ***1999***, 2661.
[518]Iglesias, B.; Alvarez, R.; de Lera, A.R. *Tetrahedron* ***2001***, *57*, 3125.
[519]Hirabayashi, K.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T. *Org. Lett.* ***1999***, *1*, 299.
[520]Mowery, M.E.; DeShong, P. *Org. Lett.* ***1999***, *1*, 2137.
[521]Chaumeil, H.; Signorella, S.; Le Drian, C. *Tetrahedron* ***2000***, *56*, 9655.
[522]Cioffi, C.L.; Spencer, W.T.; Richards, J.J.; Herr, R.J. *J. Org.Chem.* ***2004***, *69*, 2210.
[523]For a review, see Esponet, P.; Echavarren, A.M. *Angew. Chem. Int. Ed.* ***2004***, *43*, 4704.

elimination to afford biaryls.[524] Several intermediates of the oxidative coupling process have been identified by electrospray ionization mass spectrometry.[525]



25

A Suzuki-type coupling reaction has been reported involving acyl halides. When arylboronic acids were reacted with benzoyl chloride and $PdCl_2$, the product was the diaryl ketone.[526] This coupling reaction was also accomplished using a palladium(0) catalyst.[527] Cyclopropylboronic acids couple with benzoyl chloride, in the presence of Ag_2O and a palladium catalyst, to give the cyclopropyl ketone.[528] A nickel catalyst has been used,[529] and Ph_3P/Ni/C—BuLi has also been used.[530] Arylboronic acids have also been coupled to anhydrides,[531] and the methoxy group of anisole derivatives has been replaced with phenyl using phenylboronic acid and a ruthenium catalyst.[532]

In a related reaction, aryltrifluoroborates $PhBF_3^+ X^-$ (**12-28**), are coupled to aryl halides with a palladium catalyst to give the biaryl.[533]

OS **75**, 53, 61

The coupling reactions of alkylboronic acids are covered in **13-17**.

OS X, 102, 467; **81**, 89.

13-13 Aryl–Alkyne Coupling Reactions

Alkynyl-de-halogenation, and so on

$$ArI + RC{\equiv}CCu \longrightarrow ArC{\equiv}CR$$

When aryl halides react with copper acetylides to give 1-aryl alkynes, the reaction is known as *Stephens–Castro coupling*.[534] Both aliphatic and aromatic

[524]Moreno-Mañas, M.; Pérez, M.; Pleixats, R. *J. Org. Chem.* ***1996***, *61*, 2346.

[525]Aramendia, M.A.; Lafont, F.; Moreno-Mañas, M.; Pleixats, R.; Roglans, A. *J. Org. Chem.* ***1999***, *64*, 3592.

[526]Bumagin, N.A.; Korolev, D.N. *Tetrahedron Lett.* ***1999***, *40*, 3057.

[527]Haddach, M.; McCarthy, J.R. *Tetrahedron Lett.* ***1999***, *40* , 3109.

[528]Chen, H.; Deng, M.-Z. *Org. Lett.* ***2000***, *2*, 1649.

[529]Leadbeater, N.E.; Resouly, S.M. *Tetrahedron* ***1999***, *55*, 11889.

[530]Lipshutz, B.H.; Sclafani, J.A.; Blomgren, P.A. *Tetrahedron* ***2000***, *56*, 2139.

[531]Gooßen, L.J.; Ghosh, K. *Angew. Chem. Int. Ed.* ***2001***, *40*, 3458.

[532]Kakiuchi, F.; Usai, M.; Ueno, S.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* ***2004***, *126*, 2706.

[533]Batey, R.A.; Quach, T.D. *Tetrahedron Lett.* ***2001***, *42*, 9099; Barder, T.E.; Buchwald, S.L. *Org. Lett.* ***2004***, *6*, 2649; Molander, G. A.; Biolatto, B. *J. Org. Chem.* ***2003***, *68*, 4302. See Ito, T.; Iwai, T.; Mizuno, T.; Ishino, Y. *Synlett* ***2003***, 1435.

[534]Castro, C.E.; Stephens, R.D. *J. Org. Chem.* ***1963***, *28*, 2163; Stephens, R.D.; Castro, C.E. *J. Org. Chem.* ***1963***, *28*, 3313; Sladkov, A.M.; Ukhin, L.Yu.; Korshak, V.V. *Bull. Acad. Sci. USSR., Div. Chem. Sci.* ***1963***, 2043. For a review, see Sladkov, A.M.; Gol'ding, I.R. *Russ. Chem. Rev.* ***1979***, *48*, 868. For an improved procedure, see Bumagin, N.A.; Kalinovskii, I.O.; Ponomarov, A.B.; Beletskaya, I.P. *Doklad. Chem.* ***1982***, *265*, 262.

substituents can be attached to the alkyne unit, and a variety of aryl iodides has been used. Benzonitrile was shown to react with alkynyl zinc bromides, with a nickel catalyst and after electrolysis to give the diarylalkyne, where the cyano unit was replaced with an alkyne unit.[535]

$$\text{Ar-X} + \text{RC}{\equiv}\text{CH} \xrightarrow{\text{Pd(0)}} \text{Ar-C}{\equiv}\text{CR}$$

A palladium–catalyzed variation is also known in which an aryl halide reacts with a terminal alkyne to give 1-aryl alkynes is called the *Sonogashira coupling*.[536] Terminal aryl alkynes react with aryl iodides and palladium(0)[537] to give the corresponding diaryl alkyne.[538] As with all of the metal-catalyzed reactions in this chapter, work has been done to vary reaction conditions, including the catalyst,[539] the ligand, the solvent,[540] and additives.[541] copper-free palladium/DABCO catalysts have been used.[542] Aryl iodides are more reactive than aryl fluorides.[543] Alkynes can be coupled to heteroaromatic compounds via the heteroaryl halide.[544] The coupling reaction has been done neat, with microwave irradiation on KF-alumina,[545] and in aqueous polyethylene glycol.[546] The aryl–alkyne coupling has also been done in solution with microwave irradiation.[547] Sonogashira coupling

[535]Penney, J.M.; Miller, J.A. *Tetrahedron Lett.* ***2004***, *45*, 4989.

[536]Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* ***1975***, 4467; Sonogashira, K., in Trost, B.M.; Fleming, I.*Comprehensive Organic Synthesis*, Pergamon Press, NY, ***1991***, Vol. 3, Chapter 2.4; Rossi, R.; Carpita, A.; Bellina, F. *Org. Prep. Proceed. Int.* ***1995***, *27*, 127; Sonogashira, K., in Diederich, F.; Stang, P.J. *Metal–Catalyzed Cross–Coupling Reactions*, Wiley–VCH, NY, ***1998***, Chapter 5.

[537]Pd/C has also been used as a catalyst, see Novák, Z.; Szabó, A.; Répási, J.; Kotschy, A. *J. Org. Chem.* ***2003***, *68*, 3327.

[538]Böhm, V.P.W.; Herrmann, W.A. *Eur. J. Org. Chem.* ***2000***, 3679. For an example with a CuI catalyst, see Nakamura, K.; Okubo, H.; Yamaguchi, M. *Synlett* ***1999***, 549; Mori, A.; Shimada, T.; Kondo, T.; Sekiguchi, A. *Synlett* ***2001***, 649.

[539]Köllhofer, A.; Pullmann, T.; Plenio, H. *Angew. Chem. Int. Ed.* ***2003***, *42*, 1056; Feuerstein, M.; Berthiol, F.; Doucet, H.; Santelli, M. *Org. Biomol. Chem.* ***2003***, *1*, 2235. For a reaction with a nickel catalyst, see Wang, L.; Li, P.; Zhang, Y. *Chem. Commun.* ***2004***, 514; Hundertmark, T.; Littke, A.F.; Buchwald, S.L.; Fu, G.C. *Org. Lett.* ***2000***, *2*, 1729.

[540]The reaction has been done in aqueous media, see Bhattacharya, S.; Sengupta, S. *Tetrahedron Lett.* ***2004***, *45*, 8733.

[541]See Soheili, A.; Albaneze-Walker, J.; Murry, J.A.; Dormer, P.G.; Hughes, D.L. *Org. Lett.* ***2003***, *5*, 4191; Sakai, N.; Annaka, K.; Konakahara, T. *Org. Lett.* ***2004***, *6*, 1527; Leadbeater, N.E.; Tominack, B.J. *Tetrahedron Lett.* ***2003***, *44*, 8653; Djakovitch, L.; Rollet, P. *Tetrahedron Lett.* ***2004***, *45*, 1367; Hierso, J.-C.; Fihri, A.; Amardeil, R.; Meunier, P.; Doucet, H.; Santelli, M.; Ivanov, V. V. *Org. Lett.* ***2004***, *6*, 3473.

[542]See Li, J.-H.; Zhang, X.-D.; Xie, Y.-X. *Synthesis* ***2005***, 804.

[543]See, for example, Mio, M.J.; Kopel, L.C.; Braun, J.B.; Gadzikwa, T.L.; Hull, K..; Brisbois, R.G.; Markworth, C.J.; Grieco, P.A. *Org. Lett.* ***2002***, *4*, 3199.

[544]Elangovan, A.; Wang, Y.-H.; Ho, T.-I. *Org. Lett.* ***2003***, *5*, 1841; García, D.; Cuadro, A.M.; Alvarez-Builla, J.; Vaquero, J.J. *Org. Lett.* ***2004***, *6*, 4175; Wolf, C.; Lerebours, R. *Org. Biomol. Chem.* ***2004***, *2*, 2161.

[545]Kabalka, G.W.; Wang, L.; Namboodiri, V.; Pagni, R.M. *Tetrahedron Lett.* ***2000***, *41*, 5151.

[546]Leadbeater, N.E.; Marco, M.; Tominack, B.J. *Org. Lett.* ***2003***, *5*, 3919.

[547]Erdélyi, M.; Gogoll, A. *J. Org. Chem.* ***2001***, *66*, 4165; Appukkuttan, P.; Dehaen, W.; van der Eyken, E. *Eur. J. Org. Chem.* ***2003***, 4713.

was reported on microbeads,[548] with nanoparticulate nickel powder,[549] and the aryl iodide was tethered to a polymer for a solid-state reaction that included the use of microwave irradiation, and cleavage from the polymer using trifluoroacetic acid.[550] Polymer supported catalysts are known.[551] Conversion of 1-lithioalkynes to the corresponding alkynyl zinc reagent allows coupling with aryl iodides when a palladium catalyst is used.[552] Coupling with alkynyl tin compounds is also known.[553] The 1-lithioalkyne was directly coupled to aryl bromides in the presence of $B(OiPr)_3$ and a palladium catalyst,[554] where an alkynylboronic acid was generated *in situ*.

A variation was reported with environmental importance, where the triphenylphosphine by-product was scavenged by addition of Merrifield resin.[555] A copper-free Sonogashira coupling has been reported, in triethylamine[556] and in an ionic liquid.[557] A copper and amine-free reaction was reported in normal solvents, such as THF.[558] An interesting example of the versatility of the coupling reaction is the coupling of propargyl bromide and an aryl iodide, in the presence of an amine, giving the aryl aminomethylalkyne.[559] The coupling of 4-chloroacetophenone with 1-phenylethyne shows that the carbonyl group is compatible with this reaction.[560]

Diaryliodonium salts react with terminal alkynes to give the phenyl alkyne.[561] A variation couples the phenyl group of $Ph_2I^+OTf^-$ with an en-yne using a palladium catalyst.[562] Aryl sulfonate esters can be coupled to terminal alkynes using a palladium catalyst in polymethylhydrosiloxane.[563] Aryl halides are coupled to alkynyltrifluoroborates ($R{-}C{\equiv}C{-}BF_3K$, **12-28**) using a palladium catalyst.[564] The boron trifluoride induced palladium-catalyzed cross-coupling reaction of 1-aryltriazenes with areneboronic acids has been reported.[565]

A variation of this aryl–alkyne coupling reaction reacted methylthioalkynes ($R{-}C{\equiv}C{-}SMe$) with arylboronic acids and a palladium catalyst to give the aryl alkyne ($R{-}C{\equiv}C{-}Ar$).[566] 1-Trialkylsilylalkynes ($R_3Si{-}C{\equiv}C{-}R'$) were coupled

[548]Liao, Y.; Fathi, R.; Reitman, M.; Zhang, Y.; Yang, Z. *Tetrahedron Lett.* ***2001***, *42*, 1815; Gonthier, E.; Breinbauer, R. *Synlett* ***2003***, 1049.

[549]Wang, M.; Li, P.; Wang, L. *Synth. Commun.* ***2004***, *34*, 2803.

[550]Erdélyi, M.; Gogoll, A. *J. Org. Chem.* ***2003***, *68*, 6431.

[551]Lin, C.-A.; Luo, F.-T. *Tetrahedron Lett.* ***2003***, *44*, 7565.

[552]Anastasia, L.; Negishi, E. *Org. Lett.* ***2001***, *3*, 3111.

[553]See Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* ***2004***, *6*, 2821.

[554]Castanet, A.-S.; Colobert, F.; Schlama, T. *Org. Lett.* ***2000***, *2*, 3559.

[555]Lipshutz, B.H.; Blomgren, P.A. *Org. Lett.* ***2001***, *3*, 1869.

[556]Méry, D.; Heuzé, K.; Astruc, D. *Chem. Commun.* ***2003***, 1934.

[557]In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Fukuyama, T.; Shinmen, M.; Nishitani, S.; Sato, M.; Ryu, I. *Org. Lett.* ***2002***, *4*, 1691; Park, S.B.; Alper, H. *Chem. Commun.* ***2004***, 1306.

[558]Cheng, J.; Sun, Y.; Wang, F.; Guo, M.; Xu, J.-H.; Pan, Y.; Zhang, Z. *J. Org. Chem.* ***2004***, *69*, 5428; Urgaonkar, S.; Verkade, J.G. *J. Org. Chem.* ***2004***, *69*, 5752.

[559]Olivi, N.; Spruyt, P.; Peyrat, J.-F.; Alami, M.; Brion, J.-D. *Tetrahedron Lett.* ***2004***, *45*, 2607.

[560]Feuerstein, M.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* ***2004***, *45*, 8443.

[561]Kang, S.-K.; Yoon, S.-K.; Kim, Y.-M. *Org. Lett.* ***2001***, *3*, 2697.

[562]Radhakrishnan, U.; Stang, P.J. *Org. Lett.* ***2001***, *3*, 859.

[563]Gallagher, W.P.; Maleczka, Jr., R.E. *J. Org. Chem.* ***2003***, *68*, 6775.

[564]Molander, G.A.; Katona, B.W.; Machrouhi, F. *J. Org. Chem.* ***2002***, *67*, 8416.

[565]Saeki, T.; Son, E.-C.; Tamao, K. *Org.Lett.* ***2004***, *6*, 617.

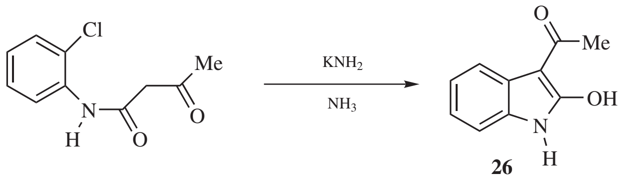
[566]Savarin, C.; Srogl, J.; Liebeskind, L.S. *Org. Lett.* ***2001***, *3*, 91.

to aryl iodides using a palladium catalyst.[567] A triphenylstibine, $Ph_3Sb(OAc)_2$, was used to transfer a phenyl group to the alkyne carbon of PhC≡$CSiMe_3$, using palladium and CuI catalysts.[568] Aryl iodides were also coupled to lithium alkynyl borate complexes, Li[R—C≡C—B(OR′)$_3$], to give the aryl alkyne.[569] Note that diphenylethyne was prepared from bromobenzene and 2-chloro-1-bromoethane using KOH, 18-crown-6 and a palladium catalyst.[570]

13-14 Arylation at a Carbon Containing an Active Hydrogen

Bis(ethoxycarbonyl)methyl-de-halogenation, and so on

The arylation of compounds of the form ZCH_2Z' is analogous to **10-67**, where Z is as defined as an electron withdrawing group (ester, cyano, sulfonyl, etc.). Activated aryl halides generally give good results.[571] Even unactivated aryl halides can be employed if the reaction is carried out in the presence of a strong base, such as $NaNH_2$[572] or LDA. Compounds of the form ZCH_2Z', even simple ketones[573] and carboxylic esters have been arylated in this manner. The reaction with unactivated halides proceeds by the benzyne mechanism and represents a method for extending the malonic ester (and similar) syntheses to aromatic compounds. The base performs two functions: it removes a proton from ZCH_2Z' and catalyzes the benzyne mechanism. The reaction has been used for ring closure, as in the formation of **26**.[574]



26

[567]Chang, S.; Yang, S.H.; Lee, P.H. *Tetahedron Lett.* ***2001***, *42*, 4833; Kabalka, G.W.; Wang, L.; Pagni, R.M. *Tetrahedron* ***2001***, *57*, 8017; Denmark, S.E.; Tymonko, S.A. *J. Org. Chem.* ***2003***, *68*, 9151.
[568]Kang, S.-K.; Ryu, H.-C.; Hong, Y-T. *J. Chem. Soc. Perkin Trans. 1* ***2001***, 736.
[569]Oh, C.H.; Jung, S.H. *Tetrahedron Lett.* ***2000***, *41*, 8513.
[570]Abele, E.; Abele, R.; Arsenyan, P.; Lukevics, E. *Tetrahedron Lett.* ***2003***, *44*, 3911.
[571]There is evidence for both the S_NAr mechanism (see Leffek, K.T.; Matinopoulos-Scordou, A.E. *Can. J. Chem.* ***1977***, *55*, 2656, 2664) and the $S_{RN}1$ mechanism (see Zhang, X.; Yang, D.; Liu, Y.; Chen, W.; Cheng, J. *Res. Chem. Intermed.* ***1989***, *11*, 281).
[572]Leake, W.W.; Levine, R. *J. Am. Chem. Soc.* ***1959***, *81*, 1169, 1627.
[573]For example, see Caubere, P.; Guillaumet, G. *Bull. Soc. Chim. Fr.* ***1972***, 4643, 4649.
[574]Bunnett, J.F.; Kato, T.; Flynn, R.; Skorcz, J.A. *J. Org. Chem.* ***1963***, *28*, 1. For reviews, see Biehl, E.R.; Khanapure, S.P. *Acc. Chem. Res.* ***1989***, *22*, 275; Hoffmann, R.W. *Dehydrobenzene and Cycloalkynes*, Academic Press, NY, ***1967***, pp. 150–164. See also, Kessar, S.V. *Acc. Chem. Res.* ***1978***, *11*, 283.

The coupling of active methylene compounds and unactivated aryl halides can also be done with copper halide catalysts[93] (the *Hurtley reaction*).[575] A palladium catalyst can be used for the coupling of malonate esters with unactivated aryl halides.[576] Bis(sulfones), $CH_2(SO_2Ar)_2$, react with aryl halides in the presence of a palladium catalyst.[577] Similar coupling was accomplished with $CH_2(CN)_2$ and a nickel catalyst.[578] Malonic and β-keto esters can be arylated at the α-carbon in high yields by treatment with aryllead tricarboxylates [$ArPb(OAc)_3$],[579] and with triphenylbismuth carbonate (Ph_3BiCO_3)[580] and other bismuth reagents.[581] In a related process, manganese(III) acetate was used to convert a mixture of ArH and ZCH_2Z' to ArCHZZ′.[582]

The reaction of the enolate anions ketones and aldehydes, generated *in situ* by addition of a suitable base, with aryl halides can be accomplished by treatment with a palladium catalyst.[583] Formation of an enolate anion of a conjugated ketone (cyclohexenone) via reaction with LDA (see p. 389), in the presence of Ph_3BiCl_2, leads to the α-phenyl conjugated ketone (6-phenylcyclohex-2-enone).[584] An ester reacted with $TiCl_4$ and *N,N*-dimethylanline to give the para-substitution product. (Me_2N—Ar—$CHRCO_2Et$).[585] The enolate anion of lactams will react with aryl halides in the presence of a palladium catalyst go via the 3-aryl lactam.[586] When the enolate anion of a ketone is generated in the presence of a palladium catalyst and a chiral phosphine ligand, the α-aryl ketone is formed with good enantioselectivity.[587]

Compounds of the form CH_3Z can be arylated by treatment with an aryl halide in liquid ammonia containing Na or K, as in the formation of **27** and **28**.[588]

[575]See Bruggink, A.; McKillop, A. *Tetrahedron* ***1975***, *31*, 2607; McKillop, A.; Rao, D.P. *Synthesis* ***1977***, 759; Osuka, A.; Kobayashi, T.; Suzuki, H. *Synthesis* ***1983***, 67; Hennessy, E.J.; Buchwald, S.L. *Org. Lett.*, **2002**, 4, 269.

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[577]Kashin, A.N.; Mitin, A.V.; Beletskaya, I.P.; Wife, R. *Tetrahedron Lett.* ***2002***, *43*, 2539.

[578]Cristau, H.J.; Vogel, R.; Taillefer, M.; Gadras, A. *Tetrahedron Lett.* ***2000***, *41*, 8457.

[579]Elliott, G.I.; Konopelski, J.P.; Olmstead, M.M. *Org. Lett.* ***1999***, *1*, 1867, and Refs. 3–7 therein.

[580]For a review of the aryllead and arylbismuth, and related reactions, see Elliott, G.I.; Konopelski, J.P. *Tetrahedron* ***2001***, *57*, 5683; Abramovitch, R.A.; Barton, D.H.R.; Finet, J. *Tetrahedron* ***1988***, *44*, 3039.

[581]Barton, D.H.R.; Blazejewski, J.; Charpiot, B.; Finet, J.; Motherwell, W.B.; Papoula, M.T.B.; Stanforth, S.P. *J. Chem. Soc. Perkin Trans. 1* ***1985***, 2667; O'Donnell, M.J.; Bennett, W.D.; Jacobsen, W.N.; Ma, Y. *Tetrahedron Lett.* ***1989***, *30*, 3913.

[582]Citterio, A.; Santi, R.; Fiorani, T.; Strologo, S. *J. Org. Chem.* ***1989***, *54*, 2703; Citterio, A.; Fancelli, D.; Finzi, C.; Pesce, L.; Santi, R. *J. Org. Chem.* ***1989***, *54*, 2713.

[583]Uno, M.; Seto, K.; Ueda, W.; Masuda, M.; Takahashi, S. *Synthesis* ***1985***, 506; Kawatsura, M.; Hartwig, J.F. *J. Am. Chem. Soc.* ***1999***, *121*, 1473; Jørgensen, M.; Lee, S.; Liu, X.; Wolkowski, J.P.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2002***, *124*, 12557; Fox, J.M.; Huang, X.; Chieffi, A.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2000***, *122*, 1360. For a review, see Culkin, D.A.; Hartwig, J.F. *Acc. Chem. Res.* ***2003***, *36*, 234.

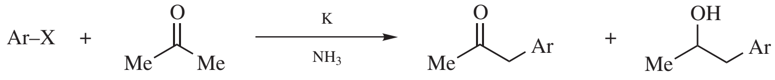
[584]Arnauld, T.; Barton, D.H.R.; Normat, J.-F.; Doris, E. *J. Org. Chem.* ***1999***, *64*, 6915.

[585]Periasamy, M.; KishoreBabu N.; Jayakumar, K.N. *Tetrahedron Lett.* ***2003***, *44*, 8939.

[586]Cossy, J.; de Filippis, A.; Pardo, D.G. *Org. Lett.* ***2003***, *5*, 3037.

[587]Hamada, T.; Chieffi, A.; Åhman, J.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2002***, *124*, 1261.

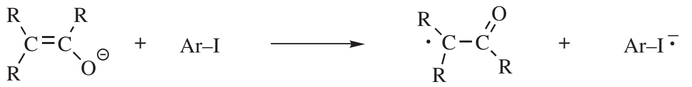
[588]Rossi, R.A.; Bunnett, J.F. *J. Org. Chem.* ***1973***, *38*, 3020; Bunnett, J.F.; Gloor, B.F. *J. Org. Chem.* ***1973***, *38*, 4156; ***1974***, *39*, 382.



27 **28**

When the solution is irradiated with near-UV light, but Na or K is omitted, the same products are obtained (though in different proportions).[589] In either case, other leaving groups can be used instead of halogens (e.g., NR_3^+, SAr) and the mechanism is the $S_{RN}1$ mechanism. Iron(II) salts have also been used to initiate this reaction.[590] The reaction can also take place without an added initiator. The reaction of 2-fluoroanisole and KHMDS, and 4 equivalents of 2-cyanopropane, leads to substitution of the fluorine atom by CMe_2CN.[591] A similar reaction as reported using a palladium catalyst.[592] Nitroethane was converted to 2-phenylnitroethane using bromobenzene and a palladium catalyst.[593]

Enolate ions of ketones react with PhI in the dark.[594] In this case, it has been suggested[595] that initiation takes place by formation of a radical, such as **29**.



29

This is an SET mechanism (see p. 444). The photostimulated reaction has also been used for ring closure.[596] In certain instances of the intermolecular reaction there is evidence that the leaving group exerts an influence on the product ratios, even when it has already departed at the time that product selection takes place.[597]

OS **V**, 12, 263; **VI**, 36, 873, 928; **VII**, 229.

13-15 Conversion of Aryl Substrates to Carboxylic Acids, Their Derivatives, Aldehydes, and Ketones[598]

[589]Hay, J.V.; Hudlicky, T.; Wolfe, J.F. *J. Am. Chem. Soc.* ***1975***, *97*, 374; Bunnett, J.F.; Sundberg, J.E. *J. Org. Chem.* ***1976***, *41*, 1702; Rajan, S.; Muralimohan, K. *Tetrahedron Lett.* ***1978***, 483; Rossi, R.A.; de Rossi, R.H.; Pierini, A.B. *J. Org. Chem.* ***1979***, *44*, 2662; Rossi, R.A.; Alonso, R.A. *J. Org. Chem.* ***1980***, *45*, 1239; Beugelmans, R. *Bull. Soc. Chim. Belg.* ***1984***, *93*, 547.

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[594]Scamehorn, R.G.; Hardacre, J.M.; Lukanich, J.M.; Sharpe, L.R. *J. Org. Chem.* ***1984***, *49*, 4881.

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[596]See Semmelhack, M.F.; Bargar, T. *J. Am. Chem. Soc.* ***1980***, *102*, 7765; Bard, R.R.; Bunnett, J.F. *J. Org. Chem.* ***1980***, *45*, 1546.

[597]Bard, R.R.; Bunnett, J.F.; Creary, X.; Tremelling, M.J. *J. Am. Chem. Soc.* ***1980***, *102*, 2852; Tremelling, M.J.; Bunnett, J.F. *J. Am. Chem. Soc.* ***1980***, *102*, 7375.

[598]For a review, see Weil, T.A.; Cassar, L.; Foà, M., in Wender, I.; Pino, P. *Organic Synthesis Via Metal Carbonyls*, Vol. 2, Wiley, NY, ***1977***, pp. 517–543.

Alkoxycarbonyl-de-halogenation, and so on

$$\text{ArX} + \text{CO} + \text{ROH} \xrightarrow[\text{Pd complex}]{\text{base}} \text{ArCOOR}$$

Carbonylation of aryl bromides and iodides with carbon monoxide, an alcohol, a base, and a palladium catalyst, give carboxylic esters. Even very sterically hindered alkoxides can be used to produce the corresponding ester.[599] The use of H_2O, RNH_2, or an alkali metal or calcium carboxylate[600] instead of ROH, gives the carboxylic acid,[601] amide,[602] or mixed anhydride, respectively.[603] Heating an aryl iodide, CO in ethanol and DBU, with a palladium catalyst, gave the ethyl ester of the aryl carboxylic acid.[604] A similar result was obtained when an aryl iodide was heated in ethanol with triethylamine, CO and Pd/C.[605] Ester formation via carbonylation was done is supercritical CO_2 (see p. 414).[606] With certain palladium catalysts, aryl chlorides[607] and aryl triflates[608] can also be substrates. Aryl carboxylic acids were also prepared from aryl iodides by heating in DMF with lithium formate, LiCl, acetic anhydride and a palladium catalyst.[609] A silica-supported palladium reagent has been used to convert iodobenzene to butyl benzoate, in the presence of CO and butanol.[610] 2-Chloropyridine was converted the butyl pyridine 2-carboxylate with this procedure.[611] Halogenated biaryls can be converted to the tricyclic ketone, 9-fluorenone, by an intramolecular carbonylation reaction with CO and a palladium catalyst.[612] A surrogate reagent used instead of CO is dicobalt octacarbonyl $CO_2(CO)_8$.[613] Aryl chlorides have been converted to carboxylic acids by an electrochemical synthesis,[614] and aryl iodides to aldehydes by treatment with

[599]Kubota, Y.; Hanaoka, T.-a.; Takeuchi, K.; Sugi, Y. *J. Chem. Soc. Chem. Commun.* ***1994***, 1553; Antebi, S.; Arya, P.; Manzer, L.E.; Alper, H. *J. Org. Chem.* ***2002***, *67*, 6623. For an interesting variation that generated a lactone ring, see Cho, C.S.; Baek, D.Y.; Shim, S.C. *J. Heterocyclic Chem.* ***1999***, *36*, 289.
[600]Pri-Bar, I.; Alper, H. *J. Org. Chem.* ***1989***, *54*, 36.
[601]For example, see Bumagin, N.A.; Nikitin, K.V.; Beletskaya, I.P. *Doklad. Chem.* ***1990***, *312*, 149.
[602]Lin, Y.-S.; Alper, H. *Angew. Chem. Int. Ed.* ***2001***, *40*, 779; Wan, Y.; Alterman, M.; Larhed, M.; Hallberg, A. *J. Org. Chem.* ***2002***, *67*, 6232. For another reagent that also gives amides, see Bumagin, N.A.; Gulevich, Yu.V.; Beletskaya, I.P. *J. Organomet. Chem.* ***1985***, *285*, 415.
[603]For a review, see Heck, R.F. *Palladium Reagents in Organic Synthesis*, Academic Press, NY, ***1985***, pp. 348–358.
[604]Ramesh, C.; Kubota, Y.; Miwa, M.; Sugi, Y. *Synthesis* ***2002***, 2171.
[605]Ramesh, C.; Nakamura, R.; Kubota, Y.; Miwa, M.; Sugi, Y. *Synthesis* ***2003***, 501.
[606]Albaneze-Walker, J.; Bazaral, C.; Leavey, T.; Dormer, P.G.; Murry, J.A. *Org. Lett.* ***2004***, *6*, 2097.
[607]Ben-David, Y.; Portnoy, M.; Milstein, D. *J. Am. Chem. Soc.* ***1989***, *111*, 8742.
[608]Cacchi, S.; Ciattini, P.G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* ***1986***, *27*, 3931; Kubota, Y.; Nakada, S.; Sugi, Y. *Synlett*, ***1998***, 183; Garrido, F.; Raeppel, S.; Mann, A.; Lautens, M. *Tetrahedron Lett.* ***2001***, *42*, 265.
[609]Cacchi, S.; Babrizi, G.; Goggiamani, A. *Org. Lett.* ***2003***, *5*, 4269.
[610]Cai, M.-Z.; Song, C.-S.; Huang, X. *J. Chem. Soc. Perkin Trans. 1*, ***1997***, 2273.
[611]Beller, M.; Mägerlein, W.; Indolese, A.F.; Fischer, C. *Synthesis* ***2001***, 1098.
[612]Campo, M.A.; Larock, R.C. *Org. Lett.* ***2000***, *2*, 3675.
[613]Brunet, J.; Sidot, C.; Caubere, P. *J. Org. Chem.* ***1983***, *48*, 1166. See also, Foà, M.; Francalanci, F.; Bencini, E.; Gardano, A. *J. Organomet. Chem.* ***1985***, *285*, 293; Kudo, K.; Shibata, T.; Kashimura, T.; Mori, S.; Sugita, N. *Chem. Lett.* ***1987***, 577.
[614]Heintz, M.; Sock, O.; Saboureau, C.; Périchon, J. *Tetrahedron* ***1988***, *44*, 1631.

CO, Bu_3SnH, and $NCCMe_2N{=}NCMe_2CN$ (AIBN).[615] Aryl ketones can be prepared from aryltrimethylsilanes $ArSiMe_3$ and acyl chlorides in the presence of $AlCl_3$.[616] Aryllithium and Grignard reagents react with iron pentacarbonyl to give aldehydes ArCHO.[617] The reaction of CO with aryllithium may occur by electron transfer.[618]

Aryl iodides are converted to unsymmetrical diaryl ketones on treatment with arylmercury halides and nickel carbonyl: $ArI + Ar'HgX + Ni(CO)_4 \rightarrow ArCOAr'$.[619] Aryl iodides are carbonylated to give the aryl alkyl ketone with CO and R_3In.[620] Arylthallium bis(trifluoroacetates), $ArTl(O_2CCF_3)_2$ (see **12-23**), can be carbonylated with CO, an alcohol, and a $PdCl_2$ catalyst to give esters.[621] Organomercury compounds undergo a similar reaction.[622] The aryllead reagent $PhPb(OAc)_3$, was converted to benzophenone using NaOMe, CO and a palladium catalyst.[623] Aryl iodides containing an ortho substituent with a β-cyano group that served as the source of a carbonyl group, was converted to a bicyclic ketone with a palladium catalyst at 130°C in aqueous DMF.[624]

Diaryl ketones can also be prepared by coupling aryl iodides with phenylboronic acid (**12-28**), in the presence of CO and a palladium catalyst.[625] This reaction has been extended to heteroaromatic systems, with the preparation of phenyl 4-pyridyl ketone from phenylboronic acid and 4-iodopyridine.[626] 2-Bromopyridine as coupled with phenylboronic acid, CO and a palladium catalyst to give phenyl 2-pyridyl ketone.[627] An interesting reaction treated a titanocycle (**30**) with CO to give the cyclobutanone.[628] Carbonylation of an alkyne and an aryl halide, with CO

[615]Ryu, I.; Kusano, K.; Masumi, N.; Yamazaki, H.; Ogawa, A.; Sonoda, N. *Tetrahedron Lett.* ***1990***, *31*, 6887.

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[617]Ryang, M.; Rhee, I.; Tsutsumi, S. *Bull. Chem. Soc. Jpn.* ***1964***, *37*, 341; Giam, C.; Ueno, K. *J. Am. Chem. Soc.* ***1977***, *99*, 3166; Yamashita, M.; Miyoshi, K.; Nakazono, Y.; Suemitsu, R. *Bull. Chem. Soc. Jpn.* ***1982***, *55*, 1663. For another method, see Gupton, J.T.; Polk, D.E. *Synth. Commun.* ***1981***, *11*, 571.

[618]Nudelman, N.S.; Doctorovich, F. *Tetrahedron* ***1994***, *50*, 4651.

[619]Rhee, I.; Ryang, M.; Watanabe, T.; Omura, H.; Murai, S.; Sonoda, N. *Synthesis* ***1977***, 776; Ryu, I.; Ryang, M.; Rhee, I.; Omura, H.; Murai, S.; Sonoda, N. *Synth. Commun.* ***1984***, *14*, 1175 and cited references. For other acylation reactions, see Tanaka, M. *Synthesis* ***1981***, 47; *Bull. Chem. Soc. Jpn.* ***1981***, *54*, 637; Bumagin, N.A.; Ponomarov, A.B.; Beletskaya, I.P. *Tetrahedron Lett.* ***1985***, *26*, 4819; Koga, T.; Makinouchi, S.; Okukado, N. *Chem. Lett.* ***1988***, 1141; Echavarren, A.M.; Stille, J.K. *J. Am. Chem. Soc.* ***1988***, *110*, 1557; Hatanaka, Y.; Hiyama, T. *Chem. Lett.* ***1989***, 2049.

[620]Lee, P.H.; Lee, S.W.; Lee, K. *Org. Lett.* ***2003***, *5*, 1103. With a palladium catalyst, see Pena, M.A.; Sestelo, J.P.; Sarandeses, L.A. *Synthesis* ***2003***, 780. For a reaction that used R_4InLi, see Lee, S.W.; Kee, K.; Seomoon, D.; Kim, S.; Kim, H.; Kim, H.; Shim, E.; Lee, M.; Lee, S.; Kim, S.; Lee, P.H. *J. Org. Chem.* ***2004***, *69*, 4852.

[621]Larock, R.C.; Fellows, C.A. *J. Am. Chem. Soc.* ***1982***, *104*, 1900.

[622]Baird Jr., W.C.; Hartgerink, R.L.; Surridge, J.H. *J. Org. Chem.* ***1985***, *50*, 4601.

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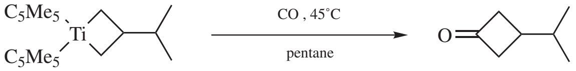
[627]Maerten, E.; Hassouna, F.; Couve-Bonnaire, S.; Mortreux, A.; Carpentiere, J.-F.; Castanet, Y. *Synlett* ***2003***, 1874.

[628]Carter, C.A.G.; Greidanus, G.; Chen, J.-X.; Stryker, J.M. *J. Am. Chem. Soc.* ***2001***, *123*, 8872.

and palladium and copper catalysts, gave the alkynyl ketone RC≡C(C=O)Ar.[629]



30

Note that seleno esters (ArCOSeAr) were prepared from aryl iodides, CO, $PhSeSnBu_3$, and a palladium catalyst.[630]

13-16 Arylation of Silanes

Silyl and Silyloxy-de-halogenation, and so on

$$\text{Ar–X} \quad + \quad \text{Ar}'\text{SiR}_2 \longrightarrow \text{Ar–SiR}_3$$

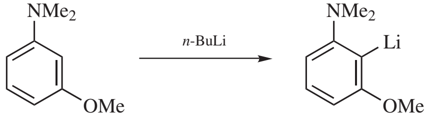
In the presence of transition-metal catalysts, such as palladium, trialkoxysilanes [$HSi(OR)_3$] react with aryl halides to give the corresponding arylsilane.[631] This transformation is an alternative to the Suzuki coupling (**13-10**).[632] A similar reaction was reported using a rhodium catalyst.[633] Arylsilanes can be coupled to aryl iodides in aqueous media.[634] Arylsilanes react with alkyl halides to give the corresponding arene, in the presence of a palladium catalyst.[635] Suzuki-type coupling using $Me_3SiSiMe_3$ leads to aryl silanes.[636]

An alternative approach reacts aryllithium reagents with siloxanes [$Si(OR)_4$], to give the aryl derivative $ArSi(OR)_3$.[637]

HYDROGEN AS LEAVING GROUP[638]

13-17 Alkylation and Arylation

Alkylation or Alkyl-de-hydrogenation, and so on



31 **32**

[629]Ahmed, M.S.M.; Mori, A. *Org. Lett.* ***2003***, *5*, 3057.

[630]Nishiyama, Y.; Tokunaga, K.; Kawamatsu, H.; Sonoda, N. *Tetrahedron Lett.* ***2002***, *43*, 1507.

[631]Manoso, A.S.; DeShong, P. *J. Org. Chem.* ***2001***, *66*, 7449.

[632]DeShong, P.; Handy, C.J.; Mowery, M.W. *Pure Appl. Chem.* ***2000***, *72*, 1655; Seganish, W.M.; DeShong, P. *Org. Lett.* ***2004***, *6*, 4379.

[633]Murata, M.; Ishikura, M.; Nagata, M.; Watanabe, S.; Masuda, Y. *Org. Lett.* ***2002***, *4*, 1843.

[634]Denmark, S.E.; Ober, M.H. *Org. Lett.* ***2003***, *5*, 1357.

[635]Mowery, M.E.; DeShong, P. *J. Org. Chem.* ***1999***, *64*, 3266; Lee, J.-y.; Fu, G.C. *J. Am. Chem. Soc.* ***2003***, *125*, 5616.

[636]Gooßen, L.J.; Ferwanah, A.-R.S. *Synlett* ***2000***, 1801.

[637]Manoso, A.S.; Ahn, C.; Soheili, A.; Handy, C.J.; Correia, R.; Seganish, W.M.; DeShong, P. *J. Org. Chem.* ***2004***, *69*, 8305.

[638]For reviews, see Chupakhin, O.N.; Postovskii, I.Ya. *Russ. Chem. Rev.* ***1976***, *45*, 454. For a review of reactivity and mechanism in these cases, see Chupakhin, O.N.; Charushin, V.N.; van der Plas, H.C. *Tetrahedron* ***1988***, *44*, 1.

The alkylation of aromatic rings was introduced, in part, in section **10-57**. The reaction of an aromatic ring with an organolithium reagent can give H—Li exchange to form an aryllithium. This reaction tends to be slow in the absence of diamine additives or if there are activating substituents on the aryl halide.[639] When heteroatom substituents are present as in **31**, however, the reaction is facile and the lithium goes into the 2 position (as in **32**).[640] This regioselectivity can be quite valuable synthetically, and is now known as *directed ortho metalation*[641] (see **10-57**). Lithiation reactions do not necessarily rely on a complex-induced proximity effect.[642] With TMEDA/*n*-butyllithium-mediate arene lithiation reactions, the viability of directive effects (complex-induced proximate effects) has been questioned,[643] although it is not clear if this extends to other systems (particularly when there is a strong coordinating group, such as carbamate).[644] The 2 position is much more acidic than the 3 position (see Table 8.1), but a negative charge at C-3 is in a more favorable position to be stabilized by the Li^+. Formation of the ortho arylmagnesium compound has been accomplished with bases of the form $(R_2N)_2Mg$.[645] Note that H—Li exchange can be faster than Cl—Li exchange. Treatment of 2-chloro-5-phenylpyridine with *tert*-butyllithium leads to lithiation on the phenyl ring rather than Li—Cl exchange, and subsequent treatment with dimethyl sulfate gave 2-chloro-5-(2-methylphenyl)pyridine.[646] Heteroaromatic rings do react, however. The reaction of 2-chloropyridine with 3 equivalents of butyllithium-$Me_2NCH_2CH_2OLi$ and then iodomethane gave 2-chloro-6-methylpyridine.[647] The reaction of *N*-triisopropylsilyl indole with *tert*-butyllithium and then iodomethane gave the 3-methyl derivative.[648] Furfural (furan 2-carboxaldehyde) reacts with aryl iodides in the presence of a palladium catalyst to give the 5-arylfuran 2-carboxaldehyde.[649]

Benzene, naphthalene, and phenanthrene have been alkylated with alkyllithium reagents, though the usual reaction with these reagents is **12-22**,[650] and Grignard reagents have been used to alkylate naphthalene.[651] The addition–elimination

[639]See, for example, Becht, J.-M.; Gissot, A.; Wagner, A.; Misokowski, C. *Tetrahedron Lett.* ***2004***, *45*, 9331.

[640]Slocum, D.W.; Jennings, C.A. *J. Org. Chem.* ***1976***, *41*, 3653. However, the regioselectivity can depend on reaction conditions: See Meyers, A.I.; Avila, W.B. *Tetrahedron Lett.* ***1980***, 3335.

[641]For a reviews of directed ortho metallation, see Snieckus, V. *Chem. Rev.* ***1990***, *90*, 879; Gschwend, H.W.; Rodriguez, H.R. *Org. React.* ***1979***, *26*, 1. See Green, L.; Chauder, B.; Snieckus, V. *J. Heterocylic Chem.* ***1999***, *36*, 1453. Also see Green, L.; Chauder, B.; Snieckus, V. *J. Heterocyclic Chem.* ***1999***, *36*, 1453. See Slocum, D.W.; Dietzel, P. *Tetrahedron Lett.* ***1999***, *40*, 1823.

[642]Chadwick, S.T.; Rennels, R.A.; Rutherford, J.L.; Collum, D.B. *J. Am. Chem. Soc.* ***2000***, *122*, 8640; Collum, D.B. *Acc. Chem. Res.* ***1992***, *25*, 448.

[643]Chadwick, S.T.; Rennels, R.A.; Rutherford, J.L.; Collum, D.B. *J. Am. Chem. Soc.* ***2000***, *122*, 8640.

[644]Hay, D. R.; Song, Z.; Smith, S.G.; Beak, P. *J. Am. Chem. Soc.* ***1988***, *110*, 8145.

[645]Eaton, P.E.; Lee, C.; Xiong, Y. *J. Am. Chem. Soc.* ***1989***, *111*, 8016.

[646]Fort, Y. Rodriguez, A.L. *J. Org. Chem.* ***2003***, *68*, 4918.

[647]Choppin, S. Gros, P.; Fort, Y. *Org. Lett.* ***2000***, *2*, 803.

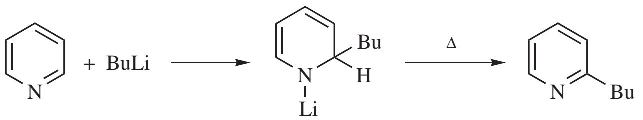
[648]Matsuzono, M.; Fukuda, T.; Iwao, M. *Tetrahedron Lett.* ***2001***, *42*, 7621.

[649]McClure, M.S.; Glover, B.; McSorley, E.; Millar, A.; Osterhout, M.H.; Roschangar, F. *Org. Lett.* ***2001***, *3*, 1677.

[650]Eppley, R.L.; Dixon, J.A. *J. Am. Chem. Soc.* ***1968***, *90*, 1606.

[651]Bryce-Smith, D.; Wakefield, B.J. *Tetrahedron Lett.* ***1964***, 3295.

mechanism apparently applies in these cases too. A protected form of benzaldehyde (protected as the benzyl imine) has been similarly alkylated at the *ortho*-position with butyllithium.[652]



The alkylation of heterocyclic nitrogen compounds[653] with alkyllithium reagents is called *Ziegler alkylation*. Aryllithium reagents give arylation. The reaction occurs by an addition–elimination mechanism and the adduct can be isolated.[654] Upon heating of the adduct, elimination of LiH occurs and an alkylated product is obtained. With respect to the 2-carbon the first step is the same as that of the S_NAr mechanism. The difference is that the unshared pair of electrons on the nitrogen combines with the lithium, so the extra pair of ring electrons has a place to go: it becomes the new unshared pair on the nitrogen. Heteroaromatic compounds can be alkylated. Pyrrole, for example, reacts with an allylic halide and zinc to give primarily the 3-substituted pyrrole.[655]

Mercuration of aromatic compounds[656] can be accomplished with mercuric salts, most often $Hg(OAc)_2$[657] to give ArHgOAc. This is ordinary electrophilic aromatic substitution and takes place by the arenium ion mechanism (p. 657).[658] Aromatic compounds can also be converted to arylthallium bis(trifluoroacetates) $ArTl(OOCCF_3)_2$ by treatment with thallium(III) trifluoroacetate[659] in trifluoroacetic acid.[660] These arylthallium compounds can be converted to phenols, aryl iodides or fluorides (**12-31**), aryl cyanides (**12-34**), aryl nitro compounds,[661] or aryl esters

[652]Flippin, L.A.; Carter, D.S.; Dubree, N.J.P. *Tetrahedron Lett.* ***1993***, *34*, 3255.

[653]For a review of substitution by carbon groups on a nitrogen heterocycle, see Vorbrüggen, H.; Maas, M. *Heterocycles*, ***1988***, *27*, 2659. For a related review, see Comins, D.L.; O'Connor, S. *Adv. Heterocycl. Chem.* ***1988***, *44*, 199.

[654]See, for example, Armstrong, D.R.; Mulvey, R.E.; Barr, D.; Snaith, R.; Reed, D. *J. Organomet. Chem.* ***1988***, *350*, 191.

[655]Yadav, J.S.; Reddy, B.V.S.; Reddy, P.M.; Srinivas, Ch. *Tetrahedron Lett.* ***2002***, *43*, 5185.

[656]For reviews, see Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, ***1985***, pp. 60–97; Wardell, J.L., in Zuckerman, J.J. *Inorganic Reactions and Methods*, Vol. 11, VCH, NY, ***1988***, pp. 308–318.

[657]For a review of mercuric acetate, see Butler, R.N., in Pizey, J.S. *Synthetic Reagents*, Vol. 4, Wiley, NY, ***1981***, pp. 1–145.

[658]For a review, see Taylor, R., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, vol. 13, Elsevier, NY, ***1972***, pp. 186–194. An alternative mechanism, involving radial cations, has been reported: Courtneidge, J.L.; Davies, A.G.; McGuchan, D.C.; Yazdi, S.N. *J. Organomet. Chem.* ***1988***, *341*, 63.

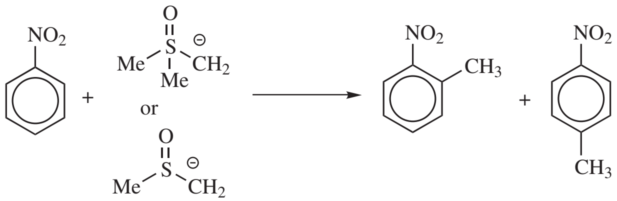
[659]For a review of this reagent, see Uemura, S., in Pizey, J.S. *Synthetic Reagents*, Vol. 5, Wiley, NY, ***1983***, pp. 165–241.

[660]Taylor, E.C.; Kienzle, F.; McKillop, A. *Org. Synth.* ***VI***, 826; Taylor, E.C.; Katz, A.H.; Alvarado, S.I.; McKillop, A. *J. Organomet. Chem.* ***1985***, *285*, C9. For reviews, see Usyatinskii, A.Ya.; Bregadze, V.I. *Russ. Chem. Rev.* ***1988***, *57*, 1054; Uemura, S., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 4, Wiley, NY, pp. 473–538.

[661]Uemura, S.; Toshimitsu, A.; Okano, M. *Bull. Chem. Soc. Jpn.* ***1976***, *49*, 2582.

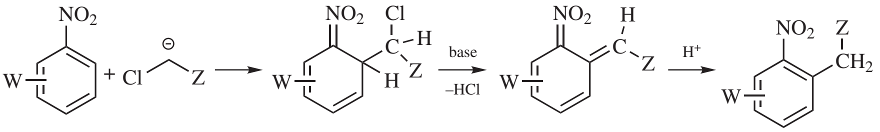
(**12-33**). The mechanism of thallation appears to be complex, with electrophilic and electron-transfer mechanisms both taking place.[662] Transient metalated aryl complexes can be formed that react with another aromatic compound. Aryl iodides reacted with benzene to form a biaryl in the presence of an iridium catalyst.[663] Aniline derivatives reacted with $TiCl_4$ to give the para-homo coupling product (R_2N—Ar—Ar—NR_2).[664]

Aromatic nitro compounds can be methylated with dimethyloxosulfonium methylid[665] or the methylsulfinyl carbanion (obtained by treatment of DMSO with a strong base):[666]



The latter reagent also methylates certain heterocyclic compounds (e.g., quinoline) and certain fused aromatic compounds (e.g., anthracene, phenanthrene).[666,667] The reactions with the sulfur carbanions are especially useful, since none of these substrates can be methylated by the Friedel–Crafts procedure (**11-10**). It has been reported[668] that aromatic nitro compounds can also be alkylated, not only with methyl but with other alkyl and substituted alkyl groups as well, in ortho and para positions, by treatment with an alkyllithium compound (or, with lower yields, a Grignard reagent), followed by an oxidizing agent, such as Br_2 or DDQ (p. 1710).

A different kind of alkylation of nitro compounds uses carbanion nucleophiles that have a chlorine at the carbanionic carbon. The following process takes place:[669]



[662]Lau, W.; Kochi, J.K. *J. Am. Chem. Soc.* ***1984***, *106*, 7100; ***1986***, *108*, 6720.
[663]Fujita, K.-i.; Nonogawa, M.; Yamaguchi, R. *Chem. Commun.* ***2004***, 1926.
[664]Periasamy, M.; Jayakumar, K.N.; Bharathi, P. *J. Org. Chem.* ***2000***, *65*, 3548.
[665]Traynelis, V.J.; McSweeney, J.V. *J. Org. Chem.* ***1966***, *31*, 243.
[666]Russell, G.A.; Weiner, S.A. *J. Org. Chem.* ***1966***, *31*, 248.
[667]Argabright, P.A.; Hofmann, J.E.; Schriesheim, A. *J. Org. Chem.* ***1965***, *30*, 3233; Trost, B.M. *Tetrahedron Lett.* ***1966***, 5761; Yamamoto, Y.; Nisimura, T.; Nozaki, H. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 541.
[668]Kienzle, F. *Helv. Chim. Acta* ***1978***, *61*, 449.
[669]In some cases, the intermediate bearing the CHCl(Z) unit has been isolated: Stahly, G.P.; Stahly, B.C.; Maloney, J.R. *J. Org. Chem.* ***1988***, *53*, 690.

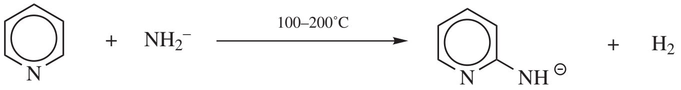
This type of process is called *vicarious nucleophilic substitution of hydrogen*.[670] The Z group is electron -withdrawing (e.g., SO_2R, SO_2OR, SO_2NR_2, COOR, or CN); it stabilizes the negative charge. The carbanion attacks the activated ring ortho or para to the nitro group.[671] Hydride ion H^- is not normally a leaving group, but in this case the presence of the adjacent Cl allows the hydrogen to be replaced. Hence, Cl is a "vicarious" leaving group. Other leaving groups have been used (e.g., OMe, SPh), but Cl is generally the best. Many groups W in ortho, meta, or para positions do not interfere. The reaction is also successful for di- and trinitro compounds, for nitronaphthalenes,[672] and for many nitro heterocycles. Z—$^{\ominus}$CR–Cl may also be used.[673] When Br_3C^- or Cl_3C^- is the nucleophile the product is $ArCHX_2$, which can easily be hydrolyzed to ArCHO.[674] This is therefore an indirect way of formylating an aromatic ring containing one or more NO_2 groups, which cannot be done by any of the formylations mentioned in Chapter 11 (**11-1–11-18**).

Replacement of an amino group is possible. When aniline derivatives were treated with allyl bromide and *tert*-butyl nitrite (*t*-BuONO), the aryl–allyl coupling product was formed ($Ar{-}NH_2 \rightarrow Ar{-}CH_2CH{=}CH_2$).[675]

For the introduction of CH_2SR groups into phenols, see **11-23**. See also **14-19**.
OS **II**, 517.

13-18 Amination of Nitrogen Heterocycles

Amination or **Amino-de-hydrogenation**



Pyridine and other heterocyclic nitrogen compounds can be aminated with alkali-metal amides in a process called the *Chichibabin reaction*.[676] The attack is always in the 2 position unless both such positions are filled, in which case the 4 position is attacked. Substituted alkali-metal amides (e.g., RNH^- and R_2N^-) have also been used. The mechanism is probably similar to that of **13-17** The existence of intermediate ions, such as **33**

[670] Goliński, J.; Mąkosza, M. *Tetrahedron Lett.* ***1978***, 3495. For reviews, see Mąkosza, M. *Synthesis* ***1991***, 103; *Russ. Chem. Rev.* ***1989***, *58*, 747; Mąkosza, M.; Winiarski, J. *Acc. Chem. Res.* ***1987***, *20*, 282.

[671] For a discussion of the mechanism, of vicarious nucleophilic aromatic substitution, see Mąkosza, M.; Lemek, T.; Kwast, A.; Terrier, F. *J. Org. Chem.* ***2002***, *67*, 394.

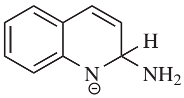
[672] Mąkosza, M.; Danikiewicz, W.; Wojciechowski, K. *Liebigs Ann. Chem.* ***1987***, 711.

[673] See Mudryk, B.; Mąkosza, M. *Tetrahedron* ***1988***, *44*, 209.

[674] Mąkosza, M.; Owczarczyk, Z. *J. Org. Chem.* ***1989***, *54*, 5094. See also, Mąkosza, M.; Winiarski, J. *Chem. Lett.* ***1984***, 1623.

[675] Ek, F.; Axelsson, O.; Wistrand, L.-G.; Frejd, T. *J. Org. Chem.* ***2002***, *67*, 6376.

[676] For reviews, see Vorbrüggen, H. *Adv. Heterocycl. Chem.* ***1990***, *49*, 117; McGill, C.K.; Rappa, A. *Adv. Heterocycl. Chem.* ***1988***, *44*, 1; Pozharskii, A.F.; Simonov, A.M.; Doron'kin, V.N. *Russ. Chem. Rev.* ***1978***, *47*, 1042.



33

(from quinoline) has been demonstrated by NMR spectra.[677] A pyridyne type of intermediate was ruled out by several observations including the facts that 3-ethylpyridine gave 2-amino-3-ethylpyridine[678] and that certain heterocycles that cannot form an aryne could nevertheless be successfully aminated. Nitro compounds do not give this reaction,[679] but they have been aminated (ArH $\rightarrow$ $ArNH_2$ or ArNHR) via the vicarious substitution principle (see **13-17**), using 4-amino- or 4-alkylamino-1,2,4-triazoles as nucleophiles.[680] The vicarious leaving group in this case is the triazole ring. Note, however, that 3-nitropyridine was converted to 6-amino-3-nitropyridine by reaction with KOH, hydroxylamine and $ZnCl_2$.[681]

Analogous reactions have been carried out with hydrazide ions, R_2NNH^-.[682] A mixture of NO_2 and O_3, with excess $NaHSO_3$, converted pyridine to 3-aminopyridine.[683] For other methods of aminating aromatic rings, see **11-6**.

There are no *Organic Syntheses* references, but see OS **V**, 977, for a related reaction.

NITROGEN AS LEAVING GROUP

The diazonium group can be replaced by a number of groups.[684] Some of these are nucleophilic substitutions, with S_N1 mechanisms (p. 432), but others are free-radical reactions and are treated in Chapter 14. The solvent in all these reactions is usually water. With other solvents it has been shown that the S_N1 mechanism is favored by solvents of low nucleophilicity, while those of high nucleophilicity favor free-radical mechanisms.[685] The N_2^+ group[686] can be replaced by Cl^-, Br^-, and CN^-, by a nucleophilic mechanism (see OS **IV**, 182), but the Sandmeyer reaction is much more useful (**14-20**). Transition metal catalyzed reactions are known involving aryldiazonium salts, and diazonium variants of the Heck reaction (**13-10**) and Suzuki coupling (**13-12**) were discussed previously. As mentioned on p. 866 it must be

[677]Zoltewicz, J.A.; Helmick, L.S.; Oestreich, T.M.; King, R.W.; Kandetzki, P.E. *J. Org. Chem.* ***1973***, *38*, 1947; Woźniak, M.; Baránski, A.; Nowak, K.; van der Plas, H.C. *J. Org. Chem.* ***1987***, *52*, 5643.

[678]Ban, Y.; Wakamatsu, T. *Chem. Ind.* (*London*) ***1964***, 710.

[679]See, for example, Levitt, L.S.; Levitt, B.W. *Chem. Ind.* (*London*) ***1975***, 520.

[680]Katritzky, A.R.; Laurenzo, K.S. *J. Org. Chem.* ***1986***, *51*, 5039; ***1988***, *53*, 3978.

[681]Bakke, J.M.; Svensen, H.; Trevisan, R. *J. Chem. Soc. Perkin Trans. 1* ***2001***, 376.

[682]Kauffmann, T.; Hansen, J.; Kosel, C.; Schoeneck, W. *Liebigs Ann. Chem.* ***1962***, *656*, 103.

[683]Suzuki, H.; Iwaya, M.; Mori, T. *Tetrahedron Lett.* ***1997***, *38*, 5647.

[684]For a review of such reactions, see Wulfman, D.S., in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 1, Wiley, NY, ***1978***, pp. 286–297.

[685]Szele, I.; Zollinger, H. *Helv. Chim. Acta* ***1978***, *61*, 1721.

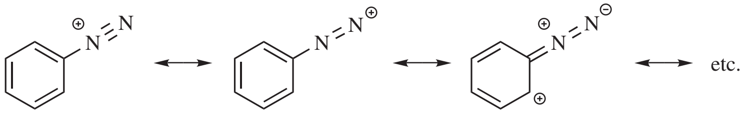
[686]For a discussion of the global and local electrophilicity patterns of diazonium ions, see Pérez, P. *J. Org. Chem.* ***2003***, *68*, 5886.

kept in mind that the N_2^+ group can activate the removal of another group on the ring. In a few cases, nitrogen groups, such as nitro or ammonium can be replaced.

13-19 Diazotization

$$\text{Ar—NH}_2 \;+\; \text{HONO} \longrightarrow \text{Ar}-\overset{\oplus}{\text{N}}\equiv\text{N}$$

When primary aromatic amines are treated with nitrous acid, diazonium salts are formed.[687] The reaction also occurs with aliphatic primary amines, but aliphatic diazonium ions are extremely unstable, even in solution (see p. 500). Aromatic diazonium ions are more stable, because of the resonance interaction between the nitrogens and the ring:



34 **35**

Incidentally, **34** contributes more to the hybrid than **35**, as shown by bond-distance measurements.[688] In benzenediazonium chloride, the C—N distance is ~1.42 Å, and the N—N distance ~1.08 Å,[689] which values fit more closely to a single and a triple bond than to two double bonds (see Table 1.5). Even aromatic diazonium salts are stable only at low temperatures, usually only $< 5°C$, although more stable ones, such as the diazonium salt obtained from sulfanilic acid, are stable up to 10 or 15°C. Diazonium salts are usually prepared in aqueous solution and used without isolation,[690] although it is possible to prepare solid diazonium salts if desired (see **13-23**). The stability of aryl diazonium salts can be increased by crown ether complexion.[691]

For aromatic amines, the reaction is very general. Halogen, nitro, alkyl, aldehyde, sulfonic acid, and so on, groups do not interfere. Since aliphatic amines do not react with

[687]For reviews, see, in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, Wiley, NY, ***1978***, the articles by Hegarty, A.F. pt. 2, pp. 511–591, and Schank, K. pt. 2, pp. 645–657; Godovikova, T.I.; Rakitin, O.A.; Khmel'nitskii, L.I. *Russ. Chem. Rev.* ***1983***, *52*, 440; Challis, B.C.; Butler, A.R., in Patai, S. *The Chemistry of the Amino Group*; Wiley, NY, ***1968***, pp. 305–320. For a review with respect to heterocyclic amines, see Butler, A.R. *Chem. Rev.* ***1975***, *75*, 241.

[688]For a review of diazonium salt structures, see Sorriso, S., in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 1, Wiley, NY, ***1978***, pp. 95–105.

[689]Rømming, C. *Acta Chem. Scand.* ***1959***, *13*, 1260; ***1963***, *17*, 1444; Sorriso, S., in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 1, Wiley, NY, ***1978***, p. 98; Ball, R.G.; Elofson, R.M. *Can. J. Chem.* ***1985***, *63*, 332.

[690]For a review of reactions of diazonium salts, see Wulfman, D.S., in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 1, Wiley, NY, ***1978***, pp. 247–339.

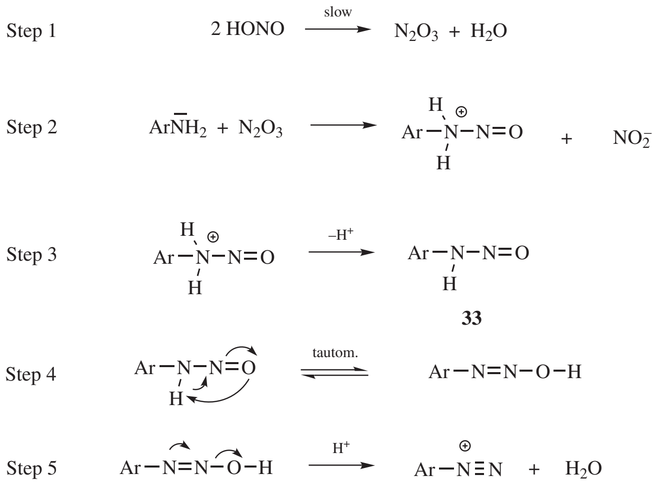
[691]Korzeniowski, S.H.; Leopold, A.; Beadle, J.R.; Ahern, M.F.; Sheppard, W.A.; Khanna, R.K.; Gokel, G.W. *J. Org. Chem.* ***1981***, *46*, 2153, and references cited therein. For reviews, see Bartsch, R.A., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C* pt. 1, Wiley, NY, ***1983***, pp. 889–915; Bartsch, R.A. *Prog. Macrocyclic Chem.* ***1981***, *2*, 1.

nitrous acid below a pH ∼ 3, it is even possible, by working at a pH ∼ 1, to diazotize an aromatic amine without disturbing an aliphatic amino group in the same molecule.[692]

$$EtOOC—CH_2—NH_2 \;+\; HONO \longrightarrow EtOOC—CH{=}\overset{\oplus}{N}{=}N$$

If an aliphatic amino group is a to a COOR, CN, CHO, COR, and so on, and has an a hydrogen, treatment with nitrous acid gives not a diazonium salt, but a *diazo compound*.[693] Such diazo compounds can also be prepared, often more conveniently, by treatment of the substrate with isoamyl nitrite and a small amount of acid.[694] Certain heterocyclic amines also give diazo compounds rather than diazonium salts.[695]

Despite the fact that diazotization takes place in acid solution, the actual species attacked is not the salt of the amine, but the small amount of free amine present.[696] It is because aliphatic amines are stronger bases than aromatic ones that at pH values < 3 there is not enough free amine present for the former to be diazotized, while the latter still undergo the reaction. In dilute acid the actual attacking species is N_2O_3, which acts as a carrier of NO^+. Evidence is that the reaction is second order in nitrous acid and, at sufficiently low acidities, the amine does not appear in the rate expression.[697] Under these conditions the mechanism is



[692]Kornblum, N.; Iffland, D.C. *J. Am. Chem. Soc.* ***1949***, *71*, 2137.

[693]For a monograph on diazo compounds, see Regitz, M.; Maas, G. *Diazo Compounds*, Academic Press, NY, ***1986***. For reviews, see, in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 1, Wiley, NY, ***1978***, the articles by Regitz, M. pt. 2, pp. 659–708, 751–820, and Wulfman, D.S.; Linstrumelle, G.; Cooper, C.F. pt. 2, pp. 821–976.

[694]Takamura, N.; Mizoguchi, T.; Koga, K.; Yamada, S. *Tetrahedron* ***1975***, *31*, 227.

[695]Butler, R.N., in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, p. 305.

[696]Challis, B.C.; Ridd, J.H. *J. Chem. Soc.* ***1962***, 5197, 5208; Challis, B.C.; Larkworthy, L.F.; Ridd, J.H. *J. Chem. Soc.* ***1962***, 5203.

[697]Hughes, E.D.; Ingold, C.K.; Ridd, J.H. *J. Chem. Soc.* ***1958***, 58, 65, 77, 88; Hughes, E.D.; Ridd, J.H. *J. Chem. Soc.* ***1958***, 70, 82.

There exists other evidence for this mechanism.[698] Other attacking species can be NOCl, $H_2NO_2^+$, and at high acidities even NO^+. Nucleophiles (e.g., Cl^-, SCN^-, thiourea) catalyze the reaction by converting the HONO to a better electrophile (e.g., $HNO_2 + Cl^- + H^+ \rightarrow NOCl + H_2O$).[699]

N-Aryl ureas are converted to the aryldiazonium nitrate upon treatment with $NaNO_2$ and H_2SO_4 in dioxane[700] or with DMF—NO_2 in DMF.[701]

There are many preparations of diazonium salts listed in *Organic Syntheses*, but they are always prepared for use in other reactions. We do not list them here, but under reactions in which they are used. The preparation of aliphatic diazo compounds can be found in OS **III**, 392; **IV**, 424. See also, OS **VI**, 840.

13-20 Hydroxylation of Aryldiazonium Salts

Hydroxy-de-diazoniation

$$ArN_2^+ \; + \; H_2O \longrightarrow ArOH$$

This reaction is formally analogous to **13-1**, but with a N_2^+ leaving group rather than a halide. Water is usually present whenever diazonium salts are made, but at these temperatures (0–5°C) the reaction proceeds very slowly. When it is *desired* to have OH replace the diazonium group, the excess nitrous acid is destroyed and the solution is usually boiled. Some diazonium salts require even more vigorous treatment, for example, boiling with aqueous sulfuric acid or with trifluoroacetic acid containing potassium trifluoroacetate.[702] The reaction can be performed on solutions of any diazonium salts, but hydrogen sulfates are preferred to chlorides or nitrates, since in these cases there is competition from the nucleophiles Cl^- or NO_3^-. A better method, which is faster, avoids side reactions, takes place at room temperature, and gives higher yields consists of adding Cu_2O to a dilute solution of the diazonium salt dissolved in a solution containing a large excess of $Cu(NO_3)_2$.[703] Aryl radicals are intermediates when this method is used. It has been shown that aryl radicals are at least partly involved when ordinary hydroxy-de-diazoniation is carried out in weakly alkaline aqueous solution.[704] Decomposition of arenediazonium tetrafluoroborates in F_3CSO_2OH gives aryl triflates directly, in high yields.[705]

OS **I**, 404; **III**, 130, 453, 564; **V**, 1130.

[698]For discussions, see Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, ***1988***, pp. 95–109; Ridd, J.H. *Q. Rev. Chem. Soc.* ***1961***, *15*, 418, p. 422.

[699]Williams, D.L.H. *Nitrosation*; Cambridge University Press, Cambridge, ***1988***, pp. 84–93.

[700]Zhang, Z.; Zhang, Q.; Zhang, S.; Liu,, X.; Zhao, G. *Synth. Commun.* ***2001***, *31*, 329.

[701]Zhang, O.Z.; Zhang, S.; Zhang, J. *Synth. Commun.* ***2001***, *31*, 1243.

[702]Horning, D.E.; Ross, D.A.; Muchowski, J.M. *Can. J. Chem.* ***1973***, *51*, 2347.

[703]Cohen, T.; Dietz, Jr., A.G.; Miser, J.R. *J. Org. Chem.* ***1977***, *42*, 2053.

[704]Dreher, E.; Niederer, P.; Rieker, A.; Schwarz, W.; Zollinger, H. *Helv. Chim. Acta* ***1981***, *64*, 488.

[705]Yoneda, N.; Fukuhara, T.; Mizokami, T.; Suzuki, A. *Chem. Lett.* ***1991***, 459.

13-21 Replacement by Sulfur-Containing Groups

Mercapto-de-diazoniation, and so on

$$ArN_2^+ + HS^- \longrightarrow ArSH$$
$$ArN_2^+ + S^{2-} \longrightarrow ArSAr$$
$$ArN_2^+ + RS^- \longrightarrow ArSR$$
$$ArN_2^+ + SCN^- \longrightarrow ArSCN + ArNCS$$

These reactions are convenient methods for incorporating a sulfur-containing group onto an aromatic ring. With Ar'S$^-$, diazosulfides Ar—N=N—S—Ar' are intermediates,[706] which can in some cases be isolated.[707] Thiophenols can be made as shown above, but more often the diazonium ion is treated with EtO–CSS$^-$ or S_2^{2-}, which give the expected products, and these are easily convertible to thiophenols. Aryldiazonium salts are prepared by the reaction of an aniline derivative with an alkyl nitrite (RONO), and when formed in the presence of dimethyl disulfide (MeS–SMe), the product is the thioether, Ar–S–Me.[708] Aryl triflates have been converted to the aryl thiol using NaST(P5) and a palladium catalyst, followed by treatment with tetrabutylammonium fluoride[709] (see also, **14-22**).

OS **II**, 580; **III**, 809 (but see OS **V**, 1050). Also see, OS **II**, 238.

13-22 Replacement by Iodine

Iodo-de-diazoniation

$$ArN_2^+ + I^- \longrightarrow ArI$$

One of the best methods for the introduction of iodine into aromatic rings (see **13-7**) is the reaction of diazonium salts with iodide ions. Analogous reactions with chloride, bromide, and fluoride ions give poorer results, and **14-20** and **13-23** are preferred for the preparation of aryl chlorides, bromides, and fluorides. However, when other diazonium reactions are carried out in the presence of these ions, halides are usually side products. Aniline has also been converted to fluorobenzene by treatment with *t*-BuONO and SiF_4 followed by heating.[710] A related reaction between PhN=N–NC_4H_8 and iodine gave iodobenzene.[711]

The actual attacking species is probably not only I^- if it is I^- at all. The iodide ion is oxidized (by the diazonium ion, nitrous acid, or some other oxidizing agent)

[706]Abeywickrema, A.N.; Beckwith, A.L.J. *J. Am. Chem. Soc.* ***1986***, *108*, 8227, and references cited therein.

[707]See, for example, Price, C.C.; Tsunawaki, S. *J. Org. Chem.* ***1963***, *28*, 1867.

[708]Allaire, F.S.; Lyga, J.W. *Synth. Commun.* ***2001***, *31*, 1857.

[709]Arnould, J.C.; Didelot, M.; Cadilhac, C.; Pasquet, M.J. *Tetrahedron Lett.* ***1996***, *37*, 4523.

[710]Tamura, M.; Shibakami, M.; Sekiya, A. *Eur. J. Org. Chem.* ***1998***, 725.

[711]Wu, Z.; Moore, J.S. *Tetrahedron Lett.* ***1994***, *35*, 5539.

to iodine, which in a solution containing iodide ions is converted to I_3^-; this is the actual attacking species, at least partly. This was shown by isolation of ArN_2^+ I_3^- salts, which, on standing, gave ArI.[712] From this, it can be inferred that the reason the other halide ions give poor results is not that they are poor nucleophiles but that they are poor reducing agents (compared with iodide). There is also evidence for a free-radical mechanism.[713]

The hydroxyl group of a phenol can be replaced with iodine. The reaction of phenol with a boronic ester and a palladium catalyst, followed by reaction with NaI and chloramine-T converts phenol to iodobenzene.[714]

OS **II**, 351, 355, 604; **V**, 1120.

13-23 The Schiemann Reaction

Fluoro-de-diazoniation (overall transformation)

$$ArN_2^+\ BF_4^- \xrightarrow{\Delta} ArF \quad + \quad N_2 \quad BF_3$$

Heating of diazonium fluoroborates (the *Schiemann* or *Balz–Schiemann reaction*) is by far the best way of introducing fluorine into an aromatic ring.[715] In the most common procedure, the fluoroborate salts are prepared by diazotizing as usual with nitrous acid and HCl and then adding a cold aqueous solution of $NaBF_4$, HBF_4, or NH_4BF_4. A precipitate forms, which is dried, and the salt is heated in the dry state. These salts are unusually stable for diazonium salts, and the reaction is usually successful. In general, any aromatic amine that can be diazotized will form a BF_4^- salt, usually with high yields. The diazonium fluoroborates can be formed directly from primary aromatic amines with *tert*-butyl nitrite and BF_3–etherate.[716] The reaction has also been carried out on ArN_2^+ PF_6^-, ArN_2^+ SbF_6^-, and ArN_2^+ AsF_6^- salts, in many cases with better yields.[717] Aryl chlorides and bromides are more commonly prepared by the Sandmeyer reaction (**14-20**). In an alternative procedure, aryl fluorides have been prepared by treatment of aryltriazenes Ar–N=N–NR_2 with 70% HF in pyridine.[718]

The mechanism is of the S_N1 type. That aryl cations are intermediates was shown by the following experiments:[719] Aryl diazonium chlorides are known to

[712]Carey, J.G.; Millar, I.T. *Chem. Ind.* (*London*) ***1960***, 97.

[713]Singh, P.R.; Kumar, R. *Aust. J. Chem.* ***1972***, *25*, 2133; Kumar, R.; Singh, P.R. *Tetrahedron Lett.* ***1972***, 613; Meyer, G.; Rössler, K.; Stöcklin, G. *J. Am. Chem. Soc.* ***1979***, *101*, 3121; Packer, J.E.; Taylor, R.E.R. *Aust. J. Chem.* ***1985***, *38*, 991; Abeywickrema, A.N.; Beckwith, A.L.J. *J. Org. Chem.* ***1987***, *52*, 2568.

[714]Thompson, A.L.S.; Kabalka, G.W.; Akula, M.R.; Huffman, J.W. *Synthesis* ***2005***, 547.

[715]For a review, see Suschitzky, H. *Adv. Fluorine Chem.* ***1965***, *4*, 1.

[716]Doyle, M.P.; Bryker, W.J. *J. Org. Chem.* ***1979***, *44*, 1572.

[717]Rutherford, K.G.; Redmond, W.; Rigamonti, J. *J. Org. Chem.* ***1961***, *26*, 5149; Sellers, C.; Suschitzky, H. *J. Chem. Soc. C* ***1968***, 2317.

[718]Rosenfeld, M.N.; Widdowson, D.A. *J. Chem. Soc. Chem. Commun.* ***1979***, 914. For another alternative procedure, see Yoneda, N.; Fukuhara, T.; Kikuchi, T.; Suzuki, A. *Synth. Commun.* ***1989***, *19*, 865.

[719]See also, Swain, C.G.; Sheats, J.E.; Harbison, K.G. *J. Am. Chem. Soc.* ***1975***, *97*, 783, 796; Becker, H.G.O.; Israel, G. *J. Prakt. Chem.* ***1979***, *321*, 579.

arylate other aromatic rings by a free-radical mechanism (see **13-27**). In radical arylation it does not matter whether the other ring contains electron-withdrawing or electron-donating groups; in either case a mixture of isomers is obtained, since the attack is not by a charged species. If an aryl radical were an intermediate in the Schiemann reaction and the reaction were run in the presence of other rings, it should not matter what kinds of groups were on these other rings: Mixtures of biaryls should be obtained in all cases. But if an aryl cation is an intermediate in the Schiemann reaction, compounds containing meta-directing groups, that is, meta directing for *electrophilic* substitutions, should be meta-arylated and those containing ortho–para-directing groups should be ortho– and para arylated, since an aryl cation should behave in this respect like any electrophile (see Chapter 11). Experiments have shown[720] that such orientation is observed, demonstrating that the Schiemann reaction has a positively charged intermediate. The attacking species, in at least some instances, is not F^- but BF_4^-.[721]

OS **II**, 188, 295, 299; **V**, 133.

13-24 Conversion of Amines to Azo Compounds

***N*-Arylimino-de-dihydro-bisubstitution**

$$ArNH_2 \quad + \quad Ar'NO \xrightarrow{\text{HOAc}} Ar{-}N{=}N{-}Ar'$$

Aromatic nitroso compounds combine with primary arylamines in glacial acetic acid to give symmetrical or unsymmetrical azo compounds (the *Mills reaction*).[722] A wide variety of substituents may be present in both aryl groups. Unsymmetrical azo compounds have also been prepared by the reaction between aromatic nitro compounds $ArNO_2$ and *N*-acyl aromatic amines Ar'NHAc.[723] The use of phase-transfer catalysis increased the yields.

13-25 Methylation, Vinylation, and Arylation of Diazonium Salts

Methyl-de-diazoniation, and so on

$$ArN_2^+ \quad + \quad Me_4Sn \xrightarrow[\text{MeCN}]{\text{Pd(OAc)}_2} ArMe$$

A methyl group can be introduced into an aromatic ring by treatment of diazonium salts with tetramethyltin and a palladium acetate catalyst.[724] The reaction has been performed with Me, Cl, Br, and NO_2 groups on the ring. A vinylic group can

[720]Makarova, L.G.; Matveeva, M.K. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1958***, 548; Makarova, L.G.; Matveeva, M.K.; Gribchenko, E.A. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1958***, 1399.

[721]Swain, C.G.; Rogers, R.J. *J. Am. Chem. Soc.* ***1975***, *97*, 799.

[722]For a review, see Boyer, J.H., in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, pt. 1, Wiley, NY, ***1969***, pp. 278–283.

[723]Ayyangar, N.R.; Naik, S.N.; Srinivasan, K.V. *Tetrahedron Lett.* ***1989***, *30*, 7253.

[724]Kikukawa, K.; Kono, K.; Wada, F.; Matsuda, T. *J. Org. Chem.* ***1983***, *48*, 1333.

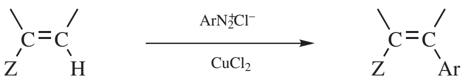
be introduced with $CH_2{=}CHSnBu_3$. When an aryl amine is treated with *tert*-butyl hyponitrite (*t*-BuONO) and allyl bromide, the nitrogen is displaced to the give allyl–aryl compound.[725]

Aryl diazonium salts can be used coupled with alkenes in a Heck-like reaction (**12-15**).[726] Other reactive aryl species also couple with aryldiazonium salts in the presence of a palladium catalyst.[727] A Suzuki type coupling (**13-9**) has also been reported using arylboronic acids, aryldiazonium salts and a palladium catalyst.[728]

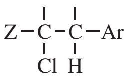
Aryltrifluoroborates (**12-28**) react with aryldiazonium salts in the presence of a palladium catalyst to give the corresponding biaryl.[729] Arylborate esters also reacat using a palladium catlsyt, and the aryl dizaonium unit reacts faster than an aryl halide.[730]

13-26 Arylation of Activated Alkenes by Diazonium Salts: Meerwein Arylation

Arylation or **Aryl-de-hydrogenation**



Alkenes activated by an electron-withdrawing group (Z may be C=C, halogen, C=O, Ar, CN, etc.) can be arylated by treatment with a diazonium salt and a cupric chloride[731] catalyst. This is called the *Meerwein*



arylation reaction.[732] Addition of ArCl to the double bond (to give) is a side reaction (**15-46**). In an improved procedure, an arylamine is treated with an alkyl nitrite (generating ArN_2^+ *in situ*) and a copper(II) halide in the presence of the alkene.[733]

The mechanism is probably of the free-radical type, with AR• (**36**) forming as in **14-20**, and then halogen transfer to give **37** or elimination to give **38**.[734]

[725]Ek, F.; Wistrand, L.-G.; Frejd, T. *J. Org. Chem.* ***2003***, *68*, 1911.

[726]Sengupta, S.; Bhattacharya, S. *J. Chem. Soc. Perkin Trans. 1* ***1993***, 1943.

[727]Darses, S.; Genêt, J.-P.; Brayer, J.-L.; Demoute, J.-P. *Tetrahedron Lett.* ***1997***, *38*, 4393.

[728]Darses, S.; Jeffery, T.; Genêt, J.-P.; Brayer, J.-L.; Demoute, J.-P. *Tetrahedron Lett.* ***1996***, *37*, 3857.

[729]Darses, S.; Michaud, G.; Genêt, J.-P. *Eur. J. Org. Chem.* ***1999***, 1875.

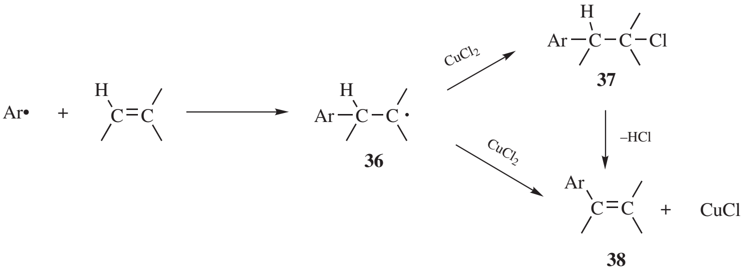
[730]Willis, D.M.; Strongin, R.M. *Tetahedron Lett.* ***2000***, *41*, 6271.

[731]$FeCl_2$ is also effective: Ganushchak, N.I.; Obushak, N.D.; Luka, G.Ya. *J. Org. Chem. USSR* ***1981***, *17*, 765.

[732]For reviews, see Dombrovskii, A.V. *Russ. Chem. Rev.*, ***1984***, *53*, 943; Rondestvedt, Jr., C.S. *Org. React.*, ***1976***, *24*, 225.

[733]Doyle, M.P.; Siegfried, B.; Elliott, R.C.; Dellaria Jr., J.F. *J. Org. Chem.* ***1977***, *42*, 2431.

[734]Dickerman, S.C.; Vermont, G.B. *J. Am. Chem. Soc.* ***1962***, *84*, 4150; Morrison, R.T.; Cazes, J.; Samkoff, N.; Howe, C.A. *J. Am. Chem. Soc.* ***1962***, *84*, 4152.



The radical **36** can react with cupric chloride by two pathways, one of which leads to addition and the other to substitution. Even when the addition pathway is taken, however, the substitution product may still be formed by subsequent elimination of HCl. Note that radical reactions are presented in Chapter 14, but the coupling of an alkene with an aromatic compound containing a leaving group prompted its placement here. Note also the similarity to the Heck reaction in **13-10**.

A variation of this reaction uses a palladium–copper catalyst on Montmorillonite clay. When aniline reacted with methyl acrylate in acetic acid and the Pd–Cu–Montmorillonite K10, $PhCH{=}CHCO_2Me$ was obtained.[735]

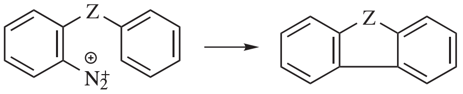
OS **IV**, 15.

13-27 Arylation of Aromatic Compounds by Diazonium Salts

Arylation or **Aryl-de-hydrogenation**

$$ArH + Ar'N_2^+ X^- \xrightarrow{OH^-} Ar{-}Ar'$$

When the normally acidic solution of a diazonium salt is made alkaline, the aryl portion of the diazonium salt can couple with another aromatic ring. Known as the *Gomberg* or *Gomberg–Bachmann reaction*,[736] it has been performed on several types of aromatic rings and on quinones. Yields are not high (usually <40%) because of the many side reactions undergone by diazonium salts, though higher yields have been obtained under phase-transfer conditions.[737] The conditions of the Meerwein reaction (**13-26**), treatment of the solution with a copper-ion catalyst, have also been used, as has the addition of sodium nitrite in Me_2SO (to benzene diazonium fluoroborate in DMSO).[738]



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[735]Waterlot, C.; Couturier, D.; Rigo, B. *Tetrahedron Lett.* ***2000*** *41*, 317.

[736]For reviews, see Bolton, R.; Williams, G.H. *Chem. Soc. Rev.*, ***1986***, *15*, 261; Hey, D.H. *Adv. Free-Radical Chem.* ***1966***, *2*, 47. For a review applied to heterocyclic substrates, see Vernin, G.; Dou, H.J.; Metzger, J. *Bull. Soc. Chim. Fr.* ***1972***, 1173.

[737]Beadle, J.R.; Korzeniowski, S.H.; Rosenberg, D.E.; Garcia-Slanga, B.J.; Gokel, G.W. *J. Org. Chem.* ***1984***, *49*, 1594.

[738]Kamigata, N.; Kurihara, T.; Minato, H.; Kobayashi, M. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 3152.

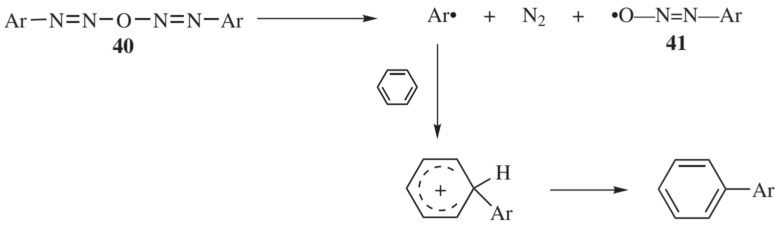
When the Gomberg–Bachmann reaction is performed intramolecularly as in the formation of **39**, either by the alkaline solution or by the copper-ion procedure, it is called the *Pschorr ring closure*[739] and yields are usually somewhat higher. Still higher yields have been obtained by carrying out the Pschorr reaction electrochemically.[740] The Pschorr reaction has been carried out for Z = CH=CH, CH_2CH_2, NH, C=O, CH_2, and quite a few others. A rapid and convenient way to carry out the Pschorr synthesis is to diazotize the amine substrate with isopropyl nitrite in the presence of sodium iodide, in which case the ring-closed product is formed in one step.[741]

Other compounds with nitrogen–nitrogen bonds have been used instead of diazonium salts. Among these are *N*-nitroso amides [ArN(NO)COR], triazenes,[742] and azo compounds. Still another method involves treatment of an aromatic primary amine directly with an alkyl nitrite in an aromatic substrate as solvent.[743]

In each case, the mechanism involves generation of an aryl radical from a covalent azo compound. In acid solution, diazonium salts are ionic and their reactions are polar. When they cleave, the product is an aryl cation (see p. 856). However, in neutral or basic solution, diazonium ions are converted to covalent compounds, and these cleave to give free radicals (Ar• and Z•). Note that radical reactions are presented in Chapter 14, but the coupling of an aromatic ring with an aromatic compound containing a leaving group prompted its placement here. Note the similarity to the Suzuki reaction in **13-12**.

$$\text{Ar—N=N—Z} \longrightarrow \text{Ar}\bullet + \text{N}\equiv\text{N} + \text{Z}\bullet$$

Under Gomberg–Bachmann conditions, the species that cleaves is the anhydride, **40**.[744]



42 **43**

[739]For a review, see Abramovitch, R.A. *Adv. Free-Radical Chem.* ***1966***, *2*, 87.

[740]Elofson, R.M.; Gadallah, F.F. *J. Org. Chem.* ***1971***, *36*, 1769.

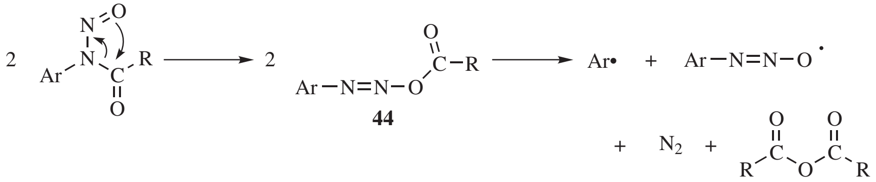
[741]Chauncy, B.; Gellert, E. *Aust. J. Chem.* ***1969***, *22*, 993. See also, Duclos, Jr., R.I.; Tung, J.S.; Rappoport, H. *J. Org. Chem.* ***1984***, *49*, 5243.

[742]See, for example, Patrick, T.B.; Willaredt, R.P.; DeGonia, D.J. *J. Org. Chem.* ***1985***, *50*, 2232; Butler, R.N.; O'Shea, P.D.; Shelly, D.P. *J. Chem. Soc. Perkin Trans. 1*, ***1987***, 1039.

[743]Cadogan, J.I.G. *J. Chem. Soc.* ***1962***, 4257; Fillipi, G.; Vernin, G.; Dou, H.J.; Metzger, J.; Perkins, M.J. *Bull. Soc. Chim. Fr.* ***1974***, 1075.

[744]Rüchardt, C.; Merz, E. *Tetrahedron Lett.* ***1964***, 2431; Eliel, E.L.; Saha, J.G.; Meyerson, S. *J. Org. Chem.* ***1965***, *30*, 2451.

The aryl radical thus formed attacks the substrate to give the intermediate **42** (see p. 940), from which the radical **41** abstracts hydrogen to give the product, **43**. *N*-Nitroso amides probably rearrange to *N*-acyloxy compounds (**44**), which cleave to give aryl radicals.[745] There is evidence that the reaction with alkyl nitrites also involves attack by aryl radicals.[746]



44

The Pschorr reaction can take place by two different mechanisms, depending on conditions: (*1*) attack by an aryl radical (as in the Gomberg–Bachmann reaction) or (*2*) attack by an aryl cation (similar to the S_N1 mechanism discussed on p. 857).[747] Under certain conditions the ordinary Gomberg–Bachmann reaction can also involve attack by aryl cations.[748]

OS **I**, 113; **IV**, 718.

13-28 Aryl Dimerization With Diazonium Salts

De-diazonio-coupling; Arylazo-de-diazonio-substitution

$$2\,ArN_2^+ \xrightarrow[\text{or}\quad Cu + H^+]{Cu^+} Ar{-}Ar + 2\,N_2 \quad \text{or} \quad Ar{-}N{=}N{-}Ar + N_2$$

When diazonium salts are treated with cuprous ion (or with copper and acid, in which case it is called the *Gatterman method*), two products are possible. If the ring contains electron-withdrawing groups, the main product is the biaryl, but the presence of electron-donating groups leads mainly to the azo compound. This reaction is different from **13-27** (and from **19-14**) in that *both* aryl groups in the product originate from ArN_2^+, that is, hydrogen is not a leaving group in this reaction. The mechanism probably involves free radicals.[749]

OS **I**, 222; **IV**, 872. Also see, OS **IV**, 273.

[745]Cadogan, J.I.G.; Murray, C.D.; Sharp, J.T. *J. Chem. Soc. Perkin Trans. 2*, ***1976***, 583, and references cited therein.

[746]Gragerov, I.P.; Levit, A.F. *J. Org. Chem. USSR* ***1968***, *4*, 7.

[747]For an alternative to the second mechanism, see Gadallah, F.F.; Cantu, A.A.; Elofson, R.M. *J. Org. Chem.* ***1973***, *38*, 2386.

[748]For examples; see Kobori, N.; Kobayashi, M.; Minato, H. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 223; Cooper, R.M.; Perkins, M.J. *Tetrahedron Lett.* ***1969***, 2477; Burri, P.; Zollinger, H. *Helv. Chim. Acta* ***1973***, *56*, 2204; Eustathopoulos, H.; Rinaudo, J.; Bonnier, J.M. *Bull. Soc. Chim. Fr.* ***1974***, 2911. For a discussion, see Zollinger, H. *Acc. Chem. Res.* ***1973***, *6*, 335, 338.

[749]See Cohen, T.; Lewarchik, R.J.; Tarino, J.Z. *J. Am. Chem. Soc.* ***1974***, *96*, 7753.

13-29 Replacement of Nitro

Alkyl-de-nitration, Hydroxy and alkoxy-de-nitration, Halo-de-nitration

$$Ar\text{-}NO_2 \longrightarrow Ar\text{-}R$$

In some cases, the nitrogen group of an aromatic nitro compound can be replaced with an alkyl group. The reaction of 1,4-dinitrobenzene with potassium *tert*-butoxide in the presence of BEt_3, for example, gave 4-ethylnitrobenzene.[750]

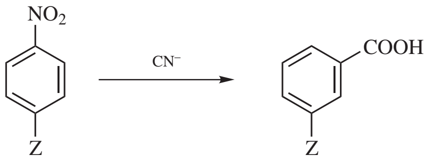
Other nucleophiles can replace a nitrogen-containing group. The reaction of hydroxide with Ar–Y, where Y = nitro,[751] azide, NR_3^+, and so on gives the corresponding phenol. This latter reaction works with alkoxide nucleophiles to give the corresponding aryl ether. The nitro can be replaced with chloro by use of NH_4Cl, PCl_5, $SOCl_2$, HCl, Cl_2, or CCl_4. Some of these reagents operate only at high temperatures and the mechanism is not always nucleophilic substitution. Activated aromatic nitro compounds can be converted to fluorides with fluoride ion.[752]

The reaction of vinyl nitro compounds ($C{=}C\text{–}NO_2$) and aryl iodide to give the styrene compound (C=C–Ar) was reported using BEt_3 and exposure to air.[753]

REARRANGEMENTS

13-30 The von Richter Rearrangement

Hydro-de-nitro-*cine*-substitution



When aromatic nitro compounds are treated with cyanide ion, the nitro group is displaced and a carboxyl group enters with cine substitution (p. 860), always ortho to the displaced group, never meta or para. The scope of this reaction, called the *von Richter rearrangement*, is variable.[754] As with other nucleophilic aromatic substitutions, the reaction gives best results when electron-withdrawing groups are in ortho and para positions, but yields are low, usually $<20\%$ and never $>50\%$.

[750]Palani, N.; Jayaprakash, K.; Hoz, S. *J. Org. Chem.* ***2003***, *68*, 4388.

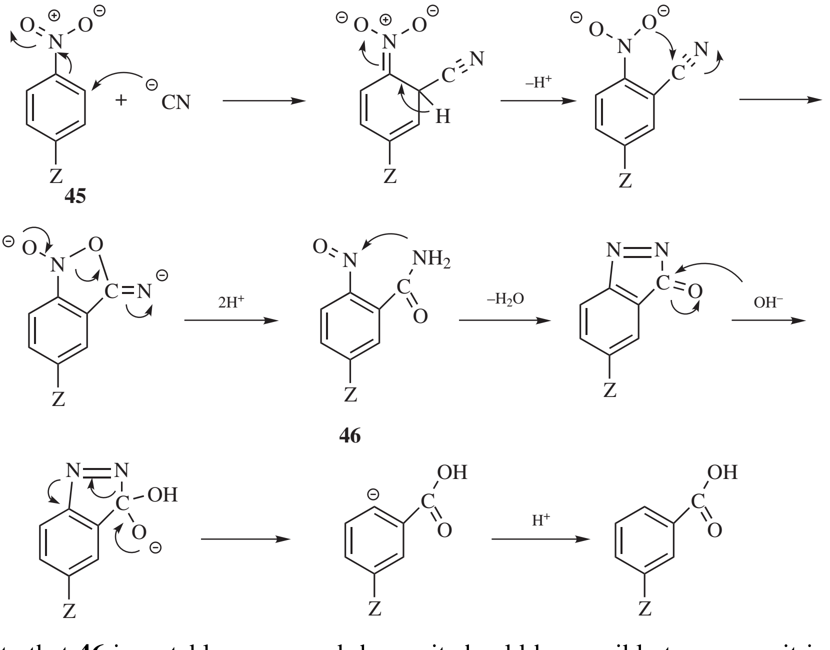
[751]For a convenient way of achieving this conversion, see Knudsen, R.D.; Snyder, H.R. *J. Org. Chem.* ***1974***, *39*, 3343.

[752]Attiná, M.; Cacace, F.; Wolf, A.P. *J. Chem. Soc. Chem. Commun.* ***1983***, 108; Clark, J.H.; Smith, D.K. *Tetrahedron Lett.* ***1985***, *26*, 2233; Suzuki, H.; Yazawa, N.; Yoshida, Y.; Furusawa,O.; Kimura, O. *Bull. Chem. Soc. Jpn.* ***1990***, *63*, 2010; Effenberger, F.; Streicher, W. *Chem. Ber.* ***1991***, *124*, 157.

[753]Liu, J.-T.; Jang, Y.-J.; Shih, Y.-K.; Hu, S.-R.; Chu, C.-M.; Yao, C.-F. *J. Org. Chem.* ***2001***, *66*, 6021.

[754]For a review, see Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 326–335.

At one time it was believed that a nitrile, ArCN, was an intermediate, since cyanide is the reagent and nitriles are hydrolyzable to carboxylic acids under the reaction conditions (**16-4**). However, a remarkable series of results proved this belief to be in error. Bunnett and Rauhut demonstrated[755] that α-naphthyl cyanide is *not* hydrolyzable to α-naphthoic acid under conditions at which β-nitronaphthalene undergoes the von Richter rearrangement to give α-naphthoic acid. This proved that the nitrile cannot be an intermediate. It was subsequently demonstrated that N_2 is a major product of the reaction.[756] It had previously been assumed that all the nitrogen in the reaction was converted to ammonia, which would be compatible with a nitrile intermediate, since ammonia is a hydrolysis product of nitriles. At the same time it was shown that NO_2^- is not a major product. The discovery of nitrogen indicated that a nitrogen–nitrogen bond must be formed during the course of the reaction. A mechanism in accord with all the facts was proposed by Rosenblum:[756]



45

46

Note that **46** is a stable compound; hence it should be possible to prepare it independently and to subject it to the conditions of the von Richter rearrangement. This was done and the correct products are obtained.[757] Further evidence is that when **45** (Z = Cl or Br) was treated with cyanide in $H_2{}^{18}O$, half the oxygen in the product was labeled, showing that one of the oxygens of the carboxyl group came from the nitro group and one from the solvent, as required by this mechanism.[758]

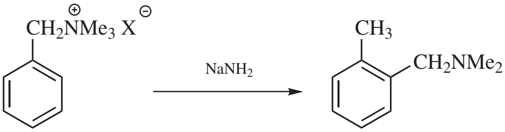
[755]Bunnett, J.F.; Rauhut, M.M. *J. Org. Chem.* ***1956***, *21*, 934, 944.

[756]Rosenblum, M. *J. Am. Chem. Soc.* ***1960***, *82*, 3796.

[757]Ibne-Rasa, K.M.; Koubek, E. *J. Org. Chem.* ***1963***, *28*, 3240.

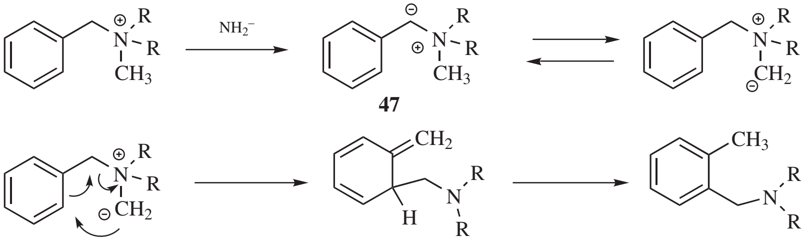
[758]Samuel, D. *J. Chem. Soc.* ***1960***, 1318. For other evidence, see Cullen, E.; L'Ecuyer, P. *Can. J. Chem.* ***1961***, *39*, 144, 155, 382; Ullman, E.F.; Bartkus, E.A. *Chem. Ind.* (*London*) ***1962***, 93.

13-31 The Sommelet–Hauser Rearrangement



Benzylic quaternary ammonium salts, when treated with alkali-metal amides, undergo a rearrangement called the *Sommelet–Hauser rearrangement.*[759] Since the product is a benzylic tertiary amine, it can be further alkylated and the product again subjected to the rearrangement. This process can be continued around the ring until an ortho position is blocked.[760]

The rearrangement occurs with high yields and can be performed with various groups present in the ring.[761] The reaction is most often carried out with three methyl groups on the nitrogen, but other groups can also be used, though if a β-hydrogen is present, Hofmann elimination (**17-7**) often competes. The *Stevens rearrangement* (**18-21**) is also a competing process.[762] When both rearrangements are possible, the Stevens is favored at high temperatures and the Sommelet–Hauser at low temperatures.[763] The mechanism is



The benzylic hydrogen is most acidic and is the one that first loses a proton to give the ylid **47**. However, **48**, which is present in smaller amount, is the species

[759]For reviews, see Pine, S.H. *Org. React.*, ***1970***, *18*, 403; Lepley, A.R.; Giumanini, A.G. *Mech. Mol. Migr.* ***1971***, *3*, 297; Wittig, G. *Bull. Soc. Chim. Fr.* ***1971***, 1921; Stevens, T.S.; Watts, W.E. *Selected Molecular Rearrangements*, Van Nostrand-Reinhold, Princeton, ***1973***, pp. 81–88; Shine, H.J.*Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 316–326. Also see, Klunder, J.M. *J. Heterocyclic Chem.* ***1995***, *32*, 1687.

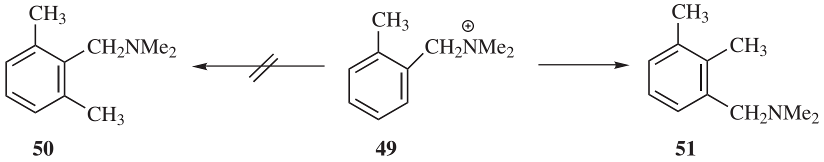
[760]Beard, W.Q.; Hauser, C.R. *J. Org. Chem.* ***1960***, *25*, 334.

[761]Jones, G.C.; Beard, W.Q.; Hauser, C.R. *J. Org. Chem.* ***1963***, *28*, 199.

[762]For a method that uses nonbasic conditions, and gives high yields of the Sommelet–Hauser product, with little or no Stevens rearrangement, see Nakano, M.; Sato, Y. *J. Org. Chem.* ***1987***, *52*, 1844; Shirai, N.; Sato, Y. *J. Org. Chem.* ***1988***, *53*, 194.

[763]Wittig, G.; Streib, H. *Liebigs Ann. Chem.* ***1953***, *584*, 1.

that undergoes the rearrangement, shifting the equilibrium in its favor. This mechanism is an example of a [2,3] sigmatropic rearrangement (see **18-35**). Another mechanism that might be proposed is one in which a methyl group actually breaks away (in some form) from the nitrogen and then attaches itself to the ring. That this is not so was shown by a product study.[764] If the second mechanism were true, **49** should give **50**, but the first mechanism predicts the formation of **51**, which is what was actually obtained.[765]



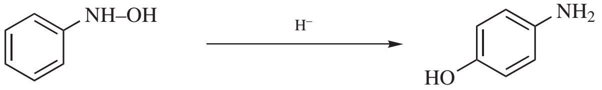
The mechanism as we have pictured it can lead only to an ortho product. However, a small amount of para product has been obtained in some cases.[766] A mechanism[767] in which there is a dissociation of the ArC—N bond (similar to the ion-pair mechanism of the Stevens rearrangement, p. 1622) has been invoked to explain the para products that are observed.

Sulfur ylids containing a benzylic group (analogous to **48**) undergo an analogous rearrangement.[768]

OS **IV**, 585.

13-32 Rearrangement of Aryl Hydroxylamines

1/*C*-Hydro-5/*N*-hydroxy-interchange



Aryl hydroxylamines treated with acids rearrange to aminophenols.[769] Although this reaction (known as the *Bamberger rearrangement*) is similar in appearance to

[764]For other evidence for the mechanism given, see Hauser, C.R.; Van Eenam, D.N. *J. Am. Chem. Soc.* ***1957***, *79*, 5512; Jones, F.N.; Hauser, C.R. *J. Org. Chem.* ***1961***, *26*, 2979; Puterbaugh, W.H.; Hauser, C.R. *J. Am. Chem. Soc.* ***1964***, *86*, 1105; Pine, S.H.; Sanchez, B.L. *Tetrahedron Lett.* ***1969***, 1319; Shirai, N.; Watanabe, Y.; Sato, Y. *J. Org. Chem.* ***1990***, *55*, 2767.

[765]Kantor, S.W.; Hauser, C.R. *J. Am. Chem. Soc.* ***1951***, *73*, 4122.

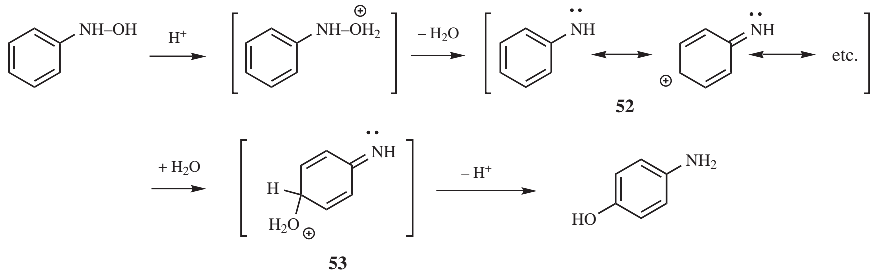
[766]Pine, S.H. *Tetrahedron Lett.* ***1967***, 3393; Pine, S.H. *Org. React.* ***1970***, *18*, 403, p. 418.

[767]Bumgardner, C.L. *J. Am. Chem. Soc.* ***1963***, *85*, 73.

[768]See Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***, pp. 118–124.

[769]For a review, see Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 182–190.

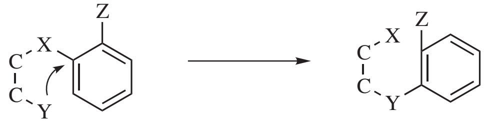
11-28–11-32, the attack on the ring is not electrophilic but nucleophilic. The rearrangement is intermolecular, with the following mechanism:



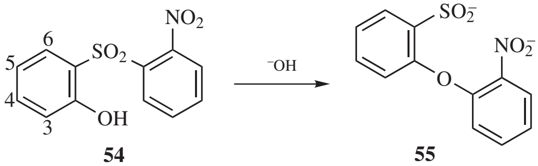
Among the evidence[770] for this mechanism are the facts that other products are obtained when the reaction is run in the presence of competing nucleophiles, for example, *p*-ethoxyaniline when ethanol is present, and that when the para position is blocked, compounds similar to **53** are isolated. In the case of 2,6-dimethylphenylhydroxylamine, the intermediate nitrenium ion **52** was trapped, and its lifetime in solution was measured.[771] The reaction of **52** with water was found to be diffusion controlled.[288]

OS **IV**, 148.

13-33 The Smiles Rearrangement



The *Smiles rearrangement* actually comprises a group of rearrangements that follow the pattern given above.[772] A specific example is the reaction of **54** with hydroxide to give **55**.



Smiles rearrangements are simply intramolecular nucleophilic substitutions. In the example given, SO_2Ar is the leaving group and ArO^- the nucleophile, and the nitro group serves to activate its ortho position. Halogens also serve as activating

[770]For additional evidence, see Sone, T.; Hamamoto, K.; Seiji, Y.; Shinkai, S.; Manabe, O. *J. Chem. Soc. Perkin Trans. 2* ***1981***, 1596; Kohnstam, G.; Petch, W.A.; Williams, D.L.H. *J. Chem. Soc. Perkin Trans. 2* ***1984***, 423; Sternson, L.A.; Chandrasakar, R. *J. Org. Chem. 1984, 49*, 4295, and references cited therein.

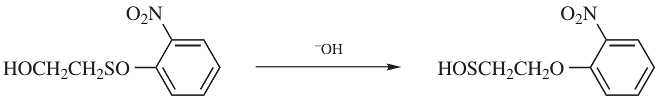
[771]Fishbein, J.C.; McClelland, R.A. *J. Am. Chem. Soc.* ***1987***, *109*, 2824.

[772]For reviews, see Truce, W.E.; Kreider, E.M.; Brand, W.W. *Org. React.*, ***1971***, *18*, 99; Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 307–316; Stevens, T.S.; Watts, W.E. *Selected Molecular Rearrangements*, Van Nostrand-Reinhold, Princeton, NJ, ***1973***, pp. 120–126.

groups.[773] The ring at which the substitution takes place is nearly always activated, usually by ortho or para nitro groups. Here X is usually S, SO, SO_2,[774] O, or COO, and Y is usually the conjugate base of OH, NH_2, NHR, or SH. The reaction has even been carried out with $Y = CH_2^-$ (phenyllithium was the base here).[775]

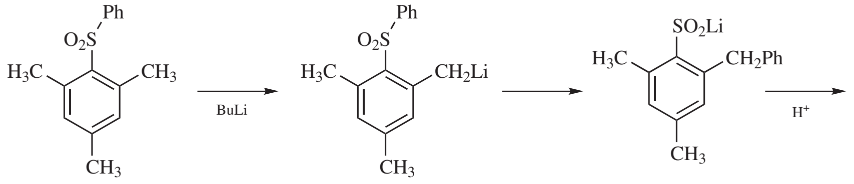
The reaction rate is greatly enhanced by substitution in the 6 position of the attacking ring, for steric reasons. For example, a methyl, chloro, or bromo group in the 6 position of **54** caused the rate to be ~10^5 times faster than when the same groups were in the 4 position,[776] though electrical effects should be similar at these positions. The enhanced rate comes about because the most favorable conformation the molecule can adopt to suit the bulk of the 6-substituent is also the conformation required for the rearrangement. Thus, less entropy of activation is required.

Although the Smiles rearrangement is usually carried out on compounds containing two rings, this need not be the case, as in the formation of **56**.[777]

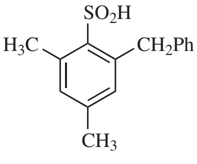


56

In this case, the sulfenic acid (**56**) is unstable[778] and the actual products isolated were the corresponding sulfinic acid (RSO_2H) and disulfide (R_2S_2).



57 **58** **59**



60

[773]Bonvicino, G.E.; Yogodzinski, L.H.; Hardy Jr., R.A. *J. Org. Chem.* ***1962***, *27*, 4272; Nodiff, E.H.; Hausman, M. *J. Org. Chem.* ***1964***, *29*, 2453; Grundon, M.F.; Matier, W.L. *J. Chem. Soc., B*, ***1966***, 266; Schmidt, D.M.; Bonvicino, G.E. *J. Org. Chem.* ***1984***, *49*, 1664.

[774]For a review for the case of $X = SO_2$, see Cerfontain, H. *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*; Wiley, NY, ***1968***, pp. 262–274.

[775]Truce, W.E.; Robbins, C.R.; Kreider, E.M. *J. Am. Chem. Soc.* ***1966***, *88*, 4027; Drozd, V.N.; Nikonova, L.A. *J. Org. Chem, USSR* ***1969***, *5*, 313.

[776]Bunnett, J.F.; Okamoto, T. *J. Am. Chem. Soc.* ***1956***, *78*, 5363.

[777]Kent, B.A.; Smiles, S. *J. Chem. Soc.* ***1934***, 422.

[778]For a stable sulfenic acid, see Nakamura, N. *J. Am. Chem. Soc.* ***1983***, *105*, 7172.

In the Smiles rearrangement, the nucleophile Y is most often the conjugate base of SH, SO_2NHR, SO_2NH_2, NH_2, NHR, OH, OR. There are few examples where Y is a carbanion, and the most common example is probably the *Truce–Smiles rearrangement*, where L—YH is an *o*-tolyl group.[779] The prototypical Truce–Smiles rearrangement requires use of a strong base to form the benzylic carbanion that undergoes the rearrangement. When sulfone **57** was treated with butyllithium, for example, deprotonation led to the benzylic lithium compound **58**. Truce–Smiles rearrangement led to **59**, and hydrolysis gave the sulfinic acid, **60**.[779] Truce–Smiles rearrangements with stabilized benzylic carbanions are known,[780] and rearrangements of carbanions in general fall under this category.[781] Relatively few examples have been reported, however.[782] Truce–Smiles rearrangements of sulfones that proceed through a six-membered transition state have been reported.[783] In another example, displacement of an activated aryl fluoride with *o*-hydroxyacetophenone gave a product that was *C*-arylated adjacent to the ketone.[784]

[779]Truce, W.E.; Ray Jr., W.J.; Norman, O.L.; Eickemeyer, D.B. *J. Am. Chem. Soc.* ***1958***, *80*, 3625.
[780]Erickson, W.R.; McKennon, M.J. *Tetrahedron Lett.* ***2000***, *41*, 4541.
[781]Fukazawa, Y.; Kato, N.; Itô, S. *Tetrahedron Lett.* ***1982***, *23*, 437.
[782]Hirota, T.; Tomita, K.; Sasaki, K.; Okuda, K.; Yoshida, M.; Kashino, S. *Heterocycles* ***2001***, *55*, 741; Bayne, D.W.; Nicol, A.J.; Tennant, G.*J. Chem. Soc. Chem. Commun.* ***1975***, 782; Hoffman, R.V.; Jankowski, B.C.; Carr, C.S.; Duesler, E.N. *J. Org. Chem.* ***1986***, *51*, 130.
[783]Truce, W.E.; Hampton, D.C. *J. Org. Chem.* ***1963***, *28*, 2276.
[784]Mitchell, L.H.; Barvian, N.C. *Tetrahedron Lett.* ***2004***, *45*, 5669.

CHAPTER 14

Substitution Reactions: Free Radicals

MECHANISMS

Free-Radical Mechanisms in General[1]

A free-radical process consists of at least two steps. The first step involves the *formation* of free radicals, usually by homolytic cleavage of bond, that is, a cleavage in which each fragment retains one electron:

$$\text{A—B} \longrightarrow \text{A}\bullet + \text{B}\bullet$$

This is called an *initiation* step. It may happen spontaneously or may be induced by heat[2] or light (see the discussion on p. 279), depending on the type of bond.[3] Peroxides, including hydrogen peroxide, dialkyl, diacyl, and alkyl acyl peroxides, and peroxyacids are the most common source of free radicals induced spontaneously or by heat, but other organic compounds with low-energy bonds, such as azo compounds, are also used. Molecules that are cleaved by light are most often chlorine, bromine, and various ketones (see Chapter 7). Radicals can also be formed

[1]For books on free-radical mechanisms, see Nonhebel, D.C.; Tedder, J.M.; Walton, J.C. *Radicals*, Cambridge University Press, Cambridge, ***1979***; Nonhebel, D.C.; Walton. J.C. *Free-Radical Chemistry*, Cambridge University Press, London, ***1974***; Huyser, E.S. *Free-Radical Chain Reactions*, Wiley, NY, ***1970***; Pryor, W.A. *Free Radicals*, McGraw-Hill, NY, ***1966***; For reviews, see Huyser, E.S., in McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, ***1973***, pp. 1–59. For monographs on the use of free-radical reactions in synthesis see Giese, B. *Radicals in Organic Synthesis, Formation of Carbon-Carbon Bonds*, Pergamon, Elmsford, NY, ***1986***; Davies, D.I.; Parrott, M.J. *Free Radicals in Organic Synthesis*, Springer, NY, ***1978***. For reviews, see Curran, D.P. *Synthesis* ***1988***, 417, 489; Ramaiah, M. *Tetrahedron* ***1987***, *43*, 3541.

[2]For a study of the thermolysis of free-radical initiators, see Engel, P.S.; Pan, L.; Ying, Y.; Alemany, L.B. *J. Am. Chem. Soc.* ***2001***, *123*, 3706.

[3]See Fokin, A.A.; Schreiner, P.R. *Chem. Rev.* ***2002***, *102*, 1551.

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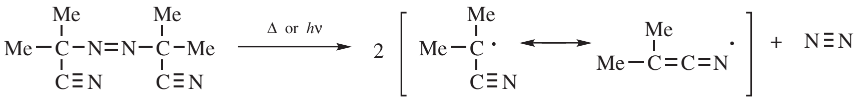
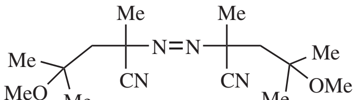
in another way, by a one-electron transfer (loss or gain), for example, $A^+ + e^- \rightarrow A\bullet$. One-electron transfers usually involve inorganic ions or electrochemical processes.

Dialkyl peroxides (ROOR) or alkyl hydroperoxides (ROOH) decompose to hydroxy radicals (HO•) or alkoxy radicals (RO•) when heated.[4] Cumene hydroperoxide ($PhCMe_2OOH$), bi-*tert*-butylperoxide ($Me_3COOCMe_3$),[5] and benzoyl peroxide [$(PhCO)O_2$] undergo homolytic cleavage at temperatures compatible with many organic reactions, allowing some control of the reaction, and they are reasonably soluble in organic solvents. In general, when a peroxide decomposes, the oxygen radical remains in a "cage" for $\sim 10^{-11}$ s before diffusing away. The radical can recombine (dimerize), or react with other molecules. Azo compounds, characterized by a —N=N— bond, are free-radical precursors that liberate nitrogen gas (N≡N) upon decomposition. azobis(isobutyronitrile) (AIBN, **1**) is a well-known example, which decomposes to give nitrogen and the cyano stabilized radical, **2**.[6] Homolytic dissociation of symmetrical diazo compounds may be stepwise.[7] A derivative has been developed that decomposes to initiate radical reactions at room temperature, 2,2′-azobis(2,4-dimethyl-4-methoxyvaleronitrile), **3**.[8] Water soluble azo compounds are known, and can be used as radical initiators.[9] Other sources of useful radicals are available. Alkyl hypochlorites (R—O—Cl) generate chlorine radicals (Cl•) and alkoxy radicals (RO•) when heated.[10] Heating *N*-alkoxydithiocarbamates is another useful source of alkoxy radicals, RO•.[11]



1 **2**



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[4]For a table of approximate decomposition temperatures for several common peroxides, see Lazár, M.; Rychlý, J.; Klimo, V.; Pelikán, P.; Valko, L. *Free Radicals in Chemistry and Biology*, CRC Press, Washington, DC, ***1989***, p. 12.

[5]Lazár, M.; Rychlý, J.; Klimo, V.; Pelikán, P.; Valko, L. *Free Radicals in Chemistry and Biology*, CRC Press, Washington, DC, ***1989***, p. 13.

[6]Yoshino, K.; Ohkatsu, J.; Tsuruta, T. *Polym. J.* ***1977***, *9*, 275; von J. Hinz, A.; Oberlinner, A.; Rüchardt, C. *Tetrahedron Lett.* ***1973***, 1975.

[7]Dannenberg, J.J.; Rocklin, D. *J. Org. Chem.* ***1982***, *47*, 4529. See also, Newman, Jr, R.C.; Lockyer Jr, G.D. *J. Am. Chem Soc.* ***1983***, *105*, 3982.

[8]Kita, Y.; Sano, A.; Yamaguchi, T.; Oka, M.; Gotanda, K.; Matsugi, M. *Tetrahedron Lett.* ***1997***, *38*, 3549.

[9]Yorimitsu, H.; Wakabayashi, K.; Shinokubo, H; Oshima, K. *Tetrahedron Lett.* ***1999***, *40* , 519.

[10]Davies, D.I.; Parrott, M.J. *Free Radicals in Organic Synthesis*, Springer–Verlag, Berlin, ***1978***, p. 9; Chattaway, F.D.; Baekeberg, O.G. *J. Chem. Soc.* ***1923***, *123*, 2999.

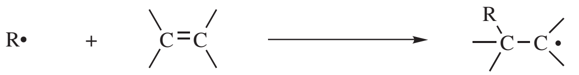
[11]Kim, S.; Lim, C.J.; Song, S.-E.; Kang, H.-Y. *Synlett* ***2001***, 688.

Note that aldehydes can also be a source of acyl radicals (•C=O) via reaction with transition metal salts such as Mn(III) acetate or Fe(II) compounds.[12] Another useful variation employs imidoyl radicals as synthons for unstable aryl radicals.[13]

The second step involves the *destruction* of free radicals. This usually happens by a process opposite to the first, namely, a combination of two like or unlike radicals to form a new bond:[14]

$$A\bullet + B\bullet \longrightarrow A{-}B$$

This type of step is called *termination*, and it ends the reaction as far as these particular radicals are concerned.[15] However, it is not often that termination follows *directly* upon initiation. The reason is that most radicals are very reactive and will react with the first available species with which they come in contact. In the usual situation, in which the concentration of radicals is low, this is much more likely to be a molecule than another radical. When a radical (which has an odd number of electrons) reacts with a molecule (which has an even number), the total number of electrons in the products must be odd. The product in a particular step of this kind may be one particle, as in the addition of a radical to a π-bond, which in this case is



4

another free radical, **4**; or abstraction of an atom such as hydrogen to give two particles, R—H and the new radical R′•.

$$R\bullet + R'H \longrightarrow RH + R'\bullet$$

In this latter case, one particle must be a neutral molecule and one a free radical. In both of these examples, a *new radical is generated.* This type of step is called *propagation*, since the newly formed radical can now react with another molecule and produce another radical, and so on, until two radicals do meet each other and terminate the sequence. The process just described is called a *chain reaction*,[16] and there may be hundreds or thousands of propagation steps between an initiation and a termination. Two other types of propagation reactions do not involve a

[12]Davies, D.I.; Parrott, M.J. *Free Radicals in Organic Synthesis* Springer–Verlag, Berlin, ***1978***, p. 69; Sosnovsky, G. *Free Radical Reactions in Preparative Organic Chemistry*, MacMillan, New York, ***1964***; Vinogradov, M.G.; Nikishin, G.I. *Usp. Khim*, ***1971***, *40*, 1960; Nikishin, G.I.; Vinogradov, M.G.; Il'ina, G.P. *Synthesis* ***1972***, 376; Nikishin, G.I.; Vinogradov, M.G.; Verenchikov, S.P.; Kostyukov, I.N.; Kereselidze, R.V. *J. Org. Chem, USSR* ***1972***, *8*, 539 (Engl, p. 544).

[13]Fujiwara, S.-i.; Matsuya, T.; Maeda, H.; Shin-ike, T.; Kambe, N.; Sonoda, N. *J. Org. Chem.* ***2001***, *66*, 2183.

[14]For a review of the stereochemistry of this type of combination reaction, see Porter, N.A.; Krebs, P.J. *Top. Stereochem.* ***1988***, *18*, 97.

[15]Another type of termination is disproportionation (see p. 280).

[16]For a discussion of radical chain reactions from a synthetic point of view, see Walling, C. *Tetrahedron* ***1985***, *41*, 3887.

molecule at all. These are (*1*) cleavage of a radical into, necessarily, a radical and a molecule and (*2*) rearrangement of one radical to another (see Chapter 18). When radicals are highly reactive, for example, alkyl radicals, chains are long, since reactions occur with many molecules; but with radicals of low reactivity, for example, aryl radicals, the radical may be unable to react with anything until it meets another radical, so that chains are short, or the reaction may be a nonchain process. In any particular chain process, there is usually a wide variety of propagation and termination steps. Because of this, these reactions lead to many products and are often difficult to treat kinetically.[17]

$$\text{R—CH}_2\bullet + n\text{-Bu}_3\text{Sn—H} \longrightarrow \text{R—CH}_2\text{—H} + n\text{-Bu}_3\text{Sn}\bullet$$

$$n\text{-Bu}_3\text{Sn}\bullet + n\text{-Bu}_3\text{Sn}\bullet \longrightarrow n\text{-Bu}_3\text{Sn—Sn}n\text{-Bu}_3$$

A useful variation of propagation and termination combines the two processes. When a carbon radical (R•) is generated in the presence of tributyltin hydride (n-Bu_3SnH), a hydrogen atom is transferred to the radical to give R—H and a new radical, n-Bu_3Sn•. The tin radical reacts with a second tin radical to give n-Bu_3 Sn—Sn—n-Bu_3. The net result is that the carbon radical is reduced to give the desired product and the tin dimer can be removed from the reaction. Tin hydride transfers a hydrogen atom in a chain propagation sequence that produces a new radical, but terminates the carbon radical sequence. Dimerization of the tin radical then terminates that radical process. Silanes, such as triethylsilane (Et_3SiH), has also been used as an effective radical reducing agent.[18] The rate constants for the reaction of both tributytin hydride and $(Me_3Si)_3Si$—H with acyl radical has been measured and the silane quenches the radical faster than the tin hydride.[19] bis(Tri-n-butylstannyl)benzopinacolate has also been used as a thermal source of n-Bu_3Sn•, used to mediate radical reactions.[20]

The following are some general characteristics of free-radical reactions:[21]

1. Reactions are fairly similar whether they are occurring in the vapor or liquid phase, though solvation of free radicals in solution does cause some differences.[22]
2. They are largely unaffected by the presence of acids or bases or by changes in the polarity of solvents, except that nonpolar solvents may suppress competing ionic reactions.

[17]For a discussion of the kinetic aspects of radical chain reactions, see Huyser, E.S. *Free-Radical Chain Reactions*, Wiley, NY, ***1970***, pp. 39–65.

[18]Chatgilialoglu, C.; Ferreri, C.; Lucarini, M. *J. Org. Chem.* ***1993***, *58*, 249.

[19]Chatgilialoglu, C.; Lucarini, M. *Tetrahedron Lett.* ***1995***, *36*, 1299.

[20]Hart, D.J.; Krishnamurthy, R.; Pook, L.M.; Seely, F.L. *Tetrahedron Lett.* ***1993***, *34*, 7819.

[21]See Beckwith, A.L.J. *Chem. Soc. Rev.* ***1993***, *22*, 143 for a discussion of selectivity in radical reactions.

[22]For a discussion, see Mayo, F.R. *J. Am. Chem. Soc.* ***1967***, *89*, 2654.

3. They are initiated or accelerated by typical free-radical sources, such as the peroxides, referred to, or by light. In the latter case, the concept of quantum yield applies (p. 349). Quantum yields can be quite high, for example, 1000, if each quantum generates a long chain, or low, in the case of nonchain processes.
4. Their rates are decreased or the reactions are suppressed entirely by substances that scavenge free radicals, for example, nitric oxide, molecular oxygen, or benzoquinone. These substances are called *inhibitors*.[23]

This chapter discusses free-radical substitution reactions. Free-radical additions to unsaturated compounds and rearrangements are discussed in Chapters 15 and 18, respectively. Fragmentation reactions are covered, in part, in Chapter 17. In addition, many of the oxidation–reduction reactions considered in Chapter 19 involve free-radical mechanisms. Several important types of free-radical reactions do not usually lead to reasonable yields of pure products and are not generally treated in this book. Among these are polymerizations and high-temperature pyrolyses.

Free-Radical Substitution Mechanisms[24]

In a free-radical substitution reaction

$$\text{R—X} \longrightarrow \text{R—Y}$$

there must first be a cleavage of the substrate RX so that R• radicals are produced. This can happen by a spontaneous cleavage

$$\text{R—X} \longrightarrow \text{R•} + \text{X•}$$

or it can be caused by light or heat, or, more often, there is no actual cleavage, but R• is produced by an *abstraction* of another atom, X but the radical W•.

$$\text{R—X} + \text{W•} \longrightarrow \text{R•} + \text{W—X}$$

The radical W• is produced by adding a compound, such as a peroxide, that spontaneously forms free radicals. Such a compound is called an *initiator* (see above). Once R• is formed, it can go to product in two ways, by another atom abstraction, such as the reaction with A—B to form R—A and a new radical B•.

$$\text{R•} + \text{A—B} \longrightarrow \text{R—A} + \text{B•}$$

Another reaction is coupling with another radical to form the neutral product R—Y.

$$\text{R•} + \text{Y•} \longrightarrow \text{R—Y}$$

[23]For a review of the action of inhibitors, see Denisov, E.T.; Khudyakov, I.V. *Chem. Rev.* ***1987***, *87*, 1313.
[24]For a review, see Poutsma, M.L., in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 113–158.

In a reaction with a moderately long chain, much more of the product will be produced by abstraction (4) than by coupling (5). Cleavage steps like (2) have been called S_H1 (H for homolytic), and abstraction steps like (3) and (4) have been called S_H2; reactions can be classified as S_H1 or SH_2 on the basis of whether RX is converted to R by (2) or (3).[25] Most chain substitution mechanisms follow the pattern (3), (4), (3), (4)••• Chains are long and reactions go well where both (3) and (4) are energetically favored (no worse that slightly endothermic (see pp. 944, 959). The IUPAC designation of a chain reaction that follows the pattern (3),(4)••• is $A_rD_R + A_RD_r$ (R stands for radical).

With certain radicals the transition state in an abstraction reaction has some polar character. For example, consider the abstraction of hydrogen from the methyl group of toluene by a bromine atom. Since bromine is more electronegative than carbon, it is reasonable to assume that in the transition state there is a separation of charge, with a partial negative charge on the halogen and a partial positive charge on the carbon:

$$\overset{\delta+}{PhCH_2}\cdots\cdots\cdots H \cdots\cdots\cdots \overset{\delta-}{Br}$$

Evidence for the polar character of the transition state is that electron-withdrawing groups in the para position of toluene (which would destabilize a positive charge) decrease the rate of hydrogen abstraction by bromine while electron-donating groups increase it.[26] However, substituents have a smaller effect here ($\rho \sim -1.4$) than they do in reactions where a completely ionic intermediate is involved, for example, the S_N1 mechanism (see p. 487). Other evidence for polar transition states in radical abstraction reactions is mentioned on p. 948. For abstraction by radicals such as methyl or phenyl, polar effects are very small or completely absent. For example, rates of hydrogen abstraction from ring-substituted toluenes by the methyl radical were relatively unaffected by the presence of electron-donating or electron-withdrawing substituents.[27] Those radicals (e.g., Br•) that have a tendency to abstract electron-rich hydrogen atoms are called *electrophilic radicals*.

When the reaction step R—X → R• takes place at a chiral carbon, racemization is almost always observed because free radicals do not retain configuration. Exceptions to this rule are found at cyclopropyl substrates, where both inversion[28] and retention[29] of configuration have been reported, and in the reactions mentioned on p. 942. Enantioselective radical processes have been reviewed.[30]

[25]Eliel, E.L., in Newman, M.S. *Steric Effects in Organic Chemistry*, Wiley, NY, ***1956***, pp. 142–143.

[26]For example, see Pearson, R.; Martin, J.C. *J. Am. Chem. Soc.* ***1963***, *85*, 354, 3142; Kim, S.S.; Choi, S.Y.; Kang, C.H. *J. Am. Chem. Soc.* ***1985***, *107*, 4234.

[27]For example, see Kalatzis, E.; Williams, G.H. *J. Chem. Soc. B* ***1966***, 1112; Pryor, W.A.; Tonellato, U.; Fuller, D.L.; Jumonville, S. *J. Org. Chem.* ***1969***, *34*, 2018.

[28]Altman, L.J.; Nelson, B.W. *J. Am. Chem. Soc.* ***1969***, *91*, 5163.

[29]Jacobus, J.; Pensak, D. *Chem. Commun.* ***1969***, 400.

[30]Sibi, M.P.; Manyem, S.; Zimmerman, J. *Chem. Rev.* ***2003***, *103*, 3263.

Mechanisms at an Aromatic Substrate[31]

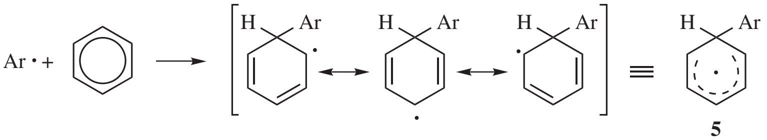
When R in reaction (1) is aromatic, the simple abstraction mechanism just discussed may be operating, especially in gas-phase reactions. However, mechanisms of this type cannot account for all reactions of aromatic substrates. In processes, such as the following (see **13-27**, **14-17**, and **14-18**):

$$\text{Ar}\bullet \quad + \quad \text{ArH} \longrightarrow \text{Ar—Ar}$$

which occur in solution, the coupling of two rings cannot be explained on the basis of a simple abstraction

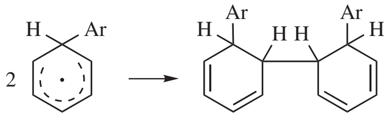
$$\text{Ar}\bullet \quad + \quad \text{ArH} \longrightarrow \text{Ar—Ar} \quad + \quad \text{H}\bullet$$

since, as discussed on p. 944, abstraction of an entire group, such as phenyl, by a free radical is very unlikely. The products can be explained by a mechanism similar to that of electrophilic and nucleophilic aromatic substitution. In the first step, the radical attacks the ring in much the same way as would an electrophile or a nucleophile:

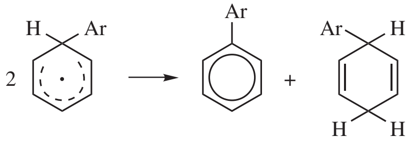


5

The intermediate radical **5** is relatively stable because of the resonance. The reaction can terminate in three ways: by simple coupling to give **6**, by disproportionation to give **7**,



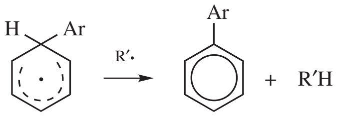
6



7

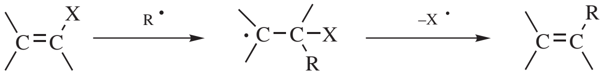
[31]For reviews, see Kobrina, L.S. *Russ. Chem. Rev.* ***1977***, *46*, 348; Perkins, M.J., in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 231–271; Bolton, R.; Williams, G.H. *Adv. Free-Radical Chem.* ***1975***, *5*, 1; Nonhebel, D.C.; Walton, J.C. *Free-Radical Chemistry*, Cambridge University Press, London, ***1974***, pp. 417–469; Minisci, F.; Porta, O. *Adv. Heterocycl. Chem.* ***1974***, *16*, 123; Bass, K.C.; Nababsing, P. *Adv. Free-Radical Chem.* ***1972***, *4*, 1; Hey, D.H. *Bull. Soc. Chim. Fr.* ***1968***, 1591.

or, if a species (R′•) is present that abstracts hydrogen, by abstraction to give **8**.[32]



8

Coupling product **6** is a partially hydrogenated quaterphenyl. Of course, the coupling need not be ortho–ortho, and other isomers can also be formed. Among the evidence for steps (9) and (10) was isolation of compounds of types **6** and **7**,[33] though normally under the reaction conditions dihydrobiphenyls like **7** are oxidized to the corresponding biphenyls. Other evidence for this mechanism is the detection of the intermediate **5** by CIDNP[34] and the absence of isotope effects, which would be expected if the rate-determining step were (7), which involves cleavage of the Ar—H bond. In the mechanism just given, the rate-determining step (8) does not involve loss of hydrogen. The reaction between aromatic rings and the HO• radical takes place by the same mechanism. Intramolecular hydrogen-transfer reactions of aryl radicals are known.[35] A similar mechanism has been shown for substitution at some vinylic[36] and acetylenic substrates, giving the substituted alkene **9**.[37] The kinetics of radical heterolysis reactions that form alkene radical cations has been studied.[38]



9

This is reminiscent of the nucleophilic tetrahedral mechanism at a vinylic carbon (p. 477).

There are a number of transition-metal mediated coupling reaction of aromatic substrates that probably proceed by radical coupling. It is also likely that many of these reactions do not proceed by free radicals, but rather by metal-mediated radicals or by ligand transfer on the metal. Reactions in these categories were presented

[32]Compound **5** can also be oxidized to the arene ArPh by atmospheric O_2. For a discussion of the mechanism of this oxidation, see Narita, N.; Tezuka, T. *J. Am. Chem. Soc.* ***1982***, *104*, 7316.

[33]De Tar, D.F.; Long, R.A.J. *J. Am. Chem. Soc.* ***1958***, *80*, 4742. See also, DeTar, D.F.; Long, R.A.J.; Rendleman, J.; Bradley, J.; Duncan, P. *J. Am. Chem. Soc.* ***1967***, *89*, 4051; DeTar, D.F. *J. Am. Chem. Soc.* ***1967***, *89*, 4058. See also, Jandu, K.S.; Nicolopoulou, M.; Perkins, M.J. *J. Chem. Res. (S)* ***1985***, 88.

[34]Fahrenholtz, S.R.; Trozzolo, A.M. *J. Am. Chem. Soc.* ***1972***, *94*, 282.

[35]Curran, D.P.; Fairweather, N. *J. Org. Chem.* ***2003***, *68*, 2972.

[36]The reaction of vinyl chloride with Cl^- favors the σ-route (nucleophilic attack at the σ-bond) over the π-route (nucleophilic attack at the π-bond), but vinyl chloride is not an experimentally viable substrate and cannot be considered as representative for the vinyl S_N2 reaction. The π-route is anticipated in substituted vinylic halide reactions, where electron-withdrawing groups are attached to the vinylic carbon. See Bach, R. D.; Baboul, A. G.; Schlegel, H. B. *J. Am. Chem. Soc*, ***2001***, *123*, 5787.

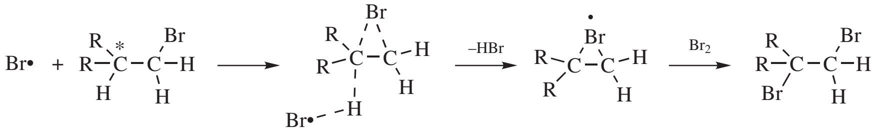
[37]Russell, G.A.; Ngoviwatchai, P. *Tetrahedron Lett.* ***1986***, *27*, 3479, and references cited therein.

[38]Horner, J.H.; Bagnol, L.; Newcomb, M. *J. Am. Chem. Soc.* ***2004***, *126*, 14979.

in Chapter 13 for convenient correlation with other displacement reactions of aryl halides, aryl diazonium salts, and so on.

Neighboring-Group Assistance in Free-Radical Reactions

In a few cases, it has been shown that cleavage steps (2) and abstraction steps (3) have been accelerated by the presence of neighboring groups. Photolytic halogenation (**14-1**) is a process that normally leads to mixtures of many products. However, bromination of carbon chains containing a bromine atom occurs with high regioselectivity. Bromination of alkyl bromides gave 84–94% substitution at the carbon adjacent to the bromine already in the molecule.[39] This result is especially surprising because, as we will see (p. 947), positions close to a polar group, such as bromine, should actually be *deactivated* by the electron-withdrawing field effect of the bromine. The unusual regioselectivity is explained by a mechanism in which abstraction (3) is assisted by a neighboring bromine atom, as in **10**.[40]



10 **11**

In the normal mechanism, Br• abstracts a hydrogen from RH, leaving R•. When a bromine is present in the proper position, it assists this process, giving a cyclic intermediate (a *bridged free radical*, **11**).[41] In the final step (very similar to R• + Br_2 → RBr + Br•), the ring is broken. If this mechanism is correct, the configuration at the substituted carbon (marked *) should be retained. This has been shown to be the case: optically active 1-bromo-2-methylbutane gave 1,2-dibromo-2-methylbutane with retention of configuration.[40] Furthermore, when this reaction was carried out in the presence of DBr, the "recovered" 1-bromo-2-methylbutane was found to be deuterated in the 2 position, and its configuration was retained.[42] This is just what would be predicted if some of the **11** present abstracted D from DBr. There is evidence that Cl can form bridged radicals,[43]

[39]Thaler, W.A. *J. Am. Chem. Soc.* ***1963***, *85*, 2607. See also, Traynham, J.G.; Hines, W.G. *J. Am. Chem. Soc.* ***1968***, *90*, 5208; Ucciani, E.; Pierri, F.; Naudet, M. *Bull. Soc. Chim. Fr.* ***1970***, 791; Hargis, J.H. *J. Org. Chem.* ***1973***, *38*, 346.

[40]Skell, P.S.; Tuleen, D.L.; Readio, P.D. *J. Am. Chem. Soc.* ***1963***, *85*, 2849. For other stereochemical evidence, see Huyser, E.S.; Feng, R.H.C. *J. Org. Chem.* ***1971***, *36*, 731. For another explanation, see Lloyd, R.V.; Wood, D.E. *J. Am. Chem. Soc.* ***1975***, *97*, 5986. Also see Cope, A.C.; Fenton, S.W. *J. Am. Chem. Soc.* ***1951***, *73*, 1668.

[41]For a monograph, see Kaplan, L. *Bridged Free Radicals*, Marcel Dekker, NY, ***1972***. For reviews, see Skell, P.S.; Traynham, J.G. *Acc. Chem. Res.* ***1984***, *17*, 160; Skell, P.S.; Shea, K.J. in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 809–852.

[42]Shea, K.J.; Skell, P.S. *J. Am. Chem. Soc.* ***1973***, *95*, 283.

[43]Everly, C.R.; Schweinsberg, F.; Traynham, J.G. *J. Am. Chem. Soc.* ***1978***, *100*, 1200; Wells, P.R.; Franke, F.P. *Tetrahedron Lett.* ***1979***, 4681.

though ESR spectra show that the bridging is not necessarily symmetrical.[44] Still more evidence for bridging by Br has been found in isotope effect and other studies.[45] However, evidence from CIDNP shows that the methylene protons of the β-bromoethyl radical are not equivalent, at least while the radical is present in the radical pair [PhCOO••CH_2CH_2Br] within a solvent cage.[46] This evidence indicates that under these conditions $BrCH_2CH_2$• is not a symmetrically bridged radical, but it could be unsymmetrically bridged. A bridged intermediate has also been invoked, when a bromo group is in the proper position, in the Hunsdiecker reaction[47] (**14-30**), and in abstraction of iodine atoms by the phenyl radical.[48] Participation by other neighboring groups (e.g. SR, SiR_3, SnR_3) has also been reported.[49]

REACTIVITY

Reactivity for Aliphatic Substrates[50]

In a chain reaction, the step that determines what the product will be is most often an abstraction step. What is abstracted by a free radical is almost never a tetra-[51] or tervalent atom[52] (except in strained systems, see p. 1027)[53] and seldom a divalent one.[54] Nearly always it is univalent, and so, for organic compounds, it is hydrogen or halogen. For example, a reaction between a chlorine atom and ethane gives an

[44]Bowles, A.J.; Hudson, A.; Jackson, R.A. *Chem. Phys. Lett.* ***1970***, *5*, 552; Cooper, J.; Hudson, A.; Jackson, R.A. *Tetrahedron Lett.* ***1973***, 831; Chen, K.S.; Elson, I.H.; Kochi, J.K. *J. Am. Chem. Soc.* ***1973***, *95*, 5341.

[45]Skell, P.S.; Pavlis, R.R.; Lewis, D.C.; Shea, K.J. *J. Am. Chem. Soc.* ***1973***, *95*, 6735; Juneja, P.S.; Hodnett, E.M. *J. Am. Chem. Soc.* ***1967***, *89*, 5685; Lewis, E.S.; Kozuka, S. *J. Am. Chem. Soc.* ***1973***, *95*, 282; Cain, E.N.; Solly, R.K. *J. Chem. Soc., Chem. Commun.* ***1974***, 148; Chenier, J.H.B.; Tremblay, J.P.; Howard, J.A. *J. Am. Chem. Soc.* ***1975***, *97*, 1618; Howard, J.A.; Chenier, J.H.B.; Holden, D.A. *Can. J. Chem.* ***1977***, *55*, 1463. See, however, Tanner, D.D.; Blackburn, E.V.; Kosugi, Y.; Ruo, T.C.S. *J. Am. Chem. Soc.* ***1977***, *99*, 2714.

[46]Hargis, J.H.; Shevlin, P.B. *J. Chem. Soc., Chem. Commun.* ***1973***, 179.

[47]Applequist, D.E.; Werner, N.D. *J. Org. Chem.* ***1963***, *28*, 48.

[48]Danen, W.C.; Winter, R.L. *J. Am. Chem. Soc.* ***1971***, *93*, 716.

[49]Tuleen, D.L.; Bentrude, W.G.; Martin, J.C. *J. Am. Chem. Soc.* ***1963***, *85*, 1938; Fisher, T.H.; Martin, J.C. *J. Am. Chem. Soc.* ***1966***, *88*, 3382; Jackson, R.A.; Ingold, K.U.; Griller, D.; Nazran, A.S. *J. Am. Chem. Soc.* ***1985***, *107*, 208. For a review of neighboring-group participation in cleavage reactions, especially those involving SiR_3 as a neighboring group, see Reetz, M.T. *Angew. Chem. Int. Ed.* ***1979***, *18*, 173.

[50]For a review of the factors involved in reactivity and regioselectivity in free-radical substitutions and additions, see Tedder, J.M. *Angew. Chem. Int. Ed.* ***1982***, *21*, 401.

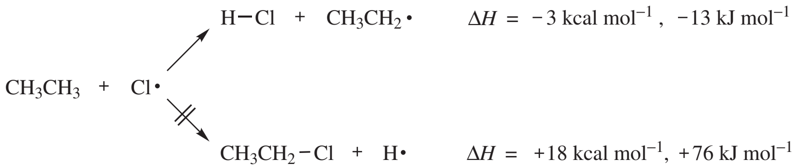
[51]Abstraction of a tetravalent carbon has been seen in the gas phase in abstraction by F• of R from RCl: Firouzbakht, M.L.; Ferrieri, R.A.; Wolf, A.P.; Rack, E.P. *J. Am. Chem. Soc.* ***1987***, *109*, 2213.

[52]See, for example, Back, R.A. *Can. J. Chem.* ***1983***, *61*, 916.

[53]For an example of an abstraction occurring to a small extent at an unstrained carbon atom, see Jackson, R.A.; Townson, M. *J. Chem. Soc. Perkin Trans. 2* ***1980***, 1452. See also, Johnson, M.D. *Acc. Chem. Res.* ***1983***, *16*, 343.

[54]For a monograph on abstractions of divalent and higher valent atoms, see Ingold, K.U.; Roberts, B.P. *Free-Radical Substitution Reactions*, Wiley, NY, ***1971***.

ethyl radical, not a hydrogen atom:



The principal reason for this is steric. A univalent atom is much more exposed to attack by the incoming radical than an atom with a higher valence. Another reason is that in many cases abstraction of a univalent atom is energetically more favored. For example, in the reaction given above, a C_2H_5—H bond is broken ($D = 100$ kcal mol^{-1}, 419 kJ mol^{-1}, from Table 5.3) whichever pathway is taken, but in the former case an H—Cl bond is formed ($D = 103$ kcal mol^{-1}, 432 kJ mol^{-1}) while in the latter case it is a C_2H_5—Cl bond ($D = 82$ kcal mol^{-1}, 343 kJ mol^{-1}). Thus the first reaction is favored because it is exothermic by 3 kcal mol^{-1} (100–103) [13 kJ mol^{-1} (419–432)], while the latter is endothermic by 18 kcal mol^{-1} (100–82) [76 kJ mol^{-1} (419–343)].[55] However, the steric reason is clearly more important, because even in cases where ΔH is not very different for the two possibilities, the univalent atom is chosen.[56] *Ab initio* studies have probed the transition structures for radical hydrogen abstractions.[57]

Most studies of aliphatic reactivity have been made with hydrogen as the leaving atom and chlorine atoms as the abstracting species.[58] In these reactions, every hydrogen in the substrate is potentially replaceable and mixtures are usually obtained. However, the abstracting radical is not totally unselective, and some positions on a molecule lose hydrogen more easily than others. *Ab initio* studies have studied the factors controlling hydrogen abstraction by radicals.[59] For hydrogen abstraction by the *tert*-butoxy radical (*t*-Bu—O•) the factors that influence rate in their order of importance are structure of the radical > substituent effects[60] > solvent effects.[61] We discuss the position of attack under several headings:[62]

[55]The parameter ΔH for a free-radical abstraction reaction can be regarded simply as the difference in D values for the bond being broken and the one formed.

[56]Giese, B.; Hartung, J. *Chem. Ber.* ***1992***, *125*, 1777.

[57]Eksterowicz, J.E.; Houk, K.N. *Tetrahedron Lett.* ***1993***, *34*, 427; Damm, W.; Dickhaut, J.; Wetterich, F.; Giese, B. *Tetrahedron Lett.* ***1993***, *34*, 431.

[58]For a review that lists many rate constants for abstraction of hydrogen at various positions of many molecules, see Hendry, D.G.; Mill, T.; Piszkiewicz, L.; Howard, J.A.; Eigenmann, H.K. *J. Phys. Chem. Ref. Data* ***1974***, *3*, 937; Roberts, B.P.; Steel, A.J. *Tetrahedron Lett.* ***1993***, *34*, 5167. See Tanko, J.M.; Blackert, J.F. *J. Chem. Soc. Perkin Trans. 2* ***1996***, 1775 for the absolute rate constants for abstraction of chlorine by alkyl radicals.

[59]Zavitsas, A.A. *J. Chem. Soc. Perkin Trans. 2* ***1998***, 499; Roberts, B.P. *J. Chem. Soc. Perkin Trans. 2* ***1996***, 2719.

[60]See Wen, Z.; Li, Z.; Shang, Z.; Cheng, J.-P. *J. Org. Chem.* ***2001***, *66*, 1466.

[61]Kim, S.S.; Kim, S.Y.; Ryou, S.S.; Lee, C.S.; Yoo, K.H. *J. Org. Chem.* ***1993***, *58*, 192.

[62]For reviews, see Tedder, J.M. *Tetrahedron* ***1982***, *38*, 313; Kerr, J.A., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 18, Elsevier, NY, ***1976***, pp. 39–109; Russell, G.A., in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 275–331; Rüchardt, C. *Angew. Chem. Int. Ed.* ***1970***, *9*, 830; Poutsma, M.L. *Methods Free-Radical Chem.* ***1969***, *1*, 79; Davidson, R.S. *Q. Rev. Chem. Soc.* ***1967***, *21*, 249; Pryor, W.A.; Fuller, D.L.; Stanley, J.P. *J. Am. Chem. Soc.* ***1972***, *94*, 1632.

TABLE 14.1. Relative Susceptibility to Attack by Cl• of Primary, Secondary, and Tertiary Positions at 100 and 600°C in the Gas Phase[63]

Temperature, °C	Primary	Secondary	Tertiary
100	1	4.3	7.0
600	1	2.1	2.6

1. *Alkanes*. The tertiary hydrogens of an alkane are the ones preferentially abstracted by almost any radical, with secondary hydrogens being next preferred. This is in the same order as *D* values for these types of C—H bonds (Table 5.3). The extent of the preference depends on the selectivity of the abstracting radical and on the temperature. Table 14.1 shows[63] that at high temperatures selectivity decreases, as might be expected.[64] An example of the effect of radical selectivity may be noted in a comparison of fluorine atoms with bromine atoms. For the former, the ratio of primary to tertiary abstraction (of hydrogen) is 1:1.4, while for the less reactive bromine atom this ratio is 1:1600. With certain large radicals there is a steric factor that may change the selectivity pattern. For example, in the photochemical chlorination of isopentane in H_2SO_4 with *N*-chloro-di-*tert*-butylamine and *N*-chloro-*tert*-butyl-*tert*-pentylamine, the primary hydrogens are abstracted 1.7 times *faster* than the tertiary hydrogen.[65] In this case, the attacking radicals (the radical ions $R_2NH\bullet^+$, see p. 958) are bulky enough for steric hindrance to become a major factor.

12

Cyclopropylcarbinyl radicals (**12**) are alkyl radicals, but they undergo rapid ring opening to give butenyl radicals.[66] The rate constant for this process has been measured by picosecond radical kinetic techniques to be in the range of $10^7\,M^{-1}\,s^{-1}$ for the parent[67] to $10^{10}\,M^{-1}\,s^{-1}$ for substituted derivatives.[68] Cyclobutylcarbinyl radicals undergo the cyclobutylcarbinyl to

[63]Hass, H.B.; McBee, E.T.; Weber, P. *Ind. Eng. Chem.* ***1936***, *28*, 333.

[64]For a similar result with phenyl radicals, see Kopinke, F.; Zimmermann, G.; Anders, K. *J. Org. Chem.* ***1989***, *54*, 3571.

[65]Deno, N.C.; Fishbein, R.; Wyckoff, J.C. *J. Am. Chem. Soc.* ***1971***, *93*, 2065. Similar steric effects, though not a reversal of primary-tertiary reactivity, were found by Dneprovskii, A.N.; Mil'tsov, S.A. *J. Org. Chem. USSR* ***1988***, *24*, 1836.

[66]Nonhebel, D.C. *Chem. Soc. Rev.* ***1993***, *22*, 347.

[67]Engel, P.S.; He, S.-L.; Banks, J.T.; Ingold, K.U.; Lusztyk, J. *J. Org. Chem.* ***1997***, *62*, 1210.

[68]Choi, S.-Y.; Newcomb, M. *Tetrahedron* ***1995***, *51*, 657; Choi, S.-Y.; Toy, P.H.; Newcomb, M. *J. Org. Chem.* ***1998***, *63*, 8609. See Martinez, F.N.; Schlegel, H.B.; Newcomb, M. *J. Org. Chem.* ***1996***, *61*, 8547; ***1998***, *63*, 3618 for *ab initio* studies to determine rate constants.

4-pentenyl radical process,[69] but examples are generally limited to the parent system and phenyl-substituted derivatives.[70] Cyclization of the 4-pentenyl radical is usually limited to systems where a stabilized radical can be formed.[71] The effect of substituents has been studied.[72] This process has been observed in bicyclo[4.1.0]heptan-4-ones.[73]

The rate of the ring-opening reaction of **5**,[74] and other substrates have been determined using an indirect method for the calibration[75] of fast radical reactions, applicable for radicals with lifetimes as short as 1 ps.[76] This 'radical clock'[77] method is based on the use of Barton's use of pyridine-2-thione-*N*-oxycarbonyl esters as radical precursors and radical trapping by the highly reactive thiophenol and benzeneselenol.[78] A number of radical clock substrates are known.[79] Other radical clock processes include: racemization of radicals with chiral conformations,[80] one-carbon ring expansion in cyclopentanones,[81] norcarane and spiro[2,5]octane,[82] α- and β-thujone radical rearrangements,[83] and cyclopropylcarbinyl radicals or alkoxycarbonyl radicals containing stabilizing substituents.[84]

[69]For a triplet radical in electron transfer cycloreversion of a cyclobutane, see Miranda, M.A.; Izquierdo, M.A.; Galindo, F. *J. Org. Chem.* ***2002***, *67*, 4138.

[70]Beckwith, A.L.J.; Moad, G. *J. Chem. Soc, Perkin Trans. 2* ***1980***, 1083; Ingold, K.U.; Maillard, B.; Walton, J.C. *J. Chem. Soc, Perkin Trans. 2* ***1981***, 970; Walton, J.C. *J. Chem. Soc, Perkin Trans. 2* ***1989***, 173; Choi, S.-Y.; Horner, J.H.; Newcomb, M. *J. Org. Chem.* ***2000***, *65*, 4447; Newcomb, M.; Horner, J.H.; Emanuel, C.J. *J. Am. Chem. Soc.* ***1997***, *119*, 7147.

[71]Clark, A.J.; Peacock, J.L. *Tetrahedron Lett.* ***1998***, *39*, 1265; Cerreti, A.; D'Annibale, A.; Trogolo, C.; Umani, F. *Tetrahedron Lett.* ***2000***, *41*, 3261; Ishibashi, H.; Higuchi, M.; Ohba, M.; Ikeda, M. *Tetrahedron Lett.* ***1998***, *39*, 75; Ishibashi, H.; Nakamura, N.; Sato, S.; Takeuchi, M.; Ikeda, M. *Tetrahedron Lett.* ***1991***, *32*, 1725; Ogura, K.; Sumitani, N.; Kayano, A.; Iguchi, H.; Fujita, M. *Chem. Lett.* ***1992***, 1487.

[72]Baker, J.M.; Dolbier Jr, W.R. *J. Org. Chem.* ***2001***, *66*, 2662.

[73]Kirschberg, T.; Mattay, J. *Tetrahedron Lett.* ***1994***, *35*, 7217.

[74]Mathew, L.; Warkentin, J. *J. Am. Chem. Soc.* ***1986***, *108*, 7981; For an article clocking tertiary cyclopropylcarbinyl radical rearrangements, see Engel, P.S.; He, S.-L.; Banks, J.T.; Ingold, K.U.; Lusztyk, J. *J. Org. Chem.* ***1997***, *62*, 1212, 5656.

[75]See Hollis, R.; Hughes, L.; Bowry, V.W.; Ingold, K.U. *J. Org. Chem.* ***1992***, *57*, 4284.

[76]Newcomb, M.; Toy, P.H. *Acc. Chem. Res.* ***2000***, *33*, 449. See Horn, A.H.C.; Clark, T. *J. Am. Chem. Soc.* ***2003***, *125*, 2809.

[77]For a review, see Griller, D.; Ingold, K.U. *Acc. Chem. Res.* ***1980***, *13*, 317.

[78]Newcomb, M.; Park, S.-U. *J. Am. Chem. Soc.* ***1986***, *108*, 4132; Newcomb, M.; Glenn, A.G. *J. Am. Chem. Soc.* ***1989***, *111*, 275; Newcomb, M.; Johnson, C.C.; Manek, M.B.; Varick, T.R. *J. Am. Chem. Soc.* ***1992***, *114*, 10915; Newcomb, M.; Varick, T.R.; Ha, C.; Manek, M.B.; Yue, X. *J. Am. Chem. Soc.* ***1992***, *114*, 8158.

[79]See Kumar, D.; de Visser, S.P.; Sharma, P.K.; Cohen, S.; Shaik, S. *J. Am. Chem. Soc.* ***2004***, *126*, 1907.

[80]Buckmelter, A.J.; Kim, A.I.; Rychnovsky, S.D. *J. Am. Chem. Soc.* ***2000***, *122*, 9386; Rychnovsky, S.D.; Hata, T.; Kim, A.I.; Buckmelter, A.J. *Org. Lett.* ***2001***, *3*, 807.

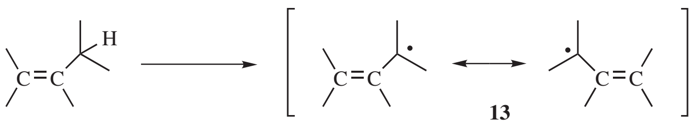
[81]Chatgilialoglu, C.; Timokhin, V. I.; Ballestri, M. *J. Org. Chem.* ***1998***, *63*, 1327.

[82]For an application and leading references, see Auclair, K.; Hu, Z.; Little, D. M.; Ortiz de Montellano, P. R.; Groves, J. T. *J. Am. Chem. Soc.* ***2002***, *124*, 6020.

[83]He, X.; Ortiz de Montellano, P. R. *J. Org. Chem.* ***2004***, *69*, 5684.

[84]Beckwith, A.L.J.; Bowry, V.W. *J. Am. Chem. Soc.* ***1994***, *116*, 2710. See Cooksy, A.L.; King, H.F.; Richardson, W.H. *J. Org. Chem.* ***2003***, *68*, 9441.

2. *Alkenes*. When the substrate molecule contains a double bond, treatment with chlorine or bromine usually leads to addition rather than substitution. However, for other radicals (and even for chlorine or bromine atoms when they do abstract a hydrogen) the position of attack is perfectly clear. Vinylic hydrogens are practically never abstracted, and allylic hydrogens are greatly preferred to other positions of the molecule. Allylic hydrogen abstraction from a cyclic alkenes is usually faster than abstraction from an acyclic alkene.[85] This is generally attributed[86] to resonance stabilization of the allylic radical, **13**. As might be expected, allylic rearrangements (see p. 469) are common in these cases.[87]



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3. *Alkyl Side Chains of Aromatic Rings*. The preferential position of attack on a side chain is usually the one to the ring. Both for active radicals, such as chlorine and phenyl, and for more selective ones, such as bromine, such attack is faster than that at a primary carbon, but for the active radicals benzylic attack is slower than for tertiary positions, while for the selective ones it is faster. Two or three aryl groups on a carbon activate its hydrogens even more, as would be expected from the resonance involved. These statements can be illustrated by the following abstraction ratios:[88]

	Me–H	$MeCH_2$–H	Me_2CH–H	Me_3C–H	$PhCH_2$–H	Ph_2CH–H	Ph_3C–H
Br	0.0007	1	220	19,400	64,000	1.1×10^6	6.4×10^6
Cl	0.004	1	4.3	6.0	1.3	2.6	9.5

However, many anomalous results have been reported for these substrates. The benzylic position is not always the most favored. One thing certain is that *aromatic* hydrogens are seldom abstracted if there are aliphatic ones to compete (note from Table 5.3, that *D* for Ph–H is higher than that for any alkyl H bond). Several σ• scales (similar to the σ, σ^+, and σ^- scales discussed in Chapter 9) have been developed for benzylic radicals.[89]

[85]Rothenberg, G.; Sasson, Y. *Tetrahedron* ***1998***, *54*, 5417.

[86]See however Kwart, H.; Brechbiel, M.; Miles, W.; Kwart, L.D. *J. Org. Chem.* ***1982***, *47*, 4524.

[87]For reviews, see Wilt, J.W., in Kochi, J.K. *Free Radicals*, Vol. 1, Wiley, NY, ***1973***, pp. 458–466.

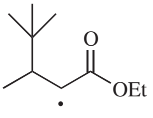
[88]Russell, G.A., in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, p. 289.

[89]See, for example, Dinçtürk, S.; Jackson, R.A. *J. Chem. Soc. Perkin Trans. 2* ***1981***, 1127; Dust, J.M.; Arnold, D.R. *J. Am. Chem. Soc.* ***1983***, *105*, 1221, 6531; Creary, X.; Mehrsheikh-Mohammadi, M.E.; McDonald, S. *J. Org. Chem.* ***1987***, *52*, 3254; ***1989***, *54*, 2904; Fisher, T.H.; Dershem, S.M.; Prewitt, M.L. *J. Org. Chem.* ***1990***, *55*, 1040.

4. *Compounds Containing Electron-Withdrawing Substituents.* In halogenations, electron-withdrawing groups greatly deactivate adjacent positions. Compounds of the type Z—CH_2—CH_3 are attacked predominantly or exclusively at the β position when Z is COOH, COCl, COOR, SO_2Cl, or CX_3. Such compounds as acetic acid and acetyl chloride are not attacked at all. This is in sharp contrast to electrophilic halogenations (**12-4–12-6**), where *only* the α position is substituted. This deactivation of a positions is also at variance with the expected stability of the resulting radicals, since they would be expected to be stabilized by resonance similar to that for allylic and benzylic radicals. This behavior is a result of the polar transition states discussed on p. 939. Halogen atoms are electrophilic radicals and look for positions of high electron density. Hydrogens on carbon atoms next to electron-withdrawing groups have low electron densities (because of the field effect of Z) and are therefore shunned. Radicals that are not electrophilic do not display this behavior. For example, the methyl radical is essentially nonpolar and does not avoid positions next to electron-withdrawing groups; relative rates of abstraction at the α and β carbons of propionic acid are:[90]

	CH_3—CH_2—COOH	
Me•	1	7.8
Cl•	1	0.02

It is possible to generate radicals adjacent to electron-withdrawing groups. Radical **14** can be generated and it undergoes coupling reactions with little selectivity. When **15** is generated, however, it rapidly disproportionates rather than couples, giving the corresponding alkene and alkane.[91] Such radicals have also been shown to have a conformational preference for orientation of the orbital containing the single electron. In such cases, hydrogen abstraction proceeds with good stereoselectivity.[92]



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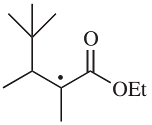

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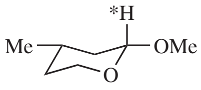
Some radicals, for example, *tert*-butyl,[93] benzyl,[94] and cyclopropyl,[95] are *nucleophilic* (they tend to abstract electron-poor hydrogen atoms). The

[90]Russell, G.A., in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, p. 311.
[91]Porter, N.A.; Rosenstein, I.J. *Tetrahedron Lett.* ***1993***, *34*, 7865.
[92]Giese, B.; Damm, W.; Wetterich, F.; Zeitz, H.-G. *Tetrahedron Lett.* ***1992***, *33*, 1863.
[93]Pryor, W.A.; Tang, F.Y.; Tang, R.H.; Church, D.F. *J. Am. Chem. Soc.* ***1982***, *104*, 2885; Dütsch, H.R.; Fischer, H. *Int. J. Chem. Kinet.* ***1982***, *14*, 195.
[94]Clerici, A.; Minisci, F.; Porta, O. *Tetrahedron* ***1973***, *29*, 2775.
[95]Stefani, A.; Chuang, L.; Todd, H.E. *J. Am. Chem. Soc.* ***1970***, *92*, 4168.

phenyl radical appears to have a very small degree of nucleophilic character.[96] For longer chains, the field effect continues, and the β position is also deactivated to attack by halogen, though much less so than the α position. We have already mentioned (p. 939) that abstraction of an α hydrogen atom from ring-substituted toluenes can be correlated by the Hammett equation.

5. *Stereoelectronic Effects*. On p. 1258, we will see an example of a stereoelectronic effect. It has been shown that such effects are important where a hydrogen is abstracted from a carbon adjacent to a C—O or C—N bond. In such cases, hydrogen is abstracted from C—H bonds that have a relatively small dihedral angle (∼30°) with the unshared orbitals of the O or N much more easily than from those with a large angle (∼90°). For example, the starred hydrogen of **16** was abstracted ∼8 times faster than the starred hydrogen of **17**.[97]



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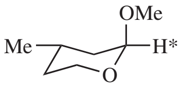

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The presence of an OR or SiR_3 substituent β- to the carbon bearing the radical accelerates the rate of halogen abstraction.[98]

Abstraction of a halogen has been studied much less,[99] but the order of reactivity is RI > RBr > RCl ≫ RF.

There are now many cases where free-radical reactions are promoted by transition metals.[100]

Reactivity at a Bridgehead[101]

Many free-radical reactions have been observed at bridgehead carbons, as in formation of bromide **18** (see **14-30**),[102] demonstrating that the free radical need not be planar. However, treatment of norbornane with sulfuryl chloride and benzoyl

[96]Suehiro, T.; Suzuki, A.; Tsuchida, Y.; Yamazaki, J. *Bull. Chem. Soc. Jpn.* ***1977***, *50*, 3324.

[97]Hayday, K.; McKelvey, R.D. *J. Org. Chem.* ***1976***, *41*, 2222. For additional examples, see Malatesta, V.; Ingold, K.U. *J. Am. Chem. Soc.* ***1981***, *103*, 609; Beckwith, A.L.J.; Easton, C.J. *J. Am. Chem. Soc.* ***1981***, *103*, 615; Beckwith, A.L.J.; Westwood, S.W. *Aust. J. Chem.* ***1983***, *36*, 2123; Griller, D.; Howard, J.A.; Marriott, P.R.; Scaiano, J.C. *J. Am. Chem. Soc.* ***1981***, *103*, 619. For a stereoselective abstraction step, see Dneprovskii, A.S.; Pertsikov, B.Z.; Temnikova, T.I. *J. Org. Chem. USSR* ***1982***, *18*, 1951. See also, Bunce, N.J.; Cheung, H.K.Y.; Langshaw, J. *J. Org. Chem.* ***1986***, *51*, 5421.

[98]Roberts, B.P.; Steel, A.J. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 2411.

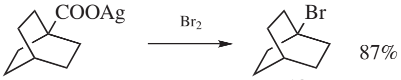
[99]For a review, see Danen, W.C. *Methods Free-Radical Chem.* ***1974***, *5*, 1.

[100]Iqbal, J.; Bhatia, B.; Nayyar, N.K. *Chem. Rev.* ***1994***, *94*, 519. See Hasegawa, E.; Curran, D.P. *Tetrahedron Lett.* ***1993***, *34*, 1717 for the rate of reaction for a primary akyl radical in the presence of SmI_2.

[101]For reviews, see Bingham, R.C.; Schleyer, P.v.R. *Fortschr. Chem. Forsch.* ***1971***, *18*, 1, see pp. 79–81; Fort, Jr, R.C.; Schleyer, P.v.R. *Adv. Alicyclic Chem.* ***1966***, *1*, 283, see p. 337.

[102]Grob, C.A.; Ohta, M.; Renk, E.; Weiss, A. *Helv. Chim. Acta* ***1958***, *41*, 1191.

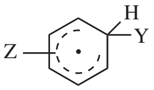
peroxide gave mostly 2-chloronorbornane, though the bridgehead position is tertiary.[103] So, while bridgehead free-radical substitution is possible, it is not preferred, presumably because of the strain involved.[104]



18

Reactivity in Aromatic Substrates

Free-radical substitution at an aromatic carbon seldom takes place by a mechanism in which a hydrogen is abstracted to give an aryl radical. Reactivity considerations here are similar to those in Chapters 11 and 13; that is, we need to know which position on the ring will be attacked to give the intermediate, **19**.



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The obvious way to obtain this information is to carry out reactions with various Z groups and to analyze the products for percent ortho, meta, and para isomers, as has so often been done for electrophilic substitution. However, this procedure is much less accurate in the case of free-radical substitutions because of the many side reactions. It may be, for example, that in a given case the ortho position is more reactive than the para, but the intermediate from the para attack may go on to product while that from ortho attack gives a side reaction. In such a case, analysis of the three products does not give a true picture of which position is most susceptible to attack. The following generalizations can nevertheless be drawn, though there has been much controversy over just how meaningful such conclusions are[105]

1. All substituents increase reactivity at ortho and para positions over that of benzene. There is no great difference between electron-donating and electron-withdrawing groups.
2. Reactivity at meta positions is usually similar to that of benzene, perhaps slightly higher or lower. This fact, coupled with the preceding one, means that all substituents are activating and ortho–para directing; none are deactivating or (chiefly) meta directing.

[103]Roberts, J.D.; Urbanek, L.; Armstrong, R. *J. Am. Chem. Soc.* ***1949***, *71*, 3049. See also, Kooyman, E.C.; Vegter, G.C. *Tetrahedron* ***1958***, *4*, 382; Walling, C.; Mayahi, M.F. *J. Am. Chem. Soc.* ***1959***, *81*, 1485.
[104]See, for example, Koch, V.R.; Gleicher, G.J. *J. Am. Chem. Soc.* ***1971***, *93*, 1657.
[105]De Tar, D.F. *J. Am. Chem. Soc.* ***1961***, *83*, 1014 (book review); Dickerman, S.C.; Vermont, G.B. *J. Am. Chem. Soc.* ***1962***, *84*, 4150; Morrison, R.T.; Cazes, J.; Samkoff, N.; Howe, C.A. *J. Am. Chem. Soc.* ***1962***, *84*, 4152; Ohta, H.; Tokumaru, K. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 3218; Vidal, S.; Court, J.; Bonnier, J. *J. Chem. Soc. Perkin Trans. 2* ***1973***, 2071; Tezuka, T.; Ichikawa, K.; Marusawa, H.; Narita, N. *Chem. Lett.* ***1983***, 1013.

TABLE 14.2. Partial Rate Factors for Attack of Substituted Benzenes by Phenyl Radicals Generated from Bz_2O_2[108]

	Partial Rate Factor		
Z	*o*	*m*	*p*
H	1	1	1
NO_2	5.50	0.86	4.90
CH_3	4.70	1.24	3.55
CMe_3	0.70	1.64	1.81
Cl	3.90	1.65	2.12
Br	3.05	1.70	1.92
MeO	5.6	1.23	2.31

3. Reactivity at ortho positions is usually somewhat greater than at para positions, except where a large group decreases ortho reactivity for steric reasons.

4. In direct competition, electron-withdrawing groups exert a somewhat greater influence than electron-donating groups. Arylation of para-disubstituted compounds XC_6H_4Y showed that substitution ortho to the group X became increasingly preferred as the electron-withdrawing character of X increases (with Y held constant).[106] The increase could be correlated with the Hammett σ_p values for X.

5. Substituents have a much smaller effect than in electrophilic or nucleophilic substitution; hence the partial rate factors (see p. 677) are not great.[107] Partial rate factors for a few groups are given in Table 14.2.[108]

6. Although hydrogen is the leaving group in most free-radical aromatic substitutions, ipso attack (p. 671) and ipso substitution (e.g., with Br, NO_2, or CH_3CO as the leaving group) have been found in certain cases.[109]

Reactivity in the Attacking Radical[110]

We have already seen that some radicals are much more selective than others (p. 944). The bromine atom is so selective that when only primary hydrogens are available, as in neopentane or *tert*-butylbenzene, the reaction is slow or nonexistent; and isobutane can be selectively brominated to give *tert*-butyl bromide in high yields.

[106]Davies, D.I.; Hey, D.H.; Summers, B. *J. Chem. Soc. C* ***1970***, 2653.

[107]For a quantitative treatment, see Charton, M.; Charton, B. *Bull. Soc. Chim. Fr.* ***1988***, 199.

[108]Davies, D.I.; Hey, D.H.; Summers, B. *J. Chem. Soc. C* ***1971***, 2681.

[109]For reviews, see Traynham, J.G. *J. Chem. Educ.* ***1983***, *60*, 937; *Chem. Rev.* ***1979***, *79*, 323; Tiecco, M. *Acc. Chem. Res.* ***1980***, *13*, 51; *Pure Appl. Chem.* ***1981***, *53*, 239.

[110]For reviews with respect to $CH_3\bullet$ and $CF_3\bullet$, see Trotman-Dickenson, A.F. *Adv. Free-Radical Chem.* ***1965***, *1*, 1; Spirin, Yu.L. *Russ. Chem. Rev.* ***1969***, *38*, 529; Gray, P.; Herod, A.A.; Jones, A. *Chem. Rev.* ***1971***, *71*, 247.

TABLE 14.3. Some Common Free Radicals in Decreasing Order of Activity[a]

	E			E	
Radical	kcal mol^{-1}e	kJ mol^{-1}e	Radical	kcal mol^{-1}	kJ mol^{-1}
F•	0.3	1.3	H•	9.0	38
Cl•	1.0	4.2	Me•	11.8	49.4
MeO•	7.1	30	Br•	13.2	55.2
CF_3•	7.5	31			

[a]The *E* values represent activation energies for the reaction

$$X\bullet + C_2H_6 \longrightarrow X\text{–}H + C_2H_5\bullet \qquad \text{(Ref. 112)}$$

i-Pr• is less active than Me• and *t*-Bu• still less so.[113]

However, toluene reacts with bromine atoms instantly. Bromination of other alkylbenzenes, for example, ethylbenzene and cumene, takes place exclusively at the a position,[111] emphasizing the selectivity of Br•. The dissociation energy *D* of the C—H bond is more important for radicals of low reactivity than for highly reactive radicals, since bond breaking in the transition state is greater. Thus, bromine shows a greater tendency than chlorine to attack α to an electron-withdrawing group because the energy of the C—H bond there is lower than in other places in the molecule.

Some radicals, for example, triphenylmethyl, are so unreactive that they abstract hydrogens very poorly if at all. Table 14.3 lists some common free radicals in approximate order of reactivity.[112]

It has been mentioned that some free radicals (e.g., chloro) are electrophilic and some (e.g., *tert*-butyl) are nucleophilic. It must be borne in mind that these tendencies are relatively slight compared with the electrophilicity of a positive ion or the nucleophilicity of a negative ion. The predominant character of a free radical is neutral, whether it has slight electrophilic or nucleophilic tendencies.

The Effect of Solvent on Reactivity[114]

As noted earlier, the solvent usually has little effect on free-radical substitutions in contrast to ionic ones: indeed, reactions in solution are often quite similar in character to those in the gas phase, where there is no solvent at all. However, in certain cases the solvent *can* make an appreciable difference. Chlorination of 2,3-dimethylbutane in aliphatic solvents gave about 60% $(CH_3)_2CHCH(CH_3)CH_2Cl$

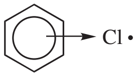
[111]Huyser, E.S. *Free-Radical Chain Reactions*, Wiley, NY, ***1970***, p. 97.

[112]Trotman-Dickenson, A.F. *Adv. Free-Radical Chem.* ***1965***, *1*, 1.

[113]Kharasch, M.S.; Hambling, J.K.; Rudy, T.P. *J. Org. Chem.* ***1959***, *24*, 303.

[114]For reviews, see Reichardt, C. *Solvent Effects in Organic Chemistry*; Verlag Chemie: Deerfield Beach, FL, ***1979***, pp. 110–123; Martin, J.C., in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 493–524; Huyser, E.S. *Adv. Free-Radical Chem.* ***1965***, *1*, 77.

and 40% $(CH_3)_2CHCCl(CH_3)_2$, while in aromatic solvents the ratio became ~10:90.[115] This result is attributed to complex formation between the aromatic solvent and the



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chlorine atom that makes the chlorine more selective.[116] This type of effect is not found in cases where the differences in ability to abstract the atom are caused by field effects of electron-withdrawing groups (p. 948). In such cases, aromatic solvents make little difference.[117] The complex **20** has been detected[118] as a very short-lived species by observation of its visible spectrum in the pulse radiolysis of a solution of benzene in CCl_4.[119] Differences caused by solvents have also been reported in reactions of other radicals.[120] Some of the anomalous results obtained in the chlorination of aromatic side chains (p. 947) can also be explained by this type of complexing, in this case not with the solvent but with the reacting species.[121] Much smaller, though real, differences in selectivity have been found when the solvent in the chlorination of 2,3-dimethylbutane is changed from an alkane to CCl_4.[122] However, these differences are not caused by formation of a complex between Cl• and the solvent. There are cases,

[115]Russell, G.A. *J. Am. Chem. Soc.* ***1958***, *80*, 4987, 4997, 5002; *J. Org. Chem.* ***1959***, *24*, 300.

[116]See also, Soumillion, J.P.; Bruylants, A. *Bull. Soc. Chim. Belg.* ***1969***, *78*, 425; Potter, A.; Tedder, J.M. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 1689; Aver'yanov, V.A.; Ruban, S.G.; Shvets,V.F. *J. Org. Chem. USSR* ***1987***, *23*, 782; Aver'yanov, V.A.; Ruban, S.G. *J. Org. Chem. USSR* ***1987***, *23*, 1119; Raner, K.D.; Lusztyk, J.; Ingold, K.U. *J. Am. Chem. Soc.* ***1989***, *111*, 3652; Ingold, K.U.; Lusztyk, J.; Raner, K.D. *Acc. Chem. Res.* ***1990***, *23*, 219.

[117]Russell, G.A. *Tetrahedron* ***1960***, *8*, 101; Nagai, T.; Horikawa, Y.; Ryang, H.S.; Tokura, N. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 2771.

[118]It has been contended that another species, a chlorocyclohexadienyl radical (the structure of which is the same as **5**, except that Cl replaces Ar), can also be attacking when the solvent is benzene: Skell, P.S.; Baxter III, H.N.; Taylor, C.K. *J. Am. Chem. Soc.* ***1983***, *105*, 120; Skell, P.S.; Baxter III, H.N.; Tanko, J.M.; Chebolu, V. *J. Am. Chem. Soc.* ***1986***, *108*, 6300. For arguments against this proposal, see Bunce, N.J.; Ingold, K.U.; Landers, J.P.; Lusztyk, J.; Scaiano, J.C. *J. Am. Chem. Soc.* ***1985***, *107*, 5464; Walling, C. *J. Org. Chem.* ***1988***, *53*, 305; Aver'yanov, V.A.; Shvets, V.F.; Semenov, A.O. *J. Org. Chem. USSR* ***1990***, *26*, 1261.

[119]Bühler, R.E. *Helv. Chim. Acta* ***1968***, *51*, 1558. For other spectral observations, see Raner, K.D.; Lusztyk, J.; Ingold, K.U. *J. Phys. Chem.* ***1989***, *93*, 564.

[120]Walling, C.; Azar, J.C. *J. Org. Chem.* ***1968***, *33*, 3885; Ito, O.; Matsuda, M. *J. Am. Chem. Soc.* ***1982***, *104*, 568; Minisci, F.; Vismara, E.; Fontana, F.; Morini, G.; Serravalle, M.; Giordano, C. *J. Org. Chem.* ***1987***, *52*, 730.

[121]Russell, G.A.; Ito, O.; Hendry, D.G. *J. Am. Chem. Soc.* ***1963***, *85*, 2976; Corbiau, J.L.; Bruylants, A. *Bull. Soc. Chim. Belg.* ***1970***, *79*, 203, 211; Newkirk, D.D.; Gleicher, G.J. *J. Am. Chem. Soc.* ***1974***, *96*, 3543.

[122]See Raner, K.D.; Lusztyk, J.; Ingold, K.U. *J. Org. Chem.* ***1988***, *53*, 5220.

however, where the rate of reaction for trapping a radical depends on the polarity of the solvent, particularly in water.[123]

REACTIONS

The reactions in this chapter are classified according to leaving group. The most common leaving groups are hydrogen and nitrogen (from the diazonium ion); these are considered first.

HYDROGEN AS LEAVING GROUP

A. Substitution by Halogen

14-1 Halogenation at an Alkyl Carbon[124]

Halogenation or **Halo-de-hydrogenation**

$$\text{R—H} \quad + \quad \text{Cl}_2 \xrightarrow{hv} \text{R—Cl}$$

Alkanes can be chlorinated or brominated by treatment with chlorine or bromine in the presence of visible or UV light.[125] These reactions require a radical chain initiator, light, or higher temperatures.[126] The reaction can also be applied to alkyl chains containing many functional groups. The chlorination reaction is usually not useful for preparative purposes precisely because it is so general: Not only does substitution take place at virtually every alkyl carbon in the molecule, but di- and polychloro substitution almost invariably occur even if there is a large molar ratio of substrate to halogen.

When functional groups are present, the principles are those outlined on p. 945; favored positions are those α to aromatic rings, while positions α to electron-withdrawing groups are least likely to be substituted. Tertiary carbons are most likely to be attacked and primary least. Positions α to an OR group are very readily attacked. Nevertheless, mixtures are nearly always obtained. This can be contrasted to the regioselectivity of electrophilic halogenation (**12-4–12-6**), which always takes place α to a carbonyl group (except when the reaction is catalyzed by $AgSbF_6$; see following). Of course, if a *mixture* of chlorides is wanted, the reaction is usually

[123]Tronche, C.; Martinez, F.N.; Horner, J.H.; Newcomb, M.; Senn, M.; Giese, B. *Tetrahedron Lett.* ***1996***, *37*, 5845.

[124]For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed, Wiley-VCH, NY, ***1999***, pp. 611–617.

[125]For reviews, see Poutsma, M.L., in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 159–229; Huyser, E.S., in Patai, S. *The Chemistry of the Carbon-Halogen Bond*, pt. 1, Wiley, NY, ***1973***, pp. 549–607; Poutsma, M.L. *Methods Free-Radical Chem.* ***1969***, *1*, 79 (chlorination); Thaler, W.A. *Methods Free-Radical Chem.* ***1969***, *2*, 121 (bromination).

[126]Hill, C.L. *Activation and Functionalization of Alkanes*, Wiley, NY, ***1989***.

quite satisfactory. For obtaining pure compounds, the chlorination reaction is essentially limited to substrates with only one type of replaceable hydrogen (e.g., ethane, cyclohexane, neopentane). The most common are methylbenzenes and other substrates with methyl groups on aromatic rings, since few cases are known where halogen atoms substitute at an aromatic position.[127] Of course, ring substitution *does* take place in the presence of a positive-ion-forming catalyst (**11-10**). In addition to mixtures of various alkyl halides, traces of other products are obtained. These include H_2, alkenes, higher alkanes, lower alkanes, and halogen derivatives of these compounds. Solvent plays an important role in this process.[128]

The bromine atom is much more selective than the chlorine atom. As indicated on p. 952, it is often possible to brominate tertiary and benzylic positions selectively. High regioselectivity can also be obtained where the neighboring-group mechanism (p. 942) can operate.

As already mentioned, halogenation can be performed with chlorine or bromine. Fluorine has also been used,[129] but seldom, because it is too reactive and hard to control.[130] It often breaks carbon chains down into smaller units, a side reaction that sometimes becomes troublesome in chlorinations too. Fluorination[131] has been achieved by the use of chlorine trifluoride ClF_3 at −75°C.[132] For example, cyclohexane gave 41% fluorocyclohexane and methylcyclohexane gave 47% 1-fluoro-1-methylcyclohexane. Fluoroxytrifluoromethane CF_3OF fluorinates tertiary positions of certain molecules in good yields with high regioselectivity.[133] For example, adamantane gave 75% 1-fluoroadamantane. Fluorine at −70°C, diluted with N_2,[134] and bromine trifluoride at 25–35°C[135] are also highly regioselective for

[127]Dermer, O.C.; Edmison, M.T. *Chem. Rev.* ***1957***, *57*, 77, pp. 110–112. An example of free-radical ring halogenation can be found in Engelsma, J.W.; Kooyman, E.C. *Revl. Trav. Chim. Pays-Bas*, ***1961***, *80*, 526, 537. For a review of aromatic halogenation in the gas phase, see Kooyman, E.C. *Adv. Free-Radical Chem.* ***1965***, *1*, 137.

[128]Dneprovskii, A.S.; Kuznetsov, D.V.; Eliseenkov, E.V.; Fletcher, B.; Tanko, J.M. *J. Org. Chem.* ***1998***, *63*, 8860.

[129]Rozen, S. *Acc. Chem. Res.* ***1988***, *21*, 307; Purrington, S.T.; Kagen, B.S.; Patrick, T.B. *Chem. Rev.* ***1986***, *86*, 997, pp. 1003–1005; Gerstenberger, M.R.C.; Haas, A. *Angew. Chem. Int. Ed.* ***1981***, *20*, 647; Hudlicky, M. *The Chemistry of Organic Fluorine Compounds*, 2nd ed., Ellis Horwood, Chichester, ***1976***; pp. 67–91. For descriptions of the apparatus necessary for handling F_2, see Vypel, H. *Chimia*, ***1985***, *39*, 305.

[130]However, there are several methods by which all the C—H bonds in a molecule can be converted to C—F bonds. For reviews, see Rozhkov, I.N., in Baizer, M.M.; Lund, H. *Organic Electrochemistry*, Marcel Dekker, NY, ***1983***, pp. 805–825; Lagow, R.J.; Margrave, J.L. *Prog. Inorg. Chem.* ***1979***, *26*, 161. See also, Adcock, J.L.; Horita, K.; Renk, E. *J. Am. Chem. Soc.* ***1981***, *103*, 6937; Adcock, J.L.; Evans, W.D. *J. Org. Chem.* ***1984***, *49*, 2719; Huang, H.; Lagow, R.J. *Bull. Soc. Chim. Fr.* ***1986***, 993.

[131]For a monograph on fluorinating agents, see German, L.; Zemskov, S. *New Fluorinating Agents in Organic Synthesis*, Springer, NY, ***1989***.

[132]Brower, K.R. *J. Org. Chem.* ***1987***, *52*, 798.

[133]Alker, D.; Barton, D.H.R.; Hesse, R.H.; Lister-James, J.; Markwell, R.E.; Pechet, M.M.; Rozen, S.; Takeshita, T.; Toh, H.T. *Nouv. J. Chem.* ***1980***, *4*, 239.

[134]Rozen, S.; Ben-Shushan, G. *J. Org. Chem.* ***1986***, *51*, 3522; Rozen, S.; Gal, C. *J. Org. Chem.* ***1987***, *52*, 4928; ***1988***, *53*, 2803; Alker, D.; Barton, D.H.R.; Hesse, R.H.; Lister-James, J.; Markwell, R.E.; Pechet, M.M.; Rozen, S.; Takeshita, T.; Toh, H.T. *Nouv. J. Chem.* ***1980***, *4*, 239.

[135]Boguslavskaya, L.S.; Kartashov, A.V.; Chuvatkin, N.N. *J. Org. Chem. USSR* ***1989***, *25*, 1835.

tertiary positions. These reactions probably have electrophilic,[136] not free-radical mechanisms. In fact, the success of the F_2 reactions depends on the suppression of free radical pathways, by dilution with an inert gas, by working at low temperatures, and/or by the use of radical scavengers.

Iodine can be used if the activating light has a wavelength of 184.9 nm,[137] but iodinations using I_2 alone are seldom attempted, largely because the HI formed reduces the alkyl iodide. The direct free-radical halogenation of aliphatic hydrocarbons with iodine is significantly endothermic relative to the other halogens, and the requisite chain reaction does not occur.[138] On the other hand, when iodine, CCl_4•2 AlI_3 react with an alkane in dibromomethane at −20°C, good yields of the iodoalkane are obtained.[139] The reaction of an alkane with *tert*-butylhypoiodite (*t*-BuOI) at 40°C gave the iodoalkane in good yield.[140] The reaction of alkanes with iodine and $PhI(OAc)_2$ generates the iodoalkane.[141] A radical protocol was developed using CI_4 with base. Cyclohexane could be iodinated, for example, with CI_4 in the presence of powdered NaOH.[142] The reaction led to the use of iodoform on solid NaOH as the iodination reagent of choice. α-Iodo ethers and α-iodolactones have been prepared from the parent ether or lactone via treatment with Et_4N•4 HF under electrolytic conditions.[143]

Many other halogenation agents have been employed, the most common of which is sulfuryl chloride SO_2Cl_2.[144] A mixture of Br_2 and HgO is a more active brominating agent than bromine alone.[145] The actual brominating agent in this case is believed to be bromine monoxide Br_2O. Among other agents used have been *N*-bromosuccinimide (NBS, see **14-3**), CCl_4,[146] $BrCCl_3$,[147] PCl_5,[148] and *N*-haloamines and sulfuric acid.[149] In all these cases, a chain-initiating catalyst is required, usually peroxides or UV light.

[136]See, for example, Rozen, S.; Gal, C. *J. Org. Chem.* ***1987***, *52*, 2769.
[137]Gover, T.A.; Willard, J.E. *J. Am. Chem. Soc.* ***1960***, *82*, 3816.
[138]Liguori, L.; Bjørsvik, H.-R.; Bravo, A.; Fontana, R.; Minisci, F. *Chem. Commun.* ***1997***, 1501; Tanner, D.D.; Gidley, G.C. *J. Am. Chem. Soc.* ***1968***, *90*, 808; Tanner, D.D.; Rowe, J.R.; Potter, A. *J. Org. Chem.* ***1986***, *51*, 457.
[139]Akhrem, I.; Orlinkov, A.; Vitt, S.; Chistyakov, A. *Tetrahedron Lett.* ***2002***, *43*, 1333.
[140]Montoro, R.; Wirth, T. *Org. Lett.* ***2003***, *5*, 4729.
[141]Barluenga, J.; González-Bobes, F.; González, J.M. *Angew. Chem. Int. Ed.* ***2002***, *41*, 2556.
[142]Schreiner, P.R.; Lauenstein, O.; Butova, E.D.; Fokin, A.A. *Angew. Chem. Int. Ed.* ***1999***, *38*, 2786.
[143]Hasegawa, M.; Ishii, H.; Fuchigami, T. *Tetrahedron Lett.* ***2002***, *43*, 1503.
[144]For a review of this reagent, see Tabushi, I.; Kitaguchi, H., in Pizey, J.S. *Synthetic Reagents*, Vol. 4, Wiley, NY, ***1981***, pp. 336–396.
[145]Bunce, N.J. *Can. J. Chem.* ***1972***, *50*, 3109.
[146]For a discussion of the mechanism with this reagent, see Hawari, J.A.; Davis, S.; Engel, P.S.; Gilbert, B.C.; Griller, D. *J. Am. Chem. Soc.* ***1985***, *107*, 4721.
[147]Huyser, E.S. *J. Am. Chem. Soc.* ***1960***, *82*, 391; Baldwin, S.W.; O'Neill, T.H. *Synth. Commun.* ***1976***, *6*, 109.
[148]Wyman, D.P.; Wang, J.Y.C.; Freeman, W.R. *J. Org. Chem.* ***1963***, *28*, 3173.
[149]For reviews, see Minisci, F. *Synthesis* ***1973***, 1; Deno, N.C. *Methods Free-Radical Chem.* ***1972***, *3*, 135; Sosnovsky, G.; Rawlinson, D.J. *Adv. Free-Radical Chem.* ***1972***, *4*, 203.

A base-induced bromination has been reported. 2-Methyl butane reacts with 50% aq. NaOH and CBr_4, in a phase-transfer catalyst, to give a modest yields of 2-bromo-2-methylbutane.[150]

When chlorination is carried out with *N*-haloamines and sulfuric acid (catalyzed by either uv light or metal ions), selectivity is much greater than with other reagents.[149] In particular, alkyl chains are chlorinated with high regioselectivity at the position next to the end of the chain (the ω - 1 position).[151] Some typical selectivity values are[152]

$CH_3-CH_2-CH_2-CH_2-CH_2-CH_2-CH_3$ Ref. 153
1 56 29 14

$CH_3-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-OH$ Ref. 154
1 92 3 1 1 2 0 0

$CH_3-CH_2-CH_2-CH_2-CH_2-CH_2-COOMe$ Ref. 155
3 72 20 4 1 0

Furthermore, di- and polychlorination are much less prevalent. Dicarboxylic acids are predominantly chlorinated in the middle of the chain,[156] and adamantane and bicyclo[2.2.2]octane at the bridgeheads[157] by this procedure. The reasons for the high ω - 1 specificity are not clearly understood.[158] Alkyl bromides can be regioselectively chlorinated one carbon away from the bromine (to give *vic*-bromochlorides) by treatment with PCl_5.[159] Alkyl chlorides can be converted to *vic*-dichlorides by treatment with $MoCl_5$.[160] Enhanced selectivity at a terminal position of *n*-alkanes has been achieved by absorbing the substrate onto a pentasil zeolite.[161] In another regioselective chlorination, alkanesulfonamides

[150]Schreiner, P.R.; Lauentstein, O.; Kolomitsyn, I.V.; Nadi, S.; Kokin, A.A. *Angew. Chem. Int. Ed.* ***1998***, *37*, 1895.

[151]The ω - 1 regioselectivity diminishes when the chains are >10 carbons; see Deno, N.C.; Jedziniak, E.J. *Tetrahedron Lett.* ***1976***, 1259; Konen, D.A.; Maxwell, R.J.; Silbert, L.S. *J. Org. Chem.* ***1979***, *44*, 3594.

[152]The ω − 1 selectivity values shown here may actually be lower than the true values because of selective solvolysis of the ω − 1 chlorides in concentrated H_2SO_4: see Deno, N.C.; Pohl, D.G. *J. Org. Chem.* ***1975***, *40*, 380.

[153]Bernardi, R.; Galli, R.; Minisci, F. *J. Chem. Soc. B* ***1968***, 324. See also, Deno, N.C.; Gladfelter, E.J.; Pohl, D.G. *J. Org. Chem.* ***1979***, *44*, 3728; Fuller, S.E.; Lindsay Smith, J.R.; Norman, R.O.C.; Higgins, R. *J. Chem. Soc. Perkin Trans. 2* ***1981***, 545.

[154]Deno, N.C.; Billups, W.E.; Fishbein, R.; Pierson, C.; Whalen, R.; Wyckoff, J.C. *J. Am. Chem. Soc.* ***1971***, *93*, 438.

[155]Minisci, F.; Gardini, G.P.; Bertini, F. *Can. J. Chem.* ***1970***, *48*, 544.

[156]Kämper, F.; Schäfer, H.J.; Luftmann, H. *Angew. Chem. Int. Ed.* ***1976***, *15*, 306.

[157]Smith, C.V.; Billups, W.E. *J. Am. Chem. Soc.* ***1974***, *96*, 4307.

[158]It has been reported that the selectivity in one case is in accord with a pure electrostatic (field effect) explanation: Dneprovskii, A.S.; Mil'tsov, S.A.; Arbuzov, P.V. *J. Org. Chem. USSR* ***1988***, *24*, 1826. See also, Tanner, D.D.; Arhart, R.; Meintzer, C.P. *Tetrahedron* ***1985***, *41*, 4261; Deno, N.C.; Pohl, D.G. *J. Org. Chem.* ***1975***, *40*, 380.

[159]Luche, J.L.; Bertin, J.; Kagan, H.B. *Tetrahedron Lett.* ***1974***, 759.

[160]San Filippo Jr, J.; Sowinski, A.F.; Romano, L.J. *J. Org. Chem.* ***1975***, *40*, 3463.

[161]Turro, N.J.; Fehlner, J.R.; Hessler, D.P.; Welsh, K.M.; Ruderman, W.; Firnberg, D.; Braun, A.M. *J. Org. Chem.* ***1988***, *53*, 3731.

RCH_2-$CH_2CH_2SO_2NHR'$ are converted primarily to $RCHClCH_2CH_2SO_2NHR'$ by sodium peroxydisulfate $Na_2S_2O_8$ and $CuCl_2$.[162] For regioselective chlorination at certain positions of the steroid nucleus, see **19-2**.

In almost all cases, the mechanism involves a free-radical chain:

$$\text{Initiation} \quad X_2 \xrightarrow{h\nu} 2\,X\bullet$$

$$RH + X\bullet \longrightarrow R\bullet + XH$$

$$\text{Propagation} \quad R\bullet + X_2 \longrightarrow RX + X\bullet$$

$$\text{Termination} \quad R\bullet + X\bullet \longrightarrow RX$$

When the reagent is halogen, initiation occurs as shown above.[163] When it is another reagent, a similar cleavage occurs (catalyzed by light or, more commonly, peroxides), followed by propagation steps that do not necessarily involve abstraction by halogen. For example, the propagation steps for chlorination by *tert*-butyl hypochlorite (*t*-BuOCl) have been formulated as[164]

$$RH + t\text{-}BuO\bullet \longrightarrow R\bullet + t\text{-}BuOH$$

$$R\bullet + t\text{-}BuOCl \longrightarrow RCl + t\text{-}BuO\bullet$$

and the abstracting radicals in the case of *N*-haloamines are the aminium radical cations $R_2NH\bullet^+$ (p. 693), with the following mechanism (in the case of initiation by Fe^{2+}):[149]

$$\text{Initiation} \quad R_2NCl \xrightarrow{H^+} R_2\overset{\oplus}{N}HCl \xrightarrow{Fe^{2+}} R_2NH\bullet^+ + \overset{\oplus}{Fe}Cl$$

$$R_2NH\bullet^+ + RH \longrightarrow R_2NH_2 + R\bullet$$

$$\text{Propagation} \quad R\bullet + R_2NHCl \longrightarrow RCl + R_2NH\bullet^+$$

This mechanism is similar to that of the Hofmann–Löffler reaction (**18-40**).

The two propagation steps shown above for X_2 are those that lead directly to the principal products (RX and HX), but many other propagation steps are possible and many occur. Similarly, the only termination step shown is the one that leads to RX, but any two radicals may combine (•H, •CH_3, •Cl, •CH_2CH_3 in all combinations).

[162]Nikishin, G.I.; Troyansky, E.I.; Lazareva, M.I. *Tetrahedron Lett.* ***1985***, *26*, 3743.

[163]There is evidence (unusually high amounts of multiply chlorinated products) that under certain conditions in the reaction of RH with Cl_2, the products of the second propagation step (RX + X•) are enclosed within a solvent cage. See Skell, P.S.; Baxter III, H.N. *J. Am. Chem. Soc.* ***1985***, *107*, 2823; Raner, K.D.; Lusztyk, J.; Ingold, K.U. *J. Am. Chem. Soc.* ***1988***, *110*, 3519; Tanko, J.M.; Anderson III, F.E. *J. Am. Chem. Soc.* ***1988***, *110*, 3525.

[164]Carlsson, D.J.; Ingold, K.U. *J. Am. Chem. Soc.* ***1967***, *89*, 4885, 4891; Walling, C.; McGuiness, J.A. *J. Am. Chem. Soc.* ***1969***, *91*, 2053. See also, Zhulin, V.M.; Rubinshtein, B.I. *Bull. Acad. Sci. USSR Div. Chem. Sci*, ***1977***, *26*, 2082.

Thus, products like H_2, higher alkanes, and higher alkyl halides can be accounted for. When methane is the substrate, the rate-determining step is

$$CH_4 + Cl\cdot \longrightarrow \cdot CH_3 + HCl$$

since an isotope effect of 12.1 was observed at 0°C.[165] For chlorinations, chains are very long, typically 10^4–10^6 propagations before a termination step takes place.

The order of reactivity of the halogens can be explained by energy considerations. For the substrate methane, ΔH values for the two principal propagation steps are

	kcal mol^{-1}				kJ mol^{-1}			
Reaction	F_2	Cl_2	Br_2	I_2	F_2	Cl_2	Br_2	I_2
$CH_4 + X\bullet \rightarrow CH_3\bullet + HX$	−31	+2	+17	+34	−132	+6	+72	+140
$CH_4 + X_2 \rightarrow CH_3X + X\bullet$	−70	−26	−24	−21	−293	−113	−100	−87

In each case, D for CH_3—H is 105 kcal mol^{-1} (438 kJ mol^{-1}), while D values for the other bonds involved are given in Table 14.4.[166] Fluorine is so reactive[167] that neither uv light nor any other initiation is needed (total $\Delta H = -101$ kcal mol^{-1}; −425 kJ mol^{-1});[168] while Br_2 and I_2 essentially do not react with methane. The second step is exothermic in all four cases, but it cannot take place before the first, and it is this step that is very unfavorable for Br_2 and I_2. It is apparent that the most important single factor causing the order of halogen reactivity to be $F_2 > Cl_2 > Br_2 > I_2$ is the decreasing strength of the HX bond in the order HF > HCl > HBr > HI. The increased reactivity of secondary and tertiary positions is in accord with the decrease in D values for R—H in the order primary > secondary > tertiary (Table 5.3). (Note that for chlorination step 1 is exothermic for practically all substrates other than CH_4, since most other aliphatic C—H bonds are weaker than those in CH_4.)

Bromination and chlorination of alkanes and cycloalkanes can also take place by an electrophilic mechanism if the reaction is catalyzed by $AgSbF_6$.[169] Direct

[165]Wiberg, K.B.; Motell, E.L. *Tetrahedron* ***1963***, *19*, 2009.

[166]Kerr, J.A., in Weast, R.C. *Handbook of Chemistry and Physics*, 69th ed., CRC Press, Boca Raton, FL, ***1988***, pp. F174–F189.

[167]It has been reported that the reaction of F atoms with CH_4 at 25 K takes place with practically zero activation energy: Johnson, G.L.; Andrews, L. *J. Am. Chem. Soc.* ***1980***, *102*, 5736.

[168]For F_2, the following initiation step is possible: $F_2 + RH \rightarrow R\bullet + F\bullet$ + HF [first demonstrated by Miller, Jr, W.T.; Koch, Jr, S.D.; McLafferty, F.W. *J. Am. Chem. Soc.* ***1956***, *78*, 4992]. ΔH for this reaction is equal to the small positive value of 5 kcal mol^{-1} (21 kJ mol^{-1}). The possibility of this reaction (which does not require an initiator) explains why fluorination can take place without UV light [which would otherwise be needed to furnish the 38 kcal mol^{-1} (159 kJ mol^{-1}) necessary to break the F—F bond]. Once the reaction has been initiated, the large amount of energy given off by the propagation steps is ample to cleave additional F_2 molecules. Indeed, it is the magnitude of this energy that is responsible for the cleavage of carbon chains by F_2.

[169]Olah, G.A.; Renner, R.; Schilling, P.; Mo, Y.K. *J. Am. Chem. Soc.* ***1973***, *95*, 7686. See also, Olah, G.A.; Wu, A.; Farooq, O. *J. Org. Chem.* ***1989***, *54*, 1463.

TABLE 14.4. Some *D* Values[166]

	D	
Bond	kcal mol^{-1}	kJ mol^{-1}
H—F	136	570
H—Cl	103	432
H—Br	88	366
H—I	71	298
F—F	38	159
Cl—Cl	59	243
Br—Br	46	193
I—I	36	151
CH_3—F	108	452
CH_3—Cl	85	356
CH_3—Br	70	293
CH_3—I	57	238

chlorination at a vinylic position by an electrophilic mechanism has been achieved with benzeneseleninyl chloride PhSe(O)Cl and $AlCl_3$ or $AlBr_3$.[170] However, while some substituted alkenes give high yields of chloro substitution products, others (e.g., styrene) undergo addition of Cl_2 to the double bond (**15-39**).[131] Electrophilic fluorination has already been mentioned (p. 956).

OS **II**, 89, 133, 443, 549; **III**, 737, 788; **IV**, 807, 921, 984; **V**, 145, 221, 328, 504, 635, 825; **VI**, 271, 404, 715; **VII**, 491; **VIII**, 161.

14-2 Halogenation at Silicon

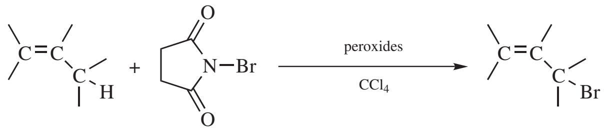
Halogenation or **Halo-de-hydrogenation**

$$R_3Si\text{–}H \longrightarrow R_3Si\text{–}X$$

Just as free-radical halogenation occurs at the carbon of an alkane, via hydrogen abstraction to form the radical, a similar reaction occurs at silicon. When triisopropylsilane (*i*Pr_3Si—H) reacts with *tert*-butyl hypochlorite at −10°C, the product is triisopropylchlorosilane (*i*Pr_3Si—Cl).[171]

14-3 Allylic and Benzylic Halogenation

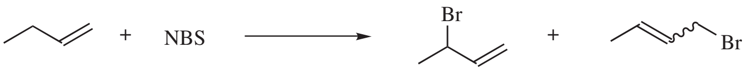
Halogenation or **Halo-de-hydrogenation**



[170]Kamigata, N.; Satoh, T.; Yoshida, M. *Bull. Chem. Soc. Jpn.* ***1988***, *44*, 449.
[171]Chawla, R.; Larson, G.L. *Synth. Commun.* ***1999***, *29*, 3499.

This reaction is a special case of **14-1**, but is important enough to be treated separately.[172] Alkenes can be halogenated in the allylic position and also a benzylic position by a number of reagents, of which NBS[173] is by far the most common. When this reagent is used, the reaction is known as *Wohl–Ziegler bromination*. A nonpolar solvent is used, most often CCl_4, but the reaction has been done in an ionic liquid.[174] A variation in the reaction used NBS with 5% $Yb(OTf)_3$ and 5% $ClSiMe_3$.[175] Other *N*-bromo amides have also been used. Allylic chlorination has been carried out, with *N*-chlorosuccinimide, *tert*-butyl hypochlorite,[176] or with $NaClO/CeCl_3{\bullet}7\ H_2O$.[177] With any reagent an initiator is needed; this is usually AIBN (**1**), a peroxide, such as di-*tert*-butyl peroxide or benzoyl peroxide or, less often, UV light.

The reaction is usually quite specific at an allylic or benzylic position and good yields are obtained. However, when the allylic radical intermediate is unsymmetrical, allylic rearrangements can take place, so that mixtures of both possible products are obtained, **21** and **22**.



21 **22**

When a double bond has two different allylic positions (e.g., $CH_3CH{=}CHCH_2CH_3$), a secondary position is substituted more readily than a primary. The relative reactivity of tertiary hydrogen is not clear, though many substitutions at allylic tertiary positions have been performed.[178] It is possible to brominate both sides of the double bond.[179] Because of the electron-withdrawing nature of bromine, the second bromine substitutes on the other side of the double bond rather than α to the first bromine. Molecules with a benzylic hydrogen, such as toluene, react rapidly to give α-bromomethyl benzene (e.g., $PhCH_3 \rightarrow PhCH_2Br$).

N-Bromosuccinimide is also a highly regioselective brominating agent at other positions, including positions α to a carbonyl group, to a $C{\equiv}C$ triple bond, and to an aromatic ring (benzylic position). When both a double and a triple bond are in the same molecule, the preferred position is α to the triple bond.[180]

Dauben and McCoy demonstrated that the mechanism of allylic bromination is of the free-radical type,[181] showing that the reaction is very sensitive to free-radical

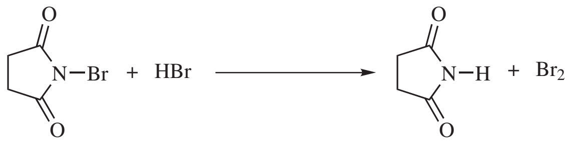
[172]For a review, see Nechvatal, A. *Adv. Free-Radical Chem.* ***1972***, *4*, 175.
[173]For a review of this reagent, see Pizey, J.S. *Synthetic Reagents*, Vol. 2, Wiley, NY, ***1974***, pp. 1–63.
[174]In bmim PF_6, 1-butyl-3-methylimidazolium hexafluoorophosphate: Togo, H.; Hirai, T. *Synlett* ***2003***, 702.
[175]Yamanaka, M.; Arisawa, M.; Nishida, A.; Nakagawa, M. *Tetahedron Lett.* ***2002***, *43*, 2403.
[176]Walling, C.; Thaler, W.A. *J. Am. Chem. Soc.* ***1961***, *83*, 3877.
[177]Moreno-Dorado, F.J.; Guerra, F.M.; Manzano, F.L.; Aladro, F.J.; Jorge, Z.S.; Massanet, G.M. *Tetrahedron Lett.* ***2003***, *44*, 6691.
[178]Dauben, Jr, H.J.; McCoy, L.L. *J. Org. Chem.* ***1959***, *24*, 1577.
[179]Ucciani, E.; Naudet, M. *Bull. Soc. Chim. Fr.* ***1962***, 871.
[180]Peiffer, G. *Bull. Soc. Chim. Fr.* ***1963***, 537.
[181]Dauben, Jr, H.J.; McCoy, L.L. *J. Am. Chem. Soc.* ***1959***, *81*, 4863.

initiators and inhibitors and indeed does not proceed at all unless at least a trace of initiator is present. Subsequent work indicated that the species that actually abstracts hydrogen from the substrate is the bromine atom. The reaction is initiated by small amounts of Br•. Once it is formed, the main propagation steps are

Step 1 $$Br\bullet + RH \longrightarrow R\bullet + HBr$$

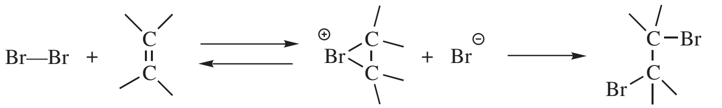
Step 2 $$R\bullet + Br_2 \longrightarrow RBr + Br\bullet$$

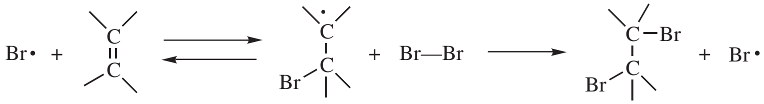
The source of the Br_2 is a fast ionic reaction between NBS and the HBr liberated in step 1:



The function of the NBS is therefore to provide a source of Br_2 in a low, steady-state concentration and to use up the HBr liberated in step 1.[182] The main evidence for this mechanism is that NBS and Br_2 show similar selectivity[183] and that the various *N*-bromo amides also show similar selectivity,[184] which is consistent with the hypothesis that the same species is abstracting in each case.[185]

It may be asked why, if Br_2 is the reacting species, it does not add to the double bond, either by an ionic or by a free-radical mechanism (see **15-39**). Apparently the concentration is too low. In bromination of a double bond, only one atom of an attacking bromine molecule becomes attached to the substrate, whether the addition is electrophilic or free radical:





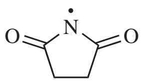
[182]This mechanism was originally suggested by Adam, J.; Gosselain, P.A.; Goldfinger, P. *Nature (London)*, ***1953***, *171*, 704; *Bull. Soc. Chim. Belg.* ***1956***, *65*, 533.

[183]Walling, C.; Rieger, A.L.; Tanner, D.D. *J. Am. Chem. Soc.* ***1963***, *85*, 3129; Russell, G.A.; Desmond, K.M. *J. Am. Chem. Soc.* ***1963***, *85*, 3139; Russell, G.A.; DeBoer, C.D.; Desmond, K.M. *J. Am. Chem. Soc.* ***1963***, *85*, 365; Pearson, R.; Martin, J.C. *J. Am. Chem. Soc.* ***1963***, *85*, 3142; Skell, P.S.; Tuleen, D.L.; Readio, P.D. *J. Am. Chem. Soc.* ***1963***, *85*, 2850.

[184]Walling, C.; Rieger, A.L. *J. Am. Chem. Soc.* ***1963***, *85*, 3134; Pearson, R.; Martin, J.C. *J. Am. Chem. Soc.* ***1963***, *85*, 3142; Incremona, J.H.; Martin, J.C. *J. Am. Chem. Soc.* ***1970***, *92*, 627.

[185]For other evidence, see Day, J.C.; Lindstrom, M.J.; Skell, P.S. *J. Am. Chem. Soc.* ***1974***, *96*, 5616.

The other bromine atom comes from another bromine-containing molecule or ion. This is clearly not a problem in reactions with benzylic species since the benzene ring is not prone to such addition reactions. If the concentration is sufficiently low, there is a low probability that the proper species will be in the vicinity once the intermediate forms. The intermediate in either case reverts to the initial species and the allylic substitution competes successfully. If this is true, it should be possible to brominate an alkene in the allylic position without competition from addition, even in the absence of NBS or a similar compound, if a very low concentration of bromine is used and if the HBr is removed as it is formed so that it is not available to complete the addition step. This has indeed been demonstrated.[186]



23

When NBS is used to brominate non-alkenyl substrates, such as alkanes, another mechanism, involving abstraction of the hydrogen of the substrate by the succinimidyl radical[187] **23** can operate.[188] This mechanism is facilitated by solvents (e.g., CH_2Cl_2, $CHCl_3$, or MeCN) in which NBS is more soluble, and by the presence of small amounts of an alkene that lacks an allylic hydrogen (e.g., ethene). The alkene serves to scavenge any Br• that forms from the reagent. Among the evidence for the mechanism involving **23** are abstraction selectivities similar to those of Cl• atoms and the isolation of β-bromopropionyl isocyanate ($BrCH_2CH_2CONCO$) which is formed by ring opening of **23**.

Allylic chlorination has also been carried out[189] with *N*-chlorosuccinimide (NCS) and either arylselenyl chlorides (ArSeCl), aryl diselenides (ArSeSeAr), or TsNSO as catalysts. Use of the selenium catalysts produces almost entirely the allylically rearranged chlorides in high yields. With TsNSO the products are the unrearranged chlorides in lower yields. Dichlorine monoxide Cl_2O, with no catalyst, also gives allylically rearranged chlorides in high yields.[190] A free-radical mechanism is unlikely in these reactions.

Allyl silanes react with transition metals bearing chlorine ligands to give allyl chlorides, where a chlorine replaces a Me_3Si unit.[191]

OS **IV**, 108; **V**, 825; **VI**, 462; **IX**, 191.

[186]McGrath, B.P.; Tedder, J.M. *Proc. Chem. Soc.* ***1961***, 80.

[187]For a review of this radical, see Chow, Y.L.; Naguib, Y.M.A. *Rev. Chem. Intermed.* ***1984***, *5*, 325.

[188]Skell, P.S.; Day, J.C. *Acc. Chem. Res.* ***1978***, *11*, 381; Tanner, D.D.; Reed, D.W.; Tan, S.L.; Meintzer, C.P.; Walling, C.; Sopchik, A. *J. Am. Chem. Soc.* ***1985***, *107*, 6576; Lüning, U.; Seshadri, S.; Skell, P.S. *J. Org. Chem.* ***1986***, *51*, 2071; Zhang, Y.; Dong, M.; Jiang, X.; Chow, Y.L. *Can. J. Chem.* ***1990***, *68*, 1668.

[189]Hori, T.; Sharpless, K.B. *J. Org. Chem.* ***1979***, *44*, 4204.

[190]Torii, S.; Tanaka, H.; Tada, N.; Nagao, S.; Sasaoka, M. *Chem. Lett.* ***1984***, 877.

[191]Fujii, T.; Hirao, Y.; Ohshiro, Y. *Tetrahedron Lett.* ***1993***, *34*, 5601.

14-4 Halogenation of Aldehydes

Halogenation or **Halo-de-hydrogenation**

$$RCHO + Cl_2 \longrightarrow RCOCl$$

The α-halogenation reaction of carbonyl compounds was mentioned in Section **14-2**. A different halogenation reaction is possible in which aldehydes can be directly converted to acyl chlorides by treatment with chlorine, but the reaction operates only when the aldehyde does not contain an α hydrogen and even then it is not very useful. When there is an α hydrogen, α halogenation (**14-2, 12-4**) occurs instead. Other sources of chlorine have also been used, among them SO_2Cl_2[192] and *t*-BOCl.[193] The mechanisms are probably of the free-radical type. *N*-Bromosuccinimide, with AIBN (p. 935) as a catalyst, has been used to convert aldehydes to acyl bromides.[194]

OS **I**, 155.

B. Substitution by Oxygen

14-5 Hydroxylation at an Aromatic Carbon[195]

Hydroxylation or **Hydroxy-de-hydrogenation**

$$ArH + H_2O_2 + FeSO_4 \longrightarrow ArOH$$

A mixture of hydrogen peroxide and ferrous sulfate,[196] called *Fenton's reagent*,[197] can be used to hydroxylate aromatic rings, though yields are usually not high.[198] Biaryls are usually side products.[199] Among other reagents used have been H_2O_2 and titanous ion; O_2 and Cu(I)[200] or Fe(III),[201] a mixture of ferrous

[192]Arai, M. *Bull. Chem. Soc. Jpn.* ***1964***, *37*, 1280; ***1965***, *38*, 252.

[193]Walling, C.; Mintz, M.J. *J. Am. Chem. Soc.* ***1967***, *89*, 1515.

[194]Markó, I.E.; Mekhalfia, A. *Tetrahedron Lett.* ***1990***, *31*, 7237. For a related procedure, see Cheung, Y. *Tetrahedron Lett.* ***1979***, 3809.

[195]For reviews, see Vysotskaya, N.A. *Russ. Chem. Rev.* ***1973***, *42*, 851; Sangster, D.F., in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, ***1971***, pp. 133–191; Metelitsa, D.I. *Russ. Chem. Rev.* ***1971***, *40*, 563; Enisov, E.T.; Metelitsa, D.I. *Russ. Chem. Rev.* ***1968***, *37*, 656; Loudon, J.D. *Prog. Org. Chem.* ***1961***, *5*, 47.

[196]For a review of reactions of H_2O_2 and metal ions with all kinds of organic compounds, including aromatic rings, see Sosnovsky, G.; Rawlinson, D.J., in Swern, D. *Organic Peroxides*, Vol. 2, Wiley, NY, ***1970***, pp. 269–336. See also, Sheldon, R.A.; Kochi, J.K. *Metal-Catalyzed Oxidations of Organic Compounds*, Academic Press, NY, ***1981***.

[197]For a discussion of Fenton's reagent, see Walling, C. *Acc. Chem. Res.* ***1975***, *8*, 125.

[198]Yields can be improved with phase transfer catalysis: Karakhanov, E.A.; Narin, S.Yu.; Filippova, T.Yu.; Dedov, A.G. *Doklad. Chem.* ***1987***, *292*, 81.

[199]See the discussion of the aromatic free-radical substitution mechanism on pp. $$$–$$$.

[200]See Karlin, K.D.; Hayes, J.C.; Gultneh, Y.; Cruse, R.W.; McKown, J.W.; Hutchinson, J.P.; Zubieta, J. *J. Am. Chem. Soc.* ***1984***, *106*, 2121; Cruse, R.W.; Kaderli, S.; Meyer, C.J.; Zuberbühler, A.D.; Karlin, K.D. *J. Am. Chem. Soc.* ***1988***, *110*, 5020; Ito, S.; Kunai, A.; Okada, H.; Sasaki, K. *J. Org. Chem.* ***1988***, *53*, 296.

[201]Funabiki, T.; Tsujimoto, M.; Ozawa, S.; Yoshida, S. *Chem. Lett.* ***1989***, 1267.

ion, oxygen, ascorbic acid, and ethylenetetraaminetetraacetic acid (*Udenfriend's reagent*);[202] O_2 and KOH in liquid NH_3;[203] and peroxyacids such as peroxynitrous and trifluoroperoxyacetic acids.

Much work has been done on the mechanism of the reaction with Fenton's reagent, and it is known that free aryl radicals (formed by a process, e.g., HO• + ArH → AR• + H_2O) are not intermediates. The mechanism is essentially that outlined on p. $$$, with HO• as the attacking species,[204] formed by

$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + OH^- + HO\bullet$$

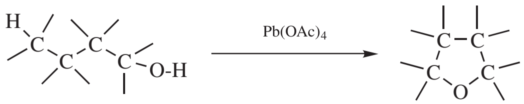
The rate-determining step is formation of HO• and not its reaction with the aromatic substrate.

An alternative oxidation of arene to phenol was reported using $Cu(NO_3)\bullet 3\ H_2O$, 30% hydrogen peroxide and a phosphate buffer.[205]

See also, **11-26**.

14-6 Formation of Cyclic Ethers

(5)*OC-cyclo*-Alkoxy-de-hydro-substitution



Alcohols with a hydrogen in the δ position can be cyclized with lead tetraacetate.[206] The reaction is usually carried out at ~80°C (most often in refluxing benzene), but can also be done at room temperature if the reaction mixture is irradiated with uv light. Tetrahydrofurans are formed in high yields. Little or no four- and six-membered cyclic ethers (oxetanes and tetrahydropyrans, respectively) are obtained even when γ and ε hydrogens are present. The reaction has also been carried out with a mixture of halogen (Br_2 or I_2) and a salt or oxide of silver or mercury (especially HgO or AgOAc),[207] with iodosobenzene diacetate and I_2,[208] and with ceric

[202] Udenfriend, S.; Clark, C.T.; Axelrod, J.; Brodie, B.B. *J. Biol. Chem.* ***1954***, *208*, 731; Brodie, B.B.; Shore, P.A.; Udenfriend, S. *J. Biol. Chem.* ***1954***, *208*, 741. See also, Tamagaki, S.; Suzuki, K.; Tagaki, W. *Bull. Chem. Soc. Jpn.* ***1989***, *62*, 148, 153, 159.

[203] Malykhin, E.V.; Kolesnichenko, G.A.; Shteingarts, V.D. *J. Org. Chem. USSR* ***1986***, *22*, 720.

[204] Jefcoate, C.R.E.; Lindsay Smith, J.R.; Norman, R.O.C. *J. Chem. Soc. B* ***1969***, 1013; Brook, M.A.; Castle, L.; Lindsay Smith, J.R.; Higgins, R.; Morris, K.P. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 687; Lai, C.; Piette, L.H. *Tetrahedron Lett.* ***1979***, 775; Kunai, A.; Hata, S.; Ito, S.; Sasaki, K. *J. Am. Chem. Soc.* ***1986***, *108*, 6012.

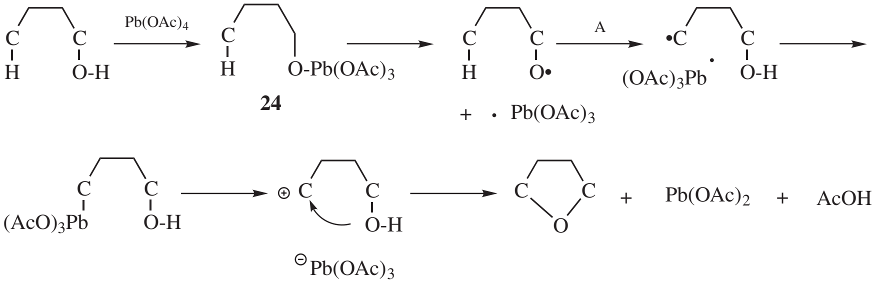
[205] Nasreen, A.; Adapa, S.R. *Org. Prep. Proceed. Int.* ***2000***, *32*, 373.

[206] For reviews, see Mihailović, M.Lj.; Partch, R. *Sel. Org. Transform.* ***1972***, *2*, 97; Milhailović, M.Lj.; Čeković, Z. *Synthesis* ***1970***, 209. For a review of the chemistry of lead tetraacetate, see Butler, R.N., in Pizey, J.S. *Synthetic Reagents*, Vol. 3, Wiley, NY, ***1977***, pp. 277–419.

[207] Akhtar, M.; Barton, D.H.R. *J. Am. Chem. Soc.* ***1964***, *86*, 1528; Sneen, R.A.; Matheny, N.P. *J. Am. Chem. Soc.* ***1964***, *86*, 3905, 5503; Roscher, N.M.; Shaffer, D.K. *Tetrahedron* ***1984***, *40*, 2643. For a review, see Kalvoda, J.; Heusler, K. *Synthesis* ***1971***, 501. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed, Wiley-VCH, NY, ***1999***, pp. 889–890.

[208] Concepción, J.I.; Francisco, C.G.; Hernández, R.; Salazar, J.A.; Suárez, E. *Tetrahedron Lett.* ***1984***, *25*, 1953; Furuta, K.; Nagata, T.; Yamamoto, H. *Tetrahedron Lett.* ***1988***, *29*, 2215.

ammonium nitrate (CAN).[209] The following mechanism is likely for the lead tetraacetate reaction:[210]

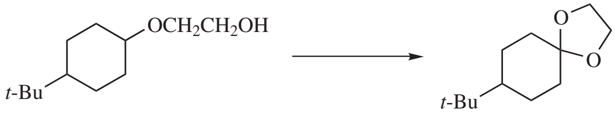


though **24** has never been isolated. The step marked **A** is a 1,5 internal hydrogen abstraction. Such abstractions are well known (see **18-40**) and are greatly favored over 1,4 or 1,6 abstractions (the small amounts of tetrahydropyran formed result from 1,6 abstractions).[211]

Reactions that sometimes compete are oxidation to the aldehyde or acid (**19-3** and **19-22**) and fragmentation of the substrate. When the OH group is on a ring of at least seven members, a transannular product can be formed, as in the cyclization reaction of 1-octanol to **25**.[212]

25

β-Hydroxy ethers can give cyclic acetals, such as **26**.[213]



26

There are no references in *Organic Syntheses*, but see OS **V**, 692; **VI**, 958, for related reactions.

[209]See, for example, Trahanovsky, W.S.; Young, M.G.; Nave, P.M. *Tetrahedron Lett.* ***1969***, 2501; Doyle, M.P.; Zuidema, L.J.; Bade, T.R. *J. Org. Chem.* ***1975***, *40*, 1454.

[210]Mihailović, M.Lj.; Čeković, Z.; Maksimović, Z.; Jeremić, D.; Lorenc, Lj.; Mamuzi, R.I. *Tetrahedron* ***1965***, *21*, 2799.

[211]Mihailović, M.Lj.; Čeković, Z.; Jeremić, D. *Tetrahedron* ***1965***, *21*, 2813.

[212]Cope, A.C.; Gordon, M.; Moon, S.; Park, C.H. *J. Am. Chem. Soc.* ***1965***, *87*, 3119; Moriarty, R.M.; Walsh, H.G. *Tetrahedron Lett.* ***1965***, 465; Mihailović, M.Lj.; Čeković, Z.; Andrejević, V.; Matić, R.; Jeremić, D. *Tetrahedron* ***1968***, *24*, 4947.

[213]Furuta, K.; Nagata, T.; Yamamoto, H. *Tetrahedron Lett.* ***1988***, *29*, 2215.

14-7 Formation of Hydroperoxides

Hydroperoxy-de-hydrogenation

$$RH + O_2 \longrightarrow R{-}O{-}O{-}H$$

The slow atmospheric oxidation (*slow* meaning without combustion) of C—H to C—O—O—H is called *autoxidation*.[214] The reaction occurs when compounds are allowed to stand in air and is catalyzed by light, so unwanted autoxidations can be greatly slowed by keeping the compounds in dark places. Most autoxidations proceed by free-radical chain processes that involve peroxyl radicals.[215] To suppress autoxidation, an antioxidant can be added that will prevent or retard the reaction with atmospheric oxygen.[216] Although some lactone compounds are sold as antioxidants, many radicals derived from lactones show poor or no reactivity toward oxygen.[216] The hydroperoxides produced often react further to give alcohols, ketones, and more complicated products, so the reaction is not often used for preparative purposes, although in some cases hydroperoxides have been prepared in good yield.[217] It is because of autoxidation that foods, rubber, paint, lubricating oils, and so on deteriorate on exposure to the atmosphere over periods of time. On the other hand, a useful application of autoxidation is the atmospheric drying of paints and varnishes. As with other free-radical reactions of C—H bonds, some bonds are attacked more readily than others,[218] and these are the ones we have seen before (pp. 943–949), though the selectivity is very low at high temperatures and in the gas phase. The reaction can be carried out successfully at tertiary (to a lesser extent, secondary), benzylic,[219] and allylic (though allylic rearrangements are common) R.[220] 2-Phenylpropane reacted with oxygen to give $PhMe_2C$—OOH, for example. Another susceptible position is aldehydic C—H,

[214]The term autoxidation actually applies to any slow oxidation with atmospheric oxygen. See Goosen, A.; Morgan, D.H. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 557. For reviews, see Sheldon, R.A.; Kochi, J.K. *Adv. Catal.*, ***1976***, *25*, 272; Howard, W.G., in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 3–62; Lloyd, W.G. *Methods Free-Radical Chem.* ***1973***, *4*, 1; Betts, J. *Q. Rev. Chem. Soc.* ***1971***, *25*, 265; Huyser, E.S. *Free-Radical Chain Reactions*, Wiley, NY, ***1970***, pp. 306–312; Chinn, L.J. *Selection of Oxidants in Synthesis* Marcel Dekker, NY, ***1971***, pp. 29–39; Ingold, K.U. *Acc. Chem. Res.* ***1969***, *2*, 1; Mayo, F.R. *Acc. Chem. Res.* ***1968***, *1*, 193. For monographs on these and similar reactions, see Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 16, Elsevier, NY, ***1980***; Sheldon, R.A.; Kochi, J.K. *Metal-Catalyzed Oxidations of Organic Compounds*, Academic Press, NY, ***1981***.

[215]Ingold, K.U. *Acc. Chem. Res.* ***1969***, *2*, 1.

[216]Bejan, E.V.; Font-Sanchis, E.; Scaiano, J.C. *Org. Lett*, ***2001***, *3*, 4059; Scaiano, J.C.; Martin, A.; Yap, G.P.A.; Ingold, K.U. *Org. Lett.* ***2000***, *2*, 899.

[217]For a review of the synthesis of alkyl peroxides and hydroperoxides, see Sheldon, R.A., in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, ***1983***, pp. 161–200.

[218]For a discussion, see Korcek, S.; Chenier, J.H.B.; Howard, J.A.; Ingold, K.U. *Can. J. Chem.* ***1972***, *50*, 2285, and other papers in this series.

[219]For a method that gives good yields at benzylic positions, see Santamaria, J.; Jroundi, R.; Rigaudy, J. *Tetrahedron Lett.* ***1989***, *30*, 4677.

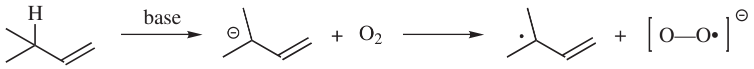
[220]For a review of autoxidation at allylic and benzylic positions, see Voronenkov, V.V.; Vinogradov, A.N.; Belyaev, V.A. *Russ. Chem. Rev.* ***1970***, *39*, 944.

but the peroxyacids so produced are not easily isolated[221] since they are converted to the corresponding carboxylic acids (**19-23**). The α positions of ethers are also easily attacked by oxygen [RO—C—H → RO—C—OOH], but the resulting hydroperoxides are seldom isolated. However, this reaction constitutes a hazard in the storage of ethers since solutions of these hydroperoxides and their rearrangement products in ethers are potential spontaneous explosives.[222]

Oxygen itself (a diradical) is not reactive enough to be the species that actually abstracts the hydrogen. But if a trace of free radical (say R′•) is produced by some initiating process, *it* reacts with oxygen[223] to give R′—O—O•; since this type of radical *does* abstract hydrogen, the chain is

$$R'OO\bullet + RH \longrightarrow R\bullet + R'OOH$$
$$R\bullet + O_2 \longrightarrow R{-}O{-}O\bullet$$
$$\text{etc.}$$

In at least some cases (in alkaline media)[224] the radical R• can be produced by formation of a carbanion and its oxidation (by O_2) to a radical, such as allylic radical **27**.[225]



27

Autoxidations in alkaline media can also proceed by a different mechanism: $R{-}H + \text{base} \rightarrow R^- + O_2 \rightarrow ROO^-$.[226]

When alkenes are treated with oxygen that has been photosensitized (p. 341), they are substituted by OOH in the allylic position in a synthetically useful reaction.[227] Although superficially similar to autoxidation, this reaction is clearly different because 100% allylic rearrangement always takes place. The reagent here is not

[221]Swern D. *Organic Peroxides*, Vol. 1, Wiley, NY, ***1970***, p. 313.

[222]For methods of detection and removal of peroxides from ether solvents, see Gordon, A.J.; Ford, R.A. *The Chemist's Companion*, Wiley, NY, ***1972***, p. 437; Burfield, D.R. *J. Org. Chem.* ***1982***, *47*, 3821.

[223]See, for example, Schwetlick, K. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 2007.

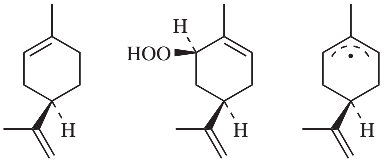
[224]For a review of base-catalyzed autoxidations in general, see Sosnovsky, G.; Zaret, E.H., in Swern, D. *Organic Peroxides*, Vol. 1, Wiley, NY, ***1970***, pp. 517–560.

[225]Barton, D.H.R.; Jones, D.W. *J. Chem. Soc.* ***1965***, 3563; Russell, G.A.; Bemis, A.G. *J. Am. Chem. Soc.* ***1966***, *88*, 5491.

[226]Gersmann, H.R.; Bickel, A.F. *J. Chem. Soc. B* ***1971***, 2230.

[227]For reviews, see Frimer, A.A.; Stephenson, L.M. in Frimer, A.A. *Singlet O_2*, Vol. 2, CRC Press, Boca Raton, FL, ***1985***, pp. 67–91; Wasserman, H.H.; Ives, J.L. *Tetrahedron* ***1981***, *37*, 1825; Gollnick, K.; Kuhn, H.J., in Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, ***1979***, pp. 287–427; Denny, R.W.; Nickon, A. *Org. React.* ***1973***, *20*, 133; Adams, W.R., in Augustine, R.L. *Oxidation*, Vol. 2, Marcel Dekker, NY, ***1969***, pp. 65–112.

the ground-state oxygen (a triplet), but an excited singlet state[228] (in which all electrons are paired), and the function of the photosensitization is to promote the oxygen to this singlet state. Singlet oxygen can also be produced by nonphotochemical means,[229] for example, by the reaction between H_2O_2 and NaOCl[230] or sodium molybdate,[231] or between ozone and triphenyl phosphite.[232] Calcium peroxide diperoxohydrate (CaO_2,2 H_2O_2) has been reported as a storable compound used for the chemical generation of singlet oxygen.[233] The oxygen generated by either photochemical or nonphotochemical methods reacts with alkenes in the same way;[234] this is evidence that singlet oxygen is the reacting species in the photochemical reaction and not some hypothetical complex between triplet oxygen and the photosensitizer, as had previously been suggested. The fact that 100% allylic rearrangement always takes place is incompatible with a free-radical mechanism, and



28 **29** **30**

further evidence that free radicals are not involved comes from the treatment of optically active limonene (**28**) with singlet oxygen. Among other products is the optically active hydroperoxide **29**, though if **30** were an intermediate, it could not give an optically active product since it possesses a plane of symmetry.[235] In contrast, autoxidation of **28** gave optically inactive **29** (a mixture of four diastereomers in which the two pairs of enantiomers are present as racemic mixtures). As this example shows, singlet oxygen reacts faster with more-highly substituted than with less-highly substituted alkenes. The order of alkene reactivity is

[228]For books on singlet oxygen, see Frimer, A.A. *Singlet O_2*, 4 vols., CRC Press, Boca Raton, FL, ***1985***; Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, ***1979***. For reviews, see Frimer, A.A., in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, ***1983***, pp. 201–234; Gorman, A.A.; Rodgers, M.A.J. *Chem. Soc. Rev.* ***1981***, *10*, 205; Shinkarenko, N.V.; Aleskovskii, V.B. *Russ. Chem. Rev.* ***1981***, *50*, 220; Shlyapintokh, V.Ya.; Ivanov, V.B. *Russ. Chem. Rev.* ***1976***, *45*, 99; Ohloff, G. *Pure Appl. Chem.* ***1975***, *43*, 481; Kearns, D.R. *Chem. Rev.* ***1971***, *71*, 395; Wayne, R.P. *Adv. Photochem.* ***1969***, *7*, 311.

[229]For reviews, see Turro, N.J.; Ramamurthy, V., in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, ***1980***, pp. 1–23; Murray, R.W., in Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, ***1979***, pp. 59–114. For a general monograph, see Adam, W.; Cilento, G. *Chemical and Biological Generation of Excited States*; Academic Press, NY, ***1982***.

[230]Foote, C.S.; Wexler, S. *J. Am. Chem. Soc.* ***1964***, *86*, 3879.

[231]Aubry, J.M.; Cazin, B.; Duprat, F. *J. Org. Chem.* ***1989***, *54*, 726.

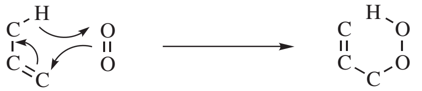
[232]Murray, R.W.; Kaplan, M.L. *J. Am. Chem. Soc.* ***1969***, *91*, 5358; Bartlett, P.D.; Mendenhall, G.D.; Durham, D.L. *J. Org. Chem.* ***1980***, *45*, 4269.

[233]Pierlot, C.; Nardello, V.; Schrive, J.; Mabille, C.; Barbillat, J.; Sombret, B.; Aubry, J.-M. *J. Org. Chem*, ***2002***, *67*, 2418.

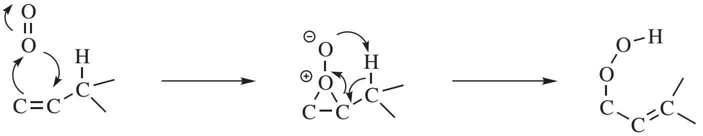
[234]Foote, C.S.; Wexler, S.; Ando, W.; Higgins, R. *J. Am. Chem. Soc.* ***1968***, *90*, 975. See also, McKeown, E.; Waters, W.A. *J. Chem. Soc. B* ***1966***, 1040.

[235]Schenck, G.O.; Gollnick, K.; Buchwald, G.; Schroeter, S.; Ohloff, G. *Liebigs Ann. Chem.* ***1964***, *674*, 93; Schenck, G.O.; Neumüller, O.; Ohloff, G.; Schroeter, S. *Liebigs Ann. Chem.* ***1965***, *687*, 26.

tetrasubstituted > trisubstituted > disubstituted. Electron-withdrawing substituents deactivate the alkene.[236] In simple trisubstituted alkenes, there is a general preference for the hydrogen to be removed from the more highly congested side of the double bond.[237] With *cis*-alkenes of the form RCH=CHR′, the hydrogen is removed from the larger R group.[238] Many functional groups in an allylic position cause the hydrogen to be removed from that side rather than the other (geminal selectivity).[239] Also, in alkyl-substituted alkenes, the hydrogen that is preferentially removed is the one geminal to the larger substituent on the double bond.[240]



Several mechanisms have been proposed for the reaction with singlet oxygen.[241] One of these is a pericyclic mechanism, similar to that of the ene synthesis (**15-23**) and to the first step of the reaction between alkenes and SeO_2 (**19-14**). However, there is strong evidence against this mechanism,[242] and a more likely mechanism involves addition of singlet oxygen to the double bond to give a perepoxide (**31**),[243] followed by internal proton transfer.[244]



31

Still other proposed mechanisms involve diradicals or dipolar intermediates.[245]

OS **IV**, 895.

[236]For example, see Foote, C.S.; Denny, R.W. *J. Am. Chem. Soc.* ***1971***, *93*, 5162.

[237]Orfanopoulos, M.; Bellamine, M.; Grdina, M.J.; Stephenson, L.M. *J. Am. Chem. Soc.* ***1979***, *101*, 275; Rautenstrauch, V.; Thommen, W.; Schulte-Elte, K.H. *Helv. Chim. Acta* ***1986***, *69*, 1638 and references cited therein.

[238]Orfanopoulos, M.; Stratakis, M.; Elemes, Y. *Tetrahedron Lett.* ***1989***, *30*, 4875.

[239]Clennan, E.L.; Chen, X.; Koola, J.J. *J. Am. Chem. Soc.* ***1990***, *112*, 5193, and references cited therein.

[240]Orfanopoulos, M.; Stratakis, M.; Elemes, Y. *J. Am. Chem. Soc.* ***1990***, *112*, 6417.

[241]For reviews of the mechanism, see Frimer, A.A.; Stephenson, L.M., in Frimer, A.A. *Singlet O_2*, Vol. 2, CRC Press, Boca Raton, FL, ***1985***, pp. 80–87; Stephenson, L.M.; Grdina, M.J.; Orfanopoulos, M. *Acc. Chem. Res.* ***1980***, *13*, 419; Gollnick, K.; Kuhn, H.J. Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, ***1979***, pp. 288–341; Frimer, A.A. *Chem. Rev.* ***1979***, *79*, 359; Foote, C.S. *Acc. Chem. Res.* ***1968***, *1*, 104; *Pure Appl. Chem.* ***1971***, *27*, 635; Gollnick, K. *Adv. Photochem.* ***1968***, *6*, 1; Kearns, D.R. *Chem. Rev.* ***1971***, *71*, 395.

[242]Asveld, E.W.H.; Kellogg, R.M. *J. Org. Chem.* ***1982***, *47*, 1250.

[243]For a review of perepoxides as intermediates in organic reactions, see Mitchell, J.C. *Chem. Soc. Rev.* ***1985***, *14*, 399, p. 401.

[244]For evidence in favor of this mechanism, at least with some kinds of substrates, see Jefford, C.W.; Rimbault, C.G. *J. Am. Chem. Soc.* ***1978***, *100*, 6437; Okada, K.; Mukai, T. *J. Am. Chem. Soc.* ***1979***, *100*, 6509; Paquette, L.A.; Hertel, L.W.; Gleiter, R.; Böhm, M. *J. Am. Chem. Soc.* ***1978***, *100*, 6510; Wilson, S.L.; Schuster, G.B. *J. Org. Chem.* ***1986***, *51*, 2056; Davies, A.G.; Schiesser, C.H. *Tetrahedron Lett.* ***1989***, *30*, 7099; Orfanopoulos, M.; Smonou, I.; Foote, C.S. *J. Am. Chem. Soc.* ***1990***, *112*, 3607.

[245]See, for example, Jefford, C.W. *Helv. Chim. Acta* ***1981***, *64*, 2534.

14-8 Formation of Peroxides

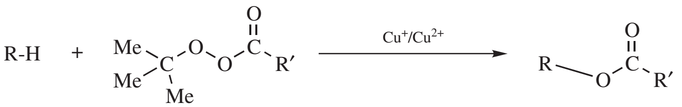
Alkyldioxy-de-hydrogenation

$$RH + R'OOH \xrightarrow{CuCl} ROOR'$$

Peroxy groups (ROO) can be introduced into susceptible organic molecules by treatment with a hydroperoxide in the presence of cuprous chloride or other catalysts, for example, cobalt and manganese salts.[246] Very high yields can be obtained. The type of hydrogen replaced is similar to that with NBS (**14-3**), that is, mainly benzylic, allylic, and tertiary. The mechanism is therefore of the free-radical type, involving ROO• formed from ROOH and the metal ion. The reaction can be used to demethylate tertiary amines of the form R_2NCH_3, since the product R_2NHCH_2OOR' can easily be hydrolyzed by acid (**10-6**) to give R_2NH.[247]

14-9 Acyloxylation

Acyloxylation or Acyloxy-de-hydrogenation



Susceptible positions of organic compounds can be directly acyloxylated[248] by *tert*-butyl peroxyesters, the most frequently used being acetic and benzoic (R′ = Me or Ph).[249] The reaction requires a catalyst (cuprous ion is the actual catalyst, but a trace is all that is necessary, and such traces are usually present in cupric compounds, so that these are often used) and without it is not selective. Susceptible positions are similar to those in **14-6**: benzylic, allylic, and the a position of ethers and sulfides. Terminal alkenes are substituted almost entirely in the 3 position, that is, with only a small amount of allylic rearrangement, but internal alkenes generally give mixtures containing a large amount of allylic-shift product. If the reaction with alkenes is carried out in an excess of

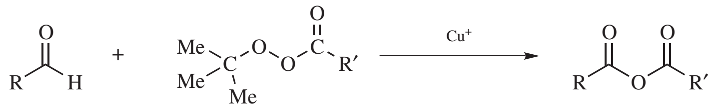
[246]For a review, see Sosnovsky, G.; Rawlinson, D.J., in Swern, D. *Organic Peroxides*, Vol. 2, Wiley, NY, ***1970***, pp. 153–268. See also, Murahashi, S.; Naota, T.; Kuwabara, T.; Saito, T.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* ***1990***, *112*, 7820; Sheldon, R.A., in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, ***1983***, p. 161.

[247]See Murahashi, S.; Naota, T.; Yonemura, K. *J. Am. Chem. Soc.* ***1988***, *110*, 8256.

[248]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed, Wiley-VCH, NY, ***1999***, pp. 1625–1630 *ff*, 1661–1663.

[249]For reviews, see Rawlinson, D.J.; Sosnovsky, G. *Synthesis* ***1972***, 1; Sosnovsky, G.; Rawlinson, D.J., in Swern, D. *Organic Peroxides*, Vol. 1, Wiley, NY, ***1970***, pp. 585–608; Doumaux, Jr, A.R. in Augustine, R.L. *Oxidation*, Vol. 2, Marcel Dekker, NY, ***1971***, pp. 141–185.

another acid R″COOH, the ester produced is of *that* acid ROCOR″. Aldehydes give anhydrides:



Acyloxylation has also been achieved with metallic acetates, such as lead tetraacetate,[250] mercuric acetate,[251] and palladium(II) acetate.[252] In the case of the lead and mercuric acetates, not only does the reaction take place at allylic and benzylic positions and at those α to an OR or SR group, but also at positions α to the carbonyl groups of aldehydes, ketones, or esters and at those a to two carbonyl groups (ZCH_2Z'). It is likely that in the latter cases it is the enol forms that react. Ketones can be α-acyloxylated indirectly by treatment of various enol derivatives with metallic acetates, for example, silyl enol ethers with silver carboxylates-iodine,[253] enol thioethers with lead tetraacetate,[254] and enamines[255] with lead tetraacetate[256] or thallium triacetate.[257] α,β-Unsaturated ketones can be acyloxylated in good yields in the α′ position with manganese triacetate.[258] Palladium acetate converts alkenes to vinylic and/or allylic acetates.[259] Lead tetraacetate even acyloxylates alkanes, in a slow reaction (10 days to 2 weeks), with tertiary and secondary positions greatly favored over primary ones.[260] Yields are as high as 50%. Acyloxylation of certain alkanes has also been reported with palladium(II) acetate.[261]

[250]For a review of lead tetraacetate, see Butler, R.N., in Pizey, J.S. *Synthetic Reagents*, Vol. 3, Wiley, NY, p. 277.

[251]For reviews, see Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, ***1985***, pp. 190–208; Rawlinson, D.J.; Sosnovsky, G. *Synthesis* ***1973***, 567.

[252]Hansson, S.; Heumann, A.; Rein, T.; Åkermark, B. *J. Org. Chem.* ***1990***, *55*, 975; Byström, S.E.; Larsson, E.M.; Åkermark, B. *J. Org. Chem.* ***1990***, *55*, 5674.

[253]Rubottom, G.M.; Mott, R.C.; Juve Jr, H.D. *J. Org. Chem.* ***1981***, *46*, 2717.

[254]Trost, B.M.; Tanigawa, Y. *J. Am. Chem. Soc.* ***1979***, *101*, 4413.

[255]For a review, see Cook, A.G., in Cook, A.G. *Enamines*, 2nd ed., Marcel Dekker, NY, ***1988***, pp. 251–258.

[256]See Butler, R.N. *Chem. Ind. (London)* ***1976***, 499.

[257]Kuehne, M.E.; Giacobbe, T.J. *J. Org. Chem.* ***1968***, *33*, 3359.

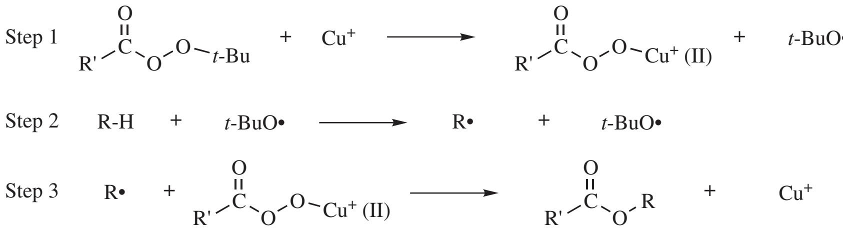
[258]Demir, A.S.; Sayrac, T.; Watt, D.S. *Synthesis* ***1990***, 1119.

[259]For reviews, see Rylander, P.N. *Organic Synthesis with Noble Metal Catalysts*, Academic Press, NY, ***1973***, pp. 80–87; Jira, R.; Freiesleben, W. *Organomet. React.* ***1972***, *3*, 1, pp. 44–84; Heck, R.F. *Fortschr. Chem. Forsch.* ***1971***, *16*, 221, pp. 231–237; Tsuji, J. *Adv. Org. Chem.* ***1969***, *6*, 109, pp. 132–143.

[260]Bestre, R.D.; Cole, E.R.; Crank, G. *Tetrahedron Lett.* ***1983***, *24*, 3891; Mosher, M.W.; Cox, J.L. *Tetrahedron Lett.* ***1985***, *26*, 3753.

[261]This was done in trifluoroacetic acid, and the products were trifluoroacetates: Sen, A.; Gretz, E.; Oliver, T.F.; Jiang, Z. *New J. Chem.* ***1989***, *13*, 755.

Studies of the mechanism of the cuprous-catalyzed reaction show that the most common mechanism is the following:[262]



32

This mechanism, involving a free radical R•, is compatible with the allylic rearrangements found.[263] The finding that *tert*-butyl peroxyesters labeled with ^{18}O in the carbonyl oxygen gave ester with 50% of the label in each oxygen[264] is in accord with a combination of R• with the intermediate **32**, in which the copper is ionically bound, so that the oxygens are essentially equivalent. Other evidence is that *tert*-butoxy radicals have been trapped with dienes.[265] Much less is known about the mechanisms of the reactions with metal acetates.[266]

Free-radical acyloxylation of aromatic substrates[267] has been accomplished with a number of reagents including copper(II) acetate,[268] benzoyl peroxide-iodine,[269] silver(II) complexes,[270] and cobalt(III) trifluoroacetate.[271]

OS **III**, 3; **V**, 70, 151; **VIII**, 137.

C. Substitution by Sulfur

14-10 Chlorosulfonation or Chlorosulfo-de-hydrogenation

$$RH + SO_2 + Cl_2 \xrightarrow{h\nu} RSO_2Cl$$

[262] Kharasch, M.S.; Sosnovsky, G.; Yang, N.C. *J. Am. Chem. Soc.* ***1959***, *81*, 5819; Kochi, J.K.; Mains, H.E. *J. Org. Chem.* ***1965***, *30*, 1862. See also, Beckwith, A.L.J.; Zavitsas, A.A. *J. Am. Chem. Soc.* ***1986***, *108*, 8230.

[263] Goering, H.L.; Mayer, U. *J. Am. Chem. Soc.* ***1964***, *86*, 3753; Denney, D.B.; Appelbaum, A.; Denney, D.Z. *J. Am. Chem. Soc.* ***1962***, *84*, 4969.

[264] Denney, D.B.; Denney, D.Z.; Feig, G. *Tetrahedron Lett.* ***1959***, no. 15, p. 19.

[265] Kochi, J.K. *J. Am. Chem. Soc.* ***1962***, *84*, 2785, 3271; Story, P.R. *Tetrahedron Lett.* ***1962***, 401.

[266] See, for example, Jones, S.R.; Mellor, J.H. *J. Chem. Soc. Perkin Trans. 2* ***1977***, 511.

[267] For a review, see Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Academic Press, NY, ***1985***, pp. 177–180, 351–355.

[268] Takizawa, Y.; Tateishi, A.; Sugiyama, J.; Yoshida, H.; Yoshihara, N. *J. Chem. Soc., Chem. Commun.* ***1991***, 104. See also Kaeding, W.W.; Kerlinger, H.O.; Collins, G.R. *J. Org. Chem.* ***1965***, *30*, 3754.

[269] For example, see Kovacic, P.; Reid, C.G.; Brittain, T.J. *J. Org. Chem.* ***1970***, *35*, 2152.

[270] Nyberg, K.; Wistrand, L.G. *J. Org. Chem.* ***1978***, *43*, 2613.

[271] Kochi, J.K.; Tank, R.T.; Bernath, T. *J. Am. Chem. Soc.* ***1973***, *95*, 7114; DiCosimo, R.; Szabo, H. *J. Org. Chem.* ***1986***, *51*, 1365.

The chlorosulfonation of organic molecules with chlorine and sulfur dioxide is called the *Reed reaction*.[272] In scope and range of products obtained, the reaction is similar to **14-1**. The mechanism is also similar, except that there are two additional main propagation steps:

$$\mathrm{R}\bullet + \mathrm{SO_2} \longrightarrow \mathrm{R{-}SO_2}\bullet$$
$$\mathrm{R{-}SO_2}\bullet + \mathrm{Cl_2} \longrightarrow \mathrm{R{-}SO_2Cl} + \mathrm{Cl}\bullet$$

Chlorosulfenation[273] can be accomplished by treatment with SCl_2 and UV light: $\mathrm{RH} + \mathrm{SCl_2} \xrightarrow{h\nu} \mathrm{RSCl}$.

D. Substitution by Nitrogen

14-11 The Direct Conversion of Aldehydes to Amides

Amination or **Amino-de-hydrogenation**

$$\mathrm{ArCHO} \xrightarrow[\text{NBS−AIBN}]{\mathrm{NH_3}} \mathrm{ArCONH_2}$$

Aliphatic and aromatic aldehydes have been converted to the corresponding amides with ammonia or a primary or secondary amine, NBS, and a catalytic amount of AIBN (p. 935).[274] In a reaction of more limited scope, amides are obtained from aromatic and α,β-unsaturated aldehydes by treatment with dry ammonia gas and nickel peroxide.[275] Best yields (80–90%) are obtained at −25 to −20°C. In the nickel peroxide reaction the corresponding alcohols ($ArCH_2OH$) have also been used as substrates.

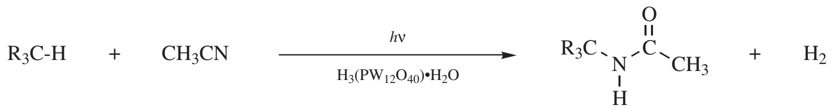
The reaction has also been performed with MnO_2 and NaCN along with ammonia or an amine at 0°C in isopropyl alcohol.[276] Aldehydes were also shown to react with hydroxylamine hydrochloride at 140°C in the presence of aluminum oxide and methanesulfonic acid.[277] Treatment of a aldehyde with iodine in aqueous ammonia, followed by oxidation with aqueous hydrogen peroxide generates a primary amide.[278] Secondary amines react with aldehydes to the an amide in using a palladium catalyst[279] or a rhodium catalyst.[280] For an indirect way of converting aldehydes to amides, see **12-32**. Thioamides $RCSNR'_2$ have been prepared in good yield

[272]For a review, see Gilbert, E.E. *Sulfonation and Related Reactions*, Wiley, NY, ***1965***, pp. 126–131.
[273]Müller, E.; Schmidt, E.W. *Chem. Ber.* ***1963***, *96*, 3050; ***1964***, *97*, 2614. For a review of the formation and reactions of sulfenyl halides, see Kühle, E. *Synthesis* ***1970***, 561; ***1971***, 563, 617.
[274]Markó, I.E.; Mekhalfia, A. *Tetrahedron Lett.* ***1990***, *31*, 7237.
[275]Nakagawa, K.; Onoue, H.; Minami, K. *Chem. Commun.* ***1966***, 17.
[276]Gilman, N.W. *Chem. Commun.* ***1971***, 733.
[277]Sharghi, H.; Sarvari, M.H. *J. Chem. Res. (S)* ***2001***, 446.
[278]Shie, J.-J.; Fang, J.-M. *J. Org. Chem.* ***2003***, *68*, 1158.
[279]Tamaru, Y.; Yamada, Y.; Yoshida, Z. *Synthesis* ***1983***, 474.
[280]Tillack, A.; Rudloff, I.; Beller, M. *Eur. J. Org. Chem.* ***2001***, 523.

from thioaldehydes (produced *in situ* from phosphoranes and sulfur) and secondary amines.[281]

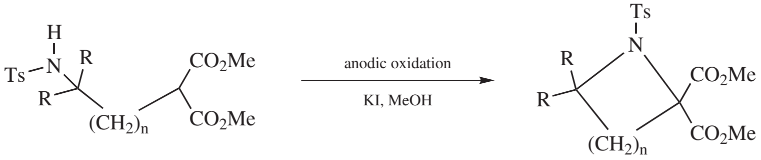
14-12 Amidation and Amination at an Alkyl Carbon

Acylamino-de-hydrogenation



When alkanes bearing a tertiary hydrogen are exposed to UV light in acetonitrile containing a heteropolytungstic acid, they are amidated.[282] The oxygen in the product comes from the tungstic acid. When the substrate bears two adjacent tertiary hydrogens, alkenes are formed (by loss of two hydrogens), rather than amides (**19-2**). Amidyl radicals can be generated by other means.[283]

An electrochemical method for amination has been reported by Shono and coworkers.[284] Derivatives of malonic esters containing an *N*-tosyl group were cyclized in high yields by anodic oxidation:



Three-, four-, and five-membered rings were synthesized by this procedure.

14-13 Substitution by Nitro

Nitro-de-carboxylation

In a reaction termed a "nitro-Hunsdiecker" (see **14-30**), vinyl carboxylic acids (conjugated acids) are treated with nitric acid and a catalytic amount of AIBN (p. 935). The product is the vinyl nitro compound, generated via decarboxylation of a radical intermediate.[285]

[281]Okuma, K.; Komiya, Y.; Ohta, H. *Chem. Lett.* ***1988***, 1145.
[282]Renneke, R.F.; Hill, C.L. *J. Am. Chem. Soc.* ***1986***, *108*, 3528.
[283]Moutrille, C.; Zard, S.Z. *Chem. Commun.* ***2004***, 1848.
[284]Shono, T.; Matsumura, Y.; Katoh, S.; Ohshita, J. *Chem. Lett.* ***1988***, 1065.
[285]Das, J.P.; Sinha, P.; Roy, S. *Org. Lett.* ***2002***, *4*, 3055.

E. Substitution by Carbon

In these reactions, a new carbon–carbon bond is formed and they may be given the collective title *coupling reactions*. In each case, an alkyl or aryl radical is generated and then combines with another radical (a termination process) or attacks an aromatic ring or alkene to give the coupling product.[286]

14-14 Simple Coupling at a Susceptible Position

De-hydrogen-coupling

$$2\ \text{RH} \longrightarrow \text{R—R}$$

Alkane and alkyl substrates RH are treated with peroxides, which decompose to give a radical that abstracts a hydrogen from RH to give R•, which dimerizes. Dialkyl and diacyl peroxides have been used, as well as Fenton's reagent (p. 964). This reaction is far from general, though in certain cases respectable yields have been obtained. Among susceptible positions are those at a tertiary carbon,[287] as well as those α to a phenyl group (especially if there is also an α-alkyl or α-chloro group),[288] an ether group,[289] a carbonyl group,[290] a cyano group,[291] a dialkylamino group,[292] or a carboxylic ester group, either the acid or alcohol side.[293] Cross-coupling is possible in some cases. When toluene was heated with allyl bromide, in the presence of di-*tert*-butyl peroxide, 4-phenyl-1-butene was formed quantitatively.[294]

Conjugated amide were coupled via the γ-carbon to give good yields of the dimeric diamide, with an excess of samarium (II) iodide, and with modest enantioselectivity using a chiral additive.[295]

$$2\ \text{RH} \xrightarrow[\text{Hg}]{h\nu} \text{R—R} + H_2$$

[286]For a monograph on the formation of C–C bonds by radical reactions, see Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, Pergamon, Elsmsford, NY, ***1986***. For a review of arylation at carbon, see Abramovitch, R.A.; Barton, D.H.R.; Finet, J. *Tetrahedron* ***1988***, *44*, 3039. For a review of aryl–aryl coupling, see Sainsbury, M. *Tetrahedron* ***1980***, *36*, 3327.

[287]Meshcheryakov, A.P.; Érzyutova, E.I. *Bull. Acad. Sci. USSR Div. Chem. Sci*, ***1966***, 94.

[288]McBay, H.C.; Tucker, O.; Groves, P.T. *J. Org. Chem.* ***1959***, *24*, 536; Johnston, K.M.; Williams, G.H. *J. Chem. Soc.* ***1960***, 1168.

[289]Pfordte, K.; Leuschner, G. *Liebigs Ann. Chem.* ***1961***, *643*, 1.

[290]Kharasch, M.S.; McBay, H.C.; Urry, W.H. *J. Am. Chem. Soc.* ***1948***, *70*, 1269; Leffingwell, J.C. *Chem. Commun.* ***1970***, 357; Hawkins, E.G.E.; Large, R. *J. Chem. Soc. Perkin Trans. 1* ***1974***, 280.

[291]Kharasch, M.S.; Sosnovsky, G. *Tetrahedron* ***1958***, *3*, 97.

[292]Schwetlick, K.; Jentzsch, J.; Karl, R.; Wolter, D. *J. Prakt. Chem.* ***1964***, *[4] 25*, 95.

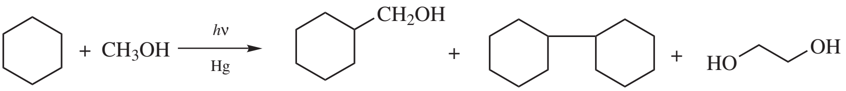
[293]Boguslavskaya, L.S.; Razuvaev, G.A. *J. Gen. Chem. USSR* ***1963***, *33*, 1967.

[294]Tanko, J.M.; Sadeghipour, M. *Angew. Chem. Int. Ed.* ***1999***, *38*, 159.

[295]Kikukawa, T.; Hanamoto, T.; Inanaga, J. *Tetrahedron Lett.* ***1999***, *40*, 7497.

Alkanes can be dimerized by vapor-phase mercury photosensitization[296] in a synthetically useful process. Best results are obtained for coupling at tertiary positions, but compounds lacking tertiary hydrogens (e.g., cyclohexane) also give good yields. Dimerization of *n*-alkanes gives secondary-secondary coupling in a nearly statistical distribution, with primary positions essentially unaffected. Alcohols and ethers dimerize at the position α to the oxygen [e.g., 2 EtOH → MeCH(OH)CH(OH)Me].

When a mixture of compounds is treated, cross-dimerization (to give **33**) and homodimerization take place statistically.



33

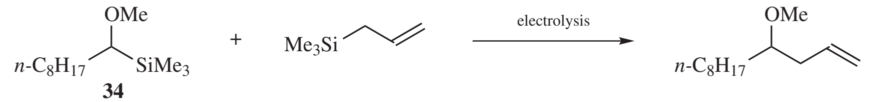
Even with the limitation on yield implied by the statistical process, cross-dimerization is still useful when one of the reactants is an alkane, because the products are easy to separate, and because of the few other ways to functionalize an alkane. The cross-coupling of an alkane with trioxane is especially valuable, because hydrolysis of the product (**10-6**) gives an aldehyde, thus achieving the conversion RH → RCHO. The mechanism probably involves abstraction of H by the excited Hg atom, and coupling of the resulting radicals.

The reaction has been extended to ketones, carboxylic acids and esters (all of which couple a to the C=O group), and amides (which couple α to the nitrogen) by running it in the presence of H_2.[297] Under these conditions it is likely that the excited Hg abstracts H• from H_2, and that the remaining H• abstracts H from the substrate. Radicals have also been generated at benzylic positions and shown to couple with epoxides, forming an alcohol.[298]

OS **IV**, 367; **V**, 1026; **VII**, 482.

14-15 Coupling at a Susceptible Position Via Silanes

De-silyl-coupling



34

Under electrochemical conditions it is possible to couple two silanes. The reaction of **34** and allyltrimethylsilane, for example, gave the corresponding homoallylic ether.[299]

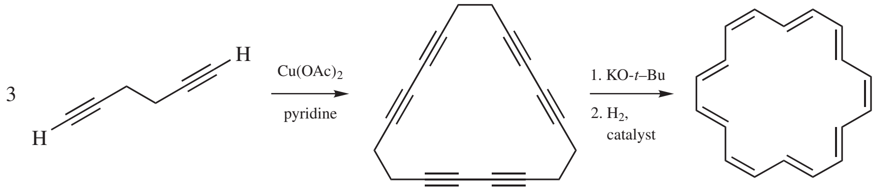
[296]Brown, S.H.; Crabtree, R.H. *J. Am. Chem. Soc.* ***1989***, *111*, 2935, 2946; *J. Chem. Educ.* ***1988***, *65*, 290.
[297]Boojamra, C.G.; Crabtree, R.H.; Ferguson, R.R.; Muedas, C.A. *Tetrahedron Lett.* ***1989***, *30*, 5583.
[298]Rawal, V.H.; Krishnamurthy, V.; Fabre, A. *Tetrahedron Lett.* ***1993***, *34*, 2899.
[299]Suga, S.; Suzuki, S.; Yamamoto, A.; Yoshida, J.-i. *J. Am. Chem. Soc.* ***2000***, *122*, 10244.

14-16 Coupling of Alkynes[300]

De-hydrogen-coupling

$$2\ R{-}C{\equiv}C{-}H \xrightarrow[\text{pyridine}]{CuX_2} R{-}C{\equiv}C{-}C{\equiv}C{-}R$$

Terminal alkynes can be coupled by heating with stoichiometric amounts of cupric salts in pyridine or a similar base. This reaction, which produces symmetrical diynes in high yields, is called the *Eglinton reaction*.[301] The large-ring annulenes of Sondheimer et al. (see p. 71) were prepared by rearrangement and hydrogenation of cyclic polyynes,[302] prepared by the Eglinton reaction with terminal diynes to give **35**, a cyclic trimer of 1,5-hexadiyne.[303] The corresponding tetramers (C_{24}), pentamers (C_{30}), and hexamers (C_{36}) were also formed. The Eglinton reaction is of wide scope. Many functional groups can be present on the alkyne. The oxidation is usually quite specific for triple-bond hydrogen.



35

Another common procedure is the use of catalytic amounts of cuprous salts in the presence of ammonia or ammonium chloride (this method is called the *Glaser reaction*). Atmospheric oxygen or some other oxidizing agent, such as permanganate or hydrogen peroxide is required in the latter procedure. This method is not satisfactory for cyclic coupling. Hydrogen peroxide, potassium permanganate, potassium ferricyanide, iodine or Cu(II) can be used instead of oxygen as oxidants.[304] Isolation of copper acetylide during the reaction can be avoided by doing the reaction in pyridine or cyclohexylamine, in the presence of catalytic amount of

[300]For a review, see Siemsen, P.; Livingston, R.C.; Diederich, F. *Angew. Chem. Int. Ed.* ***2000***, *39*, 2632.

[301]For reviews, see Simándi, L.I., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C* pt. 1, Wiley, NY, ***1983***, pp. 529–534; Nigh, W.G., in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B, Academic Press, NY, ***1973***, pp. 11–31; Cadiot, P.; Chodkiewicz, W., in Viehe, H.G. *Acetylenes*; Marcel Dekker, NY; ***1969***, pp. 597–647.

[302]For a review of cyclic alkynes, see Nakagawa, M., in Patai, S. *The Chemistry of the Carbon-Carbon Triple Bond*, pt. 2, Wiley, NY, ***1978***, pp. 635–712.

[303]Sondheimer, F.; Wolovsky, R. *J. Am. Chem. Soc.* ***1962***, *84*, 260; Sondheimer, F.; Wolovsky, R.; Amiel, Y. *J. Am. Chem. Soc.* ***1962***, *84*, 274.

[304]Gunter, H.V. *Chemistry of Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 597–647 and references cited therein.

$CuCl_3$.[305] If the Glaser reaction is done with a *N*,*N*,*N'*,*N'*-tetramethylethylenediamine–CuCl complex, the reaction proceeds in good yield in virtually any organic solvent.[306] When molecular oxygen is the oxidant, this modification of Glaser condensation is known as the *Hay reaction*. A variation couples terminal alkynes using $CuCl_2$ in supercritical CO_2 (see p. 414),[307] and in ionic liquids.[308] Coupling was also achieved using $CuCl_2$ on KF—Al_2O_3 with microwave irradiation.[309] Homocoupling of alkynyl amines $R_2N—C{\equiv}CH$ to give the diyne $R_2N—C{\equiv}C—C{\equiv}C\text{-}NR_2$ was reported in aerated acetone with 10% CuI and 20% TMEDA.[310]

Unsymmetrical diynes can be prepared by *Cadiot–Chodkiewicz* coupling:[311]

$$R{-}C{\equiv}C{-}H \quad + \quad R'{-}C{\equiv}C{-}Br \xrightarrow{Cu^+} R{-}C{\equiv}C{-}C{\equiv}C{-}R' \quad + \quad HBr$$

This may be regarded as a variation of **10-74**, but it must have a different mechanism since acetylenic halides give the reaction but ordinary alkyl halides do not, which is hardly compatible with a nucleophilic mechanism. However, the mechanism is not fully understood. One version of this reaction binds the alkynyl bromide unit to a polymer, and the di-yne is released from the polymer after the solid state transformation.[312] Alkynes have also been coupled using CuI and a palladium catalyst.[313] Propargyl halides also give the reaction,[314] as do 1-bromo propargylic alcohols ($Br—C{\equiv}C—CH_2OH$).[315] A variation of the Cadiot–Chodkiewicz method consists of treating a haloalkyne ($R'C{\equiv}CX$) with a copper acetylide ($RC{\equiv}CCu$).[316] The Cadiot–Chodkiewicz procedure can be adapted to the preparation of diynes in which $R' = H$ by the use of $BrC{\equiv}CSiEt_3$ and subsequent cleavage of the $SiEt_3$ group.[317] This protecting group can also be used in the Eglinton or Glaser methods.[318]

The mechanism of the Eglinton and Glaser reactions probably begins with loss of a proton

$$R{-}C{\equiv}C{-}H \xrightarrow{\text{base}} R{-}C{\equiv}C^-$$

[305]Stansbury, H A.; Proops, W.R. *J. Org. Chem.* ***1962***, *27*, 320.
[306]Hay, A.S. *J. Org. Chem.* ***1960***, *25*, 1275; Hay, A S. *J. Org. Chem.* ***1962***, *27*, 3320.
[307]Li, J.; Jiang, H. *Chem. Commun.* ***1999***, 2369.
[308]In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Yadav, J.S.; Reddy, B.V.S.; Reddy, K.B.; Gayathri, K.U.; Prasad, A.R. *Tetrahedron Lett.* ***2003***, *44*, 6493.
[309]Kabalka, G.W.; Wang, L.; Pagni, R.M. *Synlett* ***2001***, 108.
[310]Rodríguez, D.; Castedo, L.; Saá, C. *Synlett* ***2004***, 377.
[311]Chodkiewicz, W. *Ann. Chim. (Paris)* ***1957***, *[13]* 2, 819.
[312]Montierth, J.M.; DeMario, D.R.; Kurth, M.J.; Schore, N.E. *Tetrahedron* ***1998***, *54*, 11741.
[313]Liu, Q.; Burton, D.J. *Tetrahedron Lett.* ***1997***, *38*, 4371.
[314]Sevin, A.; Chodkiewicz, W.; Cadiot, P. *Bull. Soc. Chim. Fr.* ***1974***, 913.
[315]Marino, J.P.; Nguyen, H.N. *J. Org. Chem.* ***2002***, *67*, 6841.
[316]Curtis, R.F.; Taylor, J.A. *J. Chem. Soc. C* ***1971***, 186.
[317]Eastmond, R.; Walton, D.R.M. *Tetrahedron* ***1972***, *28*, 4591; Ghose, B.N.; Walton, D.R.M. *Synthesis* ***1974***, 890.
[318]Johnson, T.R.; Walton, D.R.M. *Tetrahedron* ***1972***, *28*, 5221.

since there is a base present and acetylenic protons are acidic. It is known, of course, that cuprous ion can form complexes with triple bonds. The last step is probably the coupling of two radicals:

$$R{-}C{\equiv}C\bullet \longrightarrow R{-}C{\equiv}C{-}C{\equiv}C{-}R$$

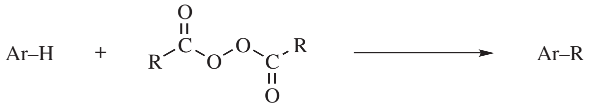
but just how the carbanion becomes oxidized to the radical and what part the cuprous ion plays (other than forming the acetylide salt) are matters of considerable speculation,[319] and depend on the oxidizing agent. One proposed mechanism postulated Cu(II) as the oxidant.[320] It has been shown that molecular oxygen forms adducts with Cu(I) supported by tertiary amines, which might be the intermediates in the Glaser reaction where molecular oxygen is the oxidant.[321] For the Hay reaction, the mechanism involves a $Cu^{I}/Cu^{III}/Cu^{II}/Cu^{I}$ catalytic cycle, and the key step for this reaction is the dioxygen activation during complexation of two molecules of acetylide with molecular oxygen, giving a Cu(III) complex.[322] This mechanism is supported by isolation and characterization of Cu(III) complexes formed under the conditions of the Glaser coupling.

Terminal alkynes are not the only reaction partners. 1-Trimethylsilyl alkynes (R—C≡C—$SiMe_3$) give the diyne R—C≡C—C≡C—R) upon reaction with CuCl[323] or $Cu(OAc)_2/Bu_4NF$.[324]

OS **V**, 517; **VI**, 68, 925; **VIII**, 63.

14-17 Alkylation and Arylation of Aromatic Compounds by Peroxides

Alkylation or **Alkyl-de-hydrogenation**



This reaction is most often carried out with R = aryl, so the net result is the same as in **13-27**, though the reagent is different.[325] It is used less often than **13-27**, but

[319]See the discussions, in Nigh, W.G., in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B, Academic Press, NY, ***1973***, pp. 27–31; Fedenok, L.G.; Berdnikov, V.M.; Shvartsberg, M.S. *J. Org. Chem. USSR* ***1973***, *9*, 1806; Clifford, A.A.; Waters, W.A. *J. Chem. Soc.* ***1963***, 3056.

[320]Bohlmann, F.; Schönowsky, H.; Inhoffen, E.; Grau, G. *Chem. Ber.* ***1964***, *97*, 794.

[321]Wieghardt, K.; Chaudhuri, P. *Prog. Inorg. Chem.* ***1987***, *37*, 329.

[322]Fomina, L.; Vazquez, B.; Tkatchouk, E.; Fomine, S. *Tetrahedron* ***2002***, *58*, 6741.

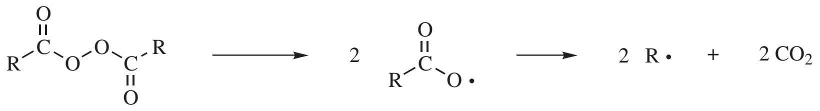
[323]Nishihara, Y.; Ikegashira, K.; Hirabayashi, K.; Ando, J.-i.; Mori, A.; Hiyama, T. *J. Org. Chem.* ***2000,*** *65*, 1780.

[324]Heuft, M.A.; Collins, S.K.; Yap, G.P.A.; Fallis, A.E. *Org. Lett.* ***2001***, *3*, 2883.

[325]For reviews, see Bolton, R.; Williams, G.H. *Chem. Soc. Rev.* ***1986***, *15*, 261; Hey, D.H. *Adv. Free-Radical Chem.* ***1966***, *2*, 47.

the scope is similar. When R = alkyl, the scope is more limited.[326] Only certain aromatic compounds, particularly benzene rings with two or more nitro groups, and fused ring systems, can be alkylated by this procedure. 1,4-Quinones can be alkylated with diacyl peroxides or with lead tetraacetate (methylation occurs with this reagent).

The mechanism is as shown on p. 940 (CIDNP has been observed[327]); the radicals are produced by



Since no relatively stable free radical is present (such as •O—N=N—Ar in **13-27**), most of the product arises from dimerization and disproportionation.[328] The addition of a small amount of nitrobenzene increases the yield of arylation product because the nitrobenzene is converted to diphenyl nitroxide, which abstracts the hydrogen from **5** and reduces the extent of side reactions.[329]

$$\text{ArH} + \text{Ar}'\text{Pb(OAc)}_3 \longrightarrow \text{ArAr}'$$

Aromatic compounds can also be arylated by aryllead tricarboxylates.[330] Best yields (~70–85%) are obtained when the substrate contains alkyl groups; an electrophilic mechanism is likely. Phenols are phenylated ortho to the OH group (and enols are a phenylated) by triphenylbismuth dichloride or by certain other Bi(V) reagents.[331] *O*-Phenylation is a possible side reaction. As with the aryllead tricarboxylate reactions, a free-radical mechanism is unlikely.[332]

OS **V**, 51. See also, OS **V**, 952; **VI**, 890.

14-18 Photochemical Arylation of Aromatic Compounds

Arylation or **Aryl-de-hydrogenation**

$$\text{ArH} + \text{Ar}'\text{I} \xrightarrow{h\nu} \text{ArAr}'$$

[326]For reviews of the free-radical alkylation of aromatic compounds, see Tiecco, M.; Testaferri, L. *React. Intermed. (Plenum)* ***1983***, *3*, 61; Dou, H.J.; Vernin, G.; Metzger, J. *Bull. Soc. Chim. Fr.* ***1971***, 4593.

[327]Kaptein, R.; Freeman, R.; Hill, H.D.W.; Bargon, J. *J. Chem. Soc., Chem. Commun.* ***1973***, 953.

[328]We have given the main steps that lead to biphenyls. The mechanism is actually more complicated than this and includes >100 elementary steps resulting in many side products, including those mentioned on p. $$$: DeTar, D.F.; Long, R.A.J.; Rendleman, J.; Bradley, J.; Duncan, P. *J. Am. Chem. Soc.* ***1967***, *89*, 4051; DeTar, D.F. *J. Am. Chem. Soc.* ***1967***, *89*, 4058. See also, Jandu, K.S.; Nicolopoulou, M.; Perkins, M.J. *J. Chem. Res. (S)* ***1985***, 88.

[329]Chalfont, G.R.; Hey, D.H.; Liang, K.S.Y.; Perkins, M.J. *J. Chem. Soc. B* ***1971***, 233.

[330]Bell, H.C.; Kalman, J.R.; May, G.L.; Pinhey, J.T.; Sternhell, S. *Aust. J. Chem.* ***1979***, *32*, 1531.

[331]For a review, see Abramovitch, R.A.; Barton, D.H.R.; Finet, J. *Tetrahedron* ***1988***, *44*, 3039, pp. 3040–3047.

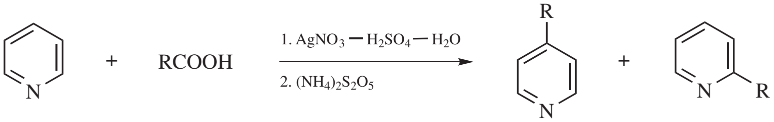
[332]Barton, D.H.R.; Finet, J.; Giannotti, C.; Halley, F. *J. Chem. Soc. Perkin Trans. 1* ***1987***, 241.

Another free-radical arylation method consists of the photolysis of aryl iodides in an aromatic solvent.[333] Yields are generally higher than in **13-27** or **14-17**. The aryl iodide may contain OH or COOH groups. The coupling reaction of iodobenzene and azulene to give a phenylazulene was reported (41% conversion and 85% yield).[334] The mechanism is similar to that of **13-27**. The aryl radicals are generated by the photolytic cleavage ArI → AR• + I•. The reaction has been applied to intramolecular arylation (analogous to the Pschorr reaction).[335] A similar reaction is photolysis of an arylthallium bis(trifluoroacetate) (**12-23**) in an aromatic solvent. Here too, an unsymmetrical biaryl is produced in good yields.[336] In this case, it is the C—Tl bond that is cleaved to give aryl radicals.

$$\text{Ar}'\text{Tl(OCOCF}_3)_2 \xrightarrow[\text{ArH}]{h\nu} \text{ArAr}'$$

14-19 Alkylation, Acylation, and Carbalkoxylation of Nitrogen Heterocycles[337]

Alkylation or **Alkyl-de-hydrogenation**, and so on



Alkylation of protonated nitrogen heterocycles (e.g., pyridines, quinolines) can be accomplished by treatment with a carboxylic acid, silver nitrate, sulfuric acid, and ammonium peroxydisulfate.[338] The R group can be primary, secondary, or tertiary. The attacking species is R•, formed by[339]

$$2\,\text{Ag}^{+} + \text{S}_2\text{O}_8^{\,2-} \longrightarrow 2\,\text{Ag}^{2+} + 2\,\text{SO}_4^{\,2-}$$

$$\text{RCOOH} + \text{Ag}^{2+} \longrightarrow \text{RCOO}\bullet + \text{H}^{+} + \text{Ag}^{+}$$

$$\text{RCOO}\bullet \longrightarrow \text{R}\bullet + \text{CO}_2$$

[333]Wolf, W.; Kharasch, N. *J. Org. Chem.* ***1965***, *30*, 2493. For a review, see Sharma, R.K.; Kharasch, N. *Angew. Chem. Int. Ed.* ***1968***, *7*, 36.

[334]Ho, T.-I.; Ku, C.-K.; Liu, R.S.H. *Tetrahedron Lett.* ***2001***, *42*, 715.

[335]See, for example, Kupchan, S.M.; Wormser, H.C. *J. Org. Chem.* ***1965***, *30*, 3792; Jeffs, P.W.; Hansen, J.F. *J. Am. Chem. Soc.* ***1967***, *89*, 2798; Thyagarajan, B.S.; Kharasch, N.; Lewis, H.B.; Wolf, W. *Chem. Commun.* ***1967***, 614.

[336]Taylor, E.C.; Kienzle, F.; McKillop, A. *J. Am. Chem. Soc.* ***1970***, *92*, 6088.

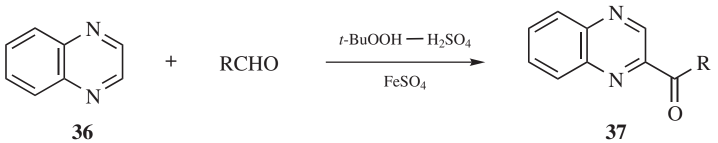
[337]For reviews; see Heinisch, G. *Heterocycles* ***1987***, *26*, 481; Minisci, F.; Vismara, E.; Fontana, F. *Heterocycles* ***1989***, *28*, 489; Minisci, F. *Top. Curr. Chem.* ***1976***, *62*, 1, pp. 17; *Synthesis* ***1973***, 1, pp. 12–19. For a review of substitution of carbon groups on nitrogen heterocycles see Vorbrüggen, H.; Maas, M. *Heterocycles* ***1988***, *27*, 2659.

[338]Fontana, F.; Minisci, F.; Barbosa, M.C.N.; Vismara, E. *Tetrahedron* ***1990***, *46*, 2525.

[339]Anderson, J.M.; Kochi, J.K. *J. Am. Chem. Soc.* ***1970***, *92*, 1651.

A hydroxymethyl group can be introduced (ArH → $ArCH_2OH$) by several variations of this method.[340] Alkylation of these substrates can also be accomplished by generating the alkyl radicals in other ways: from hydroperoxides and $FeSO_4$,[341] from alkyl iodides and H_2O_2—Fe(II),[342] from carboxylic acids and lead tetraacetate, or from the photochemically induced decarboxylation of carboxylic acids by iodosobenzene diacetate.[343]

Protonated nitrogen heterocycles, such as quinoxaline (**36**), can be acylated by treatment with an aldehyde, *tert*-butyl hydroperoxide, sulfuric acid, and ferrous sulfate, in this case giving **37**.[344]



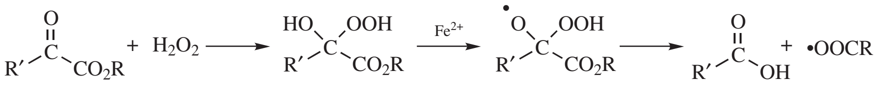
36 **37**

Photochemical alkylation of protonated quinoline occurred with $Ph_2Se(O_2Cc\text{-}C_6H_{11})_2$.[345]

Other positively charged heterocycles react as well. When *N*-fluoropyridinium triflate was treated with the enolate anion of acetone, 2-(2-oxopropyl)pyridine was formed in modest yield.[346]

These alkylation and acylation reactions are important because Friedel–Crafts alkylation and acylation (**11-11**, **11-17**) cannot be applied to most nitrogen heterocycles (see also **13-17**).

Protonated nitrogen heterocycles can be carbalkoxylated[347] by treatment with esters of α-keto acids and Fenton's reagent. Pyridine is carbalkoxylated at C-2 and C-4, for example. The attack is by •COOR radicals generated from the esters via a hydroperoxide (**38**).



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[340]See Citterio, A.; Gentile, A.; Minisci, F.; Serravalle, M.; Ventura, S. *Tetrahedron* ***1985***, *41*, 617; Katz, R.B.; Mistry, J.; Mitchell, M.B. *Synth. Commun.* ***1989***, *19*, 317.

[341]Minisci, F.; Selva, A.; Porta, O.; Barilli, P.; Gardini, G.P. *Tetrahedron* ***1972***, *28*, 2415.

[342]Fontana, F.; Minisci, F.; Barbosa, M.C.N.; Vismara, E. *Acta Chem. Scand*, ***1989***, *43*, 995.

[343]Minisci, F.; Vismara, E.; Fontana, F.; Barbosa, M.C.N. *Tetrahedron Lett.* ***1989***, *30*, 4569.

[344]Caronna, T.; Gardini, G.P.; Minisci, F. *Chem. Commun.* ***1969***, 201; Arnoldi, A.; Bellatti, M.; Caronna, T.; Citterio, A.; Minisci, F.; Porta, O.; Sesana, G. *Gazz. Chim. Ital.* ***1977***, *107*, 491.

[345]Togo, H.; Miyagawa, N.; Yokoyama, M. *Chem. Lett*, ***1992***, 1677.

[346]Kiselyov, A.S.; Strekowski, L. *J. Org. Chem.* ***1993***, *58*, 4476.

[347]Bernardi, R.; Caronna, T.; Galli, R.; Minisci, F.; Perchinunno, M. *Tetrahedron Lett.* ***1973***, 645; Heinisch, G.; Lötsch, G. *Angew. Chem. Int. Ed.* ***1985***, *24*, 692.

Similarly, a carbamoyl group can be introduced[348] by the use of the radicals $H_2N{-}\overset{\displaystyle \cdot}{C}(=O)$ or $Me_2N{-}\overset{\displaystyle \cdot}{C}(=O)$ generated from formamide or DMF and H_2SO_4, H_2O_2, and $FeSO_4$ or other oxidants.

N_2 AS LEAVING GROUP[349]

In these reactions diazonium salts are cleaved to aryl radicals,[350] in most cases with the assistance of copper salts. Reactions **13-27** and **13-26** may also be regarded as belonging to this category with respect to the attacking compound. For nucleophilic substitutions of diazonium salts (see **13-20–13-23**). Removal of nitrogen and replacement with a hydrogen atom is a reduction, found in Chapter 19.

14-20 Replacement of the Diazonium Group by Chlorine or Bromine

Chloro-de-diazoniation, and so on

$$ArN_2^+ + CuCl \longrightarrow ArCl$$

Treatment of diazonium salts with cuprous chloride or bromide leads to aryl chlorides or bromides, respectively. In either case, the reaction is called the *Sandmeyer reaction.*[351] The reaction can also be carried out with copper and HBr or HCl, in which case it is called the *Gatterman reaction* (not to be confused with **11-18**). The Sandmeyer reaction is not useful for the preparation of fluorides or iodides, but for bromides and chlorides it is of wide scope and is probably the best way of introducing bromine or chlorine into an aromatic ring. The yields are usually high.

The mechanism is not known with certainty, but is believed to take the following course:[352]

$$ArN_2^+X^- + CuX \longrightarrow Ar\bullet + N_2 + CuX_2$$
$$Ar\bullet + CuX_2 \longrightarrow ArX + CuX$$

[348]Minisci, F.; Citterio, A.; Vismara, E.; Giordano, C. *Tetrahedron* ***1985***, *41*, 4157.

[349]For a review, see Wulfman, D.S., in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 1, Wiley, NY, ***1978***, pp. 286–297.

[350]For reviews, see Galli, C. *Chem. Rev.* ***1988***, *88*, 765; Zollinger, H. *Acc. Chem. Res.* ***1973***, *6*, 355, pp. 339–341.

[351]Rate constants for this reaction have been determined. See Hanson, P.; Hammond, R.C.; Goodacre, P.R.; Purcell, J.; Timms, A.W. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 691.

[352]Dickerman, S.C.; Weiss, K.; Ingberman, A.K. *J. Am. Chem. Soc.* ***1958***, *80*, 1904; Kochi, J.K. *J. Am. Chem. Soc.* ***1957***, *79*, 2942; Dickerman, S.C.; DeSouza, D.J.; Jacobson, N. *J. Org. Chem.* ***1969***, *34*, 710; Galli, C. *J. Chem. Soc. Perkin Trans. 2* ***1981***, 1459; ***1982***, 1139; ***1984***, 897. See also, Hanson, P.; Jones, J.R.; Gilbert, B.C.; Timms, A.W. *J. Chem. Soc. Perkin Trans. 2* ***1991***, 1009.

The first step involves a reduction of the diazonium ion by the cuprous ion, which results in the formation of an aryl radical. In the second step, the aryl radical abstracts halogen from cupric chloride, reducing it. The CuX is regenerated and is thus a true catalyst.

Aryl bromides and chlorides can be prepared from primary aromatic amines in one step by several procedures,[353] including treatment of the amine (*1*) with *tert*-butyl nitrite and anhydrous $CuCl_2$ or $CuBr_2$ at 65°C,[354] and (*2*) with *tert*-butyl thionitrite or *tert*-butyl thionitrate and $CuCl_2$ or $CuBr_2$ at room temperature.[355] These procedures are, in effect, a combination of **13-19** and the Sandmeyer reaction. A further advantage is that cooling to 0°C is not needed. A mixture of Me_3SiCl and $NaNO_2$ was used to convert aniline to chlorobenzene in a related reaction.[356]

For the preparation of fluorides and iodides from diazonium salts (see **13-32** and **13-31**).

$$ArN_2^+ + CuCN \longrightarrow ArCN$$

It is noted that the reaction of aryl diazonium salts with CuCN to give benzonitrile derivatives is also called the *Sandmeyer reaction*. It is usually conducted in neutral solution to avoid liberation of HCN.

OS **I**, 135, 136, 162, 170; **II**, 130; **III**, 185; **IV**, 160. Also see, OS **III**, 136; **IV**, 182. For the reaction with CuCN, see OS **I**, 514.

14-21 Replacement of the Diazonium Group by Nitro

Nitro-de-diazoniation

$$ArN_2^+ + NaNO_2 \xrightarrow{Cu^+} ArNO_2$$

Nitro compounds can be formed in good yields by treatment of diazonium salts with sodium nitrite in the presence of cuprous ion. The reaction occurs only in neutral or alkaline solution. This is not usually called the Sandmeyer reaction, although, like **14-20**, it was discovered by Sandmeyer. Tetrafluoroborate (BF_4–) is often used as the negative ion since the diminished nucleophilicity avoids competition from the chloride ion. The mechanism is probably like that of **14-20**.[357] If electron-withdrawing groups are present, the catalyst is not needed; $NaNO_2$ alone gives nitro compounds in high yields.[358]

[353]For other procedures, see Brackman,W.; Smit, P.J. *Recl. Trav. Chim. Pays-Bas*, ***1966***, *85*, 857; Cadogan, J.I.G.; Roy, D.A.; Smith, D.M. *J. Chem. Soc. C* ***1966***, 1249.

[354]Doyle, M.P.; Siegfried, B.; Dellaria, Jr, J.F. *J. Org. Chem.* ***1977***, *42*, 2426.

[355]Oae, S.; Shinhama, K.; Kim, Y.H. *Bull. Chem. Soc. Jpn.* ***1980***, *53*, 1065.

[356]Lee, J.G.; Cha, H.T. *Tetrahedron Lett.* ***1992***, *33*, 3167.

[357]For discussions, see Opgenorth, H.; Rüchardt, C. *Liebigs Ann. Chem.* ***1974***, 1333; Singh, P.R.; Kumar, R.; Khanna, R.K. *Tetrahedron Lett.* ***1982***, *23*, 5191.

[358]Bagal, L.I.; Pevzner, M.S.; Frolov, A.N. *J. Org. Chem. USSR* ***1969***, *5*, 1767.

An alternative procedure used electrolysis, in 60% HNO_3 to convert 1-aminonaphthalene to naphthalene.[359]

OS **II**, 225; **III**, 341.

14-22 Replacement of the Diazonium Group by Sulfur-Containing Groups

Chlorosulfo-de-diazoniation

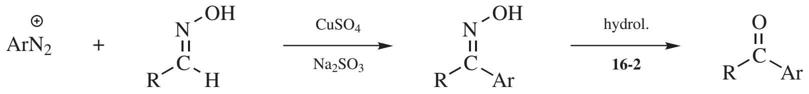
$$ArN_2^+ \; + \; SO_2 \xrightarrow[HCl]{CuCl_2} ArSO_2Cl$$

Diazonium salts can be converted to sulfonyl chlorides by treatment with sulfur dioxide in the presence of cupric chloride.[360] The use of $FeSO_4$ and copper metal instead of $CuCl_2$ gives sulfinic acids ($ArSO_2H$)[361] (see also, **13-21**).

OS **V**, 60; **VII**, 508.

14-23 Conversion of Diazonium Salts to Aldehydes, Ketones, or Carboxylic Acids

Acyl-de-diazoniation, and so on



Diazonium salts react with oximes to give aryl oximes, which are easily hydrolyzed to aldehydes (R = H) or ketones.[362] A copper sulfate-sodium sulfite catalyst is essential. In most cases higher yields (40–60%) are obtained when the reaction is used for aldehydes than for ketones. In another method[363] for achieving the conversion $ArN_2^+ \rightarrow ArCOR$, diazonium salts are treated with R_4Sn and CO with palladium acetate as catalyst.[364] In a different kind of reaction, silyl enol ethers of aryl ketones $Ar'C(OSiMe_3){=}CHR$ react with solid diazonium fluoroborates (ArN_2^+ BF_4^-) to give ketones (ArCHRCOAr′).[365] This is, in effect, an arylation of the aryl ketone.

Carboxylic acids can be prepared in moderate-to-high yields by treatment of diazonium fluoroborates with carbon monoxide and palladium acetate[366] or

[359]Torii, S.; Okumoto, H.; Satoh, H.; Minoshima, T.; Kurozumi, S. *SynLett*, ***1995***, 439.

[360]Gilbert, E.E. *Synthesis* ***1969***, 1, p. 6.

[361]Wittig, G.; Hoffmann, R.W. *Org. Synth. V*, 60.

[362]Beech, W.F. *J. Chem. Soc.* ***1954***, 1297.

[363]For still another method, see Citterio, A.; Serravalle, M.; Vimara, E. *Tetrahedron Lett.* ***1982***, *23*, 1831.

[364]Kikukawa, K.; Idemoto, T.; Katayama, A.; Kono, K.; Wada, F.; Matsuda, T. *J. Chem. Soc. Perkin Trans. 1* ***1987***, 1511.

[365]Sakakura, T.; Hara, M.; Tanaka, M. *J. Chem. Soc., Chem. Commun.* ***1985***, 1545.

[366]Nagira, K.; Kikukawa, K.; Wada, F.; Matsuda, T. *J. Org. Chem.* ***1980***, *45*, 2365.

copper(II) chloride.[367] The mixed anhydride ArCOOCOMe is an intermediate that can be isolated. Other mixed anhydrides can be prepared by the use of other salts instead of sodium acetate.[368] An arylpalladium compound is probably an intermediate.[368]

OS **V**, 139.

METALS AS LEAVING GROUPS

14-24 Coupling of Grignard Reagents

De-metallo-coupling

$$2\,RMgX \xrightarrow{TlBr} RR$$

This organometallic coupling reaction is clearly related to the Wurtz coupling, discussed in **10-56**, and the coupling of other organometallic compounds is discussed in **14-25**. Grignard reagents can be coupled to give symmetrical dimers[369] by treatment with either thallium(I) bromide[370] or with a transition-metal halide, such as $CrCl_2$, $CrCl_3$, $CoCl_2$, $CoBr_2$, or $CuCl_2$.[371] The metallic halide is an oxidizing agent and becomes reduced. Both aryl and alkyl Grignard reagents can be dimerized by either procedure, though the TlBr method cannot be applied to R = primary alkyl or to aryl groups with ortho substituents. Aryl Grignard reagents can also be dimerized by treatment with 1,4-dichloro-2-butene, 1,4-dichloro-2-butyne, or 2,3-dichloropropene.[372] Vinylic and alkynyl Grignard reagents can be coupled (to give 1,3-dienes and 1,3-diynes, respectively) by treatment with thionyl chloride.[373] Primary alkyl, vinylic, aryl, and benzylic Grignard reagents give symmetrical dimers in high yield (~90%) when treated with a silver(I) salt (e.g., $AgNO_3$, AgBr, $AgClO_4$) in the presence of a nitrogen-containing oxidizing agent, such as lithium nitrate, methyl nitrate, or NO_2.[374] This method has been used to close rings of four, five, and six members.[375]

[367]Olah, G.A.; Wu, A.; Bagno, A.; Prakash, G.K.S. *Synlett*, ***1990***, 596.

[368]Kikukawa, K.; Kono, K.; Nagira, K.; Wada, F.; Matsuda, T. *J. Org. Chem.* ***1981***, *46*, 4413.

[369]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed, Wiley-VCH, NY, ***1999***, pp. 85–88.

[370]McKillop, A.; Elsom, L.F.; Taylor, E.C. *Tetrahedron* ***1970***, *26*, 4041.

[371]For reviews, see Kauffmann, T. *Angew. Chem. Int. Ed.* ***1974***, *13*, 291; Elsom, L.F.; Hunt, J.D.; McKillop, A. *Organomet. Chem. Rev. Sect. A* ***1972***, *8*, 135; Nigh, W.G., in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B, Academic Press, NY, ***1973***, pp. 85–91.

[372]Taylor, S.K.; Bennett, S.G.; Heinz, K.J.; Lashley, L.K. *J. Org. Chem.* ***1981***, *46*, 2194; Cheng, J.; Luo, F. *Tetrahedron Lett.* ***1988***, *29*, 1293.

[373]Uchida, A.; Nakazawa, T.; Kondo, I.; Iwata, N.; Matsuda, S. *J. Org. Chem.* ***1972***, *37*, 3749.

[374]Tamura, M.; Kochi, J.K. *Bull. Chem. Soc. Jpn.* ***1972***, *45*, 1120.

[375]Whitesides, G.M.; Gutowski, F.D. *J. Org. Chem.* ***1976***, *41*, 2882.

The mechanisms of the reactions with metal halides, at least in some cases, probably begin with conversion of RMgX to the corresponding RM (**12-36**), followed by its decomposition to free radicals.[376]

OS **VI**, 488.

14-25 Coupling of Other Organometallic Reagents[332]

De-metallo-coupling

$$R_2CuLi \xrightarrow[-78°C,\ THF]{O_2} RR$$

Lithium dialkylcopper reagents can be oxidized to symmetrical dimers by O_2 at −78°C in THF.[377] The reaction is successful for R = primary and secondary alkyl, vinylic, or aryl. Other oxidizing agents, for example, nitrobenzene, can be used instead of O_2. Vinylic copper reagents dimerize on treatment with oxygen, or simply on standing at 0°C for several days or at 25°C for several hours, to yield 1,3-dienes.[378] The finding of retention of configuration for this reaction demonstrates that free-radical intermediates are not involved.

The coupling reaction of Grignard reagents was discussed in **14-24**. Lithium organoaluminates ($LiAlR_4$) are dimerized to RR by treatment with $Cu(OAc)_2$.[379] Terminal vinylic alanes (prepared by **15-17**) can be dimerized to 1,3-dienes with CuCl in THF.[380] Symmetrical 1,3-dienes can also be prepared in high yields by treatment of vinylic mercury chlorides[381] with LiCl and a rhodium catalyst[382] and by treatment of vinylic tin compounds with a palladium catalyst.[383] Arylmercuric salts are converted to biaryls by treatment with copper and a catalytic amount of $PdCl_2$.[384] Vinylic, alkynyl, and aryl tin compounds were dimerized with

[376]For a review of the mechanism, see Kashin, A.N.; Beletskaya, I.P. *Russ. Chem. Rev.* ***1982***, *51*, 503.

[377]Whitesides, G.M.; San Filippo, Jr, J.; Casey, C.P.; Panek, E.J. *J. Am. Chem. Soc.* ***1967***, *89*, 5302. See also, Kauffmann, T.; Kuhlmann, D.; Sahm, W.; Schrecken, H. *Angew. Chem. Int. Ed.* ***1968***, *7*, 541; Bertz, S.H.; Gibson, C.P. *J. Am. Chem. Soc.* ***1986***, *108*, 8286.

[378]Whitesides, G.M.; Casey, C.P.; Krieger, J.K. *J. Am. Chem. Soc.* ***1971***, *93*, 1379; Walborsky, H.M.; Banks, R.B.; Banks, M.L.A.; Duraisamy, M. *Organometallics* ***1982***, *1*, 667; Rao, S.A.; Periasamy, M. *J. Chem. Soc., Chem. Commun.* ***1987***, 495. See also, Lambert, G.J.; Duffley, R.P.; Dalzell, H.C.; Razdan, R.K. *J. Org. Chem.* ***1982***, *47*, 3350.

[379]Sato, F.; Mori, Y.; Sato, M. *Chem. Lett.* ***1978***, 1337.

[380]Zweifel, G.; Miller, R.L. *J. Am. Chem. Soc.* ***1970***, *92*, 6678.

[381]For reviews of coupling with organomercury compounds, see Russell, G.A. *Acc. Chem. Res.* ***1989***, *22*, 1; Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, ***1985***, pp. 240–248.

[382]Larock, R.C.; Bernhardt, J.C. *J. Org. Chem.* ***1977***, *42*, 1680. For extension to unsymmetrical 1,3-dienes, see Larock, R.C.; Riefling, B. *J. Org. Chem.* ***1978***, *43*, 1468.

[383]Tolstikov, G.A.; Miftakhov, M.S.; Danilova, N.A.; Vel'der, Ya.L.; Spirikhin, L.V. *Synthesis* ***1989***, 633.

[384]Kretchmer, R.A.; Glowinski, R. *J. Org. Chem.* ***1976***, *41*, 2661. See also, Bumagin, N.A.; Kalinovskii, I.O.; Beletskaya, I.P. *J. Org. Chem. USSR* ***1982***, *18*, 1151; Larock, R.C.; Bernhardt, J.C. *J. Org. Chem.* ***1977***, *42*, 1680.

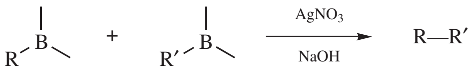
$Cu(NO_3)_2$.[385] Alkyl- and aryllithium compounds can be dimerized by transition-metal halides in a reaction similar to **14-24**.[386] Triarylbismuth compounds Ar_3Bi react with palladium(0) complexes to give biaryls ArAr.[387] Diethylzinc reacted with $Ph_2I^+ BF_4^-$ in the presence of palladium acetate, to give biphenyl.[388]

Unsymmetrical coupling of vinylic, alkynyl, and arylmercury compounds was achieved in moderate-to-good yields by treatment with alkyl and vinylic dialkylcopper reagents, for example, $PhCH{=}CHHgCl + Me_2CuLi \rightarrow PhCH{=}CHMe$.[389] Unsymmetrical biaryls were prepared by treating a cyanocuprate (ArCu(CN)Li, prepared from ArLi and CuCN) with an aryllithium (Ar′Li).[390]

A radical coupling reaction has been reported, in which an aryl halide reacted with Bu_3SnH, AIBN, and benzene, followed by treatment with methyllithium to give the biaryl.[391]

14-26 Coupling of Boranes

Alkyl-de-dialkylboration

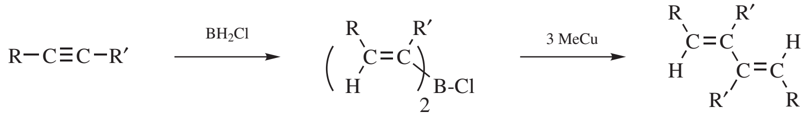


Alkylboranes can be coupled by treatment with silver nitrate and base.[392] Since alkylboranes are easily prepared from alkenes (**15-16**), this is essentially a way of coupling and reducing alkenes; in fact, alkenes can be hydroborated and coupled in the same flask. For symmetrical coupling (R = R′) yields range from 60 to 80% for terminal alkenes and from 35 to 50% for internal ones. Unsymmetrical coupling has also been carried out,[393] but with lower yields. Arylboranes react similarly, yielding biaryls.[394] The mechanism is probably of the free-radical type.

Dimerization of two vinylborane units to give a conjugated diene can be achieved by treatment of divinylchloroboranes (prepared by addition of BH_2Cl to alkynes; see **15-16**) with methylcopper. (*E*,*E*)-1,3-Dienes are prepared in high

[385]Ghosal, S.; Luke, G.P.; Kyler, K.S. *J. Org. Chem.* ***1987***, *52*, 4296.
[386]Morizur, J. *Bull. Soc. Chim. Fr.* ***1964***, 1331.
[387]Barton, D.H.R.; Ozbalik, N.; Ramesh, M. *Tetrahedron* ***1988***, *44*, 5661.
[388]Kang, S.-K.; Hong, R.-K.; Kim, T.-H.; Pyun, S.-J. *Synth. Commun.* ***1997***, *27*, 2351.
[389]Larock, R.C.; Leach, D.R. *Tetrahedron Lett.* ***1981***, *22*, 3435; *Organometallics* ***1982***, *1*, 74. For another method, see Larock, R.C.; Hershberger, S.S. *Tetrahedron Lett.* ***1981***, *22*, 2443.
[390]Lipshutz, B.H.; Siegmann, K.; Garcia, E. *J. Am. Chem. Soc.* ***1991***, *113*, 8161.
[391]Studer, A. ; Bossart, M.; Vasella, T. *Org. Lett.* ***2000***, *2*, 985.
[392]Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, pp. 306–308.
[393]Brown, H.C.; Verbrugge, C.; Snyder, C.H. *J. Am. Chem. Soc.* ***1961***, *83*, 1001.
[394]Breuer, S.W.; Broster, F.A. *Tetrahedron Lett.* ***1972***, 2193.

yields.[395]



In a similar reaction, symmetrical conjugated diynes RC≡C—C≡CR can be prepared by reaction of lithium dialkyldialkynylborates, Li^+ $[R'_2B(C{\equiv}CR)_2]^-$, with iodine.[396]

HALOGEN AS LEAVING GROUP

The conversion of RX to RH can occur by a free-radical mechanism but is treated at **19-53**.

SULFUR AS LEAVING GROUP

14-27 Desulfurization

Hydro-de-thio-substitution, and so on

$$RSH \xrightarrow[\text{Ni}]{H_2} RH$$

$$RSR' \xrightarrow[\text{Ni}]{H_2} RH + R'H$$

Thiols and thioethers,[397] both alkyl and aryl, can be desulfurized by hydrogenolysis with Raney nickel.[398] The hydrogen is usually not applied externally, since Raney nickel already contains enough hydrogen for the reaction. Other sulfur compounds can be similarly desulfurized, among them disulfides (RSSR),

[395]Yamamoto, Y.; Yatagai, H.; Maruyama, K.; Sonoda, A.; Murahashi, S. *J. Am. Chem. Soc.* ***1977***, *99*, 5652; *Bull. Chem. Soc. Jpn.* ***1977***, *50*, 3427. For other methods of dimerizing vinylic boron compounds, see Rao, V.V.R.; Kumar, C.V.; Devaprabhakara, D. *J. Organomet. Chem.* ***1979***, *179*, C7; Campbell, Jr, J.B.; Brown, H.C. *J. Org. Chem.* ***1980***, *45*, 549.

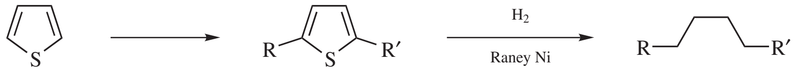
[396]Pelter, A.; Smith, K.; Tabata, M. *J. Chem. Soc., Chem. Commun.* ***1975***, 857. For extensions to unsymmetrical conjugated diynes, see Pelter, A.; Hughes, R.; Smith, K.; Tabata, M. *Tetrahedron Lett.* ***1976***, 4385; Sinclair, J.A.; Brown, H.C. *J. Org. Chem.* ***1976***, *41*, 1078.

[397]For a review of the reduction of thioethers, see Block, E., in Patai, S. *The Chemistry of Functional Groups, Supplement E*, pt. 1, Wiley, NY, ***1980***, pp. 585–600.

[398]For reviews, see Belen'kii, L.I., in Belen'kii, L.I. *Chemistry of Organosulfur Compounds*, Ellis Horwood, Chichester, ***1990***, pp. 193–228; Pettit, G.R.; van Tamelen, E.E. *Org. React.* ***1962***, *12*, 356; Hauptmann, H.; Walter, W.F. *Chem. Rev.* ***1962***, *62*, 347.

thiono esters (RCSOR′),[399] thioamides (RCDNHR′), sulfoxides, and dithioacetals. The last reaction, which is an indirect way of accomplishing reduction of a carbonyl to a methylene group (see **19-61**), can also give the alkene if an a hydrogen is present.[400] In most of the examples given, R can also be aryl. Other reagents[401] have also been used,[402] including samarium in acetic acid for desulfurization of vinyl sulfones.[403]

An important special case of RSR reduction is desulfurization of thiophene derivatives. This proceeds with concomitant reduction of the double bonds. Many compounds have been made by alkylation of thiophene (see **39**), followed by reduction to the corresponding alkane.



39

Thiophenes can also be desulfurized to alkenes ($RCH_2CH{=}CHCH_2R'$ from **39**) with a nickel boride catalyst prepared from nickel(II) chloride and $NaBH_4$ in methanol.[404] It is possible to reduce just one SR group of a dithioacetal by treatment with borane–pyridine in trifluoroacetic acid or in CH_2Cl_2 in the presence of $AlCl_3$.[405] Phenyl selenides RSePh can be reduced to RH with Ph_3SnH[406] and with nickel boride.[407]

The exact mechanisms of the Raney nickel reactions are still in doubt, though they are probably of the free-radical type.[408] It has been shown that reduction of thiophene proceeds through butadiene and butene, not through 1-butanethiol or other sulfur compounds, that is, the sulfur is removed before the double bonds

[399]See Baxter, S.L.; Bradshaw, J.S. *J. Org. Chem.* ***1981***, *46*, 831.

[400]Fishman, J.; Torigoe, M.; Guzik, H. *J. Org. Chem.* ***1963***, *28*, 1443.

[401]For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed, Wiley-VCH, NY, ***1999***, pp. 53–60. For a review with respect to transition-metal reagents, see Luh, T.; Ni, Z. *Synthesis* ***1990***, 89. For some very efficient nickel-containing reagents, see Becker, S.; Fort, Y.; Vanderesse, R.; Caubère, P. *J. Org. Chem.* ***1989***, *54*, 4848.

[402]For example, diphosphorus tetraiodide by Suzuki, H.; Tani, H.; Takeuchi, S. *Bull. Chem. Soc. Jpn.* ***1985***, *58*, 2421; Shigemasa, Y.; Ogawa, M.; Sashiwa, H.; Saimoto, H. *Tetrahedron Lett.* ***1989***, *30*, 1277; $NiBr_2$—Ph_3P—$LiAlH_4$ by Ho, K.M.; Lam, C.H.; Luh, T. *J. Org. Chem.* ***1989***, *54*, 4474.

[403]Liu, Y.; Zhang, Y. *Org. Prep. Proceed. Int.* ***2001***, *33*, 376.

[404]Schut, J.; Engberts, J.B.F.N.; Wynberg, H. *Synth. Commun.* ***1972***, *2*, 415.

[405]Kikugawa, Y. *J. Chem. Soc. Perkin Trans. 1* ***1984***, 609.

[406]Clive, D.L.J.; Chittattu, G.; Wong, C.K. *J. Chem. Soc., Chem. Commun.* ***1978***, 41.

[407]Back, T.G. *J. Chem. Soc., Chem. Commun.* ***1984***, 1417.

[408]For a review, see Bonner, W.A.; Grimm, R.A., in Kharasch, N.; Meyers, C.Y. *The Chemistry of Organic Sulfur Compounds*, Vol. 2, Pergamon, NY, ***1966***, pp. 35–71, 410–413. For a review of the mechanism of desulfurization on molybdenum surfaces, see Friend, C.M.; Roberts, J.T. *Acc. Chem. Res.* ***1988***, *21*, 394.

are reduced. This was demonstrated by isolation of the olefins and the failure to isolate any potential sulfur-containing intermediates.[409]

OS **IV**, 638; **V**, 419; **VI**, 109, 581, 601. See also OS **VII**, 124, 476.

14-28 Conversion of Sulfides to Organolithium Compounds

Lithio-de-phenylthio-substitution

$$\text{RSPh} \xrightarrow[\text{THF}]{\text{Li naphthalenide}} \text{RLi}$$

Sulfides can be cleaved, with a phenylthio group replaced by a lithium,[410] by treatment with lithium or lithium naphthalenide in THF.[411] Good yields have been obtained with R = primary, secondary, or tertiary alkyl, or allylic,[412] and containing groups, such as double bonds or halogens. Dilithio compounds can be made from compounds containing two separated SPh groups, but it is also possible to replace just one SPh from a compound with two such groups on a single carbon, to give an α-lithio sulfide.[413] The reaction has also been used to prepare α-lithio ethers and α-lithio organosilanes.[410] For some of these compounds lithium 1-(dimethylamino)naphthalenide is a better reagent than either Li or lithium naphthalenide.[414] The mechanism is presumably of the free-radical type.

CARBON AS LEAVING GROUP

14-29 Decarboxylative Dimerization: The Kolbe Reaction

De-carboxylic-coupling

$$2\,\text{RCOO}^- \xrightarrow{\text{electrolysis}} \text{R—R}$$

Electrolysis of carboxylate ions, results in decarboxylation and combination of the resulting radicals to give the coupling product R—R. This coupling

[409]Owens, P.J.; Ahmberg, C.H. *Can. J. Chem.* ***1962***, *40*, 941.

[410]For a review, see Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* ***1989***, *22*, 152.

[411]Screttas, C.G.; Micha-Screttas, M. *J. Org. Chem.* ***1978***, *43*, 1064; ***1979***, *44*, 713.

[412]See Cohen, T.; Guo, B. *Tetrahedron* ***1986***, *42*, 2803.

[413]See, for example, Cohen, T.; Sherbine, J.P.; Matz, J.R.; Hutchins, R.R.; McHenry, B.M.; Willey, P.R. *J. Am. Chem. Soc.* ***1984***, *106*, 3245; Ager, D.J. *J. Chem. Soc. Perkin Trans. 1* ***1986***, 183; Screttas, C.G.; Micha-Screttas, M. *J. Org. Chem.* ***1978***, *43*, 1064; ***1979***, *44*, 713.

[414]See Cohen, T.; Matz, J.R. *Synth. Commun.* ***1980***, *10*, 311.

reaction is called the *Kolbe reaction* or the *Kolbe electrosynthesis*.[415] It is used to prepare symmetrical R—R, where R is straight chained, since little or no yield is obtained when there is a branching. The reaction is not successful for R = aryl. Many functional groups may be present, though many others inhibit the reaction.[415] Unsymmetrical RR′ have been made by coupling mixtures of acid salts.

A free-radical mechanism is involved:

$$\text{RCOO}^- \xrightarrow[\text{oxidation}]{\text{electrolytic}} \text{RCOO}\bullet \xrightarrow{-\text{CO}_2} \text{R}\bullet \longrightarrow \text{R–R}$$

There is much evidence[416] for this mechanism, including side products (RH, alkenes) characteristic of free-radical intermediates and the fact that electrolysis of acetate ion in the presence of styrene caused some of the styrene to polymerize to polystyrene (such polymerizations can be initiated by free radicals, see p. 1015). Other side products (ROH, RCOOR) are sometimes found, stemming from further oxidation of the radical R• to a carbocation R^+.[417]

When the reaction is conducted in the presence of 1,3-dienes, additive dimerization can occur:[418]

$$2\,\text{RCOO}^- + \text{CH}_2\text{=CH–CH=CH}_2 \longrightarrow \text{RCH}_2\text{CH=CHCH}_2\text{CH}_2\text{CH=CHCH}_2\text{R}$$

The radical R• adds to the conjugated system to give $RCH_2CH{=}CHCH_2\bullet$, which dimerizes. Another possible product is $RCH_2CH{=}CHCH_2R$, from coupling of the two kinds of radicals.[419]

In a nonelectrolytic reaction, which is limited to R = primary alkyl, the thiohydroxamic esters **40** give dimers when irradiated at −64°C in an argon

[415]For reviews, see Nuding, G.; Vögtle, F.; Danielmeier, K.; Steckhan, E. *Synthesis* ***1996***, 71; Schäfer, H.J. *Top. Curr. Chem.* ***1990***, *152*, 91; *Angew. Chem. Int. Ed.* ***1981***, *20*, 911; Fry, A.J. *Synthetic Organic Electrochemistry*, 2nd ed, Wiley, NY, ***1989***, pp. 238–253; Eberson, L.; Utley, J.H.P., in Baizer, M.M.; Lund, H. *Organic Electrochemistry*, Marcel Dekker, NY, ***1983***, pp. 435–462; Gilde, H. *Methods Free-Radical Chem.* ***1972***, *3*, 1; Eberson, L., in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 53–101; Vijh, A.K.; Conway, B.E. *Chem. Rev.* ***1967***, *67*, 623.

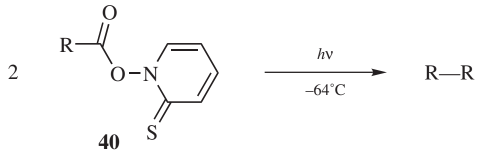
[416]For other evidence, see Kraeutler, B.; Jaeger, C.D.; Bard, A.J. *J. Am. Chem. Soc.* ***1978***, *100*, 4903.

[417]See Corey, E.J.; Bauld, N.L.; La Londe, R.T.; Casanova, Jr, J.; Kaiser, E.T. *J. Am. Chem. Soc.* ***1960***, *82*, 2645.

[418]Lindsey, Jr, R.V.; Peterson, M.L. *J. Am. Chem. Soc.* ***1959***, *81*, 2073; Khrizolitova, M.A.; Mirkind, L.A.; Fioshin, M.Ya. *J. Org. Chem. USSR* ***1968***, *4*, 1640; Bruno, F.; Dubois, J.E. *Bull. Soc. Chim. Fr.* ***1973***, 2270.

[419]Smith, W.B.; Gilde, H. *J. Am. Chem. Soc.* ***1959***, *81*, 5325; ***1961***, *83*, 1355; Schäfer, H.; Pistorius, R. *Angew. Chem. Int. Ed.* ***1972***, *11*, 841.

atmosphere:[420]



40

In another nonelectrolytic process, aryl acetic acids are converted to *vic*-diaryl compounds $2ArCR_2COOH \rightarrow ArCR_2CR_2Ar$ by treatment with sodium persulfate $Na_2S_2O_8$ and a catalytic amount of $AgNO_3$.[421] Photolysis of carboxylic acids in the presence of Hg_2F_2 leads to the dimeric alkane via decarboxylation.[422] Both of these reactions involve dimerization of free radicals. In still another process, electron-deficient aromatic acyl chlorides are dimerized to biaryls (2 ArCOCl → Ar—Ar) by treatment with a disilane R_3SiSiR_3 and a palladium catalyst.[423]

OS **III**, 401; **V**, 445, 463; **VII**, 181.

14-30 The Hunsdiecker Reaction

Bromo-de-carboxylation

$$RCOOAg + Br_2 \longrightarrow RBr + CO_2 + AgBr$$

Reaction of a silver salt of a carboxylic acid with bromine is called the *Hunsdiecker reaction*[424] and is a way of decreasing the length of a carbon chain by one unit.[425] The reaction is of wide scope, giving good results for *n*-alkyl R from 2 to 18 carbons and for many branched R too, producing primary, secondary, and tertiary bromides. Many functional groups may be present as long as they are not a substituted. The group R may also be aryl. However, if R contains unsaturation, the reaction seldom gives good results. Although bromine is the most often used halogen, chlorine and iodine have also been used. Catalytic Hunsdiecker reactions are known.[426]

When iodine is the reagent, the ratio between the reactants is very important and determines the products. A 1:1 ratio of salt/iodine gives the alkyl halide, as above.

[420]Barton, D.H.R.; Bridon, D.; Fernandez-Picot, I.; Zard, S.Z. *Tetrahedron* ***1987***, *43*, 2733.

[421]Fristad, W.E.; Klang, J.A. *Tetrahedron Lett.* ***1983***, *24*, 2219.

[422]Habibi, M.H.; Farhadi, S. *Tetrahedron Lett.* ***1999***, *40*, 2821.

[423]Krafft, T.E.; Rich, J.D.; McDermott, P.J. *J. Org. Chem.* ***1990***, *55*, 5430.

[424]This reaction was first reported by the Russian composer–chemist Alexander Borodin: *Liebigs Ann. Chem.* ***1861***, *119*, 121.

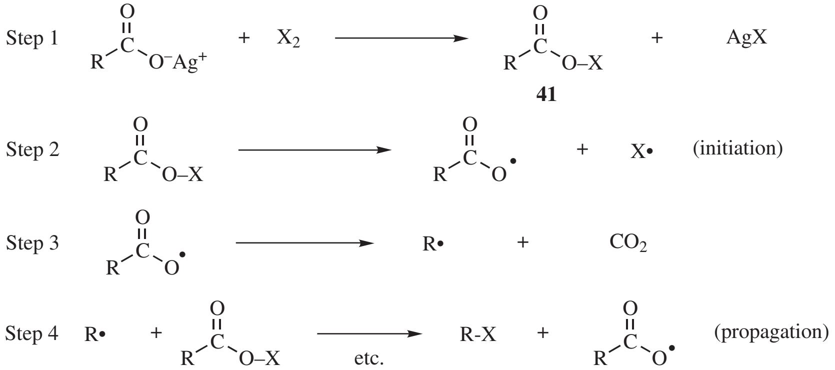
[425]For reviews, see Wilson, C.V. *Org. React.* ***1957***, *9*, 332; Johnson, R.G.; Ingham, R.K. *Chem. Rev.* ***1956***, *56*, 219. Also see, Naskar, D.; Chowdhury, S.; Roy, S. *Tetrahedron Lett.* ***1998***, *39*, 699.

[426]Das, J.P.; Roy, S. *J. Org. Chem.* ***2002***, *67*, 7861.

A 2:1 ratio, however, gives the ester RCOOR. This is called the *Simonini reaction* and is sometimes used to prepare carboxylic esters. The Simonini reaction can also be carried out with lead salts of acids.[427] A more convenient way to perform the Hunsdiecker reaction is by use of a mixture of the acid and mercuric oxide instead of the salt, since the silver salt must be very pure and dry and such pure silver salts are often not easy to prepare.[428]

Other methods for accomplishing the conversion RCOOH → RX are[429] (*1*) treatment of thallium(I) carboxylates[430] with bromine;[431] (*2*) treatment of carboxylic acids with lead tetraacetate and halide *ions* (Cl^-, Br^-, or I^-);[432] (*3*) reaction of the acids with lead tetraacetate and NCS, which gives tertiary and secondary chlorides in good yields, but is not good for R = primary alkyl or phenyl;[433] (*4*) treatment of thiohydroxamic esters with CCl_4, $BrCCl_3$ (which gives bromination), CHI_3, or CH_2I_2 in the presence of a radical initiator;[434] (*5*) photolysis of benzophenone oxime esters of carboxylic acids in CCl_4 ($RCON{=}CPh_2 \rightarrow RCl$).[435] Alkyl fluorides can be prepared in moderate to good yields by treating carboxylic acids RCOOH with XeF_2.[436] This method works best for R = primary and tertiary alkyl, and benzylic. Aromatic and vinylic acids do not react.

The mechanism of the Hunsdiecker reaction is believed to be as follows:



[427] Bachman, G.B.; Kite, G.F.; Tuccarbasu, S.; Tullman, G.M. *J. Org. Chem.* ***1970***, *35*, 3167.

[428] Cristol, S.J.; Firth, W.C. *J. Org. Chem.* ***1961***, *26*, 280. See also, Meyers, A.I.; Fleming, M.P. *J. Org. Chem.* ***1979***, *44*, 3405, and references cited therein.

[429] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed, Wiley-VCH, NY, ***1999***, pp. 741–744.

[430] These salts are easy to prepare and purify; see Ref. 501.

[431] McKillop, A.; Bromley, D.; Taylor, E.C. *J. Org. Chem.* ***1969***, *34*, 1172; Cambie, R.C.; Hayward, R.C.; Jurlina, J.L.; Rutledge, P.S.; Woodgate, P.D. *J. Chem. Soc. Perkin Trans. 1* ***1981***, 2608.

[432] Kochi, J.K. *J. Am. Chem. Soc.* ***1965***, *87*, 2500; *J. Org. Chem.* ***1965***, *30*, 3265. For a review, see Sheldon, R.A.; Kochi, J.K. *Org. React.* ***1972***, *19*, 279, pp. 326–334, 390–399.

[433] Becker, K.B.; Geisel, M.; Grob, C.A.; Kuhnen, F. *Synthesis* ***1973***, 493.

[434] Barton, D.H.R.; Lacher, B.; Zard, S.Z. *Tetrahedron* ***1987***, *43*, 4321; Stofer, E.; Lion, C. *Bull. Soc. Chim. Belg.* ***1987***, *96*, 623; Della, E.W.; Tsanaktsidis, J. *Aust. J. Chem.* ***1989***, *42*, 61.

[435] Hasebe, M.; Tsuchiya, T. *Tetrahedron Lett.* ***1988***, *29*, 6287.

[436] Patrick, T.B.; Johri, K.K.; White, D.H.; Bertrand, W.S.; Mokhtar, R.; Kilbourn, M.R.; Welch, M.J. *Can. J. Chem.* ***1986***, *64*, 138. For another method, see Grakauskas, V. *J. Org. Chem.* ***1969***, *34*, 2446.

The first step is not a free-radical process, and its actual mechanism is not known.[437] Compound **41** is an acyl hypohalite and is presumed to be an intermediate, though it has never been isolated from the reaction mixture. Among the evidence for the mechanism is that optical activity at R is lost (except when a neighboring bromine atom is present, see p. 942); if R is neopentyl, there is no rearrangement, which would certainly happen with a carbocation; and the side products, notably RR, are consistent with a free-radical mechanism. There is evidence that the Simonini reaction involves the same mechanism as the Hunsdiecker reaction, but that the alkyl halide formed then reacts with excess RCOOAg (**10-17**) to give the ester[438] (see also **19-12**).

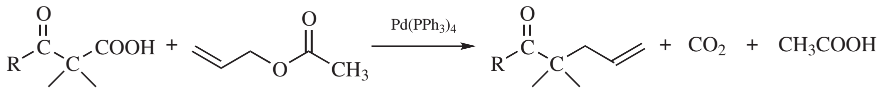
Vinyl carboxylic acids (conjugated acids) were shown to react with NBS and lithium acetate in aqueous acetonitrile, to give the corresponding vinyl bromide (C=C–COOH → C=C–Br), using microwave irradiation.[439] A similar reaction was reported using Na_2MoO_4, KBr and aqueous hydrogen peroxide.[440]

A related reaction reacts the sodium salt of an alkylsulfonic acid with thionyl chloride at 100°C, to give the alkyl chloride.[441]

OS **III**, 578; **V**, 126; **VI**, 179; **75**, 124; **X**, 237. See also OS **VI**, 403.

14-31 Decarboxylative Allylation

Allyl-de-carboxylation



The COOH group of a β-keto acid is replaced by an allylic group when the acid is treated with an allylic acetate and a palladium catalyst at room temperature.[442] The reaction is successful for various substituted allylic groups. The less highly substituted end of the allylic group forms the new bond. Thus, both CH_2=CHCHMeOAc and MeCH=$CHCH_2$OAc gave O=C(R)–C–CH_2CH=CHMe as the product.

[437]When Br_2 reacts with aryl R, at low temperature in inert solvents, it is possible to isolate a complex containing both Br_2 and the silver carboxylate: see Bryce-Smith, D.; Isaacs, N.S.; Tumi, S.O. *Chem. Lett.* ***1984***, 1471.

[438]Oae, S.; Kashiwagi, T.; Kozuka, S. *Bull. Chem. Soc. Jpn.* ***1966***, *39*, 2441; Bunce, N.J.; Murray, N.G. *Tetrahedron* ***1971***, *27*, 5323.

[439]Kuang, C.; Senboku, H.; Tokuda, M. *Synlett* ***2000***, 1439.

[440]Sinha, J.; Layek, S.; Bhattacharjee, M.; Mandal, G.C. *Chem. Commun.* ***2001***, 1916.

[441]Carlsen, P.H.J.; Rist, Ø.; Lund, T.; Helland, I. *Acta Chem. Scand. B* ***1995***, *49*, 701.

[442]Tsuda, T.; Okada, M.; Nishi, S.; Saegusa, T. *J. Org. Chem.* ***1986***, *51*, 421.

14-32 Decarbonylation of Aldehydes and Acyl Halides

Carbonyl-Extrusion

$$\text{RCHO} \xrightarrow{\text{RhCl(Ph}_3\text{P)}_3} \text{RH}$$

Aldehydes, both aliphatic and aromatic, can be decarbonylated[443] by heating with a rhodium catalyst[444] or other catalysts, such as palladium.[445] $RhCl(Ph_3P)_3$ is often called *Wilkinson's catalyst*.[446] In an older reaction, aliphatic (but not aromatic) aldehydes are decarbonylated by heating with di-*tert*-butyl peroxide or other peroxides,[447] usually in a solution containing a hydrogen donor, such as a thiol. The reaction has also been initiated with light, and thermally (without an initiator) by heating at ~500°C.

Wilkinson's catalyst has also been reported to decarbonylate aromatic acyl halides at 180°C (ArCOX → ArX).[448] This reaction has been carried out with acyl iodides,[449] bromides, and chlorides. Aliphatic acyl halides that lack an a hydrogen also give this reaction,[450] but if an α hydrogen is present, elimination takes place instead (**17-17**). Aromatic acyl cyanides give aryl cyanides (ArCOCN → ArCN).[451] Aromatic acyl chlorides and cyanides can also be decarbonylated with palladium catalysts.[452]

It is possible to decarbonylate acyl halides in another way, to give alkanes (RCOCl → RH). This is done by heating the substrate with tripropylsilane Pr_3SiH

[443]For reviews, see Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, CA ***1987***, pp. 768–775; Baird, M.C., in Patai, S. *The Chemistry of Functional Groups, Supplement B* pt. 2, Wiley, NY, ***1979***, pp. 825–857; Tsuji, J., in Wender, I.; Pino, P. *Organic Syntheses Via Metal Carbonyls*, Vol. 2, Wiley, NY, ***1977***, pp. 595–654; Tsuji, J.; Ohno, K. *Synthesis* ***1969***, 157; Bird, C.W. *Transition Metal Intermediates in Organic Synthesis*, Academic Press, NY, ***1967***, pp. 239–247.

[444]Ohno, K.; Tsuji, J. *J. Am. Chem. Soc.* ***1968***, *90*, 99; Baird, C.W.; Nyman, C.J.; Wilkinson, G. *J. Chem. Soc. A* ***1968***, 348.

[445]For a review, see Rylander, P.N. *Organic Synthesis with Noble Metal Catalysts*, Academic Press, NY, ***1973***, pp. 260–267.

[446]For a review of this catalyst, see Jardine, F.H. *Prog. Inorg. Chem.* ***1981***, *28*, 63.

[447]For reviews of free-radical aldehyde decarbonylations, see Vinogradov, M.G.; Nikishin, G.I. *Russ. Chem. Rev.* ***1971***, *40*, 916; Schubert, W.M.; Kintner, R.R., in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 711–735.

[448]Kampmeier, J.A.; Rodehorst, R.; Philip, Jr, J.B. *J. Am. Chem. Soc.* ***1981***, *103*, 1847; Blum, J.; Oppenheimer, E.; Bergmann, E.D. *J. Am. Chem. Soc.* ***1967***, *89*, 2338.

[449]Blum, J.; Rosenman, H.; Bergmann, E.D. *J. Org. Chem.* ***1968***, *33*, 1928.

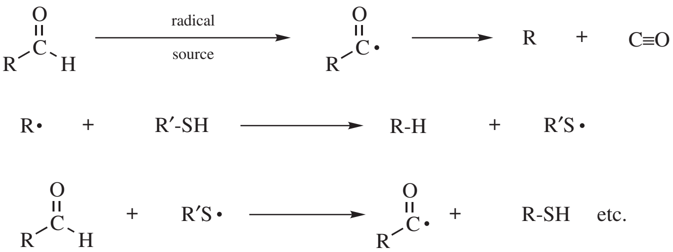
[450]Tsuji, J.; Ohno, K. *Tetrahedron Lett.* ***1966***, 4713; *J. Am. Chem. Soc.* ***1966***, *88*, 3452.

[451]Blum, J.; Oppenheimer, E.; Bergmann, E.D. *J. Am. Chem. Soc.* ***1967***, *89*, 2338.

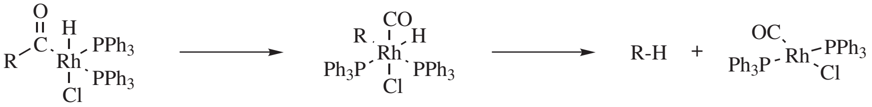
[452]Verbicky, Jr, J.W.; Dellacoletta, B.A.; Williams, L. *Tetrahedron Lett.* ***1982***, *23*, 371; Murahashi, S.; Naota, T.; Nakajima, N. *J. Org. Chem.* ***1986***, *51*, 898.

in the presence of *tert*-butyl peroxide.[453] Yields are good for R = primary or secondary alkyl and poor for R = tertiary alkyl or benzylic. There is no reaction when R = aryl. (See also the decarbonylation ArCOCl → ArAr mentioned in **14-29**.)

The mechanism of the peroxide- or light-induced reaction seems to be as follows (in the presence of thiols):[454]



The reaction of aldehydes with Wilkinson's catalyst goes through complexes of the form **42** and **43**, which have been trapped.[455] The reaction has been shown to give retention of configuration at a chiral R;[456] and deuterium labeling demonstrates that the reaction is intramolecular: RCOD give RD.[457] Free radicals are not involved.[458] The mechanism with acyl halides appears to be more complicated.[459]



42 **43**

For aldehyde decarbonylation by an electrophilic mechanism (see **11-34**).

[453]Billingham, N.C.; Jackson, R.A.; Malek, F. *J. Chem. Soc. Perkin Trans. 1* ***1979***, 1137.

[454]Slaugh, L.H. *J. Am. Chem. Soc.* ***1959***, *81*, 2262; Berman, J.D.; Stanley, J.H.; Sherman, V.W.; Cohen, S.G. *J. Am. Chem. Soc.* ***1963***, *85*, 4010.

[455]Suggs, J.W. *J. Am. Chem. Soc.* ***1978***, *100*, 640; Kampmeier, J.A.; Harris, S.H.; Mergelsberg, I. *J. Org. Chem.* ***1984***, *49*, 621.

[456]Walborsky, H.M.; Allen, L.E. *J. Am. Chem. Soc.* ***1971***, *93*, 5465. See also, Tsuji, J.; Ohno, K. *Tetrahedron Lett.* ***1967***, 2173.

[457]Prince, R.H.; Raspin, K.A. *J. Chem. Soc. A* ***1969***, 612; Walborsky, H.M.; Allen, L.E. *J. Am Chem. Soc.* ***1971***, *93*, 5465. See, however, Baldwin, J.E.; Bardenm, T.C.; Pugh, R.L.; Widdison, W.C. *J. Org. Chem.* ***1987***, *52*, 3303.

[458]Kampmeier, J.A.; Harris, S.H.; Wedegaertner, D.K. *J. Org. Chem.* ***1980***, *45*, 315.

[459]Kampmeier, J.A.; Liu, T. *Organometallics* ***1989***, *8*, 2742.

CHAPTER 15

Addition to Carbon–Carbon Multiple Bonds

There are four fundamental ways in which addition to a double or triple bond can take place. Three of these are two-step processes, with initial attack by a nucleophile, or attack upon an electrophile or a free radical. The second step consists of combination of the resulting intermediate with, respectively, a positive species, a negative species, or a neutral entity. In the fourth type of mechanism, attack at the two carbon atoms of the double or triple bond is simultaneous (concerted). Which of the four mechanisms is operating in any given case is determined by the nature of the substrate, the reagent, and the reaction conditions. Some of the reactions in this chapter can take place by all four mechanistic types.

MECHANISMS

Electrophilic Addition[1]

In this mechanism, a positive species approaches the double or triple bond and in the first step forms a bond by donation of the π pair of electrons[2] to the electrophilic

[1]For a monograph, see de la Mare, P.B.D.; Bolton, R. *Electrophilic Additions to Unsaturated Systems*, 2nd ed.; Elsevier, NY, ***1982***. For reviews, see Schmid, G.H., in Patai, S. *Supplement A: The Chemistry of Double-bonded Functional Groups*, Vol. 2, pt. 1, Wiley, NY, ***1989***, pp. 679–731; Smit, W.A. *Sov. Sci. Rev. Sect. B* ***1985***, *7*, 155; V'yunov, K.A.; Ginak, A.I. *Russ. Chem. Rev.* ***1981***, *50*, 151; Schmid, G.H.; Garratt, D.G., in Patai, S. *Supplement A: The Chemistry of Double-bonded Functional Groups*, Vol. 1, pt. 2, Wiley, NY, ***1977***, pp. 725–912; Freeman, F. *Chem. Rev.* ***1975***, *75*, 439; Bolton, R., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 1–86; Dolbier, Jr., W.R. *J. Chem. Educ.* ***1969***, *46*, 342.

[2]For a review of the π-nucleophilicity in carbon–carbon bond-forming reactions, see Mayr, H.; Kempf, B.; Ofial, A.R. *Acc. Chem. Res.* ***2003***, *36*, 66.

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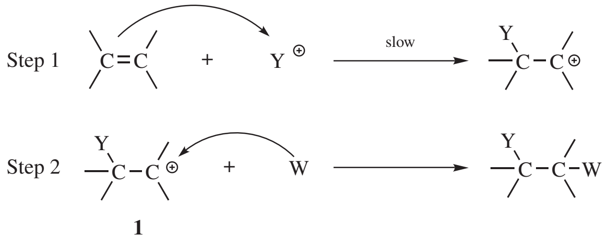
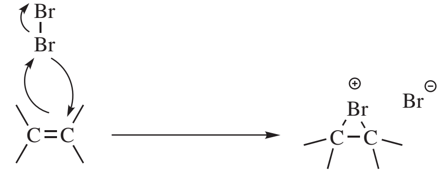
species to form a σ pair:



The IUPAC designation for this mechanism is $A_E + A_N$ (or $A_H + A_N$ if $Y^+ = H^+$). As in electrophilic substitution (p. 658), Y need not actually be a positive ion but can be the positive end of a dipole or an induced dipole, with the negative part breaking off either during the first step or shortly after. The second step is a combination of **1** with a species carrying an electron pair and often bearing a negative charge. This step is the same as the second step of the S_N1 mechanism. Not all electrophilic additions follow the simple mechanism given above. In many brominations it is fairly certain that **1**, if formed at all, very rapidly cyclizes to a bromonium ion (**2**):

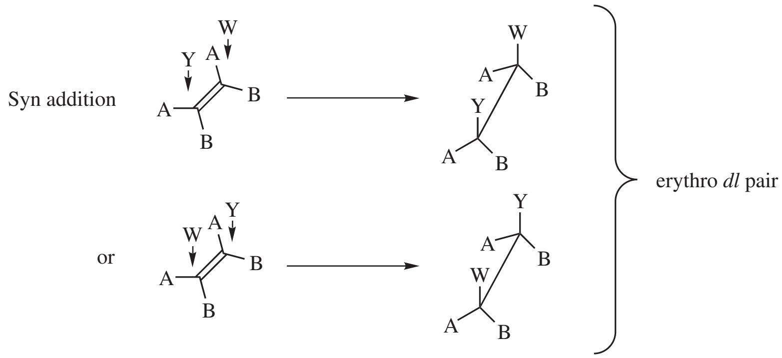


This intermediate is similar to those encountered in the neighboring-group mechanism of nucleophilic substitution (see p. 446). The attack of $\overline{\mathrm{w}}$ on an intermediate like **2** is an S_N2 step. Whether the intermediate is **1** or **2**, the mechanism is called Ad_E2 (electrophilic addition, bimolecular).

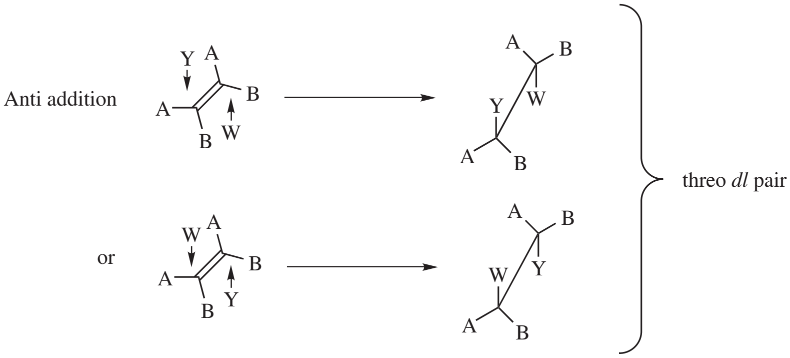
In investigating the mechanism of addition to a double bond, perhaps the most useful type of information is the stereochemistry of the reaction.[3] The two carbons of the double bond and the four atoms immediately attached to them are all in a plane (p. 9); there are thus three possibilities. Both Y and W may enter from the same side of the plane, in which case the addition is stereospecific and syn; they may enter from opposite sides for stereospecific anti addition; or the reaction may be nonstereospecific. In order to determine which of these possibilities is occurring in a given reaction, the following type of experiment is often done: YW is added to the cis and trans isomers of an alkene of the form ABC=CBA. We may use the cis alkene as an example. If the addition is syn, the product

[3]For a review of the stereochemistry of electrophilic additions to double and triple bonds, see Fahey, R.C. *Top. Stereochem.* ***1968***, *3*, 237. For a review of the synthetic uses of stereoselective additions, see Bartlett, P.A. *Tetrahedron* ***1980***, *36*, 2, pp. 3–15.

will be the erythro *dl* pair, because each carbon has a 50% chance of being attacked by Y:



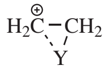
On the other hand, if the addition is anti, the threo *dl* pair will be formed:



Of course, the trans isomer will give the opposite results: the threo pair if the addition is syn and the erythro pair if it is anti. The threo and erythro isomers have different physical properties. In the special case, where Y = W (as in the addition of Br_2), the "erythro pair" is a meso compound. In addition to triple-bond compounds of the type AC≡CA, syn addition results in a cis alkene and anti addition in a trans alkene. By the definition given on p. 194 addition to triple bonds cannot be stereospecific, although it can be, and often is, stereoselective.

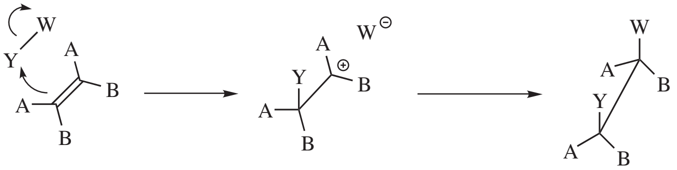
It is easily seen that in reactions involving cyclic intermediates like **2**, addition must be anti, since the second step is an S_N2 step and must occur from the back side. It is not so easy to predict the stereochemistry for reactions involving **1**. If **1** has a relatively long life, the addition should be nonstereospecific, since there will be free rotation about the single bond. On the other hand, there may be some factor that maintains the configuration, in which case W may come in from the same side or the opposite side, depending on the circumstances. For example, the positive charge might be stabilized by an attraction for Y that does not involve

a full bond (see **3**).



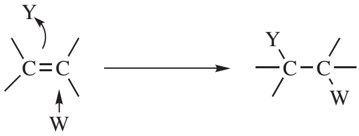
3

The second group would then come in anti. A circumstance that would favor syn addition would be the formation of an ion pair after the addition of Y:[4]



Since W is already on the same side of the plane as Y, collapse of the ion pair leads to syn addition.

Another possibility is that anti addition might, at least in some cases, be caused by the operation of a mechanism in which attack by W and Y are essentially simultaneous but from opposite sides:



This mechanism, called the Ad_E3 mechanism (*termolecular addition*, IUPAC A_NA_E),[5] has the disadvantage that three molecules must come together in the transition state. However, it is the reverse of the E2 mechanism for elimination, for which the transition state is known to possess this geometry (p. 1478).

There is much evidence that when the attack is on Br^+ (or a carrier of it), the bromonium ion **2** is often an intermediate and the addition is anti. As long ago as 1911, McKenzie and Fischer independently showed that treatment of maleic acid with bromine gave the *dl* pair of 2,3-dibromosuccinic acid, while fumaric acid (the trans isomer) gave the meso compound.[6] Many similar experiments have been performed since with similar results. For triple bonds, stereoselective anti addition was shown even earlier. Bromination of dicarboxyacetylene gave 70%

[4]Dewar, M.J.S. *Angew. Chem. Int. Ed.* ***1964***, *3*, 245; Heasley, G.E.; Bower, T.R.; Dougharty, K.W.; Easdon, J.C.; Heasley, V.L.; Arnold, S.; Carter, T.L.; Yaeger, D.B.; Gipe, B.T.; Shellhamer, D.F. *J. Org. Chem.* ***1980***, *45*, 5150.

[5]For evidence for this mechanism, see, for example, Hammond, G.S.; Nevitt, T.D. *J. Am. Chem. Soc.* ***1954***, *76*, 4121; Bell, R.P.; Pring, M. *J. Chem. Soc. B* ***1966***, 1119; Pincock, J.A.; Yates, K. *J. Am. Chem. Soc.* ***1968***, *90*, 5643; Fahey, R.C.; Payne, M.T.; Lee, D. *J. Org. Chem.* ***1974***, *39*, 1124; Roberts, R.M.G. *J. Chem. Soc. Perkin Trans. 2*, ***1976***, 1374; Pasto, D.J.; Gadberry, J.F. *J. Am. Chem. Soc.* ***1978***, *100*, 1469; Naab, P.; Staab, H.A. *Chem. Ber.* ***1978***, *111*, 2982.

[6]This was done by Fischer, E. *Liebigs Ann. Chem.* ***1911***, *386*, 374; McKenzie, A. *Proc. Chem. Soc.* ***1911***, 150; *J. Chem. Soc.* ***1912***, *101*, 1196.

of the trans isomer.[7]

70% trans

There is other evidence for mechanisms involving **2**. We have already mentioned (p. 449) that bromonium ions have been isolated in stable solutions in nucleophilic substitution reactions involving bromine as a neighboring group. Such ions have also been isolated in reactions involving addition of a Br^+ species to a double bond.[8] The following is further evidence. If the two bromines approach the double bond from opposite sides, it is very unlikely that they could come from the same bromine molecule. This means that if the reaction is performed in the presence of nucleophiles, some of these will compete in the second step with the bromide liberated from the bromine. It has been found, indeed, that treatment of ethylene with bromine in the presence of chloride ions gives some 1-chloro-2-bromoethane along with the dibromoethane.[9] Similar results are found when the reaction is carried out in the presence of water (**15-40**) or of other nucleophiles.[10] *Ab initio* molecular orbital studies show that **2** is more stable than its open isomer **1** ($Y = Br$).[11] There is evidence that formation of **2** is reversible.[12]

However, a number of examples have been found where addition of bromine is not stereospecifically anti. For example, the addition of Br_2 to *cis*- and *trans*-1-phenylpropenes in CCl_4 was nonstereospecific.[13] Furthermore, the stereospecificity of bromine addition to stilbene depends on the dielectric constant of the solvent. In solvents of low dielectric constant, the addition was 90–100% anti, but with an increase in dielectric constant, the reaction became less stereospecific, until, at a dielectric constant of ~35, the addition was completely nonstereospecific.[14] Likewise in the case of triple bonds, stereoselective anti addition was found in bromi-

[7]Michael, A. *J. Prakt. Chem.* ***1892***, *46*, 209.

[8]Strating, J.; Wieringa, J.H.; Wynberg, H. *Chem. Commun.* ***1969***, 907; Olah, G.A. *Angew. Chem. Int. Ed.* ***1973***, *12*, 173, p. 207; Slebocka-Tilk, H.; Ball, R.G.; Brown, R.S. *J. Am. Chem. Soc.* ***1985***, *107*, 4504.

[9]Francis, A.W. *J. Am. Chem. Soc.* ***1925***, *47*, 2340.

[10]See, for example, Zefirov, N.S.; Koz'min, A.S.; Dan'kov, Yu.V.; Zhdankin, V.V.; Kirin, V.N. *J. Org. Chem. USSR* ***1984***, *20*, 205.

[11]Hamilton, T.P.; Schaefer III, H.F. *J. Am. Chem. Soc.* ***1990***, *112*, 8260.

[12]Brown, R.S.; Gedye, R.; Slebocka-Tilk, H.; Buschek, J.M.; Kopecky, K.R. *J. Am. Chem. Soc.* ***1984***, *106*, 4515; Ruasse, M.; Motallebi, S.; Galland, B. *J. Am. Chem. Soc.* ***1991***, *113*, 3440; Bellucci, G.; Bianchini, R.; Chiappe, C.; Brown, R.S.; Slebocka-Tilk, H. *J. Am. Chem. Soc.* ***1991***, *113*, 8012; Bennet, A.J.; Brown, R.S.; McClung, R.E.D.; Klobukowski, M.; Aarts, G.H.M.; Santarsiero, B.D.; Bellucci, G.; Bianchini, R. *J. Am. Chem. Soc.* ***1991***, *113*, 8532.

[13]Fahey, R.C.; Schneider, H. *J. Am. Chem. Soc.* ***1968***, *90*, 4429. See also, Rolston, J.H.; Yates, K. *J. Am. Chem. Soc.* ***1969***, *91*, 1469, 1477, 1483.

[14]Heublein, G. *J. Prakt. Chem.* ***1966***, *[4] 31*, 84. See also, Buckles, R.E.; Miller, J.L.; Thurmaier, R.J. *J. Org. Chem.* ***1967***, *32*, 888; Heublein, G.; Lauterbach, H. *J. Prakt. Chem.* ***1969***, *311*, 91; Ruasse, M.; Dubois, J.E. *J. Am. Chem. Soc.* ***1975***, *97*, 1977. For the dependence of stereospecificity in this reaction on the solvent concentration, see Bellucci, G.; Bianchini, R.; Chiappe, C.; Marioni, F. *J. Org. Chem.* ***1990***, *55*, 4094.

nation of 3-hexyne, but both cis and trans products were obtained in bromination of phenylacetylene.[15] These results indicate that a bromonium ion is not formed where the open cation can be stabilized in other ways (e.g., addition of Br^+ to 1-phenylpropene gives the ion $PhC^{\oplus}HCHBrCH_3$, which is a relatively stable benzylic cation) and that there is probably a spectrum of mechanisms between complete bromonium ion (**2**, no rotation) formation and completely open-cation (**1**, free rotation) formation, with partially bridged bromonium ions (**3**, restricted rotation) in between.[16] We have previously seen cases (e.g., p. 461) where cations require more stabilization from outside sources as they become intrinsically less stable themselves.[17] Further evidence for the open cation mechanism where aryl stabilization is present was reported in an isotope effect study of addition of Br_2 to ArCH=CHCHAr' (Ar = *p*-nitrophenyl, Ar' = *p*-tolyl). The ^{14}C isotope effect for one of the double-bond carbons (the one closer to the NO_2 group) was considerably larger than for the other one.[18]

When the π-bond of an alkene attacks Cl^+,[19] I^+,[20] and RS^+,[21] the result is similar to that when the electrophile is Br^+; there is a spectrum of mechanisms between cyclic intermediates and open cations. As might be expected from our discussion in Chapter 10 (p. 446), iodonium ions compete with open carbocations more effectively than bromonium ions, while chloronium ions compete less effectively. There is kinetic and spectral evidence that at least in some cases, for example, in the addition of Br_2 or ICl, the electrophile forms a π complex with the alkene before a covalent bond is formed.[22]

[15]Pincock, J.A.; Yates, K. *Can. J. Chem.* ***1970***, *48*, 3332.

[16]For other evidence for this concept, see Pincock, J.A.; Yates, K. *Can. J. Chem.* ***1970***, *48*, 2944; Heasley, V.L.; Chamberlain, P.H. *J. Org. Chem.* ***1970***, *35*, 539; Dubois, J.E.; Toullec, J.; Barbier, G. *Tetrahedron Lett.* ***1970***, 4485; Dalton, D.R.; Davis, R.M. *Tetrahedron Lett.* ***1972***, 1057; Wilkins, C.L.; Regulski, T.W. *J. Am. Chem. Soc.* ***1972***, *94*, 6016; Sisti, A.J.; Meyers, M. *J. Org. Chem.* ***1973***, *38*, 4431; McManus, S.P.; Peterson, P.E. *Tetrahedron Lett.* ***1975***, 2753; Abraham, R.J.; Monasterios, J.R. *J. Chem. Soc. Perkin Trans. 1*, ***1973***, 1446; Schmid, G.H.; Modro, A.; Yates, K. *J. Org. Chem.* ***1980***, *45*, 665; Ruasse, M.; Argile, A. *J. Org. Chem.* ***1983***, *48*, 202; Cadogan, J.I.G.; Cameron D.K.; Gosney, I.; Highcock, R.M.; Newlands, S.F. *J. Chem. Soc., Chem. Commun.* ***1985***, 1751. For a review, see Ruasse, M. *Acc. Chem. Res.* ***1990***, *23*, 87.

[17]In a few special cases, stereospecific syn addition of Br_2 has been found, probably caused by an ion pair mechanism as shown on p. 1002: Naae, D.G. *J. Org. Chem.* ***1980***, *45*, 1394.

[18]Kokil, P.B.; Fry, A. *Tetrahedron Lett.* ***1986***, *27*, 5051.

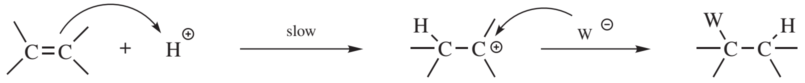
[19]Fahey, R.C. *Top. Stereochem.* ***1968***, *3*, 237, pp. 273–277.

[20]Hassner, A.; Boerwinkle, F.; Levy, A.B. *J. Am. Chem. Soc.* ***1970***, *92*, 4879.

[21]For reviews of thiiranium and/or thiirenium ions, see Capozzi, G.; Modena, G., in Bernardi, F.; Csizmadia, I.G.; Mangini, A. *Organic Sulfur Chemistry*, Elsevier, NY, ***1985***, pp. 246–298; Smit, W.A. *Sov. Sci. Rev. Sect. B* ***1985***, *7*, 155, see pp. 180–202; Dittmer, D.C.; Patwardhan, B.H., in Stirling, C.J.M. *The Chemistry of the Sulphonium Group*, pt. 1, Wiley, NY, ***1981***, pp. 387–412; Capozzi, G.; Lucchini, V.; Modena, G.; *Rev. Chem. Intermed.* ***1979***, *2*, 347; Schmid, G.H. *Top. Sulfur Chem.* ***1977***, *3*, 102; Mueller, W.H. *Angew. Chem. Int. Ed.* ***1969***, *8*, 482. The specific nature of the three-membered sulfur-containing ring is in dispute; see Smit, W.A.; Zefirov, N.S.; Bodrikov, I.V.; Krimer, M.Z. *Acc. Chem. Res.* ***1979***, *12*, 282; Bodrikov, I.V.; Borisov, A.V.; Chumakov, L.V.; Zefirov, N.S.; Smit, W.A. *Tetrahedron Lett.* ***1980***, *21*, 115; Schmid, G.H.; Garratt, D.G.; Dean, C.L. *Can. J. Chem.* ***1987***, *65*, 1172; Schmid, G.H.; Strukelj, M.; Dalipi, S. *Can. J. Chem.* ***1987***, *65*, 1945.

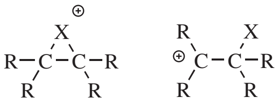
[22]See Nordlander, J.E.; Haky, J.E.; Landino, J.P. *J. Am. Chem. Soc.* ***1980***, *102*, 7487; Fukuzumi, S.; Kochi, J.K. *Int. J. Chem. Kinet.* ***1983***, *15*, 249; Schmid, G.H.; Gordon, J.W. *Can. J. Chem.* ***1984***, *62*, 2526; ***1986***, *64*, 2171; Bellucci, G.; Bianchini, R.; Chiappe, C.; Marioni, F.; Ambrosetti, R.; Brown, R.S.; Slebocka-Tilk, H. *J. Am. Chem. Soc.* ***1989***, *111*, 2640.

When the electrophile is a proton,[23] a cyclic intermediate is not possible, and the mechanism is the simple $A_H + A_N$ process shown before



This is an A-S_E2 mechanism (p. 525). There is a great deal of evidence[24] for it, including:

1. The reaction is general-acid, not specific-acid-catalyzed, implying rate-determining proton transfer from the acid to the double bond.[25]
2. The existence of open carbocation intermediates is supported by the contrast in the pattern of alkyl substituent effects[26] with that found in brominations, where cyclic intermediates are involved. In the latter case, substitution of alkyl groups on $H_2C{=}CH_2$ causes a cumulative rate acceleration



until all four hydrogens have been replaced by alkyl groups, because each group helps to stabilize the positive charge.[27] In addition of HX, the effect is not cumulative. Replacement of the two hydrogens on one carbon causes great rate increases (primary → secondary → tertiary carbocation), but additional substitution on the other carbon produces little or no acceleration.[28] This is evidence for open cations when a proton is the electrophile.[29]

[23]For a review of the addition of HCl, see Sergeev, G.B.; Smirnov, V.V.; Rostovshchikova, T.N. *Russ. Chem. Rev.* ***1983***, *52*, 259.

[24]For other evidence, see Baliga, B.T.; Whalley, E. *Can. J. Chem.* ***1964***, *42*, 1019; ***1965***, *43*, 2453; Gold, V.; Kessick, M.A. *J. Chem. Soc.* ***1965***, 6718; Corriu, R.; Guenzet, J. *Tetrahedron* ***1970***, *26*, 671; Simandoux, J.; Torck, B.; Hellin, M.; Coussemant, F. *Bull. Soc. Chim. Fr.* ***1972***, 4402, 4410; Bernasconi, C.F.; Boyle, Jr., W.J. *J. Am. Chem. Soc.* ***1974***, *96*, 6070; Hampel, M.; Just, G.; Pisanenko, D.A.; Pritzkow, W. *J. Prakt. Chem.* ***1976***, *318*, 930; Allen, A.D.; Tidwell, T.T. *J. Am. Chem. Soc.* ***1983***, *104*, 3145.

[25]Loudon, G.M.; Noyce, D.S. *J. Am. Chem. Soc.* ***1969***, *91*, 1433; Schubert, W.M.; Keeffe, J.R. *J. Am. Chem. Soc.* ***1972***, *94*, 559; Chiang, Y.; Kresge, A.J. *J. Am. Chem. Soc.* ***1985***, *107*, 6363.

[26]Bartlett, P.D.; Sargent, G.D. *J. Am. Chem. Soc.* ***1965***, *87*, 1297; Schmid, G.H.; Garratt, D.G. *Can. J. Chem.* ***1973***, *51*, 2463.

[27]See, for example, Anantakrishnan, S.V.; Ingold, C.K. *J. Chem. Soc.* ***1935***, 1396; Swern, D. in Swern *Organic Peroxides*, Vol. 2, Wiley, NY, ***1971***, pp. 451–454; Nowlan, V.J.; Tidwell, T.T. *Acc. Chem. Res.* ***1977***, *10*, 252.

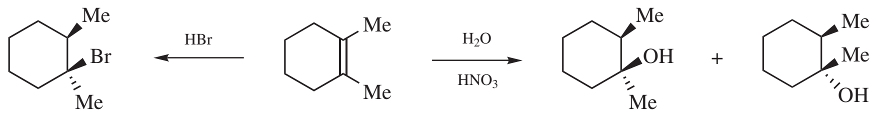
[28]Bartlett, P.D.; Sargent, G.D. *J. Am. Chem. Soc.* ***1965***, *87*, 1297; Riesz, P.; Taft, R.W.; Boyd, R.H. *J. Am. Chem. Soc.* ***1957***, *79*, 3724.

[29]A similar result (open cations) was obtained with carbocations Ar_2CH^+ as electrophiles: Mayr, H.; Pock, R. *Chem. Ber.* ***1986***, *119*, 2473.

3. Open carbocations are prone to rearrange (Chapter 18). Many rearrangements have been found to accompany additions of HX and H_2O.[30]

It may also be recalled that vinylic ethers react with proton donors in a similar manner (see **10-6**).

The stereochemistry of HX addition is varied. Examples are known of predominant syn, anti, and nonstereoselective addition. It was found that treatment of 1,2-dimethylcyclohexene (**4**) with HBr gave predominant anti addition,[31] while addition of water to **4** gave equal amounts of the cis and trans alcohols:[32]



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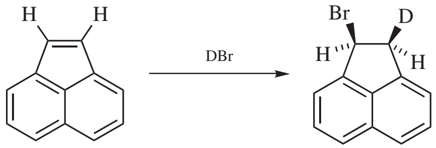
On the other hand, addition of DBr to acenaphthylene (**5**) and to indene and 1-phenylpropene gave predominant syn addition.[33]



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In fact, it has been shown that the stereoselectivity of HCl addition can be controlled by changing the reaction conditions. Addition of HCl to **4** in CH_2Cl_2 at −98°C gave predominantly syn addition, while in ethyl ether at 0°C, the addition was mostly anti.[34]

[30]For example, see Whitmore, F.C.; Johnston, F. *J. Am. Chem. Soc.* ***1933***, *55*, 5020; Fahey, R.C.; McPherson, C.A. *J. Am. Chem. Soc.* ***1969***, *91*, 3865; Bundel, Yu.G.; Ryabstev, M.N.; Sorokin, V.I.; Reutov, O.A. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1969***, 1311; Pocker, Y.; Stevens, K.D. *J. Am. Chem. Soc.* ***1969***, *91*, 4205; Staab, H.A.; Wittig, C.M.; Naab, P. *Chem. Ber.* ***1978***, *111*, 2965; Stammann, G.; Griesbaum, K. *Chem. Ber.* ***1980***, *113*, 598.

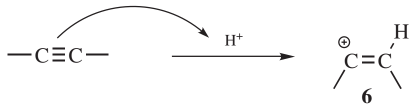
[31]Hammond, G.S.; Nevitt, T.D. *J. Am. Chem. Soc.* ***1954***, *76*, 4121; See also, Fahey, R.C.; Monahan, M.W. *J. Am. Chem. Soc.* ***1970***, *92*, 2816; Pasto, D.J.; Meyer, G.R.; Lepeska, B. *J. Am. Chem. Soc.* ***1974***, *96*, 1858.

[32]Collins, C.H.; Hammond, G.S. *J. Org. Chem.* ***1960***, *25*, 911.

[33]Dewar, M.J.S.; Fahey, R.C. *J. Am. Chem. Soc.* ***1963***, *85*, 2245, 2248. For a review of syn addition of HX, see Dewar, M.J.S. *Angew. Chem. Int. Ed.* ***1964***, *3*, 245; Heasley, G.E.; Bower, T.R.; Dougharty, K.W.; Easdon, J.C.; Heasley, V.L.; Arnold, S.; Carter, T.L.; Yaeger, D.B.; Gipe, B.T.; Shellhamer, D.F. *J. Org. Chem.* ***1980***, *45*, 5150.

[34]Becker, K.B.; Grob, C.A. *Synthesis* ***1973***, 789. See also, Marcuzzi, F.; Melloni, G.; Modena, G. *Tetrahedron Lett.* ***1974***, 413; Naab, P.; Staab, H.A. *Chem. Ber.* ***1978***, *111*, 2982.

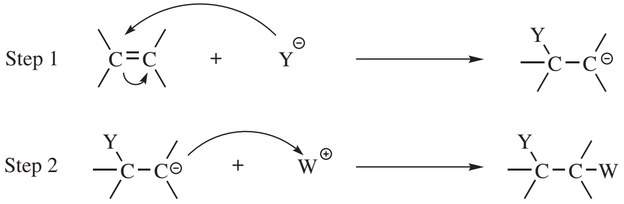
Addition of HX to triple bonds has the same mechanism, although the intermediate in this case is a vinylic cation, **6**.[35]



In all these cases (except for the Ad_E3 mechanism), we assumed that formation of the intermediate (**1**, **2**, or **3**) is the slow step and attack by the nucleophile on the intermediate is rapid, and this is probably true in most cases. However, some additions have been found in which the second step is rate determining.[36]

Nucleophilic Addition[37]

In the first step of nucleophilic addition, a nucleophile brings its pair of electrons to one carbon atom of the double or triple bond, creating a carbanion. The second step is combination of this carbanion with a positive species:



This mechanism is the same as the simple electrophilic one shown on p. 999 except that the charges are reversed (IUPAC $A_N + A_E$ or $A_N + A_H$). When the alkene contains a good leaving group (as defined for nucleophilic substitution), substitution is a side reaction (this is nucleophilic substitution at a vinylic substrate, see p. $$$).

In the special case of addition of HY to a substrate of the form —C=C—Z, where Z = CHO, COR[38] (including quinones[39]), COOR, $CONH_2$, CN, NO_2, SOR,

[35]For reviews of electrophilic addition to alkynes, including much evidence, see Rappoport, Z. *React. Intermed. (Plenum)* ***1983***, *3*, 427, pp. 428–440; Stang, P.J.; Rappoport, Z.; Hanack, M.; Subramanian, L.R. *Vinyl Cations*; Academic Press, NY, ***1979***, pp. 24–151; Stang, P.J. *Prog. Phys. Org. Chem.* ***1973***, *10*, 205; Modena, G.; Tonellato, U. *Adv. Phys. Org. Chem.* ***1971***, *9*, 185, pp. 187–231; Richey, Jr., H.G.; Richey, J.M., in Olah, G.A.; Schleyer, P.V.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, pp. 906–922.

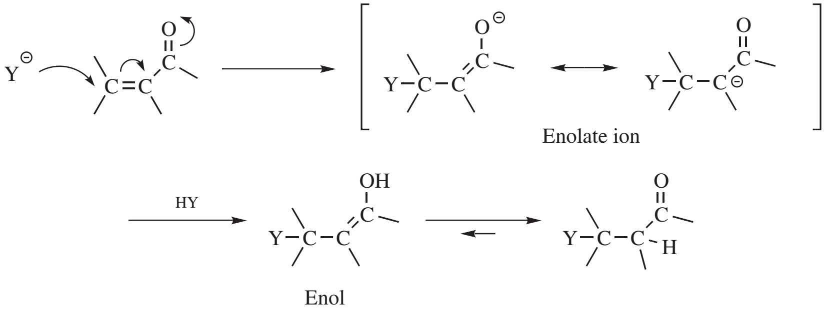
[36]See, for example, Rau, M.; Alcais, P.; Dubois, J.E. *Bull. Soc. Chim. Fr.* ***1972***, 3336; Bellucci, G.; Berti, G.; Ingrosso, G.; Mastrorilli, E. *Tetrahedron Lett.* ***1973***, 3911.

[37]For a review, see Patai, S.; Rappoport, Z., in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, ***1964***, pp. 469–584.

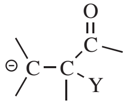
[38]For reviews of reactions of C=C—C=O compounds, see, in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 1, Wiley, NY, ***1989***, the articles by Boyd, G.V. pp. 281–315; Duval, D.; Géribaldi, S. pp. 355–469.

[39]For reviews of addition reactions of quinones, see Kutyrev, A.A.; Moskva, V.V. *Russ. Chem. Rev.* ***1991***, *60*, 72; Finley, K.T., in Patai, S.; Rappoport, Z. *The Chemistry of the Quinonoid Compounds*, Vol. 2, pt. 1, Wiley, NY, ***1988***, pp. 537–717, see pp. 539–589; Finley, K.T., in Patai, S. *The Chemistry of the Quinonoid Compounds*, pt. 2, Wiley, NY, ***1974***, pp. 877–1144.

SO_2R,[40] and so on, addition nearly always follows a nucleophilic mechanism,[41] with Y^- bonding with the carbon *away* from the Z group, for example,



Protonation of the enolate ion is chiefly at the oxygen, which is more negative than the carbon, but this produces the enol, which tautomerizes (see p. 102). So although the net result of the reaction is addition to a carbon–carbon double bond, the *mechanism* is 1,4-nucleophilic addition to the C=C—C=O (or similar) system and is thus very similar to the mechanism of addition to carbon–oxygen double and similar bonds (see Chapter 16). When Z is CN or a C=O group, it is also possible for Y^- to attack at *this* carbon, and this reaction sometimes competes. When it happens, it is called 1,2-addition. 1,4-Addition to these substrates is also known as *conjugate addition*. The Y^- ion almost never attacks at the 3 position, since the resulting carbanion would have no resonance stabilization:[42]



An important substrate of this type is acrylonitrile, and 1,4-addition to it is called *cyanoethylation* because the Y is cyanoethylated:

$$H_3C{=}CH{-}CN \quad + \quad H{-}Y \quad \longrightarrow \quad Y{-}CH_2{-}CH_2{-}CV$$

With any substrate, when Y is an ion of the type $Z{-}C^{\ominus}R_2$ (Z is as defined above; R may be alkyl, aryl, hydrogen, or another Z), the reaction is called the *Michael reaction* (see **15-24**). In this book we will call all other reactions that follow this mechanism *Michael-type additions*. Systems of the type C=C—C=C—Z can give

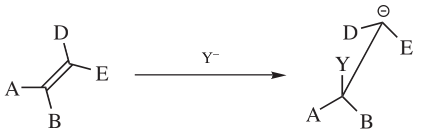
[40]For a review of vinylic sulfones, see Simpkins, N.S. *Tetrahedron* ***1990***, *46*, 6951. For a review of conjugate addition to cycloalkenyl sulfones, see Fuchs, P.L.; Braish, T.F. *Chem. Rev.* ***1986***, *86*, 903.

[41]For a review of the mechanism with these substrates, see Bernasconi, C.F. *Tetrahedron* ***1989***, *45*, 4017.

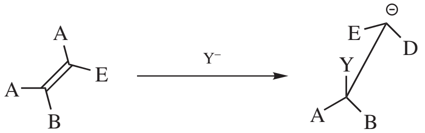
[42]For 1,8-addition to a trienone, see Barbot, F.; Kadib-Elban, A.; Miginiac, P. *J. Organomet. Chem.* ***1988***, *345*, 239.

1,2-1,4- or 1,6-addition.[43] Michael-type reactions are reversible, and compounds of the type YCH_2CH_2Z can often be decomposed to YH and $CH_2{=}CHZ$ by heating, either with or without alkali.

If the mechanism for nucleophilic addition is the simple carbanion mechanism outlined on p. 1007, the addition should be nonstereospecific, although it might well be stereoselective (see p. 194 for the distinction). For example, the (*E*) and (*Z*) forms of an alkene ABC=CDE would give **7** and **8**.



7



8

If the carbanion has even a short lifetime, **7** and **8** will assume the most favorable conformation before the attack of W. This is of course the same for both, and when W attacks, the same product will result from each. This will be one of two possible diastereomers, so the reaction will be stereoselective; but since the cis and trans isomers do not give rise to different isomers, it will not be stereospecific. Unfortunately, this prediction has not been tested on open-chain alkenes. Except for Michael-type substrates, the stereochemistry of nucleophilic addition to double bonds has been studied only in cyclic systems, where only the cis isomer exists. In these cases the reaction has been shown to be stereoselective, with syn addition reported in some cases[44] and anti addition in others.[45] When the reaction is performed on a Michael-type substrate, C=C–Z, the hydrogen does not arrive at the carbon directly but only through a tautomeric equilibrium. The product naturally assumes the most thermodynamically stable configuration, without relation to the direction of original attack of Y. In one such case (the addition of EtOD and of Me_3CSD to *trans*-MeCH=CHCOOEt) predominant anti addition was found; there is evidence that the stereoselectivity here results from the final protonation of the enolate, and not from the initial attack.[46] For obvious reasons, additions to triple bonds cannot be stereospecific. As with electrophilic additions, nucleophilic additions to triple bonds are usually stereoselective and

[43]However, attack at the 3 position has been reported when the 4 position contains one or two carbanion-stabilizing groups such as $SiMe_3$: Klumpp, G.W.; Mierop, A.J.C.; Vrielink, J.J.; Brugman, A.; Schakel, M. *J. Am. Chem. Soc.* ***1985***, *107*, 6740.

[44]For example, Truce, W.E.; Levy, A.J. *J. Org. Chem.* ***1963***, *28*, 679.

[45]For example, Truce, W.E.; Levy, A.J. *J. Am. Chem. Soc.* ***1961***, *83*, 4641; Zefirov, N.S.; Yur'ev, Yu.K.; Prikazchikova, L.P.; Bykhovskaya, M.Sh. *J. Gen. Chem. USSR* ***1963***, *33*, 2100.

[46]Mohrig, J.R.; Fu, S.S.; King, R.W.; Warnet, R.; Gustafson, G. *J. Am. Chem. Soc.* ***1990***, *112*, 3665.

anti,[47] although syn addition[48] and nonstereoselective addition[49] have also been reported.

Free-Radical Addition

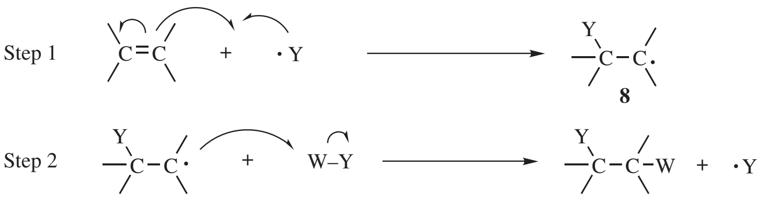
The mechanism of free-radical addition[50] follows the pattern discussed in Chapter 14 (pp. 934–939). The method of principal component analysis has been used to analyze polar and enthalpic effect in radical addition reactions.[51] A radical is generated by

$$\text{YW} \xrightarrow[\text{dissociation}]{h\nu \text{ or spontaneous}} \text{Y}\bullet + \text{W}\bullet$$

or

$$\text{R}\bullet \ \text{(from some other source)} + \text{YW} \longrightarrow \text{RW} + \text{Y}\bullet$$

Propagation then occurs by



[47]Truce, W.E.; Simms, J.A. *J. Am. Chem. Soc.* ***1956***, *78*, 2756; Shostakovskii, M.F.; Chekulaeva, I.A.; Kondrat'eva, L.V.; Lopatin, B.V. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1962***, 2118; Théron F.; Vessière, R. *Bull. Soc. Chim. Fr.* ***1968***, 2994; Bowden, K.; Price, M.J. *J. Chem. Soc. B* ***1970***, 1466, 1472; Raunio, E.K.; Frey, T.G. *J. Org. Chem.* ***1971***, *36*, 345; Truce, W.E.; Tichenor, G.J.W. *J. Org. Chem.* ***1972***, *37*, 2391.

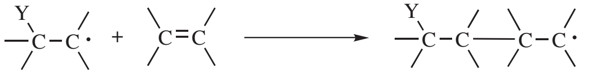
[48]Truce, W.E.; Goldhamer, D.M.; Kruse, R.B. *J. Am. Chem. Soc.* ***1959***, *81*, 4931; Dolfini, J.E. *J. Org. Chem.* ***1965***, *30*, 1298; Winterfeldt, E.; Preuss, H. *Chem. Ber.* ***1966***, *99*, 450; Hayakawa, K.; Kamikawaji, Y.; Wakita, A.; Kanematsu, K. *J. Org. Chem.* ***1984***, *49*, 1985.

[49]Gracheva, E.P.; Laba, V.I.; Kul'bovskaya, N.K.; Shostakovskii, M.F. *J. Gen. Chem. USSR* ***1963***, *33*, 2431; Truce, W.E.; Brady, D.G. *J. Org. Chem.* ***1966***, *31*, 3543; Prilezhaeva, E.N.; Vasil'ev, G.S.; Mikhaleshvili, I.L.; Bogdanov, V.S. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1970***, 1820.

[50]For a monograph on this subject, see Huyser, E.S. *Free-Radical Chain Reactions*, Wiley, NY, ***1970***. Other books with much of interest in this field are Nonhebel, D.C.; Walton, J.C. *Free-Radical Chemistry*; Cambridge University Press: London, ***1974***; Pyor, W.A. *Free Radicals*; McGraw-Hill, NY, ***1965***. For reviews, see Giese, B. *Rev. Chem. Intermed.* ***1986***, *7*, 3; *Angew. Chem. Int. Ed.* ***1983***, *22*, 753; Amiel, Y., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C* pt. 1, Wiley, NY, ***1983***, pp. 341–382; Abell, P.I., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 18; Elsevier, NY, ***1976***, pp. 111–165; Abell, P.I. in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 63–112; Minisci, F. *Acc. Chem. Res.* ***1975***, *8*, 165; Julia, M., in Viehe, H.G. *Acetylenes*; Marcel Dekker, NY, ***1969***, pp. 335–354; Elad, D. *Org. Photochem.* ***1969***, *2*, 168; Schönberg, A. *Preparative Organic Photochemistry*, Springer, NY, ***1968***, pp. 155–181; Cadogan, J.I.G.; Perkins, M.J., in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, ***1964***, pp. 585–632.

[51]Héberger, K.; Lopata, A. *J. Chem. Soc. Perkin Trans. 2*, ***1995***, 91.

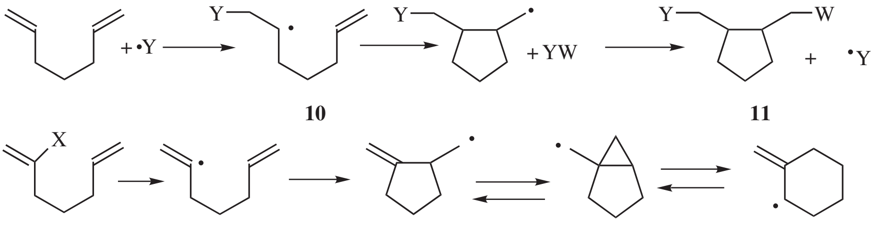
Step 2 is an abstraction (an atom transfer), so W is nearly always univalent, either hydrogen or halogen (p. 943). Termination of the chain can occur in any of the ways discussed in Chapter 14. If **9** adds to another alkene molecule,



9

a dimer is formed. This can add to still another, and chains, long or short, may be built up. This is the mechanism of free-radical polymerization. Short polymeric molecules (called *telomers*), formed in this manner, are often troublesome side products in free-radical addition reactions.

When free radicals are added to 1,5- or 1,6-dienes, the initially formed radical (**10**) can add intramolecularly to the other bond, leading to a cyclic product (**11**).[52] When the radical is generated from an precursor that gives vinyl radical **12**, however, cyclization leads to **13**, which is in equilibrium with cyclopropylcarbinyl radical (**14**) via a 5-exo-trig reaction.[53] A 6-endo-trig reaction leads to **15**, but unless there are perturbing substituent effects, however, cyclopropanation should be the major process.



10 **11**

12 **13** **14** **15**

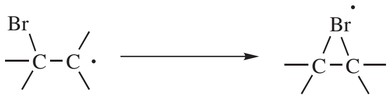
Radicals of the type **10**, generated in other ways, also undergo these cyclizations. Both five- and six-membered rings can be formed in these reactions (see p. 1021).

The free-radical addition mechanism just outlined predicts that the addition should be non-stereospecific, at least if **9** has any, but an extremely short lifetime. However, the reactions may be stereoselective, for reasons similar to those discussed for nucleophilic addition on p. 1007. Not all free-radical additions have been found to be selective, but many are. For example, addition of HBr to 1-bromocyclohexene is regioselective in that it gave only *cis*-1,2-dibromocyclohexane

[52]For reviews of these and other free-radical cyclization reactions, see RajanBabu, T.V. *Acc. Chem. Res.* ***1991***, *24*, 139; Beckwith, A.L.J. *Rev. Chem. Intermed.* ***1986***, *7*, 143; Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*, Pergamon, Elmsford, NY, ***1986***, pp. 141–209; Surzur, J. *React. Intermed. (Plenum)* ***1982***, *2*, 121–295; Julia, M. *Acc. Chem. Res.* ***1972***, *4*, 386; *Pure Appl. Chem.* ***1974***, *40*, 553; ***1967***, *15*, 167–183; Nonhebel, D.C.; Walton, J.C. *Free-Radical Chemistry*, Cambridge University Press, London, ***1974***, pp. 533–544; Wilt, J.W., in Kochi, J.K. *Free Radicals*, Vol. 1, Wiley, NY, ***1973***, pp. 418–446. For a review of cyclizations in general, see Thebtaranonth, C.; Thebtaranonth, Y. *Tetrahedron* ***1990***, *46*, 1385.

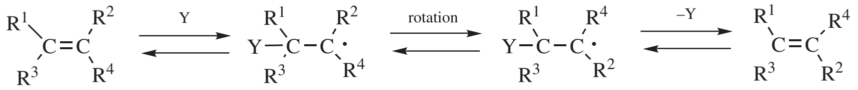
[53]Denis, R.C.; Rancourt, J.; Ghiro, E.; Boutonnet, F.; Gravel, D. *Tetrahedron Lett.* ***1993***, *34*, 2091.

and none of the trans isomer (anti addition),[54] and propyne (at −78 to −60°C) gave only *cis*-1-bromopropene (anti addition), making it stereoselective.[55] However, stereospecificity has been found only in a few cases. Selectivity was observed in radical cyclization reactions of functionalized alkenes, which proceeded via a trans-ring closure.[56] The most important case is probably addition of HBr to 2- bromo-2-butene under free-radical conditions at −80°C. Under these conditions, the cis isomer gave 92% of the meso product, while the trans isomer gave mostly the *dl* pair.[57] This stereospecificity disappeared at room temperature, where both alkenes gave the same mixture of products (~78% of the *dl* pair and 22% of the meso compound), so the addition was still stereoselective but no longer stereospecific. The stereospecificity at low temperatures is probably caused by a stabilization of the intermediate radical through the formation of a bridged bromine radical, of the type mentioned on p. 942:



This species is similar to the bromonium ion that is responsible for stereospecific anti addition in the electrophilic mechanism. Further evidence for the existence of such bridged radicals was obtained by addition of Br• to alkenes at 77 K. The ESR spectra of the resulting species were consistent with bridged structures.[58]

For many radicals, step 1 (C=C + Y• → •C—C—Y) is reversible. In such cases, free radicals can cause cis → trans isomerization of a double bond by the pathway[59]



Cyclic Mechanisms

There are some addition reactions where the initial attack is not at one carbon of the double bond, but both carbons are attacked simultaneously. Some of these are

[54]Goering, H.L.; Abell, P.I.; Aycock, B.F. *J. Am. Chem. Soc.* ***1952***, *74*, 3588. See also, LeBel, N.A.; Czaja, R.F.; DeBoer, A. *J. Org. Chem.* ***1969***, *34*, 3112.

[55]Skell, P.S.; Allen, R.G. *J. Am. Chem. Soc.* ***1958***, *80*, 5997.

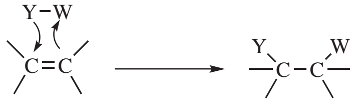
[56]Ogura, K.; Kayano, A.; Fujino, T.; Sumitani, N.; Fujita, M. *Tetrahedron Lett.* ***1993***, *34*, 8313.

[57]Goering, H.L.; Larsen, D.W. *J. Am. Chem. Soc.* ***1957***, *79*, 2653; ***1959***, *81*, 5937. Also see, Skell, P.S.; Freeman, P.K. *J. Org. Chem.* ***1964***, *29*, 2524.

[58]Abell, P.I.; Piette, L.H. *J. Am. Chem. Soc.* ***1962***, *84*, 916. See also, Leggett, T.L.; Kennerly, R.E.; Kohl, D.A. *J. Chem. Phys.* ***1974***, *60*, 3264.

[59]Benson, S.W.; Egger, K.W.; Golden, D.M. *J. Am. Chem. Soc.* ***1965***, *87*, 468; Golden, D.M.; Furuyama, S.; Benson, S.W. *Int. J. Chem. Kinet.* ***1969***, *1*, 57.

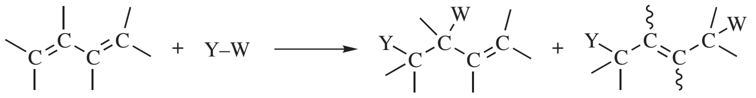
four-center mechanisms, which follow this pattern:



In others, there is a five- or a six-membered transition state. In these cases the addition to the double or triple bond must be syn. The most important reaction of this type is the Diels–Alder reaction (**15-60**).

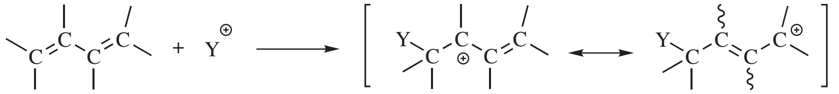
Addition to Conjugated Systems

When electrophilic addition is carried out on a compound with two double bonds in conjugation, a 1,2-addition product (**16**) is often obtained, but in most cases there is also a 1,4-addition product (**17**), often in larger yield:[60]

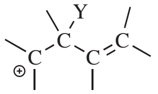


16 **17**

If the diene is unsymmetrical, there may be two 1,2-addition products. The competition between two types of addition product comes about because the carbocation resulting from attack on Y^+ is a resonance hybrid, with partial positive charges at the 2 and 4 positions:



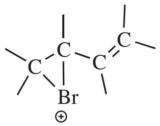
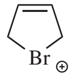
W^- may then attack either position. The original attack of Y^+ is always at the end of the conjugated system because an attack at a middle carbon would give a cation unstabilized by resonance:



In the case of electrophiles like Br^+, which can form cyclic intermediates, both 1,2- and 1,4-addition products can be rationalized as stemming from an intermediate like **18**. Direct nucleophilic attack by W^- would give the 1,2-product, while the 1,4-product could be formed by attack at the 4 position, by an S_N2'-type mechanism (see p. 470). Intermediates like **19** have been postulated, but ruled out for Br and Cl

[60]For a review of electrophilic addition to conjugated dienes, see Khristov, V.Kh.; Angelov, Kh.M.; Petrov, A.A. *Russ. Chem. Rev.* ***1991***, *60*, 39.

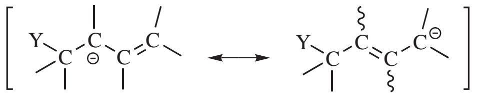
by the observation that chlorination

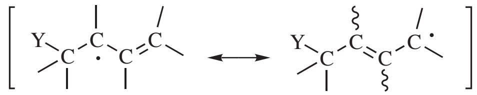



18 **19**

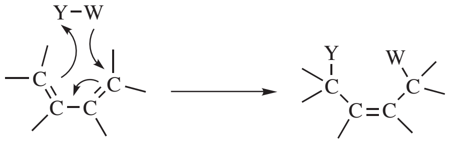
or bromination of butadiene gives trans 1,4-products.[61] If an ion like **19** were the intermediate, the 1,4-products would have to have the cis configuration.

In most cases, more 1,4- than 1,2-addition product is obtained. This may be a consequence of thermodynamic control of products, as against kinetic. In most cases, under the reaction conditions, **16** is converted to a mixture of **16** and **17** which is richer in **17**. That is, either isomer gives the same mixture of both, which contains more **17**. It was found that at low temperatures, butadiene and HCl gave only 20–25% 1,4-adduct, while at high temperatures, where attainment of equilibrium is more likely, the mixture contained 75% 1,4-product.[62] 1,2-Addition predominated over 1,4- in the reaction between DCl and 1,3-pentadiene, where the intermediate was the symmetrical (except for the D label) $H_3CHC\overset{\oplus}{\overline{-CH-}}CHCH_2D$[63] Ion pairs were invoked to explain this result, since a free ion would be expected to be attacked by Cl^- equally well at both positions, except for the very small isotope effect.





Addition to conjugated systems can also be accomplished by any of the other three mechanisms. In each case, there is competition between 1,2- and 1,4-addition. In the case of nucleophilic or free-radical attack,[64] the intermediates are resonance hybrids and behave like the intermediate from electrophilic attack. Dienes can give 1,4-addition by a cyclic mechanism in this way:



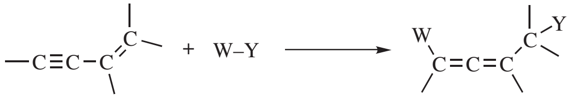
[61]Mislow, K. *J. Am. Chem. Soc.* ***1953***, *75*, 2512.

[62]Kharasch, M.S.; Kritchevsky, J.; Mayo, F.R. *J. Org. Chem.* ***1938***, *2*, 489.

[63]Nordlander, J.E.; Owuor, P.O.; Haky, J.E. *J. Am. Chem. Soc.* ***1979***, *101*, 1288.

[64]For a review of free-radical addition to conjugated dienes, see Afanas'ev, I.B.; Samokhvalov, G.I. *Russ. Chem. Rev.* ***1969***, *38*, 318.

Other conjugated systems, including trienes, enynes, diynes, and so on, have been studied much less, but behave similarly. 1,4-Addition to enynes is an important way of making allenes:



Radical addition to conjugated systems is an important part of chain propagation reactions. The rate constants for addition of cyclohexyl radical to conjugated amides have been measured, and shown to be faster than addition to styrene.[65] In additions to $RCH{=}C(CN)_2$ systems, where the R group has a chiral center, the Felkin–Ahn rule (p. 169) is followed and the reaction proceeds with high selectivity.[66] Addition of some radicals, such as $(Me_3Si)_3Si\bullet$, is reversible and this can lead to poor selectivity or isomerization.[67]

ORIENTATION AND REACTIVITY

Reactivity

As with electrophilic aromatic substitution (Chapter 11), electron-donating groups increase the reactivity of a double bond toward electrophilic addition and electron-withdrawing groups decrease it. This is illustrated in Tables 15.1 and 15.2.[68] As a further illustration it may be mentioned that the reactivity toward electrophilic addition of a group of alkenes increased in the order $CCl_3CH{=}CH_2 < Cl_2CHCH{=}CH_2 < ClCH_2CH{=}CH_2 < CH_3CH_2{=}CH_2$.[69] For nucleophilic addition the situation is reversed. These reactions are best carried out on substrates containing three or four electron-withdrawing groups, two of the most common being $F_2C{=}CF_2$[70] and $(NC)_2C{=}C(CN)_2$.[71] The effect of substituents is so great that it is possible to make the statement that *simple alkenes do not react by the nucleophilic mechanism, and polyhalo or polycyano alkenes do not generally react by the electrophilic mechanism.*[72]

[65]Curran, D.P.; Qi, H.; Porter, N.A.; Su, Q.; Wu, W.-X. *Tetrahedron Lett.* ***1993***, *34*, 4489.

[66]Giese, B.; Damm, W.; Roth, M.; Zehnder, M. *Synlett* ***1992***, 441.

[67]Ferreri, C.; Ballestri, M.; Chatgilialoglu, C. *Tetrahedron Lett.* ***1993***, *34*, 5147.

[68]Table 15.1 is from de la Mare, P.B.D. *Q. Rev. Chem. Soc.* ***1949***, *3*, 126, p. 145. Table 15.2 is from Dubois, J.E.; Mouvier, G. *Tetrahedron Lett.* ***1963***, 1325. See also, Dubois, J.E.; Mouvier, G. *Bull. Soc. Chim. Fr.* ***1968***, 1426; Grosjean, D.; Mouvier, G.; Dubois, J.E. *J. Org. Chem.* ***1976***, *41*, 3869, 3872.

[69]Shelton, J.R.; Lee, L. *J. Org. Chem.* ***1960***, *25*, 428.

[70]For a review of additions to $F_2C{=}CF_2$ and other fluoroalkenes, see Chambers, R.D.; Mobbs, R.H. *Adv. Fluorine Chem.* ***1965***, *4*, 51.

[71]For reviews of additions to tetracyanoethylene, see Fatiadi, A.J. *Synthesis* ***1987***, 249, 749; Dhar, D.N. *Chem. Rev.* ***1967***, *67*, 611.

[72]Such reactions can take place under severe conditions. For example, electrophilic addition could be accomplished with $F_2C{=}CHF$ in super acid solutions [Olah, G.A.; Mo, Y.K. *J. Org. Chem.* ***1972***, *37*, 1028] although $F_2C{=}CF_2$ did not react under these conditions. For reviews of electrophilic additions to fluoroalkenes, see Belen'kii, G.G.; German, L.S. *Sov. Sci. Rev. Sect. B* ***1984***, *5*, 183; Dyatkin, B.L.; Mochalina, E.P.; Knunyants, I.L. *Russ. Chem. Rev.* ***1966***, *35*, 417; *Fluorine Chem. Rev.* ***1969***, *3*, 45; Chambers, R.D.; Mobbs, R.H. *Adv. Fluorine Chem.* ***1965***, *4*, 51, pp. 77–81.

TABLE 15.1. Relative Reactivity of Some Alkenes Toward Bromine in Acetic Acid at 24°C[68]

Alkene	Relative Rate
$PhCH{=}CH_2$	Very fast
$PhCH{=}CHPh$	18
$CH_2{=}CHCH_2Cl$	1.6
$CH_2{=}CHCH_2Br$	1.0
$PhCH{=}CHBr$	0.11
$CH_2{=}CHBr$	0.0011

TABLE 15.2. Relative Reactivity of Some Alkenes Toward Bromine in Methanol[68]

Alkene	Relative Rate
$CH_2{=}CH_2$	3.0×10^1
$CH_3CH_2CH{=}CH_2$	$2/9 \times 10^3$
cis-$CH_3CH_2CH{=}CHCH_3$	1.3×10^5
$(CH_3)_2C{=}C(CH_3)_2$	2.8×10^7

There are some reagents that attack only as nucleophiles, for example, ammonia, and these add only to substrates susceptible to nucleophilic attack. Other reagents attack only as electrophiles, and, for example, $F_2C{=}CF_2$ does not react with these. In still other cases, the same reagent reacts with a simple alkene by the electrophilic mechanism and with a polyhalo alkene by a nucleophilic mechanism. For example, Cl_2 and HF are normally electrophilic reagents, but it has been shown that Cl_2 adds to $(N{\equiv}C)_2C{=}CHC{\equiv}N$ with initial attack by Cl^-[73] and that HF adds to $F_2C{=}CClF$ with initial attack by F^-.[74] Compounds that have a double bond conjugated with a Z group (as defined on p. 1007) nearly always react by a nucleophilic mechanism.[75] These are actually 1,4-additions, as discussed on p. 1008. A number of studies have been made of the relative activating abilities of various Z groups.[76] On the basis of these studies, the following order of decreasing activating ability has been suggested: Z = NO_2, COAr, CHO, COR, SO_2Ar, CN, COOR, SOAr, $CONH_2$, CONHR.[77]

It seems obvious that electron-withdrawing groups enhance nucleophilic addition and inhibit electrophilic addition because they lower the electron density of

[73]Dickinson, C.L., Wiley, D.W.; McKusick, B.C. *J. Am. Chem. Soc.* ***1960***, *82*, 6132. For another example, see Atkinson, R.C.; de la Mare, P.B.D.; Larsen, D.S. *J. Chem. Soc. Perkin Trans. 2*, ***1983***, 271.

[74]Miller, Jr., W.T.; Fried, J.H.; Goldwhite, H. *J. Am. Chem. Soc.* ***1960***, *82*, 3091.

[75]For a review of electrophilic reactions of such compounds, see Müllen, K.; Wolf, P., in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 1, Wiley, NY, ***1989***, pp. 513–558.

[76]See, for example, Friedman, M.; Wall, J.S. *J. Org. Chem.* ***1966***, *31*, 2888; Ring, R.N.; Tesoro, G.C.; Moore, D.R. *J. Org. Chem.* ***1967***, *32*, 1091.

[77]Shenhav, H.; Rappoport, Z.; Patai, S. *J. Chem. Soc. B* ***1970***, 469.

the double bond. Addition of electrophilic radicals to electron rich alkenes has been reported,[78] so the reaction is possible in some cases. This is probably true, and yet similar reasoning does not always apply to a comparison between double and triple bonds.[79] There is a higher concentration of electrons between the carbons of a triple bond than in a double bond, and yet triple bonds are *less* subject to attack at an electrophilic site and *more* subject to nucleophilic attack than double bonds.[80] This statement is not universally true, but it does hold in most cases. In compounds containing both double and triple bonds (nonconjugated), bromine, an electrophilic reagent, always adds to the double bond.[81] In fact, all reagents that form bridged intermediates like **2** react faster with double than with triple bonds. On the other hand, addition of electrophilic H^+ (acid-catalyzed hydration, **15-3**; addition of hydrogen halides, **15-2**) takes place at about the same rates for alkenes as for corresponding alkynes.[82] Furthermore, the presence of electron-withdrawing groups lowers the alkene/alkyne rate ratio. For example, while styrene $PhCH{=}CH_2$ was brominated 3000 times faster than $PhC{\equiv}CH$, the addition of a second phenyl group ($PhCH{=}CHPh$ versus $PhC{\equiv}CPh$) lowered the rate ratio to about 250.[83] In the case of *trans*-$MeOOCCH{=}CHCOOMe$ versus $MeOOCC{\equiv}CCOOMe$, the triple bond compound was actually brominated faster.[84]

As mentioned, it is true that in general triple bonds are more susceptible to nucleophilic and less to attack on an electrophilic site than double bonds, in spite of their higher electron density. One explanation is that the electrons in the triple bond are held more tightly because of the smaller carbon–carbon distance; it is thus harder for an attacking electrophile to pull out a pair. There is evidence from far-UV spectra to support this conclusion.[85] Another possible explanation has to do with the availability of the unfilled orbital in the alkyne. It has been shown that a π^* orbital of bent alkynes (e.g., cyclooctyne) has a lower energy than the π^* orbital of alkenes, and it has been suggested[86] that linear alkynes can achieve a bent structure in their transition states when reacting with an electrophile. Where electrophilic addition involves bridged-ion intermediates, those arising from triple bonds (**20**) are more strained than the corresponding **21** and furthermore are antiaromatic systems

[78]Curran, D.P.; Ko, S.-B. *Tetrahedron Lett.* ***1998***, *39*, 6629.

[79]For reviews of ionic additions to triple bonds, see, in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, Wiley, NY, ***1978***, the articles by Schmid, G.H. pt. 1, pp. 275–341, and by Dickstein, J.I.; Miller, S.I. pt. 2, pp. 813–955; Miller, S.I.; Tanaka, R. *Sel. Org. Transform.* ***1970***, *1*, 143; Winterfeldt, E., in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 267–334. For comparisons of double and triple bond reactivity, see Melloni, G.; Modena, G.; Tonellato, U. *Acc. Chem. Res.* ***1981***, *14*, 227; Allen, A.D.; Chiang, Y.; Kresge, A.J.; Tidwell, T.T. *J. Org. Chem.* ***1982***, *47*, 775.

[80]For discussions, see Daniels, R.; Bauer, L. *J. Chem. Educ.* ***1958***, *35*, 444; DeYoung, S.; Ehrlich, S.; Berliner, E. *J. Am. Chem. Soc.* ***1977***, *99*, 290; Strozier, R.W.; Caramella, P.; Houk, K.N. *J. Am. Chem. Soc.* ***1979***, *101*, 1340.

[81]Petrov, A.A. *Russ. Chem. Rev.* ***1960***, *29*, 489.

[82]Melloni, G.; Modena, G.; Tonellato, U. *Acc. Chem. Res.* ***1981***, *14*, 227, p. 228.

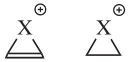
[83]Robertson, P.W.; Dasent, W.E.; Milburn, R.M.; Oliver, W.H. *J. Chem. Soc.* ***1950***, 1628.

[84]Wolf, S.A.; Ganguly, S.; Berliner, E. *J. Am. Chem. Soc.* ***1985***, *50*, 1053.

[85]Walsh, A.D. *Q. Rev. Chem. Soc.* ***1948***, *2*, 73.

[86]Ng, L.; Jordan, K.D.; Krebs, A.; Rüger, W. *J. Am. Chem. Soc.* ***1982***, *104*, 7414.

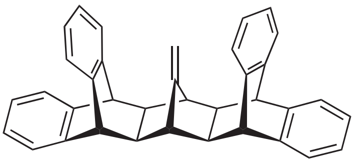
(see p. 73), which **21** are not. This may be a reason why electrophilic addition by such electrophiles as Br, I, SR, and so on, is slower for triple than for double bonds.[87] As might be expected, triple bonds connected to a Z group (C≡C–Z) undergo nucleophilic addition especially well.[88]



20 **21**

Although alkyl groups in general increase the rates of electrophilic addition, we have already mentioned (p. 1005) that there is a different pattern depending on whether the intermediate is a bridged ion or an open carbocation. For brominations and other electrophilic additions in which the first step of the mechanism is rate determining, the rates for substituted alkenes correlate well with the ionization potentials of the alkenes, which means that steric effects are not important.[89] Where the second step is rate determining [e.g., oxymercuration (**15-3**), hydroboration (**15-17**)], steric effects are important.[88]

Free-radical additions can occur with any type of substrate. The determining factor is the presence of a free-radical attacking species. Some reagents (e.g., HBr, RSH) attack by ionic mechanisms if no initiator is present, but in the presence of a free-radical initiator, the mechanism changes and the addition is of the free-radical type. Nucleophilic radicals (see p. 938) behave like nucleophiles in that the rate is increased by the presence of electron-withdrawing groups in the substrate. The reverse is true for electrophilic radicals.[90] However, nucleophilic radicals react with alkynes more slowly than with the corresponding alkenes,[91] which is contrary to what might have been expected.[92]



22

[87]Nevertheless, bridged ions **15** have been implicated in some additions to triple bonds. See, for example, Pincock, J.A.; Yates, K. *Can. J. Chem.* ***1970***, *48*, 3332; Mauger, E.; Berliner, E. *J. Am. Chem. Soc.* ***1972***, *94*, 194; Bassi, P.; Tonellato, U. *J. Chem. Soc. Perkin Trans. 1*, ***1973***, 669; Schmid, G.H.; Modro, A.; Lenz, F.; Garratt, D.G.; Yates, K. *J. Org. Chem.* ***1976***, *41*, 2331.

[88]For a review of additions to these substrates, see Winterfeldt, E. *Angew. Chem. Int. Ed.* ***1967***, *6*, 423; *Newer Methods Prep. Org. Chem.* ***1971***, *6*, 243.

[89]Nelson, D.J.; Cooper, P.J.; Soundararajan, R. *J. Am. Chem. Soc.* ***1989***, *111*, 1414; Nelson, D.J.; Soundararajan, R. *Tetrahedron Lett.* ***1988***, *29*, 6207.

[90]For reviews of reactivity in free-radical additions, see Tedder, J.M. *Angew. Chem. Int. Ed.* ***1982***, *21*, 401; Tedder, J.M.; Walton, J.C. *Tetrahedron* ***1980***, *36*, 701.

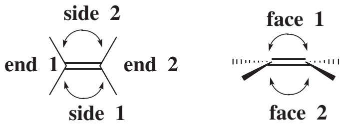
[91]Giese, B.; Lachhein, S. *Angew. Chem. Int. Ed.* ***1982***, *21*, 768.

[92]For a discussion of reactivity and orientation of polar radicals, see Volovik, S.V.; Dyadyusha, G.G.; Staninets, V.I. *J. Org. Chem. USSR* ***1986***, *22*, 1224.

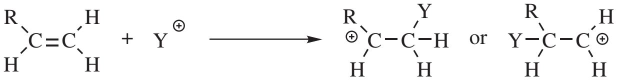
Steric influences are important in some cases. In catalytic hydrogenation, where the substrate must be adsorbed onto the catalyst surface, the reaction becomes more difficult with increasing substitution. The hydrocarbon **22**, in which the double bond is entombed between the benzene rings, does not react with Br_2, H_2SO_4, O_3, BH_3, **:**CBr_2, or other reagents that react with most double bonds.[93] A similarly inactive compound is tetra-*tert*-butylallene $(t\text{-Bu})_2C{=}C{=}C(t\text{-Bu})_2$, which is inert to Br_2, Cl_2, O_3, and catalytic hydrogenation.[94]

Orientation

When an unsymmetrical reagent is added to an unsymmetrical substrate, the question arises: Which side of the reagent goes to which side of the double or triple bond? The terms side and face are arbitrary, and a simple guide is shown to help understand the arguments used here. For electrophilic attack, the answer is given by

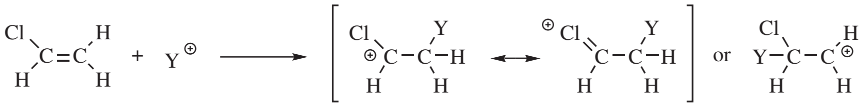


Markovnikov's rule: The positive portion of the reagent goes to the side of the double or triple bond that has more hydrogens.[95] A number of explanations have been suggested for this regioselectivity, but the most probable is that Y^+ adds to that side that will give the more stable carbocation. This premise has been examined by core electron spectroscopy and by theoretical analysis.[96] Thus, when an alkyl group is present, secondary carbocations are more stable than primary:



More stable

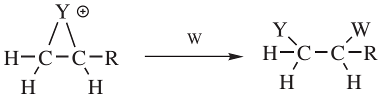
We may ask: Why does Y^+ add to give the more stable carbocation? As in the similar case of electrophilic aromatic substitution (p. 658), we invoke the Hammond postulate and say that the lower energy carbocation is preceded by the lower energy transition state. Markovnikov's rule also applies for halogen substituents because the halogen stabilizes the carbocation by resonance:



More stable

[93]Butler, D.N.; Gupt, I.; Ng, W.W.; Nyburg, S.C. *J. Chem. Soc., Chem. Commun.* ***1980***, 596.
[94]Bolze, R.; Eierdanz, H.; Schlüter, K.; Massa, W.; Grahn, W.; Berndt, A. *Angew. Chem. Int. Ed.* ***1982***, *21*, 924.
[95]For discussions of Markovnikov's rule, see Isenberg, N.; Grdinic, M. *J. Chem. Educ.* ***1969***, *46*, 601; Grdinic, M.; Isenberg, N. *Intra-Sci. Chem. Rep.*, ***1970***, *4*, 145–162.
[96]Sæthre, L.J.; Thomas, T.D.; Svensson, S. *J. Chem. Soc. Perkin Trans. 2*, ***1997***, 749.

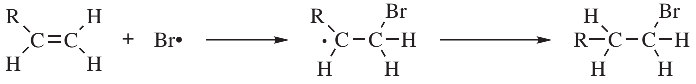
Markovnikov's rule is also usually followed where bromonium ions or other three-membered rings are intermediates.[97] This means that in these cases attack by W must resemble the S_N1 rather than the S_N2 mechanism (see p. 517), although the overall stereospecific anti addition in these reactions means that the nucleophilic substitution step is taking place with inversion of configuration.



Alkenes containing strong electron-withdrawing groups may violate Markovnikov's rule. For example, attack at the Markovnikov position of Me_3N^+—CH=CH_2 would give an ion with positive charges on adjacent atoms. The compound CF_3CH=CH_2 has been reported to give electrophilic addition with acids in an anti-Markovnikov direction, but it has been shown[98] that, when treated with acids, this compound does not give simple electrophilic addition at all; the apparently anti-Markovnikov products are formed by other pathways. Molecular electrostatic potentials for the π-region of substituted alkenes were studied, with electron donating and withdrawing substituents (based on the increase or decrease in the negative character of V_{min}-most negative-valued point), and plots of V_{min} shows a good linear correlation with the Hammett σρ constants, suggesting similar substituent electronic effects for substituted ethylenes and substituted benzenes.[99]

For nucleophilic addition the direction of attack has been studied very little, except for Michael-type addition, with compounds of the type C=C—Z. Here the negative part of the reagent almost always attacks regioselectively at the carbon that does not carry the Z (see p. 1008).

In free-radical addition[100] the main effect seems to be steric.[101] All substrates CH_2=CHX preferentially react at the CH_2, regardless of the identity of X or of the radical. With a reagent such as HBr, this means that the addition is anti-Markovnikov:



Preferentially formed intermediate

Product

[97]This has been graphically demonstrated by direct treatment of stabilized bromonium ions by nucleophiles: Dubois, J.E.; Chrétien, J.R. *J. Am. Chem. Soc.* ***1978***, *100*, 3506.

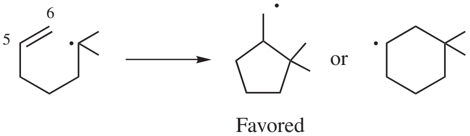
[98]Myhre, P.C.; Andrews, G.D. *J. Am. Chem. Soc.* ***1970***, *92*, 7595, 7596. See also, Newton, T.A. *J. Chem. Educ.* ***1987***, *64*, 531.

[99]Suresh, C.H.; Koga, N.; Gadre, S.R. *J. Org. Chem.* ***2001***, *66*, 6883.

[100]For reviews of orientation in free-radical additions, see Tedder, J.M.; Walton, J.C. *Tetrahedron* ***1980***, *36*, 701; *Adv. Phys. Org. Chem.* ***1978***, *16*, 51; *Acc. Chem. Res.* ***1976***, *9*, 183. See also, Giese, B. *Rev. Chem. Intermed.* ***1986***, *7*, 3; Tedder, J.M. *J. Chem. Educ.* ***1984***, *61*, 237.

[101]See, however, Riemenschneider, K.; Bartels, H.M.; Dornow, R.; Drechsel-Grau, E.; Eichel, W.; Luthe, H.; Matter, Y.M.; Michaelis, W.; Boldt, P. *J. Org. Chem.* ***1987***, *52*, 205; Gleicher, G.J.; Mahiou, B.; Aretakis, A.J. *J. Org. Chem.* ***1989***, *54*, 308.

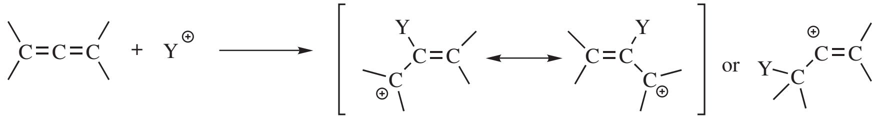
Thus the observed orientation in both kinds of HBr addition (Markovnikov electrophilic and anti-Markovnikov free radical) is caused by formation of the secondary intermediate. In the electrophilic case it forms because it is more stable than the primary; in the free-radical case because it is sterically preferred. The stability order of the free-radical intermediates is also usually in the same direction: 3° > 2° > 1° (p. 272), but this factor is apparently less important than the steric factor. Internal alkenes with no groups present to stabilize the radical usually give an ~1:1 mixture via 5-exo–trig and 6-endo–trig (see Badwin's rules p. $$$) reactions.



Favored

In *intramolecular* additions of radicals containing a 5,6 double bond,[52] both five- and six-membered rings can be formed, but in most cases[102] the five-membered rings are greatly preferred kinetically, even (as in the case shown) where five-membered ring closure means generating a primary radical and six-membered ring closure a secondary radical. This phenomenon may be caused by more favorable entropy factors leading to a five-membered ring, as well as by stereoelectronic factors, but other explanations have also been offered.[103] Similar behavior is found when the double bond is in other positions (from the 3,4 to the 7,8 position). In each case, the smaller ring (exo–trig addition) is preferred to the larger (endo–trig addition)[104] (see the Baldwin rules, p. 305). However, when a radical that is unsaturated in the 5,6 position contains an alkyl group in the 5 position, formation of the six-membered ring is generally favored.[105]

For conjugated dienes, attack by a positive ion, a negative ion, or a free radical is almost always at the *end* of the conjugated system, since in each case this gives an intermediate stabilized by resonance. In the case of an unsymmetrical diene, the more stable ion is formed. For example, isoprene ($CH_2{=}CMeCH{=}CH_2$), treated with HCl gives only $Me_2CClCH{=}CH_2$ and $Me_2C{=}CHCH_2Cl$, with none of the product arising from attack at the other end. $PhCH{=}CHCH{=}CH_2$ gives only $PhCH{=}CHCHClCH_3$ since it is the only one of the eight possible products that has a double bond in conjugation with the ring and that results from attack by H^+ at an end of the conjugated system.



[102]For an exception, see Wilt, J.W. *Tetrahedron* ***1985***, *41*, 3979.

[103]For discussions, see Beckwith, A.L.J. *Tetrahedron* ***1981***, *37*, 3073; Verhoeven, J.W. *Revl. Trav. Chim. Pays-Bas* ***1980***, *99*, 143. For molecular mechanics force-field approaches to this problem, see Beckwith, A.L.J.; Schiesser, C.H. *Tetrahedron* ***1985***, *41*, 3925; Spellmeyer, D.C.; Houk, K.N. *J. Org. Chem.* ***1987***, *52*, 959.

[104]See Beckwith, A.L.J.; Easton, C.J.; Serelis, A.K. *J. Chem. Soc., Chem. Commun.* ***1980***, 482.

[105]See Chuang, C.; Gallucci, J.C.; Hart, D.J.; Hoffman, C. *J. Org. Chem.* ***1988***, *53*, 3218, and references cited therein.

When allenes attack electrophilic reagents,[106] Markovnikov's rule would predict that the formation of the new bond should be at the end of the system, since there are no hydrogens in the middle. Reaction at the center gives a carbocation stabilized by resonance, but not immediately. In order for such stabilization to be in effect the three *p* orbitals must be parallel, and it requires a rotation about the C—C bond for this to happen.[107] Therefore, the stability of the allylic cation has no effect on the transition state, which still has a geometry similar to that of the original allene (p. 148). Probably because of this, attack on the unsubstituted $CH_2{=}C{=}CH_2$ is most often at the end carbon, to give a vinylic cation, although center attack has also been reported. However, as alkyl or aryl groups are substituted on the allene carbons, attack at the middle carbon becomes more favorable because the resulting cation is stabilized by the alkyl or aryl groups (it is now a secondary, tertiary, or benzylic cation). For example, allenes of the form $RCH{=}C{=}CH_2$ are still attacked most often at the end, but with RCH=C=CHR' center attack is more prevalent. Tetramethylallene is also attacked predominantly at the center carbon.[108] Free radicals[109] attack allenes most often at the end,[110] although attack at the middle has also been reported.[111] As with electrophilic attack and for the same reason, the stability of the allylic radical has no effect on the transition state of the reaction between a free radical and an allene. Again, as with electrophilic attack, the presence of alkyl groups increases the extent of attack by a radical at the middle carbon.[112]

Stereochemical Orientation

It has already been pointed out that some additions are syn, with both groups, approaching from the same side, and that others are anti, with the groups approaching from opposite sides of the double or triple bond. For cyclic compounds steric orientation must be considered. In syn addition to an unsymmetrical cyclic alkene,

[106]For a monograph on addition to allenes, see Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis* Wiley, NY, ***1984***. For reviews, see Pasto, D.J. *Tetrahedron* ***1984***, *40*, 2805; Smadja, W. *Chem. Rev.* ***1983***, *83*, 263; in Landor, S.R. *The Chemistry of Allenes*, Vol. 2; Academic Press, NY, ***1982***, articles by Landor, S.R., Jacobs, T.L.; Hopf, H. pp. 351–577; Stang, P.J.; Rappoport, Z.; Hanack, M.; Subramanian, L.R. *Vinyl Cations*, Academic Press, NY, ***1979***, pp. 152–167; Blake, P., in Patai, S. *The Chemistry of Ketenes, Allenes and Related Compounds*, pt. 1, Wiley, NY, ***1980***; pp. 342–357; Modena, G.; Tonellato, U. *Adv. Phys. Org. Chem.* ***1971***, *9*, 185, pp. 215–231; Richey, Jr., H.G.; Richey, J.M., in Olah, G.A.; Schleyer, P.V.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, pp. 917–922; Caserio, M.C. *Sel. Org. Transform.*, ***1970***, *1*, 239; Taylor, D.R. *Chem. Rev.* ***1967***, *67*, 317, 338–346; Mavrov, M.V.; Kucherov, V.F. *Russ. Chem. Rev.* ***1967***, *36*, 233; Griesbaum, K. *Angew. Chem. Int. Ed.* ***1966***, *5*, 933.

[107]For evidence that this is so, see Okuyama, T.; Izawa, K.; Fueno, T. *J. Am. Chem. Soc.* ***1973***, *95*, 6749.

[108]For example, see Bianchini, J.; Guillemonat, A. *Bull. Soc. Chim. Fr.* ***1968***, 2120; Pittman Jr., C.U. *Chem. Commun.* ***1969***, 122; Poutsma, M.L.; Ibarbia, P.A. *J. Am. Chem. Soc.* ***1971***, *93*, 440.

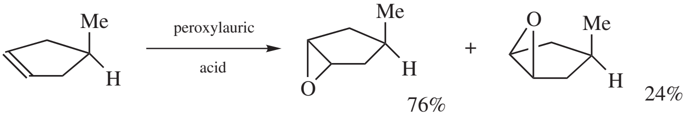
[109]For a review, see Jacobs, T.L., in Landor, S.R. *The Chemistry of Allenes*, Vol. 2, Academic Press, NY, ***1982***, pp. 399–415.

[110]Griesbaum, K.; Oswald, A.A.; Quiram, E.R.; Naegele, W. *J. Org. Chem.* ***1963***, *28*, 1952.

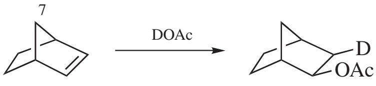
[111]See, for example, Pasto, D.J.; L'Hermine, G. *J. Org. Chem.* ***1990***, *55*, 685.

[112]For example, see Byrd, L.R.; Caserio, M.C. *J. Org. Chem.* ***1972***, *37*, 3881; Pasto, D.J.; Warren, S.E.; Morrison, M.A. *J. Org. Chem.* ***1981***, *46*, 2837. See, however, Bartels, H.M.; Boldt, P. *Liebigs Ann. Chem.* ***1981***, 40.

the two groups can come in from the more- or from the less-hindered face of the double bond. The rule is that syn addition is usually, although not always, from the less-hindered face. For example, epoxidation of 4-methylcyclopentene gave 76% addition from the less-hindered and 24% from the more-hindered face.[113]

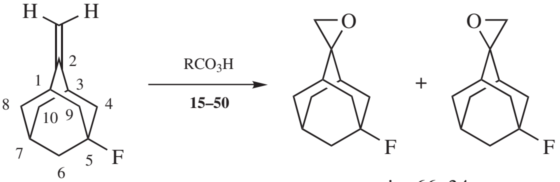


In anti addition to a cyclic substrate, the initial attack on the electrophile is also from the less-hindered face. However, many (although not all) electrophilic additions to norbornene and similar strained bicycloalkenes are syn additions.[114] In these cases reaction is always from the exo side, as in formation of **23**,[115]



23

unless the exo side is blocked by substituents in the 7 position, in which case endo attack may predominate; for example, 7,7-dimethylnorbornene undergoes syn–endo epoxidation (**15-50**) and hydroboration[116] (**15-16**). However, addition of DCl and F_3CCOOD to, and oxymercuration (**15-2**) of, 7,7-dimethylnorbornene proceeds syn–exo in spite of the methyl groups in the 7 position.[117] Similarly, free-radical additions to norbornene and similar molecules are often syn–exo, although anti additions and endo attacks are also known.[118]



ratio 66:34

24 **25** **26**

Electronic effects can also play a part in determining which face reacts preferentially with the electrophilic species. In the adamantane derivative **24**, steric

[113]Henbest, H.B.; McCullough, J.J. *Proc. Chem. Soc.* ***1962***, 74.

[114]For a discussion, see Traylor, T.G. *Acc. Chem. Res.* ***1969***, *2*, 152.

[115]Cristol, S.J.; Morrill, T.C.; Sanchez, R.A. *J. Org. Chem.* ***1966***, *31*, 2719; Brown, H.C.; Kawakami, J.H.; Liu, K. *J. Am. Chem. Soc.* ***1970***, *92*, 5536; Alvernhe, G.; Anker, D.; Laurent, A.; Haufe, G.; Beguin, C. *Tetrahedron* ***1988***, *44*, 3551; Koga, N.; Ozawa, T.; Morokuma, K. *J. Phys. Org. Chem.* ***1990***, *3*, 519.

[116]Brown, H.C.; Kawakami, J.H.; Liu, K. *J. Am. Chem. Soc.* ***1973***, *95*, 2209.

[117]Brown, H.C.; Liu, K. *J. Am. Chem. Soc.* ***1975***, *97*, 600, 2469; Tidwell, T.T.; Traylor, T.G. *J. Org. Chem.* ***1968***, *33*, 2614.

[118]For a review of free-radical addition to these systems, see Azovskaya, V.A.; Prilezhaeva, E.N. *Russ. Chem. Rev.* ***1972***, *41*, 516.

effects are about the same for each face of the double bond. Yet epoxidation, dibromocarbene reactions (**15-64**), and hydroboration (**15-16**) all predominantly take place from the face that is syn to the electron-withdrawing fluorine.[119] In the case shown, about twice as much **25** was formed, compared to **26**. Similar results have been obtained on other substrates:[120] groups that are electron withdrawing by the field effect ($-I$) direct attack from the syn face; $+I$ groups from the anti face, for both electrophilic and nucleophilic attack. These results are attributed[121] to hyperconjugation: For the adamantane case, there is overlap between the σ^* orbital of the newly forming bond (between the attacking species and C-2 in **24**) and the filled σ orbitals of the C_α—C_β bonds on the opposite side. This is called the *Cieplak effect*. The $LiAlH_4$ reduction of 2-axial methyl or methoxy cyclohexanones supports Cieplak's proposal.[122] In addition reactions of methanol to norbornanones, however, little evidence was found to support the Cieplak effect.[123] The four possible bonds are C-3–C-4 and C-1–C-9 on the syn side and C-3–C-10 and C-1–C-8 on the anti side. The preferred pathway is the one where the incoming group has the more electron-rich bonds on the side *opposite* to it (these are the ones it overlaps with). Since the electron-withdrawing F has its greatest effect on the bonds closest to it, the C-1–C-8 and C-3–C-10 bonds are more electron rich, and the group comes in on the face syn to the F.

It has been mentioned that additions of Br_2 and HOBr are often anti because of formation of bromonium ions and that free-radical addition of HBr is also anti. When the substrate in any of these additions is a cyclohexene, the addition is not only anti but the initially formed product is conformationally specific too, being mostly diaxial.[124] This is so because diaxial opening of the three-membered ring preserves a maximum coplanarity of the participating centers in the transition state; indeed, on opening, epoxides also give diaxial products.[125] However, the initial diaxial product may then pass over to the diequatorial conformer unless other groups on the ring render the latter less stable than the former. In free-radical additions to cyclohexenes in which cyclic intermediates are not involved, the initial reaction with the radical is also usually from the axial direction,[126] resulting in a diaxial initial product if the overall addition is anti. The direction from which unsymmetrical radicals react has also been studied.[127] For example, when the radical **27** adds

[119]Srivastava, S.; le Noble, W.J. *J. Am. Chem. Soc.* ***1987***, *109*, 5874. See also, Bodepudi, V.R.; le Noble, W.J. *J. Org. Chem.* ***1991***, *56*, 2001.

[120]Cieplak, A.S.; Tait, B.D.; Johnson, C.R. *J. Am. Chem. Soc.* ***1989***, *111*, 8447.

[121]Cieplak, A.S. *J. Am. Chem. Soc.* ***1981***, *103*, 4540. See also, Jorgensen, W.L. *Chemtracts: Org. Chem.* ***1988***, *1*, 71.

[122]Senda, Y.; Nakano, S.; Kunii, H.; Itoh, H. *J. Chem. Soc. Perkin Trans. 2*, ***1993***, 1009.

[123]Coxon, J.M.; McDonald, D.Q. *Tetrahedron* ***1992***, *48*, 3353.

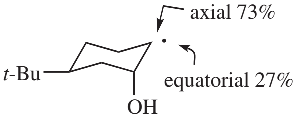
[124]Barton, D.H.R., in *Theoretical Organic Chemistry The Kekulé Symposium*, Butterworth: London, ***1959***, pp. 127–143; Goering, H.L.; Sims, L.L. *J. Am. Chem. Soc.* ***1955***, *77*, 3465; Shoppee, C.W.; Akhtar, M.I.; Lack, R.E. *J. Chem. Soc.* ***1964***, 877; Readio, P.D.; Skell, P.S. *J. Org. Chem.* ***1966***, *31*, 753, 759.

[125]For example, see Anselmi, C.; Berti, G.; Catelani, G.; Lecce, L.; Monti, L. *Tetrahedron* ***1977***, *33*, 2771.

[126]Huyser, E.S.; Benson, H.; Sinnige, H.J. *J. Org. Chem.* ***1967***, *32*, 622; LeBel, N.A.; Czaja, R.F.; DeBoer, A. *J. Org. Chem.* ***1969***, *34*, 3112

[127]For a review, see Giese, B. *Angew. Chem. Int. Ed.* ***1989***, *28*, 969.

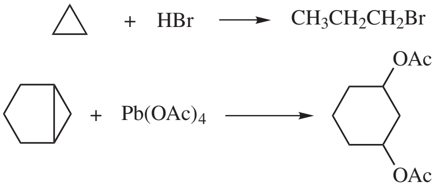
to a double bond it preferentially does so anti to the OH group, leading to a diaxial trans product.[125]



27

Addition to Cyclopropane Rings[128]

We have previously seen (p. 218) that in some respects, cyclopropane rings resemble double bonds.[129] It is not surprising, therefore, that cyclopropanes undergo addition reactions analogous to those undergone by double-bond compounds, resulting in the opening of the three-membered rings, as in the two examples shown where reaction numbers relating the reaction to alkene chemistry are in parentheses.

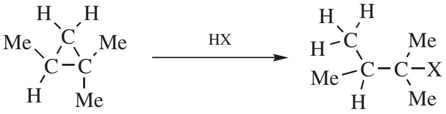


(**15-2**)

(**15-47**) Ref. [130]

Other examples are discussed at **15-3**, **15-15**, and **15-63**.

Additions to cyclopropanes can take place by any of the four mechanisms already discussed in this chapter, but the most important type involves attack on an electrophile.[131] For substituted cyclopropanes, these reactions usually follow Markovnikov's rule, although exceptions are known and the degree of regioselectivity is often small. The application of Markovnikov's rule to these substrates can be illustrated by the reaction of 1,1,2-trimethylcyclopropane with HX.[132] The rule predicts that the electrophile (in this case H^+) goes to the carbon



[128]For a review, see Charton, M., in Zabicky, J. *The Chemistry of Alkenes*, Vol 2., Wiley, NY, ***1970***, pp. 569–592. For reviews of the use of cyclopropanes in organic synthesis see Reissig, H. *Top. Curr. Chem.* ***1988***, *144*, 73; Wong, H.N.C.; Hon, M.; Tse, C.; Yip, Y.; Tanko, J.; Hudlicky, T. *Chem. Rev.* ***1989***, *89*, 165.

[129]The analogies are by no means complete: see Gordon, A.J. *J. Chem. Educ.* ***1967***, *44*, 461.

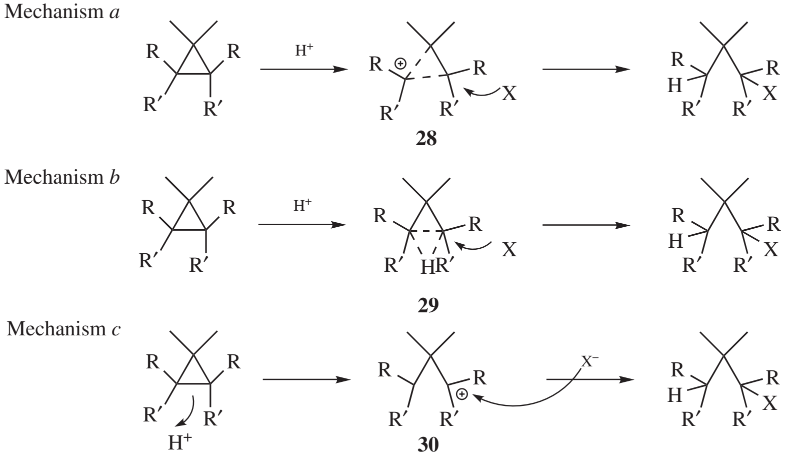
[130]Moon, S. *J. Org. Chem.* ***1964***, *39*, 3456.

[131]For a review, see DePuy, C.H. *Top. Curr. Chem.* ***1973***, *40*, 73–101. For a list of references to pertinent mechanistic studies, see Wiberg, K.B.; Kass, S.R. *J. Am. Chem. Soc.* ***1985***, *107*, 988.

[132]Kramer, G.M. *J. Am. Chem. Soc.* ***1970***, *92*, 4344.

with the most hydrogens and the nucleophile goes to the carbon that can best stabilize a positive charge (in this case the tertiary rather than the secondary carbon). The stereochemistry of the reaction can be investigated at two positions the one that becomes connected to the electrophile and the one that becomes connected to the nucleophile. The results at the former position are mixed. Additions have been found to take place with 100% retention,[133] 100% inversion,[134] and with mixtures of retention and inversion.[135] At the carbon that becomes connected to the nucleophile the result is usually inversion, although retention has also been found,[136] and elimination, rearrangement, and racemization processes often compete, indicating that in many cases a positively charged carbon is generated at this position.

At least three mechanisms have been proposed for electrophilic addition (these mechanisms are shown for attack by HX, but analogous mechanisms can be written for other electrophiles).



Mechanism *a* involves a corner-protonated cyclopropane[137] (**28**); we have already seen examples of such ions in the 2-norbornyl and 7-norbornenyl cations (pp. 453, 460). Mechanism *b* involves an edge-protonated cyclopropane (**29**). Mechanism *c*

[133]For example, see DePuy, C.H.; Breitbeil, F.W.; DeBruin, K.R. *J. Am. Chem. Soc.* ***1966***, *88*, 3347; Hendrickson, J.B.; Boeckman, Jr., R.K. *J. Am. Chem. Soc.* ***1969***, *91*, 3269.

[134]For example, see LaLonde, R.T.; Ding, J.; Tobias, M.A. *J. Am. Chem. Soc.* ***1967***, *89*, 6651; Warnet, R.J.; Wheeler, D.M.S. *Chem. Commun.* ***1971***, 547; Hogeveen, H.; Roobeek, C.F.; Volger, H.C. *Tetrahedron Lett.* ***1972***, 221; Battiste, M.A.; Mackiernan, J. *Tetrahedron Lett.* ***1972***, 4095. See also, Jensen, F.R.; Patterson, D.B.; Dinizo, S.E. *Tetrahedron Lett.* ***1974***, 1315; Coxon, J.M.; Steel, P.J.; Whittington, B.I. *J. Org. Chem.* ***1990***, *55*, 4136.

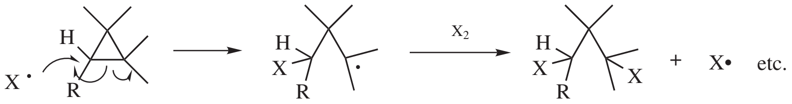
[135]Nickon, A.; Hammons, J.H. *J. Am. Chem. Soc.* ***1964***, *86*, 3322; Hammons, J.H.; Probasco, E.K.; Sanders, L.A.; Whalen, E.J. *J. Org. Chem.* ***1968***, *33*, 4493; DePuy, C.H.; Fünfschilling, P.C.; Andrist, A.H.; Olson, J.M. *J. Am. Chem. Soc.* ***1977***, *99*, 6297.

[136]Cristol, S.J.; Lim, W.Y.; Dahl, A.R. *J. Am. Chem. Soc.* ***1970***, *92*, 4013; Hendrickson, J.B.; Boeckman, Jr., R.K. *J. Am. Chem. Soc.* ***1971***, *93*, 4491.

[137]For reviews of protonated cyclopropanes, see Collins, C.J. *Chem. Rev.* ***1969***, *69*, 543; Lee, C.C. *Prog. Phys. Org. Chem.* ***1970***, *7*, 129.

consists of a one-step S_E2-type attack on H^+ to give the classical cation **30**, which then reacts with the nucleophile. Although the three mechanisms as we have drawn them show retention of configuration at the carbon that becomes attached to the proton, mechanisms *a* and *c* at least can also result in inversion at this carbon. Unfortunately, the evidence on hand at present does not allow us unequivocally to select any of these as the exclusive mechanism in all cases. Matters are complicated by the possibility that more than one edge-protonated cyclopropane is involved, at least in some cases. There is strong evidence for mechanism *b* with the electrophiles Br^+ and Cl^+;[138] and for mechanism *a* with D^+ and Hg^{2+}.[139] *Ab initio* studies show that the corner-protonated **28** is slightly more stable (~1.4 kcal mol^{-1}, 6 kJ mol^{-1}) than the edge-protonated **29**.[140] There is some evidence against mechanism *c*.[141]

Free-radical additions to cyclopropanes have been studied much less, but it is known that Br_2 and Cl_2 add to cyclopropanes by a free-radical mechanism in the presence of UV light. The addition follows Markovnikov's rule, with the initial radical reacting at the least-substituted carbon and the second group going to the most-substituted position. Several investigations have shown that the reaction is stereospecific at one carbon, taking place with inversion there, but nonstereospecific at the other carbon.[142] A mechanism that accounts for this behavior is[143]



In some cases, conjugate addition has been performed on systems where a double bond is "conjugated" with a cyclopropyl ring. An example is the formation of **31**.[144]

31

(15-6)

[138]Coxon, J.M.; Steel, P.J.; Whittington, B.I.; Battiste, M.A. *J. Org. Chem.* ***1989***, *54*, 1383; Coxon, J.M.; Steel, P.J.; Whittington, B.I. *J. Org. Chem.* ***1989***, *54*, 3702.

[139]Lambert, J.B.; Chelius, E.C.; Bible, Jr., R.H.; Hadju, E. *J. Am. Chem. Soc.* ***1991***, *113*, 1331.

[140]Koch, W.; Liu, B.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1989***, *111*, 3479, and references cited therein.

[141]Wiberg, K.B.; Kass, S.R. *J. Am. Chem. Soc.* ***1985***, *107*, 988.

[142]Maynes, G.G.; Applequist, D.E. *J. Am. Chem. Soc.* ***1973***, *95*, 856; Incremona, J.H.; Upton, C.J. *J. Am. Chem. Soc.* ***1972***, *94*, 301; Shea, K.J.; Skell, P.S. *J. Am. Chem. Soc.* ***1973***, *95*, 6728; Poutsma, M.L. *J. Am. Chem. Soc.* ***1965***, *87*, 4293; Jarvis, B.B. *J. Org. Chem.* ***1970***, *35*, 924; Upton, C.J.; Incremona, J.H. *J. Org. Chem.* ***1976***, *41*, 523.

[143]For free-radical addition to [1.1.1]propellane and bicyclo[1.1.0]butane, see Wiberg, K.B.; Waddell, S.T.; Laidig, K. *Tetrahedron Lett.* ***1986***, *27*, 1553.

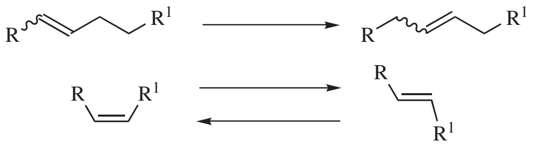
[144]Sarel, S.; Ben-Shoshan, B. *Tetrahedron Lett.* ***1965***, 1053. See also, Danishefsky, S. *Acc. Chem. Res.* ***1979***, *12*, 66.

REACTIONS

Reactions are classified by type of reagent. Isomerization of double and triple bonds is followed by examination of all reactions, where hydrogen adds to one side of the double or triple bond.

ISOMERIZATION OF DOUBLE AND TRIPLE BONDS

15-1 Isomerization



There are several reagents that lead to isomerization of a double bond to form a new alkene. In general, there is an energetic preference of an α,β- versus. β,γ-double bond.[145] Transition metals have been used to induce isomerization of alkenes. Allylic arenes (Ar-$CH_2CH{=}CH_2$) have been converted to the corresponding (*Z*-)1-propenyl arene (Ar-CH=CHMe using a ruthenium catalyst[146] or a polymer-supported iridium catalyst.[147] Allyl decyl ether ($CH_2{=}CHCH_2OC_{10}H_{21}$) was isomerized to 1-decyloxy-1-propene ($CH_3CH{=}CHOC_{10}H_{21}$) by treatment with $NaHFe(CO)_4$.[148] Double-bond migration has been observed in sulfide photo-irradiation, induced by singlet oxygen.[149] *N*-Acyl allylamine can be isomerized to the *N*-acyl enamine by heating with a ruthenium catalyst.[150] Many of these reactions were discussed in **12-2**.

For conjugated carbonyl compounds that have a hydrogen atom at the γ-position (C-4), it is possible to move a double bond *out* of conjugation. Photolysis of conjugated esters, at −40°C in the presence of *N,N*- dimethylaminoethanol, gave the nonconjugated ester.[151] Heating an *N*-allylic amide (*N*-C—C=C) with $Fe(CO)_5$, neat, gave the enamide (*N*-C=C—C).[152]

Isomerization of (*E/Z*) isomers is another important transformation.[153] Isomerization of (*E*)- and (*Z*)-conjugated amides is effected photochemically[154]

[145]Lee, P.S.; Du, W.; Boger, D.L.; Jorgensen, W.L. *J. Org. Chem.* ***2004***, *69*, 5448.

[146]Sato, T.; Komine, N.; Hirano, M.; Komiya, S. *Chem. Lett.* ***1999***, 441.

[147]Baxendale, I.R.; Lee, A.-L.; Ley, S.V. *Synlett* ***2002***, 516.

[148]Crivello, J.V.; Kong, S. *J. Org. Chem.* ***1998***, *63*, 6745.

[149]Clennan, E.L.; Aebisher, D. *J. Org. Chem.* ***2002***, *67*, 1036.

[150]Krompiec, S.; Pigulla, M.; Krompiec, M.; Baj, S.; Mrowiec-Bialon, J.; Kasperczyk, J. *Tetrahedron Lett.* ***2004***, *45*, 5257.

[151]Bargiggia, F.; Piva, O. *Tetrahedron Asymmetry* ***2001***, *12*, 1389.

[152]Sergeyev, S.; Hesse, M. *Synlett* ***2002***, 1313.

[153]For a review, see Dugave, C.; Demange, L. *Chem. Rev.* ***2003***, *103*, 2475.

[154]Kinbara, K.; Saigo, K. *Bull. Chem. Soc. Jpn.* ***1996***, *69*, 779; Wada, T.; Shikimi, M.; Inoue, Y.; Lem, G.; Turro, N.J. *Chem. Commun.* ***2001***, 1864.

(photoisomerization[155]). There is a rather high energy barrier for the excited state required for (*E/Z*) isomerization.[156] Isomerization of the C=C units in dienes is also induced photochemically.[157] Isomerization of cyclic alkenes is more difficult but cyclooctene is isomerized photochemically.[158] The photosensitized cis–trans isomerization of 1,2-dichloroethylenes have been reported,[159] and also the photoisomerization of cis/trans cyclooctene.[160] Radical-induced (*E/Z*) isomerization is known.[161]

Conjugated aldehydes have been isomerized using thiourea in DMF.[162] A 1:1 mixture of cis/trans styrene derivatives was isomerized to a 90% yield of the trans styrene derivatives was reported using a palladium catalyst.[163] Thermal cis–trans isomerization of 1,3-diphenyltriazenes has been reported, in aqueous solution.[164]

REACTIONS IN WHICH HYDROGEN ADDS TO ONE SIDE

A. Halogen on the Other Side

15-2 Addition of Hydrogen Halides

Hydro-halo-addition

Any of the four hydrogen halides can be added to double bonds.[165] HI, HBr, and HF[166] add at room temperature. The addition of HCl is more difficult and usually requires heat,[23] although HCl adds easily in the presence of silica gel.[167] The reaction has been carried out with a large variety of double-bond compounds, including

[155]Inoue, Y.; Yamasaki, N.; Yokoyama, T.; Tai, A. *J. Org. Chem.* ***1992***, *57*, 1332.

[156]Arai, T.; Takahashi, O. *J. Chem. Soc., Chem. Commun.* ***1995***, 1837.

[157]Wakamatsu, K.; Takahashi, Y.; Kikuchi, K.; Miyashi, T. *J. Chem. Soc. Perkin Trans. 2*, ***1996***, 2105.

[158]Tsuneishi, H.; Hakushi, T.; Inoue, Y. *J. Chem. Soc. Perkin Trans. 2*, ***1996***, 1601; Inoue, Y.; Tsuneishi, H.; Hakushi, T.; Yagi, K.; Awazu, K.; Onuki, H. *Chem. Commun.* ***1996***, 2627; Tsuneishi, H.; Hakushi, T.; Tai, A.; Inoue, Y. *J. Chem. Soc. Perkin Trans. 2*, ***1995***, 2057.

[159]Kokubo, K.; Kakimoto, H.; Oshima, T. *J. Am. Chem. Soc.* ***2002***, *124*, 6548.

[160]Wada, T.; Sugahara, N.; Kawano, M.; Inoue, Y. *Chem. Lett.* ***2000***, 1174.

[161]Baag, Md.M.; Kar, A.; Argade, N.P. *Tetrahedron* ***2003***, *59*, 6489.

[162]Phillips, O.A.; Eby, P.; Maiti, S.N. *Synth. Commun.* ***1995***, *25*, 87.

[163]Yu, J.; Gaunt, M.J.; Spencer, J.B. *J. Org. Chem.* ***2002***, *67*, 4627.

[164]Chen, N.; Barra, M.; Lee, I.; Chahal, N. *J. Org. Chem.* ***2002***, *67*, 2271.

[165]For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 633–636.

[166]For reviews of addition of HF, see Sharts, C.M.; Sheppard, W.A. *Org. React.* ***1974***, *21*, 125, 192–198, 212–214; Hudlický, M. *The Chemistry of Organic Fluorine Compounds*, 2nd ed., Ellis Horwood, Chichester, ***1976***, pp. 36–41.

[167]Kropp, P.J.; Daus, K.A.; Tubergen, M.W.; Kepler, K.D.; Wilson, V.P.; Craig, S.L.; Baillargeon, M.M.; Breton, G.W. *J. Am. Chem. Soc.* ***1993***, *115*, 3071.

conjugated systems, where both 1,2- and 1,4-addition are possible. A convenient method for the addition of HF involves the use of a polyhydrogen fluoride-pyridine solution.[168] When the substrate is mixed with this solution in a solvent, such as THF at 0°C, alkyl fluorides are obtained in moderate-to-high yields.

The addition of hydrogen halides to simple alkenes, in the absence of peroxides, takes place by an electrophilic mechanism, and the orientation is in accord with Markovnikov's rule.[169] The addition follows second order kinetics.[170] When peroxides are added, the addition of HBr occurs by a free-radical mechanism and the orientation is anti-Markovnikov (p. 1021).[171] It must be emphasized that this is true *only* for HBr. Free-radical addition of HF and HI has never been observed, even in the presence of peroxides, and of HCl only rarely. In the rare cases where free-radical addition of HCl was noted, the orientation was still Markovnikov, presumably because the more stable *product* was formed.[172] Free-radical addition of HF, HI, and HCl is energetically unfavorable (see the discussions on pp. 943, 959). It has often been found that anti-Markovnikov addition of HBr takes place even when peroxides have not been added. This happens because the substrate alkenes absorb oxygen from the air, forming small amounts of peroxides (**14-7**). Markovnikov addition can be ensured by rigorous purification of the substrate, but in practice this is not easy to achieve, and it is more common to add inhibitors, for example, phenols or quinones, which suppress the free-radical pathway. The presence of free-radical precursors, such as peroxides does not inhibit the ionic mechanism, but the radical reaction, being a chain process, is much more rapid than the electrophilic reaction. In most cases, it is possible to control the mechanism (and hence the orientation) by adding peroxides to achieve complete free-radical addition, or inhibitors to achieve complete electrophilic addition, although there are some cases where the ionic mechanism is fast enough to compete with the free-radical mechanism and complete control cannot be attained. Markovnikov addition of HBr, HCl, and HI has also been accomplished, in high yields, by the use of phase-transfer catalysis.[173] For alternative methods of adding HBr (or HI) with anti-Markovnikov orientation, see **12-31**.

It is also possible to add 1[174] or 2 equivalents of any of the four hydrogen halides to triple bonds. Markovnikov's rule ensures that *gem*-dihalides and not *vic*-dihalides

[168]Olah, G.A.; Welch, J.T.; Vankar, Y.D.; Nojima, M.; Kerekes, I.; Olah, J.A. *J. Org. Chem.* ***1979***, *44*, 3872. For related methods, see Yoneda, N.; Abe, T.; Fukuhara, T.; Suzuki, A. *Chem. Lett.* ***1983***, 1135; Olah, G.A.; Li, X. *Synlett* ***1990***, 267.

[169]For reviews of electrophilic addition of HX, see Sergeev, G.B.; Smirnov, V.V.; Rostovshchikova, T.N.; *Russ. Chem. Rev.* ***1983***, *52*, 259, and Dewar, M.J.S. *Angew. Chem. Int. Ed.* ***1964***, *3*, 245.

[170]Boregeaud, R.; Newman, H.; Schelpe, A.; Vasco, V.; Hughes, D.E.P. *J. Chem. Soc., Perkin Trans. 2*, ***2002***, 810.

[171]For reviews of free-radical addition of HX, see Thaler, W.A. *Methods Free-Radical Chem.* ***1969***, *2*, 121, see pp. 182–195.

[172]Mayo, F.R. *J. Am. Chem. Soc.* ***1962***, *84*, 3964.

[173]Landini, D.; Rolla, F. *J. Org. Chem.* ***1980***, *45*, 3527.

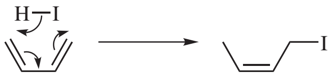
[174]For a convenient method of adding one mole of HCl or HBr to a triple bond, see Cousseau, J.; Gouin, L. *J. Chem. Soc. Perkin Trans. 1*, ***1977***, 1797; Cousseau, J. *Synthesis* ***1980***, 805. For the addition of one mole of HI, see Kamiya, N.; Chikami, Y.; Ishii, Y. *Synlett* ***1990***, 675.

are the products of the addition of two equivalents.

$$—C \quad C— \xrightarrow{HX} —CH{=}CX— \xrightarrow{HX} —CH_2—CX_2—$$

Chlorotrimethylsilane can be added to alkenes to give alkyl chlorides. 1-Hexene reacts with Me_3SiCl in water to give 2-chlorohexane.[175] Treatment of an alkene with KHF_2 and SiF_4 leads to the alkyl fluoride,[176] and bromotrimethylsilane adds to alkynes to give the vinyl bromide.[177] Trichloroisocyanuric acid reacts with terminal alkenes in water to give the 1-chloro alkane.[178]

HX are electrophilic reagents, and many polyhalo and polycyano alkenes, for example, $Cl_2C{=}CHCl$, do not react with them at all in the absence of free-radical conditions. Vinylcyclopropanes, however, react with opening of the cyclopropane ring to give a homoallylic chloride.[179] When such reactions do occur, however, they take place by a nucleophilic addition mechanism, that is, initial attack is by X^-. This type of mechanism also occurs with Michael-type substrates C=C—Z,[180] There the orientation is always such that the halogen goes to the carbon that does not bear the Z, so the product is of the form X—C—CH—Z, even in the presence of free-radical initiators. Hydrogen iodine adds 1,4 to conjugated dienes in the gas phase by a pericyclic mechanism:[181]



HX can be added to ketenes[182] to give acyl halides:

OS **I**, 166; **II**, 137, 336; **III**, 576; **IV**, 238, 543; **VI**, 273; **VII**, 59; **80**, 129.

[175]Boudjouk, P.; Kim, B.-K.; Han, B.-H. *Synth. Commun.* ***1996***, *26*, 3479.

[176]Tamura, M.; Shibakami, M.; Kurosawa, S.; Arimura, T.; Sekiya, A. *J. Chem. Soc., Chem. Commun.* ***1995***, 1891.

[177]Su, M.; Yu, W.; Jin, Z. *Tetrahedron Lett.* ***2001***, *42*, 3771.

[178]Mendonça, G.F.; Sanseverino, A.M.; de Mattos, M.C.S. *Synthesis* ***2003***, 45.

[179]Siriwardana, A.I.; Nakamura, I.; Yamamoto, Y. *Tetrahedron Lett.* ***2003***, *44*, 985.

[180]For an example, see Marx, J.N. *Tetrahedron* ***1983***, *39*, 1529.

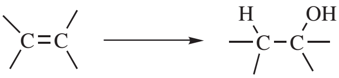
[181]Gorton, P.J.; Walsh, R. *J. Chem. Soc., Chem. Commun.* ***1972***, 782. For evidence that a pericyclic mechanism may be possible, even for an isolated double bond, see Sergeev, G.B.; Stepanov, N.F.; Leenson, I.A.; Smirnov, V.V.; Pupyshev, V.I.; Tyurina, L.A.; Mashyanov, M.N. *Tetrahedron* ***1982***, *38*, 2585.

[182]For reviews of additions to ketenes, and their mechanisms, see Tidwell, T.T. *Acc. Chem. Res.* ***1990***, *23*, 273; Seikaly, H.R.; Tidwell, T.T. *Tetrahedron* ***1986***, *42*, 2587; Satchell, D.P.N.; Satchell, R.S. *Chem. Soc. Rev.* ***1975***, *4*, 231.

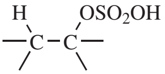
B. Oxygen on the Other Side

15-3 Hydration of Double bonds

Hydro-hydroxy-addition

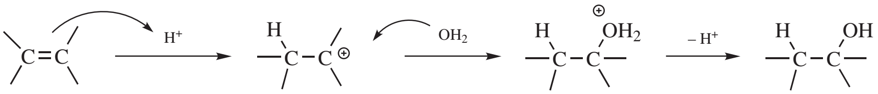


Double bonds can be hydrated by treatment with water and an acid catalyst. The most common catalyst is sulfuric acid, but other acids that have relatively non-nucleophilic counterions, such as nitric or perchloric can also be used. The mechanism is electrophilic and begins with attack of the π-bond on an acidic proton (see p. 1005). The resulting carbocation is then attacked by negative species, such as HSO_4^- (or similar counterion in the case of other acids), to give the initial product **32**, which can be isolated in some cases, but under the conditions of the



32

reaction, is usually hydrolyzed to the alcohol (**10-4**). However, the conjugate base of the acid is not the only possible species that attacks the initial carbocation. The attack can also be by water to form **33**.



33

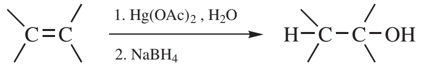
When the reaction proceeds by this pathway, **32** and similar intermediates are not involved and the mechanism is exactly (by the principle of microscopic reversibility) the reverse of El elimination of alcohols (**17-1**).[183] It is likely that the mechanism involves both pathways. *The initial carbocation occasionally rearranges to a more stable one.* For example, hydration of CH_2=$CHCH(CH_3)_2$ gives $CH_3CH_2COH(CH_3)_2$. With ordinary alkenes the addition predominantly follows Markovnikov's rule. Another method for Markovnikov addition of water consists of simultaneously adding an oxidizing agent (O_2) and a reducing agent (either Et_3SiH[184] or a secondary alcohol, e.g., 2-propanol[185]) to the alkene in the presence of a cobalt-complex catalyst. No rearrangement is observed with this

[183]For discussions of the mechanism, see Vinnik, M.I.; Obraztsov, P.A. *Russ. Chem. Rev.* ***1990***, *59*, 63; Liler, M. *Reaction Mechanisms in Sulphuric Acid*, Academic Press, NY, ***1971***, pp. 210–225.

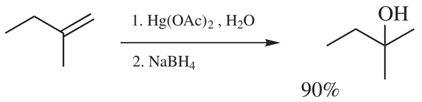
[184]Isayama, S.; Mukaiyama, T. *Chem. Lett.* ***1989***, 569.

[185]Inoki, S.; Kato, K.; Takai, T.; Isayama, S.; Yamada, T.; Mukaiyama, T. *Chem. Lett.* ***1989***, 515.

method. The corresponding alkane and ketone are usually side products.



Alkenes can be hydrated quickly under mild conditions in high yields without rearrangement products by the use of *oxymercuration*[186] (addition of oxygen and mercury) followed by *in situ* treatment with sodium borohydride[187] (**12-24**). For example, 2-methyl-1-butene treated with mercuric acetate,[188] followed by $NaBH_4$, gave 2-methyl-2-butanol.



This method, which is applicable to mono-, di-, tri-, and tetraalkyl as well as phenyl-substituted alkenes, gives almost complete Markovnikov addition. Hydroxy, methoxy, acetoxy, halo, and other groups may be present in the substrate without, in general, causing difficulties.[189] When two double bonds are present in the same molecule, the use of ultrasound allows oxymercuration of the less-substituted one without affecting the other.[190] A related reaction treats an alkene with zinc borohydride on silica gel to give a 35:65 mixture of secondary:primary alcohols.[191]

Water can be added indirectly, with anti-Markovnikov orientation, by treatment of the alkene with a 1:1 mixture of $PhCH_2NEt_3^+ \ BH_4^-$ and Me_3SiCl, followed by addition of an aqueous solution of K_2CO_3.[192] Reaction of alkenes with $Ti(BH_4)_3$, and then aqueous K_2CO_3 also leads to the anti-Markovnikov alcohol.[193] Reaction of

[186]For a monograph, see Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, ***1986***. For reviews of this and other oxymetallation reactions, see Kitching, W. *Organomet. React.* ***1972***, *3*, 319; *Organomet. Chem. Rev.* ***1968***, *3*, 61; Oullette, R.J., in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B; Academic Press, NY, ***1973***, pp. 140–166; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 387–396; Zefirov, N.S. *Russ. Chem. Rev.* ***1965***, *34*, 527.

[187]Brown, H.C.; Geoghegan, Jr., P.J. *J. Org. Chem.* ***1972***, *37*, 1937; Brown, H.C.; Geoghegan, Jr., P.J.; Lynch, G.J.; Kurek, J.T. *J. Org. Chem.* ***1972***, *37*, 1941; Moon, S.; Takakis, I.M.; Waxman, B.H. *J. Org. Chem.* ***1969***, *34*, 2951; Moon, S.; Ganz, C.; Waxman, B.H. *Chem. Commun.* ***1969***, 866; Johnson, M.R.; Rickborn, B. *Chem. Commun.* ***1968***, 1073; Klein, J.; Levene, R. *Tetrahedron Lett.* ***1969***, 4833; Chamberlain, P.; Whitham, G.H. *J. Chem. Soc. B* ***1970***, 1382; Barrelle, M.; Apparu, M. *Bull. Soc. Chim. Fr.* ***1972***, 2016.

[188]For a review of this reagent, see Butler, R.N., in Pizey, J.S. *Synthetic Reagents*, Vol. 4, Wiley, NY, ***1981***, pp. 1–145.

[189]See the extensive tables, in Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, ***1986***, pp. 4–71.

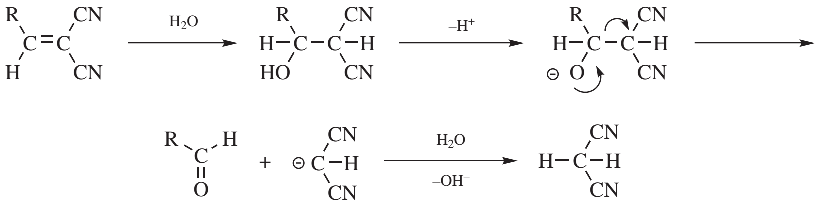
[190]Einhorn, J.; Einhorn, C.; Luche, J.L. *J. Org. Chem.* ***1989***, *54*, 4479.

[191]Ranu, B.C.; Sarkar, A.; Saha, M.; Chakraborty, R. *Tetrahedron* ***1994***, *50*, 6579; Campelo, J.M.; Chakraborty, R.; Marinas, J.M. *Synth. Commun.* ***1996***, *26*, 1639; Ranu, B.C.; Chakraborty, R.; Saha, M. *Tetrahedron Lett.* ***1993***, *34*, 4659.

[192]Baskaran, S.; Gupta, V.; Chidambaram, N.; Chandrasekaran, S. *J. Chem. Soc., Chem. Commun.* ***1989***, 903.

[193]Kumar, K.S.R.; Baskaran, S.; Chandrasekaran, S. *Tetrahedron Lett.* ***1993***, *34*, 171.

terminal alkynes with water and ruthenium catalyst, followed by sequential treatment with long chain sulfates and then ammonium salts gave the aldehyde via anti-Markovnikov addition of water.[194] With substrates of the type C=C–Z (Z is as defined on p. 1007) the product is almost always HO—C—CH—Z and the mechanism is usually nucleophilic,[195] although electrophilic addition gives the same product[196] since a cation CH—C—Z would be destabilized by the positive charges (full or partial) on two adjacent atoms. However, the α-hydroxy compound HC—CH(OH)Z, was obtained by treatment of the substrate with O_2, $PhSiH_3$, and a manganese- complex catalyst.[197] When the substrate is of the type RCH=CZZ′, CZZ′, addition of water may result in cleavage of the adduct, to give an aldehyde and CH_2ZZ', **34**.[198] The cleavage step is an example of **12-41**



34

For another method of anti-Markovnikov hydration, see hydroboration (**15-16**).

Alkenes react with PhO_2BH and a niobium catalyst, followed by oxidation with $NaOO^-$, to give the alcohol,[199] and Cp_2TiCl_4 can also be used.[200] Reaction with $HSiCl_3$ and a chiral palladium catalyst, followed by reaction with KF and hydrogen peroxide, leads to the alcohol with high asymmetric induction.[201] Conjugated alkenes also react with $PhSiH_2$ and oxygen, with a manganese catalyst, to give an α-hydroxy ketone.[202] Alkenes react with molecular oxygen in the presence of a cobalt porphyrin catalyst, and reduction with $P(OMe)_3$ leads to the secondary alcohol.[203] This procedure has also been used to hydrate conjugated dienes,[204] although conjugated dienes are seldom hydrated.

[194]Alvarez, P.; Basetti, M.; Gimeno, J.; Mancini, G. *Tetrahedron Lett.* ***2001***, *42*, 8467.

[195]For example, see Fedor, L.R.; De, N.C.; Gurwara, S.K. *J. Am. Chem. Soc.* ***1973***, *95*, 2905; Jensen, J.L.; Hashtroudi, H. *J. Org. Chem.* ***1976***, *41*, 3299; Bernasconi, C.F.; Leonarduzzi, G.D. *J. Am. Chem. Soc.* ***1982***, *104*, 5133, 5143.

[196]For example, see Noyce, D.S.; DeBruin, K.E. *J. Am. Chem. Soc.* ***1968***, *90*, 372.

[197]Inoki, S.; Kato, K.; Isayama, S.; Mukaiyama, T. *Chem. Lett.* ***1990***, 1869; Magnus, P.; Scott, D.A.; Fielding, M.R. *Tetrahedron Lett.* ***2001***, *42*, 4127.

[198]Bernasconi, C.F.; Fox, J.P.; Kanavarioti, A.; Panda, M. *J. Am. Chem. Soc.* ***1986***, *108*, 2372; Bernasconi, C.F.; Paschalis, P. *J. Am. Chem. Soc.* ***1989***, *111*, 5893, and other papers in this series.

[199]Burgess, K.; Jaspars, M. *Tetrahedron Lett.* ***1993***, *34*, 6813.

[200]Burgess, K.; van der Donk, W.A. *Tetrahedron Lett.* ***1993***, *34*, 6817.

[201]Uozumi, Y.; Hayashi, T. *Tetrahedron Lett.* ***1993***, *34*, 2335.

[202]Magnus, P.; Payne, A.H.; Waring, M.J.; Scott, D.A.; Lynch, V. *Tetrahedron Lett.* ***2000***, *41*, 9725.

[203]Matsushita, Y.; Sugamoto, K.; Matsui, T. *Chem. Lett.* ***1993***, 925.

[204]Matshshita, Y.; Sugamoto, K.; Nakama, T.; Sakamoto, T.; Matsui, T.; Nakayama, M. *Tetrahedron Lett.* ***1995***, *36*, 1879.

The addition of water to enol ethers causes hydrolysis to aldehydes or ketones (**10-6**). Ketenes add water to give carboxylic acids ($R_2C{=}C{=}O \rightarrow R_2COOH$) in a reaction catalyzed by acids:[205]

OS **IV**, 555, 560; **VI**, 766. Also see, OS **V**, 818.

15-4 Hydration of Triple Bonds

Dihydro-oxo-biaddition

The hydration of triple bonds is generally carried out with mercuric ion salts (often the sulfate or acetate) as catalysts.[206] Mercuric oxide in the presence of an acid is also a common reagent. Since the addition follows Markovnikov's rule, only acetylene gives an aldehyde. All other triple-bond compounds give ketones (for a method of reversing the orientation for terminal alkynes, see **15-16**). With alkynes of the form RC≡CH methyl ketones are formed almost exclusively, but with RC≡CR′ both possible products are usually obtained. The reaction can be conveniently carried out with a catalyst prepared by impregnating mercuric oxide onto Nafion-H (a superacidic perfluorinated resinsulfonic acid, see p. 236).[207] Terminal alkynes react with water at 200°C with microwave irradiation to give the corresponding methyl ketone.[208] A gold catalyst was used in aqueous methanol with 50% sulfuric acid to convert terminal alkynes to the ketone.[209] Conversion of phenyl acetylene to acetophenone was accomplished in water at 100°C with a catalytic amount of Tf_2NH (trifluoromethanesulfonimide).[210] In a modified reaction, internal alkynes were treated with 2-aminophenol in refluxing dioxane using a palladium catalyst to produce the corresponding ketone.[211]

Hydration of terminal alkynes can proceed with anti-Markovnikov addition. When 1-octyne was heated with water, isopropanol and a ruthenium catalyst, for example, the product was octanal.[212] A similar reaction was reported in aqueous acetone using a ruthenium catalyst.[213] The presence of certain functionality can

[205]For discussions of the mechanism, see Poon, N.L.; Satchell, D.P.N. *J. Chem. Soc. Perkin Trans. 2*, ***1983***, 1381; ***1986***, 1485; Tidwell, T.T. *Acc. Chem. Res.* ***1990***, *23*, 273; Seikaly, H.R.; Tidwell, T.T. *Tetrahedron* ***1986***, *42*, 2587; Satchell, D.P.N.; Satchell, R.S. *Chem. Soc. Rev.* ***1975***, *4*, 231.

[206]For reviews, see Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, ***1986***, pp. 123–148; Khan, M.M.T.; Martell, A.E. *Homogeneous Catalysis by Metal Complexes*, Vol. 2, Academic Press, NY, ***1974***, pp. 91–95. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1217–1219.

[207]Olah, G.A.; Meidar, D. *Synthesis* ***1978***, 671.

[208]Vasudevan, A.; Verzas, M.K. *Synlett* ***2004***, 631.

[209]Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angew. Chem. Int. Ed.* ***2002***, *41*, 4563.

[210]Tsuchimoto, T.; Joya, T.; Shirakawa, E.; Kawakami, Y. *Synlett* ***2000***, 1777.

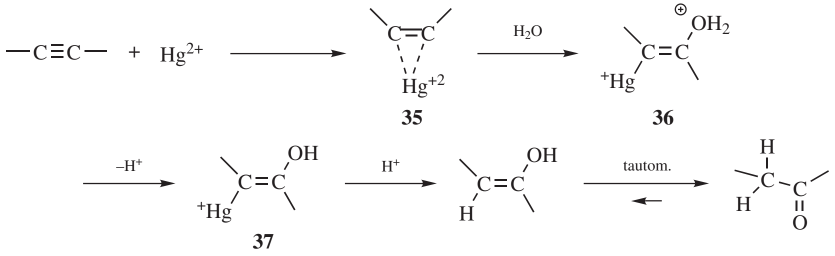
[211]Shimada, T.; Yamamoto, Y. *J. Am. Chem. Soc.* ***2002***, *124*, 12670.

[212]Suzuki, T.; Tokunaga, M.; Wakatsuki, Y. *Org. Lett.* ***2001***, *3*, 735.

[213]Grotjahn, D.B.; Lev, D.A. *J. Am. Chem. Soc.* ***2004***, *126*, 12232.

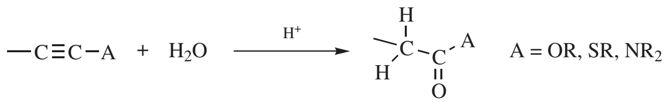
influence the regioselectivity of hydration. 1-Seleno alkynes, such as PhSe-C≡C-Ph, react with tosic acid in dichloromethane to give a seleno ester PhSeC(=O)SH_2Ph after treatment with water.[214]

The first step of the mechanism is formation of a complex (**35**) (ions like Hg^{2+} form complexes with alkynes, p. 115). Water then attacks in an S_N2-type process to give the intermediate **36**,



which loses a proton to give **37**. Hydrolysis of **37** (an example of **12-34**) gives the enol, which tautomerizes to the product. A spectrum of the enol was detected by flash photolysis when phenylacetylene was hydrated photolytically.[215]

Carboxylic esters, thiol esters, and amides can be made, respectively, by acid-catalyzed hydration of acetylenic ethers, thioethers,[216] and ynamines, without a mercuric catalyst:[217]



This is ordinary electrophilic addition, with rate-determining protonation as the first step.[218] Certain other alkynes have also been hydrated to ketones with strong acids in the absence of mercuric salts.[219] Simple alkynes can also be converted to ketones by heating with formic acid, without a catalyst.[220] Lactones have been prepared from trimethylsilyl alkenes containing an hydroxyl unit elsewhere in the molecule, when reacted with molecular oxygen, $CuCl_2$, and a palladium catalyst.[221]

[214]Sheng, S.; Liu, X. *Org. Prep. Proceed. Int.* ***2002***, *34*, 499.

[215]Chiang, Y.; Kresge, A.J.; Capponi, M.; Wirz, J. *Helv. Chim. Acta* ***1986***, *69*, 1331.

[216]Braga, A.L.; Martins, T.L.C.; Silveira, C.C.; Rodrigues, O.E.D. *Tetrahedron* ***2001***, *57*, 3297. For a review of acetylenic ethers and thioethers, see Brandsma, L.; Bos, H.J.T.; Arens, J.F., in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 751–860.

[217]Arens, J.F. *Adv. Org. Chem.* ***1960***, *2*, 163; Brandsma, L.; Bos, H.J.T.; Arens, J.F., in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 774–775.

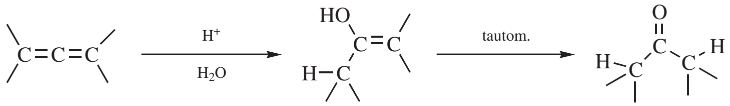
[218]Hogeveen, H.; Drenth, W. *Recl. Trav. Chim. Pays-Bas* ***1963***, *82*, 375, 410; Verhelst, W.F.; Drenth, W. *J. Am. Chem. Soc.* ***1974***, *96*, 6692; Banait, N.; Hojatti, M.; Findlay, P.; Kresge, A.J. *Can. J. Chem.* ***1987***, *65*, 441.

[219]See, for example, Noyce, D.S.; Schiavelli, M.D. *J. Org. Chem.* ***1968***, *33*, 845; *J. Am. Chem. Soc.* ***1968***, *90*, 1020, 1023.

[220]Menashe, N.; Reshef, D.; Shvo, Y. *J. Org. Chem.* ***1991***, *56*, 2912.

[221]Compain, P.; Goré, J.; Vatèle, J.-M. *Tetrahedron* ***1996***, *52*, 10405.

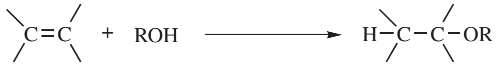
Allenes can also be hydrolyzed to ketones, with an acid catalyst.[222]



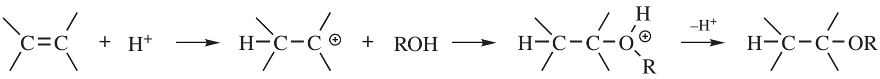
OS **III**, 22; **IV**, 13; **V**, 1024.

15-5 Addition of Alcohols and Phenols

Hydro-alkoxy-addition



The addition of alcohols and phenols to double bonds is catalyzed by acids or bases. When the reactions are acid catalyzed, the mechanism is electrophilic, with H^+ as the species attacked by the π-bond. The resulting carbocation combines with a molecule of alcohol to give an oxonium ion, **38**.



38

The addition, therefore, follows Markovnikov's rule. Primary alcohols give better results than secondary, and tertiary alcohols are very inactive. This is a convenient method for the preparation of tertiary ethers by the use of a suitable alkene, such as $Me_2C{=}CH_2$. Addition of alcohols to allylic systems can proceed with rearrangement, and the use of chiral additive can lead to asymmetric induction.[223]

Alcohols add intramolecularly to alkenes to generate cyclic ethers, often bearing a hydroxyl unit,.[224] but not always.[225] Furan derivatives are available for alkene-ketones using $CuCl_2$ and a palladium catalyst,[226] but chromium catalysts have been used for a similar purpose.[227] A gold catalyst was used with conjugated ketones bearing an alkyne substituent to give fused-ring furans.[228] Pyrone derivatives are available by the coupling of conjugated ketones bearing an alcohol unit, via an addition

[222]For example, see Fedorova, A.V.; Petrov, A.A. *J. Gen. Chem. USSR* ***1962***, *32*, 1740; Mühlstadt, M.; Graefe, J. *Chem. Ber.* ***1967***, *100*, 223; Cramer, P.; Tidwell, T.T. *J. Org. Chem.* ***1981***, *46*, 2683.

[223]See Nakamura, H.; Ishihara, K.; Yamamoto, H. *J. Org. Chem.* ***2002***, *67*, 5124.

[224]Bhaumik, A.; Tatsumi, T. *Chem. Commun.* ***1998***, 463; Gruttadauria, M.; Aprile, C.; Riela, S.; Noto, R. *Tetrahedron Lett.* ***2001***, *42*, 2213.

[225]Miura, K.; Hondo, T.; Okajima, S.; Nakagawa, T.; Takahashi, T.; Hosomi, A. *J. Org. Chem.* ***2002***, *67*, 6082; Marotta, E.; Foresti, E.; Marcelli, T.; Peri, F.; Righi, P.; Scardovi, N.; Rosini, G. *Org. Lett.* ***2002***, *4*, 4451.

[226]Han, X.; Widenhoefer, R.A. *J. Org. Chem.* ***2004***, *69*, 1738.

[227]Miki, K.; Nishino, F.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc.* ***2002***, *124*, 5260.

[228]Yao, T.; Zhang, X.; Larock, R.C. *J. Am. Chem. Soc.* ***2004***, *126*, 11164.

elimination process mediated by a palladium catalyst.[229] Intramolecular addition of alcohols to alkenes can be promoted by a palladium catalyst, with migration of the double bond in the final product.[230] Rhenium compounds,[231] titanium compounds,[232] or platinum compounds[233] facilitate this cyclization reaction to form functionalized tetrahydrofurans or tetrahydrofurans. Allylic alcohols have been converted to 2-bromo oxetanes using $Br(collidine)_2^+\ PF_6$.[234] It is noted that the reaction of an alkene–alcohol and *N*-iodosuccinimide with a chiral titanium catalyst leads to a tetrahydrofuran with a pendant iodoalkyl group, with modest enantioselectivity.[235]

Allenes react with alcohols and allenic alcohols have been converted to tetrahydrofuran derivatives bearing a vinyl group at the α-position, using diphenyliodonium salts.[236] In the presence of allylic bromide and a palladium catalyst, allenic alcohols lead to allylically substituted dihydrofurans.[237] Intramolecular addition of alcohols to allenes leads to cyclic vinyl ethers.[238] Alcohols add intramolecularly to a vinylidene dithiane under electrolytic conditions to form a tetrahydrofuran derivative with a pendant dithiane group.[239]

In the presence of other reagents, functionalized ethers can be formed. In methanol with an R—Se—Br reagent, alkenes are converted to selenoalkyl ethers (MeO—C—C—SeR).[240]

An interesting "double" addition was reported in which 2-(hydroxymethyl)phenol reacted with 2,3-dimethyl-2-butene in the presence of lithium perchlorate and Montmorillonite clay/water to give benzopyrans, but the reaction proceeded via an *O*-quinomethane generated *in situ*.[241]

Alcohols add to alkynes under certain conditions to give vinyl ethers. In an excess of alcohol, and in the presence of a platinum catalyst, internal alkynes are converted to ketals.[242] The alcohol to alkyne addition reaction is quite useful for the preparation of heterocycles. Dihydrofurans,[243] furans,[244] benzofurans,[245] and pyran

[229]Reiter, M.; Ropp, S.; Gouverneur, V. *Org. Lett.* ***2004***, *6*, 91

[230]Rönn, M.; Bäckvall, J.-E.; Andersson, P.G. *Tetrahedron Lett.* ***1995***, *36*, 7749; Semmelhack, M.F.; Epa, W.R. *Tetrahedron Lett.* ***1993***, *34*, 7205. See Tiecco, M.; Testaferri, L.; Santi, C. *Eur. J. Org. Chem.* ***1999***, 797.

[231]Kennedy, R.M.; Tang, S. *Tetrahedron Lett.* ***1992***, *33*, 3729; McDonald, F.E.; Towne, T.B. *J. Org. Chem.* ***1995***, *60*, 5750.

[232]Lattanzi, A.; Della Sala, G.G.D.; Russo, M.; Screttri, A. *Synlett* ***2001***, 1479.

[233]Qian, H.; Han, X.; Widenhoefer, R.A. *J. Am. Chem. Soc.* ***2004***, *126*, 9536.

[234]Albert, S.; Robin, S.; Rousseau, G. *Tetrahedron Lett.* ***2001***, *42*, 2477.

[235]Kang, S.H.; Park, C.M.; Lee, S.B.; Kim, M. *Synlett* ***2004***, 1279.

[236]In this case, the phenyl group also added to the allene. Kang, S.-K.; Baik, T.-G.; Kulak, A.N. *Synlett* ***1999***, 324.

[237]Ma, S.; Gao, W. *J. Org. Chem.* ***2002***, *67*, 6104.

[238]Mukai, C.; Ohta, M.; Yamashita, H.; Kitagaki, S. *J. Org. Chem.* ***2004***, *69*, 6867.

[239]Sun, Y.; Liu, B.; Kao, J.; Andred′Avignon, D.; Moeller, K.D. *Org. Lett.* ***2001***, *3*, 1729. See also, Mukai, C.; Yamashita, H.; Hanaoka, M. *Org. Lett.* ***2001***, *3*, 3385.

[240]Back, T.G.; Moussa, Z.; Parvez, M. *J. Org. Chem.* ***2002***, *67*, 499.

[241]Chiba, K.; Hirano, T.; Kitano, Y.; Tada, M. *Chem. Commun.* ***1999***, 691.

[242]Hartman, J.W.; Sperry, L. *Tetrahedron Lett.* ***2004***, *45*, 3787.

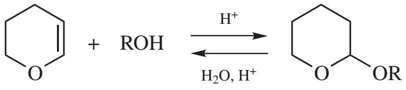
[243]Gabriele, B.; Salerno, G.; Lauria, E. *J. Org. Chem.* ***1999***, *64*, 7687.

[244]Qing, F.L.; Gao, W.-Z.; Ying, J. *J. Org. Chem.* ***2000***, *65*, 2003. See Kel'in, A.V.; Gevorgyan, V. *J. Org. Chem.* ***2002***, *67*, 95.

[245]Nan, Y.; Miao, H.; Yang, Z. *Org. Lett.* ***2000***, *2*, 297. See also, Arcadi, A.; Cacchi, S.; DiGiuseppe, S.; Fabrizi, G.; Marinelli, F. *Synlett* ***2002***, 453.

derivatives[246] have been prepared using this approach. Tetrahydrofurans bearing an exocyclic double bond (vinylidene tetrahydrofurans) were prepared from alkynyl alcohols and a silver carbonate catalyst.[247]

For those substrates, more susceptible to nucleophilic attack, for example, polyhalo alkenes and alkenes of the type C=C—Z, it is better to carry out the reaction in basic solution, where the attacking species is RO^-.[248] The reactions with C=C—Z are of the Michael type, and OR goes to the side away from the Z.[249] Since triple bonds are more susceptible to nucleophilic attack than double bonds, it might be expected that bases would catalyze addition to triple bonds particularly well. This is the case, and enol ethers and acetals can be produced by this reaction.[250] Because enol ethers are more susceptible than triple bonds to electrophilic attack, the addition of alcohols to enol ethers can also be catalyzed by acids.[251] One utilization of this reaction involves the compound dihydropyran



39 **40**

(**39**), which is often used to protect the OH groups of primary and secondary[252] alcohols and phenols.[253] The tetrahydropyranyl acetal formed by this reaction (**40**) is stable to bases, Grignard reagents, $LiAlH_4$, and oxidizing agents, any of which can be used to react with functional groups located within the R group. When the reactions are completed, **40** is easily cleaved by treatment with dilute acids (**10-6**). The addition of alcohols to enol ethers is also catalyzed by $CoCl_2$.[254]

Conjugate addition of alcohols to conjugated esters, using ceric ammonium nitrate and LiBr, gave the corresponding α-bromo-β-alkoxy ester.[255]

In base-catalyzed addition to triple bonds, the rate falls in going from a primary to a tertiary alcohol, and phenols require more severe conditions. Other catalysts, namely, BF_3 and mercuric salts, have also been used in addition of ROH to triple bonds.

[246]Davidson, M.H.; McDonald, F.E. *Org. Lett.* ***2004***, *6*, 1601.
[247]Pale, P.; Chuche, J. *Eur. J. Org. Chem.* ***2000***, 1019.
[248]For a review with respect to fluoroalkenes, see Chambers, R.D.; Mobbs, R.H. *Adv. Fluorine Chem.* ***1965***, *4*, 51, pp. 53–61.
[249]For an example using a rhodium catalyst, See Farnsworth, M.V.; Cross, M.J.; Louie, J. *Tetrahedron Lett.* ***2004***, *45*, 7441.
[250]For a review, see Shostakovskii, M.F.; Trofimov, B.A.; Atavin, A.S.; Lavrov, V.I. *Russ. Chem. Rev.* ***1968***, *37*, 907.
[251]For discussions of the mechanism, see Toullec, J.; El-Alaoui, M.; Bertrand, R. *J. Chem. Soc. Perkin Trans. 2*, ***1987***, 1517; Kresge, A.J.; Yin, Y. *J. Phys. Org. Chem.* ***1989***, *2*, 43.
[252]Tertiary alcohols can also be protected in this way if triphenylphosphine hydrobromide is used as a catalyst: Bolitt, V.; Mioskowski, C.; Shin, D.; Falck, J.R. *Tetrahedron Lett.* ***1988***, *29*, 4583.
[253]For useful catalysts for this reaction, some of which are also applicable to tertiary alcohols, see Miyashita, M.; Yoshikoshi, A.; Grieco, P.A. *J. Org. Chem.* ***1977***, *42*, 3772; Olah, G.A.; Husain, A.; Singh, B.P. *Synthesis* ***1985***, 703; Johnston, R.D.; Marston, C.R.; Krieger, P.E.; Goem G.L. *Synthesis* ***1988***, 393.
[254]Iqbal, J.; Srivastava, R.R.; Gupta, K.B.; Khan, M.A. *Synth. Commun.* ***1989***, *19*, 901.
[255]Roy, S.C.; Guin, C.; Rana, K.K.; Maiti, G. *Synlett* ***2001***, 226.

Alcohols can be added to certain double-bond compounds (cyclohexenes, cycloheptenes) photochemically[256] in the presence of a photosensitizer such as benzene. The mechanism is electrophilic and Markovnikov orientation is found. The alkenes react in their first excited triplet states.[257]

The oxymercuration–demercuration procedure mentioned in **15-3** can be adapted to the preparation of ethers (Markovnikov orientation) if the oxymercuration is carried out in an alcohol ROH as solvent,[258] for example 2-methyl-1-butene in ethanol gives $EtMe_2COEt$.[259] Primary alcohols give good yields when mercuric acetate is used, but for secondary and tertiary alcohols it is necessary to use mercuric trifluoroacetate.[260] However, even this reagent fails where the product would be a ditertiary ether. It is possible to combine the alcohol reactant with another reagent. The reaction of an alkene with iodine and allyl alcohol, in the presence of HgO, gave the *vic*-iodo ether.[261] Alkene-alcohols react with mercuric trifluoroacetate and the aq. KBr (with $LiBH_4/BEt_3$) to give a derivative bearing an iodoalkyl substituent, —O—C—CH(I)R.[262] Alkynes generally give acetals. If the oxymercuration is carried out in the presence of a hydroperoxide instead of an alcohol, the product (after demercuration with $NaBH_4$) is an alkyl peroxide (peroxy-mercuration).[263] This can be done intramolecularly.[264]

Both alcohols and phenols add to ketenes to give carboxylic esters $[R_2C{=}C{=}O + ROH \rightarrow R_2CHCO_2R]$.[265] This has been done intramolecularly (with the ketene end of the molecule generated and used *in situ*) to form medium- and large-ring lactones.[266] In the presence of a strong acid, ketene reacts with aldehydes or ketones (in their enol forms) to give enol acetates. 1,4-Asymmetric induction is possible when chiral alcohols add to ketenes.[267]

[256]For a review of the photochemical protonation of double and triple bonds, see Wan, P.; Yates, K. *Rev. Chem. Intermed.* ***1984***, *5*, 157.

[257]Marshall, J.A. *Acc. Chem. Res.* ***1969***, *2*, 33.

[258]For a review, with tables of many examples, see Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, ***1986***, pp. 162–345.

[259]Brown, H.C.; Rei, M. *J. Am. Chem. Soc.* ***1969***, *91*, 5646.

[260]Brown, H.C.; Kurek, J.T.; Rei, M.; Thompson, K.L. *J. Org. Chem.* ***1984***, *49*, 2551; ***1985***, *50*, 1171.

[261]Talybov, G.M.; Mekhtieva, V.Z.; Karaev, S.F. *Russ. J. Org. Chem.* ***2001***, *37*, 600.

[262]Kang, S.H.; Kim, M. *J. Am. Chem. Soc.* ***2003***, *125*, 4684. For an enantioselective example, see Kang, S.H.; Lee, S.B.; Park, C.M. *J. Am. Chem. Soc.* ***2003***, *125*, 15748.

[263]Ballard, D.H.; Bloodworth, A.J. *J. Chem. Soc. C* ***1971***, 945; Sokolov, V.I.; Reutov, O.A. *J. Org. Chem. USSR* ***1969***, *5*, 168. For a review, see Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, ***1986***, pp. 346–366.

[264]Garavelas, A.; Mavropoulos, I.; Perlmutter, P.; Westman, F. *Tetrahedron Lett.* ***1995***, *36*, 463.

[265]Quadbeck, G. *Newer Methods Prep. Org. Chem.* ***1963***, *2*, 133–161. See also, Chihara, T.; Teratini, S.; Ogawa, H. *J. Chem. Soc., Chem. Commun.* ***1981***, 1120. For discussions of the mechanism, see Tille, A.; Pracejus, H. *Chem. Ber.* ***1967***, *100*, 196–210; Brady, W.T.; Vaughn, W.L.; Hoff, E.F. *J. Org. Chem.* ***1969***, *34*, 843; Tidwell, T.T. *Acc. Chem. Res.* ***1990***, *23*, 273; Seikaly, H.R.; Tidwell, T.T. *Tetrahedron* ***1986***, *42*, 2587; Satchell, D.P.N.; Satchell, R.S. *Chem. Soc. Rev.* ***1975***, *4*, 231.; Jähme, J.; Rüchardt, C. *Tetrahedron Lett.* ***1982***, *23*, 4011; Poon, N.L.; Satchell, D.P.N. *J. Chem. Soc. Perkin Trans. 2*, ***1984***, 1083; ***1985***, 1551.

[266]Boeckman, Jr., R.K.; Pruitt, J.R. *J. Am. Chem. Soc.* ***1989***, *111*, 8286.

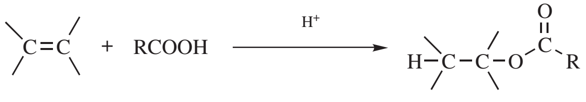
[267]Cannizzaro, C.E.; Strassner, T.; Houk, K.N. *J. Am. Chem. Soc.* ***2001***, *123*, 2668.

Alcohols can also add to alkenes via the α-carbon (see **15-33**).

OS **III**, 371, 774, 813; **IV**, 184, 558; **VI**, 916; **VII**, 66, 160, 304, 334, 381; **VIII**, 204, 254; **IX**, 472.

15-6 Addition of Carboxylic Acids to Form Esters

Hydro-acyloxy-addition



Carboxylic esters are produced by the addition of carboxylic acids to alkenes, a reaction that is usually acid-catalyzed (by proton or Lewis acids[268]) and similar in mechanism to **15-5**. Since Markovnikov's rule is followed, hard-to-get esters of tertiary alcohols can be prepared from alkenes of the form $R_2C{=}CHR$.[269] A combination of V_2O_5 and trifluoroacetic acid converts alkenes to trifluoroacetate esters.[270] When a carboxylic acid that contains a double bond in the chain is treated with a strong acid, the addition occurs internally and the product is a γ- and/or a δ-lactone, regardless of the original position of the double bond in the chain, since strong acids catalyze double-bond shifts (**12-2**).[271] The double bond always migrates (also see, **15-1**) to a position favorable for the reaction, whether this has to be toward or away from the carboxyl group. The use of a chiral *Cinchonidine* alkaloid additive leads to lactone formation with modest enantioselectivity.[272] In the presence of diphenyl diselenide and DDQ, alkene carboxylic acids react of form the lactone with a phenylselenomethyl group ($PhSeCH_2$—) at C-5.[273] Carboxylic esters have also been prepared by the acyloxymercuration-demercuration of alkenes (similar to the procedures mentioned in **15-3** and **15-4**).[274] Conjugated esters has been converted to β-lactones with photolysis and added tributyltin hydride, radical cyclization conditions (**15-30**).[275] Addition of carboxylic acids to alkenes to form esters or lactones is catalyzed by palladium compounds.[276] Thallium acetate also promotes this cyclization reaction.[277]

[268]See, for example, Guenzet, J.; Camps, M. *Tetrahedron* ***1974***, *30*, 849; Ballantine, J.A.; Davies, M.; Purnell, H.; Rayanakorn, M.; Thomas, J.M.; Williams, K.J. *J. Chem. Soc., Chem. Commun.* ***1981***, 8.

[269]See, for example, Peterson, P.E.; Tao, E.V.P. *J. Org. Chem.* ***1964***, *29*, 2322.

[270]Choudary, B.M.; Reddy, P.N. *J. Chem. Soc., Chem. Commun.* ***1993***, 405.

[271]For a review of such lactonizations, see Ansell, M.F.; Palmer, M.H. *Q. Rev. Chem. Soc.* ***1964***, *18*, 211.

[272]Wang, M.; Gao, L.X.; Mai, W.P.; Xia, A.X.; Wang, F.; Zhang, S.B. *J. Org. Chem.* ***2004***, *69*, 2874.

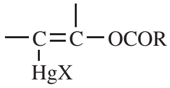
[273]Tiecco, M.; Testaferri, L.; Temperini, A.; Bagnoli, L.; Marini, F.; Santi, C. *Synlett* ***2001***, 1767.

[274]For a review, see Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, ***1986***, pp. 367–442.

[275]Castle, K.; Hau, C.-S.; Sweeney, J.B.; Tindall, C. *Org. Lett.* ***2003***, *5*, 757.

[276]Larock, R.C.; Hightower, T.R. *J. Org. Chem.* ***1993***, *58*, 5298; Annby, U.; Stenkula, M.; Andersson, C.-M. *Tetrahedron Lett.* ***1993***, *34*, 8545.

[277]Ferraz, H.M.C.; Ribeiro, C.M.R. *Synth. Commun.* ***1992***, *22*, 399.

Triple bonds can give enol esters[278] or acylals when treated with carboxylic acids. Mercuric salts are usually catalysts,[279] and vinylic mercury compounds  are intermediates.[280] Terminal alkynes RC≡CH react with CO_2, a secondary amine R'_2 NH, and a ruthenium complex catalyst, to give enol carbamates RCH=CHOC(=O)NR. [281] This reaction has also been performed intramolecularly, to produce unsaturated lactones.[282] Cyclic unsaturated lactones (internal vinyl esters) have been generated from alkyne-carboxylic acids using a palladium catalyst[283] or a ruthenium catalyst.[284] Carboxylic esters can also be obtained by the addition to alkenes of diacyl peroxides.[285] These reactions are catalyzed by copper and are free-radical processes.

Allene carboxylic acids have been cyclized to butenolides with copper(II) chloride.[286] Allene esters were converted to butenolides by treatment with acetic acid and LiBr.[287] Cyclic carbonates can be prepared from allene alcohols using carbon dioxide and a palladium catalyst, and the reaction was accompanied by arylation when iodobenzene was added.[288] Diene carboxylic acids have been cyclized using acetic acid and a palladium catalyst to form lactones that have an allylic acetate elsewhere in the molecule.[289] With ketenes, carboxylic acids give anhydrides[290] and acetic anhydride is prepared industrially in this manner [$CH_2{=}C{=}O + MeCO_2H \rightarrow (MeC{=}O)_2O$].

[278]Goossen, L.J.; Paetzold, J.; Koley, D. *Chem. Commun.* ***2003***, 706. For a rhenium catalyzed example, see Hua, R.; Tian, X. *J. Org. Chem.* ***2004***, *69*, 5782.

[279]For the use of rhodium complex catalysts, see Bianchini, C.; Meli, A.; Peruzzini, M.; Zanobini, F.; Bruneau, C.; Dixneuf, P.H. *Organometallics* ***1990***, *9*, 1155.

[280]See for example, Bach, R.D.; Woodard, R.A.; Anderson, T.J.; Glick, M.D. *J. Org. Chem.* ***1982***, *47*, 3707; Bassetti, M.; Floris, B. *J. Chem. Soc. Perkin Trans. 2*, ***1988***, 227; Grishin, Yu.K.; Bazhenov, D.V.; Ustynyuk, Yu.A.; Zefirov, N.S.; Kartashov, V.R.; Sokolova, T.N.; Skorobogatova, E.V.; Chernov, A.N. *Tetrahedron Lett.* ***1988***, *29*, 4631. Ruthenium complexes have also been used as catalysts. See Rotem, M.; Shvo, Y. *Organometallics* ***1983***, *2*, 1689; Mitsudo, T.; Hori, Y.; Yamakawa, Y.; Watanabe, Y. *J. Org. Chem.* ***1987***, *52*, 2230.

[281]Mitsudo, T.; Hori, Y.; Yamakawa, Y.; Watanabe, Y. *Tetrahedron Lett.* ***1987***, *28*, 4417; Mahé, R.; Sasaki, Y.; Bruneau, C.; Dixneuf, P.H. *J. Org. Chem.* ***1989***, *54*, 1518.

[282]See, for example, Sofia, M.J.; Katzenellenbogen, J.A. *J. Org. Chem.* ***1985***, *50*, 2331. For a list of other examples, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, p. 1895.

[283]Liao, H.-Y.; Cheng, C.-H. *J. Org. Chem.* ***1995***, *60*, 3711

[284]Jiménez-Tenorio, M.; Puerta, M.C.; Valerga, P.; Moreno-Dorado, F.J.; Guerra, F.M.; Massanet, G.M. *Chem. Commun.* ***2001***, 2324.

[285]Kharasch, M.S.; Fono, A. *J. Org. Chem.* ***1959***, *24*, 606; Kochi, J.K. *J. Am. Chem. Soc.* ***1962***, *84*, 1572.

[286]Ma, S.; Wu, S. *J. Org. Chem.* ***1999***, *64*, 9314.

[287]Ma, S.; Li, L.; Wei, Q.; Xie, H.; Wang, G.; Shi, Z.; Zhang, J. *Pure. Appl. Chem.* ***2000***, *72*, 1739.

[288]Uemura, K.; Shiraishi, D.; Noziri, M.; Inoue, Y. *Bull. Chem. Soc. Jpn.* ***1999***, *72*, 1063.

[289]Verboom, R.C.; Persson, B.A.; Bäckvall, J.-E. *J. Org. Chem.* ***2004***, *69*, 3102.

[290]For discussions of the mechanism, see Briody, J.M.; Lillford, P.J.; Satchell, D.P.N. *J. Chem. Soc. B* ***1968***, 885; Corriu, R.; Guenzet, J.; Camps, M.; Reye, C. *Bull. Soc. Chim. Fr.* ***1970***, 3679; Blake, P.G.; Vayjooee, M.H.B. *J. Chem. Soc. Perkin Trans. 2*, ***1976***, 1533.

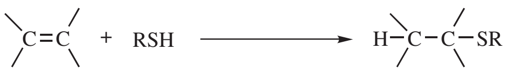
Sulfonic acids add to alkenes and alkynes. The reaction of an alkyne with *para*-toluenesulfonic acid and treatment with silica gives the vinyl sulfonate (C=C–OSO_2Tol).[291] Cyclic sulfonates can be generated by the reaction of an allylic sulfonate salt (C=C–C–OSO_3^-) with silver nitrate in acetonitrile containing an excess of bromine and a catalytic amount of water.[292] Sultones are formed when alkenes react with PhIO and two equivalents of Me_2SiSO_3Cl.[293]

OS **III**, 853; **IV**, 261, 417, 444; **V**, 852, 863; **VII**, 30, 411. Also see, OS **I**, 317.

C. Sulfur on the Other Side

15-7 Addition of H_2S and Thiols

Hydro-alkylthio-addition



Hydrogen sulfide (H_2S) and thiols add to alkenes to give alkyl thiols or sulfides by electrophilic, nucleophilic, or free-radical mechanisms.[294] In the absence of initiators, the addition to simple alkenes is by an electrophilic mechanism, similar to that in **15-5**, and Markovnikov's rule is followed. However, this reaction is usually very slow and often cannot be done or requires very severe conditions unless a proton or Lewis acid catalyst is used. For example, the reaction can be performed in concentrated H_2SO_4[295] or together with $AlCl_3$.[296] In the presence of free-radical initiators, H_2S and thiols add to double and triple bonds by a free-radical mechanism and the orientation is anti-Markovnikov.[297] The addition of thiophenol to an alkene with a zeolite also leads to the anti-Markovnikov sulfide.[298] Additives can influence the regioselectivity. Styrene reacts with thiophenol to give primarily the anti-Markovnikov product, whereas addition of thiophenol in the presence of Montmorillonite K10 clay gives primarily the Markovnikov addition product.[299] In fact, the orientation can be used as a diagnostic tool to indicate which mechanism is operating. Free-radical addition can be done with H_2S, RSH (R may be primary,

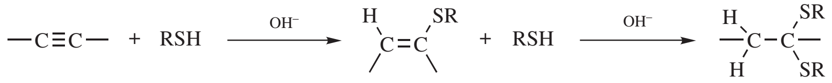
[291]Braga, A.L.; Emmerich, D.J.; Silveira, C.C.; Martins, T.L.C.; Rodrigues, O.E.D. *Synlett* ***2001***, 371.
[292]Steinmann, J.E.; Phillips, J.H.; Sanders, W.J.; Kiessling, L.L. *Org. Lett.* **2001**, *3*, 3557.
[293]Bassindale, A.R.; Katampe, I.; Maesano, M.G.; Patel, P.; Taylor, P.G. *Tetrahedron Lett.* ***199***, *40*, 7417.
[294]For a review, see Wardell, J.L., in Patai, S. *The Chemistry of the Thiol Group*, pt. 1, Wiley, NY, ***1974***, pp. 69–178.
[295]Shostakovskii, M.F.; Kul'bovskaya, N.K.; Gracheva, E.P.; Laba, V.I.; Yakushina, L.M. *J. Gen. Chem. USSR* ***1962***, *32*, 707.
[296]Belley, M.; Zamboni, R. *J. Org. Chem.* ***1989***, *54*, 1230.
[297]For reviews of free-radical addition of H_2S and RSH, see Voronkov, M.G.; Martynov, A.V.; Mirskova, A.N. *Sulfur Rep.*, ***1986***, *6*, 77; Griesbaum, K. *Angew. Chem. Int. Ed.* ***1970***, *9*, 273; Oswald, A.A.; Griesbaum, K., in Kharasch, N.; Meyers, C.Y. *Organic Sulfur Compounds*, Vol. 2, Pergamon, Elmsford, NY, ***1966***, pp. 233–256; Stacey, F.W.; Harris Jr., J.F. *Org. React.* ***1963***, *13*, 150, pp. 165–196, 247–324.
[298]Kumar, P.; Pandey, R.K.; Hegde, V.R. *Synlett* ***1999***, 1921.
[299]Kanagasabapathy, S.; Sudalai, A.; Benicewicz, B.C. *Tetrahedron Lett.* ***2001***, *42*, 3791.

secondary, or tertiary), ArSH, or RCOSH.[300] The R group may contain various functional groups. The alkenes may be terminal, internal, contain branching, be cyclic, and have various functional groups including OH, COOH, COOR, NO_2, RSO_2, and so on. Addition of Ph_3SiSH to terminal alkenes under radical conditions also leads to the primary thiol.[301]

Alkynes react with thiols to give vinyl sulfides. With alkynes it is possible to add 1 or 2 equivalents of RSH, giving a vinyl sulfide[302] or a dithioketal, respectively. Alternative preparations are available, as in the reaction of a terminal alkyne with $Cp_2Zr(H)Cl$ followed by PhSCl to give the vinyl sulfide with the SPh unit at the less substituted position (PhCH=CHSPh).[303] The intramolecular addition of a thiol to an ene-yne, with a palladium catalyst, leads to substituted thiophene derivatives.[304]

The fundamental addition reaction can be modified by the use of transition metals and different reagents. Alkenes react with diphenyl disulfide in the presence of $GaCl_3$ to give the product with two phenylthio units, PhS–C–C–SPh).[305] The reaction of an alkyne with diphenyl disulfide and a palladium catalyst leads to the bis-vinyl sulfide, PhS–C=C–SPh.[306]

When thiols are added to substrates susceptible to nucleophilic attack, bases catalyze the reaction and the mechanism is nucleophilic. These substrates may be of the Michael type[307] or may be polyhalo alkenes or alkynes.[250] As with the free-radical mechanism, alkynes can give either vinylic thioethers or dithioacetals:



Thiols add to alkenes under photochemical conditions to form thioethers, and the reaction can be done intramolecularly to give cyclic thioethers.[308] Thiols also add to alkynes and with a palladium catalyst, vinyl sulfides can be formed.[309] Thiocarbonates function as thiol surrogates, converting alkenes to alkyl thiol in the presence of $TiCl_4$; and CuO.[310]

By any mechanism, the initial product of addition of H_2S to a double bond is a thiol, which is capable of adding to a second molecule of alkene, so that sulfides

[300]For a review of the addition of thio acids, see Janssen, M.J., in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 720–723.

[301]Haché, B.; Gareau, Y. *Tetrahedron Lett.* ***1994***, *35*, 1837.

[302]See Arjona, O.; Medel, R.; Rojas, J.; Costa, A.M.; Vilarrasa, J. *Tetrahedron Lett.* ***2003***, *44*, 6369.

[303]Huang, X.; Zhong, P.; Guo, W.-r. *Org. Prep. Proceed. Int.* ***1999***, *31*, 201.

[304]Gabriele, B.; Salerno, G.; Fazio, A. *Org. Lett.* ***2000***, *2*, 351.

[305]Usugi, S.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* ***2004***, *6*, 601.

[306]Ananikov, V.P.; Beletskaya, I.P. *Org. Biomol. Chem.* ***2004***, *2*, 284.

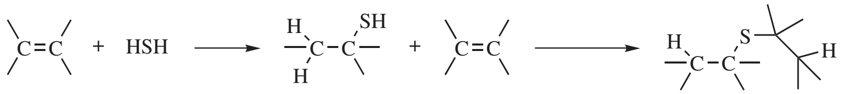
[307]Michael substrates usually give the expected orientation. For a method of reversing the orientation for RS groups (the RS group goes a to the C=O bond of a C=C–C=O system), see Gassman, P.G.; Gilbert, D.P.; Cole, S.M. *J. Org. Chem.* ***1977***, *42*, 3233.

[308]Kirpichenko, S.V.; Tolstikova, L.L.; Suslova, E.N.; Voronkov, M.G. *Tetrahedron Lett.* ***1993***, *34*, 3889.

[309]Kuniyasu, H.; Ogawa, A.; Sato, K.-I.; Ryu, I.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* ***1992***, *114*, 5902.

[310]Mukaiyama, T.; Saitoh, T.; Jona, H. *Chem. Lett.* ***2001***, 638.

are often produced:



As with alcohols, ketenes add thiols to give thiol esters [$R_2C{=}C{=}O + RSH \rightarrow R_2CHCOSR$].[311]

Selenium compounds (RSeH) add in a similar manner to thiols.[312] Vinyl selenides can be prepared from alkynes using diphenyl diselenide and sodium borohydride.[313]

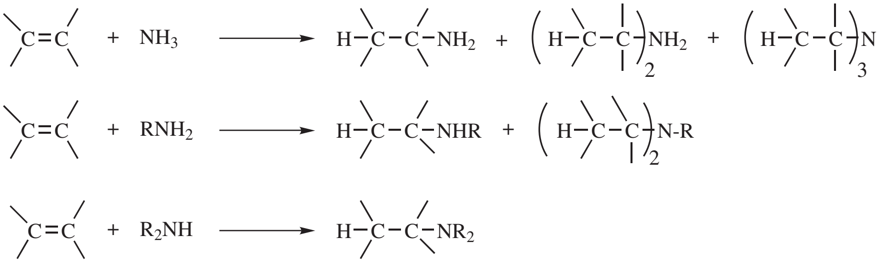
The conjugate addition of thiols to α,β-unsaturated carbonyl derivatives is discussed in **15-31**.

OS **III**, 458; **IV**, 669; **VIII**, 302. See also, OS **VIII**, 458.

D. Nitrogen or Phosphorus on the Other Side

15-8 Addition of Ammonia and Amines, Phosphines, and Related Compounds

Hydro-amino-addition
Hydro-phosphino-addition



Ammonia and primary and secondary amines add to alkenes *that are susceptible* to nucleophilic attack.[314] Ammonia and amines are much weaker acids than water, alcohols, and thiols (see **15-3**, **15-5**, **15-7**) and since acids turn NH_3 into the weak

[311]For an example, see Blake, A.J.; Friend, C.L.; Outram, R.J.; Simpkins, N.S.; Whitehead, A.J. *Tetrahedron Lett.* ***2001***, *42*, 2877.

[312]Kuniyasu, H.; Ogawa, A.; Sato, K.-I.; Ryu, I.; Sonoda, N. *Tetrahedron Lett.* ***1992***, *33*, 5525.

[313]Dabdoub, M.J.; Baroni, A.C.M.; Lenardão, E.J.; Gianeti, T.R.; Hurtado, G.R. *Tetrahedron* ***2001***, *57*, 4271.

[314]For reviews, see Gasc, M.B.; Lattes, A.; Périé, J.J. *Tetrahedron* ***1983***, *39*, 703; Pines, H.; Stalick, W.M. *Base-Catalyzed Reactions of Hydrocarbons and Related Compounds*, Academic Press, NY, ***1977***, pp. 423–454; Suminov, S.I.; Kost, A.N. *Russ. Chem. Rev.* ***1969***, *38*, 884; Gibson, M.S., in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, pp. 61–65; Beller, M.; Breindl, C.; Eichberger, M.; Hartung, C.G.; Seayad, J.; Thiel, O.R.; Tillack, A.; Trauthwein, H. *Synlett* ***2002***, 1579. For a discussion of Markovnikov versus anti-Markovnikov selectivity, see Tillack, A.; Khedkar, V.; Beller, M. *Tetrahedron Lett.* ***2004***, *45*, 8875.

acid, the ammonium ion NH_4^+, this reaction does not occur by an electrophilic mechanism. The reaction tends to give very low yields, if any, with ordinary alkenes, unless extreme conditions are used (e.g., 178–200°C, 800–1000 atm, and the presence of metallic Na, for the reaction between NH_3 and ethylene[315]). Amine alkenes give cyclic amines as the major product, in good yield, when treated with *n*-butyllithium.[316] Ammonia gives three possible products, since the initial product is a primary amine, which may add to a second molecule of alkene, and so on. Similarly, primary amines give both secondary and tertiary products. In practice it is usually possible to control which product predominates. The mechanism is nearly always nucleophilic, and the reaction is generally performed on polyhalo alkenes[317] and alkynes.[318] Ammonia adds to alkenes photochemically.[319] Reaction of a secondary amine with butyllithium generates an amide base, which reacts with alkenes to give alkyl amines,[320] and can add intramolecularly to an alkene to form a pyrrolidine.[321] Pyrroles can be generated in this manner.[322] *N*-Chloroamines add to alkenes intramolecularly to give β-chloropyrrolidines.[323]

Conjugated carbonyl compounds react via conjugate addition with amines to give β-amino derivatives (see **15-31**)[324] As expected, on Michael-type substrates the nitrogen goes to the carbon that does not carry the Z. With substrates of the form RCH=CZZ′, the same type of cleavage of the adduct can take place as in **15-3**.[325]

There are many examples of transition catalyzed addition of nitrogen compounds to alkenes, alkynes,[326] and so on. Secondary amines can be added to certain nonactivated alkenes if palladium(II) complexes are used as catalysts.[327]

[315]Howk, B.W.; Little, E.L.; Scott, S.L.; Whitman, G.M. *J. Am. Chem. Soc.* ***1954***, *76*, 1899.

[316]Ates, A.; Quinet, C. *Eur. J. Org. Chem.* ***2003***, 1623.

[317]For a review with respect to fluoroalkenes, see Chambers, R.D.; Mobbs, R.H. *Adv. Fluorine Chem.* ***1965***, *4*, 51–112, pp. 62–68.

[318]For an intramolecular example see Cossy, J.; Belotti, D.; Bellosta, V.; Boggio, C. *Tetrahedron Lett.* ***1997***, *38*, 2677. For intramolecular addition to a 1-ethoxy alkyne, see MaGee, D.I.; Ramaseshan, M. *Synlett* ***1994***, 743.

[319]Yasuda, M.; Kojima, R.; Ohira, R.; Shiragami, T.; Shima, K. *Bull. Chem. Soc. Jpn.* ***1998***, *71*, 1655.

[320]Hartung, C.G.; Breindl, C.; Tillack, A.; Beller, M. *Tetrahedron* ***2000***, *56*, 5157.

[321]Fujita, H.; Tokuda, M.; Nitta, M.; Suginome, H. *Tetrahedron Lett.* ***1992***, *33*, 6359.

[322]Dieter, R.K.; Yu, H. *Org. Lett.* ***2000***, *2*, 2283.

[323]Göttlich, R. *Synthesis* ***2000***, 1561; Göttlich, R.; Noack, M. *Tetrahedron Lett* ***2001***, *42*, 7771 For a reaction with an *N*-bromoamine, see Outurquin, F.; Pannecoucke, X.; Berthe, B.; Paulmier, C. *Eur. J. Org. Chem.* ***2002***, 1007. For a $TiCl_3$—$AlMe_3$ mediated reaction, see Sjöholm, Å.; Hemmerling, M.; Pradeille, N.; Somfai, P. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 891. For a variation with a sulfonamide and iodine, see Jones, A.D.; Knight, D.W.; Hibbs, D.E. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 1182

[324]See Cossu, S.; DeLucchi, O.; Durr, R. *Synth. Commun.* ***1996***, *26*, 4597 for an example involing methyl 2-propynoate.

[325]See, for example, Bernasconi, C.F.; Murray, C.J. *J. Am. Chem. Soc.* ***1986***, *108*, 5251, 5257; Bernasconi, C.F.; Bunnell, R.D. *J. Org. Chem.* ***1988***, *53*, 2001.

[326]For a review, see Doye, S. *Synlett* ***2004***, 1653.

[327]For a review, see Gasc, M.B.; Lattes, A.; Périé, J.J. *Tetrahedron* ***1983***, *39*, 703. For a review of metal-catalyzed nucleophilic addition, see Bäckvall, J. *Adv. Met.-Org. Chem.* ***1989***, *1*, 135. See Löber, O.; Kawatsura, M.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2001***, *123*, 4366.

The complexation lowers the electron density of the double bond, facilitating nucleophilic attack.[328] Markovnikov orientation is observed and the addition is anti.[329] Molybdenum,[330] titanium,[331] Yttrium,[332] and rhodium compounds[333] have been used in the addition of amines to alkenes. An intramolecular addition of an amine unit to an alkene to form a pyrrolidine was reported using a palladium catalyst,[334] a lanthanide reagent,[335] or an yttrium reagent.[336] Aniline reacts with dienes and a palladium catalyst to give allylic amines.[337] Diene amines react with samarium catalysts to give 2-alkenyl pyrrolidines.[338] Addition of secondary amines to dihydropyrans using a palladium catalyst gave the corresponding aminal (an α-amino ether).[339] Reduction of nitro compounds in the presence of rhodium catalysts, in the presence of alkenes, CO and H_2, leads to an amine unit adding to the alkene moiety.[340] Secondary amines react with alkenes to give the alkyl amine using a rhodium catalyst in a CO/H_2 atmosphere,[341] but modification of the chromium catalyst and conditions led to an enamine.[342] Note that the reaction of an alkene and a secondary amine with a rhodium catalyst can also give an enamine.[343]

Other nitrogen compounds, among them hydroxylamine and hydroxylamines,[344] hydrazines, and amides (**15-9**), also add to alkenes. Azodicarboxylates (Boc-N=N-Boc) react with alkenes, in the presence of $PhSiH_3$ and a cobalt catalyst, to give

[328]For a discussion of the mechanism, see Hegedus, L.S.; Åkermark, B.; Zetterberg, K.; Olsson, L.F. *J. Am. Chem. Soc.* ***1984***, *106*, 7122.

[329]Åkermark, B.; Zetterberg, K. *J. Am. Chem. Soc.* ***1984***, *106*, 5560; Utsunomiya, M.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2003***, *125*, 14286.

[330]Srivastava, R.S.; Nicholas, K.M. *Chem. Commun.* ***1996***, 2335.

[331]Ackermann, L.; Kaspr, L.T.; Gschrei, C.J. *Org. Lett.* ***2004***, *6*, 2515. See Castro, I.G.; Tillack, A.; Hartung, C.G.; Beller, M. *Tetrahedron Lett.* ***2003***, *44*, 3217.

[332]O'Shaughnessy, P.N.; Scott, P. *Tetrahedron Asymmetry* ***2003***, *14*, 1979.

[333]The anti-Markovkinov amine is produced: Utsunomiya, M.; Kuwano, R.; Kawatsura, M.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2003***, *125*, 5608; Utsonomiya, M.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2004***, *126*, 2702; Ahmed, M.; Seayad, A.M.; Jackstell, R.; Beller, M. *J. Am. Chem. Soc.* ***2003***, *125*, 10311.

[334]Fix, S.R.; Brice, J.L.; Stahl, S.S. *Angew. Chem. Int. Ed.* ***2002***, *41*, 164.

[335]Molander, G.A.; Dowdy, E.D. *J. Org. Chem.* ***1998***, *63*, 8983; Ryu, J.-S.; Marks, T.J.; McDonald, F.E. *Org. Lett.* ***2001***, *3*, 3091. The use of a chiral lanthanum catalyst led to pyrrolidines with modest asymmetric induction: Hong, S.; Tian, S.; Metz, M.V.; Marks, T.J. *J. Am. Chem. Soc.* ***2003***, *125*, 14768.

[336]Kim, Y.K.; Livinghouse, T.; Bercaw, J.E. *Tetrahedron Lett.* ***2001***, *42*, 2933.

[337]Minami, T.; Okamoto, H.; Ikeda, S.; Tanaka, R.; Ozawa, F.; Yoshifuji, M. *Angew. Chem. Int. Ed.* ***2001***, *40*, 4501.

[338]Hong, S.; Marks, T.J. *J. Am. Chem. Soc.* ***2002***, *124*, 7886.

[339]Cheng, X.; Hii, K.K. *Tetrahedron* ***2001***, *57*, 5445.

[340]Rische, T.; Eilbracht, P. *Tetrahedron* ***1998***, *54*, 8441; Akazome, M.; Kondo, T.; Watanabe, Y. *J. Org. Chem.* ***1994***, *59*, 3375.

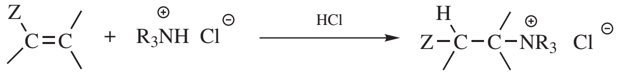
[341]Rische, J.; Bärfacker, L.; Eilbracht, P. *Eur. J. Org. Chem.* ***1999***, 653; Lin, Y.-S.; El Ali, B.; Alper, H. *Tetrahedron Lett.* ***2001***, *42*, 2423.

[342]Ahmed, M.; Seayad, A.M.; Jackstell, R.; Beller, M. *Angew. Chem. Int. Ed.* ***2003***, *42*, 5615.

[343]Tillack, A.; Trauthwein, H.; Hartung, C.G.; Eichberger, M.; Pitter, S.; Jansen, A.; Beller, M. *Monat. Chem.* ***2000***, *131*, 1327.

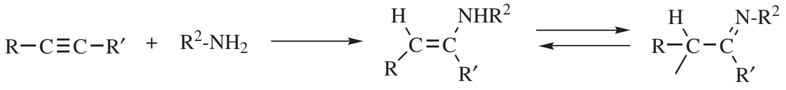
[344]Lin, X.; Stien, D.; Weinreb, S.M. *Tetrahedron Lett.* ***2000***, *41*, 2333; Singh, S.; Nicholas, K.M. *Synth. Commun.* ***2001***, *31*, 3087.

alkylhydrazides [RN(Boc)–NHBoc].[345] Even with amines, basic catalysts are sometimes used, so that RNH^- or R_2N^- is the actual nucleophile. Tertiary amines (except those that are too bulky) add to Michael-type substrates in a reaction that is catalyzed by acids like HCl or HNO_3 to give the corresponding quaternary ammonium salts.[346]



The tertiary amine can be aliphatic, cycloalkyl, or heterocyclic (including pyridine). The reaction of NaOH with an amine containing two distal alkene units, followed by addition of a neodymium catalyst leads to a bicyclic amine.[347]

Primary amines add to triple bonds[348] to give enamines that have a hydrogen on the nitrogen and (analogously to enols) tautomerize to the more stable imines, **41**.[349]



41

The reaction has been done with a palladium catalyst,[350] a titanium catalyst,[351] a tantalum catalyst,[352] and with a gold catalyst.[353] An intramolecular addition of amines to an alkyne unit in the presence of a palladium catalyst generated heterocyclic or cyclic amine compounds.[354] The titanium catalyzed addition of primary

[345]Waser, J.; Carreira, E.M. *J. Am. Chem. Soc.* ***2004***, *126*, 5676.

[346]Le Berre, A.; Delacroix, A. *Bull. Soc. Chim. Fr.* ***1973***, 640, 647. See also, Vogel, D.E.; Büchi, G. *Org. Synth., 66*, 29.

[347]Molander, G.A.; Pack, S.K. *J. Org. Chem.* ***2003***, *68*, 9214.

[348]For a review of addition of ammonia and amines to triple bonds, see Chekulaeva, I.A.; Kondrat'eva, L.V. *Russ. Chem. Rev.* ***1965***, *34*, 669. For reactions with aniline, see Haak, E.; Bytschkov, I.; Doye, S. *Angew. Chem. Int. Ed.* ***1999***, *38*, 3389; Hartung, C.G.; Tillack, A.; Trauthwein, H.; Beller, M. *J. Org. Chem.* ***2001***, *66*, 6339.

[349]For example, see Kruse, C.W.; Kleinschmidt, R.F. *J. Am. Chem. Soc.* ***1961***, *83*, 213, 216.

[350]Kadota, I.; Shibuya, A.; Lutete, L.M.; Yamamoto, Y. *J. Org. Chem.* ***1999***, *64*, 4570.

[351]Khedkar, V.; Tillack, A.; Beller, M. *Org. Lett.* ***2003***, *5*, 4767; Tillack, A.; Castro, I.G.; Hartung, C.G.; Beller, M. *Angew. Chem. Int. Ed.* ***2002***, *41*, 2541.

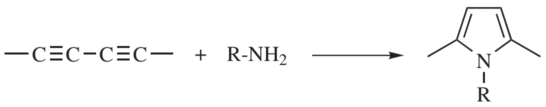
[352]Anderson, L.L.; Arnold, J.; Bergman R.G. *Org. Lett.* ***2004***, *6*, 2519; Shi, Y.; Hall, C.; Ciszewski, J.T.; Cao, C.; Odom, A.L. *Chem. Commun.* ***2003***, 586; Cao, C.; Li, Y.; Shi, Y.; Odom, A.L. *Chem. Commun.*, ***2004***, 2002.

[353]Mizushima, E.; Hayashi, T.; Tanaka, M. *Org. Lett.* ***2003***, *5*, 3349.

[354]Müller, T.E. *Tetrahedron Lett.* ***1998***, *39*, 5961; Hiroya, K.; Matsumoto, S.; Sakamoto, T. *Org. Lett.* ***2004***, *6*, 2953; Lutete, L.M.; Kadota, I.; Yamamoto, Y. *J. Am. Chem. Soc.* ***2004***, *126*, 1622; Hiroya, K.; Itoh, S.; Ozawa, M.; Kanamori, Y.; Sakamoto, T. *Tetrahedron Lett.* ***2002***, *43*, 1277. See also, Karur, S.; Kotti, S.R.S.S.; Xu, X.; Cannon, J.F.; Headley, A.; Li, G. *J. Am. Chem. Soc.* ***2003***, *125*, 13340.

amines to alkynes give the enamine, which can be hydrogenated (**15-11**) to give the corresponding amine.[355] A variation treats an alkynyl imine with CuI to form pyrroles.[356] *N,N*-Diphenylhydrazine reacts with diphenyl acetylene and a titanium catalyst to give indole derivatives.[357] Treatment of an imine of 2-alkynyl benzaldehyde with iodide gave a functionalized isoquinoline.[358] When ammonia is used instead of a primary amine, the corresponding $RH_2C{-}C({=}NH){-}R'$ is not stable enough for isolation, but polymerizes. Ammonia and primary amines (aliphatic and aromatic) add to conjugated diynes to give pyrroles, **42**.[359] A similar preparation of pyrroles was reported by heating non-conjugated diynes with aniline and a titanium catalyst.[360] This is not 1,4-addition, but 1,2-addition twice. Conjugated ene-ynes containing an amino group also give pyrroles with a palladium catalyst.[361]

Allenes are reaction partners,[362] and amines add to allenes in the presence of a catalytic amount of CuBr[363] or palladium compounds.[364] Intramolecular reaction of allene amines lead to dihydropyrroles, using a gold catalyst.[365]



42

Treatment of an allene amine with a ruthenium catalyst, 10% of $TiCl_4$ and methyl vinyl ketone to give a product of amine addition followed by Michael addition, a pyrrolidine derivative with a pendant alkenyl ketone unit.[366] Cyclic imines can be prepared from allene amines using a titanium catalyst.[367]

[355]Haak, E.; Siebeneicher, H.; Doye, S. *Org. Lett.* ***2000***, *2*, 1935; Bytschkov, I.; Doye, S. *Eur. J. Org. Chem.* ***2001***, 4411. For a variation using sodium cyanoborohydride and zinc chloride as the reducing agent, see Heutling, A.; Doye, S. *J. Org. Chem.* ***2002***, *67*, 1961.

[356]Kel'in, A.; Sromek, A.W.; Gevorgyan, V. *J. Am. Chem. Soc.* ***2001***, *123*, 2074. Another variation used a chromium carbene species to generate pyrroles from imino ene-ynes: Zhang, Y.; Herndon, J.W. *Org. Lett.* ***2003***, *5*, 2043.

[357]Ackermann, L.; Born, R. *Tetrahedron Lett.* ***2004***, *45*, 9541. For a different approach using hypervalent iodine, see Barluenga, J.; Trincado, M.; Rubio, E.; González, J.M. *Angew. Chem. Int. Ed.* ***2003***, *42*, 2406.

[358]Huang, Q.; Hunter, J.A.; Larock, R.C *J. Org. Chem.* ***2002***, *67*, 3437.

[359]Schult, K.E.; Reisch, J.; Walker, H. *Chem. Ber.* ***1965***, *98*, 98.

[360]Ramanathan, B.; Keith, A.J.; Armstrong, D.; Odom, A.L. *Org. Lett.* ***2004***, *6*, 2957.

[361]Gabriele, B.; Salerno, G.; Fazio, A.; Bossio, M.R. *Tetrahedron Lett.* ***2001***, *42*, 1339; Gabriele, B.; Salerno, G.; Fazio, A. *J. Org. Chem.* ***2003***, *68*, 7853.

[362]Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* ***1998***, *39*, 5421.

[363]Geri, R.; Polizzi, C.; Lardicci, L.; Caporusso, A.M. *Gazz. Chim. Ital.*, ***1994***, *124*, 241.

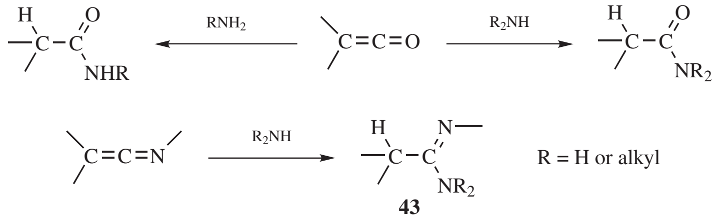
[364]Davies, I.W.; Scopes, D.I.C.; Gallagher, T. *Synlett* ***1993***, 85.

[365]Morita, N.; Krause, N. *Org. Lett.* ***2004***, *6*, 4121.

[366]Trost, B.M.; Pinkerton, A.B.; Kremzow, D. *J. Am. Chem. Soc.* ***2000***, *122*, 12007.

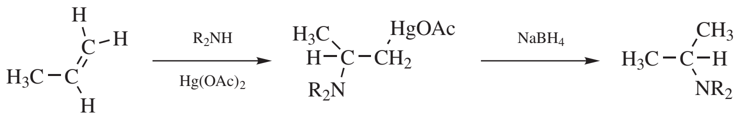
[367]Ackermann, L.; Bergman, R.G. *Org. Lett.* ***2002***, *4*, 1475; Ackerman, L.; Bergman, R.G.; Loy, R.N. *J. Am. Chem. Soc.* ***2003***, *125*, 11956.

Primary and secondary amines add to ketenes to give, respectively, *N*-substituted and *N,N*-disubstituted amides:[368] and to ketenimines to give amidines, **43**.[369]



43

NH_3 can be added to double bonds (even ordinary double bonds) in an indirect manner by the use of hydroboration (**15-16**) followed by treatment with NH_2Cl or NH_2OSO_2OH (**12-32**). This produces a primary amine with anti-Markovnikov orientation. An indirect way of adding a primary or secondary amine to a double bond consists of aminomercuration followed by reduction (see **15-3** for the analogous oxymercuration–demercuration procedure), to give amine **45**.[370]



44 **45**

The addition of a secondary amine (shown above) produces a tertiary amine, while addition of a primary amine gives a secondary amine. The overall orientation follows Markovnikov's rule. For conversion of **44** to other products, see **15-53**.

Phosphines add to alkenes to give alkyl phosphines and to alkynes to give vinyl phosphines. In the presence of an ytterbium (Yb) catalyst, diphenylphosphine added to diphenyl acetylene to give the corresponding vinyl phosphine.[371] A palladium catalyst was used for the addition *o*-diphenylphosphine to terminal alkynes, giving the anti-Markovnikov vinyl phosphine but a nickel catalyst led to the Markovnikov vinyl phosphine.[372] Alkenes also react with diarylphosphines

[368]For discussions of the mechanism of this reaction, see Briody, J.M.; Satchell, D.P.N. *Tetrahedron* ***1966***, *22*, 2649; Tidwell, T.T. *Acc. Chem. Res.* ***1990***, *23*, 273; Satchell, D.P.N.; Satchell, R.S. *Chem. Soc. Rev.* ***1975***, *4*, 231. For an enantioselective reaction, see Hodous, B.L.; Fu, G.C. *J. Am. Chem. Soc.* ***2002***, *124*, 10006.

[369]Stevens, C.L.; Freeman, R.C.; Noll, K. *J. Org. Chem.* ***1965***, *30*, 3718.

[370]For a review, see Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, ***1986***, pp. 443–504. See also, Barluenga, J.; Perez-Prieto, J.; Asensio, G. *Tetrahedron* ***1990***, *46*, 2453.

[371]Takaki, K.; Koshoji, G.; Komeyama, K.; Takeda, M.; Shishido, T.; Kitani, A.; Takehira, K. *J. Org. Chem.* ***2003***, *68*, 6554.

[372]Kazankova, M.A.; Efimova, I.V.; Kochetkov, A.N.; Atanas'ev, V.V.; Beletskaya, I.P.; Dixneuf, P.H. *Synlett* ***2001***, 497.

and a nickel catalyst. to give the alkyl phosphine[373] Silylphosphines ($R_3Si{-}PAr_2$) react with alkenes and Bu_4NF to give the anti-Markovnikov ally phosphine.[374] Phosphine oxides can be prepared by the reaction of an aryl substituted alkene and diphenylphosphine oxide, $Ph_2P(=O)H$.[375] Diphenylphosphine oxide also reacted with terminal alkynes to give the anti-Markovnikov vinyl phosphine oxide using a rhodium catalyst.[376] Phosphonate esters were similar prepared from alkenes and diethyl phosphite, $(EtO_2)P(=O)H$, and a manganese catalyst in a reaction exposed to oxygen.[377] Similar addition was observed in the reaction of an alkene with NaH_2PO_2 to give the phosphinate, $RCH{=}CH_2 \rightarrow RCH_2CH_2PH(=O)ONa$.[378] Palladium catalysts were used for the preparation of similar compounds from alkenes[379] and the reaction of terminal alkynes with dimethyl phosphite and a nickel catalyst gave the Markovnikov vinyl phosphonate ester.[380] Other phosphites were added to dienes to give an allylic phosphonate ester using a palladium catalyst.[381] Diarylphosphines react with vinyl ethers and a nickel catalyst to give α-alkoxy phosphonate esters.[382]

OS **I**, 196; **III**, 91, 93, 244, 258; **IV**, 146, 205; **V**, 39, 575, 929; **VI**, 75, 943; **VIII**,188, 190, 536; **80**, 75. See also, OS **VI**, 932.

15-9 Addition of Amides

Hydro-amido-addition

Under certain conditions, amides can add directly to alkenes to form *N*-alkylated amides. Sulfonamides react in a similar manner. 3-Pentenamide was cyclized to 5-methyl-2-pyrrolidinone by treatment with trifluorosulfonic acid.[383] Acyl hydrazine derivatives also cyclized in the presence of hypervalent iodine reagents to give lactams.[384] When a carbamate was treated with Bu_3SnH, and AIBN, addition to an alkene led to a bicyclic lactam.[385]

[373]Shulyupin, M.O.; Kazankova, M.A.; Beletskaya, I.P. *Org. Lett.*, ***2002***, *4*, 761.
[374]Hayashi, M.; Matsuura, Y.; Watanabe, Y. *Tetrahedron Lett.* ***2004***, *45*, 9167.
[375]Bunlaksananusorn, T.; Knochel, P. *J. Org. Chem.* ***2004***, *69*, 4595; Rey, P.; Taillades, J.; Rossi, J.C.; Gros, G. *Tetrahedron Lett.* ***2003***, *44*, 6169.
[376]Han, L.-B.; Zhao, C.-Q.; Tanaka, M. *J. Org. Chem.* ***2001***, *66*, 5929.
[377]Tayama, O.; Nakano, A.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* ***2004***, *69*, 5494.
[378]Deprèle, S.; Montchamp, J.-L. *J. Org. Chem.* ***2001***, *66*, 6745.
[379]Deprèle, S.; Montchamp, J.-L. *J. Am. Chem. Soc.* ***2002***, *124*, 9386.
[380]Han, L.-B.; Zhang, C.; Yazawa, H.; Shimada, S. *J. Am. Chem. Soc.* ***2004***, *126*, 5080.
[381]Mirzaei, F.; Han, L.-B.; Tanaka, M. *Tetrahedron Lett.* ***2001***, *42*, 297.
[382]Kazankova, M.A.; Shulyupin, M.O.; Beletskaya, I.P. *Synlett* ***2003***, 2155.
[383]Marson, C.M.; Fallah, A. *Tetrahedron Lett.* ***1994***, *35*, 293.
[384]Scartozzi, M.; Grondin, R.; Leblanc, Y. *Tetrahedron Lett.* ***1992***, *33*, 5717.
[385]Callier, A.-C.; Quiclet-Sire, B.; Zard, S.Z. *Tetrahedron Lett.* ***1994***, *35*, 6109.

The reaction can be done intramolecularly. *N*-Benzyl pent-4-ynamide reacted with tetrabutylammonium fluoride to an alkylidene lactam.[386] Similar addition of a tosylamide-alkene, with a palladium catalyst, led to a vinyl *N*-tosyl pyrrolidine.[387] Similar cyclization reactions occur with tosylamide-alkynes.[388]

Treatment of triflamide alkenes with triflic acid gives the corresponding *N*-triflyl cyclic amine.[389] Using an alkene halide and an *N*-chlorosulfonamide, an amide is generated *in situ*, and addition to the alkene gives a pyrrolidine derivative.[390] *N*-Bromocarbamates also add to alkenes, in the presence of $BF_3•OEt_2$ to give a *vic*-bromo *N*-Boc amine.[391] The titanium catalyzed reaction of alkenyl *N*-tosylamines give *N*-tosyl cyclic amines.[392]

Alkynes and allenes also react with amides. Phenylthiomethyl alkynes were converted to *N*-Boc-*N*-phenylthio allenes with Boc azide and an iron catalyst.[393] The palladium-catalyzed reaction of an allene amide, with iodobenzene, leads to *N*-sulfonyl aziridines having an allylic group at C1.[394] Other allene *N*-tosylamines similarly give *N*-tosyl tetrahydropyridines.[395]

Imides can also add to alkenes or alkynes. Ethyl 2-propynoate reacted with phthalimide, in the presence of a palladium catalyst, to give ethyl 2-phthalimido-2-propenoate.[396]

15-10 Addition of Hydrazoic Acid

Hydro-azido-addition

Hydrazoic acid (HN_3) can be added to certain Michael-type substrates (Z is as defined on p. 1007) to give β-azido compounds.[397] The reaction apparently fails if R

[386]Jacobi, P.A.; Brielmann, H.L.; Hauck, S.I. *J. Org. Chem.* ***1996***, *61*, 5013.

[387]Larock, R.C.; Hightower, T.R.; Hasvold, L.A.; Peterson, K.P. *J. Org. Chem.* ***1996***, *61*, 3584; Harris, Jr., G.D.; Herr, R.J.; Weinreb, S.M. *J. Org. Chem.* ***1993***, *58*, 5452. See also, Pinho, P.; Minnaard, A.J.; Feringa, B.L. *Org. Lett.* ***2003***, *5*, 259.

[388]Luo, F.-T.; Wang, R.-T. *Tetrahedron Lett.* ***1992***, *33*, 6835.

[389]Schlummer, B.; Hartwig, J.F. *Org. Lett.* ***2002***, *4*, 1471; Haskins, C.M.; Knight, D.W. *Chem. Commun.* ***2002***, 2724.

[390]Minakata, S.; Kano, D.; Oderaotoshi, Y.; Komatsu, M. *Org. Lett.* ***2002***, *4*, 2097.

[391]Ś liwnń ska, A.; Zwierzak, A. *Tetrahedron* ***2003***, *59*, 5927.

[392]Miura, K.; Hondo, T.; Nakagawa, T.; Takahashi, T.; Hosomi, A. *Org. Lett.* ***2000***, *2*, 385.

[393]Bacci, J.P.; Greenman, K.L.; van Vranken, D.L. *J. Org. Chem.* ***2003***, *68*, 4955.

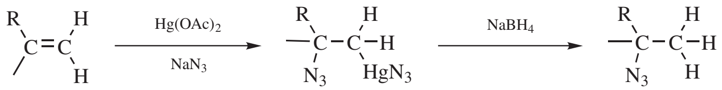
[394]Ohno, H.; Toda, A.; Miwa, Y.; Taga, T.; Osawa, E.; Yamaoka, Y.; Fujii, N.; Ibuka, T. *J. Org. Chem.* ***1999***, *64*, 2992.

[395]Rutjes, F.P.J.T.; Tjen, K.C.M.F.; Wolf, L.B.; Karstens, W.F.J.; Schoemaker, H.E.; Hiemstra, H. *Org. Lett.* ***1999***, *1*, 717; Na, S.; Yu, F.; Gao, W. *J. Org. Chem.* ***2003***, *68*, 5943; Ma. S.; Gao, W. *Org. Lett.* ***2002***, *4*, 2989.

[396]Trost, B.M.; Dake, G.R. *J. Am. Chem. Soc.* ***1997***, *119*, 7595.

[397]Boyer, J.H. *J. Am. Chem. Soc.* ***1951***, *73*, 5248; Harvey, G.R.; Ratts, K.W. *J. Org. Chem.* ***1966***, *31*, 3907. For a review, see Biffin, M.E.C.; Miller, J.; Paul, D.B., in Patai, S. *The Chemistry of the Azido Group*, Wiley, NY, ***1971***, pp. 120–136.

is phenyl. The HN_3 also adds to enol ethers $CH_2{=}CHOR$ to give $CH_3{-}CH(OR)N_3$, and to silyl enol ethers,[398] but it does not add to ordinary alkenes unless a Lewis acid catalyst, such as $TiCl_4$, is used, in which case good yields of azide can be obtained.[398] Hydrazoic acid can also be added indirectly to ordinary alkenes by azidomercuration, followed by demercuration,[399] analogous to the similar procedures

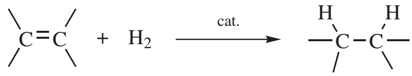


mentioned in **15-3**, **15-5**, **15-6**, and **15-8**. The method can be applied to terminal alkenes or strained cycloalkenes (e.g., norbornene) but fails for unstrained internal alkenes.

E. Hydrogen on Both Sides

15-11 Hydrogenation of Double and Triple Bonds[400]

Dihydro-addition



Most carbon–carbon double bonds, whether substituted by electron-donating or electron-withdrawing substituents, can be catalytically hydrogenated, usually in quantitative or near-quantitative yields.[401] Almost all known alkenes added hydrogen at temperatures between 0 and 275°C. The catalysts used can be divided into

[398]Hassner, A.; Fibiger, R.; Andisik, D. *J. Org. Chem.* ***1984***, *49*, 4237.

[399]Heathcock, C.H. *Angew. Chem. Int. Ed.* ***1969***, *8*, 134. For a review, see Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, ***1986***, pp. 522–527.

[400]For a review, see Mitsui, S.; Kasahara, A., in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, ***1970***, pp. 175–214. Also see, Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY, ***2001***, pp. 369–382.

[401]For books on catalytic hydrogenation, see Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, ***1985***; *Catalytic Hydrogenation in Organic Synthesis*, Academic Press, NY, ***1979***; *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, ***1967***; Červený, L. *Catalytic Hydrogenation*, Elsevier, NY, ***1986*** (this book deals mostly with industrial aspects); Freifelder, M. *Catalytic Hydrogenation in Organic Synthesis*, Wiley, NY, ***1978***; *Practical Catalytic Hydrogenation*, Wiley, NY, ***1971***; Augustine, R.L. *Catalytic Hydrogenation*, Marcel Dekker, NY, ***1965***. For reviews, see Parker, D., in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 979–1047; Carruthers, W. *Some Modern Methods of Organic Synthesis* 3rd ed., Cambridge University Press, Cambridge, ***1986***, pp. 411–431; Colquhoun, H.M.; Holton, J.; Thompson, D.J.; Twigg, M.V. *New Pathways for Organic Synthesis*, Plenum, NY, ***1984***, pp. 266–300, 325–334; Kalinkin, M.I.; Kolomnikova, G.D.; Parnes, Z.N.; Kursanov, D.N. *Russ. Chem. Rev.* ***1979***, *48*, 332; Candlin, J.P.; Rennie, R.A.C. in Bentley, K.W.; Kirby, G.W. *Elucidation of Organic Structures by Physical and Chemical Methods*, 2nd ed. (Vol. 4 of Weissberger, A. *Techniques of Chemistry*), pt. 2, Wiley, NY, ***1973***, pp. 97–117; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp, 1–34.

two broad classes, both of which mainly consist of transition metals and their compounds: (*1*) catalysts insoluble in the reaction medium (*heterogeneous catalysts*). Among the most effective are Raney nickel,[402] palladium-on-charcoal (perhaps the most common),[403] $NaBH_4$-reduced nickel[404] (also called nickel boride), platinum metal or its oxide, rhodium, ruthenium, and zinc oxide.[405] (*2*) Catalysts soluble in the reaction medium (*homogeneous catalysts*).[406] An important example is chlorotris(triphenylphosphine)rhodium, $RhCl(Ph_3P)_3$,[407] (**100**, *Wilkinson's catalyst*),[408] which catalyzes the hydrogenation of many alkenyl compounds without disturbing such groups as COOR, NO_2, CN, or COR present in the same molecule.[409] Even unsaturated aldehydes can be reduced to saturated aldehydes,[410] although in this case decarbonylation (**14-32**) may be a side reaction. In general, for catalytic hydrogenation, many functional groups may be present in the molecule, for example, OH, COOH, NR_2 including NH_2, N(R)COR′ including carbamates,[411] CHO, COR, COOR, or CN. Vinyl esters can be hydrogenated using homogeneous rhodium catalyst.[412] Enamides are hydrogenated, with excellent enantioselectivity, using chiral rhodium catalysts.[413] Some of these groups are also susceptible to catalytic reduction, but it is usually possible to find conditions

[402]For a review of Raney nickel, see Pizey, J.S. *Synthetic Reagents*, Vol. 2, Wiley, NY, ***1974***, pp. 175–311. Double bonds have been reduced with Raney nickel alone; with no added H_2. The hydrogen normally present in this reagent was sufficient: Pojer, P.M. *Chem. Ind. (London)* ***1986***, 177.

[403]A recyclable $Pd/CaCO_3$ catalyst in polyethylene glycol (PEG) as been reported. See Chandrasekhar, S.; Narsihmulu, Ch.; Chandrashekar, G.; Shyamsunder, T. *Tetrahedron Lett.* ***2004***, *45*, 2421.

[404]Paul, R.; Buisson, P.; Joseph, N. *Ind. Eng. Chem.* ***1952***, *44*, 1006; Brown, C.A. *Chem. Commun.* ***1969***, 952; *J. Org. Chem.* ***1970***, *35*, 1900. For a review of reductions with nickel boride and related catalysts, see Ganem, B.; Osby, J.O. *Chem. Rev.* ***1986***, *86*, 763.

[405]For reviews of hydrogenation with metal oxides, see Minachev, Kh.M.; Khodakov, Yu.S.; Nakhshunov, V.S. *Russ. Chem. Rev.* ***1976***, *45*, 142; Kokes, R.J.; Dent, A.L. *Adv. Catal.* ***1972***, *22*, 1 (ZnO).

[406]For a monograph, see James, B.R. *Homogeneous Hydrogenation*, Wiley, NY, ***1973***. For reviews, see Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, CA ***1987***, pp. 523–564; Birch, A.J.; Williamson, D.H. *Org. React.* ***1976***, *24*, 1; James, B.R. *Adv. Organomet. Chem.* ***1979***, *17*, 319; Harmon, R.E.; Gupta, S.K.; Brown, D.J. *Chem. Rev.* ***1973***, *73*, 21; Strohmeier, W. *Fortschr. Chem. Forsch.* ***1972***, *25*, 71; Heck, R.F. *Organotransition Metal Chemistry*, Academic Press, NY, ***1974***, pp. 55–65; Rylander, P.N. *Organic Syntheses with Noble Metal Catalysts*, Academic Press, NY, ***1973***, pp. 60–76; Lyons, J.E.; Rennick, L.E.; Burmeister, J.L. *Ind. Eng. Chem. Prod. Res. Dev.* ***1970***, *9*, 2; Vol'pin, M.E.; Kolomnikov, I.S. *Russ. Chem. Rev.* ***1969***, *38*, 273.

[407]Osborn, J.A.; Jardine, F.H.; Young, J.F.; Wilkinson, G. *J. Chem. Soc, A* ***1966***, 1711; Osborn, J.A.; Wilkinson, G. *Inorg. Synth.*, ***1967***, *10*, 67; Biellmann, J.F. *Bull. Soc. Chim. Fr.* ***1968***, 3055; van Bekkum, H.; van Rantwijk, F.; van de Putte, T. *Tetrahedron Lett.* ***1969***, 1.

[408]For a review of Wilkinson's catalyst, see Jardine, F.H. *Prog. Inorg. Chem.* ***1981***, *28*, 63–202.

[409]Harmon, R.E.; Parsons, J.L.; Cooke, D.W.; Gupta, S.K.; Schoolenberg, J. *J. Org. Chem.* ***1969***, *34*, 3684. See also, Mohrig, J.R.; Dabora, S.L.; Foster, T.F.; Schultz, S.C. *J. Org. Chem.* ***1984***, *49*, 5179.

[410]Jardine, F.H.; Wilkinson, G. *J. Chem. Soc. C* ***1967***, 270.

[411]Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron* ***2000***, *56*, 8433.

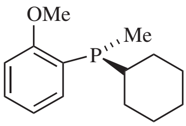
[412]Tang, W.; Liu, D.; Zhang, X *Org. Lett.* ***2003***, *5*, 205.

[413]Jia, X.; Guo, R.; Li, X.; Yao, X.; Chan, A.S.C. *Tetrahedron Lett.* ***2002***, *43*, 5541; Reetz, M.T.; Mehler, G.; Meiswinkel, A.; Sell, T. *Tetrahedron Lett.* ***2002***, *43*, 7941; Reetz, M.T.; Mehler, G. *Tetrahedron Lett.* ***2003***, *44*, 4593.

under which double bonds can be reduced selectively[414] (see Table 19.2). Controlling the solvent allows catalytic hydrogenation of an alkene in the presence of an aromatic nitro group.[415]

Among other homogeneous catalysts are chlorotris(triphenylphosphine)hydridoruthenium(II), $(Ph_3P)_3RuClH$,[416] which is specific for terminal double bonds (other double bonds are hydrogenated slowly or not at all), and pentacyanocobaltate(II), $Co(CN)_5^{3-}$, which is effective for double and triple bonds only when they are part of conjugated systems[417] (the conjugation may be with C=C, C=O, or an aromatic ring). Colloidal palladium has also been used as a catalyst,[418] and a polymer bound ruthenium catalyst has also been used.[419] A polymer incarcerated palladium catalyst gave the hydrogenated product in quantitative yields.[420] Rhodium on mesoporous silica can be used to hydrogenate alkenes.[421] A nanoparticulate palladium catalyst in an ionic liquid has been used for the hydrogenation of alkenes.[422]

Homogeneous catalysts often have the advantages of better catalyst reproducibility and better selectivity. They are also less susceptible to catalyst poisoning[423] (heterogeneous catalysts are usually poisoned by small amounts of sulfur, often found in rubber stoppers, or by sulfur-containing compounds, such as thiols and sulfides).[424] On the other hand, heterogeneous catalysts are usually easier to separate from the reaction mixture.



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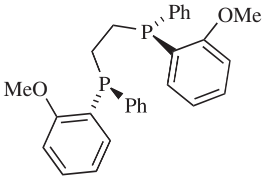


102

[414]For a discussion, see Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, ***1967***, pp. 59–120. Also see, Hudlický, M. *Reductions in Organic Chemistry*, Ellis Horwood Ltd., Chichester, ***1984***.

[415]Jourdant, A.; González-Zamora, E.; Zhu, J. *J. Org. Chem.* ***2002***, *67*, 3163.

[416]Hallman, P.S.; McGarvey, B.R.; Wilkinson, G. *J. Chem. Soc. A* ***1968***, 3143; Jardine, F.H.; McQuillin, F.J. *Tetrahedron Lett.* ***1968***, 5189.

[417]Kwiatek, J.; Mador, I.L.; Seyler, J.K. *J. Am. Chem. Soc.* ***1962***, *84*, 304; Jackman, L.M.; Hamilton, J.A.; Lawlor, J.M. *J. Am. Chem. Soc.* ***1968***, *90*, 1914; Funabiki, T.; Matsumoto, M.; Tarama, K. *Bull. Chem. Soc. Jpn.* ***1972***, *45*, 2723; Reger, D.L.; Habib, M.M.; Fauth, D.J. *Tetrahedron Lett.* ***1979***, 115.

[418]Fowley, L.A.; Michos, D.; Luo, X.-L.; Crabtree, R.H. *Tetrahedron Lett.* ***1993***, *34*, 3075.

[419]Taylor, R.A.; Santora, B.P.; Gagné, M.R. *Org. Lett.* ***2000***, *2*, 1781.

[420]Okamoto, K.; Akiyama, R.; Kobayashi, S. *J. Org. Chem.* ***2004***, *69*, 2871. See also, Bremeyer, N.; Ley, S.V.; Ramarao, C.; Shirley, I.M.; Smith, S.C. *Synlett* ***2002***, 1843.

[421]Crudden, C.M.; Allen, D.; Mikoluk, M.D.; Sun, J. *Chem. Commun.* ***2001***, 1154.

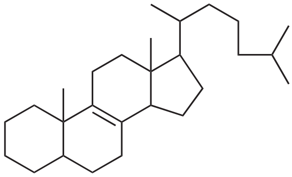
[422]In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Huang, J.; Jiang, T.; Han, B.; Gao, H.; Chang, Y.; Zhao, G.; Wu, W. *Chem. Commun.* ***2003***, 1654.

[423]Birch, A.J.; Walker, K.A.M. *Tetrahedron Lett.* ***1967***, 1935.

[424]For a review of catalyst poisoning by sulfur, see Barbier, J.; Lamy-Pitara, E.; Marecot, P.; Boitiaux, J.P.; Cosyns, J.; Verna, F. *Adv. Catal.* ***1990***, *37*, 279–318.

Unfunctionalized alkenes are hydrogenated with good diastereoselectivity and enantioselectivity using various metal catalysts and chiral ligands.[425] Soluble, chiral homogeneous catalysts are usually the best choice, especially for alkenes. The transition-metal catalyst (rhodium and ruthenium are probably the most common) is usually prepared with suitable chiral ligands prior to addition to the reaction, or an achiral catalyst, such as Wilkinson's catalyst, **100**: $RhCl(Ph_3P)_3$, is added along with a chiral ligand. The chiral ligand is typically a phosphine. In one case, the phosphorous may be chiral, as in **101** (called R-camp),[426] but pyramidal inversion at elevated temperatures (see p. 142) limits the utility of such ligands. The alliterative is to prepare a phosphine containing a chiral carbon, and bis(phosphines), such as **102** (called dipamp)[427] are the most common. There are many variations of chiral bis(phosphine) ligands. Mono-phosphine ligands have also been used.[428] Titanocenes[429] with chiral cyclopentadienyl ligands have given enantioselective hydrogenation of unfunctionalized alkenes, such as 2-phenyl-1-butene.[430] Chiral poisoning has been used as a strategy for asymmetric catalysis.[431]

Hydrogenations in most cases are carried out at room temperature and just above atmospheric pressure, but some double bonds are more resistant and require higher temperatures and pressures. The resistance is usually a function of increasing substitution and is presumably caused by steric factors. Trisubstituted double bonds require, say, 25°C and 100 atm, while tetrasubstituted double bonds may require 275°C and 1000 atm. Among



103

the double bonds most difficult to hydrogenate or which cannot be hydrogenated at all are those common to two rings, as in steroid **103**. Hydrogenations, even at about atmospheric pressure, are ordinarily performed in a special hydrogenator, but this is

[425]**Zr**: Troutman, M.V.; Appella, D.H.; Buchwald, S.L. *J. Am. Chem. Soc.* ***1999***, *121*, 4916. **Ir**: Xu, G.; Gilbertson, S.R. *Tetrahedron Lett.* ***2003***, *44*, 953; Tang, W.; Wang, W.; Zhang, X. *Angew. Chem. Int. Ed.* ***2003***, *42*, 943; Cozzi, P.G.; Menges, F.; Kaiser, S. *Synlett* ***2003***, 833. Special ligands: Perry, M.C.; Cui, X.; Powell, M.T.; Hou, D.-R.; Reibenspies, J.H.; Burgess, K. *J. Am. Chem. Soc.* ***2003***, *125*, 113.

[426]Knowles, W.S.; Sabacky, M.J.; Vineyard, B.D. *Adv. Chem. Ser* ***1974***, *132*, 274.

[427]Brown, J.M.; Chaloner, P.A. *J. Chem. Soc., Chem. Commun.* ***1980***, 344; ***1978***, 321; *Tetrahedron Lett.* ***1978***, 1877; *J. Am. Chem. Soc.* ***1980***, *102*, 3040.

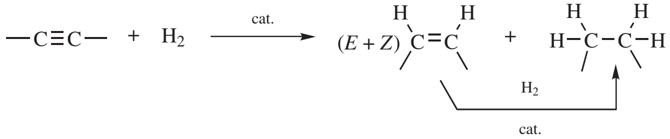
[428]Huang, H.; Zheng, Z.; Luo, H.; Bai, C.; Hu, X.; Chen, H. *J. Org. Chem.* ***2004***, *69*, 2355; Hua, Z.; Vassar, V.C.; Ojima, I. *Org. Lett.* ***2003***, *5*, 3831. For a review, see Jerphagnon, T.; Renaud, J.-L.; Bruneau, C. *Tetrahedron Asymmetry* ***2004***, *15*, 2101.

[429]Burk, M.J.; Gross, M.F. *Tetrahedron Lett.* ***1994***, *35*, 9363.

[430]Halterman, R.L.; Vollhardt, K.P.C.; Welker, M.E.; Bläser, D.; Boese, R. *J. Am. Chem. Soc.* ***1987***, *109*, 8105; Lee, N.E.; Buchwald, S.L. *J. Am. Chem. Soc.* ***1994***, *116*, 5985.

[431]Faller, J.W.; Parr, J. *J. Am. Chem. Soc.* ***1993***, *115*, 804.

not always necessary. Both the catalyst and the hydrogen can be generated *in situ*, by treatment of H_2PtCl_6 or $RhCl_3$ with $NaBH_4$;[432] ordinary glassware can then be used. The great variety of catalysts available often allows an investigator to find one that is highly selective. For example, the catalyst Pd(salen) encapsulated in zeolites permitted the catalytic hydrogenation of 1-hexene in the presence of cyclohexene.[433] It has been shown that the pressure of the reaction can influence enantioselectivity in asymmetric catalytic hydrogenations.[434]



Triple bonds can be reduced, either by catalytic hydrogenation or by the other methods mentioned in the following two sections. The comparative reactivity of triple and double bonds depends on the catalyst. With most catalysts (e.g., Pd), triple bonds are hydrogenated more easily, and therefore it is possible to add just 1 equivalent of hydrogen and reduce a triple bond to a double bond (usually a stereoselective syn addition) or to reduce a triple bond without affecting a double bond present in the same molecule.[435] A particularly good catalyst for this purpose is the Lindlar catalyst (Pd-$CaCO_3$—PbO).[436] An alternative catalyst used for selective hydrogenation to cis-alkenes is palladium on barium sulfate ($BaSO_4$) catalyst, poisoned with quinoline[437] (sometimes called the *Rosenmund catalyst*). Palladium on calcium carbonate in polyethylene glycol (PEG) has also bee used as a recyclable catalyst system.[438] Hydrogenation using a palladium catalyst on pumice was shown to give the cis-alkene with excellent selectivity.[439] Hydrogenation of a C≡C unit occurs in the presence of other functional groups, including NR_2 including NH_2,[440] and sulfonyl.[441]

[432]Brown, C.A.; Sivasankaran, K. *J. Am. Chem. Soc.* ***1962***, *84*, 2828; Brown, C.A.; Brown, H.C. *J. Am. Chem. Soc.* ***1962***, *84*, 1494, 1945, 2829; *J. Org. Chem.* ***1966***, *31*, 3989.

[433]Kowalak, S.; Weiss, R.C.; Balkus Jr., K.J. *J. Chem. Soc., Chem. Commun.* ***1991***, 57.

[434]Sun, Y.; Landau, R.N.; Wang, J.; LeBlond, C.; Blackmond, D.G. *J. Am. Chem. Soc.* ***1996***, *118*, 1348.

[435]For reviews of the hydrogenation of alkynes, see Hutchins, R.O.; Hutchins, M.G.K., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C* pt. 1, Wley, NY, ***1983***, pp. 571–601; Marvell, E.N.; Li, T. *Synthesis* ***1973***, 457; Gutmann, H.; Lindlar, H., in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 355–363.

[436]Lindlar, H.; Dubuis, R. *Org. Synth.* ***V***, 880. See also, Rajaram, J.; Narula, A.P.S.; Chawla, H.P.S.; Dev, S. *Tetrahedron* ***1983***, *39*, 2315; McEwen, A.B.; Guttieri, M.J.; Maier, W.F.; Laine, R.M.; Shvo, Y. *J. Org. Chem.* ***1983***, *48*, 4436.

[437]Cram, D.J.; Allinger, N.L. *J. Am. Chem. Soc.* ***1956***, *78*, 2518; Rosenmund, K.W. *Ber.* ***1918***, *51*, 585; Mosettig, E.; Mozingo, R. *Org. React.* ***1948***, *4*, 362.

[438]Chandrasekhar, S.; Narsihmulu, Ch.; Chandrashekar, G.; Shyamsunder, T. *Tetrahedron Lett.* ***2004***, *45*, 2421.

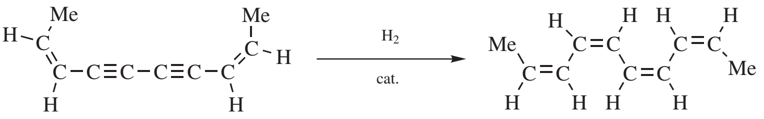
[439]Gruttadauria, M.; Noto, R.; Deganello, G.; Liotta, L.F. *Tetrahedron Lett.* ***1999***, *40*, 2857; Gruttadauria, M.; Liotta, L.F.; Noto, R.; Deganello, G. *Tetrahedron Lett.* ***2001***, *42*, 2015.

[440]Campos, K.R.; Cai, D.; Journet, M.; Kowal, J.J.; Larsen, R.D.; Reider, P.J. *J. Org. Chem.* ***2001***, *66*, 3634.

[441]Zhong, P.; Huang, X.; Ping-Guo, M. *Tetrahedron* ***2000***, *56*, 8921.

Conjugated dienes can add hydrogen by 1,2- or 1,4-addition. Selective 1,4-addition can be achieved by hydrogenation in the presence of carbon monoxide, with bis(cyclopentadienyl)chromium as catalyst.[442] With allenes[443] catalytic hydrogenation usually reduces both double bonds.

Most catalytic reductions of double or triple bonds, whether heterogeneous or homogeneous, have been shown to be syn, with the hydrogens entering from the less-hindered side of the molecule.[444] Stereospecificity can be investigated only for tetrasubstituted alkenes (except when the reagent is D_2), which are the hardest to hydrogenate, but the results of these investigations show that the addition is usually 80–100% syn, although some of the anti addition product is normally also found and in some cases predominates. Catalytic hydrogenation of alkynes is nearly always stereoselective, giving the cis alkene (usually at least 80%), even when it is thermodynamically less stable. For example, **104** gave **105**, even although the steric hindrance is such that a planar molecule is impossible.[445] This is thus a useful method for preparing cis alkenes.[446] However, when



104 **105**

steric hindrance is too great, the trans alkene may be formed. One factor that complicates the study of the stereochemistry of heterogeneous catalytic hydrogenation is that exchange of hydrogens takes place, as can be shown by hydrogenation with deuterium.[447] Thus deuterogenation of ethylene produced all the possible deuterated ethylenes and ethanes (even C_2H_6), as well as HD.[448] With 2-butene, it was found that double-bond migration, cis–trans isomerization, and even exchange of hydrogen with groups not on the double bond could occur; for example, $C_4H_2D_8$ and C_4HD_9 were detected on treatment of *cis*-2-butene with deuterium and a catalyst.[449] Indeed, *alkanes* have been found to exchange with deuterium over a catalyst,[450] and even without deuterium, for example, $CH_4 + CD_4 \rightarrow CHD_3 + CH_3D$

[442]Miyake, A.; Kondo, H. *Angew. Chem. Int. Ed.* ***1968***, *7*, 631. For other methods, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 403–404.

[443]For a review, see Schuster, H.F.; Coppola, G.M. *Allenes in Organoic Synthesis* Wiley, NY, ***1984***, pp. 57–61.

[444]For a review of homogeneous hydrogenation directed to only one face of a substrate molecule, see Brown, J.M. *Angew. Chem. Int. Ed.* ***1987***, *26*, 190.

[445]Holme, D.; Jones, E.R.H.; Whiting, M.C. *Chem. Ind. (London)* ***1956***, 928.

[446]For a catalyst that leads to trans alkenes, see Burch, R.R.; Muetterties, E.L.; Teller, R.G.; Williams, J.M. *J. Am. Chem. Soc.* ***1982***, *104*, 4257.

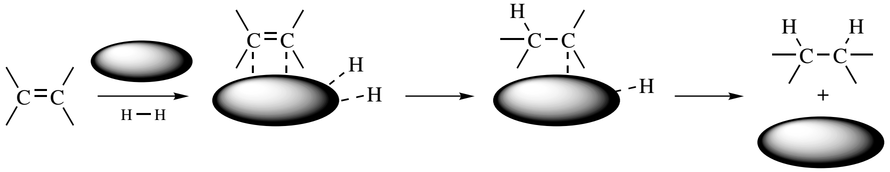
[447]For a review of the use of deuterium to study the mechanism of heterogeneous organic catalysis see Gudkov, B.S. *Russ. Chem. Rev.* ***1986***, *55*, 259.

[448]Turkevich, J.; Schissler, D.O.; Irsa, P. *J. Phys. Chem.* ***1951***, *55*, 1078.

[449]Wilson, J.N.; Otvos, J.W.; Stevenson, D.P.; Wagner, C.D. *Ind. Eng. Chem.* ***1953***, *45*, 1480.

[450]For a review, see Gudkov, B.S.; Balandin, A.A. *Russ. Chem. Rev.* ***1966***, *35*, 756. For an example of intramolecular exchange, see Lebrilla, C.B.; Maier, W.F. *Tetrahedron Lett.* ***1983***, *24*, 1119. See also, Poretti, M.; Gäumann, T. *Helv. Chim. Acta* ***1985***, *68*, 1160.

D in the gas phase, with a catalyst. All this makes it difficult to investigate the stereochemistry of heterogeneous catalytic hydrogenation.



The mechanism of the heterogeneous catalytic hydrogenation of double bonds is not thoroughly understood because it is a very difficult reaction to study.[451] Because the reaction is heterogeneous, kinetic data, although easy to obtain (measurement of decreasing hydrogen pressure), are difficult to interpret. Furthermore, there are the difficulties caused by the aforementioned hydrogen exchange. The currently accepted mechanism for the common two-phase reaction was originally proposed in 1934.[452] According to this, the alkene is adsorbed onto the surface of the metal, although the nature of the actual bonding is unknown,[453] despite many attempts to elucidate it.[454] In the 1934 work, the metallic site was indicated by an asterisk, but here we use . For steric reasons it is apparent that adsorption of the alkene takes place with its less-hindered side attached to the catalyst surface, probably as an η^2 complex (see p. 116). The fact that addition of hydrogen is generally also from the less-hindered side indicates that the hydrogen too is probably adsorbed on the catalyst surface before it reacts with the alkene. It is likely that as the H_2 molecule is adsorbed on (coordinated to) the metal catalyst, cleavage occurs to give η^1- coordinated hydrogen atoms (see p. $$$). Note that this model suggest a single metal particle for coordination of the alkene and the hydrogen atoms, but the hydrogen atoms and the alkene could be coordinated to different metal particles. It has been shown that platinum catalyzes homolytic cleavage of hydrogen molecules.[455] In the second step, one of the adsorbed (η^1-coordinated) hydrogen atoms becomes attached to a carbon atom, creating in effect, an alkyl radical (which is still bound to the catalyst although only by one bond, probably η^1-coordination). Transfer of a hydrogen atom to carbon opens a site on the metal catalyst for coordination to additional hydrogen atoms. Finally, another hydrogen atom (not necessarily the one originally connected to the first hydrogen) combines with the radical

[451]For reviews, see Webb, G., in Bamford, CH.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 20, Elsevier, NY, ***1978***, pp. 1–121; Clarke, J.K.A.; Rooney, J.J. *Adv. Catal.* ***1976***, *25*, 125–183; Siegel, S. *Adv. Catal.* ***1966***, *16*, 123–177; Burwell, Jr., R.L. *Chem. Eng. News* ***1966***, *44(34)*, 56–67.
[452]Horiuti, I.; Polanyi, M. *Trans. Faraday Soc.* ***1934***, *30*, 1164.
[453]See, for example, Burwell, Jr., R.L.; Schrage, K. *J. Am. Chem. Soc.* ***1965***, *87*, 5234.
[454]See, for example, McKee, D.W. *J. Am. Chem. Soc.* ***1962***, *84*, 1109; Ledoux, M.J. *Nouv. J. Chim.* ***1978***, *2*, 9; Bautista, F.M.; Campelo, J.M.; Garcia, A.; Guardeño, R.; Luna, D.; Marinas, J.M. *J. Chem. Soc. Perkin Trans. 2*, ***1989***, 493.
[455]Krasna, A.I. *J. Am. Chem. Soc.* ***1961***, *83*, 289.

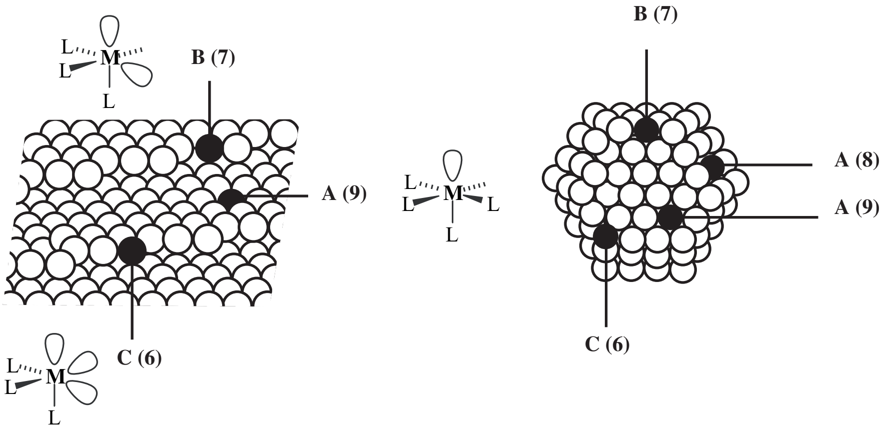


Fig. 15.1. The principal surface and particle sites for heterogeneous catalysts.

to give the reaction product, freed from the catalyst surface, and the metal catalyst that is now available for coordination of additional hydrogen atoms and/or alkenes. All the various side reactions, including hydrogen exchange and isomerism, can be explained by this type of process.[456] Although this mechanism is satisfactory as far as it goes,[457] there are still questions it does not answer, among them questions[458] involving the nature of the asterisk, the nature of the bonding, and the differences caused by the differing nature of each catalyst.[459]

Heterogeneous catalysis occurs at the surface of the metal catalyst, and there are different types of metal particles on the surface. Maier suggested the presence of **terrace-**, **step-**, and **kink**-type atoms (in Fig. 6.1)[460] on the surface of a heterogeneous catalyst. These terms refer to different atom types, characterized by the number of nearest neighbors,[460] which correspond to different transition-metal fragments, as well as to different coordination states of that metal.[461] A terrace-type atom (A in Fig. 15.1) typically has eight or nine neighbors and corresponds to a geometry shown for the ML_5 particle. The step type of atom (B) usually has seven neighbors and can be correlated with the geometry shown for the ML_4

[456]Smith, G.V.; Burwell Jr., R.L. *J. Am. Chem. Soc.* ***1962***, *84*, 925.

[457]A different mechanism has been proposed by Zaera, F.; Somorjai, G.A. *J. Am. Chem. Soc.* ***1984***, *106*, 2288, but there is evidence against it: Beebe, Jr., T.P.; Yates Jr., J.T. *J. Am. Chem. Soc.* ***1986***, *108*, 663. See also, Thomson, S.J.; Webb, G. *J. Chem. Soc., Chem. Commun.* ***1976***, 526.

[458]For discussions, see Augustine, R.L.; Yaghmaie, F.; Van Peppen, J.F. *J. Org. Chem.* ***1984***, *49*, 1865; Maier, W.F. *Angew. Chem. Int. Ed.* ***1989***, *28*, 135.

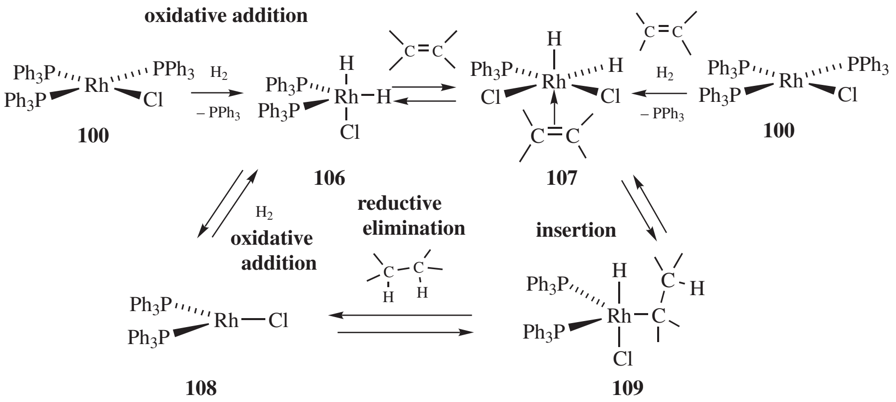
[459]For a study of the detailed structure of Lindlar catalysts (which were shown to consist of seven distinct chemical phases), see Schlögl, R.; Noack, K.; Zbinden, H.; Reller, A. *Helv. Chim. Acta* ***1987***, *70*, 627.

[460]Maier, W.F. *Angew. Chem. Int. Ed.* ***1989***, *28*, 135.

[461]Maier, W.F., in Rylander, P.N.; Greenfield, H.; Augustine, R.L. *Catalysis of Organic Reactions*, Marcel Dekker, NY, ***1988***, pp. 211–231, Cf. p. 220.

particle. Finally, the kink-type atom (C) has six neighbors and corresponds to geometry shown for the ML_3 particle. In general, as the particle size increases, the relative concentration of terrace atoms will increase, whereas small particle size favors the kink type of surface atoms.

The mechanism of homogeneous hydrogenation[462] catalyzed by $RhCl(Ph_3P)_3$ (**100**, Wilkinson's catalyst)[463] involves reaction of the catalyst with hydrogen to form a metal hydride $(PPh_3)_2RhH_2Cl$ (**106**).[464] Replacement of a triphenylphosphine ligand with two toms of hydrogen constitutes an oxidative addition.



After coordination of the alkene to form **107**, transfer of hydrogen to carbon is an insertion process, presumably generating **109**, and a second insertion liberates the hydrogenated compound, and rhodium species **108**, which adds hydrogen by oxidative addition to give **106**. Alternatively, replacement of triphenylphosphine can lead to **107**, with two hydrogen atoms and a η^2-alkene complex. If a mixture of H_2 and D_2 is used, the product contains only dideuterated and non-deuterated compounds; no mono-deuterated products are found, indicating that (unlike the case of heterogeneous catalysis) H_2 or D_2 has been added to one alkene molecule and that no exchange takes place.[330] Although conversion of **107** to the products takes place in two steps,[465] the addition of H_2 to the double bond is syn, although bond rotation in **109** can lead to stereochemical mixtures.

The occurrence of hydrogen exchange and double-bond migration in heterogeneous catalytic hydrogenation means that the hydrogenation does not necessarily

[462]For reviews, see Crabtree, R.H. *Organometallic Chemistry of the Transition Metals*, Wiley, NY, ***1988***, pp. 190–200; Jardine, F.H. in Hartley, F.R. *The Chemistry of the Metal-Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 1049–1071.

[463]Montelatici, S.; van der Ent, A.; Osborn, J.A.; Wilkinson, G. *J. Chem. Soc. A* ***1968***, 1054; Wink, D.; Ford, P.C. *J. Am. Chem. Soc.* ***1985***, *107*, 1794; Koga, N.; Daniel, C.; Han, J.; Fu, X.Y.; Morokuma, K. *J. Am. Chem. Soc.* ***1987***, *109*, 3455.

[464]Tolman, C.A.; Meakin, P.Z.; Lindner, D.L.; Jesson, J.P. *J. Am. Chem. Soc.* ***1976***, *96*, 2762.

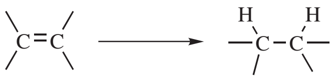
[465]Biellmann, J.F.; Jung, M.J. *J. Am. Chem. Soc.* ***1968***, *90*, 1673; Hussey, A.S.; Takeuchi, Y. *J. Am. Chem. Soc.* ***1969***, *91*, 672; Heathcock, C.H.; Poulter, S.R. *Tetrahedron Lett.* ***1969***, 2755; Smith, G.V.; Shuford, R.J. *Tetrahedron Lett.* ***1970***, 525; Atkinson, J.G.; Luke, M.O. *Can. J. Chem.* ***1970***, *48*, 3580.

take place by straightforward addition of two hydrogen atoms at the site of the original double bond. Consequently, this method is not synthetically useful for adding D_2 to a double or triple bond in a regioselective or stereospecific manner. However, this objective can be achieved (with syn addition) by a homogeneous catalytic hydrogenation, which usually adds D_2 without scrambling[466] or by the use of one of the diimide methods (**15-12**). Deuterium can also be regioselectively added by the hydroboration–reduction procedure previously mentioned.

Reductions of double and triple bonds are found at OS **I**, 101, 311; **II**, 191, 491; **III**, 385, 794; **IV**, 298, 304, 408; **V**, 16, 96, 277; **VI**, 68, 459; **VII**, 226, 287; **VIII**, 420. 609; **IX**, 169, 533.

Catalysts and apparatus for hydrogenation are found at OS **I**, 61, 463; **II**, 142; **III**, 176, 181, 685; **V**, 880; **VI**, 1007.

15-12 Other Reductions of Double and Triple Bonds



Although catalytic hydrogenation is the method most often used, double or triple bonds can be reduced by other reagents, as well. Among these are sodium in ethanol, sodium and *tert*-butyl alcohol in HMPA,[467] lithium and aliphatic amines[468] (see also, **15-13**), zinc and acids, sodium hypophosphate and Pd—C,[469] $(EtO)_3$-$SiHPd(OAc)_2$,[470] triethylsilane Et_3SiH and trifluoroacetic acid[471] or palladium chloride,[472] and hydroxylamine and ethyl acetate.[473] Trialkylsilanes (R_3SiH) in conjunction with an acid will reduce double bonds.[474] Siloxanes (RO_3SiH) and a ruthenium catalyst, followed by treatment with AgF convert alkynes to *trans*-alkenes.[475] Poly(methylhydrosiloxane) was used for reduction of conjugated alkenes using a copper carbene complex.[476] Reduction of alkynes with silanes and a ruthenium catalyst, followed by treatment with CuI and Bu_4NF gave the

[466]Biellmann, J.F.; Liesenfelt, H. *Bull. Soc. Chim. Fr.* ***1966***, 4029; Birch, A.J.; Walker, K.A.M. *Tetrahedron Lett.* ***1966***, 4939, *J. Chem. Soc. C* ***1966***, 1894; Morandi, J.R.; Jensen, H.B. *J. Org. Chem.* ***1969***, *34*, 1889. See, however, Atkinson, J.G.; Luke, M.O. *Can. J. Chem.* ***1970***, *48*, 3580.

[467]Angibeaud, P.; Larchevêque, M.; Normant, H.; Tchoubar, B. *Bull. Soc. Chim. Fr.* ***1968***, 595; Whitesides, G.M.; Ehmann, W.J. *J. Org. Chem.* ***1970***, *35*, 3565.

[468]Benkeser, R.A.; Schroll, G.; Sauve, D.M. *J. Am. Chem. Soc.* ***1955***, *77*, 3378.

[469]Sala, R.; Doria, G.; Passarotti, C. *Tetrahedron Lett.* ***1984***, *25*, 4565.

[470]Tour, J.M.; Pendalwar, S.L. *Tetrahedron Lett.* ***1990***, *31*, 4719.

[471]For a review, see Kursanov, D.N.; Parnes, Z.N.; Loim, N.M. *Synthesis* ***1974***, 633. Also see, Doyle, M.P.; McOsker, C.C. *J. Org. Chem.* ***1978***, *43*, 693. For a monograph, see Kursanov, D.N.; Parnes, Z.N.; Kalinkin, M.I.; Loim, N.M. *Ionic Hydrogenation and Related Reactions*, Harwood Academic Publishers, Chur, Switzerland, ***1985***.

[472]Mirza-Aghayan, M.; Boukherroub, R.; Bolourtchian, M.; Hosseini, M. *Tetrahedron Lett.* ***2003***, *44*, 4579.

[473]Wade, P.A.; Amin, N.V. *Synth. Commun.* ***1982***, *12*, 287.

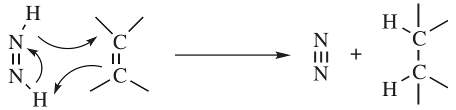
[474]Masuno, M.N.; Molinski, T.F. *Tetrahedron Lett.* ***2001***, *42*, 8263.

[475]Fürstner, A.; Radkowski, K. *Chem. Commun.* ***2002***, 2182.

[476]Jurkauskas, V.; Sakighi, J.P.; Buchwald, S.L. *Org. Lett.* ***2003***, *5*, 2417.

trans- alkene.[477] Samarium iodide in water and a triamine additive led to reduction of alkenes.[478] Similar reduction was reported using $Co_2(CO)_8$ and an excess of water in dimethoxyethane.[479] Reduction of an alkyne to an alkene can be done via an organometallic, by heating the alkyne with indium metal in aqueous ethanol.[480] Alkynes are reduced with palladium acetate and sodium ethoxide. In methanol the product is the alkane, whereas in THF the product is the cis-alkene.[481]

In the above-mentioned reactions with hydrazine and hydroxylamine, the actual reducing species is diimide NH=NH, which is formed from N_2H_4 by the oxidizing agent and from NH_2OH by the ethyl acetate.[482] The rate of this reaction has been studied.[483] Although both the syn and anti forms of diimide are produced, only the syn form reduces the double bond,[484] at least in part by a cyclic mechanism:[485]



The addition is therefore stereospecifically syn[486] and, like catalytic hydrogenation, generally takes place from the less-hindered side of a double bond, although not much discrimination in this respect is observed where the difference in bulk effects is small.[487] Diimide reductions are most successful with symmetrical multiple bonds (C=C, C≡C, N=N) and are not useful for those inherently polar (C≡N, C=N, C=O, etc.). Diimide is not stable enough for isolation at ordinary temperatures, although it has been prepared[488] as a yellow solid at −196°C. *N*-Arylsulfonylhydrazines bearing a phosphonate ester unit converted 1,1-diiodoalkenes ($C{=}CI_2$) to *gem*-diiodides, ($CH{-}CHI_2$).[489]

An indirect method[490] of double-bond reduction involves hydrolysis of boranes (prepared by **15-16**). Trialkylboranes can be hydrolyzed by refluxing with carboxylic

[477]Trost, B.M.; Ball, Z.T.; Jöge, T. *J. Am. Chem. Soc.* ***2002***, *124*, 7922.
[478]Dahlén, A.; Hilmersson, G. *Tetrahedron Lett.* ***2003***, *44*, 2661.
[479]Lee, H.-Y.; An, M. *Tetrahedron Lett.* ***2003***, *44*, 2775.
[480]Ranu, B.C.; Dutta, J.; Guchhait, S.K. *J. Org. Chem.* ***2001***, *66*, 5624.
[481]Wei, L.-L.; Wei, L.-M.; Pan, W.-B.; Leou, S.-P.; Wu, M.-J. *Tetrahedron Lett.* ***2003***, *44*, 1979.
[482]For reviews of hydrogenations with diimide, see Pasto, D.J.; Taylor, R.T. *Org. React.* ***1991***, *40*, 91; Miller, C.E. *J. Chem. Educ.* ***1965***, *42*, 254; House, H.O. *Modern Synthetic Reaction*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 248–256. For reviews of diimides, see Back, R.A. *Rev. Chem. Intermed.* ***1984***, *5*, 293; Hünig, S.; Müller, H.R.; Thier, W. *Angew. Chem. Int. Ed.* ***1965***, *4*, 271.
[483]Nelson, D.J.; Henley, R.L.; Yao, Z.; Smith, T.D. *Tetrahedron Lett.* ***1993***, *34*, 5835.
[484]Aylward, F.; Sawistowska, M.H. *J. Chem. Soc.* ***1964***, 1435.
[485]van Tamelen, E.E.; Dewey, R.S.; Lease, M.F.; Pirkle, W.H. *J. Am. Chem. Soc.* ***1961***, *83*, 4302; Willis, C.; Back, R.A.; Parsons, J.A.; Purdon, J.G. *J. Am. Chem. Soc.* ***1977***, *99*, 4451.
[486]Corey, E.J.; Pasto, D.J.; Mock, W.L. *J. Am. Chem. Soc.* ***1961***, *83*, 2957.
[487]van Tamelen, E.E.; Timmons, R.J. *J. Am. Chem. Soc.* ***1962***, *84*, 1067.
[488]Wiberg, N.; Fischer, G.; Bachhuber, H. *Chem. Ber.* ***1974***, *107*, 1456; *Angew. Chem. Int. Ed.* ***1977***, *16*, 780. See also, Trombetti, A. *Can. J. Phys.* ***1968***, *46*, 1005; Bondybey, V.E.; Nibler, J.W. *J. Chem. Phys.* ***1973***, *58*, 2125; Craig, N.C.; Kliewer, M.A.; Shih, N.C. *J. Am. Chem. Soc.* ***1979***, *101*, 2480.
[489]Cloarec, J.-M.; Charette, A.B. *Org. Lett.* ***2004***, *6*, 4731.
[490]For a review, see Zweifel, G. *Intra-Sci. Chem. Rep.* ***1973***, *7(2)*, 181–189.

acids,[491] while monoalkylboranes, RBH_2, can be hydrolyzed with base.[492] Triple bonds can be similarly reduced, to cis alkenes.[493] Further reduction is also possible. When an alkyne was treated with decaborane and Pd/C in methanol, two equivalents of hydrogen are transferred to give the alkane.[494] Hydrogenation with Ni_2B on borohydride exchange resin (BER) has also been used.[495] Reduction occurs *in situ* when an alkene is treated with $NaBH_4$, $NiCl_2$•6 H_2O with moist alumina.[496] Reduction of alkenes occurs with *tert*-butylamine•borane complex in methanol with 10% Pd/C.[497]

Metallic hydrides, such as lithium aluminum hydride and sodium borohydride, do not in general reduce carbon–carbon double bonds, although this can be done in special cases where the double bond is polar, as in 1,1-diarylethenes[498] and in enamines.[499] Lithium aluminum hydride reduces cyclopropenes with a pendant alcohol in the allylic position to the corresponding cyclopropane.[500]

Triple bonds can also be selectively reduced to double bonds with diisobutylaluminum hydride (Dibal-H),[501] with activated zinc (see **12-38**),[502] with hydrogen and Bi_2B–borohydride exchange resin,[503] or (internal triple bonds only) with alkali metals (Na, Li) in liquid ammonia or a low-molecular-weight amine.[504] Terminal alkynes are not reduced by the Na—NH_3 procedure because they are converted to acetylide ions under these conditions. However, terminal triple bonds can be reduced to double bonds by the addition to the Na—NH_3 solution of $(NH_4)_2SO_4$, which liberates the free ethynyl group.[505] The reaction of a terminal alkyne with

[491]Brown, H.C.; Murray, K.J. *Tetrahedron* ***1986***, *42*, 5497; Kabalka, G.W.; Newton, Jr., R.J.; Jacobus, J. *J. Org. Chem.* ***1979***, *44*, 4185.

[492]Weinheimer, A.J.; Marisco, W.E. *J. Org. Chem.* ***1962***, *27*, 1926.

[493]Brown, H.C.; Zweifel, G. *J. Am. Chem. Soc.* ***1959***, *81*, 1512.

[494]Lee, S.H.; Park, Y.J.; Yoon, C.M. *Tetrahedron Lett.* ***2000***, *41*, 887.

[495]Choi, J.; Yoon, N.M. *Synthesis* ***1996***, 597.

[496]Yakabe, S.; Hirano, M.; Morimoto, T. *Tetrahedron Lett.* ***2000***, *41*, 6795.

[497]Couturier, M.; Andresen, B.M.; Tucker, J.L.; Dubé, P.; Brenek, S.J.; Negri, J.J. *Tetrahedron Lett.* ***2001***, *42*, 2763.

[498]See Granoth, I.; Segall, Y.; Leader, H.; Alkabets, R. *J. Org. Chem.* ***1976***, *41*, 3682.

[499]For a review of the reduction of enamines and indoles with $NaBH_4$ and a carboxylic acid, see Gribble, G.W.; Nutaitis, C.F. *Org. Prep. Proced. Int.* ***1985***, *17*, 317. Enamines can also be reduced by formic acid; see Nilsson, A.; Carlson, R. *Acta Chem. Scand. Sect. B* ***1985***, *39*, 187.

[500]Zohar, E.; Marek, I. *Org. Lett.* ***2004***, *6*, 341.

[501]Wilke, G.; Müller, H. *Chem. Ber.* ***1956***, *89*, 444, *Liebigs Ann. Chem.* ***1960***, *629*, 224; Gensler, W.J.; Bruno, J.J. *J. Org. Chem.* ***1963***, *28*, 1254; Eisch, J.J.; Kaska, W.C. *J. Am. Chem. Soc.* ***1966***, *88*, 2213. For a catalyst with even better selectivity for triple bonds, see Ulan, J.G.; Maier, W.F.; Smith, D.A. *J. Org. Chem.* ***1987***, *52*, 3132.

[502]Aerssens, M.H.P.J.; van der Heiden, R.; Heus, M.; Brandsma, L. *Synth. Commun.* ***1990***, *20*, 3421; Chou, W.; Clark, D.L.; White, J.B. *Tetrahedron Lett.* ***1991***, *32*, 299. See Sakai, M.; Takai, Y.; Mochizuki, H.; Sasaki, K.; Sakakibara, Y. *Bull. Chem. Soc. Jpn.* ***1994***, *67*, 1984 for reduction with a $NiBr_2$–Zn reagent.

[503]Choi, J.; Yoon, N.M. *Tetrahedron Lett.* ***1996***, *37*, 1057.

[504]For a list of methods of reducing triple to double bonds, with syn or anti addition, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 405–410.

[505]Henne, A.L.; Greenlee, K.W. *J. Am. Chem. Soc.* ***1943***, *65*, 2020.

lithium naphthalenide and $NiCl_2$ effectively reduced the alkyne unit (i.e., $PhC{\equiv}CH \rightarrow PhCH_2CH_3$).[506] This reagent is also effect for the reduction of simple alkenes.[507] A mixture of $NaBH_4$ and $BiCl_3$ also reduced certain alkenes[508] and An alkyne unit was reduced to an alkene, in the presence of a phenylthio group elsewhere in the molecule, using $Cp_2Zr(H)Cl$.[509]

Reduction of just one double bond of an allene, to give an alkene, has been accomplished by treatment with Na—NH_3[510] or with Dibal-H,[511] and by hydrogenation with $RhCl(PPh_3)_3$ as catalyst.[512]

When double bonds are reduced by lithium in ammonia or amines, the mechanism is similar to that of the Birch reduction (**15-13**).[513] The reduction with trifluoroacetic acid and Et_3SiH has an ionic mechanism, with H^+ coming in from the acid and H^- from the silane.[290] In accord with this mechanism, the reaction can be applied only to those alkenes, which when protonated can form a tertiary carbocation or one stabilized in some other way, for example, by a OR substitution.[514] It has been shown, by the detection of CIDNP, that reduction of α-methylstyrene by hydridopentacarbonylmanganese(I), $HMn(CO)_5$, involves free-radical addition.[515]

Catalytic hydrogenation of triple bonds and the reaction with Dibal-H usually give the cis-alkene (**15-11**). Most of the other methods of triple-bond reduction lead to the more thermodynamically stable trans alkene. However, this is not the case with the method involving hydrolysis of boranes or with the reductions with activated zinc, hydrazine, or NH_2OSO_3H, which also give the cis products.

The fact that ordinary double bonds are inert toward metallic hydrides is quite useful, since it permits reduction of, say, a carbonyl or nitro group, without disturbing a double bond in the same molecule (see Chapter 19 for a discussion of selectivity in reduction reactions). Sodium in liquid ammonia also does not reduce ordinary double bonds,[516] although it does reduce alkynes, allenes, conjugated dienes,[517] and aromatic rings (**15-13**).

[506]Alonso, F.; Yus, M. *Tetrahedron Lett.* ***1997***, *38*, 149.

[507]Alonso, F.; Yus, M. *Tetrahedron Lett.* ***1996***, *37*, 6925.

[508]Ren, P.-D.; Pan, S.-F.; Dong, T.-W.; Wu, S.-H. *Synth. Commun.* ***1996***, *26*, 763.

[509]Lipshutz, B.H.; Lindsley, C.; Bhandari, A. *Tetrahedron Lett.* ***1994***, *35*, 4669.

[510]Gardner, P.D.; Narayana, M. *J. Org. Chem.* ***1961***, *26*, 3518; Vaidyanathaswamy, R.; Joshi, G.C.; Devaprabhakara, D. *Tetrahedron Lett.* ***1971***, 2075.

[511]Montury, M.; Goré, J. *Tetrahedron Lett.* ***1980***, *21*, 51.

[512]Bhagwat, M.M.; Devaprabhakara, D. *Tetrahedron Lett.* ***1972***, 1391.

[513]For a review of the steric course of this reaction, see Toromanoff, E. *Bull. Soc. Chim. Fr.* ***1987***, 893–901. For a review of this reaction as applied to α,β-unsaturated ketones, see Russell, G.A., in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 2, Wiley, NY, ***1989***, pp. 471–512.

[514]Parnes, Z.N.; Bolestova, G.I.; Kursanov, D.N. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1972***, *21*, 1927.

[515]Sweany, R.L.; Halpern, J. *J. Am. Chem. Soc.* ***1977***, *99*, 8335. See also, Thomas, M.J.; Shackleton, T.A.; Wright, S.C.; Gillis, D.J.; Colpa, J.P.; Baird, M.C. *J. Chem. Soc., Chem. Commun.* ***1986***, 312; Garst, J.F.; Bockman, T.M.; Batlaw, R. *J. Am. Chem. Soc.* ***1986***, *108*, 1689; Bullock, R.M.; Samsel, E.G. *J. Am. Chem. Soc.* ***1987***, *109*, 6542.

[516]There are some exceptions. See, for example, Butler, D.N. *Synth. Commun.* ***1977***, *7*, 441, and references cited therein.

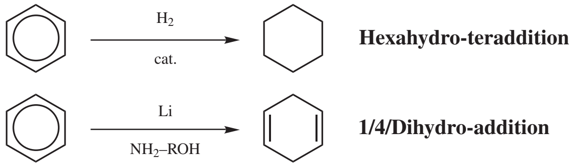
[517]For a review of reductions of α,β-unsaturated carbonyl compounds with metals in liquid NH_3, see Caine, D. *Org. React.* ***1976***, *23*, 1–258.

Another hydrogenation method is called *transfer hydrogenation*.[518] In this method the hydrogen comes from another organic molecule, which is itself oxidized. A transition-metal catalyst, heterogeneous or homogeneous, is frequently employed. Dendritic catalysts have been used for asymmetric transfer hydrogenation.[519] A common reducing agent is cyclohexene, which, when a palladium catalyst is used, is oxidized to benzene, losing 2 mol of hydrogen.

Enantioselective reduction of certain alkenes has also been achieved by reducing with baker's yeast.[520]

Reductions of double and triple bonds are found at OS **III**, 586, 742; **IV**, 136, 302, 887; **V**, 281, 993; **VII**, 524; **80**, 120.

15-13 Hydrogenation of Aromatic Rings



Aromatic rings can be reduced by catalytic hydrogenation,[521] but higher temperatures (100–200°C) are required than for ordinary double bonds.[522] although the reaction is usually carried out with heterogeneous catalysts, homogeneous catalysts have also been used; conditions are much milder with these.[523] Mild conditions are also successful in hydrogenations with phase transfer catalysts.[524] Hydrogenation in ionic liquids is known,[525] and also hydrogenation in supercritical ethane containing water.[526] Many functional groups, such as OH, O^-, COOH, COOR, NH_2, do not interfere with the reaction, but some groups may be preferentially reduced. Among these are CH_2OH groups, which undergo hydrogenolysis to CH_3 (**19-54**). Phenols may be reduced to cyclohexanones, presumably through the enol. Heterocyclic compounds are often reduced. Thus furan gives THF. The

[518]For reviews, see Johnstone, R.A.W.; Wilby, A.H.; Entwistle, I.D. *Chem. Rev.* ***1985***, *85*, 129; Brieger, G.; Nestrick, T.J. *Chem. Rev.* ***1974***, *74*, 567.

[519]Chen, Y.-C.; Wu, T.-F.; Deng, J.-G.; Liu, H.; Cui, X.; Zhu, J.; Kiang, Y.-Z.; Choi, M.C.K.; Chan, A.S.C. *J. Org. Chem.* ***2002***, *67*, 5301.

[520]See, for example, Ferraboschi, P.; Reza-Elahi, S.; Verza, E.; Santaniello, E. *Tetrahedron Asymmetry* ***1999***, *10*, 2639. For reviews of baker's yeast, see Csuk, R.; Glänzer, B.I. *Chem. Rev.* ***1991***, *91*, 49; Servi, S. *Synthesis* ***1990***, 1.

[521]For reviews, see Karakhanov, E.A.; Dedov, A.G.; Loktev, A.S. *Russ. Chem. Rev.* ***1985***, *54*, 171.

[522]For a highly active heterogeneous Rh catalyst, see Timmer, K.; Thewissen, D.H.M.W.; Meinema, H.A.; Bulten, E.J. *Recl. Trav. Chim. Pays-Bas* ***1990***, *109*, 87.

[523]For reviews, see Bennett, M. *CHEMTECH* ***1980***, *10*, 444–446; Muetterties, E.L.; Bleeke, J.R. *Acc. Chem. Res.* ***1979***, *12*, 324. See also, Tsukinoki, T.; Kanda, T.; Liu, G.-B.; Tsuzuki, H.; Tashiro, M. *Tetrahedron Lett.* ***2000***, *41*, 5865.

[524]Januszkiewicz, K.R.; Alper, H. *Organometallics* ***1983***, *2*, 1055.

[525]In bmim BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate: Dyson, P.J.; Ellis, D.J.; Parker, D.G.; Welton, T. *Chem. Commun.* ***1999***, 25.

[526]Bonilla, R.J.; James, B.R.; Jessop, P.G. *Chem. Commun.* ***2000***, 941.

nitrogen-containing ring of quinolines is reduced by hydrogenation using iodine and an iridium catalyst.[527] Catalytic hydrogenation of the five-membered ring in indole derivatives using a chiral rhodium catalyst gave hydroindoles with excellent enantioselectivity.[528]

With benzene rings it is usually impossible to stop the reaction after only one or two bonds have been reduced, since alkenes are more easily reduced than aromatic rings.[529] Thus, 1 equivalent of benzene, treated with 1 equivalent of hydrogen, gives no cyclohexadiene or cyclohexene, but $\frac{1}{3}$ equivalent of cyclohexane and $\frac{2}{3}$ equivalent of recovered benzene. This is not true for all aromatic systems. With anthracene, for example, it is easy to stop after only the 9,10-bond has been reduced (see p. 59). Hydrogenation of phenol derivatives can lead to conjugated cyclohexenones.[530] Hydrogenation of toluene in an ionic liquid using a ruthenium catalyst gave methylcyclohexane.[531]

When aromatic rings are reduced by lithium (or potassium or sodium) in liquid ammonia (such reductions are known as *dissolving metal reductions*), usually in the presence of an alcohol (often ethyl, isopropyl, or *tert*-butyl alcohol), 1,4-addition of hydrogen takes place and nonconjugated cyclohexadienes are produced.[532] This reaction is called the *Birch reduction*.[533] Heterocycles, such as pyrroles,[534] furans,[535] pyridines,[536] and indolones,[537] can be reduced using Birch reduction. Ammonia obtained commercially often has iron salts as impurities that lower the yield in the Birch reduction. Therefore it is often necessary to distill the ammonia. When substituted aromatic compounds are subjected to the Birch reduction, electron-donating groups, such as alkyl or alkoxyl decrease the rate of the reaction and are generally found on the nonreduced positions of the product. For example, anisole gives 1-methoxy-1,4-cyclohexadiene, not 3-methoxy-1,4-cyclohexadiene. On the other hand, electron-withdrawing groups, such as COOH or $CONH_2$,

[527]Wang, W.-B.; Lu, S.-M.; Yang, P.-Y.; Han, X.-W.; Zhou, Y.-G. *J. Am. Chem. Soc.* ***2003***, *125*, 10536.

[528]Kuwano, R.; Kaneda, K.; Ito, T.; Sato, K.; Kurokawa, T.; Ito, Y. *Org. Lett.* ***2004***, *6*, 2213.

[529]For an indirect method of hydrogenating benzene to cyclohexene, see Harman, W.D.; Taube, H. *J. Am. Chem. Soc.* ***1988***, *110*, 7906.

[530]Higashijima, M.; Nishimura, S. *Bull. Chem. Soc. Jpn.* ***1992***, *65*, 824.

[531]In bmim BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate: Boxwell, C.J.; Dyson, P.J.; Ellis, D.J.; Welton, T. *J. Am. Chem. Soc.* ***2002***, *124*, 9334.

[532]For a procedure that converts benzene to pure 1,4-cyclohexadiene, see Brandsma, L.; van Soolingen, J.; Andringa, H. *Synth. Commun.* ***1990***, *20*, 2165. Also see, Weitz, I.S.; Rabinovitz, M. *J. Chem. Soc. Perkin Trans. 1*, ***1993***, 117.

[533]For a monograph, see Akhrem, A.A.; Reshotova, I.G.; Titov, Yu.A. *Birch Reduction of Aromatic Compounds*, Plenum, NY, ***1972***. For reviews, see Birch, A.J. *Pure Appl. Chem.* ***1996***, *68*, 553; Rabideau, P.W. *Tetrahedron* ***1989***, *45*, 1579; Birch, A.J.; Subba Rao, G. *Adv. Org. Chem.* ***1972***, *8*, 1; Kaiser, E.M. *Synthesis* ***1972***, 391; Harvey, R.G. *Synthesis* ***1970***, 161; House, H.O. *Modern Synthetic Reaction*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 145–150, 173–209; Hückel, W. *Fortschr. Chem. Forsch.* ***1966***, *6*, 197; Smith, M., in Augustine, R.L. *Reduction Techniques and Applications in Organic Synthesis*, Marcel Dekker, NY, ***1968***, pp. 95–170.

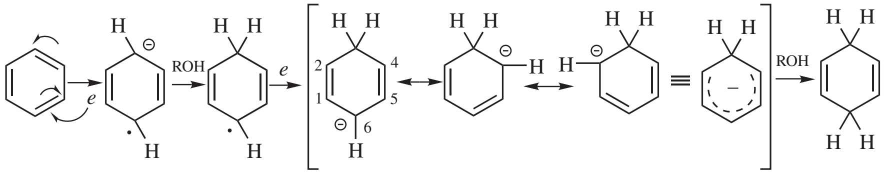
[534]Donohoe, T.J.; House, D. *J. Org. Chem.* ***2002***, *67*, 5015.

[535]Kinoshita, T.; Ichinari, D.; Sinya, J. *J. Heterocyclic Chem.* ***1996***, *33*, 1313.

[536]Donohoe, T.J.; McRiner, A.J.; Helliwell, M.; Sheldrake, P. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 1435.

[537]Guo, Z.; Schultz, A.G. *J. Org. Chem.* ***2001***, *66*, 2154.

increase the reaction rate and are found on the reduced positions of the product.[538] The regioselectivity of the reaction has been examined.[539] The mechanism involves solvated electrons,[540] which are transferred from the metal to the solvent, and hence to the ring:[541]



110 **111**

The sodium becomes oxidized to Na^+ and creates a radical ion (**110**).[542] There is a great deal of evidence from ESR spectra for these species.[543] The radical ion accepts a proton from the alcohol to give a radical, which is reduced to a carbanion by another sodium atom. Finally, **111** accepts another proton. Thus the function of the alcohol is to supply protons, since with most substrates ammonia is not acidic enough for this purpose. In the absence of the alcohol, products arising from dimerization of **110** are frequently obtained. There is evidence[544] at least with some substrates, for example, biphenyl, that the radical ion corresponding to **110** is converted to the carbanion corresponding to **111** by a different pathway, in which the order of the steps is reversed: first a second electron is gained to give a dianion,[542] which then acquires a proton, producing the intermediate corresponding to **111**.

Ordinary alkenes are usually unaffected by Birch-reduction conditions, and double bonds may be present in the molecule if they are not conjugated with the ring. However, phenylated alkenes, internal alkynes (**15-12**),[545] and conjugated alkenes (with C=C or C=O) are reduced under these conditions.

Note that **111** is a resonance hybrid; that is, we can write the two additional canonical forms shown. The question therefore arises: Why does the carbanion pick up a proton at the 6 position to give the 1,4-diene? Why not at the 2 position

[538]These regioselectivities have generally been explained by molecular-orbital considerations regarding the intermediates involved. For example, see Birch, A.J.; Hinde, A.L.; Radom, L. *J. Am. Chem. Soc.* ***1980***, *102*, 3370, 4074, 6430; ***1981***, *103*, 284; Zimmerman, H.E.; Wang, P.A. *J. Am. Chem. Soc.* ***1990***, *112*, 1280. For methods of reversing the regioselectivities, see Epling, G.A.; Florio, E. *Tetrahedron Lett.* ***1986***, *27*, 1469; Rabideau, P.W.; Karrick, G.L. *Tetrahedron Lett.* ***1987***, *28*, 2481.

[539]Zimmerman, H.E.; Wang, P.A. *J. Am. Chem. Soc.* ***1993***, *115*, 2205.

[540]For reviews of solvated electrons and related topics, see Dye, J.L. *Prog. Inorg. Chem.* ***1984***, *32*, 327–441; Alpatova, N.M.; Krishtalik, L.I.; Pleskov, Y.V. *Top. Curr. Chem.* ***1987***, *138*, 149–219.

[541]Birch, A.J.; Nasipuri, D. *Tetrahedron* ***1959***, *6*, 148.

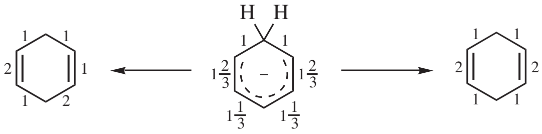
[542]For a review of radical ions and diions generated from aromatic compounds, see Holy, N.L. *Chem. Rev.* ***1974***, *74*, 243.

[543]For example, see Jones, M.T., in Kaiser, E.T.; Kevan, L. *Radical Ions*, Wiley, NY, ***1968***, pp. 245–274; Bowers, K.W. *Adv. Magn. Reson.*, ***1965***, *1*, 317; Carrington, A. *Q. Rev. Chem. Soc.* ***1963***, *17*, 67.

[544]Lindow, D.F.; Cortez, C.N.; Harvey, R.G. *J. Am. Chem. Soc.* ***1972***, *94*, 5406; Rabideau, P.W.; Peters, N.K.; Huser, D.L. *J. Org. Chem.* ***1981***, *46*, 1593.

[545]See Brandsma, L.; Nieuwenhuizen, W.F.; Zwikker, J.W. Mäeorg, U. *Eur. J. Org. Chem.* ***1999***, 775.

to give the 1,3-diene?[546] An answer to this question has been proposed by Hine, who has suggested that this case is an illustration of the operation of the *principle of least motion*.[547] According to this principle, "those elementary reactions will be favored that involve the least change in atomic position and electronic configuration."[547] The principle can be applied to the case at hand in the following manner (simplified): The valence-bond bond orders (p. 32) for the six carbon–carbon bonds (on the assumption that each of the three forms contributes equally) are (going around the ring) $1\frac{2}{3}$, 1, 1, $1\frac{2}{3}$, $1\frac{1}{3}$, and $1\frac{1}{3}$. When the carbanion is converted to the diene, these bond orders change as follows:



It can be seen that the two bonds whose bond order is 1 are unchanged in the two products, but for the other four bonds there is a change. If the 1,4-diene is formed, the change is $\frac{1}{3}+\frac{1}{3}+\frac{1}{3}+\frac{1}{3}$, while formation of the 1,3-diene requires a change of $\frac{1}{3}+\frac{2}{3}+\frac{2}{3}+\frac{1}{3}$. Since a greater change is required to form the 1,3-diene, the principle of least motion predicts formation of the 1,4-diene. This may not be the only factor, because the ^{13}C NMR spectrum of **111** shows that the 6 position has a somewhat greater electron density than the 2 position, which presumably would make the former more attractive to a proton.[548]

Reduction of aromatic rings with lithium[549] or calcium[550] in amines (instead of ammonia: called *Benkeser reduction*) proceeds further and cyclohexenes are obtained. It is thus possible to reduce a benzene ring, by proper choice of reagent, so that one, two, or all three double bonds are reduced.[551] Lithium triethylborohydride ($LiBEt_3H$) has also been used, to reduce pyridine derivatives to piperidine derivatives.[552]

Transition metals and metal compounds can reduce aromatic rings in the proper medium. Indium metal reduces the pyridine ring in quinoline in aqueous ethanol solution[553] as well as the C=C unit in the five-membered ring of indole

[546]For a discussion of this question, see Rabideau, P.W.; Huser, D.L. *J. Org. Chem.* ***1983***, *48*, 4266.

[547]Hine, J. *J. Org. Chem.* ***1966***, *31*, 1236. For a review of this principle, see Hine, J. *Adv. Phys. Org. Chem.* ***1977***, *15*, 1. See also, Tee, O.S. *J. Am. Chem. Soc.* ***1969***, *91*, 7144; Jochum, C.; Gasteiger, J.; Ugi, I. *Angew. Chem. Int. Ed.* ***1980***, *19*, 495.

[548]Bates, R.B.; Brenner, S.; Cole, C.M.; Davidson, E.W.; Forsythe, G.D.; McCombs, D.A.; Roth, A.S. *J. Am. Chem. Soc.* ***1973***, *95*, 926.

[549]Reggel, L.; Friedel, R.A.; Wender, I. *J. Org. Chem.* ***1957***, *22*, 891; Benkeser, R.A.; Agnihotri, R.K.; Burrous, M.L.; Kaiser, E.M.; Mallan, J.M.; Ryan, P.W. *J. Org. Chem.* ***1964***, *29*, 1313; Kwart, H.; Conley, R.A. *J. Org. Chem.* ***1973***, *38*, 2011.

[550]Benkeser, R.A.; Belmonte, F.G.; Kang, J. *J. Org. Chem.* ***1983***, *48*, 2796. See also, Benkeser, R.A.; Laugal, J.A.; Rappa, A. *Tetrahedron Lett.* ***1984***, *25*, 2089.

[551]One, two, or all three double bonds of certain aromatic nitrogen heterocycles can be reduced with metallic hydrides, such as $NaBH_4$ or $LiAlH_4$. For a review, see Keay, J.G. *Adv. Heterocycl. Chem.* ***1986***, *39*, 1.

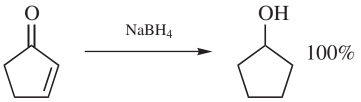
[552]Blough, B.E.; Carroll, F.I. *Tetrahedron Lett.* ***1993***, *34*, 7239.

[553]Moody, C.J.; Pitts, M.R. *Synlett* ***1998***, 1029.

derivatives.[554] Samarium iodide (SmI_2) reduces pyridine in aq. THF[555] and phenol in MeOH/KOH.[556] Ammonium formate and a Pd—C catalyst reduces pyridine *N*-oxide to piperidine in methanol.[557] The nitrogen-containing ring of quinolines is reduced with an iridium catalyst in isopropanol.[558]

OS **I**, 99, 499; **II**, 566; **III**, 278, 742; **IV**, 313, 887, 903; **V**, 398, 400, 467, 591, 670, 743, 989; **VI**, 371, 395, 461, 731, 852, 856, 996; **VII**, 249.

15-14 Reduction Of The Double or Triple Bonds Conjugated to Carbonyls, Cyano, and so on.



In certain cases,[559] metallic hydride reagents may also reduce double bonds in conjugation with C=O bonds, as well as reducing the C=O bonds, as in the conversion of cyclopentenone to cyclopentanol.[560] The reagent $NaBH_4$ has a greater tendency than $LiAlH_4$ to effect this double reduction, although even with $NaBH_4$ the product of single reduction (of the C=O bond) is usually formed in larger amount than the doubly reduced product. Lithium aluminium hydride gives significant double reduction only in cinnamyl systems, for example, with PhCH=CHCOOH.[561] Lithium aluminium hydride also reduces the double bonds of allylic alcohols[562] and $NaBH_4$ in MeOH—THF[563] or $NaCNBH_3$ on a zeolite[564] reduces α,β-unsaturated nitro compounds to nitroalkanes. The C=C unit proximal to the carbonyl in dienyl amides is selectively reduced with $NaBH_4/I_2$.[565] Mixed hydride reducing agents, such as $NaBH_4$—$BiCl_3$,[566] $NaBH_4$—$InCl_3$,[567] borohydride exchange resin (BER)—$CuSO_4$,[568] and Dibal—$Co(acac)_2$[569] have been

[554]Pitts, M.R.; Harrison, J.R.; Moody, C.J. *J. Chem. Soc., Perkin Trans. 1*, **2001**, 955.
[555]Kamochi, Y.; Kudo, T. *Heterocycles* ***1993***, *36*, 2383.
[556]Kamochi, Y.; Kudo, T. *Tetrahedron Lett.* ***1994***, *35*, 4169.
[557]Zacharie, B.; Moreau, N.; Dockendorff, C. *J. Org. Chem.* ***2001***, *66*, 5264.
[558]Fujita, K.; Kitatsuji, C.; Furukawa, S.; Yamaguchi, R. *Tetrahedron Lett.* ***2004***, *45*, 3215.
[559]For discussion, see Meyer, G.R. *J. Chem. Educ.* ***1981***, *58*, 628.
[560]Brown, H.C.; Hess, H.M. *J. Org. Chem.* ***1969***, *34*, 2206. For other methods of reducing both double bonds, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, p. 1096.
[561]Nystrom, R.F.; Brown, W.G. *J. Am. Chem. Soc.* ***1947***, *69*, 2548; ***1948***, *70*, 3738; Gammill, R.B.; Gold, P.M.; Mizsak, S.A. *J. Am. Chem. Soc.* ***1980***, *102*, 3095.
[562]For discussions of the mechanism of this reaction, see Snyder, E.I. *J. Org. Chem.* ***1967***, *32*, 3531; Borden, W.T. *J. Am. Chem. Soc.* ***1968***, *90*, 2197; Blunt, J.W.; Hartshorn, M.P.; Soong, L.T.; Munro, M.H.G. *Aust. J. Chem.* ***1982***, *35*, 2519; Vincens, M.; Fadel, R.; Vidal, M. *Bull. Soc. Chim. Fr.* ***1987***, 462.
[563]Varma, R.S.; Kabalka, G.W. *Synth. Commun.* ***1985***, *15*, 151.
[564]Gupta, A.; Haque, A.; Vankar, Y.D. *Chem. Commun.* ***1996***, 1653.
[565]Das, B.; Kashinatham, A.; Madhusudhan, P. *Tetrahedron Lett.* ***1998***, *39*, 677.
[566]Ren, P.-D.; Pan, S.-F.; Dong, T.-W.; Wu, S.-H. *Synth. Commun.* ***1995***, *25*, 3395.
[567]Ranu, B.C.; Samanta, S. *Tetrahedron Lett.* ***2002***, *43*, 7405.
[568]Sim, T.B.; Yoon, N.M. *Synlett* ***1995***, 726.
[569]Ikeno, T.; Kimura, T.; Ohtsuka, Y.; Yamada, T. *Synlett* ***1999***, 96.

used. The $InCl_3$–$NaBH_4$ reagent was used to covert conjugated diene ketones (C=C–C=C–C=O) selectively to the nonconjugated alkenyl ketone (C=C–CH_2CH_2–C=O).[570]

Note that both $LiAlH_4$ and $NaBH_4$, as well as NaH, reduce ordinary alkenes and alkynes when complexed with transition-metal salts, such as $FeCl_2$ or $CoBr_2$.[571]

Reduction of only the C=C bond of conjugated C=C–C=O and C=C–C≡N systems[572] has been achieved by many reducing agents,[573] a few of which are H_2 and a Rh catalyst,[574] a Ru catalyst,[575] a Pd catalyst,[576] or an Ir catalyst,[577] and Raney nickel alone.[578] Reagents such as SmI_2,[579] and catecholborane[580] are effective. Conjugated ketones react with 2 equivalents of Cp_2TiCl in THF/MeOH to give the corresponding saturated ketone.[581] Indium metal in aqueous ethanol with ammonium chloride converts alkylidene dimalononitriles to the saturated dinitrile.[582] Zinc and acetic acid has been used for the conjugate reduction of dihydropyridin-4-ones.[583] Formic acid with a palladium catalysts reduced conjugated carboxylic acids.[584]

Silanes can be effective for the reduction of the C=C unit in conjugated systems in the presence of copper species.[585] $PhSiH_3$ and a nickel catalyst,[586] CuCl,[587] or a manganese catalyst.[588] In addition, PhR_2SiH with a copper catalyst,[589] and

[570]Ranu, B.C.; Samanta, S. *J. Org. Chem.* ***2003***, *68*, 7130.

[571]See, for example, Ashby, E.C.; Lin, J.J. *J. Org. Chem.* ***1978***, *43*, 2567; Chung, S. *J. Org. Chem.* ***1979***, *44*, 1014. See also, Osby, J.O.; Heinzman, S.W.; Ganem, B. *J. Am. Chem. Soc.* ***1986***, *108*, 67.

[572]For a review of the reduction of α,β-unsaturated carbonyl compounds, see Keinan, E.; Greenspoon, N., in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 2, Wiley, NY, ***1989***, pp. 923–1022. For a review of the stereochemistry of catalytic hydrogenation of α,β-unsaturated ketones, see Augustine, R.L. *Adv. Catal.* ***1976***, *25*, 56.

[573]For a long list of these, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 13–27.

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[579]Cabrera, A.; Alper, H. *Tetrahedron Lett.* ***1992***, *33*, 5007. See also, Guo, H.; Zhang, Y. *Synth. Commun.* ***2000***, *30*, 1879.

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[581]Moisan, L.; Hardouin, C.; Rousseau, B.; Doris, E. *Tetrahedron Lett.* ***2002***, *43*, 2013.

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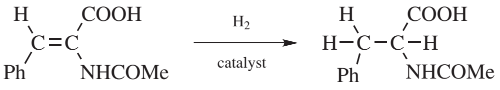
$PhSiH_3$—$Mo(CO)_6$[590] have been used. Triphenylsilane was also used for the asymmetric reduction of nitro alkenes (C=C—NO_2).[591] Poly(methylhydrosiloxane) with a chiral copper catalyst gave conjugate reduction of conjugated esters to give the saturated derivative with high enantioselectivity.[592]

A β-bromo conjugated lactone was reduced to the β-bromolactone with modest enantioselectivity using an excess of Ph_3SiH and a CuCl catalyst with a chiral ligand.[593] A copper complex with a chiral ligand and poly(methylhydrosiloxane) gave reduction of the C=C unit in conjugated carbonyl systems with good enantioselectivity.[594] Tributyltin hydride, in the presence of $MgBr_2$•OEt_2 gave 1,4-reduction of conjugated esters.[595]



(+) or (–)

112 **113**

Optically active catalysts, primarily homogeneous, have been used to achieve enantioselective hydrogenations[596] of many prochiral conjugated substrates.[597] For example,[598] hydrogenation of **112** with a suitable catalyst gives (+) or (−)

[590]Keinan, E.; Perez, D. *J. Org. Chem.* ***1987***, *52*, 2576.

[591]Czekelius, C.; Carreira, E.M. *Org. Lett.* ***2004***, *6*, 4575.

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[593]Hughes, G.; Kimura, M.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2003***, *125*, 11253.

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[595]Hirasawa, S.; Nagano, H.; Kameda, Y. *Tetrahedron Lett.* ***2004***, *45*, 2207.

[596]For a discussion of the mechanism of asymmetric hydrogenation of such systems using a ruthenium catalyst, see Kitamura, M.; Tsukamoto, M.; Bessho, Y.; Yoshimura, M.; Kobs, U.; Widhalm, M.; Noyori, R. *J. Am. Chem. Soc.* ***2002***, *124*, 6649. For a review of the mechanism of stereoselection in rhodium-catalyzed asymmetric hydrogenations, see Gridnev, I.D.; Imamoto, T. *Acc. Chem. Res.* ***2004***, *37*, 633.

[597]For reviews, see, in Morrison, J.D. *Asymmetric Synthesis*, Vol. 5, Academic Press, NY, ***1985***, the reviews by Halpern, J. pp. 41–69, Koenig, K.E. pp. 71–101, Harada, K. pp. 345–383; Ojima, I.; Clos, N.; Bastos, C. *Tetrahedron* ***1989***, *45*, 6901, 6902–6916; Jardine, F.H., in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 751–775; Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, ***1986***, pp. 53–87; Knowles, W.S. *Acc. Chem. Res.* ***1983***, *16*, 106; Brunner, H. *Angew. Chem. Int. Ed.* ***1983***, *22*, 897; Klabunovskii, E.I. *Russ. Chem. Rev.* ***1982***, *51*, 630; Čaplar, V.; Comisso, G.;Šunjić, V. *Synthesis* ***1981***, 85; Morrison, J.D.; Masler, W.F.; Neuberg, M.K. *Adv. Catal.* ***1976***, *25*, 81; Kagan, H.B. *Pure Appl. Chem.* ***1975***, *43*, 401; Bogdanović, B. *Angew. Chem. Int. Ed.* ***1973***, *12*, 954. See also, Brewster, J.H. *Top. Stereochem.* ***1967***, *2*, 1, *J. Am. Chem. Soc.* ***1959***, *81*, 5475, 5483, 5493; Davis, D.D.; Jensen, F.R. *J. Org. Chem.* ***1970***, *35*, 3410; Jullien, F.R.; Requin, F.; Stahl-Larivière, H. *Nouv. J. Chim.* ***1979***, *3*, 91; Sathyanarayana, B.K.; Stevens, E.S. *J. Org. Chem.* ***1987***, *52*, 3170; Wroblewski, A.E.; Applequist, J.; Takaya, A.; Honzatko, R.; Kim, S.; Jacobson, R.A.; Reitsma, B.H.; Yeung, E.S.; Verkade, J.G. *J. Am. Chem. Soc.* ***1988***, *110*, 4144; Knowles, W.S. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1999.

[598]For some other recent examples, see Hayashi, T.; Kawamura, N.; Ito, Y. *Tetrahedron Lett.* ***1988***, *29*, 5969; Muramatsu, H.; Kawano, H.; Ishii, Y.; Saburi, M.; Uchida, Y. *J. Chem. Soc., Chem. Commun.* ***1989***, 769; Amrani, Y.; Lecomte, L.; Sinou, D.; Bakos, J.; Toth, I.; Heil, B. *Organometallics* ***1989***, *8*, 542; Yamamoto, K.; Ikeda, K.; Lin, L.K. *J. Organomet. Chem.* ***1989***, *370*, 319; Waymouth, R.; Pino, P. *J. Am. Chem. Soc.* ***1990***, *112*, 4911; Ohta, T.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* ***1990***, *31*, 7189; Ashby, M.T.; Halpern, J. *J. Am. Chem. Soc.* ***1991***, *113*, 589; Heiser, B.; Broger, E.A.; Crameri, Y. *Tetrahedron: Asymmetry* ***1991***, *2*, 51; Burk, M.J. *J. Am. Chem. Soc.* ***1991***, *113*, 8518.

113 (depending on which enantiomer of the catalyst is used) with an enantiomeric excess as high as 96%.[599] Prochiral substrates that give such high optical yields generally contain functional groups, such as a carbonyl group,[600] amide groups, cyano groups, or combinations of such groups as in **112**.[601] The catalyst in such cases[602] is usually a ruthenium[603] or rhodium complex with chiral phosphine ligands.[604] Iridium complexes have been used with excellent enantioselectivity.[605] Good asymmetric induction[606] has been achieved using chiral rhodium complexes with other chiral additives.[607] The role of solvent has been examined.[608] A pressure dependent enantioselective hydrogenation has been reported.[609] There are many examples for the reduction of alkylidene amino acids, amino esters or amido acids or esters that vary the catalyst and/or the chiral ligand.[610] Asymmetric catalytic hydrogenation has been reported for conjugated carboxylic acids[611] and conjugated ketones.[612] A ruthenium catalyst with a polymer supported chiral ligand has also

[599]Koenig, K.E., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 5, Academic Press, NY, ***1985***, p. 74.

[600]Reetz, M.T.; Mehler, G. *Angew. Chem. Int. Ed.* ***2000***, *39*, 3889.

[601]For tables of substrates that have been enantioselectively hydrogenated, see Koenig, K.E., in Morrison, J.D. *Asymmetric Synthesis* Vol. 5, Academic Press, NY, ***1985***, pp. 83–101.

[602]For a list of these, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 8–12. For reviews of optically active nickel catalysts, see Izumi, Y. *Adv. Catal.* ***1983***, *32*, 215; *Angew. Chem. Int. Ed.* ***1971***, *10*, 871. For a review of the synthesis of some of these phosphines, see Mortreux, A.; Petit, F.; Buono, G.; Peiffer, G. *Bull. Soc. Chim. Fr.* ***1987***, 631.

[603]Wu, H.-P.; Hoge, G. *Org. Lett.* ***2004***, *6*, 3645; Tang, W.; Wu, S.; Zhang, X. *J. Am. Chem. Soc.* ***2003***, *125*, 9570.

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[608]Maki, S.; Harada, Y.; Matsui, R.; Okawa, M.; Hirano, T.; Niwa, H.; Koizumi, M.; Nishiki, Y.; Furuta, T.; Inoue, H.; Iwakura, C. *Tetrahedron Lett.* ***2001***, *42*, 8323; Heller, D.; Drexler, H.-J.; Spannenberg, A.; Heller, B.; You, J.; Baumann, W. *Angew. Chem. Int. Ed.* ***2002***, *41*, 777.

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[610]Rhodium catalyst with a chiral bis(phosphine): Li. W.; Zhang, Z.; Xiao, D.; Zhang, X. *Tetrahedron Lett.* ***1999***, *40*, 6701. New chiral phosphines: Ohashi, A.; Imamoto, T. *Org. Lett.* ***2001***, *3*, 373.

[611]Uemura, T.; Zhang, X.; Matsumura, K.; Sayo, N.; Kumobayashi, H.; Ohta, T.; Nozaki, K.; Takaya, H. *J. Org. Chem.* ***1996***, *61*, 5510; Suárez, A.; Pizzano, A. *Tetrahedron Asymmetry* ***2001***, *12*, 2501. See, Okano, T.; Kaji, M.; Isotani, S.; Kiji, J. *Tetrahedron Lett.* ***1992***, *33*, 5547 for the influence of water on the regioselectivity of this reduction.

[612]Yamaguchi, M.; Nitta, A.; Reddy, R.S.; Hirama, M. *Synlett* ***1997***, 117.

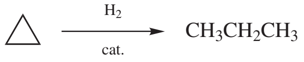
been used for conjugated acids.[613] Asymmetric hydrogenation of conjugated carboxylic acids in an ionic liquid is known using a chiral ruthenium complex[614] Enamino esters have been hydrogenated with high enantioselectivity using chiral rhodium catalysts.[615]

See **19-36** for methods of reducing C=O bonds in the presence of conjugated C=C bonds.

The C=C unit of conjugated aldehydes has been reduced using $AlMe_3$ with a catalytic amount of CuBr[616] and with ammonium formate/Pd–C.[617] Polymer-supported formate has been used for the 1,4-reduction of conjugated ketones[618] and conjugated acids using a rhodium catalyst and microwave irradiation.[619] Selective reduction of the C=C unit in conjugated ketones was accomplished with $Na_2S_2O_4$ in aqueous dioxane, and nonconjugated alkenes were not reduced.[620] Isopropanol and an iridium catalyst gives conjugate reduction of conjugated ketones.[621] Conjugate hydrostannation by an iodotin hydride ate complex, followed by hydrolysis converts unsaturated esters to saturated esters.[622] The reaction of conjugated ketones with aluminum chlorides, followed by treatment with water generates the saturated ketone.[623]

Baker's yeast reduces conjugated nitro compounds to nitroalkanes[624] and also the C=C unit of conjugated ketones.[625] Other enzymatic reductions are possible. A reductase from *Nicotiana tabacum* reduced a conjugated ketone to the saturated ketone, with excellent enantioselectivity.[626] Enzyme YNAR-I and NADP-H reduces conjugated nitro compounds to nitroalkanes.[627]

15-15 Reductive Cleavage of Cyclopropanes



[613]Fan, Q.H.; Deng, G.-J.; Lin, C.-C.; Chan, A.S.C. *Tetrahedron Asymmetry* ***2001***, *12*, 1241.

[614]In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Brown, R.A.; Pollet, P.; McKoon, E.; Eckert, C.A.; Liotta, C.L.; Jessop, P.G. *J. Am. Chem. Soc.* ***2001***, *123*, 1254.

[615]Hsiao, Y.; Rivera, N.R.; Rosner, T.; Krska, S.W.; Njolito, E.; Wang, F.; Sun, Y.; Armstrong III, J.D.; Grabowski, E.J.J.; Tillyer, R.D.; Spindler, F.; Malan, C. *J. Am. Chem. Soc.* ***2004***, *126*, 9918.

[616]Kabbara, J.; Flemming, S.; Nickisch, K.; Neh, H.; Westermann, J. *Synlett* ***1994***, 679.

[617]Ranu, B.C.; Sarkar, A. *Tetrahedron Lett.* ***1994***, *35*, 8649.

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[620]Dhillon, R.S.; Singh, R.P.; Kaur, D. *Tetrahedron Lett.* ***1995***, *36*, 1107.

[621]Sakaguchi, S.; Yamaga, T.; Ishii, Y. *J. Org. Chem.* ***2001***, *66*, 4710.

[622]Shibata, I.; Suwa, T.; Ryu, K.; Baba, A. *J. Org. Chem.* ***2001***, *66*, 8690.

[623]Koltunov, K.Yu.; Repinskaya, I.B.; Borodkin, G.I. *Russ. J. Org. Chem.* ***2001***, *37*, 1534.

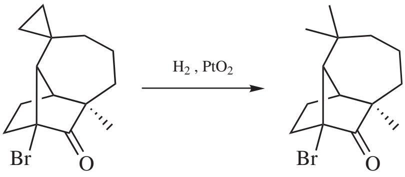
[624]Bak, R.R.; McAnda, A.F.; Smallridge, A.J.; Trewhella, M.A. *Aust. J. Chem.* ***1996***, *49*, 1257; Takeshita, M.; Yoshida, S.; Kohno, Y. *Heterocycles* ***1994***, *37*, 553; Kawai, Y.; Inaba,Y.; Tokitoh, N. *Tetrahedron Asymmetry* ***2001***, *12*, 309.

[625]Kawai, Y.; Saitou, K.; Hida, K.; Ohno, A. *Tetrahedron Asymmetry* ***1995***, *6*, 2143; Filho, E.P.S.; Rodrigues, J.A.R.; Moran, P.J.S. *Tetrahedron Asymmetry* ***2001***, *12*, 847; Kawai, Y.; Hayashi, M.; Tokitoh, N. *Tetrahedron Asymmetry* ***2001***, *12*, 3007.

[626]Shimoda, K.; Kubota, N.; Hamada, H. *Tetrahedron Asymmetry* ***2004***, *15*, 2443; Hirata, T.; Shimoda, K.; Gondai, T. *Chem. Lett.* ***2000***, 850.

[627]Kawai, Y.; Inaba, Y.; Hayashi, M.; Tokitoh, N. *Tetrahedron Lett.* ***2001***, *42*, 3367.

Cyclopropanes can be cleaved by catalytic hydrogenolysis.[628] Among the catalysts used have been Ni, Pd, Rh,[629] and Pt. The reaction can often be run under mild conditions.[630] Certain cyclopropane rings, especially cyclopropyl ketones and aryl-substituted cyclopropanes,[631] can be reductively cleaved by an alkali metal (generally Na or Li) in liquid ammonia.[632] Similar reduction has been accomplished photochemically in the presence of $LiClO_4$.[633] This reaction is an excellent way to introduce a *gem*-dimethyl unit into a molecule. Hydrogenation of the cyclopropane ring in **114**, for example, gave the *gem*-dimethyl unit in **115** using PtO_2 (Adam's catalyst).[634]



114 **115**

F. A Metal on the Other Side

15-16 Hydroboration

When alkenes are treated with borane[635] in ether solvents, BH_3 adds across the double bond.[636] Borane cannot be prepared as a stable pure compound[637] (it dimerizes to diborane, B_2H_6), but it is commercially available in the form of

[628]For reviews, see Charton, M., in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, ***1970***, pp. 588–592; Newham, J. *Chem. Rev.* ***1963***, *63*, 123; Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals*, *Academic Press, NY*, ***1967***, pp. 469–474.

[629]Bart, S.C.; Chirik, P.J. *J. Am. Chem. Soc.* ***2003***, *125*, 886.

[630]See, for example, Woodworth, C.W.; Buss, V.; Schleyer, P.v.R. *Chem. Commun.* ***1968***, 569.

[631]See, for example, Walborsky, H.M.; Aronoff, M.S.; Schulman, M.F. *J. Org. Chem.* ***1970***, *36*, 1036.

[632]For a review, see Staley, S.W. *Sel. Org. Transform.* ***1972***, *2*, 309.

[633]Cossy, J.; Furet, N. *Tetrahedron Lett.* ***1993***, *34*, 8107.

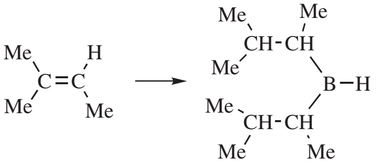
[634]Karimi, S.; Tavares, P. *J. Nat. Prod.* ***2003***, *66*, 520.

[635]For a review of this reagent, see Lane, C.F., in Pizey, J.S. *Synthetic Reagents*, Vol. 3, Wiley, NY, ***1977***, pp. 1–191.

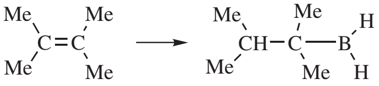
[636]For books on this reaction and its many applications, see Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***; Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, ***1972***, *Organic Syntheses Via Boranes, Wiley*, NY, ***1975***; Cragg, G.M.L. *Organoboranes in Organic Synthesis*, Marcel Dekker, NY, ***1973***. For reviews, see Matteson, D.S., in Hartley, F.R. *The Chemistry of the Metal-Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 307–409, 315–337; Smith, K. *Chem. Ind. (London)* ***1987***, 603; Brown, H.C.; Vara Prasad, J.V.N. *Heterocycles* ***1987***, *25*, 641; Suzuki, A.; Dhillon, R.S. *Top. Curr. Chem.* ***1986***, *130*, 23.

[637]Fehlner, T.P. *J. Am. Chem. Soc.* ***1971***, *93*, 6366.

'ate' complexes with THF, Me_2S,[638] phosphines, or tertiary amines. The alkenes can be treated with a solution of one of these complexes ($THF—BH_3$ reacts at 0°C and is the most convenient to use; $R_3N—BH_3$ generally require temperatures of ~100°C; however, the latter can be prepared as air-stable liquids or solids, while the former can only be used as relatively dilute solutions in THF and are decomposed by moisture in air) or with a mixture of $NaBH_4$ and BF_3 etherate, which generates borane *in situ*.[639] With relatively unhindered alkenes, the process cannot be stopped with the addition of one molecule of BH_3 because the resulting RBH_2 adds to another molecule of alkene to give R_2BH, which in turn adds to a third alkene molecule, so that the isolated product is a trialkylborane R_3B. The reaction can be performed on alkenes with one to four substituents, including cyclic alkenes, but when the alkene is moderately hindered, the product *is* the dialkylborane R_2BH or even the monalkylborane RBH_2.[640] For example, **116** (*disiamylborane*) and **117** (*thexylborane*)[641] have been prepared in this manner. Monoalkylboranes RBH_2 (which can be prepared from hindered alkenes, as above) and dialkylboranes R_2BH also add to alkenes, to give the mixed trialkylboranes RR'_2 B and $R_2R'B$, respectively. Surprisingly, when methylborane $MeBH_2$,[642] which is not a bulky molecule, adds to alkenes in the solvent THF, the reaction can be stopped with one addition to give the dialkylboranes RMeBH.[643] Reaction of this with a second alkene produces the trialkylborane RR'MeB.[644] Other monoalkylboranes, *i*$PrBH_2$, *n*-$BuBH_2$, *s*-$BuBH_2$, and *t*-$BuBH_2$, behave similarly with internal alkenes, but not with alkenes of the type $RCH{=}CH_2$.[645]



Disiamylborane, **116**



Thexylborane, **117**

[638]For a review of BH_3•SMe_2, see Hutchins, R.O.; Cistone, F. *Org. Prep. Proced. Int.* ***1981***, *13*, 225. See Cadot, C.; Dalko, P.I.; Cossy, J. *Tetrahedron Lett.* ***2001***, *42*, 1661.

[639]For a list of hydroborating reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1005–1009.

[640]Unless coordinated with a strong Lewis base such as a tertiary amine, mono and dialkylboranes actually exist as dimers, for example, $R_2B\overset{H}{\underset{H}{\cdots}}BR_2$ Brown, H.C.; Klender, G.J. *Inorg. Chem.* ***1962***, *1*, 204.

[641]For a review of the chemistry of thexylborane, see Negishi, E.; Brown, H.C. *Synthesis* ***1974***, 77.

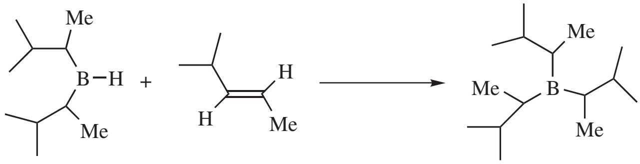
[642]Prepared from lithium methylborohydride and HCl: Brown, H.C.; Cole, T.E.; Srebnik, M.; Kim, K. *J. Org. Chem.* ***1986***, *51*, 4925.

[643]Srebnik, M.; Cole, T.E.; Brown, H.C. *J. Org. Chem.* ***1990***, *55*, 5051.

[644]For a method of synthesis of RR^1R^2B, see Kulkarni, S.U.; Basavaiah, D.; Zaidlewicz, M.; Brown, H.C. *Organometallics* ***1982***, *1*, 212.

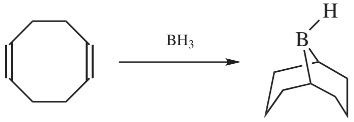
[645]Srebnik, M.; Cole, T.E.; Ramachandran, P.V.; Brown, H.C. *J. Org. Chem.* ***1989***, *54*, 6085.

In all cases, the boron goes to the side of the double bond that has more hydrogens, whether the substituents are aryl or alkyl.[646] This actually follows Markovnikov's rule, since boron is more positive than hydrogen. However, the regioselectivity is caused mostly by steric factors, although electronic factors also play a part. Studies of the effect of ring substituents on rates and on the direction of attack in hydroboration of substituted styrenes showed that the reaction with boron and the alkene has electrophilic character.[647] When both sides of the double bond are monosubstituted or both disubstituted, about equal amounts of each isomer are obtained. However, it is possible in such cases to make the addition regioselective by the use of a large borane molecule. For example, treatment of *i*PrCH=CHMe with borane gave 57% of product with boron on the methyl-bearing carbon and 43% of the other, while treatment with **116** gave 95% **118** and only 5% of the other isomer.[648]



116 **118**

Another reagent with high regioselectivity is 9-borabicyclo[3.3.1]nonane (9-BBN), which is prepared by hydroboration of 1,5-cyclooctadiene,[649] and has the advantage that it is stable in air. Borane is quite unselective and attacks all sorts of double bonds. Disiamylborane, 9-BBN, and similar molecules are far more selective and preferentially attack less-hindered bonds, so it is often possible to hydroborate one double bond in a molecule and leave others unaffected or to hydroborate one alkene in the presence of a less reactive alkene.[650] For example, 1-pentene can be removed from a mixture of 1- and 2-pentenes, and a cis alkene can be selectively hydroborated in a mixture of the cis and trans isomers.



9-BBN

[646]For a thorough discussion of the regioselectivity with various types of substrate and hydroborating agents, see Cragg, G.M.L.*Organoboranes in Organic Synthesis* Marcel Dekker, NY, ***1973***, pp.63–84, 137–197. See also, Brown, H.C.; Vara Prasad, J.V.N.; Zee, S. *J. Org. Chem.* ***1986***, *51*, 439.

[647]Brown, H.C.; Sharp, R.L. *J. Am. Chem. Soc.* ***1966***, *88*, 5851; Klein, J.; Dunkelblum, E.; Wolff, M.A. *J. Organomet. Chem.* ***1967***, *7*, 377. See also, Marshall, P.A.; Prager, R.H. *Aust. J. Chem.* ***1979***, *32*, 1251. For a study of hyperconjugation effects in substituted methylboranes, see Mo, Y.; Jiao, H. Schleyer, P.v.R. *J. Org. Chem.* ***2004***, *69*, 3493.

[648]Brown, H.C.; Zweifel, G. *J. Am. Chem. Soc.* ***1961***, *83*, 1241.

[649]See Knights, E.F.; Brown, H.C. *J. Am. Chem. Soc.* ***1968***, *90*, 5280, 5281; Brown, H.C.; Chen, J.C. *J. Org. Chem.* ***1981***, *46*, 3978; Soderquist, J.A.; Brown, H.C. *J. Org. Chem.* ***1981***, *46*, 4599.

[650]Brown, H.C.; Moerikofer, A.W. *J. Am. Chem. Soc.* ***1963***, *85*, 2063; Zweifel, G.; Brown, H.C. *J. Am. Chem. Soc.* ***1963***, *85*, 2066; Zweifel, G.; Ayyangar, N.R.; Brown, H.C. *J. Am. Chem. Soc.* ***1963***, *85*, 2072; Brown, H.C.; Sharp, R.L. *J. Am. Chem. Soc.* ***1966***, *88*, 5851; Klein, J.; Dunkelblum, E.; Wolff, M.A. *J. Organomet. Chem.* ***1967***, *7*, 377.

For most substrates, the addition in hydroboration is stereospecific and syn, with attack taking place from the less-hindered side.[651] Note that organoboranes can be analyzed using ^{11}B nmr.[652] The mechanism[653] may be a cyclic four-center one:[654]

When the substrate is an allylic alcohol or amine, the addition is generally anti,[655] although the stereoselectivity can be changed to syn by the use of catecholborane and the rhodium complexes mentioned above.[656] Because the mechanism is different, use of this procedure can result in a change in regioselectivity as well, for example, styrene $PhCH{=}CH_2$ gave $PhCH(OH)CH_3$.[657]

Monochloroborane[658] BH_2Cl coordinated with dimethyl sulfide shows greater regioselectivity than BH_3 for terminal alkenes or those of the form $R_2C{=}CHR$, and the hydroboration product is a dialkylchloroborane R_2BCl).[659] For example, 1-hexene gave 94% of the anti-Markovnikov product (the boron is on the less substituted carbon) with BH_3—THF, but 99.2% with BH_2Cl—SMe_2. Treatment of alkenes with dichloroboranedimethyl sulfide $BHCl_2$—SMe_2 in the presence of BF_3[660] or with BCl_3 and Me_3SiH[661] gives alkyldichloroboranes $RBCl_2$. Extensions of this basic approach are possible with dihalo alkylboranes. The reaction of an alkene with allyl dibromoborane, incorporated an allyl group and the born on adjacent carbons.[662]

[651]Brown, H.C.; Zweifel, G. *J. Am. Chem. Soc.* ***1961***, *83*, 2544; Bergbreiter, D.E.; Rainville, D.P. *J. Org. Chem.* ***1976***, *41*, 3031; Kabalka, G.W.; Newton, Jr., R.J.; Jacobus, J. *J. Org. Chem.* ***1978***, *43*, 1567.

[652]Medina, J.R.; Cruz, G.; Cabrera, C.R.; Soderquist, J.A. *J. Org. Chem.* ***2003***, *68*, 4631.

[653]For kinetic studies, see Vishwakarma. L.C.; Fry, A. *J. Org. Chem.* ***1980***, *45*, 5306; Brown, H.C.; Chandrasekharan, J.; Wang, K.K. *J. Org. Chem.* ***1983***, *48*, 2901; *Pure Appl. Chem.* ***1983***, *55*, 1387–1414; Nelson, D.J.; Cooper, P.J. *Tetrahedron Lett.* ***1986***, *27*, 4693; Brown, H.C.; Chandrasekharan, J. *J. Org. Chem.* ***1988***, *53*, 4811.

[654]Brown, H.C.; Zweifel, G. *J. Am. Chem. Soc.* ***1959***, *81*, 247; Pasto, D.J.; Lepeska, B.; Balasubramaniyan, V. *J. Am. Chem. Soc.* ***1972***, *94*, 6090; Pasto, D.J.; Lepeska, B.; Cheng, T. *J. Am. Chem. Soc.* ***1972***, *94*, 6083; Narayana, C.; Periasamy, M. *J. Chem. Soc., Chem. Commun.* ***1987***, 1857. See, however, Jones, P.R. *J. Org. Chem.* ***1972***, *37*, 1886.

[655]See Still, W.C.; Barrish, J.C. *J. Am. Chem. Soc.* ***1983***, *105*, 2487.

[656]See Evans, D.A.; Fu, G.C.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***1988***, *110*, 6917; Burgess, K.; Cassidy, J.; Ohlmeyer, M.J. *J. Org. Chem.* ***1991***, *56*, 1020; Burgess, K.; Ohlmeyer, M.J. *J. Org. Chem.* ***1991***, *56*, 1027.

[657]Hayashi, T.; Matsumoto, Y.; Ito, Y. *J. Am. Chem. Soc.* ***1989***, *111*, 3426; Zhang, J.; Lou, B.; Guo, G.; Dai, L. *J. Org. Chem.* ***1991***, *56*, 1670.

[658]For a review of haloboranes, see Brown, H.C.; Kulkarni, S.U. *J. Organomet. Chem.* ***1982***, *239*, 23.

[659]Brown, H.C.; Ravindran, N.; Kulkarni, S.U. *J. Org. Chem.* ***1979***, *44*, 2417.

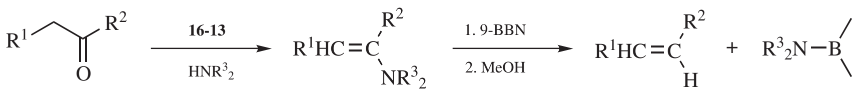
[660]Brown, H.C.; Racherla, U.S. *J. Org. Chem.* ***1986***, *51*, 895.

[661]Soundararajan, R.; Matteson, D.S. *J. Org. Chem.* ***1990***, *55*, 2274.

[662]Frantz, D.E.; Singleton, D.A. *Org. Lett.* ***1999***, *1*, 485.

An important use of the hydroboration reaction is oxidation of an organoborane to alcohols with hydrogen peroxide and NaOH (**12-27**). Organoboranes have been oxidized with Oxone®[663] and methanol/triethylamine/molecular oxygen.[664] The synthetic result is an indirect way of adding H_2O across a double bond in an anti-Markovnikov manner. However, boranes undergo many other reactions as well. Among other things, they react with α-halo carbonyl compounds to give alkylated products (**10-73**), with α,β-unsaturated carbonyl compounds to give Michael-type addition of R and H (**15-27**), with CO to give alcohols and ketones (**18-23–18-24**); they can be reduced with carboxylic acids, providing an indirect method for reduction of double bonds (**15-11**), or they can be oxidized with chromic acid or pyridinium chlorochromate to give ketones[665] or aldehydes (from terminal alkenes),[666] dimerized with silver nitrate and NaOH (**14-26**), isomerized (**18-11**), or converted to amines (**12-32**), halides (**12-31**), or carboxylic acids.[667] They are thus useful intermediates for the preparation of a wide variety of compounds. Intramolecular hydroboration reaction are possible.[668]

Such functional groups as OR, OH, NH_2, SMe, halogen, and COOR may be present in the molecule,[669] but not groups that are reducible by borane. Hydroboration of enamines with 9-BBN provides an indirect method for reducing an aldehyde or ketone to an alkene, e.g.[670]



Enamines can also be converted to amino alcohols via hydroboration.[671] Allene–boranes react with aldehydes to give alkyne–alcohols.[672]

Use of the reagent diisopinocampheylborane **119** (prepared by treating optically active α-pinene with BH_3) results in enantioselective hydroboration–oxidation.[673] Since both (+) and (−) α-pinene are readily available, both enantiomers

[663]Ripin, D.H.B.; Cai, W.; Brenek, S.J. *Tetrahedron Lett.* ***2000***, *41*, 5817.

[664]Cadot, C.; Dalko, P.I.; Cossy, J.; Ollivier, C.; Chuard, R.; Renaud, P. *J. Org. Chem.* ***2002***, *67*, 7193.

[665]Brown, H.C.; Garg, C.P. *J. Am. Chem. Soc.* ***1961***, *83*, 2951; *Tetrahedron* ***1986***, *42*, 5511; Rao, V.V.R.; Devaprabhakara, D.; Chandrasekaran, S. *J. Organomet. Chem.* ***1978***, 162, C9; Parish, E.J.; Parish, S.; Honda, H. *Synth. Commun.* ***1990***, *20*, 3265.

[666]Brown, H.C.; Kulkarni, S.U.; Rao, C.G.; Patil, V.D. *Tetrahedron* ***1986***, *42*, 5515.

[667]Soderquist, J.A.; Martinez, J.; Oyola, Y.; Kock, I. *Tetrahedron Lett.* ***2004***, *45*, 5541.

[668]See Shapland, P.; Vedejs, E. *J. Org. Chem.* ***2004***, *69*, 4094.

[669]See, for example, Brown, H.C.; Unni, M.K. *J. Am. Chem. Soc.* ***1968***, *90*, 2902; Brown, H.C.; Gallivan, Jr., R.M. *J. Am. Chem. Soc.* ***1968***, *90*, 2906; Brown, H.C.; Sharp, R.L. *J. Am. Chem. Soc.* ***1968***, *90*, 2915.

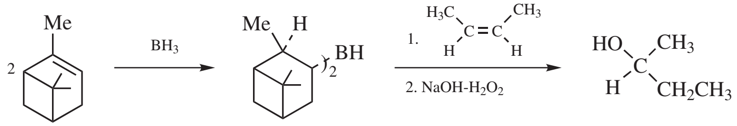
[670]Singaram, B.; Rangaishenvi, M.V.; Brown, H.C.; Goralski, C.T.; Hasha, D.L. *J. Org. Chem.* ***1991***, *56*, 1543.

[671]Goralski, C.T.; Hasha, D.L.; Nicholson, L.W.; Singaram, B. *Tetrahedron Lett.* ***1994***, *35*, 5165.

[672]Brown, H.C.; Khire, U.R.; Racherla, U.S. *Tetrahedron Lett.* ***1993***, *34*, 15.

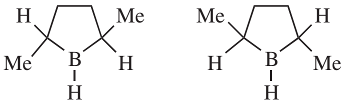
[673]Brown, H.C.; Vara Prasad, J.V.N. *J. Am. Chem. Soc.* ***1986***, *108*, 2049.

can be prepared. Alcohols with moderate-to-excellent enantioselectivities have been



α-Pinene Optically active 119 Optically active

obtained in this way.[674] However, **119** does not give good results with even moderately hindered alkenes; a better reagent for these compounds is isopinocampheylborane[675] although optical yields are lower. Limonylborane,[676] 2- and 4-dicaranylboranes,[677] a myrtanylborane,[678] and dilongifolylborane[679] have also been used. Other new asymmetric boranes have also been developed. The chiral cyclic boranes *trans*-2,15-dimethylborolanes (**51** and **52**) also add enantioselectively to alkenes (except



(*R*, *R*) **120** **121** (*S*, *S*)

alkenes of the form RR′C=CH$_2$) to give boranes of high optical purity.[680] When chiral boranes are added to trisubstituted alkenes of the form RR′C=CHR″, two new chiral centers are created, and, with **120** or **121**, only one of the four possible diastereomers is predominantly produced, in yields $> 90\%$.[680] This has been called *double-asymmetric synthesis*.[681] An alternative asymmetric synthesis of alcohols involves the reaction of catechol borane with an alkene in the presence

[674]For reviews of enantioselective syntheses with organoboranes, see Brown, H.C.; Singaram, B. *Acc. Chem. Res.* ***1988***, *21*, 287; Srebnik, M.; Ramachandran, P.V. *Aldrichimica Acta* ***1987***, *20*, 9; Brown, H.C.; Jadhav, P.K.; Singaram, B. *Mod. Synth. Methods*, ***1986***, *4*, 307; Matteson, D.S. *Synthesis* ***1986***, 973; Brown, H.C.; Jadhav, P.K., in Morrison, J.D. *Asymmetric Synthesis* Vol. 2, Academic Press, NY, ***1983***, pp. 1–43. For a study of electronic effects, see Garner, C.M.; Chiang, S.; Nething, M.; Monestel, R. *Tetrahedron Lett.* ***2002***, *43*, 8339.

[675]Brown, H.C.; Jadhav, P.K.; Mandal, A.K. *J. Org. Chem.* ***1982***, *47*, 5074. See also, Brown, H.C.; Weissman, S.A.; Perumal, P.T.; Dhokte, U.P. *J. Org. Chem.* ***1990***, *55*, 1217. For an improved method, see Brown, H.C.; Singaram, B. *J. Am. Chem. Soc.* ***1984***, *106*, 1797; Brown, H.C.; Gupta, A.K.; Vara Prasad, J.V.N. *Bull. Chem. Soc. Jpn.* ***1988***, *61*, 93. For the crystal structure of this adduct, see Soderquist, J.A.; Hwang-Lee, S.; Barnes, C.L. *Tetrahedron Lett.* ***1988***, *29*, 3385.

[676]Jadhav, P.K.; Kulkarni, S.U. *Heterocycles* ***1982***, *18*, 169.

[677]Brown, H.C.; Vara Prasad, J.V.N.; Zaidlewicz, M. *J. Org. Chem.* ***1988***, *53*, 2911.

[678]Kiesgen de Richter, R.; Bonato, M.; Follet, M.; Kamenka, J. *J. Org. Chem.* ***1990***, *55*, 2855.

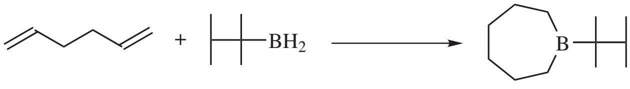
[679]Jadhav, P.K.; Brown, H.C. *J. Org. Chem.* ***1981***, *46*, 2988.

[680]Masamune, S.; Kim, B.M.; Petersen, J.S.; Sato, T.; Veenstra, J.S.; Imai, T. *J. Am. Chem. Soc.* ***1985***, *107*, 4549.

[681]For another enantioselective hydroboration method, see p. 1082.

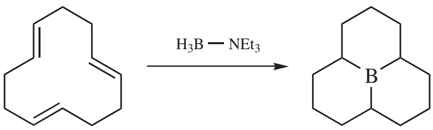
of a chiral rhodium catalyst, giving the alcohol enantioselectivity after the usual oxidation.[682]

The double bonds in a conjugated diene are hydroborated separately, that is, there is no 1,4-addition. However, it is not easy to hydroborate just one of a conjugated system, since conjugated double bonds are less reactive than isolated ones. Thexylborane[641] (**117**) is particularly useful for achieving the cyclic hydroboration of dienes, conjugated or nonconjugated, as in the formation of **122**.[683]



48 **122**

Rings of five, six, or seven members can be formed in this way. Similar cyclization can also be accomplished with other monoalkylboranes and, in some instances, with BH_3 itself.[684] One example is the formation of 9-BBN, shown above. Another is conversion of 1,5,9-cyclododecatriene to perhydro-9*b*-boraphenalene, **123**.[685] If a diene is treated with a diaminoborane and a samarium catalyst, oxidation leads to a carbocyclic ring with a pendant hydroxymethyl group.[686]



123

Triple bonds[687] can be monohydroborated to give vinylic boranes, which can be reduced with carboxylic acids to cis-alkenes or oxidized and hydrolyzed to aldehydes or ketones. Terminal alkynes give aldehydes by this method, in contrast to the mercuric or acid-catalyzed addition of water discussed at **15-4**. However, terminal alkynes give vinylic boranes[688] (and hence aldehydes) only when treated with a hindered borane, such as **116**, **117**, or catecholborane (p. 820),[689] or with $BHBr_2$—SMe_2.[690] The reaction between terminal alkynes and BH_3 produces

[682]Demay, S.; Volant, F.; Knochel, P. *Angew. Chem. Int. Ed.* ***2001***, *40*, 1235.

[683]Brown, H.C.; Negishi, E. *J. Am. Chem. Soc.* ***1972***, *94*, 3567.

[684]For a review of cyclic hydroboration, see Brown, H.C.; Negishi, E. *Tetrahedron* ***1977***, *33*, 2331. See also, Brown, H.C.; Pai, G.G.; Naik, R.G. *J. Org. Chem.* ***1984***, *49*, 1072.

[685]Rotermund, G.W.; Köster, R. *Liebigs Ann. Chem.* ***1965***, *686*, 153; Brown, H.C.; Negishi, E.; Dickason, W.C. *J. Org. Chem.* ***1985***, *50*, 520.

[686]Molander, G.A; Pfeiffer, D. *Org. Lett.* ***2001***, *3*, 361.

[687]For a review of hydroboration of triple bonds, see Hudrlik, P.F.; Hudrlik, A.M., in Patai, S. *The Chemistry of the Carbn–Carbon Triple Bond*, pt. 1, Wiley, NY, ***1978***, pp. 203–219.

[688]For a review of the preparation and reactions of vinylic boranes, see Brown, H.C.; Campbell, Jr., J.B. *Aldrichimica Acta* ***1981***, *14*, 1.

[689]Brown, H.C.; Gupta, S.K. *J. Am. Chem. Soc.* ***1975***, *97*, 5249. For a review of catecholborane, see Lane, C.F.; Kabalka, G.W. *Tetrahedron* ***1976***, *32*, 981; Garrett, C.E.; Fu, G.C. *J. Org. Chem.* ***1996***, *61*, 3224.

[690]Brown, H.C.; Campbell Jr., J.B. *J. Org. Chem.* ***1980***, *45*, 389.

1,1-dibora compounds, which can be oxidized either to primary alcohols (with NaOH—H_2O_2) or to carboxylic acids (with *m*-chloroperoxybenzoic acid).[691] Double bonds can be hydroborated in the presence of triple bonds if the reagent is 9-BBN.[692] On the other hand, dimesitylborane selectively hydroborates triple bonds in the presence of double bonds.[693] Furthermore, it is often possible to hydroborate selectively one particular double bond of a nonconjugated diene.[694] A triple bond can be hydroborated in the presence of a ketone, and treatment with acetic acid reduces the C≡C unit to a cis- alkene (see **15-12**).[695] When the reagent is catecholborane, hydroboration is catalyzed by rhodium complexes,[696] such as Wilkinson's catalyst,[697] by SmI_2,[698] or lanthanide reagents.[699] Enantioselective hydroboration–oxidation has been achieved by the use of optically active rhodium complexes.[700]

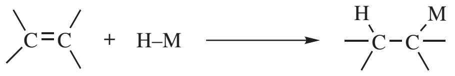
A chain extension variation involved the reaction of styrene with catecholborane and then Me_3SiCHN_2.[701] Subsequent oxidation with NaOH/H_2O_2 and the reaction with Bu_4NF gave 3-phenyl-1-propanol.

An unusual extension of hydroboration involves remote C—H activation. Aryl alkenes are treated with borane and then oxidized in the usual manner. The product is a phenol and a hydroxymethyl group (Ph—C=C—CH_3 → *o*-Ph—CH—CH—CH_2OH.[702]

OS **VI**, 719, 852, 919, 943; **VII**, 164, 339, 402, 427; **VIII**, 532.

15-17 Other Hydrometalation

Hydro-metallo-addition



Metal hydrides of Groups 13 (III A) and 14 (IV B) of the periodic table (e.g., AlH_3, GaH_3) as well as many of their alkyl and aryl derivatives (e.g., R_2AlH,

[691]Zweifel, G.; Arzoumanian, H. *J. Am. Chem. Soc.* ***1967***, *89*, 291.

[692]Brown, H.C.; Coleman, R.A. *J. Org. Chem.* ***1979***, *44*, 2328.

[693]Pelter, A.; Singaram, S.; Brown, H.C. *Tetrahedron Lett.* ***1983***, *24*, 1433.

[694]For a list of references, see Gautam, V.K.; Singh, J.; Dhillon, R.S. *J. Org. Chem.* ***1988***, *53*, 187. See also, Suzuki, A.; Dhillon, R.S. *Top. Curr. Chem.* ***1986***, *130*, 23.

[695]Kabalka, G.W.; Yu, S.; Li, N.-S. *Tetrahedron Lett.* ***1997***, *38*, 7681.

[696]Burgess, K.; van der Donk, W.A.; Westcott, S.A.; Marder, T.B.; Baker, R.T. ; Calabrese, J.C. *J. Am. Chem. Soc.* ***1992***, *114*, 9350; Wescott, S.A.; Blom, H.P.; Marder, T.B.; Baker, R.T. *J. Am. Chem. Soc.* ***1992***, *114*, 8863; Evans, D.A.; Fu, G.C.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***1992***, *114*, 6671.

[697]Männig, D.; Nöth, H. *Angew. Chem. Int. Ed.* ***1985***, *24*, 878. For a review, see Burgess, K.; Ohlmeyer, M.J. *Chem. Rev.* ***1991***, *91*, 1179.

[698]Evans, D.A.; Muci, A.R.; Stürmer, R. *J. Org. Chem.* ***1993***, *58*, 5307.

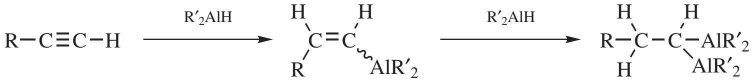
[699]Harrison, K.N.; Marks, T.J. *J. Am. Chem. Soc.* ***1992***, *114*, 9220.

[700]Burgess, K.; Ohlmeyer, M.J. *J. Org. Chem.* ***1988***, *53*, 5178; Hayashi, T.; Matsumoto, Y.; Ito, Y. *J. Am. Chem. Soc.* ***1989***, *111*, 3426; Sato, M.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* ***1990***, *31*, 231; Brown, J.M.; Lloyd-Jones, G.C. *Tetrahedron: Asymmetry* ***1990***, *1*, 869.

[701]Goddard, J.-P.; LeGall, T.; Mioskowski, C. *Org. Lett.* ***2000***, *2*, 1455.

[702]Varela, J.A.; Peña, D.; Goldfuss, B.; Polborn, K.; Knochel, P. *Org. Lett.* ***2001***, *3*, 2395.

Ar_3SnH) add to double bonds to give organometallic compounds.[703] The hydroboration reaction (**15-16**) is the most important example, but other important metals in this reaction are aluminum,[704] tin,[705] and zirconium[706] [a Group 4 (IV B) metal]. Some of these reactions are uncatalyzed, but in other cases various types of catalyst have been used.[707] Hydrozirconation is most commonly carried out with Cp_2ZrHCl (Cp = cyclopentadienyl),[708] known as *Schwartz's reagent*. The mechanism with Group 13 (III A) hydrides seems to be electrophilic (or four-centered pericyclic with some electrophilic characteristics) while with Group 14 (IV A) hydrides a mechanism involving free radicals seems more likely. Dialkylmagnesium reagents have been obtained by adding MgH_2 to double bonds.[709] With Grignard reagents such as RMgX, the Grignard reagent can be added to an alkene $R'CH{=}CH_2$ to give $R'CH_2CH_2MgX$, with $TiCl_4$ as a catalyst.[710] With some reagents triple bonds[711] can add 1 or 2 equivalents, to give **124** or **125**.[712]



124 **125**

[703]Negishi, E. *Adv. Met.-Org. Chem.* ***1989***, *1*, 177; Eisch, J.J. *The Chemistry of Organometallic Compounds*; Macmillan, NY, ***1967***, pp. 107–111. See also, Eisch, J.J.; Fichter, K.C. *J. Organomet. Chem.* ***1983***, *250*, 63.

[704]For reviews of organoaluminums in organic synthesis, see Dzhemilev, U.M.; Vostrikova, O.S.; Tolstikov, G.A. *Russ. Chem. Rev.* ***1990***, *59*, 1157; Maruoka, K.; Yamamoto, H. *Tetrahedron* ***1988***, *44*, 5001.

[705]For a review with respect to Al, Si, and Sn, see Negishi, E. *Organometallics in Organic Synthesis*, Vol. 1, Wiley, NY, ***1980***, pp. 45–48, 357–363, 406–412. For reviews of hydrosilylation, see Ojima, I. in Patai, S.; Rappoport, Z. *The Chemistry of Organic Silicon Compounds*, pt. 2, Wiley, NY, ***1989***, pp. 1479–1526; Alberti, A.; Pedulli, G.F. *Rev. Chem. Intermed.* ***1987***, *8*, 207; Speier, J.L. *Adv. Organomet. Chem.* ***1979***, *17*, 407; Andrianov, K.A.; Souč ek, J.; Khananashvili, L.M. *Russ. Chem. Rev.* ***1979***, *48*, 657.

[706]For reviews of hydrozirconation, and the uses of organozirconium compounds, see Negishi, E.; Takahashi, T. *Synthesis* ***1988***, 1; Dzhemilev, U.M.; Vostrikova, O.S.; Tolstikov, G.A. *J. Organomet. Chem.* ***1986***, *304*, 17; Schwartz, J.; Labinger, J.A. *Angew. Chem. Int. Ed.* ***1976***, *15*, 333. Also see Hoveyda, A.H.; Morken, J.P. *J. Org. Chem.* ***1993***, *58*, 4237.

[707]See, for example, Oertle, K.; Wetter, H. *Tetrahedron Lett.* ***1985***, *26*, 5511; Randolph, C.L.; Wrighton, M.S. *J. Am. Chem. Soc.* ***1986***, *108*, 3366; Maruoka, K.; Sano, H.; Shinoda, K.; Nakai, S.; Yamamoto, H. *J. Am. Chem. Soc.* ***1986***, *108*, 6036; Miyake, H.; Yamamura, H. *Chem. Lett.* ***1989***, 981; Doyle, M.P.; High, K.G.; Nesloney, C.L.; Clayton, Jr., T.W.; Lin, J. *Organometallics* ***1991***, *10*, 1225.

[708]For a method of preparing this reagent (which is also available commercially), see Buchwald, S.L.; LaMaire, S.J.; Nielsen, R.B.; Watson, B.T.; King, S.M. *Tetrahedron Lett.* ***1987***, *28*, 3895. It can also be generated *in situ*: Lipshutz, B.H.; Keil, R.; Ellsworth, E.L. *Tetrahedron Lett.* ***1990***, *31*, 7257.

[709]For a review, see Bogdanović, B. *Angew. Chem. Int. Ed.* ***1985***, *24*, 262.

[710]For a review, see Sato, F. *J. Organomet. Chem.* ***1985***, *285*, 53–64. For another catalyst, see Hoveyda, A.H.; Xu, Z. *J. Am. Chem. Soc.* ***1991***, *113*, 5079.

[711]For a review of the hydrometalation of triple bonds, see Hudrlik, P.F.; Hudrlik, A.M., in Patai, S. *The Chemistry of the Carbon-Carbon Triple Bond*, pt. 1, Wiley, NY, ***1978***, pp. 219–232.

[712]Wilke, G.; Müller, H. *Liebigs Ann. Chem.* ***1960***, *629*, 222; Eisch, J.J.; Kaska, W.C. *J. Am. Chem. Soc.* ***1966***, *88*, 2213; Eisch, J.J.; Rhee, S. *Liebigs Ann. Chem.* ***1975***, 565.

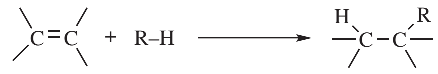
When 2 equivalents are added, electrophilic addition generally gives 1,1-dimetallic products **125** (as with hydroboration), while free-radical addition usually gives the 1,2-dimetallic products.

OS **VII**, 456; **VIII**, 268, 295, 507; **80**, 104. See also, OS **VIII**, 277, 381.

G. Carbon or Silicon on the Other Side

15-18 Addition of Alkanes

Hydro-alkyl-addition



There are two important ways of adding alkanes to alkenes: the thermal and the acid-catalysis method.[713] Both give chiefly mixtures, and neither is useful for the preparation of relatively pure compounds in reasonable yields. However, both are useful industrially. In the thermal method the reactants are heated to high temperatures (~500°C) at high pressures (150–300 atm) without a catalyst. As an example, propane and ethylene gave 55.5% isopentane, 7.3% hexanes, 10.1% heptanes, and 7.4% alkenes.[714] The mechanism is undoubtedly of a free-radical type and can be illustrated by one possible sequence in the reaction between propane and ethylene:

$$\text{Step 1}\quad CH_3CH_2CH_3 + CH_2{=}CH_2 \xrightarrow{\Delta} CH_3{-}\dot{C}H{-}CH_3 + CH_3CH_2\bullet$$

$$\text{Step 2}\quad CH_3{-}\dot{C}H{-}CH_3 + CH_2{=}CH_2 \longrightarrow (CH_3)_2CHCH_2CH_2\bullet$$

$$\text{Step 3}\quad (CH_3)_2CHCH_2CH_2\bullet + CH_3CH_2CH_3 \longrightarrow (CH_3)_2CHCH_2CH_3 + CH_3\dot{C}HCH_3$$

There is kinetic evidence that the initiation takes place primarily by steps like 1, which are called *symproportionation* steps[715] (the opposite of disproportionation, p. 280).

In the acid-catalysis method, a proton or Lewis acid is used as the catalyst and the reaction is carried out at temperatures between −30 and 100°C. This is a Friedel–Crafts process with a carbocation mechanism[716] (illustrated for a proton

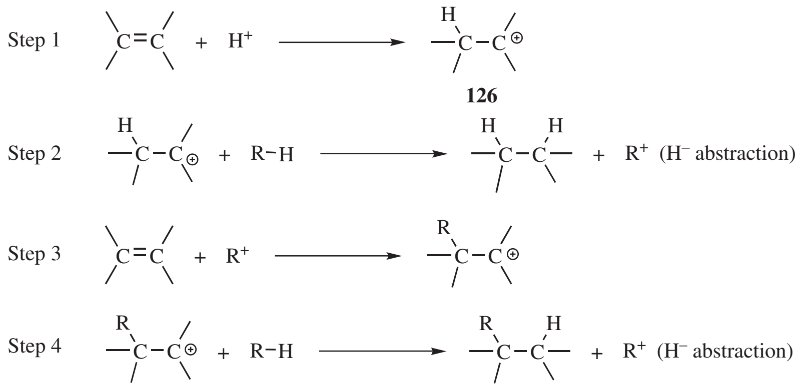
[713]For reviews, see Shuikin, N.I.; Lebedev, B.L. *Russ. Chem. Rev.* ***1966***, *35*, 448; Schmerling, L., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 2, Wiley, NY, ***1964***, pp. 1075–1111, 1121–1122.

[714]Frey, E.J.; Hepp, H.J. *Ind. Eng. Chem.* ***1936***, *28*, 1439.

[715]Metzger, J.O. *Angew. Chem. Int. Ed.* ***1983***, *22*, 889; Hartmanns, J.; Klenke, K.; Metzger, J.O. *Chem. Ber.* ***1986***, *119*, 488.

[716]For a review, see Mayr, H. *Angew. Chem. Int. Ed.* ***1990***, *29*, 1371.

acid catalyst):



127

Carbocation **127** often rearranges before it abstracts a hydride, explaining, for example, why the principal product from the reaction between isobutane and ethylene is 2,3-dimethylbutane. It is also possible for **126** (or **127**) instead of abstracting a hydride, to add to another mole of alkene, so that not only rearrangement products but also dimeric and polymeric products are frequent. If the tri- or tetrasubstituted alkenes are treated with Me_4Si, HCl, and $AlCl_3$, they become protonated to give a tertiary carbocation, which reacts with the Me_4Si to give a product that is the result of addition of H and Me to the original alkene.[717] (For a free-radical hydromethyl-addition, see **15-28**.) Addition a cation to a vinyl bromide, generated from an α-ethoxy-lactam with trifluoroacetic acid, generated a ketone.[718] An intramolecular cyclization of 1-dodecene to cyclododecane was reported using aluminum chloride in an ionic liquid.[719]

Alkanes add to alkynes under photolysis conditions to give an alkene.[720] Tetrahydrofuran adds to alkynes to give the alkene with microwave irradiation.[721]

The reaction can also be base catalyzed, in which case there is nucleophilic addition and a carbanion mechanism.[722] Carbanions most often used are those stabilized by one or more α-aryl groups. For example, toluene adds to styrene in the presence of sodium to give 1,3-diphenylpropane:[723]

$$PhCH_3 \xrightarrow{Na} Ph\overset{\ominus}{C}H_2 + PhCH{=}CH_2 \longrightarrow Ph\overset{\ominus}{C}H{-}CH_2CH_2Ph \xrightarrow{solvent} PhCH_2CH_2CH_2Ph$$

[717]Bolestova, G.I.; Parnes, Z.N.; Kursanov, D.N. *J. Org. Chem. USSR* ***1983***, *19*, 2175.

[718]Gesson, J.-P.; Jacquesy, J.-C.; Rambaud, D. *Tetrahedron* ***1993***, *49*, 2239.

[719]In bmim Cl, 1-butyl-3-methylimidazolium chloride: Qiao, K.; Deng, Y. *Tetrahedron Lett.* ***2003***, *44*, 2191.

[720]Geraghty, N.W.A.; Hannan, J.J. *Tetrahedron Lett.* ***2001***, *42*, 3211.

[721]Zhang, Y.; Li, C.-J. *Tetrahedron Lett.* ***2004***, *45*, 7581.

[722]For reviews, see Pines, H.; Stalick, W.M. *Base-Catalyzed Reactions of Hydrocarbons and Related Compounds*, Academic Press, NY, ***1977***, pp. 240–422; Pines, H. *Acc. Chem. Res.* ***1974***, *7*, 155; Pines, H.; Schaap, L.A. *Adv. Catal.* ***1960***, *12*, 117, pp. 126.

[723]Pines, H.; Wunderlich, D. *J. Am. Chem. Soc.* ***1958***, *80*, 6001.

Conjugated dienes give 1,4-addition.[724] This reaction has also been performed with salts of carboxylic acids in what amounts to a method of alkylation of carboxylic acids[725] (see also, **10-59**).

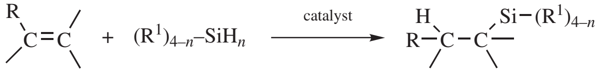
$$CH_3COOK \xrightarrow{NaNH_2} {}^{\ominus}CH_2COOK + CH_2{=}CH_2 \longrightarrow {}^{\ominus}CH_2{-}CH_2CH_2COOK$$

There are transition-metal catalyzed addition reaction of alkyl units to alkenes,[726] often proceeding with metal hydride elimination to form an alkene. An intramolecular cyclization reaction of an *N*-pyrrolidino amide alkene was reported using an iridium catalyst for addition of the carbon α to nitrogen to the alkene unit.[727]

OS **I**, 229; **IV**, 665; **VII**, 479.

15-19 Addition of Silanes

Silyl-hydro-addition



Although silanes bearing at least one Si—H unit do not generally react with alkenes or alkynes, in the presence of certain catalyst addition occurs to give the corresponding alkyl or vinyl silane. The reaction of an alkene with an yttrium,[728] ruthenium,[729] rhodium,[730] palladium,[731] lanthanum,[732] platinum[733], or samarium[734] catalyst addition occurs with high anti-Markovnikov selectivity. Silanes add to dienes with a palladium catalyst, and asymmetric induction is achieved by using a binapthyl additive.[735] Alkenes react with Li-(0) and *t*-Bu_2SiCl_2 to give a three-membered ring silane.[736] In the presence of BEt_3, silanes add to alkynes to give the corresponding vinyl silane[737] or to alkenes to give the alkylsilane, with

[724] Eberhardt, G.G.; Peterson, H.J. *J. Org. Chem.* ***1965***, *30*, 82; Pines, H.; Stalick, W.M. *Tetrahedron Lett.* ***1968***, 3723.

[725] Schmerling, L.; Toekelt, W.G. *J. Am. Chem. Soc.* ***1962***, *84*, 3694.

[726] Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* ***2002***, *35*, 826.

[727] DeBoef, B.; Pastine, S.J.; Sames, D. *J. Am. Chem. Soc.* ***2004***, *126*, 6556.

[728] Molander, G.A.; Julius, M. *J. Org. Chem.* ***1992***, *57*, 6347.

[729] Glaser, P.B.; Tilley, T.D. *J. Am. Chem.Soc.* ***2003***, *125*, 13640.

[730] Itami, K.; Mitsudo, K.; Nishino, A.; Yoshida, J.-i. *J. Org. Chem.* ***2002***, *67*, 2645; Tsuchiya, Y.; Uchimura, H.; Kobayashi, K.; Nishiyama, H. *Synlett* ***2004***, 2099.

[731] Motoda, D.; Shinokubo, H.; Oshima, K. *Synlett* ***2002***, 1529.

[732] Takaki, K.; Sonoda, K.; Kousaka, T.; Koshoji, G.; Shishido, T.; Takehira, K. *Tetrahedron Lett.* ***2001***, *42*, 9211.

[733] Perales, J.B.; van Vranken, D.L. *J. Org. Chem.* ***2001***, *66*, 7270; Sabourault, N.; Mignani, G.; Wagner, A.; Mioskowski, C. *Org. Lett.* ***2002***, *4*, 2117.

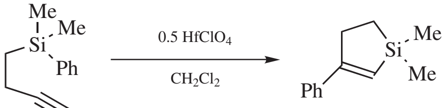
[734] Hou, Z.; Zhang, Y.; Tardif, O.; Wakatsuki, Y. *J. Am. Chem. Soc.* ***2001***, *123*, 9216.

[735] Hatanaka, Y.; Goda, K.; Yamashita, F.; Hiyama, T. *Tetrahedron Lett.* ***1994***, *35*, 7981.

[736] Driver, T.G.; Franz, A.K.; Woerpel, K.A. *J. Am. Chem. Soc.* ***2002***, *124*, 6524.

[737] Miura, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* ***1993***, *66*, 2356.

anti-Markovnikov selectivity.[738] Similar selectivity was observed when a silylated zinc reagent was added to a terminal alkyne.[739] Silanes add to alkynes to give a vinyl silane using Cp_2TiCl_2–*n*-butyllithium.[740] Siloxanes such as $(RO)_3SiH$ add to alkynes with a ruthenium catalyst to give the corresponding vinyl silane.[741] The reaction of Cl_2MeSiH and terminal alkynes, in ethanol–triethylamine with a ruthenium catalyst, to give primarily the Markovnikov vinyl silane.[742] However, Et_3SiH adds to terminal alkynes with a rhodium[743] or a platinum[744] catalyst to give the anti-Markovnikov vinyl silane. Using 0.5 equivalent of $HfClO_4$ with alkynes bearing a dimethylphenylsilyl unit gave a cyclic vinyl silane with transfer of the phenyl group to carbon (see **128**).[745] Dienes react with zirconium compounds and silanes to produce cyclic compounds in which the silyl group has also added to one C=C unit.[746] With an yttrium catalyst, $PhSiH_3$ reacts with nonconjugated dienes to give cyclic alkenes with a pendant CH_2SiH_2Ph group.[747] Rhodium compounds allow silanes to add to enamides to give the α-silylamide.[748] Allylsilanes add to certain allylic alcohols in the presence of Me_3SiOTf, via a S_N2'-like reaction, to give dienes.[749] Note that silanes open cyclopropane rings in the presence of 20% $AlCl_3$ to give the alkylsilane.[750] Formation of silanes via reaction with alkenes can be followed by reaction with fluoride ion and then oxidation to give an alcohol[751] (see **10-16**).



128

Silanes also add to alkenes under radical conditions (using AIBN) with high anti-Markovnikov selectivity.[752] An alternative route to alkylsilanes reacted an alkene with lithium metal in the presence of 3 equivalents of chlorotrimethylsilane, giving bis-1,2-trimethylsilyl compounds after treatment with water.[753] Silanes also

[738]Rubin, M.; Schwier, T.; Gevorgyan, V. *J. Org. Chem.* ***2002***, *67*, 1936.
[739]Nakamura, S.; Uchiyama, M.; Ohwada, T. *J. Am. Chem. Soc.* ***2004***, *126*, 11146.
[740]Takahashi, T.; Bao, F.; Gao, G.; Ogasawara, M. *Org. Lett.* ***2003***, *5*, 3479.
[741]Trost, B.M.; Ball, Z.T. *J. Am. Chem. Soc.* ***2001***, *123*, 12726.
[742]Kawanami, Y.; Sonoda, Y.; Mori, T.; Yamamoto, K. *Org. Lett.* ***2002***, *4*, 2825.
[743]Sato, A.; Kinoshita, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* ***2004***, *6*, 2217.
[744]Wu, W.; Li, C.-J. *Chem. Commun.* ***2003***, 1668.
[745]Asao, N.; Shimada, T.; Shimada, T.; Yamamoto, Y. *J. Am. Chem. Soc.* ***2001***, *123*, 10899. See also, Sudo, T.; Asao, N.; Yamamoto, Y. *J. Org. Chem.* ***2000***, *65*, 8919.
[746]Molander, G.A.; Corrette, C.P. *Tetrahedron Lett.* ***1998***, *39*, 5011.
[747]Muci, A.R.; Bercaw, J.E. *Tetrahedron Lett.* ***2000***, *41*, 7609.
[748]Murai, T.; Oda, T.; Kimura, F.; Onishi, H.; Kanda, T.; Kato, S. *J. Chem. Soc., Chem. Commun.* ***1994***, 2143.
[749]Toshima, K.; Ishizuka, T.; Matsuo, G.; Nakata, M. *Tetrahedron Lett.* ***1994***, *35*, 5673.
[750]Nagahara, S.; Yamakawa, T.; Yamamoto, H. *Tetrahedron Lett.* ***2001***, *42*, 5057.
[751]Jensen, J.F.; Svendsen, B.H.; la Cour, T.V.; Pedersen, H.L.; Johannsen, M. *J. Am. Chem. Soc.* ***2002***, *124*, 4558.
[752]Kopping, B.; Chatgilialoglu, C.; Zehnder, M.; Giese, B. *J. Org. Chem.* ***1992***, *57*, 3994.
[753]Yus, M.; Martínez, P.; Guijarro, D. *Tetrahedron* ***2001***, *57*, 10119.

add to alkenes to form anti-Markovnikov alkylsilane (R_3Si—C—C—R′) in the presence of a hyponitrite.[754]

Vinyl silanes add to conjugated carbonyl compounds in the presence of a ruthenium catalyst,[755] or to acrylonitriles with a cobalt catalyst.[756] Silyl phosphines react with conjugated ynones directly to give an enone with an α-trimethylsilyl and a β-phosphine group.[757] Siloxanes of the type $(RO)_3SiH$ add to the α-carbon of enamines in the presence of a dirhodium catalyst.[758] The uncatalyzed reaction of trimethylsilyl cyanide and ynamines, however, gave an enamine with a β-trimethylsilyl and an α-cyano group.[759]

15-20 Addition of Alkenes and/or Alkynes to Alkenes and/or Alkynes

Hydro-alkenyl-addition

$$CH_2{=}CH_2 + CH_2{=}CH_2 \xrightarrow{H^+} CH_2{=}CHCH_2CH_3$$

With certain substrates, alkenes can be dimerized by acid catalysts, so that the product is a dimer that contains one double bond.[760] A combination of zinc and a $CoCl_2$ catalyst accomplished the same type of coupling.[761] One alkene adds to another in the presence of a nickel catalyst.[762] Coupling conjugated alkenes with vinyl esters to give a functionalized conjugated diene is known, using a complex palladium–vanadium catalyst in an oxygen atmosphere.[763] This reaction is more often carried out internally, as in the formation of cyclohexene **129**. A palladium catalyzed cyclization is known, in which dienes are converted to cyclopentene derivatives such as **130**.[764] Ring-forming reactions with heterocyclic compounds such as indoles are known using $PtCl_2$.[765] A ruthenium catalyzed version of this reaction gave the five-membered ring with an exocyclic double bond.[766] Carbocyclization of an alkene unit to another alkene unit was reported

[754]Dang, H.-S.; Roberts, B.P. *Tetrahedron Lett.* ***1995***, *36*, 2875.

[755]Kakiuchi, F.; Tanaka, Y.; Sato, T.; Chatani, N.; Murai, S. *Chem. Lett.* ***1995***, 679; Trost, B.M.; Imi, K.; Davies, I.W. *J. Am. Chem. Soc.* ***1995***, *117*, 5371.

[756]Tayama, O.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *Eur. J. Org. Chem.* ***2003***, 2286.

[757]Reisser, M.; Maier, A.; Maas, G. *Synlett* ***2002***, 1459.

[758]Hewitt, G.W.; Somers, J.J.; Sieburth, S.Mc.N. *Tetrahedron Lett.* ***2000***, *41*, 10175.

[759]Lukashev, N.V.; Kazantsev, A.V.; Borisenko, A.A.; Beletskaya, I.P. *Tetrahedron* ***2001***, *57*, 10309.

[760]For a review, see Onsager, O.; Johansen, J.E., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 3, Wiley, NY, ***1985***, pp. 205–257.

[761]Wang, C.-C.; Lin, P.-S.; Cheng, C.-H. *Tetrahedron Lett.* ***2004***, *45*, 6203.

[762]RajanBabu, T.V.; Nomura, N.; Jin, J.; Nandi, M.; Park, H.; Sun, X. *J. Org. Chem.* ***2003***, *68*, 8431.

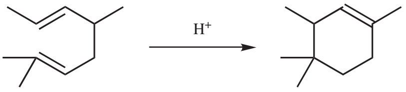
[763]Hatamoto, Y.; Sakaguchi, S.; Ishii, Y. *Org. Lett.* ***2004***, *6*, 4623.

[764]Kisanga, P.; Goj, L.A.; Widenhoefer, R.A. *J. Org. Chem.* ***2001***, *66*, 635.

[765]Liu, C.; Han, X.; Wang, X.; Widenhoefer, R.A. *J. Am. Chem. Soc.* ***2004***, *126*, 3700.

[766]Yamamoto, Y.; Nakagai, Y.-i.; Ohkoshi, N.; Itoh, K. *J. Am. Chem. Soc.* ***2001***, *123*, 6372; Mori, M.; Saito, N.; Tanaka, D.; Takimoto, M.; Sato, Y. *J. Am. Chem. Soc.* ***2003***, *125*, 5606; Michaut, M.; Santelli, M.; Parrain, J.-L. *Tetrahedron Lett.* ***2003***, *44*, 2157.

using an yttrium catalyst,[767] or a titanium catalyst.[768] In some cases, internal coupling of two alkenes can form larger rings.[769] Variations include treatment of similar dienes with $HSiMe_2OSiMe_3$ and KF-acetic acid to give a cyclopentane with a pendant trimethylsilylmethyl group trans to a methyl.[770] Exo-dig carbocyclization was reported using $HfCl_4$[771] palladium,[772] or titanium,[773] catalysts. Alkynes also add to alkenes for form rings in the presence of a palladium,[774] rhodium,[775] ruthenium,[776] iridium,[777] or a zirconium catalyst.[778] Alkene allene substrates were cyclized to form cyclic products with an exocyclic double bond using a palladium catalyst.[779] An interesting variation adds a silyl enol ether to an alkyne using $GaCl_3$ to give an unconjugated ketone (O=C–C–C=C).[780] Alkenes and alkynes can also add to each other to give cyclic products in other ways (see **15-63** and **15-65**).



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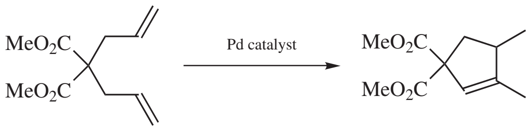

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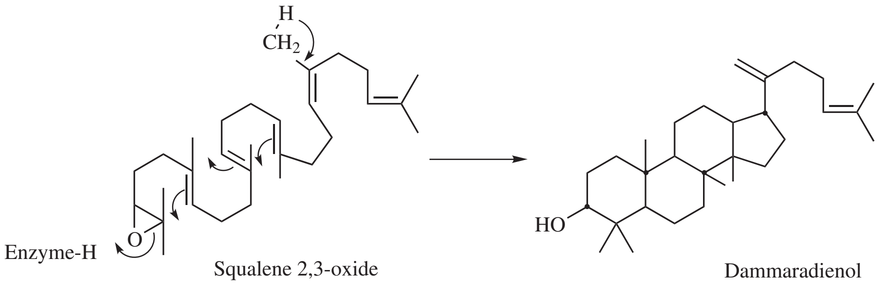
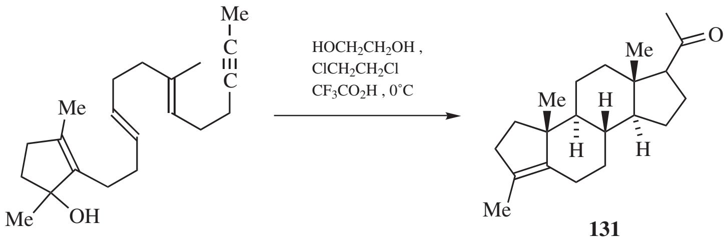
Processes of this kind are important in the biosynthesis of steroids and tetra- and pentacyclic terpenes. For example, squalene 2,3-oxide is converted by enzymatic

[767]Molander, G.A.; Dowdy, E.D.; Schumann, H. *J. Org. Chem.* ***1998***, *63*, 3386.
[768]Okamoto, S.; Livinghouse, T. *J. Am. Chem. Soc.* ***2000***, *122*, 1223. See Hart, D.J.; Bennett, C.E. *Org. Lett.* ***2003***, *5*, 1499.
[769]Toyota, M.; Majo, V.J.; Ihara, M. *Tetrahedron Lett.* ***2001***, *42*, 1555.
[770]Pei, T.; Widenhoefer, R.A. *J. Org. Chem.* ***2001***, *66*, 7639.
[771]Imamura, K.-i.; Yoshikawa, E.; Gevorgyan, V.; Yamamoto, Y. *J. Am. Chem. Soc.* ***1998***, *120*, 5339.
[772]Xie, X.; Lu, X. *Synlett* ***2000***, 707.
[773]Berk, S.C.; Grossman, R.B.; Buchwald, S.L. *J. Am. Chem. Soc.* ***1994***, *116*, 8593; *J. Am. Chem. Soc.* ***1993***, *115*, 4912.
[774]Galland, J.-C.; Savignac, M.; Genêt, J.-P. *Tetrahedron Lett.* ***1997***, *38*, 8695; Widenhoefer, R.A.; Perch, N.S. *Org. Lett.* ***1999***, *1*, 1103.
[775]Wender, P.A.; Dyckman, A.J. *Org. Lett.* ***1999***, *1*, 2089; Cao, P.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* ***2000***, *122*, 6490; Cao, P.; Zhang, X. *Angew. Chem. Int. Ed.* ***2000***, *39*, 4104.
[776]Fernández-Rivas, C.; Méndez, M.; Echavarren, A.M. *J. Am. Chem. Soc.* ***2000***, *122*, 1221; Fürstner, A.; Ackermann, L. *Chem. Commun.* ***1999***, 95.
[777]Chatani, N.; Inoue, H.; Morimoto, T.; Muto, T.; Murai, S. *J. Org. Chem.* ***2001***, *66*, 4433.
[778]Miura, K.; Funatsu, M.; Saito, H.; Ito, H.; Hosomi, A. *Tetrahedron Lett.* ***1996***, *37*, 9059; Kemp, M.I.; Whitby, R.J.; Coote, S.J. *Synlett* ***1994***, 451; Wischmeyer, U.; Knight, K.S.; Waymouth, R.M. *Tetrahedron Lett.* ***1992***, *33*, 7735. Also see Maye, J.P.; Negishi, E. *Tetrahedron Lett.* ***1993***, *34*, 3359.
[779]Iodobenzene was added and a phenyl substituent was incorporated in the product. See Ohno, H.; Takeoka, Y.; Kadoh, Y.; Miyamura, K.; Tanaka, T. *J. Org. Chem.* ***2004***, *69*, 4541.
[780]Yamaguchi, M.; Tsukagoshi, T.; Arisawa, M. *J. Am. Chem. Soc.* ***1999***, *121*, 4074.

catalysis to dammaradienol.



The squalene → lanosterol biosynthesis (which is a key step in the biosynthesis of cholesterol) is similar. The idea that the biosynthesis of such compounds involves this type of multiple ring closing was proposed in 1955 and is known as the *Stork–Eschenmoser hypothesis*.[781] Such reactions can also be carried out in the laboratory, without enzymes.[782] By putting cation-stabilizing groups at positions at which positive charges develop, Johnson and co-workers have been able to close as many as four rings stereoselectively and in high yield, in one operation.[783] An example is formation of **131**,[784] also known as the *Johnson polyene cyclization*.[785]



131

Lewis acids can be used to initiate this cyclization,[786] including $EtAlCl_2$ used for the coupling of an alkyne and an alkene.[787] Cyclization to a tricyclic systems that included formation of a dihydropyran ring was reported using mercuric

[781]Stork, G.; Burgstahler, A.W. *J. Am. Chem. Soc.* ***1955***, *77*, 5068; Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* ***1955***, *38*, 1890.

[782]For reviews, see Gnonlonfoun, N. *Bull. Soc. Chim. Fr.* ***1988***, 862; Sutherland, J.K. *Chem. Soc. Rev.* ***1980***, *9*, 265; Johnson, W.S. *Angew. Chem. Int. Ed.* ***1976***, *15*, 9; *Bioorg. Chem.* ***1976***, *5*, 51; *Acc. Chem. Res.* ***1968***, *1*, 1; van Tamelen, E.E. *Acc. Chem. Res.* ***1975***, *8*, 152. For a review of the stereochemical aspects, see Bartlett, P.A., in Morrison, J.D. *Asymmetric Synthesis* Vol. 3, Academic Press, NY, ***1985***, pp. 341–409.

[783]Guay, D.; Johnson, W.S.; Schubert, U. *J. Org. Chem.* ***1989***, *54*, 4731 and references cited therein.

[784]Johnson, W.S.; Gravestock, M.B.; McCarry, B.E. *J. Am. Chem. Soc.* ***1971***, *93*, 4332.

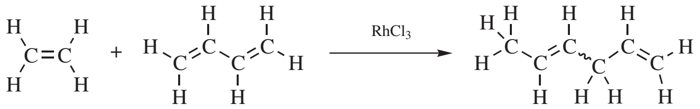
[785]Johnson, W.S. *Acc. Chem. Res.* ***1968***, *1*, 1; Hendrickson, J.B. *The Molecules of Nature*, W.A. Benjamin, NY, ***1965***, pp. 12–57; Kametani T.; Fukumoto, K. *Synthesis* ***1972***, 657.

[786]Sen, S.E.; Roach, S.L.; Smith, S.M.; Zhang, Y.Z. *Tetrahedron Lett.* ***1998***, *39*, 3969. For an asymmetric version using $SnCl_4$, see Ishihara, K.; Nakamura, S.; Yamamoto, H. *J. Am. Chem. Soc.* ***1999***, *121*, 4906.

[787]Asao, N.; Shimada, T.; Yamamoto, Y. *J. Am. Chem. Soc.* ***1999***, *121*, 3797.

bis(trifluorosulfonate) as an initiator.[788] A radical cyclization approach (**15-30**) to polyene cyclization using a seleno-ester anchor gave a tetracyclic system.[789]

The addition of alkenes to alkenes[790] can also be accomplished by bases.[791] Coupling reactions can occur using catalyst systems[792] consisting of nickel complexes and alkylaluminum compounds (known as *Ziegler catalysts*),[793] rhodium catalysts,[794] and other transition-metal catalysts, including iron.[795] The 1,4-addition of alkenes to conjugated dienes to give nonconjugated dienes[796] occurs with various transition-metal catalysts.



and the dimerization of 1,3-butadienes to octatrienes.[797] Ethylene adds to alkenes to form a new alkene in the presence of a nickel catalyst[798] or a zirconium catalyst,[799] to alkynes in the presence of a ruthenium catalyst[800] to form a diene, and allenes add to alkynes to give a diene with a titanium catalyst.[801]

In the presence of cuprous chloride and ammonium chloride, acetylene adds to another molecule of itself to give vinylacetylene.

$$HC{\equiv}CH \; + \; HC{\equiv}CH \xrightarrow[NH_4Cl]{CuCl} HC{\equiv}C{-}CH{=}CH_2$$

[788]Gopalan, A.S.; Prieto, R.; Mueller, B.; Peters, D. *Tetrahedron Lett.* ***1992***, *33*, 1679.

[789]Chen, L.; Gill, G.B.; Pattenden, G. *Tetrahedron Lett.* ***1994***, *35*, 2593.

[790]For a review of alkene dimerization and oligomerization with all catalysts, see Fel'dblyum, V.Sh.; Obeshchalova, N.V. *Russ. Chem. Rev.* ***1968***, *37*, 789.

[791]For a review, see Pines, H. *Synthesis* ***1974***, 309.

[792]For reviews, see Pillai, S.M.; Ravindranathan, M.; Sivaram, S. *Chem. Rev.* ***1986***, *86*, 353; Jira, R.; Freiesleben, W. *Organomet. React.* ***1972***, *3*, 1, 117; Heck, R.F. *Organotransition Metal Chemistry*, Academic Press, NY, ***1974***, pp. 84–94, 150–157; Khan, M.M.T.; Martell, A.E. *Homogeneous Catalysis by Metal Complexes*, Vol. 2, Academic Press, NY, ***1974***, pp. 135–15; Rylander, P.N. *Organic Syntheses with Noble Metal Catalysts*, Academic Press, NY, ***1973***, pp. 175–196; Tsuji, J. *Adv. Org. Chem.* ***1969***, *6*, 109, pp. 213. Also see, Kaur, G.; Manju, K.; Trehan, S. *Chem. Commun.* ***1996***, 581.

[793]See, for example, Onsager, O.; Wang, H.; Blindheim, U. *Helv. Chim. Acta* ***1969***, *52*, 187, 230; Fischer, K.; Jonas, K.; Misbach, P.; Stabba, R.; Wilke, G. *Angew. Chem. Int. Ed.* ***1973***, *12*, 943.

[794]Cramer, R. *J. Am. Chem. Soc.* ***1965***, *87*, 4717; *Acc. Chem. Res.* ***1968***, *1*, 186; Kobayashi, Y.; Taira, S. *Tetrahedron* ***1968***, *24*, 5763; Takahashi, N.; Okura, I.; Keii, T. *J. Am. Chem. Soc. 1975, 97*, 7489.

[795]Takacs, J.M.; Myoung, Y.C. *Tetrahedron Lett.* ***1992***, *33*, 317.

[796]Alderson, T.; Jenner, E.L.; Lindsey, Jr., R.V. *J. Am. Chem. Soc.* ***1965***, *87*, 5638; Hilt, G.; du Mesnil, F.-X.; Lüers, S. *Angew. Chem. Int. Ed.* ***2001***, *40*, 387. For a review see Su, A.C.L. *Adv. Organomet. Chem.* ***1979***, *17*, 269.

[797]See, for example, Denis, P.; Jean, A.; Croizy, J.F.; Mortreux, A.; Petit, F. *J. Am. Chem. Soc.* ***1990***, *112*, 1292.

[798]Nomura, N.; Jin, J.; Park, H.; RajanBabu, T.V. *J. Am. Chem. Soc.* ***1998***, *120*, 459; Monteiro, A.L.; Seferin, M.; Dupont, J.; de Souza, R.F. *Tetrahedron Lett.* ***1996***, *37*, 1157.

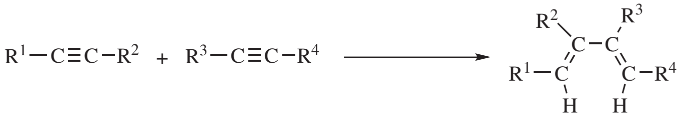
[799]Takahashi, T.; Xi, Z.; Fischer, R.; Huo, S.; Xi, C.; Nakajima, K. *J. Am. Chem. Soc.* ***1997***, *119*, 4561; Takahashi, T.; Xi, Z.; Rousset, C.J.; Suzuki, N. *Chem. Lett.* ***1993***, 1001.

[800]Kinoshita, A.; Sakakibara, N.; Mori, M. *J. Am. Chem. Soc.* ***1997***, *119*, 12388; Trost, B.M.; Indolese, A. *J. Am. Chem. Soc.* ***1993***, *115*, 4361.

[801]Urabe, H.; Takeda, T.; Hideura, D.; Sato, F. *J. Am. Chem. Soc.* ***1997***, *119*, 11295.

This type of alkyne dimerization is also catalyzed by nickel,[802] palladium,[803] lutetium,[804] and ruthenium catalysts.[805] Similar products are obtained by the cross-coupling an terminal alkynes with allene, using a combination of palladium and CuI catalysts.[806] The reaction has been carried out internally to convert diynes to large-ring cycloalkynes with an exocyclic double bond.[807] Diynes have also been cyclized to form cyclic enynes (an endocyclic double bond) using a diruthenium catalyst with ammonium tetrafluoroborate in methanol.[808] Enynes are similarly cyclized to cyclic alkenes with an endocyclic C=C unit, analogous to formation of **200** above, using a dicobalt catalyst.[809] A molecule containing two distal conjugated diene units was cyclized to give a bicyclic molecule with an exocyclic double bond using a palladium catalyst.[810] A nickel catalyst converted a similar system to a saturated five-membered ring containing an allylic group and a vinyl group.[811]

In another type of alkyne dimerization is the reductive coupling in which two molecules of alkyne, the same or different, give a 1,3-diene.[812]



In this method, one alkyne is treated with Schwartz's reagent (see **15-17**) to produce a vinylic zirconium intermediate. Addition of MeLi or MeMgBr, followed by the second alkyne, gives another intermediate, which, when treated with aqueous acid, gives the diene in moderate-to-good yields. The stereoisomer shown is the one formed in usually close to 100% purity. If the second intermediate is treated with I_2 instead of aqueous acid, the 1,4-diiodo-1,3-diene is obtained instead, in comparable yield and isomeric purity. The reaction of alkynes with two equivalents of trimethylsilyldiazomethane and a ruthenium catalyst gave a conjugated diene with trimethylsilyl groups at C-1 and C-4.[813] Alkynes can also be coupled to allylic silyl ethers with a ruthenium catalysts to give dienes.[814] Other alkyne–allylic coupling reactions are known to give dienes.[815]

[802]Ogoshi, S.; Ueta, M.; Oka, M.-A.; Kurosawa, H. *Chem. Commun.* ***2004***, 2732.

[803]Rubina, M.; Gevergyan, V. *J. Am. Chem. Soc.* ***2001***, *123*, 11107; Yang, C.; Nolan, S.P. *J. Org. Chem.* ***2002***, *67*, 591.

[804]Nishiura, M.; Hou, Z.; Wakatsuki, Y.; Yamaki, T.; Miyamoto, T. *J. Am. Chem. Soc.* ***2003***, *125*, 1184.

[805]Smulik, J.A.; Diver, S.T. *J. Org. Chem.* ***2000***, *65*, 1788.

[806]Bruyere, D.; Grigg, R.; Hinsley, J.; Hussain, R.K.; Korn, S.; Del Cierva, C.O.; Sridharan, V.; Wang, J. *Tetrahedron Lett.* ***2003***, *44*, 8669.

[807]Trost, B.M.; Matusbara, S.; Carninji, J.J. *J. Am. Chem. Soc.* ***1989***, *111*, 8745.

[808]Nishibayashi, Y.; Yamanashi, M.; Wakiji, I.; Hidai, M. *Angew. Chem. Int. Ed.* ***2000***, *39*, 2909.

[809]Ajamian, A.; Gleason, J.L. *Org. Lett.* ***2003***, *5*, 2409.

[810]Takacs, J.M.; Leonov, A.P. *Org. Lett.* ***2003***, *5*, 4317.

[811]Takimoto, M.; Mori, M. *J. Am. Chem. Soc.* ***2002***, *124*, 10008; Takimoto, M.; Nakamura, Y.; Kimura, K.; Mori, M. *J. Am. Chem. Soc.* ***2004***, *126*, 5956.

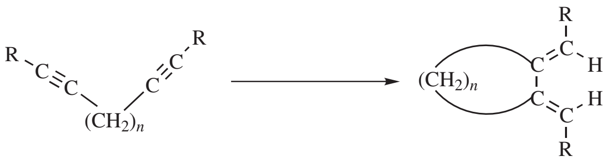
[812]Buchwald, S.L.; Nielsen, R.B. *J. Am. Chem. Soc.* ***1989***, *111*, 2870.

[813]Le Paih, J.; Dérien, S.; Özdemir, I.; Dixneuf, P.H. *J. Am. Chem. Soc.* ***2000***, *122*, 7400.

[814]Trost, B.M.; Surivet, J.-P.; Toste, F.D. *J. Am. Chem. Soc.* ***2001***, *123*, 2897.

[815]Trost, B.M.; Pinkerton, A.B.; Toste, F.D.; Sperrle, M. *J. Am. Chem. Soc.* ***2001***, *123*, 12504; Giessert, A.J.; Snyder, L.; Markham, J.; Diver, S.T. *Org. Lett.* ***2003***, *5*, 1793.

This reaction can also be done intramolecularly, as in the cyclization of diyne **132** to (*E*,*E*)-exocyclic dienes **133** by treatment with a zirconium,[816] rhodium,[817] or platinum complex.[818] A similar reaction was reported using a titanium catalyst from a diyne amide.[819]



132 **133**

Rings of four, five, and six members were obtained in high yield; seven-membered rings in lower yield. When the reaction is applied to enynes, compounds similar to **133** are formed using various catalysts, but with only one double bond[820] Internal coupling of alkene–allenes and a rhodium catalyst give similar products bearing a pendant vinyl group.[821] With a $PtCl_2$ catalyst, ring closure leads to a diene in some cases.[822] Larger rings can be formed from the appropriate enyne, including forming cyclohexadiene compounds.[823] Spirocyclic compounds can be prepared from enynes in this manner using formic acid and a palladium catalyst.[824] Enynes can also be converted to bicyclo[3.1.0]hexenes[825] or nonconjugated cyclohexadienes[826] using a gold catalyst. Internal coupling of an alkyne and a vinylidene cyclopropane unit with a palladium catalyst leads to a cyclopentene derivative with an exocyclic double bond.[827] Enynes having a conjugated alkene unit also undergo this reaction

[816]Nugent, W.A.; Thorn, D.L.; Harlow, R.L. *J. Am. Chem. Soc.* ***1987***, *109*, 2788. See also, Trost, B.M.; Lee, D.C. *J. Am. Chem. Soc.* ***1988***, *110*, 7255; Tamao, K.; Kobayashi, K.; Ito, Y. *J. Am. Chem. Soc.* ***1989***, *111*, 6478.

[817]Jang, H.-Y.; Krische, M.J. *J. Am. Chem. Soc.* ***2004***, *126*, 7875.

[818]Madine, J.W.; Wang, X.; Widenhoefer, R.A. *Org. Lett.* ***2001***, *3*, 385; Méndez, M.; Muñoz, M.P. ; Nevado, C.; Cárdenas, D.J.; Echavarren, A.M. *J. Am. Chem. Soc.* ***2001***, *123*, 10511; Wang, X.; Chakrapani, H.; Madine, J.W.; Keyerleber, M.A.; Widenhoefer, R.A. *J. Org. Chem.* ***2002***, *67*, 2778. See also, Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* ***2001***, *123*, 11863.

[819]Urabe, H.; Nakajima, R.; Sato, F. *Org. Lett.* ***2000***, *2*, 3481.

[820]RajanBabu, T.V.; Nugent, W.A.; Taber, D.F.; Fagan, P.J. *J. Am. Chem. Soc.* ***1988***, *110*, 7128; Méndez, M.; Muñoz, M.P.; Echavarren, A.M. *J. Am. Chem. Soc.* ***2000***, *122*, 11549; Chakrapani, H.; Liu, C.; Widenhoefer, R.A. *Org. Lett.* ***2003***, *5*, 157; Lei, A.; He, M.; Zhang, X. *J. Am. Chem. Soc.* ***2002***, *124*, 8198; Ojima, I.; Vu, A.T.; Lee, S.-Y.; McCullagh, J.V.; Moralee, A.C.; Fujiwara, M.; Hoang, T.H. *J. Am. Chem. Soc.* ***2002***, *124*, 9164; Lee, P.H.; Kim, S.; Lee, K.; Seomoon, D.; Kim, H.; Lee, S.; Kim, M.; Han, M.; Noh, K.; Livinghouse, T. *Org. Lett.* ***2004***, *6*, 4825.

[821]Makino, T.; Itoh, K. *Tetrahedron Lett.* ***2003***, *44*, 6335; Lei, A.; He, M.; Wu, S.; Zhang, X. *Angew. Chem. Int. Ed.* ***2002***, *41*, 3457.

[822]Harrison, T.J.; Dake, G.R. *Org. Lett.* ***2004***, *6*, 5023. See also, Ikeda, S.-i.; Sanuki, R.; Miyachi, H.; Miyashia, H.; Taniguchi, M.; Odashima, K. *J. Am. Chem. Soc.* ***2004***, *126*, 10331.

[823]Yamamoto, Y.; Kuwabara, S.; Ando, Y.; Nagata, H.; Nishiyama, H.; Itoh, K. *J. Org. Chem.* ***2004***, *69*, 6697.

[824]Hatano, M.; Mikami, K. *J. Am. Chem. Soc.* ***2003***, *125*, 4704.

[825]Luzung, M.R.; Markham, J.P.; Toste, F.D. *J. Am. Chem. Soc.* ***2004***, *126*, 10858.

[826]Zhang, L.; Kozmin, S.A. *J. Am. Chem. Soc.* ***2004***, *126*, 11806.

[827]Delgado, A.; Rodríguez, J.R.; Castedo, L.; Mascareñas, J.L. *J. Am. Chem. Soc.* ***2003***, *125*, 9282.

in the presence of $ZnBr_2$.[828] Using mercury (II) triflate in water, cyclization leads to five-membered rings having an exocyclic double bond, and a pendant alcohol group.[829] Enynes give cyclic compounds with an endocyclic double bond conjugated to another alkene unit (a conjugated diene) when treated with $GaCl_3$[830] or a platinum catalyst in an ionic liquid.[831] Allene–alkenes give a similar product with a palladium catalyst[832] or a ruthenium catalyst,[833] as do alkyne–allenes with a dirhodium catalyst.[834] Ethers having an enyne unit (propargylic and allylic) give dihydrofurans upon treatment with $Co_2(CO)_8$.[835] Amines and sulfonamides bearing two propargyl groups cyclize with a ruthenium catalyst to give the corresponding dihydropyrrole.[836]

There are many useful variations. Internal coupling of an alkyne with a vinyl halide, using triethylsilane and a palladium catalyst, gave the saturated cyclic compound with two adjacent exocyclic double bonds (a 2,3-disubstituted diene.[837] Alkynes can added to propargyl acetates using palladium catalyst to give an alkyne allene.[838] Two-Substituted malonate esters having a distal alkyne unit generated vinylidene cycloalkanes when treated with a catalytic amount of *n*-butyllithium.[839] Intramolecular coupling of alkenes and allylic sulfides using *tert*-butoxide/*n*-butyllithium, and then LiBr leads to a bicyclic compound containing a fused cyclopropane ring.[840] The reaction of an alkyne with a vinyl iodide and silver carbonate, with a palladium catalyst, gave a fulvene.[841] The reaction of a terminal alkyne and a vinyl cyclopropane, with a dirhodium catalyst, gives a cycloheptadiene.[842] Alkyne–alkenes were formed by coupling terminal alkynes and allenes in the presence of a palladium catalyst.[843] An alkyne was coupled internally to an allene using a palladium catalyst, with an exocyclic methylene

[828]Yamazaki, S.; Yamada, K.; Yamabe, S.; Yamamoto, K. *J. Org. Chem.* ***2002***, *67*, 2889.

[829]Nishizawa, M.; Yadav, V.K.; Skwarczynski, M.; Takao, H.; Imagawa, H.; Sugihara, T. *Org. Lett.* ***2003***, *5*, 1609.

[830]Chatani, N.; Inoue, H.; Kotsuma, T.; Morai, S. *J. Am. Chem. Soc.* ***2002***, *124*, 10294.

[831]In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Miyanohana, Y.; Inoue, H.; Chatani, N. *J. Org. Chem.* ***2004***, *69*, 8541.

[832]Frazén, J.; Löfstedt, J.; Dorange, I.; Bäckvall, J.-E. *J. Am. Chem. Soc.* ***2002***, *124*, 11246.

[833]Kang, S.-K.; Ko, B.-S.; Lee, D.-M. *Tetrahedron Lett.* ***2002***, *43*, 6693.

[834]Brummond, K.M.; Chen, H.; Sill, P.; You, L. *J. Am. Chem. Soc.* ***2002***, *124*, 15186. See also, Candran, N.; Cariou, K.; Hervé, G.; Aubert, C.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. *J. Am. Chem. Soc.* ***2004***, *126*, 3408.

[835]Ajamian, A.; Gleason, J.L. *Org. Lett.* ***2001***, *3*, 4161; Oh, C.H.; Han, J.W.; Kim, J.S.; Um, S.Y.; Jung, H.H.; Jang, W.H.; Won, H.S. *Tetrahedron Lett.* ***2000***, *41*, 8365; Ackermann, L.; Bruneau, C.; Dixneuf, P.H. *Synlett* ***2001***, 397.

[836]Trost, B.M.; Rudd, M.T. *Org. Lett.* ***2003***, *5*, 1467.

[837]Oh, C.H.; Park, S.J. *Tetrahedron Lett.* ***2003***, *44*, 3785.

[838]Condon-Gueugnot, S.; Linstrumelle, G. *Tetrahedron* ***2000***, *56*, 1851.

[839]Kitagawa, O.; Suzuki, T.; Fujiwra, H.; Fujita, M.; Taguchi, T. *Tetrahedron Lett.* ***1999***, *40*, 4585.

[840]Cheng, D.; Knox, K.R.; Cohen, T. *J. Am. Chem. Soc.* ***2000***, *122*, 412.

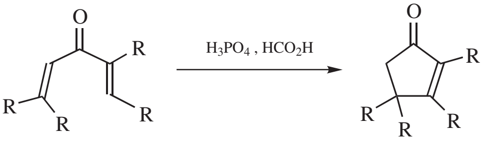
[841]Kotora, M.; Matsumura, H.; Gao, G.; Takahashi, T. *Org. Lett.* ***2001***, *3*, 3467.

[842]Wender, P.A.; Barzilay, C.M.; Dyckman, A.J. *J. Am. Chem. Soc.* ***2001***, *123*, 179.

[843]Rubin, M.; Markov, J.; Chuprakov, S.; Wink, D.J.; Gevorgyan, V. *J. Org. Chem.* ***2003***, *68*, 6251.

group trapped and a vinyltin derivative.[844] A similar process occurred with a rhodium catalyst, $RhCl(PPh_3)_3$, to incorporate a vinyl chloride.[845] Allene–allylic halide systems reacted with phenylboronic acid and a palladium catalyst to give cyclopentane rings with two pendant vinyl groups, one of which contained a phenyl group.[846]

In another reductive coupling, substituted alkenes ($CH_2{=}CH{-}Y$; Y =R, COOMe, OAc, CN, etc.) can be dimerized to substituted alkanes CH_3CHY-$CHYCH_3$ by photolysis in an H_2 atmosphere, using Hg as a photosensitizer.[847] Still another procedure involves palladium-catalyzed addition of vinylic halides to triple bonds to give 1,3-dienes.[848]



134 **135**

An important cyclization procedure involves acid-catalyzed addition of diene-ketones, such as **134**, where one conjugated alkene adds to the other conjugated alkene to form cyclopentenones (**135**). This is called the *Nazarov cyclization*.[849] Structural variations are possible that prepare a variety of cyclopentenones. When one of the C=C units is a vinyl ether, a cyclopentenone is formed with an oxygen attached to the alkenyl carbon.[850] Substituents on the C=C units, including $-CO_2Et$, lead to cyclopentenones that bear those substituents. The use of such a substrate with $AgSbF_6$, $CuBr_2$ and a chiral ligand gave the cyclopentenone with modest enantioselectivity.[851] Cyclization can also give the nonconjugated five-membered ring.[852] A reductive Nazarov cyclization was reported using $BF_3{\bullet}OEt_2$ and Et_3SiH, giving a cyclopentanone rather than a cyclopentenone.[853] A palladium catalyzed reaction that is related to the Nazarov cyclization converts terminal

[844]Shin, S.; RajanBabu, T.V. *J. Am. Chem. Soc.* ***2001***, *123*, 8416.

[845]Tong, X.; Zhang, Z.; Zhang, X. *J. Am. Chem. Soc.* ***2003***, *125*, 6370.

[846]Zhu, G.; Zhang, Z. *Org. Lett.* ***2004***, *6*, 4041.

[847]Muedas, C.A.; Ferguson, R.R.; Crabtree, R.H. *Tetrahedron Lett.* ***1989***, *30*, 3389.

[848]Arcadi, A.; Bernocchi, E.; Burini, A.; Cacchi, S.; Marinelli, F.; Pietroni, B. *Tetrahedron Lett.* ***1989***, *30*, 3465.

[849]Nazarov, I.N.; Torgov, I.B.; Terekhova, L.N. *Izv. Akad. Nauk. SSSR otd. Khim. Nauk*, ***1942***, 200; Braude, E.A.; Forbes, W.F. *J. Chem. Soc.* ***1953***, 2208. Also see, Motoyoshiya, J.; Mizuno, K.; Tsuda, T.; Hayashi, S. *Synlett* ***1993***, 237; Oda, M.; Yamazaki, T.; Kajioka, T.; Miyatake, R.; Kuroda, S. *Liebigs Ann. Chem.* ***1997***, 2563. See Smith, D.A.; Ulmer II, C.W. *J. Org. Chem.* ***1993***, *58*, 4118 for a discussion of torquoselectivity and hyperconjugation in this reaction.

[850]Using $AlCl_3$, see Liang, G.; Gradl, S.N.; Trauner, D. *Org. Lett.* ***2003***, *5*, 4931. Using a $Cu(OTf)_2$ catalyst, see He, W.; Sun, X.; Frontier, A.J. *J. Am. Chem. Soc.* ***2003***, *125*, 14278. Using a scandium catalyst, see Liang, G.; Trauner, D. *J. Am. Chem. Soc.* ***2004***, *126*, 9544.

[851]Aggarwal, V.K.; Belfield, A.J. *Org. Lett.* ***2003***, *5*, 5075.

[852]Giese, S.; West, F.G. *Tetrahedron Lett.* ***1998***, *39*, 8393.

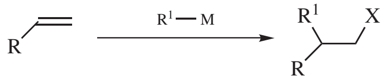
[853]Giese, S.; West, F.G. *Tetrahedron* ***2000***, *56*, 10221.

alkynes to fulvenes.[854] Note that a *retro*-Nazarov is possible with α-bromocyclopentanones.[855] In one variation using a aluminum complex, a cyclohexenone was formed.[856]

OS **VIII**, 190, 381, 505; **IX**, 310.

15-21 Addition of Organometallics to Double and Triple Bonds Not Conjugated to Carbonyls

Hydro-alkyl-addition



Neither Grignard reagents nor lithium dialkylcopper reagents generally add to ordinary C=C double bonds.[857] An exception is the reaction of $(PhMe_2Si)_2Cu(CN)Li$ to 8-oxabicyclo[3.2.1]oct-2-ene derivatives.[858] Grignard reagents usually add only to double bonds susceptible to nucleophilic attack, (e.g., fluoroalkenes and tetracyanoethylene).[859] However, active Grignard reagents (benzylic, allylic) also add to the double bonds of allylic amines,[860] and of allylic and homoallylic alcohols,[861] as well as to the triple bonds of propargyl alcohols and certain other alkynols.[862] Grignard reagents also add to alkynes in the presence of $MnCl_2$ at 100°C[863] and to alkenes in the presence of zirconium[864] or nickel[865] catalysts. It is likely that cyclic intermediates are involved in these cases, in which the magnesium coordinates with the heteroatom. Allylic, benzylic, and tertiary alkyl Grignard reagents also add to 1-alkenes and strained internal alkenes (e.g., norbornene), if the reaction is carried

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[857]For reviews of the addition of RM to isolated double bonds, see Wardell, J.L.; Paterson, E.S., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 2, Wiley, NY, ***1985***, 219–338, pp. 268–296; Vara Prasad, J.V.N.; Pillai, C.N. *J. Organomet. Chem.* ***1983***, *259*, 1.

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[863]Yorimitsu, H.; Tang, J.; Okada, K.; Shinokubo, H.; Oshima, K. *Chem. Lett.* ***1998***, 11.

[864]Rousset, C.J.; Negishi, E.; Suzuki, N.; Takahashi, T. *Tetrahedron Lett.* ***1992***, *33*, 1965; de Armas, J.; Hoveyda, A.H. *Org. Lett.* ***2001***, *3*, 2097.

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out in a hydrocarbon solvent, such as pentane rather than ether, or in the alkene itself as solvent, heated, under pressure if necessary, to 60–130°C.[866] Yields are variable. *Intramolecular* addition of RMgX to completely unactivated double and triple bonds has been demonstrated.[867] The reaction of tosylates bearing a remote alkene unit and a Grignard reagent leads to cyclization when a zirconium catalyst is used.[868] The intramolecular addition of a CH_2Br unit to the C=C unit of an allylic ether was accomplished using PhMgBr and a cobalt catalyst, give a functionalized tetrahydrofuran and incorporation of the phenyl group on the C=C unit as well.[869] Grignard reagents add to the C=C unit of $(MeO)_2CRCH{=}CH{-}R$ moieties to give a 3-alkyl substituted ketone with good enantioselectivity using a nickel catalyst and a chiral additive.[870] In a useful variation, vinyl epoxides react with Grignard reagents and CuBr to give an allylic alcohol via reaction at the C=C unit and concomitant opening of the epoxide.[871] Conjugated dienes react with arylmagnesium halides, Ph_3SiCl and a palladium catalyst to give a coupling product involving the reaction of two equivalents of the diene and incorporation of two $SiPh_3$ units.[872]

Organolithium reagents (primary, secondary, and tertiary alkyl and in some cases aryl) also add to the double and triple bonds of allylic and propargylic alcohols[873] (in this case tetramethylethylenediamine is a catalyst) and to certain other alkenes containing hetero groups, such as OR, NR_2, or SR. Addition of butyllithium to alkenes has been observed with good enantioselectivity when sparteine was added.[874] Mixing an organolithium reagent with transition metal compounds, such as $CeCl_3$[875] or $Fe(acac)_3$[876] leads to addition of the alkyl group. The intramolecular addition of RLi and R_2CuLi has been reported.[877] Organolithium reagents

[866]Lehmkuhl, H.; Reinehr, D. *J. Organomet. Chem.* ***1970***, *25*, C47; ***1973***, *57*, 29; Lehmkulhl, H.; Janssen, E. *Liebigs Ann. Chem.* ***1978***, 1854. This is actually a type of ene reaction. For a review of the intramolecular version of this reaction, see Oppolzer, W. *Angew. Chem. Int. Ed.* ***1989***, *28*, 38.

[867]See, for example, Richey Jr., H.G.; Rees, T.C. *Tetrahedron Lett.* ***1966***, 4297; Drozd, V.N.; Ustynyuk, Yu.A.; Tsel'eva, M.A.; Dmitriev, L.B. *J. Gen. Chem. USSR* ***1969***, *39*, 1951; Felkin, H.; Umpleby, J.D.; Hagaman, E.; Wenkert, E. *Tetrahedron Lett.* ***1972***, 2285; Hill, E.A.; Myers, M.M. *J. Organomet. Chem.* ***1979***, *173*, 1. See also, Yang, D.; Gu, S.; Yan, Y.-L.; Zhu, N.-Y.; Cheung, K.-K. *J. Am. Chem. Soc.* ***2001***, *123*, 8612.

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[873]For a review of the addition of organolithium compounds to double or triple bonds, see Wardell, J.L., in Zuckerman, J.J. *Inorganic Reactions and Methods*, Vol. 11; VCH, NY, ***1988***, pp. 129–142. For a tandem reaction, see García, G.V.; Budelman, N.S. *Org. Prep. Proceed. Int.* ***2003***, *35*, 445.

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containing an alkene[377,878] or alkyne[879] unit cyclize[880] at low temperatures and quenching with methanol replaces the new C—Li bond with C—H. Cyclopropane derivatives have been formed in this manner.[881] Alkyllithium and alkenyllithium derivatives containing an ester moiety can be cyclized.[882] Tandem cyclization are possible with dienes and enynes to form more than one ring,[883] including bicyclic compounds.[884] Tandem cyclization is possible with alkyne iodides[885] or alkynes with a homoallylic CH_2Li unit.[886] The organolithium reagents can contain heteroatoms, such as nitrogen elsewhere in the molecule, and the organolithium species can be generated from an intermediate organotin derivative.[887] Organolithium reagents add to the less substituted C=C unit of conjugated dienes.[888] The organolithium compound can be generated *in situ* by reaction of an organotin compound with butyllithium, allowing cyclization of occur upon treatment with an excess of LiCl.[889]

Ketones with an α-hydrogen add to alkenes, intramolecular, when heated in a sealed tube with $CuCl_2$ and a palladium catalyst.[890] A similar reaction was reported using $Yb(OTf)_3$ and a palladium catalyst.[891] Keto esters add to alkynes using 10% benzoic acid and a palladium catalyst,[892] or an indium catalyst.[893] 1,3-Diketones add to dienes (1,4-addition) using a palladium catalyst,[894] a $AuCl_3$/AgOTf catalyst,[895] and this addition has been done intramolecularly using 2.4 equivalents of $CuCl_2$ and a palladium catalyst.[896] A related cyclization reaction was reported for diesters having a remote terminal alkyne unit in the molecule, with a palladium

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[879]Bailey, W.F.; Ovaska, T.V. *J. Am. Chem. Soc.* ***1993***, *115*, 3080, and references cited therein. See Funk, R.L.; Bolton, G.L.; Brummond, K.M.; Ellestad, K.E.; Stallman, J.B. *J. Am. Chem. Soc.* ***1993***, *115*, 7023.

[880]A conformational radical clock has been developed to evaluate organolithium-mediated cyclization reactions. See Rychnovsky, S.D.; Hata, T.; Kim, A.I.; Buckmelter, A.J. *Org. Lett.* ***2001***, *3*, 807.

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[891]Yang, D.; Li, J.-H.; Gao, Q.; Yan, Y.-L. *Org. Lett.* ***2003***, *5*, 2869.

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[894]Leitner, A.; Larsen, J.; Steffens, C.; Hartwig, J.F. *J. Org. Chem.* ***2004***, *69*, 7552.

[895]Yao, X.; Li, C.-J. *J. Am. Chem. Soc.* ***2004***, *126*, 6884.

[896]Pei, T.; Wang, X.; Widenhoefer, R.A. *J. Am. Chem. Soc.* ***2003***, *125*, 648; Pei, T.; Widenhoefer, R.A. *J. Am. Chem. Soc.* ***2001***, *123*, 11290.

catalyst.[897] The intermolecular addition of diesters, such as malonates, to alkynes was accomplished in acetic acid and a palladium catalyst under microwave irradiation.[898] Enolate anions can add to allylic sulfides, forming β-lactams in some cases.[899] α-Potassio amines (from an *N*-Boc amine and KHMDS) undergoes intramolecular cyclization with an alkene unit to form a dihydropyrrole.[900] The enolate anion derived from the reaction of a nitrile with potassium *tert*-butoxide added to the less substituted carbon of the C=C unit of styrene in DMSO.[901] Similarly, the intramolecular addition of a nitrile enolate (from treatment with CsOH in *N*-methylpyrrolidinone) to an alkyne gave a cyclized product with an exocyclic methylene unit.[902] Silyl enol ethers add to alkynes using a tungsten catalyst.[903] Malonate derivatives add to alkenes in the presence of an $Al(OR)_3$ catalyst.[904]

Unactivated alkenes or alkynes[905] can react with other organometallic compounds under certain conditions. Trimethylaluminum reacts with 4-methyl-1-pentene, in the presence of Cl_2ZrCp_2, for example, and subsequent reaction with molecular oxygen leads to (2*R*),4-dimethyl-1-pentanol in good yield and 74% ee.[906] These reagents also add to alkynes.[907] Aluminum chloride mediated cyclization of α-iodo ketones to a pendant alkyne unit, in the presence of ICl, gave the spirocyclic ketone with an exocyclic C=CHI unit.[908] Isopropylchloroformate (*i*PrO_2CCl) reacts with an alkene, in conjunction with $Et_3Al_2Cl_3$, to add an isopropyl group.[909] Ruthenium catalysts have been used to add allylic alcohols to alkynes.[910] Samarium iodide (SmI_2) induces cyclization of a halide moiety to an alkyne unit[911] or an alkene unit[912] to form cyclized products. Copper complexes can catalyze similar cyclization to alkenes, even when an ester unit is present in the molecule.[913] The reaction of a dithioketal containing a remote alkene moiety, with a titanium complex, leads to cyclization and incorporation of an endocyclic C=C unit in the final product.[914] Allyl manganese compounds add to allenes to give nonconjugated dienes.[915]

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[907]Wipf, P.; Lim, S. *Angew. Chem. Int. Ed.* ***1993***, *32*, 1068.

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[915]Nishikawa, T.; Shinokubo, H.; Oshima, K. *Org. Lett.* ***2003***, *5*, 4623.

Vinyl halides add to allylic amines in the presence of $Ni(cod)_2$ where cod = 1, 5-cyclooctodine, followed by reduction with sodium borohydride.[916] Aryl iodides add to alkynes using a platinum complex in conjunction with a palladium catalyst.[917] A palladium catalyst has been used alone for the same purpose,[918] and the intramolecular addition of a arene to an alkene was accomplished with a palladium[919] or a $GaCl_3$ catalyst,[920] Alkyl iodides add intramolecularly to alkenes with a titanium catalyst,[921] or to alkynes using indium metal and additives.[922] The latter cyclization of aryl iodides to alkenes was accomplished with indium and iodine[923] or with SmI_2.[924]

Aromatic hydrocarbons, such as benzene add to alkenes using a ruthenium catalyst[925] a catalytic mixture of $AuCl_3/AgSbF_6$,[926] or a rhodium catalyst,[927] and ruthenium complexes catalyze the addition of heteroaromatic compounds, such as pyridine, to alkynes.[928] Such alkylation reactions are clearly reminiscent of the Friedel–Crafts reaction (**11-11**). Palladium catalysts can also be used to for the addition of aromatic compounds to alkynes,[929] and rhodium catalysts for addition to alkenes (with microwave irradiation).[930] Note that vinylidene cyclopropanes react with furans and a palladium catalyst to give allylically substituted furans.[931]

Arylboronic acids (p. 905) add to alkynes to give the substituted alkene using a rhodium catalyst.[932] Allenes react with phenylboronic acid and an aryl iodide, in the presence of a palladium catalyst, to give a substituted alkene.[933] 2-Bromo-1,6-dienes react with phenylboronic acid with a palladium catalyst to give a cyclopentane with an exocyclic double bond and a benzyl substituent.[934]

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[917]Denmark, S.E.; Wang, Z. *Org. Lett.* ***2001***, *3*, 1073.
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[919]Huang, Q.; Fazio, A.; Dai, G.; Campo, M.A.; Larock, R.C. *J. Am. Chem. Soc.* ***2004***, *126*, 7460.
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[922]Yanada, R.; Koh, Y.; Nishimori, N.; Matsumura, A.; Obika, S.; Mitsuya, H.; Fujii, N.; Takemoto, Y. *J. Org. Chem.* ***2004***, *69*, 2417; Yanada, R.; Obika, S.; Oyama, M.; Takemoto, Y. *Org. Lett.* ***2004***, *6*, 2825.
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[926]Reetz, M.T.; Sommer, K. *Eur. J. Org. Chem.* ***2003***, 3485.
[927]Thalji, R.K.; Ellman, J.A.; Bergman, R.G. *J. Am. Chem. Soc.* ***2004***, *126*, 7192.
[928]Murakami, M.; Hori, S. *J. Am. Chem. Soc.* ***2003***, *125*, 4720. For a review, see Alonso, F.; Beletskaya, I.P.; Yus, M. *Chem. Rev.* ***2004***, *104*, 3079.
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[934]Oh, C.H.; Sung, H.R.; Park, S.J.; Ahn, K.H. *J. Org. Chem.* ***2002***, *67*, 7155.

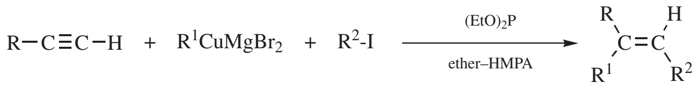
Organomanganese reagents add to alkenes.[935] Manganese triacetate [$Mn(OAc)_3$], in the presence of cupric acetate, facilitates intramolecular cyclization of a halide unit to an alkene.[936] A combination of $Mn(OAc)_2$ and $Co(OAc)_2$ catalysts, and an oxygen atmosphere in acetic acid, leads to addition of ketones to simple alkenes, give the 2-alkyl ketone.[937] Alkynes react with indium reagents, such as $(allyl)_3In_2I_3$, to form dienes (allyl substituted alkenes from the alkyne).[938] Allylic halides add to propargyl alcohols using indium metal to form the aryl organometallic *in situ*.[939] Allyltin reagents add to alkynes in a similar manner in the presence of $ZrCl_4$.[940] Alkylzinc reagents add to alkynes to give substituted alkenes in the presence of a palladium catalyst.[941] Allylzinc reagents add to alkynes in the presence of a cobalt catalyst.[942] A variation reacts dialkylzinc compounds with a 7-oxabicyclo[2.2.1]hept-2-ene system to give incorporation of the alkyl group and opening of the ring to give a cyclohexenol derivative.[943] Vinyltellurium add to alkynes in the presence of $CuI/PdCl_2$.[944]

An indirect addition converts alkynes to an organozinc compound using a palladium catalyst, which then reacts with allylic halides.[945] Similarly, the reaction of an alkyne with $Ti(OiPr)_4$/2 *i*PrMgCl followed by addition of an alkyne leads to a conjugated diene.[946]

OS 81, 121.

15-22 The Addition of Two Alkyl Groups to an Alkyne

Dialkyl-addition



Two different alkyl groups can be added to a terminal alkyne[947] in one laboratory step by treatment with an alkylcopper-magnesium bromide reagent (called *Normant*

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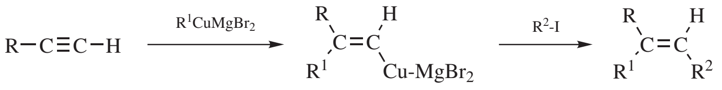
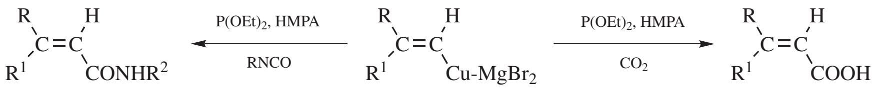
[941]Luo, F.-T.; Fwu, S.-L.; Huang, W.-S. *Tetrahedron Lett.* ***1992***, *33*, 6839.
[942]Nishikawa, T.; Yorimitsu, H.; Oshima, K. *Synlett* ***2004***, 1573.
[943]Lautens, M.; Hiebert, S. *J. Am. Chem. Soc.* ***2004***, *126*, 1437.
[944]Zeni, G.; Nogueira, C.W.; Pena, J.M.; Pialssã, C.; Menezes, P.H.; Braga, A.L.; Rocha, J.B.T. *Synlett.* ***2003***, 579.
[945]Matsubara, S.; Ukai, K.; Toda, N.; Utimoto, K.; Oshima, K. *Synlett* ***2000***, 995.
[946]Tanaka, R.; Hirano, S.; Urabe, H.; Sato, F. *Org. Lett.* ***2003***, *5*, 67.
[947]For reviews of this and related reactions, see Raston, C.L.; Salem, G., in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 159–306, pp. 233–248; Normant, J.F.; Alexakis, A. *Synthesis* ***1981***, 841; Hudrlik, P.F.; Hudrlik, A.M., in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, pt. 1, Wiley, NY, ***1978***, pp. 233–238. For a list of reagents and references for this and related reactions, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 452–460.

reagents)[948] and an alkyl iodide in ether–HMPA containing triethyl phosphite.[949] The groups add stereoselectively syn. The reaction, which has been applied to primary[950] R′ and to primary, allylic, benzylic, vinylic, and α-alkoxyalkyl R′, involves initial addition of the alkylcopper reagent,[951] followed by a coupling reaction (**10-57**):



136

Acetylene itself (R =H) undergoes the reaction with R_2CuLi instead of the Normant reagent.[952] The use of R′ containing functional groups has been reported.[953] If the alkyl iodide is omitted, the vinylic copper intermediate



136 can be converted to a carboxylic acid by the addition of CO_2 (see **16-30**) or to an amide by the addition of an isocyanate, in either case in the presence of HMPA and a catalytic amount of triethyl phosphite.[954] The use of I_2 results in a vinylic iodide.[955]

Similar reactions, in which two alkyl groups are added to a triple bond, have been carried out with trialkylalanes (R_3Al), with zirconium complexes as catalysts.[956] Allyl ethers and iodobenzene have also been added using a

[948]For the composition of these reagents see Ashby, E.C.; Smith, R.S.; Goel, A.B. *J. Org. Chem.* ***1981***, *46*, 5133; Ashby, E.C.; Goel, A.B. *J. Org. Chem.* ***1983***, *48*, 2125.

[949]Gardette, M.; Alexakis, A.; Normant, J.F. *Tetrahedron* ***1985***, *41*, 5887, and references cited therein. For an extensive list of references, see Marfat, A.; McGuirk, P.R.; Helquist, P. *J. Org. Chem.* ***1979***, *44*, 3888.

[950]For a method of using secondary and tertiary R, see Rao, S.A.; Periasamy, M. *Tetrahedron Lett.* ***1988***, *29*, 4313.

[951]The initial product, **136**, can be hydrolyzed with acid to give $RR'C{=}CH_2$. See Westmijze, H.; Kleijn, H.; Meijer, J.; Vermeer, P. *Recl. Trav. Chim. Pays-Bas* ***1981***, *100*, 98, and references cited therein.

[952]Alexakis, A.; Cahiez, G.; Normant, J.F. *Synthesis* ***1979***, 826; *Tetrahedron* ***1980***, *36*, 1961; Furber, M.; Taylor, R.J.K.; Burford, S.C. *J. Chem. Soc. Perkin Trans. 1*, ***1986***, 1809.

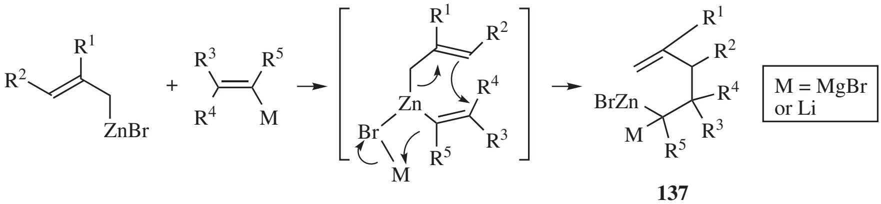
[953]Rao, S.A.; Knochel, P. *J. Am. Chem. Soc.* ***1991***, *113*, 5735.

[954]Normant, J.F.; Cahiez, G.; Chuit, C.; Villieras, J. *J. Organomet. Chem.* ***1973***, *54*, C53.

[955]Alexakis, A.; Cahiez, G.; Normant, J.F. *Org. Synth.* ***VII***, 290.

[956]Negishi, E.; Van Horn, D.E.; Yoshida, T. *J. Am. Chem. Soc.* ***1985***, *107*, 6639. For reviews, see Negishi, E. *Acc. Chem. Res.* ***1987***, *20*, 65; *Pure Appl. Chem.* ***1981***, *53*, 2333; Negishi, E.; Takahashi, T. *Aldrichimica Acta* ***1985***, *18*, 31.

zirconium complex.[957] Similarly, allyl ethers and allyl chlorides have been added.[958]



137

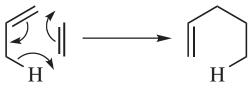
Allylic zinc bromides add to vinylic Grignard and lithium reagents to give the gem-dimetallo compounds **137**. The two metallo groups can be separately reacted with various nucleophiles.[959]

Arylboronic acids (p. 905) react with alkynes and 1 equivalent of an aryl iodide, with a palladium catalyst, to add two aryl groups across the triple bond.[960]

OS **VII**, 236, 245, 290.

15-23 The Ene Reaction

Hydro-allyl-addition



Alkenes can add to double bonds in a reaction different from those discussed in **15-20**, which, however, is still formally the addition of RH to a double bond. This is called the *ene reaction* or the *ene synthesis.*[961] For the reaction to proceed without a catalyst, one of the components must be a reactive dienophile (see **15-60** for a definition of this word), such as maleic anhydride, but the other (which supplies the hydrogen) may be a simple alkene such as propene. Rather high reaction temperatures (250–450°C) are common unless the substrates are very

[957]Hara, R.; Nishihara, Y.; Landré, P.D.; Takahashi, T. *Tetrahedron Lett.* ***1997***, *38*, 447.

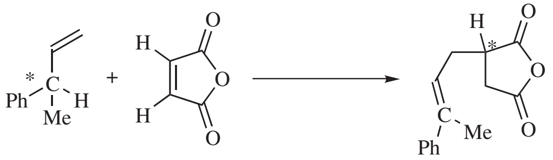
[958]Takahashi, T.; Kotora, M.; Kasai, K.; Suzuki, N. *Tetrahedron Lett.* ***1994***, *35*, 5685.

[959]Knochel, P.; Normant, J.F. *Tetrahedron Lett.* ***1986***, *27*, 1039, 1043, 4427, 4431, 5727.

[960]Zhou, C.; Emrich, D.E.; Larock, R.C. *Org. Lett.* ***2003***, *5*, 1579.

[961]Alder, K.; von Brachel, H. *Liebigs Ann. Chem.* ***1962***, *651*, 141. For a monograph, see Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*, Pergamon, Elmsford, NY, ***1990***. For reviews, see Boyd, G.V., in Patai, S. *Supplement A: The Chemistry of Double-Bonded Functional Groups*, Vol. 2, pt. 1, Wiley, NY, ***1989***, pp. 477–525; Keung, E.C.; Alper, H. *J. Chem. Educ.* ***1972***, *49*, 97–100; Hoffmann, H.M.R. *Angew. Chem. Int. Ed.* ***1969***, *8*, 556. For reviews of intramolecular ene reactions see, Taber, D.F. *Intramolecular Diels–Alder and Alder Ene Reactions*, Springer, NY, ***1984***; pp. 61–94; Oppolzer, W.; Snieckus, V. *Angew. Chem. Int. Ed.* ***1978***, *17*, 476–486; Conia, J.M.; Le Perchec, P. *Synthesis* ***1975***, 1. See Desimoni, G.; Faita, G.; Righetti, P.P.; Sfulcini, A.; Tsyganov, D. *Tetrahedron* ***1994***, *50*, 1821 for solvent effects in the ene reaction.

activated. Note that steric acceleration of the uncatalyzed ene reaction is known.[962] Cyclopropene has also been used.[963] The reaction is compatible with a variety of functional groups that can be appended to the ene and dienophile.[964] *N,N*-Diallyl amides give an ene cyclization, for example.[965] The ene reaction is known with fullerene (see p. 94) derivatives.[966] There has been much discussion of the mechanism of this reaction, and both concerted pericyclic (as shown above) and stepwise



138

mechanisms have been suggested. The mechanism of the ene reaction of singlet ($^1\Delta_g$) oxygen with simple alkenes was found to involve two steps, with no intermediate.[967] A retro-ene reaction is known with allylic dithiocarbonate.[968] The reaction between maleic anhydride and optically active $PhCHMeCH{=}CH_2$ gave an optically active product (**138**),[969] which is strong evidence for a concerted rather than a stepwise mechanism.[970] The reaction can be highly stereoselective.[971]

The reaction can be extended to less-reactive enophiles by the use of Lewis acid catalysts, especially alkylaluminum halides.[972] Titanium catalysts,[973] $Sc(OTf)_3$,[974]

[962]Choony, N.; Kuhnert, N.; Sammes, P.G.; Smith, G.; Ward, R.W. *J. Chem. Soc., Perkin Trans. 1* ***2002***, 1999.

[963]Deng, Q.; Thomas IV, B.E.; Houk, K.N.; Dowd, P. *J. Am. Chem. Soc.* ***1997***, *119*, 6902.

[964]For a review of ene reactions in which one of the reactants bears a Si or Ge atom, see Dubac, J.; Laporterie, A. *Chem. Rev.* ***1987***, *87*, 319.

[965]Cossy, J.; Bouzide, A. *Tetrahedron* ***1997***, *53*, 5775; Oppolzer, W.; Fürstner, A. *Helv. Chim. Acta* ***1993***, *76*, 2329; Oppolzer, W.; Schröder, F. *Tetrahedron Lett.* ***1994***, *35*, 7939.

[966]Wu, S.; Shu, L.; Fan, K. *Tetrahedron Lett.* ***1994***, *35*, 919.

[967]Singleton, D. A.; Hang, C.; Szymanski, M. J.; Meyer, M. P.; Leach, A. G.; Kuwata, K. T.; Chen, J. S.; Greer, A.; Foote, C. S.; Houk, K. N. *J. Am. Chem. Soc.* ***2003***, *125*, 1319.

[968]Eto, M.; Nishimoto, M.; Kubota, S.; Matsuoka, T.; Harano, K. *Tetrahedron Lett.* ***1996***, *37*, 2445.

[969]Hill, R.K.; Rabinovitz, M. *J. Am. Chem. Soc.* ***1964***, *86*, 965. See also, Garsky, V.; Koster, D.F.; Arnold, R.T. *J. Am. Chem. Soc.* ***1974***, *96*, 4207; Stephenson, L.M.; Mattern, D.L. *J. Org. Chem.* ***1976***, *41*, 3614; Nahm, S.H.; Cheng, H.N. *J. Org. Chem.* ***1986***, *51*, 5093.

[970]For other evidence for a concerted mechanism see Benn, F.R.; Dwyer, J.; Chappell, I. *J. Chem. Soc. Perkin Trans. 2*, ***1977***, 533; Jenner, G.; Salem, R.B.; El'yanov, B.; Gonikberg, E.M. *J. Chem. Soc. Perkin Trans. 2*, ***1989***, 1671. See Thomas IV, B.E.; Loncharich, R.J.; Houk, K.N. *J. Org. Chem.* ***1992***, *57*, 1354 for transition-state structures of the intramolecular ene reaction.

[971]Cossy, J.; Bouzide, A.; Pfau, M. *Tetrahedron Lett.* ***1992***, *33*, 4883; Ooi, T.; Maruoka, K.; Yamamoto, H. *Tetrahedron* ***1994***, *50*, 6505; Thomas IV, B.E.; Houk, K.N. *J. Am. Chem. Soc.* ***1993***, *115*, 790; Also see Masaya, K.; Tanino, K.; Kuwajima, I. *Tetrahedron Lett.* ***1994***, *35*, 7965.

[972]For reviews, see Chaloner, P.A., in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 456–460; Snider, B.B. *Acc. Chem. Res.* ***1980***, *13*, 426.

[973]Waratuke, S.A.; Johnson, E.S.; Thorn, M.G.; Fanwick, P.E.; Rothwell, I.P. *Chem. Commun.* ***1996***, 2617; Sturla, S.J.; Kablaoui, N.M.; Buchwald, S.L. *J. Am. Chem. Soc.* ***1999***, *121*, 1976.

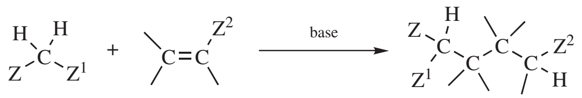
[974]Aggarwal, V.K.; Vennall, G.P.; Davey, P.N.; Newman, C. *Tetrahedron Lett.* ***1998***, *39*, 1997.

$LiClO_4$[975] yttrium,[976] nickel catalysts,[977] as well as a combination of silver and gold catalysts[978] have also been used. A magnesium-ene cyclization stereochemically directed by an allylic oxyanionic group has been reported.[979] The Lewis acid catalyzed reaction probably has a stepwise mechanism.[980] The ene reaction has also been mediated on certain resins,[981] and using formaldehyde that was encapsulated in zeolite.[982] An iridium catalyzed ene reaction has been done in an ionic liquid.[983] The carbonyl-ene reaction is also very useful, and often gives synthetically useful yields of products when catalyzed by Lewis acids,[984] including asymmetric catalysts.[985] Among the useful Lewis acids are scandium triflate[986] and chromium complexes.[987] Carbonyl ene cyclization has been reported on silica gel at high pressure (15 kbar).[988] Ene reactions with imines,[989] nitrile oxides,[990] as well as nitroso ene reactions are known.[991]

OS **IV**, 766; **V**, 459. See also, OS **VIII**, 427.

15-24 The Michael Reaction

Hydro-bis(ethoxycarbonyl)methyl-addition, and so on



Compounds containing electron-withdrawing groups (Z is defined on p. 1007) add, in the presence of bases, to alkenes of the form C=C–Z (including quinones).

[975]Davies, A.G.; Kinart, W.J. *J. Chem. Soc. Perkin Trans. 2*, ***1993***, 2281.

[976]Molander, G.A.; Corrette, C.P. *J. Org. Chem.* ***1999***, *64*, 9697.

[977]Michelet, V.; Galland, J.-C.; Charruault, L.; Savignac, M.; Genêt, J.-P. *Org. Lett.* ***2001***, *3*, 2065.

[978]Kennedy-Smith, J.J.; Staben, S.T.; Toste, F.D. *J. Am. Chem. Soc.* ***2004***, *126*, 4526.

[979]Cheng, D.; Zhu, S.; Yu, Z.; Cohen, T. *J. Am. Chem. Soc.* ***2001***, *123*, 30.

[980]See Snider, B.B.; Ron E. *J. Am. Chem. Soc.* ***1985***, *107*, 8160.

[981]Cunningham, I.D.; Brownhill, A.; Hamereton, I.; Howlin, B.J. *Tetrahedron* ***1997***, *53*, 13473.

[982]Okachi, T.; Onaka, M. *J. Am. Chem. Soc.* ***2004***, *126*, 2306.

[983]Shibata, T.; Yamasaki, M.; Kadowaki, S.; Takagi, K. *Synlett* ***2004***, 2812.

[984]See Achmatowicz, O.; Bialeck-Florjańczyk, E. *Tetrahedron* ***1996***, *52*, 8827; Marshall, J.A.; Andersen, M.W. *J. Org. Chem.* ***1992***, *57*, 5851 for mechanistic discussions of this reaction.

[985]Mikami, K.; Terada, M.; Narisawa, S.; Nakai, T. *Synlett* ***1992***, 255; Wu, X.-M.; Funakoshi, K.; Sakai, K. *Tetrahedron Lett.* ***1993***, *34*, 5927. For a discussion of the mechanism of the chiral copper complex-catalyzed carbonyl ene reaction, see Morao, I.; McNamara, J.P.; Hillier, I.H. *J. Am. Chem. Soc.* ***2003***, *125*, 628.

[986]See Aggarwal, V.K.; Vennall, G.P.; Davey, P.N.; Newman, C. *Tetrahedron Lett.* ***1998***, *39*, 1997.

[987]Ruck, R.T.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2002***, *124*, 2882.

[988]Dauben, W.G.; Hendricks, R.T. *Tetrahedron Lett.* ***1992***, *33*, 603.

[989]Tohyama, Y.; Tanino, K.; Kuwajima, I. *J. Org. Chem.* ***1994***, *59*, 518; Yamanaka, M.; Nishida, A.; Nakagawa, M.; *Org. Lett.* ***2000***, *2*, 159.

[990]For a discussion of the mechanism of the intramolecular reaction, see Yu, Z.-X.; Houk, K.N. *J. Am. Chem. Soc.* ***2003***, *125*, 13825.

[991]Lu, X. *Org. Lett.* ***2004***, *6*, 2813. See also, Leach, A.G.; Houk, K.N. *J. Am. Chem. Soc.* ***2002***, *124*, 14820. For a review, see Adam, W.; Krebs, O. *Chem. Rev.* ***2003***, *103*, 4131.

This is called the *Michael reaction* and involves conjugate addition.[992] The compound RCH_2Z or RCHZZ′ can include aldehydes,[993] ketones,[994] esters[995] and diesters,[996] diketones,[997] keto-esters,[998] carboxylic acids and dicarboxylic acids,[999] nitriles,[1000] and nitro compounds,[1001] often with chiral catalysts or additives that give asymmetric induction. Enamines can also be used as the nucleophilic partner in Michael additions.[1002] In the most common examples, a base removes the acidic proton and then the mechanism is as outlined on p. 1008. The reaction has been carried out with conjugated substrates that include malonates, cyanoacetates, acetoacetates, other β-keto esters, and compounds of the form ZCH_3, ZCH_2R, $ZCHR_2$, and ZCHRZ′, including carboxylic esters, amides,[1003] ketones, aldehydes, nitriles, nitro compounds,[1004]

[992]For reviews, see Yanovskaya, L.A.; Kryshtal, G.V.; Kulganek, V.V. *Russ. Chem. Rev.* ***1984***, *53*, 744; Bergmann, E.D.; Ginsburg, D.; Pappo, R. *Org. React.* ***1959***, *10*, 179; House, H.O. *Modern Synthetic Reaction*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 595–623. The subject is also discussed at many places, in Stowell, J.C. *Carbanions in Organic Synthesis*, Wiley, NY, ***1979***.

[993]Hagiwara, H.; Okabe, T.; Hakoda, K.; Hoshi, T.; Ono, H.; Kamat, V.P.; Suzuki, T.; Ando, M. *Tetrahedron Lett.* ***2001***, *42*, 2705; Melchiorre, P.; Jørgensen, K.A. *J. Org. Chem.* ***2003***, *68*, 4151; Shimizu, K.; Suzuki, H.; Hayashi, E.; Kodama, T.; Tsuchiya, Y.; Hagiwara, H.; Kityama, Y. *Chem. Commun.* ***2002***, 1068; Willis, M.C.; McNally, S.J.; Beswick, P.J. *Angew. Chem. Int. Ed.* ***2004***, *43*, 340. For an intramolecular example, see Fonseca, M.T.H.; List, B. *Angew. Chem. Int. Ed.* ***2004***, *43*, 3958.

[994]Betancort, J.M.; Sakthivel, K.; Thayumanavan, R.; Barbas III, C.F. *Tetahedron Lett.* ***2001***, *42*, 4441; Enders, D.; Seki, A. *Synlett* ***2002***, 26. For an example using an α-hydroxy ketone, see Andrey, O.; Alexakis, A.; Bernardinelli, G. *Org. Lett.* ***2003***, *5*, 2559; Harada, S.; Kumagai, N.; Kinoshita, T.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* ***2003***, *125*, 2582.

[995]Kim, S.-G.; Ahn, K.H. *Tetrahedron Lett.* ***2001***, *42*, 4175.

[996]Halland, N.; Aburel, P.S.; Jørgensen, K.A. *Angew. Chem. Int. Ed.* ***2003***, *42*, 661.

[997]da silva, F.M.; Gomes, A.K.; Jones Jr., J. *Can. J. Chem.* ***1999***, *77*, 624.

[998]Suzuki, T.; Torii, T. *Tetrahedron Asymmetry* ***2001***, *12*, 1077; García-Gómez, G.; Moretó, J.M. *Eur. J. Org. Chem.* ***2001***, 1359; Kobayashi, S.; Kakumoto, K.; Mori, Y.; Manabe, K. *Isr. J. Chem.* ***2001***, *41*, 247.

[999]Méou, A.; Lamarque, L.; Brun, P. *Tetrahedron Lett.* ***2002***, *43*, 5301.

[1000]Kraus, G.A.; Dneprovskaia, E. *Tetrahedron Lett.* ***2000***, *41*, 21. For an example using an α-cyano amide, see Wolckenhauer, S.A.; Rychnovsky, S.D. *Org. Lett.* ***2004***, *6*, 2745. For a review of conjugate addition to this relatively unreactive class of compounds, see Fleming, F.F.; Wang, Q. *Chem. Rev.* ***2003***, *103*, 2035.

[1001]Sebti, S.; Boukhal, H.; Hanafi, N.; Boulaajaj, S. *Tetrahedron Lett.* ***1999***, *40*, 6207; Novák, T.; Tatai, J.; Bakó, P.; Czugler, M.; Keglevich, G. Töke, L. *Synlett* ***2001***, 424; Halland, N.; Hazell, R.G.; Jørgensen, K.A. *J. Org. Chem.* ***2002***, *67*, 8331; Ooi, T.; Fujioka, S.; Maruoka, K. *J. Am. Chem. Soc.* ***2004***, *126*, 11790. For a reaction using nitromethane and a Mg–Al hydrotalcite catalyst, see Choudary, B.M.; Kantam, M.L.; Kavita, B.; Reddy, Ch.V.; Figueras, F. *Tetrahedron* ***2000***, *56*, 9357. For the importance of the aggregation state, see Strzalko, T.; Seyden-Penne, J.; Wartski, L.; Froment, F.; Corset, J. *Tetrahedron Lett.* ***1994***, *35*, 3935.

[1002]Sharma, U.; Bora, U.; Boruah, R.C.; Sandhu, J.S. *Tetrahedron Lett.* ***2002***, *43*, 143.

[1003]Taylor, M.S.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2003***, *125*, 11204.

[1004]For reviews of Michael reactions, where Z or Z′ is nitro, see Yoshikoshi, A.; Miyashita, M. *Acc. Chem. Res.* ***1985***, *18*, 284; Baer, H.H.; UrBas L., in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, pt. 2, Wiley, NY, ***1970***, pp. 130–148. See Kumar, H.M.S.; Reddy, B.V.S.; Reddy, P.T.; Yadav, J.S. *Tetrahedron Lett.* ***1999***, *40*, 5387; Ji, J.; Barnes, D.M.; Zhang, J.; King, S.A.; Wittenberger, S.J.; Morton, H.E. *J. Am. Chem. Soc.* ***1999***, *121*, 10215; List, B.; Pojarliev, P.; Martin, H.J. *Org. Lett.* ***2001***, *3*, 2423; Alexakis, A.; Andrey, O. *Org. Lett.* ***2002***, *4*, 3611; Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas III, C.F. *Org. Lett.* ***2004***, *6*, 2527; Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* ***2003***, *125*, 12672; Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* ***2004***, *126*, 9558; Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* ***2004***, *126*, 9906; Watanabe, M.; Ikagawa, A.; Wang, H.; Murata, K.; Ikariya, T. *J. Am. Chem. Soc.* ***2004***, *126*, 11148.

and sulfones, as well as other compounds with relatively acidic hydrogens, such as indenes and fluorenes. Vinylogous Michael reaction are well known, using a variety of nucleophilic species.[1005] Michael addition of methyl 2,2-dichloroacetate/ $LiN(TMS)_2$ where TMS = trinethysilyl, leads to formation of a cyclopropane ring.[1006] Similarly, the intramolecular Michael addition of an α-chloro ketone enolate anion, formed *in situ* using DABCO, leads to formation of a bicyclo[4.1.0] diketone.[1007] It is noted that activated aryl compounds undergo Michael addition in the presence of an imidazolidinone catalyst.[1008] Conjugate addition of nitrones using SmI_2 has been reported.[1009]

These reagents do not add to ordinary double bonds, except in the presence of free-radical initiators (**15-33**). 1,2 Addition (to the C=O or C≡N group) often competes and sometimes predominates (**16-38**).[1010] In particular, α,β-unsaturated *aldehydes* seldom give 1,4 addition.[1011] The Michael reaction has traditionally been performed in protic solvents, with catalytic amounts of base,[1012] but more recently better yields with fewer side reactions have been obtained in some cases by using an equimolar amount of base to convert the nucleophile to its enolate form (*preformed enolate*). In particular, preformed enolates are often used where stereoselective reactions are desired.[1013] Silyl enol ethers can also be used, and in conjunction with chiral additives.[1014] Phase-transfer catalysts have been used,[1015] and ionic liquids have been used in conjunction with phase-transfer catalysis.[1016] Michael addition has been done in ionic liquids, adding aldehydes to conjugated nitro compounds using proline as a catalyst.[1017] Transition-metal compounds, such as $CeCl_3$,[1018] $Yb(OTf)_3$,[1019] $Bi(OTf)_3$,[1020] ferric chloride hexahydrate,[1021]

[1005]Ballini, R.; Bosica, G.; Fiorini, D. *Tetrahedron Lett.* ***2001***, *42*, 8471.

[1006]Escribano, A.; Pedregal, C.; González, R.; Fernádez, A.; Burton, K.; Stephenson, G.A. *Tetrahedron* ***2001***, *57*, 9423.

[1007]Bremeyer, N.; Smith, S.C.; Ley, S.V.; Gaunt, M.J. *Angew. Chem. Int. Ed.* ***2004***, *43*, 2681.

[1008]Paras, N.A.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2002***, *124*, 7894.

[1009]Masson, G.; Cividino, P.; Py, S.; Vallée, Y. *Angew. Chem. Int. Ed.* ***2003***, *42*, 2265.

[1010]For a discussion of 1,2 versus 1,4-addition, see, Oare, D.A.; Heathcock, C.H. *Top. Stereochem.* ***1989***, *19*, 227, pp. 232–236.

[1011]For reports of successful 1,4-additions to α,β-unsaturated aldehydes, see Kryshtal, G.V.; Kulganek, V.V.; Kucherov, V.F.; Yanovskaya, L.A. *Synthesis* ***1979***, 107; Yamaguchi, M.; Yokota, N.; Minami, T. *J. Chem. Soc., Chem. Commun.* ***1991***, 1088.

[1012]See Macquarrie, D.J. *Tetrahedron Lett.* ***1998***, *39*, 4125 for the use of supported phenolates as catalysts.

[1013]For reviews of stereoselective Michael additions, see Oare, D.A.; Heathcock, C.H. *Top. Stereochem.* ***1991***, *20*, 87; ***1989***, *19*, 227.

[1014]Harada, T.; Adachi, S.; Wang, X. *Org. Lett.* ***2004***, *6*, 4877.

[1015]Kim, D.Y.; Huh, S.C. *Tetrahedron* ***2001***, *57*, 8933.

[1016]Dere, R.T.; Pal, R.R.; Patil, P.S.; Salunkhe, M.M. *Tetrahedron Lett.* ***2003***, *44*, 5351.

[1017]In bmim PF_6, 3-butyl-1-methylimidazolium hexafluorophosphate: Kotrusz, P.; Toma, S.; Schamlz, H.-G.; Adler, A. *Eur. J. Org. Chem.* ***2004***, 1577.

[1018]Boruah, A.; Baruah, M.; Prajapati, D.; Sandhu, J.S. *Synth. Commun.* ***1998***, *28*, 653; Bartoli, G.; Bosco, M.; Bellucci, M.C.; Marcantoni, E.; Sambri, L.; Torregiani, E. *Eur. J. Org. Chem.* ***1999***, 617.

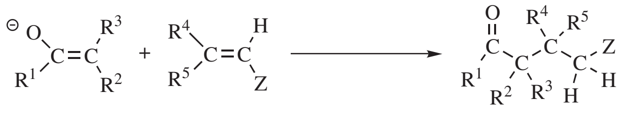
[1019]Keller, E.; Feringa, B.L. *Tetrahedron Lett.* ***1996***, *37*, 1879; Kotsuki, H.; Arimura, K. *Tetrahedron Lett.* ***1997***, *38*, 7583.

[1020]Varala, R.; Alam, M.M.; Adapa, S.R. *Synlett* ***2003***, 720.

[1021]For a review, see Christoffers, J. *Synlett* ***2001***, 723.

copper compounds,[1022] lanthanum complexes,[1023] ruthenium complexes,[1024] or scandium complexes[1025] also induce the reaction. In many cases, such compounds lead to catalytic enantioselective Michael additions.[1026] Conjugate addition has also been promoted by Y-zeolite,[1027] and water-promoted Michael additions have also been reported.[1028] Other catalysts have also been used.[1029] Vinylzinc complexes add to conjguated keotnes in the presence of a CuBr catlayst.[1030]

In a Michael reaction with suitably different R groups, two new stereogenic centers are created (see **139**).



139

In a diastereoselective process, one of the two pairs is formed exclusively or predominantly, as a racemic mixture.[1031] Many such examples have been reported.[672] In many of these cases, both the enolate anion and substrate can exist as (*Z*) or (*E*) isomers. With enolates derived from ketones or carboxylic esters, The (*E*) enolates gave the syn pair of enantiomers (p. 166), while (*Z*) enolates gave the anti pair.[1032] Nitro compounds add to conjugated ketones in the presence of a dipeptide and a piperazine.[1033] Malonate derivatives also add to conjugated ketones,[1034] and keto esters add to conjugated esters.[1035] Addition of chiral additives to the reaction, such as metal–salen complexes,[1036] proline derivatives,[1037] or (−)-sparteine,[1038]

[1022]Iguchi, Y.; Itooka, R.; Miyaura, N. *Synlett* ***2003***, 1040; Meyer, O.; Becht, J.-M.; Helmchen, G. *Synlett* ***2003***, 1539. For a discussion of the mechanism, see Comelles, J.; Moreno-Mañas, M.; Pérez, E.; Roglans, A.; Sebastián, R.M.; Vallribera, A. *J. Org. Chem.* ***2004***, *69*, 6834.

[1023]Kim, Y.S.; Matsunaga, S.; Das, J.; Sekine, A.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* ***2000***, *122*, 6506.

[1024]Watanabe, M.; Murata, K.; Ikariya, T. *J. Am. Chem. Soc.* ***2003***, *125*, 7508; Wadsworth, K.J.; Wood, F.K.; Chapman, C.J.; Frost, C.G. *Synlett* ***2004***, 2022. For a review, see Hayashi, T.; Yamasaki, K. *Chem. Rev.* ***2003***, *103*, 2829.

[1025]Mori, Y.; Kakumoto, K.; Manabe, K.; Kobayashi, S. *Tetahedron Lett.* ***2000***, *41*, 3107.

[1026]For a review, see Krause, N.; Hoffmann-Röder, A. *Synthesis* ***2001***, 171.

[1027]Sreekumar, R.; Rugmini, P.; Padmakumar, R. *Tetrahedron Lett.* ***1997***, *38*, 6557.

[1028]Lubineau, A.; Augé, J. *Tetrahedron Lett.* ***1992***, *33*, 8073.

[1029]Phosphoramidites: Grossman, R.B.; Comesse, S.; Rasne, R.M.; Hattori, K.; Delong, M.N. *J. Org. Chem.* ***2003***, *68*, 871. Fluorapatite: Zahouily, M.; Abrouki, Y.; Rayadh, A.; Sebti, S.; Dhimane, H.; David, M. *Tetrahedron Lett.* ***2003***, *44*, 2463.

[1030]Huang, X.; Pi, J. *Synlett* ***2003***, 481.

[1031]For a more extended analysis, see Oare, D.A.; Heathcock, C.H. *Top. Stereochem.* ***1989***, *19*, p. 237.

[1032]For example, see Oare, D.A.; Heathcock, C.H. *J. Org. Chem.* ***1990***, *55*, 157.

[1033]Tsogoeva, S.B.; Jagtap, S.B. *Synlett* ***2004***, 2624; Ballini, R.; Barboni, L.; Bosica, G.; Fiorini, D. *Synthesis* ***2002***, 2725.

[1034]Zhang, Z.; Dong, Y.-W.; Wang, G.-W.; Komatsu, K. *Synlett* ***2004***, 61.

[1035]Yadav, J.S.; Geetha, V.; Reddy, B.V.S. *Synth. Commun.* ***2002***, *32*, 3519.

[1036]Jha, S.C.; Joshi, N.N. *Tetrahedron Asymmetry* ***2001***, *12*, 2463.

[1037]Yamaguchi, M.; Shiraishi, T.; Hirama, M. *J. Org. Chem.* ***1996***, *61*, 3520.

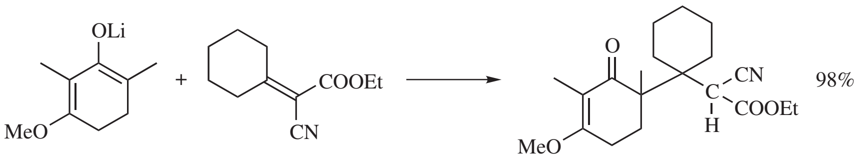
[1038]Xu, F.; Tillyer, R.D.; Tschaen, D.M.; Grabowski, E.J.J.; Reider, P.J. *Tetrahedron Assymetry* ***1998***, *9*, 1651.

lead to product formation with good-to-excellent asymmetric induction. Ultrasound has also been used to promote asymmetric Michael reactions.[1039] Intramolecular versions of Michael addition are known.[1040] A double Michael process is possible, where conjugate addition to an alkynyl ketone is followed by an intramolecular Michael to form a functionalized ring.[1041]

When either or both of the reaction components has a chiral substituent, the reaction can be enantioselective (only one of the four diastereomers formed predominantly).[1042] Enantioselective addition has also been achieved by the use of a chiral catalyst[1043] and by using optically active enamines instead of enolates.[1044] Chiral imines have also been used.[1045]

Mannich bases (see **16-19**) and β-halo carbonyl compounds can also be used as substrates; these are converted to the C=C–Z compounds *in situ* by the base (**16-19**, **17-13**).[1046] Substrates of this kind are especially useful in cases where the C=C–Z compound is unstable. The reaction of C=C–Z compounds with enamines (**10-69**) can also be considered a Michael reaction. Michael reactions are reversible.

When the substrate contains *gem*-Z groups (e.g., **141**), bulky groups can be added, if the reaction is carried out under aprotic conditions. For example, addition of enolate **140** to **141** gave **142** in which two adjacent quaternary centers have been formed.[1047]



140 **141** **142**

[1039]Mirza-Aghayan, M.; Etemad-Moghadam, G.; Zaparucha, A.; Berlan, J.; Loupy, A.; Koenig, M. *Tetrahedron Asymmetry* ***1995***, *6*, 2643.

[1040]Christoffers, J. *Tetrahedron Lett.* ***1998***, *39*, 7083.

[1041]Holeman, D.S.; Rasne, R.M.; Grossman, R.B. *J. Org. Chem.* ***2002***, *67*, 3149.

[1042]See, for example, Töke, L.; Fenichel, L.; Albert, M. *Tetrahedron Lett.* ***1995***, *36*, 5951; Corey, E.J.; Peterson, R.T. *Tetrahedron Lett.* ***1985***, *26*, 5025; Calderari, G.; Seebach, D. *Helv. Chim. Acta* ***1985***, *68*, 1592; Tomioka, K.; Ando, K.; Yasuda, K.; Koga, K. *Tetrahedron Lett.* ***1986***, *27*, 715; Posner, G.H.; Switzer, C. *J. Am. Chem. Soc.* ***1986***, *108*, 1239; Enders, D.; Demir, A.S.; Rendenbach, B.E.M. *Chem. Ber.* ***1987***, *120*, 1731. Also see, Hawkins, J.M.; Lewis, T.A. *J. Org. Chem.* ***1992***, *57*, 2114.

[1043]Yura, T.; Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* ***1988***, 1021; Yura, T.; Iwasawa, N.; Narasaka, K.; Mukaiyama, T. *Chem. Lett.* ***1988***, 1025; Desimoni, G.; Quadrelli, P.; Righetti, P.P. *Tetrahedron* ***1990***, *46*, 2927.

[1044]See d'Angelo, J.; Revial, G.; Volpe, T.; Pfau, M. *Tetrahedron Lett.* ***1988***, *29*, 4427.

[1045]d'Angelo, J.; Desmaële, D.; Dumas, F.; Guingant, A. *Tetrahedron Asymmetry* ***1992***, *3*, 459.

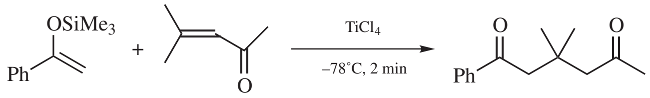
[1046]Mannich bases react with ketones *without* basic catalysts to give 1,5-diketones, but this process, known as the *thermal-Michael reaction*, has a different mechanism: Brown, H.L.; Buchanan, G.L.; Curran, A.C.W.; McLay, G.W. *Tetrahedron* ***1968***, *24*, 4565; Gill, N.S.; James, K.B.; Lions, F.; Potts, K.T. *J. Am. Chem. Soc.* ***1952***, *74*, 4923.

[1047]Holton, R.A.; Williams, A.D.; Kennedy, R.M. *J. Org. Chem.* ***1986***, *51*, 5480.

In certain cases, Michael reactions can take place under acidic conditions.[1048] Michael-type addition of radicals to conjugated carbonyl compounds is also known.[1049] Radical addition can be catalyzed by $Yb(OTf)_3$,[1050] but radicals add under standard conditions as well, even intramolecularly.[1051] Electrochemical-initiated Michael additions are known.

Michael reactions are sometimes applied to substrates of the type C≡C—Z, where the coproducts are conjugated systems of the type C=C—Z.[1052] Indeed, because of the greater susceptibility of triple bonds to nucleophilic attack, it is even possible for nonactivated alkynes (e.g., acetylene), to be substrates in this reaction.[1053]

In a closely related reaction, silyl enol ethers add to α,β-unsaturated ketones and esters when catalyzed[1054] by $TiCl_4$, for example,[1055]



$InCl_3$ also catalyzes this reaction.[1056] Aluminum compounds also catalyze this reaction[1057] and the reaction has been done in neat tri-*n*-propylaluminum.[1058] A solid-state version of the reaction used alumina•$ZnCl_2$.[1059] This reaction, also, has been performed diastereoselectively.[1060] Tin enolates have been used.[1061]

OS **I**, 272; **II**, 200; **III**, 286; **IV**, 630, 652, 662, 776; **V**, 486, 1135; **VI**, 31, 648, 666, 940; **VII**, 50, 363, 368, 414, 443; **VIII**, 87, 210, 219, 444, 467; **IX**, 526. See also, OS **VIII**, 148.

[1048] See Hajos, Z.G.; Parrish, D.R. *J. Org. Chem.* ***1974***, *39*, 1612; *Org. Synth.* ***VII***, 363.

[1049] Undheim, K.; Williams, K. *J. Chem. Soc., Chem. Commun.* ***1994***, 883; Bertrand, S.; Glapski, C.; Hoffmann, N.; Pete, J.-P. *Tetrahedron Lett.* ***1999***, *40*, 3169.

[1050] Sibi, M.P.; Jasperse, C.P.; Ji, J. *J. Am. Chem. Soc.* ***1995***, *117*, 10779. See Wu, J.H.; Radinov, R.; Porter, N.A. *J. Am. Chem. Soc.* ***1995***, *117*, 11029 for a related reaction involving $Zn(OTf)_2$.

[1051] Enholm, E.J.; Kinter, K.S. *J. Org. Chem.* ***1995***, *60*, 4850.

[1052] Rudorf, W.-D.; Schwarz, R. *Synlett* ***1993***, 369.

[1053] See, for example, Makosza, M. *Tetrahedron Lett.* ***1966***, 5489.

[1054] Other catalysts have also been used. For a list of catalysts, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1576–1582. See also, Mukaiyama, T.; Kobayashi, S.; Tamura, M.; Sagawa, Y. *Chem. Lett.* ***1987***, 491; Mukaiyama, T.; Kobayashi, S. *J. Organomet. Chem.* ***1990***, *382*, 39.

[1055] Narasaka, K.; Soai, K.; Aikawa, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* ***1976***, *49*, 779; Saigo, K.; Osaki, M.; Mukaiyama, T. *Chem. Lett.* ***1976***, 163; Matsuda, I. *J. Organomet. Chem.* ***1987***, *321*, 307; Narasaka, K. *Org. Synth,. 65*, 12. See also, Yoshikoshi, A.; Miyashita, M. *Acc. Chem. Res.* ***1985***, *18*, 284.

[1056] Loh, T.-P.; Wei, L.-L. *Tetrahedron* ***1998***, *54*, 7615.

[1057] Tucker, J.A.; Clayton, T.L.; Mordas, D.M. *J. Org. Chem.* ***1997***, *62*, 4370.

[1058] Kabbara, J.; Flemming, S.; Nickisch, K.; Neh, H.; Westermann, J. *Tetrahedron* ***1995***, *51*, 743.

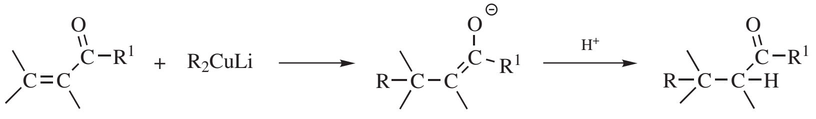
[1059] Ranu, B.C.; Saha, M.; Bhar, S. *Tetrahedron Lett.* ***1993***, *34*, 1989.

[1060] See Heathcock, C.H.; Uehling, D.E. *J. Org. Chem.* ***1986***, *51*, 279; Mukaiyama, T.; Tamura, M.; Kobayashi, S. *Chem. Lett.* ***1986***, 1017, 1817, 1821; ***1987***, 743.

[1061] Yasuda, M.; Ohigashi, N.; Shibata, I.; Baba, A. *J. Org. Chem.* ***1999***, *64*, 2180; Yasuda, M.; Chiba, K.; Ohigashi, N.; Katoh, Y.; Baba, A. *J. Am. Chem. Soc.* ***2003***, *125*, 7291.

15-25 1,4 Addition of Organometallic Compounds to Activated Double Bonds

Hydro-alkyl-addition



143

Lithium dialkylcopper reagents (see **10-57**) add to α,β-unsaturated aldehydes[1062] and ketones (R′ =H, R, Ar) to give conjugate addition products[1063] in a reaction closely related to the Michael reaction. α,β-Unsaturated esters are less reactive,[1064] and the corresponding acids do not react at all. R can be primary alkyl, vinylic,[1065] or aryl. If Me_3SiCl is present, the reaction takes place much faster and with higher yields; in this case the product is the silyl enol ether of **143** (see **12-17**).[1066] The use of Me_3SiCl also permits good yields with allylic R groups.[1067] Conjugated alkynyl-ketones also react via 1,4-addition to give substituted alkenyl-ketones.[1068]

Various functional groups, such as OH and unconjugated C=O groups, may be present in the substrate.[1069] Conjugated sulfones are also good substrates.[1070] An excess of the cuprate reagent relative to the conjugated substrate is often required. In general, only one of the R groups of R_2CuLi adds to the substrate; the other is wasted. This can be a limitation where the precursor (RLi or RCu, see **12-36**) is expensive or available in limited amounts, particularly if an excess of the reagent

[1062]For reviews, see Alexakis, A.; Chuit, C.; Commerçon-Bourgain, M.; Foulon, J.P.; Jabri, N.; Mangeney, P.; Normant, J.F. *Pure Appl. Chem.* ***1984***, *56*, 91.

[1063]House, H.O.; Respess, W.L.; Whitesides, G.M. *J. Org. Chem.* ***1966***, *31*, 3128. For reviews, see Posner, G.H. *Org. React.* ***1972***, *19*, 1; House, H.O. *Acc. Chem. Res.* ***1976***, *9*, 59. For a discussion of the mechanism and regioselectivity, see Yamanaka, M.; Kato, S.; Nakamura, E. *J. Am. Chem. Soc.* ***2004***, *126*, 6287. For examples of the use of this reaction in the synthesis of natural products, see Posner, G.H. *An Introduction to Synthesis Using Organocopper Reagents*, Wiley, NY, ***1980***, pp. 10–67. For a list of organocopper reagents that give this reaction, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1599–1613, 1814–1824.

[1064]R_2CuLi also add to *N*-tosylated α,β-unsaturated amides: Nagashima, H.; Ozaki, N.; Washiyama, M.; Itoh, K. *Tetrahedron Lett.* ***1985***, *26*, 657.

[1065]Bennabi, S.; Narkunan, K.; Rousset, L.; Bouchu, D.; Ciufolini, M.A. *Tetrahedron Lett.* ***2000***, *41*, 8873.

[1066]Corey, E.J.; Boaz, N.W. *Tetrahedron Lett.* ***1985***, *26*, 6019; Alexakis, A.; Berlan, J.; Besace,Y. *Tetrahedron Lett.* ***1986***, *27*, 1047; Matsuza, S.; Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron* ***1989***, *45*, 349; Horiguchi, Y.; Komatsu, M.; Kuwajima, I. *Tetrahedron Lett.* ***1989***, *30*, 7087; Linderman, R.J.; McKenzie, J.R. *J. Organomet. Chem.* ***1989***, *361*, 31; Bertz, S.H.; Smith, R.A.J. *Tetrahedron* ***1990***, *46*, 4091. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1491–1492.

[1067]Lipshutz, B.H.; Ellsworth, E.L.; Dimock, S.H.; Smith, R.A.J. *J. Am. Chem. Soc.* ***1990***, *112*, 4404; Lipshutz, B.H.; James, B. *Tetrahedron Lett.* ***1993***, *34*, 6689.

[1068]Degl'Innocenti, A.; Stucchi, E.; Capperucci, A.; Mordini, A.; Reginato, G.; Ricci, A. *Synlett* ***1992***, *329*, 332.

[1069]For the use of enol tosylates of 1,2-diketones as substrates, see Charonnat, J.A.; Mitchell, A.L.; Keogh, B.P. *Tetrahedron Lett.* ***1990***, *31*, 315.

[1070]Domínguez, E.; Carretero, J.C. *Tetrahedron Lett.* ***1993***, *34*, 5803.

is required. The difficulty of group transfer can be overcome by using one of the mixed reagents $R(R'C{\equiv}C)CuLi$,[1071] $R(O{-}t{-}Bu)CuLi$,[1072] $R(PhS)CuLi$,[1073] each of which transfers only the R group. Mixed reagents are easily prepared by the reaction of RLi with $R'C{\equiv}CCu$ ($R' = n$-Pr or t-Bu), t-BuOCu, or PhSCu, respectively. A further advantage of the mixed reagents is that good yields of addition product are achieved when R is tertiary, so that use of one of them permits the introduction of a tertiary alkyl group. The mixed reagents R(CN)CuLi[1074] (prepared from RLi and CuCN) and $R_2Cu(CN)Li_2$[1075] also selectively transfer the R group.[1076] Other mixed reagents incorporate a ligand that is not easily transferred, such as $R(R'Se)Cu(CN)Li_2$, leading to selective transfer of the R group.[1077] The reaction has also been carried out[1078] with α,β-acetylenic ketones,[1079] esters, and nitriles.

Both Grignard and R_2CuLi reagents[1080] have also been added to systems of the form $C{\equiv}C{-}C{=}O$.[1081] Conjugate addition to α,β-unsaturated and acetylenic acids and esters, as well as ketones, can be achieved by the use of the coordinated reagents $RCu{\bullet}BF_3$ (R = primary).[1082] Alkylcopper compounds RCu (R = primary or secondary alkyl) have also been used with tetramethylethylenediamine and Me_3SiCl to give silyl enol ethers from α,β-unsaturated ketones in high yield.[1083] Amine units have been transferred in this manner using α-lithio amides, CuCN, and additives ranging from LiCl to $Me_2NCH_2SnBu_3$, which gave conjugate addition of an amidomethyl unit, $-CH_2N(Me)Boc$.[1084] Other amino-cuprates are known to give conjugate addition reactions.[1085]

[1071]House, H.O.; Umen, M.J. *J. Org. Chem.* ***1973***, *38*, 3893; Corey, E.J.; Floyd, D.; Lipshutz, B.H. *J. Org. Chem.* ***1978***, *43*, 3419.

[1072]Posner, G.H.; Whitten, C.E. *Tetrahedron Lett.* ***1973***, 1815.

[1073]Posner, G.H.; Whitten, C.E.; Sterling, J.J. *J. Am. Chem. Soc.* ***1973***, *95*, 7788.

[1074]Gorlier, J.; Hamon, L.; Levisalles, J.; Wagnon, J. *J. Chem. Soc., Chem. Commun.* ***1973***, 88. For another useful mixed reagent, see Ledlie, D.B.; Miller, G. *J. Org. Chem.* ***1979***, *44*, 1006.

[1075]Lipshutz, B.H.; Wilhelm, R.S.; Kozlowski, J. *Tetrahedron Lett.* ***1982***, *23*, 3755; Lipshutz, B.H. *Tetrahedron Lett.* ***1983***, *24*, 127.

[1076]When the two R groups of $R_2Cu(CN)Li_2$ are different, one can be selectively transferred: Lipshutz, B.H.; Wilhelm, R.S.; Kozlowski, J.A. *J. Org. Chem.* ***1984***, *49*, 3938.

[1077]Zinn, F.K.; Ramos, E.C.; Comasseto, J.V. *Tetahedron Lett.* ***2001***, *42*, 2415.

[1078]For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 456–457.

[1079]Lee, P.H.; Park, J.; Lee, K.; Kim, H.-C. *Tetrahedron Lett.* ***1999***, *40*, 7109.

[1080]For example, see Corey, E.J.; Kim, C.U.; Chen, H.K.; Takeda, M. *J. Am. Chem. Soc.* ***1972***, *94*, 4395; Anderson, R.J.; Corbin, V.L.; Cotterrell, G.; Cox, G.R.; Henrick, C.A.; Schaub, F.; Siddall, J.B. *J. Am. Chem. Soc.* ***1975***, *97*, 1197.

[1081]For a review of the addition of organometallic reagents to conjugated enynes see Miginiac, L. *J. Organomet. Chem.* ***1982***, *238*, 235.

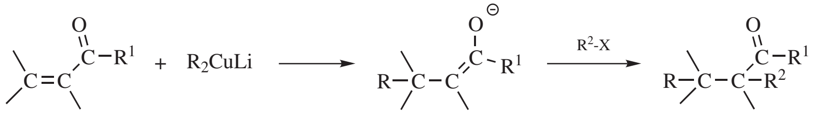
[1082]For a review, see Yamamoto, Y. *Angew. Chem. Int. Ed.* ***1986***, *25*, 947. For a discussion of the role of the BF_3, see Lipshutz, B.H.; Ellsworth, E.L.; Siahaan, T.J. *J. Am. Chem. Soc.* ***1988***, *110*, 4834; ***1989***, *111*, 1351.

[1083]Johnson, C.R.; Marren, T.J. *Tetrahedron Lett.* ***1987***, *28*, 27.

[1084]Dieter, R.K.; Velu, S.E. *J. Org. Chem.* ***1997***, *62*, 3798; Dieter, R.K.; Alexander, C.W. *Synlett* ***1993***, 407; Dieter, R.K.; Alexander, C.W.; Nice, L.E. *Tetrahedron* ***2000***, *56*, 2767; Dieter, R.K.;Lu, K.; Velu, S.E. *J. Org. Chem.* ***2000***, *65*, 8715. See Dieter, R.K.; Topping, C.M.; Nice, L.E. *J. Org. Chem.* ***2001***, *66*, 2302.

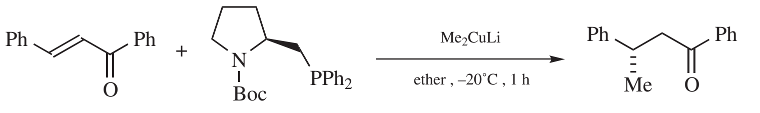
[1085]Yamamoto, Y.; Asao, N.; Uyehara, T. *J. Am. Chem. Soc.* ***1992***, *114*, 5427.

There is generally little or no competition from 1,2-addition (to the C=O). However, when R is allylic, 1,4-addition is observed with some substrates and 1,2-addition with others.[1086] R_2CuLi also add to α,β-unsaturated sulfones[1087] but not to simple α,β-unsaturated nitriles.[1088] Organocopper reagents (RCu), as well as certain R_2CuLi add to α,β-unsaturated and acetylenic sulfoxides.[1089]



143

Conjugate addition of the cuprate to the α,β-unsaturated ketone leads to an enolate ion, **143**. It is possible to have this enolate anion reacts with an electrophilic species (*tandem vicinal difunctionalization*), in some cases at the O and in other cases at the C.[1090] For example, if an alkyl halide R^2X is present (R^2 = primary alkyl or allylic), the enolate **143** can be alkylated directly.[1091] Thus, by this method, both the α and β positions of a ketone are alkylated in one synthetic operation (see also, **15-22**).



144

As with the Michael reaction (**15-24**) the 1,4-addition of organometallic compounds has been performed diastereoselectively[1092] and enantioselectively.[1093]

[1086]House, H.O.; Fischer, Jr., W.F. *J. Org. Chem.* ***1969***, *34*, 3615. See also, Daviaud, G.; Miginiac, P. *Tetrahedron Lett.* ***1973***, 3345.

[1087]Posner, G.H.; Brunelle, D.J. *Tetrahedron Lett.* ***1973***, 935.

[1088]House, H.O.; Umen, M.J. *J. Org. Chem.* ***1973***, *38*, 3893.

[1089]Truce, W.E.; Lusch, M.J. *J. Org. Chem.* ***1974***, *39*, 3174; ***1978***, *43*, 2252.

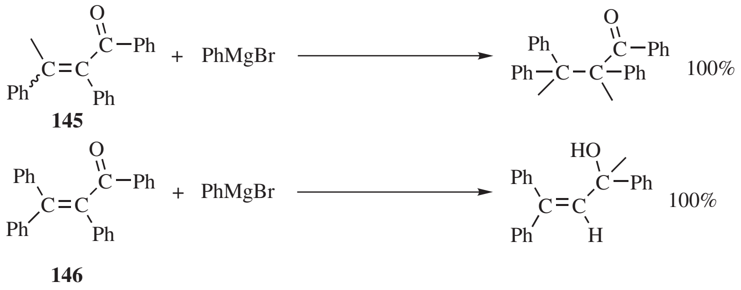
[1090]For reviews of such reactions, see Chapdelaine, M.J.; Hulce, M. *Org. React.* ***1990***, *38*, 225; Taylor, R.J.K. *Synthesis* ***1985***, 364. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1609–1612, 1826.

[1091]Coates, R.M.; Sandefur, L.O. *J. Org. Chem.* ***1974***, *39*, 275; Posner, G.H.; Lentz, C.M. *Tetrahedron Lett.* ***1977***, 3215.

[1092]For some examples, see Isobe, M.; Funabashi, Y.; Ichikawa, Y.; Mio, S.; Goto, T. *Tetrahedron Lett.* ***1984***, *25*, 2021; Kawasaki, H.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* ***1985***, *26*, 3031; Yamamoto, Y.; Nishii, S.; Ibuka, T. *J. Chem. Soc., Chem. Commun.* ***1987***, 464, 1572; Smith III, A.B.; Dunlap, N.K.; Sulikowski, G.A. *Tetrahedron Lett.* ***1988***, *29*, 439; Smith III, A.B.; Trumper, P.K. *Tetrahedron Lett.* ***1988***, *29*, 443; Alexakis, A.; Sedrani, R.; Mangeney, P.; Normant, J.F. *Tetrahedron Lett.* ***1988***, *29*, 4411; Larchevêque, M.; Tamagnan, G.; Petit, Y. *J. Chem. Soc., Chem. Commun.* ***1989***, 31; Page, P.C.B.; Prodger, J.C.; Hursthouse, M.B.; Mazid, M. *J. Chem. Soc. Perkin Trans. 1*, ***1990***, 167; Corey, E.J.; Hannon, F.J. *Tetrahedron Lett.* ***1990***, *31*, 1393.

[1093]For reviews, see Posner, G.H. *Acc. Chem. Res.* ***1987***, *20*, 72; in Morrison, J.D. *Assymmetric Synthesis* Vol. 2, Academic Press, NY, ***1983***, the articles by Tomioka, K.; Koga, K. pp. 201–224; Posner, G. pp. 225–241.

The influence of solvent and additives on yield and selectivity has been examined.[1094] The conjugate addition of dimethyl cuprate in the presence of a chiral ligand, such as **144**, is an example.[1095] The use of chiral ligands with MgI_2/I_2 and Bu_3SnI gave conjugate addition products with α,β-unsaturated amides with good % ee.[1096] Chiral bis(oxazoline) copper catalysts have been used for the conjugate addition of indoles to α,β-unsaturated esters.[1097] Chiral templates have also been used with Grignard reagents, directly[1098] and in the presence of $AlMe_2Cl$.[1099] Many of the examples cited below involve the use of chiral additives, chiral catalysts, or chiral templates.



Grignard reagents also add to conjugated substrates such as α,β-unsaturated ketones, cyano-ketones,[1100] esters, and nitriles,[1101] but 1,2-addition may seriously compete:[1102] The product is often controlled by steric factors. Thus **145** with phenylmagnesium bromide gives 100% 1,4-addition, while **146** gives 100% 1,2-addition. In general, substitution at the carbonyl group increases 1,4-addition, while substitution at the double bond increases 1,2-addition. In most cases, both products are obtained, but α,β-unsaturated *aldehydes* nearly always give exclusive 1,2-addition when treated with Grignard reagents. However, the extent of 1,4-addition of Grignard reagents can be increased by the use of a copper ion catalyst, for example, CuCl, $Cu(OAc)_2$.[1103] A dialkyl copper–magnesium iodide complex (R_2Cu•MgI) has been used for conjugate addition to chiral α,β-unsaturated amides.[1104] Grignard reagents mixed with $CeCl_3$ generates a reactive species that gives primarily 1,4-addition.[1105] It is likely that alkylcopper reagents, formed from RMgX and

[1094] Christenson, B.; Ullenius, C.; Håkansson, M.; Jagner, S. *Tetrahedron* ***1992***, *48*, 3623.

[1095] Kanai, M.; Koga, K.; Tomioka, K. *Tetrahedron Lett.* ***1992***, *33*, 7193.

[1096] Sibi, M.P.; Ji, J.; Wu, J.H.; Gürtler, S.; Porter, N.A. *J. Am. Chem. Soc.* ***1996***, *118*, 9200.

[1097] Jensen, K.B.; Thorhauge, J.; Hazell, R.G.; Jørgensen, K.A. *Angew. Chem. Int. Ed.* ***2001***, *40*, 160.

[1098] Han, Y.; Hruby, V.J. *Tetrahedron Lett.* ***1997***, *38*, 7317.

[1099] Bongini, A.; Cardillo, G.; Mingardi, A.; Tomasini, C. *Tetrahedron Asymmetry* ***1996***, *7*, 1457.

[1100] Kung, L.-R.; Tu, C.-H.; Shia, K.-S.; Liu, H.-J. *Chem. Commun.* ***2003***, 2490.

[1101] Fleming, F.F.; Wang, Q.; Zhang, Z.; Steward, O.W. *J. Org. Chem.* ***2002***, *67*, 5953.

[1102] For a discussion of the factors affecting 1,2- versus 1,4-addition, see Negishi, E. *Organometallics in Organic Synthesis* Vol. 1, Wiley, NY, ***1980***, pp. 127–133.

[1103] Posner, G.H. *Org. React.* ***1972***, *19*, 1; López, F.; Harutyanyan, S.R.; Minnaard, A.J.; Feringa, B.L. *J. Am. Chem. Soc.* ***2004***, *126*, 12784.

[1104] Schneider, C.; Reese, O. *Synthesis* ***2000***, 1689.

[1105] Bartoli, G.; Bosco, M.; Sambri, L.; Marcantoni, E. *Tetrahedron Lett.* ***1994***, *35*, 8651.

Cu^+ (cupric acetate is reduced to cuprous ion by excess RMgX), are the actual attacking species in these cases.[1063] Alkylidene malonic ester derivatives, $C{=}C(CO_2R)$, increase the facility of 1,4-addition with the two electron withdrawing groups.[1106] Alkylidene amido esters, $C{=}C(CO_2R)NHCOAr$, react with $EtI/Mg(ClO_4)_2$ and Bu_3SnH, in the presence of BEt_3/O_2 and a chiral ligand, to give the ethylated product $EtCHCH(CO_2R)NHCOAr$.[1107] This is probably a radical process (see **15-35**).

Organolithium reagents[1108] generally react with conjugated aldehydes, ketones and esters by 1,2-addition,[1109] but 1,4-addition was achieved with esters of the form C=C–COOAr, where Ar was a bulky group such as 2,6-di-*tert*-butyl-4-methoxyphenyl.[1110] Alkyllithium reagents can be made to give 1,4-addition with α,β-unsaturated ketones[1111] and aldehydes[1112] if the reactions are conducted in the presence of HMPA.[1113] Among organolithium reagents that have been found to add 1,4 in this manner are 2-lithio-1,3-dithianes (see **10-71**),[1114] vinyllithium reagents,[1115] and α-lithio allylic amides.[1116] Lithium–halogen exchange (**12-22**) generates an organolithium species that adds intramolecularly to conjugated esters to give cyclic and bicyclic products.[1117] 1,4-Addition of alkyllithium reagents to α,β-unsaturated aldehydes can also be achieved by converting the aldehyde to a benzothiazole derivative (masking the aldehyde function),[1118] from which the aldehyde group can be regenerated. When some conjugated acids are added to organolithium reagents, the conjugate addition product was isolated in good yield.[1119] α,β-Unsaturated nitro compounds undergo conjugate addition with aryllithium reagents, and subsequent treatment with acetic acid gives the α-aryl ketone.[1120]

[1106]See Kim, Y.M.; Kwon, T.W.; Chung, S.K.; Smith, M.B. *Synth. Commun.* ***1999***, *29*, 343.

[1107]Sibi, M.P.; Asano, Y.; Sausker, J.B. *Angew. Chem. Int. Ed.* ***2001***, *40*. 1293.

[1108]For a review of addition of organolithium compounds to double bonds, see Hunt, D.A. *Org. Prep. Proced. Int.* ***1989***, *21*, 705–749.

[1109]Rozhkov, I.N.; Makin, S.M. *J. Gen. Chem. USSR* ***1964***, *34*, 57. For a discussion of 1,2- versus 1,4-addition with organolithiums, see Cohen, T.; Abraham, W.D.; Myers, M. *J. Am. Chem. Soc.* ***1987***, *109*, 7923.

[1110]Cooke, Jr., M.P. *J. Org. Chem.* ***1986***, *51*, 1637.

[1111]Roux, M.C.; Wartski, L.; Seyden-Penne, J. *Tetrahedron* ***1981***, *37*, 1927; *Synth. Commun.* ***1981***, *11*, 85.

[1112]El-Bouz, M.; Wartski, L. *Tetrahedron Lett.* ***1980***, *21*, 2897.

[1113]Sikorski, W.H.; Reich, H.J. *J. Am. Chem. Soc.* ***2001***, *123*, 6527.

[1114]Lucchetti, J.; Dumont, W.; Krief, A. *Tetrahedron Lett.* ***1979***, 2695; Brown, C.A.; Yamaichi, A. *J. Chem. Soc., Chem. Commun.* ***1979***, 100; El-Bouz, M.; Wartski, L. *Tetrahedron Lett.* ***1980***, *21*, 2897. See also, Bürstinghaus, R.; Seebach, D. *Chem. Ber.* ***1977***, *110*, 841.

[1115]For an intramolecular example, see Maezaki, N.; Sawamoto, H.; Yuyama, S.; Yoshigami, R.; Suzuki, T.; Izumi, M.; Ohishi, H.; Tanaka, T. *J. Org. Chem.* ***2004***, *69*, 6335.

[1116]For an example using sparteine as a chiral additive, see Curtis, M.D.; Beak, P. *J. Org. Chem.* ***1999***, *64*, 2996.

[1117]Cooke Jr., M.P.; Gopal, D. *Tetrahedron Lett.* ***1994***, *35*, 2837. For an example involving the intramolecular addition of a vinyllithium reagent, see Piers, E.; Harrison, C.L.; Zetina-Rocha, C. *Org. Lett.* ***2001***, *3*, 3245.

[1118]Corey, E.J.; Boger, D.L. *Tetrahedron Lett.* ***1978***, 9. For another indirect method, see Sato, T.; Okazaki, H.; Otera, J.; Nozaki, H. *Tetrahedron Lett.* ***1988***, *29*, 2979.

[1119]Aurell, M.J.; Mestres, R.; Muñoz, E. *Tetrahedron Lett.* ***1998***, *39*, 6351. Also see, Plunian, B.; Vaultier, M.; Mortier, J. *Chem. Commun.* ***1998***, 81. For a discussion of the mechansim, see Aurell, M.J.; Bañuls, M.J.; Mestres, R.; Muñoz, E. *Tetrahedron* ***2001***, *57*, 1067.

[1120]Santos, R.P.; Lopes, R.S.C.; Lopes, C.C. *Synthesis* ***2001***, 845.

If the organolithium reagent is modified, 1,4-addition is more successful. The reaction of an aryllithium reagent with $B(OMe)_3$, for example, led to a rhodium-catalyzed conjugate addition with excellent enantioselectivity in when a chiral ligand was employed.[1121] Allylic tellurium reagents that are treated with lithium diisopropyl amide, and then conjugated esters give the 1,4-addition product, which cyclizes to form the corresponding cyclopropane derivative.[1122]

Boron reagents add to conjugated carbonyl compounds.[1123] Alkynyl borate esters (p. 815) give conjugate addition in the presence of boron trifluoride etherate,[1124] as do arylboronic acids (p. 815) with a rhodium,[1125] palladium,[1126] or a bismuth catalyst.[1127] Diethylzinc has also been used.[1128] Aryl boronic acids add to the double bond of vinyl sulfones in the presence of a rhodium catalyst.[1129] Similarly, $LiBPh(OMe)_3$ and a rhodium catalyst gave conjugate addition of the phenyl group to α,β-unsaturated esters.[1130] Potassium vinyltrifluoroborates (see p. 607) give 1,4-addition with a rhodium catalyst,[1131] as do aryltrifluoroborates.[1132]

Organozinc compounds add to conjugated systems. The use of chiral ligands is effective for conjugate addition of dialkylzinc compounds to α,β-unsaturated ketones, esters, and so on,[1133] including conjugated lactones.[1134] Many dialkylzinc compounds can be used, including vinylzinc compounds.[1135] Dialkylzinc

[1121]Takaya, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron Lett.* ***1999***, *40*, 6957.

[1122]Liao, W.-W.; Li, K.; Tang, Y. *J. Am. Chem. Soc.* ***2003***, *125*, 13030.

[1123]Kabalka, G.W.; Das, B.C.; Das, S. *Tetrahedron Lett.* ***2002***, *43*, 2323.

[1124]Chong, J.M.; Shen, L.; Taylor, N.J. *J. Am. Chem. Soc.* ***2000***, *122*, 1822.

[1125]Itooka, R.; Iguchi, Y.; Miyaura, N. *J. Org. Chem.* ***2003***, *68*, 6000; Ramnauth, J.; Poulin, O.; Bratovanov, S.S.; Rakhit, S.; Maddaford, S.P. *Org. Lett.* ***2001***, *3*, 2571; Reetz, M.T.; Moulin, D.; Gosberg, A. *Org. Lett.* ***2001***, *3*, 4083; Kuriyama, M.; Nagai, K.; Yamada, K.-i.; Miwa, Y.; Taga, T.; Tomioka, K. *J. Am. Chem. Soc.* ***2002***, *124*, 8932; Boiteau, J.-G.; Minnaard, A.J.; Feringa, B.L. *J. Org. Chem.* ***2003***, *68*, 9481; Boiteau, J.-G.; Imbos, R.; Minnaard, A.J.; Feringa, B.L. *Org. Lett.* ***2003***, *5*, 681; Shintani, R.; Ueyama, K.; Yamada, I.; Hayashi, T. *Org. Lett.* ***2004***, *6*, 3425; Shi, Q.; Xu, L.; Li, X.; Wang, R.; Au-Yeung, T.T.-L.; Chan, A.S.C.; Hayashi, T.; Cao, R.; Hong, M. *Tetrahedron Lett.* ***2003***, *44*, 6505; Amengual, R.; Michelet, V.; Genêt, J.-P. *Synlett.* ***2002***, 1791. For a review, see Hayashi, T. *Synlett* ***2001***, 879.

[1126]Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Angew. Chem. Int. Ed.* ***2003***, *42*, 2768.

[1127]Sakuma, S.; Miyaura, N. *J. Org. Chem.* ***2001***, *66*, 8944.

[1128]Dong, L.; Xu, Y.-J.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z. *Synthesis* ***2004***, 1057.

[1129]With a chiral ligand, see Mauleón, P.; Carretero, J.C. *Org. Lett.* ***2004***, *6*, 3195.

[1130]Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. *Tetrahedron Asymmetry* ***1999***, *10*, 4047.

[1131]Duursma, A.; Boiteau, J.-G.; Lefort, L.; Boogers, J.A.F.; de Vries, A.H.M.; de Vires, J.G.; Minnaard, A.J.; Feringa, B.L. *J. Org. Chem.* ***2004***, *69*, 8045.

[1132]Moss, R.J.; Wadsworth, K.J.; Chapman, C.J.; Frost, C.G. *Chem. Commun.* ***2004***, 1984; Pucheault, M.; Darses, S.; Genêt, J.-P. *Eur. J. Org. Chem.* ***2002***, 3552.

[1133]Alexakis, A.; Burton, J.; Vastra, J.; Mangeney, P. *Tetrahedron Asymm.*, ***1997***, *8*, 3987. Yan, M.; Yang, L.,-W.; Wong, K.-Y.; Chan, A.S.C. *Chem. Commun.* ***1999***, 11; Tong, P.-E.; Li, P.; Chan, A.S.C. *Tetrahedron Asymmetry* ***2001***, *12*, 2301; Liang, L.; Au-Yeung, T.T.-L.; Chan, A.S.C. *Org. Lett.* ***2002***, *4*, 3799.

[1134]Reetz, M.T.; Gosberg, A.; Moulin, D. *Tetrahedron Lett.* ***2002***, *43*, 1189.

[1135]For an example using a nickel catalyst with a chiral ligand, see Ikeda, S.-i.; Cui, D.-M.; Sato, Y. *J. Am. Chem. Soc.* ***1999***, *121*, 4712.

compounds and a chiral complex leads to enantioselective conjugate addition in conjunction with $Cu(OTf)_2$[1136] or other copper compounds.[1137] Diethylzinc adds to conjugated nitro compounds in the presence of a catalytic amount of $Cu(OTf)_2$ to give the conjugate addition product.[1138] Other transition-metal compounds can be used in conjunction with dialkylzinc compounds[1139] or with arylzinc halides (ArZnCl).[1140] Reaction of alkyl iodides with Zn/CuI with ultrasound generates an organometallic that adds to conjugated esters.[1141] Diarylzinc compounds (prepared with the aid of ultrasound) in the presence of nickel acetylacetonate, undergo 1,4-addition not only to α,β-unsaturated ketones, but also to α,β-unsaturated aldehydes.[1142] Mixed alkylzinc compounds also add to conjugated systems.[1143] Functionalized allylic groups can be added to terminal alkynes with allylic halides, zinc, and ultrasound, to give 1,4-dienes.[1144] Internal alkynes undergo 1,4-addition to conjugated esters using a combination of zinc metal and a cobalt complex as catalysts.[1145]

[1136]Liang, L.; Yan, M.; Li, Y.-M.; Chan, A.S.C. *Tetrahedron Asymmetry* ***2004***, *15*, 2575, and references cited therein; Pàmies, O.; Net, G.; Ruiz, A.; Claver, C.; Woodward, S. *Tetrahedron Asymmetry* ***2000***, *11*, 871; Diéguez, M. Ruiz, A.; Claver, C. *Tetrahedron Asymmetry* ***2001***, *12*, 2861; Arena, C.G.; Calabrò, G.P.; Franciò, G.; Faraone, F. *Tetrahedron Asymmetry* ***2000***, *11*, 2387; Mandoli, A.; Arnold, L.A.; de Vries, A.H.M.; Salvadori, P.; Feringa, B.L. *Tetrahedron Asymmetry* ***2001***, *12*, 1929; Martorell, A.; Naasz, R.; Feringa, B.L.; Pringle, P.G. *Tetrahedron Asymmetry* ***2001***, *12*, 2497; Escher, I.H.; Pfaltz, A. *Tetrahedron* ***2000***, *56*, 2879; Morimoto, T.; Yamaguchi, Y.; Suzuki, M.; Saitoh, A. *Tetrahedron Lett.* ***2000***, *41*, 10025; Alexakis, A.; Polet, D.; Rosset, S.; March, S. *J. Org. Chem.* ***2004***, *69*, 5660, and references cited therein; Pytkowicz, J.; Roland, S.; Mangeney, P. *Tetrahedron Asymmetry* ***2001***, *12*, 2087; Zhou, H.; Wang, W.-H.; Fu, Y.; Xie, J.-H.; Shi, W.-J.; Wang, L.-X.; Zhou, Q.-L. *J. Org. Chem.* ***2003***, *68*, 1582; Duncan, A.P.; Leighton, J.L. *Org. Lett.* ***2004***, *6*, 4117, and references cited therein; Choi, Y.H.; Choi, J.Y.; Yang, H.-Y.; Kim, H.Y. *Tetrahedron Asymmetry* ***2002***, *13*, 801; Kang, J.; Lee, J.H.; Lim, D.S. *Tetrahedron Asymmetry* ***2003***, *14*, 305; Scafato, P.; Labano, S.; Cunsolo, G.; Rosini, C. *Tetrahedron Asymmetry* ***2003***, *14*, 3873; Hird, A.W.; Hoveyda, A.H. *Angew. Chem. Int. Ed.* ***2003***, *42*, 1276.

[1137]Delapierre, G.; Brunel, J.M.; Constantieux, T.; Buono, G. *Tetrahedron Asymmetry* ***2001***, *12*, 1345; Hu, Y.; Liang, X.; Wang, J.; Zheng, Z.; Hu, X. *J. Org. Chem.* ***2003***, *68*, 4542; Wan, H.; Hu, Y.; Liang, Y.; Gao, S.; Wang, J.; Zheng, Z.; Hu, X. *J. Org. Chem.* ***2003***, *68*, 8277; Alexakis, A.; Polet, D.; Benhaim, C.; Rosset, S. *Tetrahedron Asymmetry* ***2004***, *15*, 2199; Breit, B.; Laungani, A.Ch. *Tetrahedron Asymmetry* ***2003***, *14*, 3823; Shi, M.; Wang, C.-J.; Zhang, W. *Chem. Eur. J.* ***2004***, *10*, 5507.

[1138]Yan, M.; Chan, A.S.C. *Tetrahedron Lett.* ***1999***, *40*, 6645; Rimkus, A.; Sewald, N. *Org. Lett.* ***2002***, *4*, 3289; Choi, H.; Hua, Z.; Ojima, I. *Org. Lett.* ***2004***, *6*, 2689; Mampreian, D.M.; Hoveyda, A.H. *Org. Lett.* ***2004***, *6*, 2829; Duursma, A.; Minnaard, A.J.; Feringa, B.L. *J. Am. Chem. Soc.* ***2003***, *125*, 3700.

[1139]With a vanadium complex: Hirao, T.; Takada, T.; Sakurai, H. *Org. Lett.* ***2000***, *2*, 3659. With a nickel complex: Yin, Y.; Li, X.; Lee, D.-S.; Yang, T.-K. *Tetrahedron Asymmetry* ***2000***, *11*, 3329; Shadakshari, U.; Nayak, S.K. *Tetrahedron* ***2001***, *57*, 8185.

[1140]Shitani, R.; Tokunaga, N.; Doi, H.; Hayashi, T. *J. Am. Chem. Soc.* ***2004***, *126*, 6240.

[1141]Sarandeses, L.A.; Mouriño, A.; Luche, J.-L. *J. Chem. Soc., Chem. Commun.* ***1992***, 798. See also, Das, B.; Banerjee, J.; Mahender, G.; Majhi, A. *Org. Lett.* ***2004***, *6*, 3349.

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[1143]Berger, S.; Langer, F.; Lutz, C.; Knochel, P.; Mobley, T.A.; Reddy, C.K. *Angew. Chem. Int. Ed.* ***1997***, *36*, 1496.

[1144]Knochel, P.; Normant, J.F. *J. Organomet. Chem.* ***1986***, *309*, 1.

[1145]Wang, C.-C.; Lin, P.-S.; Cheng, C.-H. *J. Am. Chem. Soc.* ***2002***, *124*, 9696.

Trialkylalanes R_3Al add 1,4 to α,β-unsaturated carbonyl compounds in the presence of nickel acetylacetonate[1146] or $Cu(OTf)_2$.[1147] In the presence of aluminum chloride, benzene reacts with conjugated amides to add a phenyl group to C-4.[1148] Alkyl halides react via conjugate addition using BEt_3 or $AlEt_3$.[1149] An alkynyl group can be added to the double bond of an α,β-unsaturated ketone by use of the diethylalkynylalane reagents $Et_2AlC{\equiv}CR$.[1150] In a similar manner, the alkenyl reagents $R_2AlCH{=}CR$ transfer an alkenyl group.[1151]

Terminal alkynes add to conjugated systems when using a ruthenium,[1152] palladium,[1153] or a rhodium catalyst.[1154] Triphenylbismuth (Ph_3Bi) and a rhodium catalyst gives conjugate addition of the phenyl group upon exposure to air.[1155] Similar reactivity is observed with a palladium catalyst in aqueous media.[1156] Lithium tetraalkylgallium reagents give 1,4-addition.[1157] Trimethyl(phenyl)tin and a rhodium catalyst gives conjugate addition of a methyl group[1158] and tetraphenyltin and a palladium catalyst adds a phenyl group.[1159] Allyltin compounds add an allyl group in the presence of a scandium catalyst.[1160] Benzylic bromides add to conjugated nitriles using a 2:1 mixture of $CrCl_3$ and manganese metal.[1161] Electrochemical conjugate addition to α,β-unsaturated ketones was reported using aryl halides and a cobalt catalyst.[1162] Aryl halides add in the presence of $NiBr_2$.[1163] Vinyl zirconium complexes undergo conjugate addition when using a rhodium catalyst.[1164] Pyrrole adds to conjugated alkynyl esters in the presence

[1146]Bagnell, L.; Meisters, A.; Mole, T. *Aust. J. Chem.* ***1975***, *28*, 817; Ashby, E.C.; Heinsohn, G. *J. Org. Chem.* ***1974***, *39*, 3297. See also, Sato, F.; Oikawa, T.; Sato, M. *Chem. Lett.* ***1979***, 167; Kunz, H.; Pees, K.J. *J. Chem. Soc. Perkin Trans. 1*, ***1989***, 1168.

[1147]Su, L.; Li, X.; Chan, W.L.; Jia, X.; Chan, A.S.C. *Tetrahedron Asymmetry* ***2003***, *14*, 1865.

[1148]Koltunov, K.Yu.; Walspurger, S.; Sommer, J. *Tetrahedron Lett.* ***2004***, *45*, 3547.

[1149]Liu, J.-Y.,; Jang, Y.-J.; Lin, W.-W.; Liu, J.-T.; Yao, C.-F. *J. Org. Chem.* ***2003***, *68*, 4030.

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[1151]Hooz, J.; Layton, R.B. *Can. J. Chem.* ***1973***, *51*, 2098. For a similar reaction with an alkenylzirconium reagent, see Dayrit, F.M.; Schwartz, J. *J. Am. Chem. Soc.* ***1981***, *103*, 4466.

[1152]With $SnCl_4$, see Trost, B.M.; Pinkerton, A.B. *J. Am. Chem. Soc.* ***1999***, *121*, 1988. See Chang, S.; Na, Y.; Choi, E.; Kim, S. *Org. Lett.* ***2001***, *3*, 2089.

[1153]Chen, L.; Li, C.-J. *Chem. Commun.* ***2004***, 2362.

[1154]Hayashi, T.; Tokunaga, N.; Yoshida, K.; Han, J.W. *J. Am. Chem. Soc.* ***2002***, *124*, 12102; Lerum, R.V.; Chisholm, J.D. *Tetrahedron Lett.* ***2004***, *45*, 6591.

[1155]Venkatraman, S.; Li, C.-J. *Tetrahedron Lett.* ***2001***, *42*, 781.

[1156]Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Chem. Commun.* ***2004***, 1822.

[1157]Han, Y.; Huang, Y.-Z.; Fang, L.; Tao, W.-T. *Synth. Commun.* ***1999***, *29*, 867.

[1158]Venkatraman, S.; Meng, Y.; Li, C.-J. *Tetrahedron Lett.* ***2001***, *42*, 4459; Oi, S.; Moro, M.; Ito, H.; Honma, Y.; Miyano, S.; Inoue, Y. *Tetrahedron* ***2002***, *58*, 91.

[1159]Ohe, T.; Wakita, T.; Motofusa, S.-i; Cho, C.S.; Ohe, K.; Uemura, S. *Bull. Chem. Soc. Jpn.* ***2000***, *73*, 2149; Ohe, T.; Uemura, S. *Tetrahedron Lett.* ***2002***, *43*, 1269.

[1160]Williams, D.R.; Mullins, R.J.; Miller, N.A. *Chem. Commun.* ***2003***, 2220.

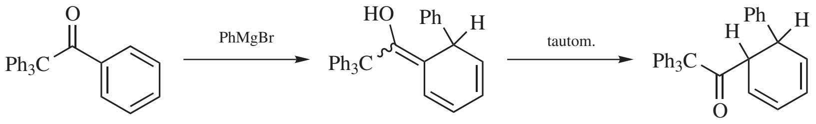
[1161]Augé, J.; Gil, R.; Kalsey, S. *Tetrahedron Lett.* ***1999***, *40*, 67.

[1162]Gomes, P.; Gosmini, C.; Nédélec, J.-Y.; Périchon, J. *Tetrahedron Lett.* ***2000***, *41*, 3385.

[1163]Condon, S.; Dupré, D.; Falgayrac, G.; Nédélec, J.-Y. *Eur. J. Org. Chem.* ***2002***, 105.

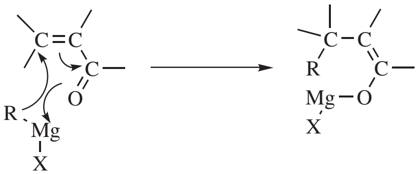
[1164]Kakuuchi, A.; Taguchi, T.; Hanzawa, Y. *Tetrahedron* ***2004***, *60*, 1293.

of palladium acetate, to give the 2-alkenyl pyrrole.[1165]



147

In certain cases, Grignard reagents add 1,4 to *aromatic* systems to give **147** after tautomerization (p. $$$) of the initial formed enol.[1166] Such cyclohexadienes are easily oxidizable to benzenes (often by atmospheric oxygen), so this reaction becomes a method of alkylating and arylating suitably substituted (usually hindered) aryl ketones. A similar reaction has been reported for aromatic nitro compounds where 1,3,5-trinitrobenzene reacts with excess methylmagnesium halide to give 2,4,6-trinitro-1,3,5-trimethylcyclohexane.[1167]



The mechanisms of most of these reactions are not well known. The 1,4 uncatalyzed Grignard reaction has been postulated to proceed by the cyclic mechanism shown, but there is evidence against it.[1168] The R_2CuLi[1169] and copper-catalyzed Grignard additions may involve a number of mechanisms, since the actual attacking species and substrates are so diverse.[1170] A free-radical mechanism of some type

[1165]Lu, W.; Jia, C.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* ***2000***, *2*, 2927.

[1166]This example is from Schmidlin, J.; Wohl, J. *Ber.* ***1910***, *43*, 1145; Mosher, W.A.; Huber, M.B. *J. Am. Chem. Soc.* ***1953***, *75*, 4604. For a review of such reactions see Fuson, R.C. *Adv. Organomet. Chem.* ***1964***, *1*, 221.

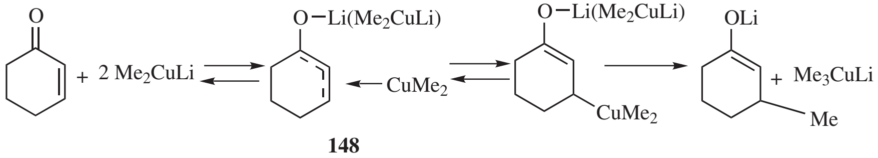
[1167]Severin, T.; Schmitz, R. *Chem. Ber.* ***1963***, *96*, 3081. See also, Bartoli, G. *Acc. Chem. Res.* ***1984***, *17*, 109; Bartoli, G.; Dalpozzo, R.; Grossi, L. *J. Chem. Soc. Perkin Trans. 2*, ***1989***, 573. For a study of the mechanism, see Bartoli, G.; Bosco, M.; Cantagalli, G.; Dalpozzo, R.; Ciminale, F. *J. Chem. Soc. Perkin Trans. 2*, ***1985***, 773.

[1168]House, H.O.; Thompson, H.W. *J. Org. Chem.* ***1963***, *28*, 360; Klein, J. *Tetrahedron* ***1964***, *20*, 465. See, however, Marets, J.; Rivière, H. *Bull. Soc. Chim. Fr.* ***1970***, 4320.

[1169]See Kingsbury, C.L.; Smith, R.A.J. *J. Org. Chem.* ***1997***, *62*, 4629. Also see, Bertz, S.H.; Miao, G.; Rossiter, B.E.; Snyder, J.P. *J. Am. Chem. Soc.* ***1995***, *117*, 11023; Snyder, J.P. *J. Am. Chem. Soc.* ***1995***, *117*, 11025; Vellekoop, A.S.; Smith, R.A.J. *J. Am. Chem. Soc.* ***1994***, *116*, 2902.

[1170]For some mechanistic investigations, see Berlan, J.; Battioni, J.; Koosha, K. *J. Organomet. Chem.* ***1978***, *152*, 359; *Bull. Soc. Chim. Fr.* ***1979***, II-183; Four, P.; Riviere, H.; Tang, P.W. *Tetrahedron Lett.* ***1977***, 3879; Casey, C.P.; Cesa, M.C. *J. Am. Chem. Soc.* ***1979***, *101*, 4236; Krauss, S.R.; Smith, S.G. *J. Am. Chem. Soc.* ***1981***, *103*, 141; Bartoli, G.; Bosco, M.; Dal Pozzo, R.; Ciminale, F. *J. Org. Chem.* ***1982***, *47*, 5227; Corey, E.J.; Boaz, N.W. *Tetrahedron Lett.* ***1985***, *26*, 6015; Yamamoto, Y.; Yamada, J.; Uyehara, T. *J. Am. Chem. Soc.* ***1987***, *109*, 5820; Ullenius, C.; Christenson, B. *Pure Appl. Chem.* ***1988***, *60*, 57; Christenson, B.; Olsson, T.; Ullenius, C. *Tetrahedron* ***1989***, *45*, 523; Krause, N. *Tetrahedron Lett.* ***1989***, *30*, 5219.

(perhaps SET) has been suggested[1171] although the fact that retention of configuration at R has been demonstrated in several cases rules out a completely free R• radical.[1172] For simple α,β-unsaturated ketones, such as 2-cyclohexenone, and Me_2CuLi, there is evidence[1173] for this mechanism:

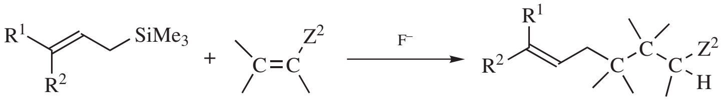


148 is a *d*,π* complex, with bonding between copper, as a base supplying a pair of *d* electrons, and the enone as a Lewis acid using the π* orbital of the allylic system.[1173] The ^{13}C NMR spectrum of an intermediate similar to **148** has been reported.[1174]

For the addition of organocopper reagents to alkynes and conjugated dienes, see **15-22**.

OS **IV**, 93; **V**, 762; **VI**, 442, 666, 762, 786; **VIII**, 112, 257, 277, 479; **IX**, 328, 350, 640.

15-26 The Sakurai Reaction



Allylic silanes $R_2C{=}CHCH_2SiMe_3$ can be used instead of silyl enol ethers (the *Sakurai reaction*).[1175] An allyl group can be added, to α,β-unsaturated carboxylic esters, amides and nitriles, with $CH_2{=}CHCH_2SiMe_3$ and F^- ion (see **15-47**).[1176] This reagent gave better results than lithium diallylcuprate (**15-25**). Catalytic Sakurai reactions are known.[1177] The palladium catalyzed reaction of conjugated ketones with $PhSi(OEt)_3$ with $SbCl_3$ and Bu_4NF in acetic acid gave the 1,4-addition product.[1178] A similar reaction was reported using $PhSi(OMe)_3$

[1171]See, for example, Ruden, R.A.; Litterer, W.E. *Tetrahedron Lett.* ***1975***, 2043; House, H.O.; Snoble, K.A.J. *J. Org. Chem.* ***1976***, *41*, 3076; Wigal, C.T.; Grunwell, J.R.; Hershberger, J. *J. Org. Chem.* ***1991***, *56*, 3759.

[1172]Näf, F.; Degen, P. *Helv. Chim. Acta* ***1971***, *54*, 1939; Whitesides, G.M.; Kendall, P.E. *J. Org. Chem.* ***1972***, *37*, 3718. See also, Ref. 1063.

[1173]Corey, E.J.; Hannon, F.J.; Boaz, N.W. *Tetrahedron* ***1989***, *45*, 545.

[1174]Bertz, S.H.; Smith, R.A.J. *J. Am. Chem. Soc.* ***1989***, *111*, 8276.

[1175]Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* ***1977***, *99*, 1673; Jellal, A.; Santelli, M. *Tetrahedron Lett.* ***1980***, *21*, 4487; Sakurai, H.; Hosomi, A.; Hayashi, J. *Org. Synth.* ***VII***, 443; Kuhnert, N.; Peverley, J.; Robertson, J. *Tetrahedron Lett.* ***1998***, *39*, 3215. For a review, see Fleming, I.; Dunoguès, J.; Smithers, R. *Org. React.* ***1989***, *37*, 57, see pp. 127, 335–370. For a review of intramolecular additions, see Schinzer, D. *Synthesis* ***1988***, 263.

[1176]Majetich, G.; Casares, A.; Chapman, D.; Behnke, M. *J. Org. Chem.* ***1986***, *51*, 1745.

[1177]$InCl_3$: Lee, P.H.; Lee, K.; Sung, S.-y.; Chang, S. *J. Org. Chem.* ***2001***, *66*, 8646.

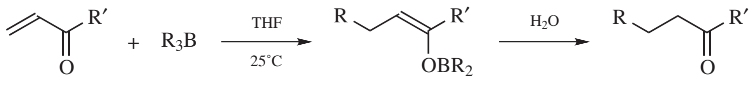
[1178]Denmark, S.E.; Amishiro, N. *J. Org. Chem.* ***2003***, *68*, 6997.

with a rhodium catalyst.[1179] In a related reaction, Ph_2SiCl_2, NaF and a rhodium catalyst gives conjugate addition of a phenyl group to α,β-unsaturated ketones.[1180] An interesting rhodium-catalyzed, conjugate addition of a phenyl group was reported using a siloxane polymer bearing Si—Ph units.[1181]

Silyl ketene acetals, RCH=C(OMe)$OSiMe_3$, add to conjugated ketones to give δ-keto esters, in $MeNO_2$ as solvent.[1182]

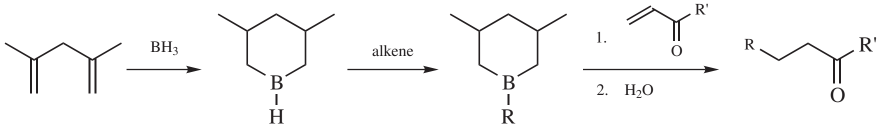
15-27 Conjugate Addition of Boranes to Activated Double Bonds

Hydro-alkyl-addition (overall transformation)



R′ = H, Me

Just as trialkylboranes add to simple alkenes (**15-16**), they rapidly add to the double bonds of acrolein, methyl vinyl ketone, and certain of their derivatives in THF at 25°C to give enol borinates (also see, p. 631), which can be hydrolyzed to aldehydes or ketones.[1183] If water is present in the reaction medium from the beginning, the reaction can be run in one laboratory step. Since the boranes can be prepared from alkenes (**15-16**), this reaction provides a means of lengthening a carbon chain by three or four carbons, respectively. Compounds containing a terminal alkyl group, such as crotonaldehyde (CH_3CH=CHCHO) and 3-penten-2-one, fail to react under these conditions, as does acrylonitrile, but these compounds can be induced to react by the slow and controlled addition of O_2 or by initiation with peroxides or UV light.[1184] A disadvantage is



149

[1179]Oi, S.; Honma, Y.; Inoue, Y. *Org. Lett.* ***2002***, *4*, 667; Oi, S.; Taira, A.; Honma, Y.; Inoue, Y. *Org. Lett.* ***2003***, *5*, 97.

[1180]Huang, T.-S.; Li, C.-J. *Chem. Commun.* ***2001***, 2348.

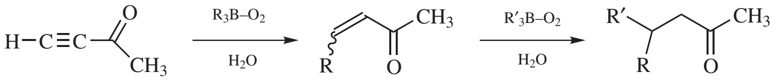
[1181]Koike, T.; Du, X.; Mori, A.; Osakada, K. *Synlett* ***2002***, 301.

[1182]RajanBabu, T.V. *J. Org. Chem.* ***1984***, *49*, 2083.

[1183]Suzuki, A.; Arase, A.; Matsumoto, H.; Itoh, M.; Brown, H.C.; Rogić, M.M.; Rathke, M.W. *J. Am. Chem. Soc.* ***1967***, *89*, 5708; Köster, R.; Zimmermann, H.; Fenzl, W. *Liebigs Ann. Chem.* ***1976***, 1116. For reviews, see Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, pp. 301–305, 318–323; Brown, H.C.; Midland, M.M. *Angew. Chem. Int. Ed.* ***1972***, *11*, 692, sse pp. 694–698; Kabalka, G.W. *Intra-Sci. Chem. Rep.* ***1973***, *7(1)*, 57; Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithica, NY, ***1972***, pp. 413–433.

[1184]Brown, H.C.; Kabalka, G.W. *J. Am. Chem. Soc.* ***1970***, *92*, 712, 714. See also, Utimoto, K.; Tanaka, T.; Furubayashi, T.; Nozaki, H. *Tetrahedron Lett.* ***1973***, 787; Miyaura, N.; Kashiwagi, M.; Itoh, M.; Suzuki, A. *Chem. Lett.* ***1974***, 395.

that only one of the three R groups of R_3B adds to the substrate, so that the other two are wasted. This difficulty is overcome by the use of a β-alkyl borinate, such as **149**,[1185] which can be prepared as shown. **149** (R = *tert*-butyl) can be made by treatment of **149** (R = OMe) with *t*-BuLi. The use of this reagent permits *tert*-butyl groups to be added. β-1-Alkenyl-9-BBN compounds β-RCH = CR′-9-BBN (prepared by treatment of alkynes with 9-BBN or of RCH=CR′Li with β-methoxy-9-BBN[1186]) add to methyl vinyl ketones to give, after hydrolysis, γ,δ-unsaturated ketones,[1187] although β-R-9-BBN, where R = a saturated group, are not useful here, because the R group of these reagents does not preferentially add to the substrate.[1184] The corresponding β-1-alkynyl-9-BBN compounds also give the reaction.[1188] Like the three substrates mentioned above, 3-butyn-2-one fails to react in the absence of air, but undergoes the reaction when exposed to a slow stream of air:[1189] Since the product, **150**, is an α,β-unsaturated ketone, it can be made to react with another BR_3, the same or different, to produce a wide variety of ketones **151**.



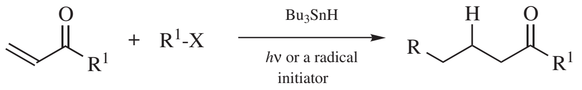
150 **151**

Vinyl boranes add to conjugated ketones in the presence of a rhodium catalyst (with high asymmetric induction in the presence of BINAP).[1190] Alkynyl-boranes also add to conjugated ketones, in the presence of BF_3.[1191]

The fact that these reactions are catalyzed by free-radical initiators and inhibited by galvinoxyl[1192] (a free-radical inhibitor) indicates that free-radical mechanisms are involved.

15-28 Radical Addition to Activated Double Bonds

Hydro-alkyl-addition



[1185]Brown, H.C.; Negishi, E. *J. Am. Chem. Soc.* ***1971***, *93*, 3777.

[1186]Brown, H.C.; Bhat, N.G.; Rajagopalan, S. *Organometallics* ***1986***, *5*, 816.

[1187]Jacob III, P.; Brown, H.C. *J. Am. Chem. Soc.* ***1976***, *98*, 7832; Satoh, Y.; Serizawa, H.; Hara, S.; Suzuki, A. *J. Am. Chem. Soc.* ***1985***, *107*, 5225. See also, Molander, G.A.; Singaram, B.; Brown, H.C. *J. Org. Chem.* ***1984***, *49*, 5024. Alkenyldialkoxyboranes, together with BF_3–etherate, also transfer vinylic groups: Hara, S.; Hyuga, S.; Aoyama, M.; Sato, M.; Suzuki, A. *Tetrahedron Lett.* ***1990***, *31*, 247.

[1188]Sinclair, J.A.; Molander, G.A.; Brown, H.C. *J. Am. Chem. Soc.* ***1977***, *99*, 954. See also, Molander, G.A.; Brown, H.C. *J. Org. Chem.* ***1977***, *42*, 3106.

[1189]Suzuki, A.; Nozawa, S.; Itoh, M.; Brown, H.C.; Kabalka, G.W.; Holland, G.W. *J. Am. Chem. Soc.* ***1970***, *92*, 3503.

[1190]Takaya, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron Lett.* ***1998***, *39*, 8479.

[1191]Fujishima, H.; Takada, E.; Hara, S.; Suzuki, A. *Chem. Lett.* ***1992***, 695.

[1192]Kabalka, G.W.; Brown, H.C.; Suzuki, A.; Honma, S.; Arase, A.; Itoh, M. *J. Am. Chem. Soc.* ***1970***, *92*, 710. See also, Arase, A.; Masuda, Y.; Suzuki, A. *Bull. Chem. Soc. Jpn.* ***1976***, *49*, 2275.

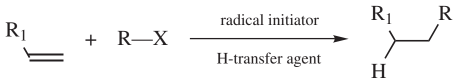
In a reaction similar to **15-25**, alkyl groups can be added to alkenes activated by, such groups as COR′, COOR′, CN, and even Ph.[1193] In the method illustrated above, the R group comes from an alkyl halide (R = primary, secondary, or tertiary alkyl; X = Br or I) and the hydrogen from the tin hydride. The reaction of *tert*-butyl bromide, Bu_3SnH and AIBN (p. 935), for example, adds a *tert*-butyl group to a conjugated ester via 1,4-addition.[1194] An alkene is converted to an alkylborane with catecholborane (p. 817) and when treated with a conjugated ketone and O_2, radical conjugate addtion leads to the β-substituted ketone.[1195] Organomercury hydrides (RHgH) generated *in situ* from RHgX and $NaBH_4$, can also be used.[1196] When the tin method is used, Bu_3SnH can also be generated in a similar way, from R_3SnX and $NaBH_4$. The tin method has a broader scope (e.g., it can be used on $CH_2{=}CCl_2$), but the mercury method uses milder reaction conditions. Like **15-27**, these additions have free-radical mechanisms. The reaction has been used for free-radical cyclizations of the type discussed on p. 1125.[1197] Such cyclizations normally give predominant formation of 15-membered rings, but large rings (11–20 members) have also been synthesized by this reaction.[1198]

Free-radical addition of an aryl group and a hydrogen has been achieved by treatment of activated alkenes with a diazonium salt and $TiCl_3$.[1199] The addition of R_3Al takes place by a free-radical mechanism.[1146]

OS **VII**, 105.

15-29 Radical Addition to Unactivated Double Bonds[1200]

Alkyl-hydro-addition



[1193]For reviews, see Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, Pergamon, Elmsford, NY, ***1986***, pp. 36–68; Giese, B. *Angew. Chem. Int. Ed.* ***1985***, *24*, 553; Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, ***1985***, pp. 263–273. The last review includes a table with many examples of the mercury method. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1809–1813.

[1194]Hayen, A.; Koch, R.; Metzger, J.O. *Angew. Chem. Int. Ed.* ***2000***, *39*, 2758.

[1195]Ollivier, C.; Renaud, P. *Chem. Eur. J.* ***1999***, *5*, 1468.

[1196]For the use of tris(trimethylsilyl)silane, see Giese, B.; Kopping, B.; Chatgilialoglu, C. *Tetrahedron Lett.* ***1989***, *30*, 681.

[1197]For reviews, see Jasperse, C.P.; Curran, D.P.; Fevig, T.L. *Chem. Rev.* ***1991***, *91*, 1237; Curran, D.P. *Adv. Free Radical Chem. (Greenwich, Conn.)* ***1990***, *1*, 121; Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*, Pergamon, Elmsford, NY, ***1986***, pp. 151–169. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 413–418.

[1198]See Porter, N.A.; Chang, V.H. *J. Am. Chem. Soc.* ***1987***, *109*, 4976.

[1199]Citterio, A.; Vismara, E. *Synthesis* ***1980***, 291. For other methods of adding an alkyl or aryl group and a hydrogen to activated double bonds by free-radical processes, see Cacchi, S.; Palmieri, G. *Synthesis* ***1984***, 575; Lebedev, S.A.; Lopatina, V.S.; Berestova, S.S.; Petrov, E.S.; Beletskaya, I.P. *J. Org. Chem. USSR* ***1986***, *22*, 1238; Luche, J.L.; Allavena, C. *Tetrahedron Lett.* ***1988***, *29*, 5369; Varea, T.; González-Núñez, M.E.; Rodrigo-Chiner, J.; Asensio, G. *Tetrahedron Lett.* ***1989***, *30*, 4709; Barton, D.H.R.; Sarma, J.C. *Tetrahedron Lett.* ***1990***, *31*, 1965.

[1200]See Smith, M.B. *Organic Synthesis,* 2nd ed., McGraw-Hill, NY ***2001***, pp. 1167–1172

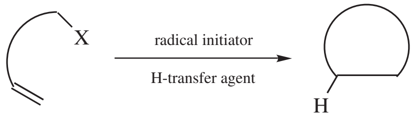
Radical addition to alkenes is usually difficult, except when addition occurs to conjugated carbonyl compounds (**15-24**). An important exception involves radicals bearing a heteroatom α to the carbon bearing the radical center. These radical are much more stable and can add to alkenes, usually with anti-Markovnikov orientation, as in the radical induced addition of HBr to alkenes (**15-2**).[1201] Examples of this type of reaction include the use of alcohol-, ester-,[1202] amino-, and aldehyde-stabilized radicals.[455] Carbon tetrachloride can be cleaved homolytically to generate Cl• and Cl_3C•, which can add to alkenes. The alkyl group of alkyl iodides adds to alkenes with BEt_3/O_2 as the initiator and in the presence of a tetraalkylammonium hypophosphite.[1203] When chloroform was treated with a ruthenium carbene complex, Cl_2CH add to the less substituted carbon of an alkene, and Cl to the more substituted carbon.[1204] The radical generated from $(EtO)_2POCH_2Br$ adds to alkenes to generate a new phosphonate ester.[1205] α-Bromo esters add to alkenes in the presence of BEt_3/air to give a γ-bromo ester.[1206] α-Bromo amides add the Br and the acyl carbon to an alkene using $Yb(OTf)_3$ with BEt_3/O_2 as the radical initiator.[1207] α-Iodo amides add to alkenes using a water soluble azobis initiator to give the iodo ester, which cyclizes under the reaction conditions to give a lactone.[1208] β-Keto dithiocarbonates, RC(=O)—C—SC(=S)OEt, generate the radical in the presence of a peroxide and add to alkenes.[1209] Malonate derivatives add to alkenes in the presence of a mixture of Mn/Co catalyst, in oxygenated acetic acid.[1210]

Other radicals can add to alkenes, and the rate constant for the addition of methyl radicals to alkenes has been studied,[1211] and the rate of radical additions to alkenes in general has also been studied.[1212] The kinetic and thermodynamic control of a radical addition regiochemistry has also been studied.[1213] Alkynes are generally less reactive than alkenes in radical coupling reactions.[1214] Nonradical nucleophiles usually react faster with alkynes than with alkenes, however.[1215]

[1201]See Curran, D.P. *Synthesis* ***1988***, 489 (see pp. 497–498).
[1202]Deng, L.X.; Kutateladze, A.G. *Tetrahedron Lett.* ***1997***, *38*, 7829.
[1203]Jang, D.O.; Cho, D.H.; Chung, C.-M. *Synlett* ***2001***, 1923.
[1204]Tallarico, J.A.; Malnick, L.M.; Snapper, M.L. *J. Org. Chem.* ***1999***, *64*, 344.
[1205]Baczewski, P.; Mikoajczyk, M. *Synthesis* ***1995***, 392.
[1206]Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K.; Omoto, K.; Fujimoto, H. *J. Org. Chem.* ***2001***, *66*, 7776.
[1207]Mero, C.L.; Porter, N.A. *J. Am. Chem. Soc.* ***1999***, *121*, 5155.
[1208]Yorimitsu, H.; Wakabayashi, K.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* ***2001***, *74*, 1963.
[1209]Ouvry, G.; Zard, S.Z. *Chem. Commun.* ***2003***, 778.
[1210]Hirase, K.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* ***2002***, *67*, 970.
[1211]Zytowski, T.; Fischer, H. *J. Am. Chem. Soc.* ***1996*** *118*, 437.
[1212]Avila, D.V.; Ingold, K.U.; Lusztyk, J.; Dolbier Jr., W.R.; Pan, H.-Q. *J. Org. Chem.* ***1996***, *61*, 2027.
[1213]Leach, A.G.; Wang, R.; Wohlhieter, G.E.; Khan, S.I.; Jung, M.E.; Houk, K.N. *J. Am. Chem. Soc.* ***2003***, *125*, 4271.
[1214]Giese, B.; Lachhein, S. *Angew. Chem. Int. Ed.* ***1982***, *21*, 768; Giese, B.; Meixner, J. *Angew. Chem. Int. Ed.* ***1979*** *18* 154.
[1215]Dickstein, J.I.; Miller, G.I., in *The Chemistry of Carbon Carbon Triple Bonds*, Vol. 2, Patai, S., Ed., Wiley, NY ***1978***.

15-30 Radical Cyclization[1216]

Alkyl-hydro-addition



ω-Haloalkenes generate radicals upon treatment with reagents, such as AIBN or under photolysis conditions,[1217] and the radical carbon adds to the alkene to form cyclic compounds.[1218] This intramolecular addition of a radical to an alkene is called radical cyclization. In a typical example, haloalkene **154** reacts with the radical produced by AIBN to give radical **153**. The radical can add to the more substituted carbon to give **155** via a 5-exo–trig reaction (p. 305).[1219] If the radical adds to the less substituted carbon, **156** is formed via a 6-endo–trig reaction.[1220] In both cases, the product is another radical, which must be converted to an unreactive product. This is generally accomplished by adding a hydrogen transfer agent,[1221] such as tributyltin hydride (Bu_3SnH), which reacts with **155** to form methylcyclopentane and Bu_3Sn•, or with **156** to give cyclohexane. The Bu_3Sn• formed in both cases usually dimerizes to form $Bu_3SnSnBu_3$. Cyclization can compete with hydrogen transfer[1222] of Bu_3SnH to **153** to give **152**, the reduction product. In general, formation of the five-membered ring dominates the cyclization, but if addition to the C=C unit is relatively slow, the reduction product is formed preferentially. Radical rearrangements can also diminish the yield of the desired product.[1223] Given a choice between a larger and a smaller ring, radical cyclization generally gives the smaller ring,[1224] but not

[1216]See Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY ***2001***, pp. 1172–1181. For a review of radical-mediated annulation reactions, see Rheault, T.R.; Sibi, M.P. *Synthesis* ***2003***, 803.

[1217]For example, see Pandey, G.; Reddy, G.D.; Chakrabarti, D. *J. Chem. Soc., Perkin Trans. 1* ***1996***, 219; Abe, M.; Hayashi, T.; Kurata, T. *Chem. Lett.* ***1994*** 1789; Pandey, G.; Hajra, S.; Ghorai, M.K. *Tetrahedron Lett.* ***1994***, *35*, 7837; Pandey, G.; Reddy, G.D. *Tetrahedron Lett.* ***1992***, *33*, 6533.

[1218]Curran, D.P. *Synthesis* ***1988***, 417, 489; Chang, S.-Y.; Jiang, W.-T.; Cherng, C.-D.; Tang, K.-H.; Huang, C.-H.; Tsai, Y.-M. *J. Org. Chem.* ***1997***, *62*, 9089. For a review of applications to organic synthesis see McCarroll, A.J.; Walton, J.C. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 3215.

[1219]For a discussion of whether 5-endo–trig radical cyclizations are favored or disfavored, see Chatgilialoglu, C.; Ferreri, C.; Guerra, M.; Timokhin, V.; Froudakis, G.; Gimisis, Z.T. *J. Am. Chem. Soc.* ***2002***, *124*, 10765.

[1220]For a review of 5-endo–trig radical cyclizations, see Ishibashi, H.; Sato, T.; Ikeda, M. *Synthesis* ***2002***, 695.

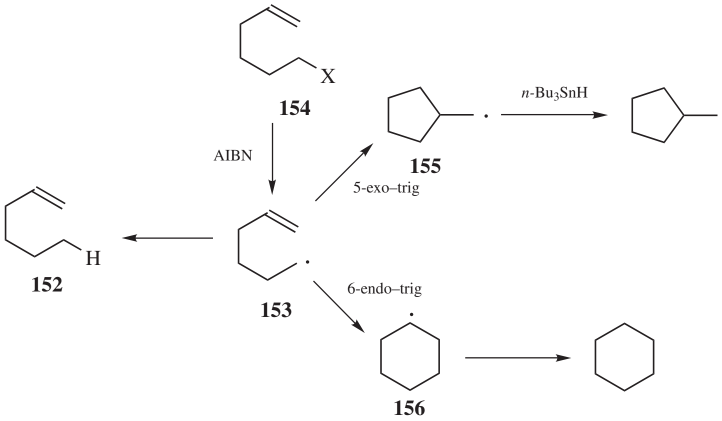
[1221]See Ha, C.; Horner, J.H.; Newcomb, M.; Varick, T.R.; Arnold, B.R.; Lusztyk, J. *J. Org. Chem.* ***1993***, *58* 1194.

[1222]For a discussion of the kinetics of radical cyclization, see Furxhi, E.; Horner, J.H.; Newcomb, M. *J. Org. Chem.* ***1999***, *64*, 4064. Rate constants have been determined for selected reactions: Tauh, P.; Fallis, A.G. *J. Org. Chem.* ***1999***, *64*, 6960.

[1223]Mueller, A.M.; Chen, P. *J. Org. Chem.* ***1998***, *63*, 4581.

[1224]Bogen, S; Malacria, M. *J. Am. Chem. Soc.* ***1996*** *118*, 3992.; Beckwith, A.L.J.; Ingold, K.U., in Vol 1 of *Rearrangements in Ground States and Excited States*, de Mayo, P., Ed., Academic Press, NY ***1980***, pp. 162–283. For a discussion of six- versus five-membered rings, see Gómez, A.M.; Company, M.D.; Uriel, C.; Valverde, S.; López, J.C. *Tetrahedron Lett.* ***2002***, *43*, 4997.

always.[1225] The mechanism of this reaction has been discussed.[1226] Formation of other size rings is possible of course. A 4-exo–trig radical cyclization has been studied,[1227] selectivity in a 7-endo versus 6-exo cyclization,[1228] and also an 8-endo-trig reaction.[1229] In radical cyclization to form large rings, 1,5- and 1,9-hydrogen atom abstractions can pose a problem[1230]



In cases where hydrogen atom transfer gives primarily reduced products, $Bu_3Sn{-}SnBu_3$ under photochemical generates the radical which can cyclize (see **15-46**),[1231] but a halogen atom transfer agent, such as iodoethane, is used rather than a hydrogen-transfer agent, so the final product is an alkyl iodide.

A mixture of a Grignard reagent and $CoCl_2$ has also been used to initiate aryl radical cyclizations.[1232] Titanium(III)-mediated radical cyclizations are known,[1233] and SmI_2-mediate reactions are possible in the presence of a nickel catalyst.[1234] Organoborane-mediated radical cyclizations are known.[1235] Electrochemically generated radicals also cyclize.[1236] The influence of the halogen atom on radical cyclization has been studied.[1237] Both phenylthio[1238] and phenylseleno

[1225]Mayon, P.; Chapleur, Y. *Tetrahedron Lett.* ***1994***, *35*, 3703; Marco-Contelles, J.; Sánchez, B. *J. Org. Chem.* ***1993***, *58*, 4293.

[1226]Bailey, W.F.; Carson, M.W. *Tetrahedron Lett.* ***1999***, *40*, 5433.

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[1231]A polymer-bound tin catalyst has been used under photochemical conditions. See Hernán, A.G.; Kilburn, J.D. *Tetrahedron Lett.* ***2004***, *45*, 831.

[1232]Clark, A.J.; Davies, D.I.; Jones, K.; Millbanks, C. *J. Chem. Soc., Chem. Commun.* ***1994***, 41.

[1233]Barrero, A.F.; Oltra, J.E.; Cuerva, J.M.; Rosales, A. *J. Org. Chem.* ***2002***, *67*, 2566.

[1234]Molander, G.A.; St. Jean, Jr., D.J. *J. Org. Chem.* ***2002***, *67*, 3861.

[1235]Becattini, B.; Ollivier, C.; Renaud, P. *Synlett* ***2003***, 1485.

[1236]Olivero, S.; Clinet, J.C.; Duñach, E. *Tetrahedron Lett.* ***1995***, *36*, 4429; Ozaki, S.; Horiguchi, I.; Matsushita, H.; Ohmori, H. *Tetrahedron Lett.* ***1994***, *35*, 725.

[1237]Tamura, O.; Matsukida, H.; Toyao, A.; Takeda, Y.; Ishibashi, H. *J. Org. Chem.* ***2002***, *67*, 5537.

[1238]See, for example, Ikeda, M.; Shikaura, J.; Maekawa, N.; Daibuzono, K.; Teranishi, H.; Teraoka, Y.; Oda, N.; Ishibashi, H. *Heterocycles* ***1999***, *50*, 31.

groups[1239] can be used as 'leaving groups' for radical cyclization, where sulfur or selenium atom transfer leads to formation of the radical. A seleno ester, R_2N—CH_2C(—O)SeMe, has also been used with $(Me_3Si)_3SiH$ (tristrimethylsilylsilane, TTMSS) and AIBN to generate R_2NCH_2•.[1240] *O*-Phosphonate esters have also served as the leaving group.[1241] *N*-(2-bromophenylbenzyl)methylamino groups have been used as leaving groups for formation of a radical.[1242] Alkenes also serve as radical precursors, adding to another alkene,[1243] including conjugated systems.[1244]

Radical cyclization reaction often proceeds with high diastereoselectivity[1245] and high asymmetric induction when chiral precursors are used. Internal alkynes are good substrates for radical cyclization,[1246] but terminal alkynes tend to give mixtures of *exo/endo–dig* products (p. 305).[1247] *N*-Alkenyl pyridinium salts, with ortho-halogen substituents generate the aryl radical with Bu_3SnH/AIBN, which cyclizes on the pendant alkene unit.[1248] Cyclization of vinyl radicals[1249] and allenyl radicals[1250] are also well known. Ring expansion during radical cyclization is possible when the terminal intermediate is a cyclobutylcarbinyl radical.[1251]

Aryl radicals participate in radical cyclization reactions when the aromatic ring has an alkene or alkyne substituent. *o*-Iodo aryl allyl ethers cyclize to benzofuran derivatives, for example, when treated with AIBN, aqueous H_3PO_2 and $NaHCO_3$ in ethanol.[1252] Cyclization of an *o*-bromo-*N*-acyl aniline (a methacrylic acid derivative) with AIBN/Bu_3SnH gave an indolone under the typical conditions used for cyclization of alkenes.[1253]

Radical cyclization is compatible with the presence of other functional groups. Treatment of $XCH_2CON(R)$—$C(R^1)$=CH_2 derivatives (X = Cl, Br, I) with Ph_3SnH

[1239]See, for example, Ericsson, C.; Engman, L. *Org. Lett.* ***2001***, *3*, 3459.

[1240]Quirante, J.; Vila, X.; Escolano, C.; Bonjoch, J. *J. Org. Chem.* ***2002***, *67*, 2323.

[1241]Crich, D.; Ranganathan, K.; Huang, X. *Org. Lett.* ***2001***, *3*, 1917.

[1242]Andrukiewicz, R.; Loska, R.; Prisyahnyuk, V.; Staliński, K. *J. Org. Chem.* ***2003***, *68*, 1552.

[1243]See Jessop, C.M.; Parsons, A.F.; Routledge, A.; Irvine, D. *Tetrahedron Lett.* ***2003***, *44*, 479.

[1244]Bebbington, D.; Bentley, J.; Nilsson, P.A.; Parsons, A.F. *Tetrahedron Lett.* ***2000***, *41*, 8941; Menes-Arzate, M.; Martínez, R.; Cruz-Almanza, R.; Muchowski, J.M.; Osornio, Y.M.; Miranda, L.D. *J. Org. Chem.* ***2004***, *69*, 4001. For a review, see Zhang, W. *Tetrahedron* ***2001***, *57*, 7237.

[1245]For a discussion of stereocontrol in radical processes, see Bouvier, J.-P.; Jung, G.; Liu, Z.; Guérin, B.; Guindon, Y. *Org. Lett.* ***2001***, *3*, 1391. See Bailey, W.F.; Longstaff, S.C. *Org. Lett.* ***2001***, *3*, 2217; Stalinski, K.; Curran, D.P. *J. Org. Chem.* ***2002***, *67*, 2982.

[1246]See Sha, C.-K.; Shen, C.-Y.; Jean, T.-S.; Chiu, R.-T.; Tseng, W.-H. *Tetrahedron Lett.* ***1993***, *34*, 764.

[1247]Choi, J.-K.; Hart, D.J.; Tsai, Y.-M. *Tetrahedron Lett.* ***1982***, *23*, 4765; Burnett, D.A.; Choi, J.-K.; Hart, D.-J.; Tsai, Y.-M. *J. Am. Chem. Soc.* ***1984*** *106*, 8201; Hart, D.J.; Tsai, Y.-M. *Ibid* ***1984*** *106*, 8209; Choi, J.-K.; Hart, D.J. *Tetrahedron* ***1985***, *41*, 3959; Hart, D.J.; Tsai, Y.-M. *J. Am. Chem. Soc.* ***1982*** *104* 1430; Kano, S.; Yuasa, Y.; Asami, K.; Shibuya, S. *Chem. Lett.* ***1986***, 735; Robertson, J.; Lam, H.W.; Abazi, S.; Roseblade, S.; Lush, R.K. *Tetrahedron* ***2000***, *56*, 8959.

[1248]Dobbs, A.P.; Jones, K.; Veal, K.T. *Tetrahedron Lett.* ***1997***, *38*, 5383.

[1249]Crich, D.; Hwang, J.-T.; Liu, H. *Tetrahedron Lett.* ***1996***, *37*, 3105; Sha, C.-K.; Zhan, Z.-P.; Wang, F.-S. *Org. Lett.* ***2000***, *2*, 2011.

[1250]Wartenberg, F.-H.; Junga, H.; Blechert, S. *Tetrahedron Lett.* ***1993***, *34*, 5251.

[1251]Zhang, W.; Dowd, P. *Tetrahedron Lett.* ***1995***, *36*, 8539.

[1252]Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Chem. Lett.* ***2000***, 104.

[1253]Jones, K.; Brunton, S.A.; Gosain, R. *Tetrahedron Lett.* ***1999***, *40*, 8935.

and AIBN led to formation of a lactam via radical cyclization.[1254] Cyclization of *N*-iodoethyl-5-vinyl-2-pyrrolidinone led to the corresponding bicyclic lactam,[1255] and there are other examples of radical cyclization with molecules containing a lactam unit[1256] or an amide unit.[1257] β-Lactams can be produced by radical cyclization, using $Mn(OAc)_3$.[1258] Radical cyclization occurs with enamines as well.[1259] Photochemical irradiation of *N,N*-diallyl acrylamide leads to formation of a lactam ring, and in this case thiophenol was added to generate the phenylthio derivative.[1260] Phenylseleno *N*-allylamines lead to cyclic amines.[1261] ω-Iodo acrylate esters cyclize to form lactones,[1262] and allylic acetoxy compounds of the type $C{=}C{-}C{-}O_2C{-}CH_2I$ cyclize in a similar manner to give lactones.[1263] Iodolactonization (p. 1154) occurs under standard radical cyclization conditions using allylic acetoxy compounds[1264] and $HGaCl_2/BEt_3$ has been used to initiate the radical process.[1265] α-Bromo mixed acetals give α-alkoxy tetrahydrofuran derivatives[1266] and α-iodoacetals cyclize to give similar products.[1267] The reaction of an ortho-alkynyl aryl isonitrile with AIBN and 2.2 equivalents of Bu_3SnH gave an indole via 5-exo–digcyclization.[1268] Indole derivatives have also been prepared from ortho-iodo aniline derivatives, using AIBN and tristrimethylsilylsilane (TTMSS).[1269]

Acyl radicals can be generated and they cyclize in the usual manner.[1270]A polyene-cyclization reaction generated four rings, initiating the sequence by treatment

[1254]Baker, S.R.; Parsons, A.F.; Pons, J.-F.; Wilson, M. *Tetrahedron Lett.* ***1998***, *39*, 7197; Sato, T.; Chono, N.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc, Perkin Trans. 1* ***1995*** 1115; Goodall, K.; Parsons, A.F. *J. Chem. Soc., Perkin Trans. 1* ***1994***, 3257; Sato, T.; Machigashira, N.; Ishibashi, H.; Ikeda, M. *Heterocycles* ***1992***, *33* 139; Bryans, J.S.; Large, J.M.; Parsons, A.F. *Tetrahedron Lett.* ***1999***, *40*, 3487; Gilbert, B.C.; Kalz, W.; Lindsay, C.I.; McGrail, P.T.; Parsons, A.F.; Whittaker, D.T.E. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 1187. For a tandem cyclization to give a tricyclic compound, see Parsons, A.F.; Williams, D.A.J. *Tetrahedron* ***2000***, *56*, 7217; Wakabayashi, K.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* ***2000***, *73*, 2377; El Bialy, S.A.A.; Ohtani, S.; Sato, T.; Ikeda, M. *Heterocycles* ***2001***, *54*, 1021; Liu, L.; Wang, X.; Li, C. *Org. Lett.* ***2003***, *5*, 361.

[1255]Keusenkothen, P.F.; Smith, M.B. *J. Chem. Soc., Perkin Trans. 1* ***1994***, 2485; Keusenkothen, P.F.; Smith, M.B. *Tetrahedron* ***1992***, *48*, 2977.

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[1264]Ollivier, C.; Bark, T.; Renaud, P. *Synthesis* ***2000***, 1598.

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[1266]Villar, F.; Equey, O.; Renaud, P. *Org. Lett.* ***2000***, *2*, 1061.

[1267]Fujioka, T.; Nakamura, T.; Yorimitsu, H.; Oshima, K. *Org. Lett.* ***2002***, *4*, 2257.

[1268]Rainer, J.D.; Kennedy, A.R.; Chase, E. *Tetrahedron Lett.* ***1999***, *40*, 6325.

[1269]Kizil, M.; Patro, B.; Callaghan, O.; Murphy, J.A.; Hursthouse, M.B.; Hobbs, D. *J. Org. Chem.* ***1999***, *64*, 7856.

[1270]See Jiaang, W.-T.; Lin, H.-C.; Tang, K.-H.; Chang, L.-B.; Tsai, Y.-M. *J. Org. Chem.* ***1999***, *64*, 618.

of a phenylseleno ester with Bu_3SnH/AIBN to form the acyl radical, which added to the first alkene unit.[1271] The newly formed carbon radical added to the next alkene, and so on. Acyl radicals generated from Ts(R)NCOSePh derivatives cyclize to form lactams.[1272]

Radical cyclization of iodo aldehydes or ketones, at the carbon of the carbonyl, is effectively an acyl addition reaction (**16-24**, **16-25**). This cyclization is often reversible, and there are many fewer examples can addition to an alkene or alkyne. In one example, a δ-iodo aldehyde was treated with BEt_3/O_2 to initiate formation of the radical, and in the presence of Bu_3SnH cyclization gave a cyclopentanol.[1273] The reaction of an aldehyde-alkene with AIBN, 0.5 $PhSiH_3$ and 0.1 Bu_3SnH generated a radical from the alkene, which cyclized at the aldehyde to give cyclopentanol derivatives.[1274] An aldehyde-*O*-methyloxime generated a radical adjacent to nitrogen under standard conditions, which cyclized at the carbonyl to give a cyclic α-hydroxy *N*-methoxyamine.[1275] Alternatively an α-bromoacetal-*O*-methyl oxime cyclized at the C=NOMe unit under electrolytic conditions in the presence of cobaloxime.[1276]

The attacking radical in radical cyclization reactions is not limited to a carbon, and a number of heterocycles can be prepared.[1277] Amidyl radical are known and give cyclization reactions.[1278] Aminyl radical cyclizations have been reported.[1279] *N*-Chloroamine-alkenes give an aminyl radical when treated with $TiCl_3$•BF_3, and cyclization give a pyrrolidine derivative with a pendant chloromethyl group.[1280] *N*-(S-substituted) amines give similar results using AIBN/Bu_3SnH.[1281] Oxime–alkenes cyclize to imines when treated with PhSSPh and TEMPO (p. 274).[1282] An oxygen radical can be generated under photochemical conditions, and they add to alkenes in a normal manner.[1283] Note that radical substitution occurs, and reaction of Ph_3SnH/AIBN and an *O*-amidyl compound having a phosphonate ester elsewhere in the molecule gave cyclization to a tetrahydrofuran derivative.[1284]

[1271]Pattenden, G.; Roberts, L.; Blake, A.J. *J. Chem. Soc., Perkin Trans. 1* ***1998***, 863; Batsanov, A.; Chen, L.; Gill, G.B.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* ***1996***, 45. Also see, Pattenden, G.; Smithies, A.J.; Tapolczay, D.; Walter, D.S. *J. Chem. Soc., Perkin Trans. 1* ***1996***, 7 for a related reaction that generates a bicyclic species from an initially generated alkyl radical.

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15-31 Conjugate Addition With Heteroatom Nucleophiles

Other nucleophiles add to conjugated systems to give Michael-type products. Aniline derivatives add to conjugated aldehydes in the presence of a catalytic amount of DBU (p. 1132).[1285] Amines add to conjugated esters in the presence of $InCl_3$,[1286] $Bi(NO)_3$,[1287] $Cu(OTf)_2$,[1288] $CeCl_3/NaI/SiO_2$,[1289] $La(OTf)_3$,[1290] or $Yb(OTf)_3$ at 3 kbar,[1291] for example, to give β-amino esters. Palladium catalysts have been used as well.[1292] Conjugate addition of amines has also been promoted by lithium perchlorate,[1293] and by clay.[1294] This reaction can be initiated photochemically[1295] or with microwave irradiation.[1296] Lithium amides add to conjugated esters to give the β-amino ester.[1297] An intramolecular addition of an amine unit to a conjugated ketone in the presence of a palladium catalyst, or photochemically, led to cyclic amines.[1298] Amines add to conjugated thio-lactams.[1299] Chiral catalysts lead to enantioselective reactions.[1300] Chiral imines add in a highly stereoselective manner.[1301] Chiral additives, such as chiral Cinchona alkaloids[1302] or chiral naphthol derivatives,[1303] have also been used. The nitrogen of carbamates add to conjugated ketones with a platinum,[1304] palladium,[1305] copper,[1306] or with a bis-(triflamide) catalyst.[1307] The amine moiety of a carbamate adds to conjugated

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[1302]Jew, S.-s.; Jeong, B.S.; Yoo, M.-S.; Huh, H.; Park, H.-g. *Chem. Commun.* ***2001***, 1244.
[1303]Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* ***2003***, *125*, 16178.
[1304]Kakumoto, K.; Kobayashi, S.; Sugiura, M. *Org. Lett.* ***2002***, *4*, 1319.
[1305]Gaunt, M.J.; Spencer, J.B. *Org. Lett.* ***2001***, *3*, 25.
[1306]Wabnitz, T.C.; Spencer, J.B. *Tetrahedron Lett.* ***2002***, *43, 3*891.
[1307]Wabnitz, T.C.; Spencer, J.B. *Org. Lett.* ***2003***, *5*, 2141.

ketones with a polymer-supported acid catalyst,[1308] or with BF_3•OEt_2.[1309] Chiral catalysts have been used for the conjugated addition of carbamates.[1310] The reaction of ammonium formate with 1,4-diphenylbut-2-en-1,4-dione, in PEG-200 and a palladium catalyst under microwave irradiation, gave 2,5-diphenylpyrrole.[1311]

Lactams have been shown to add to conjugated esters in the presence of $Si(OEt)_4$ and CsF.[1312] Phthalimide adds to alkylidene malononitriles via 1,4-addition with a palladium catalyst, and the resulting anion can be alkylated with an added allylic halide.[1313] Alkylidene amido amides, C=C(NHAc)CONHR, react with secondary amines in water to give the β-amino amido amide.[1314] Amines also add in a conjugate manner to alkynyl phosphonate esters, C≡C–$PO(OEt)_2$, using a CuI catalyst.[1315] Hydroxylamines add to conjugated nitro compounds to give 2-nitro hydroxylamines.[1316] *N,O*-Trimethylsilyl hydroxylamines add to conjugated esters, via nitrogen, using a copper catalyst.[1317] Trimethylsilyl azide with acetic acid reacts with conjugated ketones to give the β-azido ketone.[1318] Sodium azide adds to conjugated ketones in aqueous acetic acid and 20% PBu_3.[1319]

Phosphines react similarly to amines under certain conditions. Conjugate addition of R_2PH and a nickel catalyst give conjugate addition to α,β-unsaturated nitriles.[1320]

Alcohols add to conjugated ketones with a PMe_3 catalyst to give the β-alkoxy ketone.[1321] The conjugate addition of peroxide anions (HOO^- and ROO^-) to α,β-unsaturated carbonyl compounds is discussed in **15-48**.

bis(Silanes) add to alkylidene malonate derivatives in the presence of a copper catalyst to give β-silyl malonates, $RCH(SiR_3)CH(CO_2Me)_2$.[1322] Alkylsilane units add using bis(trialkylsilyl)zinc reagents with a CuCN catalyst.[1323]

Thiophenol and butyllithium (lithium phenylthiolate) adds to conjugated esters.[1324] Similar addition is observed with selenium compounds RSeLi.[1325]

[1308]Wabnitz, T.C.; Yu, J.-Q.; Spencer, J.B. *Synlett* ***2003***, 1070.

[1309]Xu, L.-W.; Li, L.; Xia, C.-G.; Zhou, S.-L.; Li, J.-W.; Hu, X.-X. *Synlett* ***2003***, 2337.

[1310]Palomo, C.; Oiarbide, M.; Halder, R.; Kelso, M.; Gómez-Bengoa, E.; García, J.M. *J. Am. Chem. Soc.* ***2004***, *126*, 9188.

[1311]Rao, H.S.P.; Jothilingam, S. *Tetrahedron Lett.* ***2004***, *42*, 6595.

[1312]Ahn, K.H.; Lee, S.J. *Tetrahedron Lett.* ***1994***, *35*, 1875.

[1313]Aoyagi, K.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* ***2002***, *67*, 5977.

[1314]Naidu, B.N.; Sorenson, M.E.; Connolly, J.P.; Ueda, Y. *J. Org. Chem.* ***2003***, *68*, 10098.

[1315]Panarina, A.E.; Dogadina, A.V.; Zakharov, V.I.; Ionin, B.I. *Tetrahedron Lett.* ***2001***, *42*, 4365.

[1316]O'Neil, I.A.; Cleator, E.; Southern, J.M.; Bickley, J.F.; Tapolczay, D.J. *Tetrahedron Lett.* ***2001***, *42*, 8251.

[1317]Cardillo, G.; Gentilucci, L.; Gianotti, M.; Kim, H.; Perciaccante, R.; Tolomelli, A. *Tetrahedron Asymmetry* ***2001***, *12*, 2395.

[1318]Guerin, D.J.; Horstmann, T.E.; Miller, S.J. *Org. Lett.* ***1999***, *1*, 1107.

[1319]Xu, L.-W.; Xia, C.-G.; Li, J.-W.; Zhou, S.-L. *Synlett* ***2003***, 2246.

[1320]Sadow, A.D.; Haller, I.; Fadini, L.; Togni, A. *J. Am. Chem. Soc.* ***2004***, *126*, 14704.

[1321]Stewart, I.C.; Bergman, R.G.; Toste, F.D. *J. Am. Chem. Soc.* ***2003***, *125*, 8696.

[1322]Clark, C.T.; Lake, J.F.; Scheidt, K.A. *J. Am. Chem. Soc.* ***2004***, *126*, 84.

[1323]Oestreich, M.; Weiner, B. *Synlett* ***2004***, 2139.

[1324]Kamimura, A.; Kawahara, F.; Omata, Y.; Murakami, N.; Morita, R.; Otake, H.; Mitsudera, H.; Shirai, M.; Kakehi, A. *Tetrahedron Lett.* ***2001***, *42*, 8497.

[1325]Zeni, G.; Stracke, M.P.; Nogueira, C.W.; Braga, A.L.; Menezes, P.H.; Stefani, H.A. *Org. Lett.* ***2004***, *6*, 1135.

Thiols react with conjugated amides via 1,4-addition with the addition of 10% $Hf(OTf)_4$ or other lanthanide triflates[1326] or to conjugated ketones in ionic solvents.[1327] Thiophenol adds in a similar manner in the presence of Na_2Ca-P_2O_7[1328] or LiAl–poly2a.[1329] Thioaryl moieties can be added in the presence of Yb[1330] or a catalytic amount of $(DHQD)_2PYR$ (a dihydroquinidine, see **15-48**).[1331] Thioalkyl units, such as BuS—, add to conjugated ketones using BuS—SnBu and In—I.[1332] Addition of conjugated lactones is possible to produce β-arylthiolated lactones.[1333]

α,β-Unsaturated sulfones undergo conjugate addition of a cyano group using Et_2AlCN.[1334] Trimethylsilyl cyanide (Me_3SiCN) adds a cyano group to α,β-unsaturated amines with a specialized aluminum salen-ytterbium catalyst.[1335]

15-32 Acylation of Activated Double Bonds and of Triple Bonds

Hydro-acyl-addition

Under some conditions, acid derivatives add directly to activated double bonds. Acetic anhydride, magnesium metal, and Me_3SiCl reacts with conjugated esters to give a γ-keto ester.[1336] Similar reaction with vinyl phosphonate esters leads to a γ-keto phosphonate ester.[1337] Thioesters undergo conjugate addition to α,β-unsaturated ketones in the presence of SmI_2.[1338] Using DBU (1,8-diazabicyclo [5.4.0] undec-7-ene) (p. 1132) and a thioimidazolium salt, acyl silanes, $Ar(C{=}O)SiMe_3$, add in a similar manner.[1339] Under microwave irradiation, aldehydes add to conjugated ketones using DBU/Al_2O_3 and a thiazolium salt.[1340] The conjugate addition

[1326]Kobayashi, S.;Ogawa, C.; Kawamura, M.; Sugiura, M. *Synlett* ***2001***, 983.

[1327]In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Yadav, J.S.; Reddy, B.V.S.; Baishya, G. *J. Org. Chem.* ***2003***, *68*, 7098.

[1328]Zahouily, M.; Abrouki, Y.; Rayadh, A. *Tetrahedron Lett.* ***2002***, *43*, 7729.

[1329]Sundararajan, G.; Prabagaran, N. *Org. Lett.* ***2001***, *3*, 389.

[1330]Taniguchi, Y.; Maruo, M.; Takaki, K.; Fujiwara, Y. *Tetrahedron Lett.* ***1994***, *35*, 7789.

[1331]McDaid, P.; Chen, Y.; Deng, L. *Angew. Chem. Int. Ed.* ***2002***, *41*, 338.

[1332]Ranu, B.C.; Mandal, T. *Synlett* ***2004***, 1239.

[1333]Nishimura, K.; Tomioka, K. *J. Org. Chem.* ***2002***, *67*, 431.

[1334]Ruano, J.L.G.; García, M.C.; Laso, N.M.; Castro, A.M.M.; Ramos, J.H.R. *Angew. Chem. Int. Ed.* ***2001***, *40*, 2507.

[1335]With high enantioselectivity, see Sammis, G.M.; Danjo, H.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2004***, *126*, 9928.

[1336]Ohno, T.; Sakai, M.; Ishino, Y.; Shibata, T.; Maekawa, H.; Nishiguchi, I. *Org. Lett.* ***2001***, *3*, 3439.

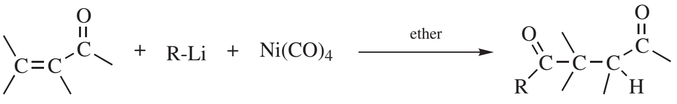
[1337]Kyoda, M.; Yokoyama, T.; Maekawa, H.; Ohno, T.; Nishiguchi, I. *Synlett* ***2001***, 1535.

[1338]Blakskjær, P.; Høj, B.; Riber, D.; Skrydstrup, T. *J. Am. Chem. Soc.* ***2003***, *125*, 4030.

[1339]Mattson, A.E.; Bharadwaj, A.R.; Scheidt, K.A. *J. Am. Chem. Soc.* ***2004***, *126*, 2314.

[1340]Yadav, J.S.; Anuradha, K.; Reddy, B.V.S.; Eeshwaraiah, B. *Tetrahedron Lett.* ***2003***, *44*, 8959.

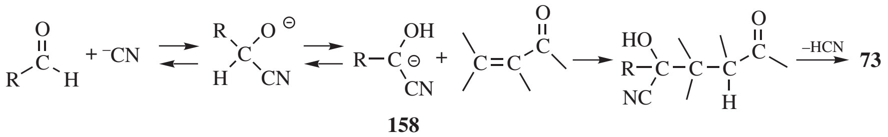
of acyl zirconium complexes in the presence of BF3•OEt_2 is catalyzed by palladium acetate.[1341]



157

An acyl group can be introduced into the 4 position of an α,β-unsaturated ketone by treatment with an organolithium compound and nickel carbonyl.[1342] The product is a 1,4-diketone, **157**. The R group may be aryl or primary alkyl. The reaction can also be applied to alkynes (which need not be activated), in which case 2 mol add and the product is also a 1,4-diketone (e.g., $R'C{\equiv}CH \rightarrow RCOCHR'CH_2COR$).[1343] In a different procedure, α,β-unsaturated ketones and aldehydes are acylated by treatment at −110°C with $R_2(CN)CuLi_2$ and CO. This method is successful for R = primary, secondary, and tertiary alkyl.[1344] For secondary and tertiary groups, R(CN)CuLi (which does not waste an R group) can be used instead.[1345]

Another method involves treatment with an aldehyde and cyanide ion (see **16-52**) in a polar aprotic solvent (e.g., DMF or DMSO).[1346]



This method has been applied to α,β-unsaturated ketones, esters, and nitriles to give the corresponding 1,4-diketones, γ-keto esters, and γ-keto nitriles, respectively (see also, **16-55**). The ion **158** is a synthon for the unavailable $R^{\ominus}$ C=O anion (see also, p. 634); it is a masked $R^{\ominus}$ C=O anion. Other masked carbanions that have been used in this reaction are the $RC^{\ominus}$(CN) NR ion,[1347] the $EtSC^{\ominus}$ RSOEt ion[1348] (see p. 634), the $CH_2{=}C^{\ominus}$ OEt ion,[1349] $CH_2{=}C(OEt)Cu_2Li$,[1350] $CH_2{=}CMe(SiMe_3)$,[750]

[1341]Hanzawa, Y.; Tabuchi, N.; Narita, K.; Kakuuchi, A.; Yabe, M.; Taguchi, T. *Tetrahedron* ***2002***, *58*, 7559.

[1342]Corey, E.J.; Hegedus, L.S. *J. Am. Chem. Soc.* ***1969***, *91*, 4926.

[1343]Sawa, Y.; Hashimoto, I.; Ryang, M.; Tsutsumi, S. *J. Org. Chem.* ***1968***, *33*, 2159.

[1344]Seyferth, D.; Hui, R.C. *J. Am. Chem. Soc.* ***1985***, *107*, 4551. See also, Lipshutz, B.H.; Elworthy, T.R. *Tetrahedron Lett.* ***1990***, *31*, 477.

[1345]Seyferth, D.; Hui, R.C. *Tetrahedron Lett.* ***1986***, *27*, 1473.

[1346]For reviews, see Stetter, H.; Kuhlmann, H. *Org. React.* ***1991***, *40*, 407–496; Stetter, H. *Angew. Chem. Int. Ed.* ***1976***, *15*, 639. For a similar method involving thiazolium salts, see Stetter, H.; Skobel, H. *Chem. Ber.* ***1987***, *120*, 643; Stetter, H.; Kuhlmann, H.; Haese, W. *Org. Synth.*, *65*, 26.

[1347]Enders, D.; Gerdes, P.; Kipphardt, H. *Angew. Chem. Int. Ed.* ***1990***, *29*, 179.

[1348]Herrmann, J.L.; Richman, J.E.; Schlessinger, R.H. *Tetrahedron Lett.* ***1973***, 3271, 3275.

[1349]Beockman Jr., R.K.; Bruza, K.J.; Baldwin, J.E.; Lever Jr., O.W. *J. Chem. Soc., Chem. Commun.* ***1975***, 519.

[1350]Boeckman Jr., R.K ; Bruza, K.J. *J. Org. Chem.* ***1979***, *44*, 4781.

and the RC$^{\ominus}$(OCHMeOEt) CN ion[1351] (see p. 640). In the last case, best results are obtained when R is a vinylic group. Anions of 1,3-dithianes (**10-71**) do not give 1,4-addition to these substrates (except in the presence of HMPA, see **15-25**), but add 1,2 to the C=O group instead (**16-38**).

In another procedure, acyl radicals derived from phenyl selenoesters ArCOSePh (by treatment of them with Bu_3SnH) add to α,β-unsaturated esters and nitriles to give γ-keto esters and γ-keto nitriles, respectively.[1352]

OS **VI**, 866; **VIII**, 620.

15-33 Addition of Alcohols, Amines, Carboxylic Esters, Aldehydes, and so on.

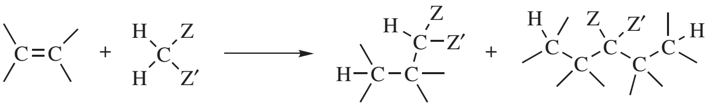
Hydro-acyl-addition, and so on.

Formates, primary, and secondary alcohols, amines, ethers, alkyl halides, compounds of the type Z—CH_2— Z′, and a few other compounds add to double bonds in the presence of free-radical initiators.[1353] This is formally the addition of RH to a double bond, but the "R" is not just any carbon but one connected to an oxygen or a nitrogen, a halogen, or to two Z groups (defined as on p. 1007). Formates and formamides[1354] add similarly:

W = OR, NH_2

Alcohols, ethers, amines, and alkyl halides add as follows (shown for alcohols):

ZCH_2Z' compounds react at the carbon bearing the active hydrogen:[1355]



[1351]Stork, G.; Maldonado, L. *J. Am. Chem. Soc.* ***1974***, *96*, 5272.

[1352]Boger, D.L.; Mathvink, R.J. *J. Org. Chem.* ***1989***, *54*, 1777.

[1353]For reviews, see Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*, Pergamon, Elmsford, NY, ***1986***, pp. 69–77; Vogel, H. *Synthesis* ***1970***, 99; Huyser, E.S. *Free-Radical Chain Reactions*, Wiley, NY, ***1970***, pp. 152–159; Elad, D. *Fortschr. Chem. Forsch.* ***1967***, *7*, 528. Hyponitrites have been used to initiate this reaction; see Dang, H.-S.; Roberts, B.P. *Chem. Commun.* ***1996***, 2201.

[1354]Elad, D. *Fortschr. Chem. Forsch.* ***1967***, *7*, 528, see pp. 530–543.

[1355]For example, see Cadogan, J.I.G.; Hey, D.H.; Sharp, J.T. *J. Chem. Soc. C* ***1966***, 1743; *J. Chem. Soc. B* ***1967***, 803; Hájek, M.; Málek, J. *Coll. Czech. Chem. Commun.* ***1979***, *44*, 3695.

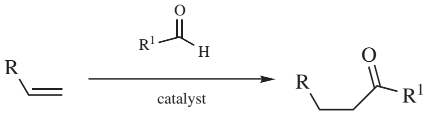
Similar additions have been successfully carried out with carboxylic acids, anhydrides,[1356] acyl halides, carboxylic esters, nitriles, and other types of compounds.[1357]

Similar reactions have been carried out on acetylene.[1358] In an interesting variation, thiocarbonates add to alkynes in the presence of a palladium catalyst to give a β-phenylthio α,β-unsaturated ester.[1359] Aldehydes add to alkynes in the presence of a rhodium catalyst to give conjugated ketones.[1360] In a cyclic version of the addition of aldehydes, 4-pentenal was converted to cyclopentanone with a rhodium–complex catalyst.[1361] An intramolecular acyl addition to an alkyne was reported using silyl ketones, acetic aid and a rhodium catalyst.[1362] In the presence of a palladium catalyst, a tosylamide group added to an alkene unit to generate *N*-tosylpyrrolidine derivatives.[1363]

OS **IV**, 430; **V**, 93; **VI**, 587, 615.

15-34 Addition of Aldehydes

Alkyl-carbonyl-addition



In the presence of metal catalysts, such as rhodium compounds[1364] or $Yb(OTf)_3$,[1365] aldehydes can add directly to alkenes to form ketones. The reaction of ω-alkenyl aldehydes with rhodium catalyst leads to cyclic ketones,[1366] with high enantioselectivity if chiral ligands are employed. Aldehydes also add to vinyl esters in the presence of hyponitrites and thioglycolates.[1367] The addition of aldehydes to activated double bonds, mediated by a catalytic amount of thiazolium salt in the presence of a

[1356]de Klein, W.J. *Recl. Trav. Chim. Pays-Bas* ***1975***, *94*, 48.

[1357]Allen, J.C.; Cadogan, J.I.G.; Hey, D.H. *J. Chem. Soc.* ***1965***, 1918; Cadogan, J.I.G. *Pure Appl. Chem.* ***1967***, *15*, 153, pp. 153–158. See also, Giese, B.; Zwick, W. *Chem. Ber.* ***1982***, *115*, 2526; Giese, B.; Erfort, U. *Chem. Ber.* ***1983***, *116*, 1240.

[1358]For example, see Cywinski, N.F.; Hepp, H.J. *J. Org. Chem.* ***1965***, *31*, 3814; DiPietro, J.; Roberts, W.J. *Angew. Chem. Int. Ed.* ***1966***, *5*, 415.

[1359]Hua, R.; Takeda, H.; Onozawa, S.-y.; Abe, Y.; Tanaka, M. *J. Am. Chem. Soc.* ***2001***, *123*, 2899.

[1360]Kokubo, K.; Matsumasa, K.; Miura, M.; Nomura, M. *J. Org. Chem.* ***1997***, *62*, 4564.

[1361]Fairlie, D.P.; Bosnich, B. *Organometallics* ***1988***, *7*, 936, 946. Also see, Barnhart, R.W.; Wang, X.; Noheda, P.; Bergens, S.H.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* ***1994***, *116*, 1821 for an enantioselective version of this cyclization.

[1362]Yamane, M.; Amemiya, T.; Narasaka, K. *Chem. Lett.* ***2001***, 1210.

[1363]Larock, R.C.; Hightower, T.R.; Hasvold, L.A.; Peterson, K.P. *J. Org. Chem.* ***1996***, *61*, 3584.

[1364]Jun, C.-H.; Lee, H.; Hong, J.-B. *J. Org. Chem.* ***1997***, *62*, 1200.

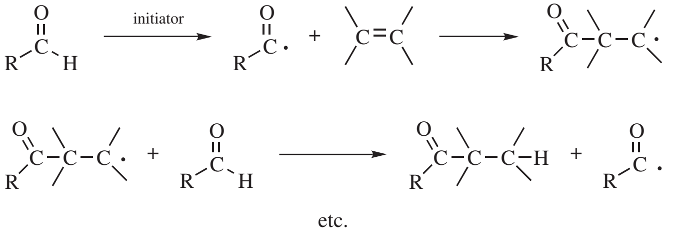
[1365]Curini, M.; Epifano, F.; Maltese, F.; Rosati, O. *Synlett* ***2003***, 552.

[1366]Barnhart, R.W.; McMorran, D.A.; Bosnich, B. *Chem. Commun.* ***1997***, 589.

[1367]Dang, H.-S.; Roberts, B.P. *J. Chem. Soc, Perkin Trans. 1*, ***1998***, 67.

weak base, is called the *Stetter reaction*,[1368] An internal addition of an alkynyl aldehyde, catalyzed by a rhodium complex, led to a cyclopentenone derivative.[1369] A similar carbonyl addition with benzaldehyde derivatives having an ortho-allylic ether led to a benzopyranone when treated with potassium hexamethyldisilazide.[1370]

These reactions are not successful when the alkene contains electron-withdrawing groups, such as halo or carbonyl groups. A free-radical initiator is required,[1371] usually peroxides or *UV* light. The mechanism is illustrated for aldehydes but is similar for the other compounds:

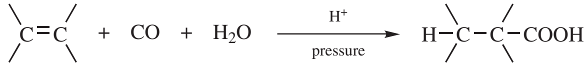


Polymers are often side products. Photochemical addition of aldehyde to conjugated C=C units can be efficient when a triplet sensitizer (p. 340), such as benzophenone is used.[1372]

A variation that is more of an acyl addition (**16-25**) involves the reaction of an allylic alcohol with benzaldehyde. With a ruthenium catalyst and in an ionic liquid, the C=C unit reacts with the aldehyde, with concomitant oxidation of the allylic alcohol unit, to give a β-hydroxy ketone, PhCHO +C=C–CH(OH)R → PhCH(OH)–CH(Me)COR.[1373] In another variation, formate esters add to alkenes using a ruthenium catalyst to give an alkyl ester via a formylation process.[1374]

15-35 Hydrocarboxylation

Hydro-carboxy-addition



[1368]Stetter, H.; Schreckenberg, M. *Angew. Chem., Int. Ed* ***1973***, *12*, 81; Stetter, H.; Kuhlmann, H. *Angew. Chem., Int. Ed.* ***1974***, *13*, 539; Stetter, H. *Angew. Chem., Int. Ed.* ***1976***, *15*, 639; Stetter, H.; Haese, W. *Chem. Ber.* ***1984***, *117*, 682; Stetter, H.; Kuhlmann, H. *Org. React.* ***1991***, *40*, 407; Enders, D.; Breuer, K.; Runsink, J.; Teles, J.H. *Helv. Chim. Acta* ***1996***, *79*, 1899; Kerr, M.S.; Rovis, T. *Synlett* ***2003***, 1934; Kerr, M.S.; Rovis, T. *J. Am. Chem. Soc.* ***2004***, *126*, 8876; Pesch, J.; Harms, K.; Bach, T. *Eur. J. Org. Chem.* ***2004***, 2025; Mennen, S.; Blank, J.; Tran-Dube, M.B.; Imbriglio, J.E.; Miller, S.J. *Chem. Commun.* ***2005***, 195. For examples of the Stetter reaction with acyl silanes, see Mattson, A.E.; Bharadwaj, A.R.; Scheidt, K.A. *J. Am. Chem. Soc.* ***2004***, *126*, 2314.

[1369]Tanaka, K.; Fu, G.C. *J. Am. Chem. Soc.* ***2002***, *124*, 10296.

[1370]Kerr, M.S.; de Alaniz, J.R.; Rovis, T. *J. Am. Chem. Soc.* ***2002***, *124*, 10298.

[1371]See Lee, E.; Tae, J.S.; Chong, Y.H.; Park, Y.C.; Yun, M.; Kim, S. *Tetrahedron Lett.* ***1994***, *35*, 129 for an example.

[1372]Kraus, G.A.; Liu, P. *Tetrahedron Lett.* ***1994***, *35*, 7723.

[1373]In bmim PF_6, 3-butyl-1-methylimidazolium hexafluorophosphate: Yang, X.-F.; Wang, M.; Varma, R.S.; Li, C.-J. *Org. Lett.* ***2003***, *5*, 657.

[1374]Na, Y.; Ko, S.; Hwang, L.K.; Chang, S. *Tetrahedron Lett.* ***2003***, *44*, 4475.

The acid-catalyzed hydrocarboxylation of alkenes (the *Koch reaction*) can be performed in a number of ways.[1375] In one method, the alkene is treated with carbon monoxide and water at 100–350°C and 500–1000-atm pressure with a mineral acid catalyst. However, the reaction can also be performed under milder conditions. If the alkene is first treated with CO and catalyst and then water added, the reaction can be accomplished at 0–50°C and 1–100 atm. If formic acid is used as the source of both the CO and the water, the reaction can be carried out at room temperature and atmospheric pressure.[1376] The formic acid procedure is called the *Koch–Haaf reaction* (the Koch–Haaf reaction can also be applied to alcohols, see **10-77**). Nearly all alkenes can be hydrocarboxylated by one or more of these procedures. However, conjugated dienes are polymerized instead. Hydrocarboxylation can also be accomplished under mild conditions (160°C and 50 atm) by the use of nickel carbonyl as catalyst. Acid catalysts are used along with the nickel carbonyl, but basic catalysts can also be employed.[1377] Other metallic salts and complexes can be used, sometimes with variations in the reaction procedure, including palladium,[1378] platinum,[1379] and rhodium[1380] catalysts. The $Ni(CO)_4$-catalyzed oxidative carbonylation with CO and water as a nucleophile is often called *Reppe carbonylation*.[1381] The toxic nature of nickel

[1375]For reviews of hydrocarboxylation of double and triple bonds catalyzed by acids or metallic compounds, see Lapidus, A.L.; Pirozhkov, S.D. *Russ. Chem. Rev.* ***1989***, *58*, 117; Anderson, G.K.; Davies, J.A., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 3, Wiley, NY, ***1985***, pp. 335–359, 335–348; in Falbe, J. *New Syntheses with Carbon Monoxide*, Springer, NY, ***1980***, the articles by Mullen, A. pp. 243–308; and Bahrmann, H. pp. 372–413; in Wender, I.; Pino, P. *Organic Syntheses via Metal Carbonyls*, Vol. 2, Wiley, NY, ***1977***, the articles by Pino, P.; Piacenti, F.; Bianchi, M. pp. 233–296; and Pino, P.; Braca, G. pp. 419–516; Eidus, Ya.T.; Lapidus, A.L.; Puzitskii, K.V.; Nefedov, B.K. *Russ. Chem. Rev.* ***1973***, *42*, 199; *Russ. Chem. Rev.* ***1971***, *40*, 429; Falbe, J. *Carbon Monoxide in Organic Synthesis*, Springer, Berlin, ***1970***, pp. 78–174.

[1376]Haaf, W. *Chem. Ber.* ***1966***, *99*, 1149; Christol, H.; Solladié, G. *Bull. Soc. Chim. Fr.* ***1966***, 1307.

[1377]Sternberg, H.W.; Markby, R.; Wender, P. *J. Am. Chem. Soc.* ***1960***, *82*, 3638.

[1378]For reviews, see Heck, R.F. *Palladium Reagents in Organic Synthesis*, Academic Press, NY, ***1985***, pp. 381–395; Bittler, K.; Kutepow, N.V.; Neubauer, D.; Reis, H. *Angew. Chem. Int. Ed.* ***1968***, *7*, 329. For a review with respect to fluoroalkenes, see Ojima, I. *Chem. Rev.* ***1988***, *88*, 1011, p. 1016. Seayad, A.; Jayasree, S.; Chaudhari, R.V. *Org. Lett.* ***1999***, *1*, 459; Mukhopadhyay, K.; Sarkar, B.R.; Chaudhari, R.V. *J. Am. Chem. Soc.* ***2002***, *124*, 9692. See also, the references cited in these latter articles.

[1379]Xu, Q.; Fujiwara, M.; Tanaka, M.; Souma, Y. *J. Org. Chem.* ***2000***, *65*, 8105.

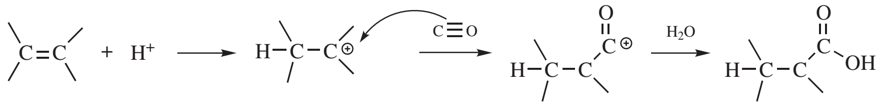
[1380]Xu, Q.; Nakatani, H.; Souma, Y. *J. Org. Chem.* ***2000***, *65*, 1540.

[1381]Tsuji, J. *Palladium Reagents and Catalysts*, Wiley, NY, ***1999***; Hohn, A., in *Applied Homogeneous Catalysis with Organometallic Compounds*, Vol. 1, VCH, NY, ***1996***, p. 137; Beller, M.; Tafesh, A.M., in *Applied Homogeneous Catalysis with Organometallic Compounds*, Vol. 1, VCH, NY, ***1996***, p. 187; Drent, E.; Jager, W.W.; Keijsper, J.J.; Niele, F.G.M., in *Applied Homogeneous Catalysis with Organometallic Compounds*, Vol. 1, VCH, NY, ***1996***, p. 1119.; Parshall, G.W.; Ittel, S.D. *Homogeneous Catalysis*, 2nd ed., Wiley, NY, ***1992***; Mullen, A. in *New Syntheses with Carbon Monoxide*, Springer-Verlag, NY, ***1980***, p. 243; Tsuji, J. *Organic Synthesis with Palladium Compounds*, Springer-Verlag, NY, ***1980***; Bertoux, F.; Monflier, E.; Castanet, Y.; Mortreux, A. *J. Mol. Catal. A: Chem.* ***1999***, *143*, 11; Beller, M.; Cornils, B.; Frohning, C. D.; Kohlpaintner, C. W. *J. Mol. Catal. A: Chem.* ***1995***, *104*, 17; Chiusoli, G. P. *Transition Met. Chem.* ***1991***, *16*, 553; Roeper, M. *Stud. Surf. Sci. Catal.* ***1991***, *64*, 381; Milstein, D. *Acc. Chem. Res.* ***1988***, *21*, 428; Escaffre, P.; Thorez, A.; Kalck, P. *J. Mol. Catal.* ***1985***, *33*, 87; Cassar, L.; Chiusoli, G. P.; Guerrieri, F. *Synthesis* ***1973***, 509; Tsuji, J. *Acc. Chem. Res.* ***1969***, *2*, 144; Bird, C. W. *Chem. Rev.* ***1962***, *62*, 283.

tetracarbonyl has led to development of other catalysts, including Co, Rh, Ir, Pd, and Pt, and Mo compounds.[1382] This reaction converts alkenes, alkynes and dienes and is tolerant of a wide variety of functional groups. When the additive is alcohol or acid, saturated or unsaturated acids, esters, or anhydrides are produced (see **15-36**). The transition-metal-catalyzed carbonylation has been done enantioselectively, with moderate-to-high optical yields, by the use of an optically active palladium complex catalyst.[1383] Dienes react with Cp_2TiCl_2/RMgCl and then with Me_2NCOCl to give amides.[1384] In the presence of formic acid, CO, and palladium acids can similarly be formed.[1385] Alkenes also react with $Fe(CO)_5$ and CO to give carboxylic acids.[1386] Electrochemical carboxylation procedures have been developed, including the conversion of alkenes to 1,4-butanedicarboxylic acids.[1387]

When applied to triple bonds, hydrocarboxylation gives α,β-unsaturated acids under very mild conditions. Triple bonds give unsaturated acids and saturated dicarboxylic acids when treated with carbon dioxide and an electrically reduced nickel complex catalyst.[1388] Alkynes also react with $NaHFe(CO)_4$, followed by $CuCl_2$•2 H_2O, to give alkenyl acid derivatives.[1389] A related reaction with CO and palladium catalysts in the presence of $SnCl_2$ also leads to conjugated acid derivatives.[1390] Terminal alkynes react with CO_2 and $Ni(cod)_2$, and subsequent treatment with DBU (p. 1132) gives the α,β-unsaturated carboxylic acid.[1391]

When acid catalysts are employed, in the absence of nickel carbonyl, the mechanism[1392] involves initial attack by a proton, followed by attack of the resulting carbocation on carbon monoxide to give an acyl cation, which, with water, gives the product, **159**. Markovnikov's rule is followed, and carbon skeleton rearrangements and double-bond isomerizations (prior to attack by CO) are frequent.



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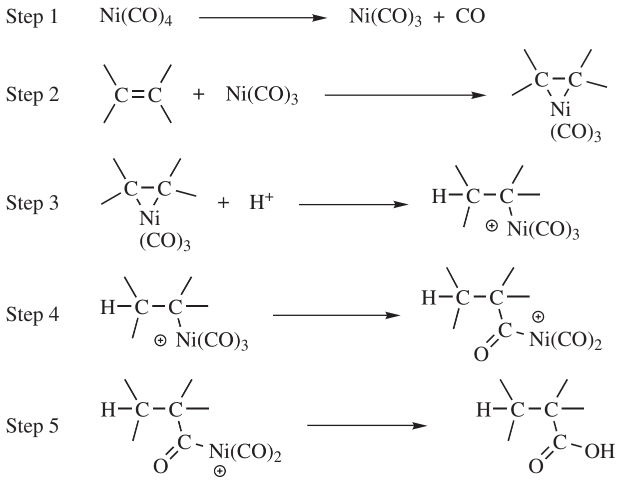
[1382]For a review, see Kiss, G. *Chem. Rev.* ***2001***, *101*, 3435.
[1383]Alper, H.; Hamel, N. *J. Am. Chem. Soc.* ***1990***, *112*, 2803.
[1384]Szymoniak, J.; Felix, D.; Moïse, C. *Tetrahedron Lett.* ***1996***, *37*, 33.
[1385]Vasapollo, G.; Somasunderam, A.; El Ali, B.; Alper, H. *Tetrahedron Lett.* ***1994***, *35*, 6203. See El Ali, B.; Vasapollo, G.; Alper, H. *J. Org. Chem.* ***1993***, *58*, 4739 and El Ali, B.; Alper, H. *J. Org. Chem.* ***1993***, *58*, 3595 for the same reaction with alkenes.
[1386]Brunet, J.-J.; Neibecker, D.; Srivastava, R.S. *Tetrahedron Lett.* ***1993***, *34*, 2759.
[1387]Senboku, H.; Komatsu, H.; Fujimura, Y.; Tokuda, M. *Synlett* ***2001***, 418.
[1388]Duñach, E.; Dérien, S.; Périchon, J. *J. Organomet. Chem.* ***1989***, *364*, C33.
[1389]Periasamy, M.; Radhakrishnan, U.; Rameshkumar, C.; Brunet, J.-J. *Tetrahedron Lett.* ***1997***, *38*, 1623.
[1390]Takeuchi, R.; Sugiura, M. *J. Chem. Soc. Perkin Trans. 1*, ***1993***, 1031.
[1391]Saito, S.; Nakagawa, S.; Koizumi, T.; Hirayama, K.; Yamamoto, Y. *J. Org. Chem.* ***1999***, *64*, 3975. See also, Takimoto, M.; Shimizu, K.; Mori, M. *Org. Lett.* ***2001***, *3*, 3345.
[1392]For a review, see Hogeveen, H. *Adv. Phys. Org. Chem.* ***1973***, *10*, 29.

For the transition metal catalyzed reactions, the nickel carbonyl reaction has been well studied and the addition is syn for both alkenes and alkynes.[1393] The following is the accepted mechanism:[785]

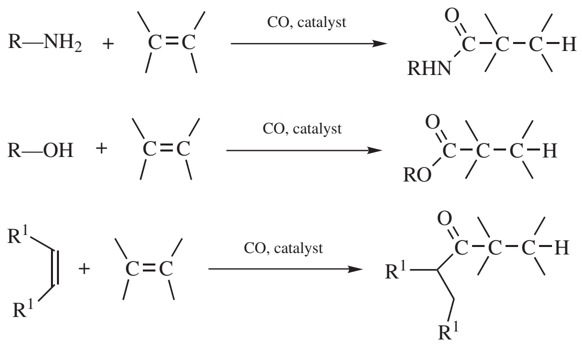


Step 3 is an electrophilic substitution. The principal step of the mechanism, step 4, is a rearrangement.

An indirect method for hydrocarboxylation involves the reaction of an alkene with a borate, $(RO)_2BH$ and a rhodium catalysts. Subsequent reaction with $LiCHCl_2$ and then $NaClO_2$ gives the Markovnikov carboxylic acid (RC=C → $RC(COOH)CH_3$.[1394] When a chiral ligand is used, the reaction proceeds with good enantioselectivity.

15-36 Carbonylation, Alkoxycarbonylation and Aminocarbonylation of Double and Triple Bonds

Alkyl, Alkoxy or Amino-carbonyl-addition



[1393]Bird, C.W.; Cookson, R.C.; Hudec, J.; Williams, R.O. *J. Chem. Soc.* ***1963***, 410.
[1394]Chen, A.; Ren, L.; Crudden, C.M. *J. Org. Chem.* ***1999***, *64*, 9704.

In the presence of certain metal catalysts, alkenes and alkynes can be carbonylated or converted to amides or esters.[1395] There are several variations. The reaction of an alkyl iodide and a conjugated ester with CO, $(Me_3Si)_3SiH$ and AIBN (p. 935) in supercritical CO_2 (p. 414) gave a γ-keto ester.[1396] Terminal alkynes react with CO and methanol, and in the presence of $CuCl_2$ and $PdCl_2$ the product is a β-chloro-α-β-unsaturated methyl ester.[1397] Conjugated dienes react with thiophenol, CO and palladium(II) acetate to give the β,γ-unsaturated thioester.[1398] Allene reacts with CO, methanol and a ruthenium catalyst go give methacrylic acid.[1399] 5-Iodo-1-pentene reacted with 40 atm of CO in butanol to give a cyclopentanone with a pendant ester ($—CH_2CO_2Bu$).[1400] Alkynes react with thiophenol and CO with a palladium[1401] or platinum[1402] catalyst to give a conjugated thioester. Terminal alkynes react with CO and methanol, using a combination of a palladium (II) halide and a copper (II) halide, to give a conjugated diester, $MeO_2C—C{=}C—CO_2Me$.[1403] A similar reaction with alkenes using a combination of a palladium and a molybdenum catalyst led to a saturated diester, $MeO_2C—C—C—CO_2Me$.[1404] Alkenes were converted to the dimethyl ester of 1,4-butanedioic acid derivatives with CO/O_2 and a combination of $PdCl_2$ and CuCl catalysts.[1405] Note that alkenes are converted to primarily the anti-Markovnikov ester upon treatment with arylmethyl formate esters ($ArCH_2OCHO$) and a ruthenium catalyst.[1406]

A bicyclic ketone was generated when 1,2-diphenylethyne was heated with CO, methanol and a dirhodium catalyst.[1407] 2-Iodostyrene reacted at 100°C with CO and a palladium catalyst to give the bicyclic ketone 1-indanone.[1408] Another variation reacted a conjugated allene–alkene with 5 atm of CO and a rhodium catalyst to give a bicyclic ketone.[1409] An intermolecular version of this reaction is known

[1395]For a review of carbometallation of alkenes and alkynes containing adjacent heteroatoms, see Fallis, A.G.; Forgione, P. *Tetrahedron* ***2001***, *57*, 5899.

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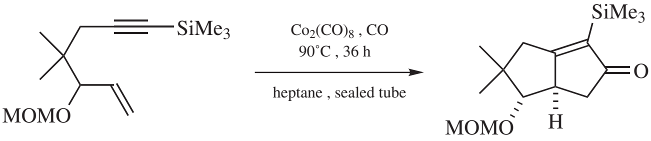
[1408]Gagnier, S.V.; Larock, R.C. *J. Am. Chem. Soc.* ***2003***, *125*, 4804.

[1409]Murakami, M.; Itami, K.; Ito, Y. *J. Am. Chem. Soc.* ***1999***, *121*, 4130.

using a cobalt catalyst, giving a cyclopentenone[1410] in a reaction related to the Pauson–Khand reaction (see below). The reaction of a conjugated diene having a distal alkene unit and CO with a rhodium catalyst led to a bicyclic conjugated ketone.[1411] When a Stille coupling (**12-15**) is done in a CO atmosphere, conjugated ketones of the type C=C—CO—C=C are formed,[1412] suitable for a Nazarov cyclization (**15-20**). Alkynes were converted to cyclobutenones using $Fe_3(CO)_{12}$ to form the initial complex, followed by reaction with copper(II) chloride.[1413] An interesting variation treated cyclohexene with 5 equivalents of Oxone® and a $RuCl_3$ catalyst to give 2-hydroxycyclohexanone.[1414]

The reaction of dienes, diynes, or en-ynes with transition metals[1415] (usually cobalt)[1416] forms organometallic coordination complexes. In the presence of carbon monoxide, the metal complexes derived primarily from enynes (alkene–alkynes) form cyclopentenone derivatives in what is known as the *Pauson–Khand reaction*.[1417] The reaction involves (*1*) formation of a hexacarbonyldicobalt–alkyne complex and (*2*) decomposition of the complex in the presence of an alkene.[1418] A typical example is formation of **160**.[1419] Cyclopentenones can be prepared by an intermolecular reaction of a vinyl silane and an alkyne using CO and a ruthenium catalyst.[1420] Carbonylation of an alkene–diene using a rhodium catalyst leads to cyclization to an α-vinyl cyclopentanone.[1421] An yne–diene can also be used for the Pauson–Khand reaction.[1422]



160

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[1415]For a discussion of catalytic precursors, see Krafft, M.E.; Hirosawa, C.; Bonaga, L.V.R. *Tetrahedron Lett.* ***1999***, *40*, 9177.

[1416]For development of practical cobalt catalysts, see Krafft, M.E.; Boñaga, L.V.R.; Hirosawa, c. *J. Org. Chem.* ***2001***, *66*, 3004.

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[1418]For a discussion of the reactivity of alkenes, see de Bruin, T.J.M.; Milet, A.; Greene, A.E.; Gimbert, Y. *J. Org. Chem.* ***2004***, *69*, 1075. See also, Rivero, M.R.; Adrio, J.; Carretero, J.C. *Eur. J. Org. Chem.* ***2002***, 2881.

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[1422]Wender, P.A; Deschamps, N.M.; Gamber, G.G. *Angew. Chem. Int. Ed.* ***2003***, *42*, 1853.

Rhodium,[1423] titanium,[1424] and tungsten[1425] complexes have also been used for this reaction. The reaction can be promoted photochemically[1426] and the rate is enhanced by the presence of primary amines.[1427] Coordinating ligands also accelerate the reaction,[1428] polymer-supported promoters have been developed[1429] and there are many possible variations in reaction conditions.[1430] The Pauson–Khand reaction has been done under heterogeneous reaction conditions,[1431] and with cobalt nanoparticles.[1432] A dendritic cobalt catalyst has been used.[1433] Ultrasound promoted[1434] and microwave promoted[1435] reactions have been developed. Polycyclic compounds (tricyclic and higher) are prepared in a relatively straightforward manner using this reaction.[1436] Asymmetric Pauson–Khand reactions are known.[1437]

The Pauson–Khand reaction is compatible with other groups or heteroatoms elsewhere in the molecule. These include ethers and aryl halides,[1438] esters,[1439]

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[1435]Iqbal, M.; Vyse, N.; Dauvergne, J.; Evans, P. *Tetrahedron Lett.* ***2002***, *43*, 7859.

[1436]Ishizaki, M.; Iwahara, K.; Niimi, Y.; Satoh, H.; Hoshino, O. *Tetrahedron* ***2001***, *57*, 2729; Son, S.U.; Chung, Y.K.; Lee, S.-G. *J. Org. Chem.* ***2000***, *65*, 6142; Son, S.U.; Yoon, Y.A.; Choi, D.S.; Park, J.K.; Kim, B.M.; Chung, Y.K. *Org. Lett.* ***2001***, *3*, 1065; Jung, J.-C.; Jung, Y.-J.; Park, O.-S. *Synth. Commun.* ***2001***, *31*, 2507; Pérez-Serrano, L.; Casarrubios, L.; Domínguez, G.; Pérez-Castells, J. *Chem. Commun.*, ***2001***, 2602.

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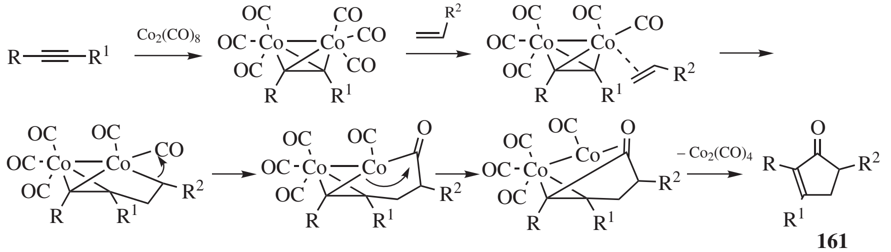
amides,[1440] alcohols,[1441] diols,[1442] and an indole unit.[1443] A silicon-tethered Pauson–Khand reaction is known.[1444] Allenes are reaction partners in the Pauson–Khand reaction.[1445] This type of reaction can be extended to form six-membered rings using a ruthenium catalyst.[1446] A double-Pauson–Khand process was reported.[1447] In some cases, an aldehyde can serve as the source of the carbonyl for carbonylation.[1448]

The accepted mechanism was proposed by Magnus,[1449] shown for the formation of **161**,[1450] and supported by Krafft's work.[1451] It has been shown that CO is lost from the Pauson–Khand complex prior to alkene coordination and insertion.[1452] Calculations concluded that the LUMO of the coordinated alkene plays a crucial role in alkene reactivity by determining the degree of back-donation in the complex.[1453]



161

Other carbonylation methods are available. Carbonylation occurs with conjugated ketones to give 1.4-diketones, using phenylboronic acid (**13-12**), CO and a rhodium catalyst.[1454] A non-carbonylation route treated a conjugated diene with an

[1440]Comely, A.C.; Gibson, S.E.; Stevenazzi, A.; Hales, N.J. *Tetrahedron Lett.* ***2001***, *42*, 1183.

[1441]Blanco-Urgoiti, J.; Casarrubios, L.; Domínguez, G.; Pérez-Castells, J. *Tetrahedron Lett.* ***2001***, *42*, 3315.

[1442]Mukai, C.; Kim, J.S.; Sonobe, H.; Hanaoka, M. *J. Org. Chem.* ***1999***, *64*, 6822.

[1443]Pérez-Serrano, L.; Domínguez, G.; Pérez-Castells, J. *J. Org. Chem.* ***2004***, *69*, 5413.

[1444]Brummond, K.M.; Sill, P.C.; Rickards, B.; Geib, S.J. *Tetrahedron Lett.* ***2002***, *43*, 3735; Reichwein, J.F.; Iacono, S.T.; Patel, U.C.; Pagenkopf, B.L. *Tetrahedron Lett.* ***2002***, *43*, 3739.

[1445]Antras, F.; Ahmar, M.; Cazes, B. *Tetrahedron Lett.* ***2001***, *42*, 8153, 8157; Brummond, K.M.; Chen, H.; Fisher, K.D.; Kerekes, A.D.; Rickards, B.; Sill, P.C.; Geib, A.D. *Org. Lett.* ***2002***, *4*, 1931. For an intramolecular version, see Shibata, T.; Kadowaki, S.; Hirase, M.; Takagi, K. *Synlett* ***2003***, 573.

[1446]Trost, B.M.; Brown, R.E.; Toste, F.D. *J. Am. Chem. Soc.* ***2000***, *122*, 5877.

[1447]Rausch, B.J.; Gleiter, R. *Tetrahedron Lett.* ***2001***, *42*, 1651.

[1448]For example, see Shibata, T.; Toshida, N.; Takagi, K. *J. Org. Chem.* ***2002***, *67*, 7446; Shibata, T.; Toshida, N.; Takagi, K. *Org. Lett.* ***2002***, *4*, 1619; Morimoto, T.; Fuji, K.; Tsutsumi, K.; Kakiuchi, K. *J. Am. Chem. Soc.* ***2002***, *124*, 3806; Fuji, K.; Morimoto, T.; Tsutsumi, K.; Kakiuchi, K. *Tetrahedron Lett.* ***2004***, *45*, 9163.

[1449]Magnus, P.; Principe, L.M. *Tetrahedron Lett.* ***1985***, *26*, 4851.

[1450]For a review, see Brummond, K.M.; Kent, J.L. *Tetrahedron* ***2000***, *56*, 3263.

[1451]Krafft, M.E. *Tetrahedron Lett.* ***1988***, *29*, 999.

[1452]Gimbert, Y.; Lesage, D.; Milet, A.; Fournier, F.; Greene, A.E.; Tabet, J.-C. *Org. Lett.* ***2003***, *5*, 4073. See Robert, F.; Milet, A.; Gimbert, Y.; Konya, D.; Greene, A.E. *J. Am. Chem. Soc.* ***2001***, *123*, 5396.

[1453]de Bruin, T.J.M.; Milet, A.; Greene, A.E.; Gimbert, Y. *J. Org. Chem.*, ***2004*** *69*, 1075.

[1454]Sauthier, M.; Castanet, Y.; Mortreux, A. *Chem. Commun.* ***2004*** 1520.

excess of *tert*-butyllithium and quenching with carbon dioxide led to a cyclopentadienone.[1455] When quenched with CO rather than CO_2, a nonconjugated cyclopentenone was formed.[1456] It is noted that a carbonylation reaction with CO, a diyne and an iridium catalyst[1457] or a cobalt catalyst[1458] provided similar molecules.

The reaction of a secondary amine, CO, a terminal alkyne and *t*-$BuMe_2SiH$ with a rhodium catalyst led to a conjugated amide bearing the silyl group of the C=C unit.[1459] Reaction of a molecule containing an amine and an alkene unit was carboxylated with CO in the presence of a palladium catalyst to give a lactam.[1460] A similar reaction with a molecule containing an amine and an alkyne also generated a lactam, in the presence of CO and a rhodium catalyst.[1461] An intramolecular carbonylation reaction of a conjugated imine, with CO, ethylene and a ruthenium catalyst, led to a highly substituted β,γ-unsaturated lactam.[1462]

With any method, if the alkene contains a functional group, such as OH, NH_2, or $CONH_2$, the corresponding lactone (**16-63**),[1463] lactam (**16-74**), or cyclic imide may be the product.[1464] Titanium,[1465] palladium,[1466] ruthenium,[1467] and rhodium[1468] catalysts have been used to generate lactones. Allenic alcohols are converted to butenolides with 10 atm of CO and a ruthenium catalyst.[1469] Larger ring conjugated lactones can also be formed by this route using the appropriate allenic alcohol.[1470] Propargylic alcohols lead to β-lactones.[1471] Allenic tosyl-amides are converted to *N*-tosyl α,β-unsaturated pyrrolidinones using 20 atm of CO and a ruthenium catalyst.[1472] Conjugated imines are converted to similar products with CO, ethylene and a ruthenium catalyst.[1473] Propargyl alcohols are converted to

[1455]Xi, Z.; Song, Q. *J. Org. Chem.* ***2000***, *65*, 9157.

[1456]Song, Q.; Chen, J.; Jin, X.; Xi, Z. *J. Am. Chem. Soc.* ***2001***, *123*, 10419; Song, Q.; Li, Z.; Chen, J.; Wang, C.; Xi, Z. *Org. Lett.* ***2002***, *4*, 4627.

[1457]Shibata, T.; Yamashita, K.; Ishida, H.; Takagi, K. *Org. Lett.* ***2001***, *3*, 1217; Shibata, T.; Yamashita, K.; Katayama, E.; Takagi, K. *Tetrahedron* ***2002***, *58*, 8661.

[1458]Sugihara, T.; Wakabayashi, A.; Takao, H.; Imagawa, H.; Nishizawa, M. *Chem. Commun.* ***2001***, 2456.

[1459]Matsuda, I.; Takeuchi, K.; Itoh, K. *Tetrahedron Lett.* ***1999***, *40*, 2553.

[1460]Okuro, K.; Kai, H.; Alper, H. *Tetrahedron Asymmetry* ***1997***, *8*, 2307.

[1461]Hirao, K.; Morii, N.; Joh, T.; Takahashi, S. *Tetrahedron Lett.* ***1995***, *36*, 6243; Shiba, T.; Zhou, D.-Y.; Onitsuka, K.; Takahashi, S. *Tetrahedron Lett.* ***2004***, *45*, 3211.

[1462]Berger, D.; Imhof, W. *Tetrahedron* ***2000***, *56*, 2015.

[1463]Dong, C.; Alper, H. *J. Org. Chem.* ***2004***, *69*, 5011.

[1464]For reviews of these ring closures see Ohshiro, Y.; Hirao, T. *Heterocycles* ***1984***, *22*, 859; Falbe, J. *New Syntheses with Carbon Monoxide*, Springer, NY, ***1980***, pp. 147–174, *Angew. Chem. Int. Ed.* ***1966***, *5*, 435; *Newer Methods Prep. Org. Chem.* ***1971***, *6*, 193. See also, Krafft, M.E.; Wilson, L.J.; Onan, K.D. *Tetrahedron Lett.* ***1989***, *30*, 539.

[1465]Kablaoui, N.M.; Hicks, F.A.; Buchwald, S.L. *J. Am. Chem. Soc.* ***1997***, *119*, 4424.

[1466]El Ali, B.; Okuro, K.; Vasapollo, G.; Alper, H. *J. Am. Chem. Soc.* ***1996***, *118*, 4264. Also see, Brunner, M.; Alper, H. *J. Org. Chem.* ***1997***, *62*, 7565.

[1467]Kondo, T.; Kodoi, K.; Mitsudo, T.-a.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* ***1994***, 755.

[1468]Yoneda, E.; Kaneko, T.; Zhang, S.-W.; Takahashi, S. *Tetrahedron Lett.* ***1998***, *39*, 5061.

[1469]Yoneda, E.; Kaneko, T.; Zhang, S.-W.; Onitsuka, K.; Takahashi, S. *Org. Lett.* ***2000***, *2*, 441.

[1470]Yoneda, E.; Zhang, S.-W.; Onitsuka, K.; Takahashi, S. *Tetrahedron Lett.* ***2001***, *42*, 5459.

[1471]Ma, S.; Wu, B.; Zhao, S. *Org. Lett.* ***2003***, *5*, 4429.

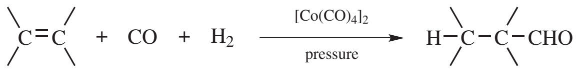
[1472]Kang, S.-K.; Kim, K.-J.; Yu, C.-M.; Hwang, J.-W.; Do, Y.-K. *Org. Lett.* ***2001***, *3*, 2851.

[1473]Chatani, N.; Kamitani, A.; Murai, S. *J. Org. Chem.* ***2002***, *67*, 7014.

butenolides with CO/H_2O and a rhodium catalyst.[1474] Propargyl alcohols generate lactones when treated with a chromium pentacarbonyl carbene complex.[1475] Amines add to allenes, in the presence of CO and a palladium catalyst, to form conjugated amides.[1476]

15-37 Hydroformylation

Hydro-formyl-addition



Alkenes can be hydroformylated[1477] by treatment with carbon monoxide and hydrogen over a catalyst. The most common catalysts are cobalt carbonyls (see below for a description of the mechanism) and rhodium complexes,[1478] but other transition metal compounds have also been used. Cobalt catalysts are less active than the rhodium type, and catalysts of other metals are generally less active.[1479] Commercially, this is called the *oxo process*, but it can be carried out in the laboratory in an ordinary hydrogenation apparatus. The order of reactivity is straight-chain terminal alkenes > straight-chain internal alkenes > branched-chain alkenes. With terminal alkenes, for example, the aldehyde unit is formed on both the primary and secondary carbon, but proper choice of catalyst and additive leads to selectivity for the secondary product[1480] or primary

[1474]Fukuta, Y.; Matsuda, I.; Itoh, K. *Tetrahedron Lett.* ***2001***, *42*, 1301.

[1475]Good, G.M.; Kemp, M.I.; Kerr, W.J. *Tetahedron Lett.* ***2000***, *41*, 9323.

[1476]Grigg, R.; Monteith, M.; Sridharan, V.; Terrier, C. *Tetrahedron* ***1998***, *54*, 3885.

[1477]For reviews, see Kalck, P.; Peres, Y.; Jenck, J. *Adv. Organomet. Chem.* ***1991***, *32*, 121; Davies, J.A., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 3, Wiley, NY, ***1985***, pp. 361–389; Pino, P.; Piacenti, F.; Bianchi, M., in Wender, I.; Pino, P. *Organic Syntheses via Metal Carbonyls*, Vol. 2, Wiley, NY, ***1977***, pp. 43–231; Cornils, B., in Falbe, J. *New Syntheses with Carbon Monoxide*, Springer, NY, ***1980***, pp. 1–225; Collman, J.P., Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, CA ***1987***, pp. 621–632; Pino, P. *J. Organomet. Chem.* ***1980***, *200*, 223; Pruett, R.L. *Adv. Organomet. Chem.* ***1979***, *17*, 1; Stille, J.K.; James, D.E., in Patai, S. *Supplement A: The Chemistry of Double-Bonded Functional Groups*, Vol. 1, pt. 2, Wiley, NY, ***1977***, pp. 1099–1166; Heck, R.F. *Organotransition Metal Chemistry*, Academic Press, NY, ***1974***, pp. 215–224; Khan, M.M.T.; Martell, A.E. *Homogeneous Catalysis by Metal Complexes*, Vol. 2, Academic Press, NY, ***1974***, pp. 39–60; Falbe, J. *Carbon Monoxide in Organic Synthesis* Springer, NY, ***1980***, pp. 3–77; Chalk, A.J.; Harrod, J.F. *Adv. Organomet. Chem.* ***1968***, *6*, 119. For a review with respect to fluoroalkenes, see Ohshiro, Y.; Hirao, T. *Heterocycles* ***1984***, *22*, 859.

[1478]For example, see Brown, J.M.; Kent, A.G. *J. Chem. Soc. Perkin Trans. 1*, ***1987***, 1597; Hanson, B.E.; Davis, M.E. *J. Chem. Ed.*, ***1987***, *64*, 928; Jackson, W.R.; Perlmutter, P.; Suh, G. *J. Chem. Soc., Chem. Commun.* ***1987***, 724; Amer, I.; Alper, H. *J. Am. Chem. Soc.* ***1990***, *112*, 3674. See the references cited in these papers. For a review of the rhodium-catalyzed process, see Jardine, F.H., in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 733–818, pp. 778–784.

[1479]Collman, J.P., Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, CA ***1987***, p. 630.

[1480]Chan, A.S.C.; Pai, C.-C.; Yang, T.-K.; Chen, S.M. *J. Chem. Soc., Chem. Commun.* ***1995***, 2031; Doyle, M.P.; Shanklin, M.S.; Zlokazov, M.V. *Synlett* ***1994***, 615; Higashizima, T.; Sakai, N.; Nozaki, K.; Takaya, H. *Tetrahedron Lett.* ***1994***, *35*, 2023.

product.[1481] Good yields for hydroformylation have been reported using rhodium catalysts in the presence of certain other additives.[1482] Among the side reactions are the aldol reaction (**16-34**), acetal formation, the Tishchenko reaction (**19-82**), and polymerization. In one case using a rhodium catalyst, 2-octene gave nonanal, presumably via a η^3-allyl complex (p. 116).[1483] Conjugated dienes give dialdehydes when rhodium catalysts are used[1484] but saturated mono-aldehydes (the second double bond is reduced) with cobalt carbonyls. Both 1,4- and 1,5-dienes may give cyclic ketones.[1485] Hydroformylation of triple bonds proceeds very slowly, and few examples have been reported.[1486] However, in the presence of a rhodium catalyst, the triple bond of a conjugated enyne is formylated.[1487] Many functional groups such as OH, CHO, COOR,[1488] CN, can be present in the molecule, although halogens usually interfere. Stereoselective syn addition has been reported,[1489] and also stereoselective anti addition.[1490] Asymmetric hydroformylation has been accomplished with a chiral catalyst,[1491] and in the presence of chiral additives.[1492] Cyclization to prolinal derivatives has been reported with allylic amines.[1493]

When dicobalt octacarbonyl, $[Co(CO)_4]_2$, is the catalyst, the species that actually adds to the double bond is tricarbonylhydrocobalt, $HCo(CO)_3$.[1494] Carbonylation $RCo(CO)_3 + CO \rightarrow RCo(CO)_4$ takes place, followed by a rearrangement and a

[1481]Fernández, E.; Castillón, S. *Tetrahedron Lett.* ***1994***, *35*, 2361; Klein, H.; Jackstell, R.; Wiese, K.-D.; Borgmann, C.; Beller, M. *Angew. Chem. Int. Ed.* ***2001***, *40*, 3408; Breit, B.; Seiche, W. *J. Am. Chem. Soc.* ***2003***, *125*, 6608.

[1482]Johnson, J.R.; Cuny, G.D.; Buchwald, S.L. *Angew. Chem. Int. Ed.* ***1995***, *34*, 1760.

[1483]van der Veen, L.A.; Kamer, P.C.J.; van Leeuwen, P.W.N.M. *Angew. Chem. Int. Ed.* ***1999***, *38*, 336.

[1484]Fell, B.; Rupilius, W. *Tetrahedron Lett.* ***1969***, 2721.

[1485]For a review of ring closure reactions with CO, see Mullen, A., in Falbe, J. *New Syntheses with Carbon Monoxide*, Springer, NY, ***1980***, pp. 414–439. See also, Eilbracht, P.; Hüttmann, G.; Deussen, R. *Chem. Ber.* ***1990***, *123*, 1063, and other papers in this series.

[1486]For examples with rhodium catalysts, see Fell, B.; Beutler, M. *Tetrahedron Lett.* ***1972***, 3455; Botteghi, C.; Salomon, C. *Tetrahedron Lett.* ***1974***, 4285. For an indirect method, see Campi, E.; Fitzmaurice, N.J.; Jackson, W.R.; Perlmutter, P.; Smallridge, A.J. *Synthesis* ***1987***, 1032.

[1487]van den Hoven, B.G.; Alper, H. *J. Org. Chem.* ***1999***, *64*, 3964.

[1488]For formylation at the β-carbon of methyl acrylate, see Hu, Y.; Chen, W.; Osuna, A.M.B.; Stuart, A.M.; Hope, E.G.; Xiao, J. *Chem. Commun.* ***2001***, 725.

[1489]See, for example, Haelg, P.; Consiglio, G.; Pino, P. *Helv. Chim. Acta* ***1981***, *64*, 1865.

[1490]Krauss, I.J.; Wang, C.C-Y.; Leighton, J.L. *J. Am. Chem. Soc.* ***2001***, *123*, 11514.

[1491]For reviews, see Ojima, I.; Hirai, K., in Morrison, J.D. *Organic Synthesis*, Vol. 5, Wiley, NY, ***1985***, pp. 103–145, 125–139; Consiglio, G.; Pino, P. *Top. Curr. Chem.* ***1982***, *105*, 77; Breit, B.; Seiche, W. *Synthesis* ***2001***, 1; Diéguez, M.; Pàmies, O.; Claver, C. *Tetrahedron Asymmetry* ***2004***, *15*, 2113. See also, Hegedüs, C.; Madrász, J.; Gulyás, H.; Szöllöy, A.; Bakos, J. *Tetrahedron Asymmetry* ***2001***, *12*, 2867.

[1492]Nozaki, K.; Itoi, Y.; Shibahara, F.; Shirakawa, E.; Ohta, T.; Takaya, H.; Hiyama, T. *J. Am. Chem. Soc.* ***1998***, *120*, 4051; Sakai, N.; Nozaki, K.; Takaya, H. *J. Chem. Soc., Chem. Commun.* ***1994***, 395; Rajan Babu, T.V.; Ayers, T.A. *Tetrahedron Lett.* ***1994***, *35*, 4295. See Gladiali, S.; Bayón, J.C.; Claver, C. *Tetrahedron Asymmetry* ***1995***, *6*, 1453.

[1493]Anastasiou, D.; Campi, E.M.; Chaouk, H.; Jackson, W.R.; McCubbin, Q.J. *Tetrahedron Lett.* ***1992***, *33*, 2211.

[1494]Heck, R.F.; Breslow, D.S. *J. Am. Chem. Soc.* ***1961***, *83*, 4023; Karapinka, G.L.; Orchin, M. *J. Org. Chem.* ***1961***, *26*, 4187; Whyman, R. *J. Organomet. Chem.* ***1974***, *81*, 97; Mirbach, M.F. *J. Organomet. Chem.* ***1984***, *265*, 205. For discussions of the mechanism, see Orchin, M. *Acc. Chem. Res.* ***1981***, *14*, 259; Versluis, L.; Ziegler, T.; Baerends, E.J.; Ravenek, W. *J. Am. Chem. Soc.* ***1989***, *111*, 2018.

reduction of the C—Co bond, similar to steps 4 and 5 of the nickel carbonyl mechanism shown in **15-35**. The reducing agent in the reduction step is tetracarbonylhydrocobalt, $HCo(CO)_4$,[1495] or, under some conditions, H_2.[1496] When $HCo(CO)_4$ was the agent used to hydroformylate styrene, the observation of CIDNP indicated that the mechanism is different, and involves free radicals.[1497] Alcohols can be obtained by allowing the reduction to continue after all the carbon monoxide is used up. It has been shown[1498] that the formation of alcohols is a second step, occurring after the formation of aldehydes, and that $HCo(CO)_3$ is the reducing agent.

OS **VI**, 338.

15-38 Addition of HCN

Hydro-cyano-addition

Ordinary alkenes do not react with HCN, but polyhalo alkenes and alkenes of the form C=C—Z add HCN to give nitriles.[1499] The reaction is therefore a nucleophilic addition and is base catalyzed. When Z is COR or, more especially, CHO, 1,2-addition (**16-53**) is an important competing reaction and may be the only reaction. Triple bonds react very well when catalyzed by an aqueous solution of CuCl, NH_4Cl, and HCl or by Ni or Pd compounds.[1500] The HCN can be generated *in situ* from acetone cyanohydrin (see **16-52**), avoiding the use of the poisonous HCN.[1501] One or 2 equivalents of HCN can be added to a triple bond, since the initial product is a Michael-type substrate. Acrylonitrile is commercially prepared this way, by the addition of HCN to acetylene. Alkylaluminum cyanides, for example, Et_2AlCN, or mixtures of HCN and trialkylalanes R_3Al are especially good reagents for conjugate addition of HCN[1502] to α,β-unsaturated ketones and α,β-unsaturated acyl halides. Hydrogen cyanide can be added to ordinary alkenes in the presence of dicobalt octacarbonyl[1503] or certain other

[1495]Alemdaroğ lu, N.H.; Penninger, J.L.M.; Oltay, E. *Monatsh. Chem.* ***1976***, *107*, 1153; Ungváry, F.; Markó, L. *Organometallics* ***1982***, *1*, 1120.

[1496]See Kovács, I.; Ungváry, F.; Markó, L. *Organometallics* ***1986***, *5*, 209.

[1497]Bockman, T.M.; Garst, J.F.; King, R.B.; Markó, L.; Ungváry, F. *J. Organomet. Chem.* ***1985***, *279*, 165.

[1498]Aldridge, C.L.; Jonassen, H.B. *J. Am. Chem. Soc.* ***1963***, *85*, 886.

[1499]For reviews see Friedrich, K., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 2, Wiley, NY, ***1983***, pp. 1345–1390; Nagata, W.; Yoshioka, M. *Org. React.* ***1977***, *25*, 255; Brown, E.S., in Wender, I.; Pino, P. *Organic Syntheses via Metal Carbonyls*, Vol. 2, Wiley, NY, ***1977***, pp. 655–672; Friedrich, K.; Wallenfels, K., in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 68–72.

[1500]Jackson, W.R.; Lovel, C.G. *Aust. J. Chem.* ***1983***, *36*, 1975.

[1501]Jackson, W.R.; Perlmutter, P. *Chem. Br.* ***1986***, 338.

[1502]For a review, see Nagata, W.; Yoshioka, M. *Org. React.* ***1977***, *25*, 255.

[1503]Arthur, Jr., P.; England, D.C.; Pratt, B.C.; Whitman, G.M. *J. Am. Chem. Soc.* ***1954***, *76*, 5364.

transition-metal compounds.[1504] An indirect method for the addition of HCN to ordinary alkenes uses an isocyanide (RNC) and Schwartz's reagent (see **15-17**); this method gives anti-Markovnikov addition.[1505] *tert*-Butyl isocyanide and $TiCl_4$ have been used to add HCN to C=C—Z alkenes.[1506] Pretreatment with NaI/Me_3SiCl followed by CuCN converts alkynes to vinyl nitriles.[1507]

When an alkene is treated with Me_3SiCN and $AgClO_4$, followed by aq. $NaHCO_3$, the product is the isonitrile (RNC) formed with Markovnikov selectivity.[1508] An alternative reagent is the cyanohydrin of acetone, which adds to alkenes to give a nitrile in the presence of a nickel complex.[1509]

OS **I**, 451; **II**, 498; **III**, 615; **IV**, 392, 393, 804; **V**, 239, 572; **VI**, 14.
For addition of ArH, see **11-12** (Friedel–Crafts alkylation).

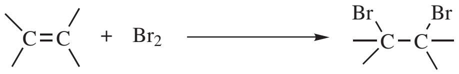
REACTIONS IN WHICH HYDROGEN ADDS TO NEITHER SIDE

Some of these reactions are *cycloadditions* (reactions **15-50**, **15-62**, **15-54**, and **15-57–15-66**). In such cases, addition to the multiple bond closes a ring:

A. Halogen on One or Both Sides

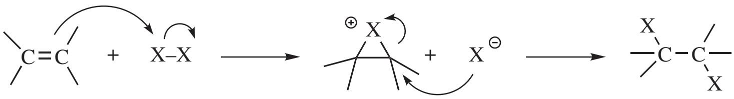
15-39 Halogenation of Double and Triple Bonds (Addition of Halogen, Halogen)

Dihalo-Addition



[1504]For a review, see Brown, E.S., in Wender, P.; Pino, P. *Organic Syntheses via Metal Carbonyls*, Vol. 2, Wiley, NY, ***1977***, pp. 658–667. For a review of the nickel-catalyzed process, see Tolman, C.A.; McKinney, R.J.; Seidel, W.C.; Druliner, J.D.; Stevens, W.R. *Adv. Catal.* ***1985***, *33*, 1. For studies of the mechanism see Tolman, C.A.; Seidel, W.C.; Druliner, J.D.; Domaille, P.J. *Organometallics* ***1984***, *3*, 33; Druliner, J.D. *Organometallics* ***1984***, *3*, 205; Bäckvall, J.E.; Andell, O.S. *Organometallics* ***1986***, *5*, 2350; McKinney, R.J.; Roe, D.C. *J. Am. Chem. Soc.* ***1986***, *108*, 5167; Funabiki, T.; Tatsami, K.; Yoshida, S. *J. Organomet. Chem.* ***1990***, *384*, 199. See also, Jackson, W.R.; Lovel, C.G.; Perlmutter, P.; Smallridge, A.J. *Aust. J. Chem.* ***1988***, *41*, 1099.
[1505]Buchwald, S.L.; LeMaire, S.J. *Tetrahedron Lett.* ***1987***, *28*, 295.
[1506]Ito, Y.; Kato, H.; Imai, H.; Saegusa, T. *J. Am. Chem. Soc.* ***1982***, *104*, 6449.
[1507]Luo, F.-T.; Ko, S.-L.; Chao, D.-Y. *Tetrahedron Lett.* ***1997***, *38*, 8061.
[1508]Kitano, Y.; Chiba, K.; Tada, M. *Synlett* ***1999***, 288.
[1509]Yan, M.; Xu, Q.-Y.; Chan, A.S.C. *Tetrahedron Asymmetry* ***2000***, *11*, 845.

Most double bonds are easily halogenated[1510] with bromine, chlorine, or inter-halogen compounds.[1511] Substitution can compete with addition in some cases.[1512] Iodination has also been accomplished, but the reaction is slower.[1513] Under free-radical conditions, iodination proceeds more easily.[1514] However, *vic*-diiodides are generally unstable and tend to revert to iodine and the alkene.



162

The mechanism is usually electrophilic (see p. 1002), involving formation of an halonium ion (**162**),[1515] followed by nucleophilic opening to give the *vic*-dihalide. Nucleophilic attack is occurs with selectivity for the less substituted carbon with unsymmetrical alkenes. When free-radical initiators (or UV light) are present, addition can occur by a free-radical mechanism.[1516] Once Br• or Cl• radicals are formed, however, substitution may compete (**14-1** and **14-3**). This is especially important when the alkene has allylic hydrogens. Under free-radical conditions (UV light) bromine or chlorine adds to the benzene ring to give, respectively, hexabromo- and hexachlorocyclohexane. These are mixtures of stereoisomers (see p. 187).[1517]

Under ordinary conditions fluorine itself is too reactive to give simple addition; it attacks other bonds and mixtures are obtained.[1518] However, F_2 has been successfully added to certain double bonds in an inert solvent at low temperatures (−78°C), usually by diluting the F_2 gas with Ar or N_2.[1519] Addition of fluorine has also been accomplished with other reagents (e.g., *p*-Tol—IF_2/Et_3N•5 HF),[1520] and a mixture of PbO_2 and SF_4.[1521]

[1510]For a list of reagents that have been used for di-halo-addition, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 629–632.

[1511]For a monograph, see de la Mare, P.B.D. *Electrophilic Halogenation*, Cambridge University Press, Cambridge, ***1976***. For a review, see House, H.O. *Modern Synthetic Reaction*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 422–431.

[1512]McMillen, D.W.; Grutzner, J.B. *J. Org. Chem.* ***1994***, *59*, 4516.

[1513]Sumrell, G.; Wyman, B.M.; Howell, R.G.; Harvey, M.C. *Can. J. Chem.* ***1964***, *42*, 2710; Zanger, M.; Rabinowitz, J.L. *J. Org. Chem.* ***1975***, *40*, 248.

[1514]Skell, P.S.; Pavlis, R.R. *J. Am. Chem. Soc.* ***1964***, *86*, 2956; Ayres, R.L.; Michejda, C.J.; Rack, E.P. *J. Am. Chem. Soc.* ***1971***, *93*, 1389.

[1515]See Lenoir, D.; Chiappe, C. *Chem. Eur. J.* ***2003***, *9*, 1037.

[1516]For example, see Poutsma, M.L. *J. Am. Chem. Soc.* ***1965***, *87*, 2161, 2172; *J. Org. Chem.* ***1966***, *31*, 4167; Dessau, R.M. *J. Am. Chem. Soc.* ***1979***, *101*, 1344.

[1517]For a review, see Cais, M., in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, ***1964***, p. 993.

[1518]See, for example, Fuller, G.; Stacey, F.W.; Tatlow, J.C.; Thomas, C.R. *Tetrahedron* ***1962***, *18*, 123.

[1519]Merritt, R.F. *J. Am. Chem. Soc.* ***1967***, *89*, 609; Barton, D.H.R.; Lister-James, J.; Hesse, R.H.; Pechet, M.M.; Rozen, S. *J. Chem. Soc. Perkin Trans. 1* ***1982***, 1105; Rozen, S.; Brand, M. *J. Org. Chem.* ***1986***, *51*, 3607.

[1520]Hara, S.; Nakahigashi, J.; Ishi-i, K.; Sawaguchi, M.; Sakai, H.; Fukuhara, T.; Yoneda, N. *Synlett* ***1998***, 495.

[1521]Bissell, E.R.; Fields, D.B. *J. Org. Chem.* ***1964***, *29*, 1591.

The reaction with bromine is very rapid and is easily carried out at room temperature,[1522] although the reaction is reversible under some conditions.[1523] In the case of bromine, an alkene•Br_2 complex has been detected in at least one case.[1524] Bromine is often used as a test, qualitative or quantitative, for unsaturation.[1525] The vast majority of double bonds can be successfully brominated. Even when aldehyde, ketone, amine, and so on functions are present in the molecule, they do not interfere, since the reaction with double bonds is faster. Bromination has been carried out in an ionic liquid.[1526]

Several other reagents add Cl_2 to double bonds, among them Me_3SiCl^- MnO_2,[1527] $NaClO_2/Mn(acac)_2$/moist Al_2O_3,[1528] $BnNEt_3MnO_4/Me_3SiCl$,[1529] and $KMnO_4$-oxalyl chloride.[1530] A convenient reagent for the addition of Br_2 to a double bond on a small scale is the commercially available pyridinium bromide perbromide $C_5H_5NH^+Br_3^-$.[1531] Potassium bromide with ceric ammonium nitrate, in water/dichloromethane, gives the dibromide.[1532] A combination of KBr and Selectfluor also give the dibromide.[1533] A combination of $CuBr_2$ in aq. THF and a chiral ligand led to the dibromide with good enantioselectivity.[1534] A mixture of (decyl)Me_3 $NMnO_4$ and Me_3SiBr is also an effective reagent.[1535] Either Br_2 or Cl_2 can also be added with $CuBr_2$ or $CuCl_2$ in the presence of a compound, such as acetonitrile, methanol, or triphenylphosphine.[1536]

[1522]See Bellucci, G.; Chiappe, C. *J. Org. Chem.* ***1993***, *58*, 7120 for a study of the rate and kinetics of alkene bromination.

[1523]Zheng, C.Y.; Slebocka-Tilk, H.; Nagorski, R.W.; Alvarado, L.; Brown, R.S. *J. Org. Chem.* ***1993***, *58*, 2122.

[1524]Bellucci, G.; Chiappe, C.; Bianchini, R.; Lenoir, D.; Herges, R. *J. Am. Chem. Soc.* ***1995***, *117*, 12001.

[1525]For a review of this, see Kuchar, E.J., in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, ***1964***, pp. 273–280.

[1526]In bmim Br, 1-butyl-3-methylimidazolium bromide: Chiappe, C.; Capraro, D.; Conte, V.; Picraccini, D. *Org. Lett.* ***2001***, *3*, 1061.

[1527]Bellesia, F.; Ghelfi, F.; Pagnoni, U.M.; Pinetti, A. *J. Chem. Res. (S)* ***1989***, *108*, 360.

[1528]Yakabe, S.; Hirano, M.; Morimoto, T. *Synth. Comun.* ***1998***, *28*, 1871.

[1529]Markó, I.E.; Richardson, P.R.; Bailey, M.; Maguire, A.R.; Coughlan, N. *Tetrahedron Lett.* ***1997***, *38*, 2339.

[1530]Markó, I.E.; Richardson, P.F. *Tetrahedron Lett.* ***1991***, *32*, 1831.

[1531]Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis*, Vol. 1, Wiley, NY, ***1967***, pp. 967–970. For a discussion of the mechanism with Br_3^-, see Bellucci, G.; Bianchini, R.; Vecchiani, S. *J. Org. Chem.* ***1986***, *51*, 4224.

[1532]Nair, V.; Panicker, S.B.; Augstine, A.; George, T.G.; Thomas, S.; Vairamani, M. *Tetrahedron* ***2001***, *57*, 7417.

[1533]Ye, C.; Shreeve, J.M. *J. Org. Chem.* ***2004***, *69*, 8561.

[1534]El-Quisairi, A.K.; Qaseer, H.A.; Katsigras, G.; Lorenzi, P.; Tribedi, U.; Tracz, S.; Hartman, A.; Miller, J.A.; Henry, P.M. *Org. Lett.* ***2003***, *5*, 439.

[1535]Hazra, B.G.; Chordia, M.D.; Bahule, B.B.; Pore, V.S.; Basu, S. *J. Chem. Soc. Perkin Trans. 1* ***1994***, 1667.

[1536]Koyano, T. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 1439, 3501; Uemura, S.; Tabata, A.; Kimura, Y.; Ichikawa, K. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 1973; Or, A.; Levy, M.; Asscher, M.; Vofsi, D. *J. Chem. Soc. Perkin Trans. 2* ***1974***, 857; Uemura, S.; Okazaki, H.; Onoe, A.; Okano, M. *J. Chem. Soc. Perkin Trans. 1* ***1977***, 676; Baird, Jr., W.C.; Surridge, J.H.; Buza, M. *J. Org. Chem.* ***191***, *36*, 2088, 3324.

Mixed halogenations have also been achieved, and the order of activity for some of the reagents is BrCl > ICl[1537] > Br_2 > IBr > I_2.[1538] Mixtures of Br_2 and Cl_2 have been used to give bromochlorination,[1539] as has tetrabutylammonium dichlorobromate, Bu_4NBrCl_2;[1540] iodochlorination has been achieved with $KICl_2$,[1541] $CuCl_2$, and either I_2, HI, or CdI_2; iodofluorination[1542] with mixtures of AgF and I_2;[1543] and mixtures of *N*-bromo amides in anhydrous HF give bromofluorination.[1544] Bromo-, iodo-, and chlorofluorination have also been achieved by treatment of the substrate with a solution of Br_2, I_2, or an *N*-halo amide in polyhydrogen fluoride-pyridine;[1545] while addition of I along with Br, Cl, or F has been accomplished with the reagent bis(pyridine)iodo(I) tetrafluoroborate $I(Py)_2BF_4$ and Br^-, Cl^-, or F^-, respectively.[1546] This reaction (which is also successful for triple bonds[1547]) can be extended to addition of I and other nucleophiles (e.g., NCO, OH, OAc, and NO_2).[1547] Cyclohexene is converted to *trans*-2-fluoroiodocyclohexane under electrolytic conditions using Et_4NI—Et_3N•HF in the reaction medium.[1548]

Conjugated systems give both 1,2- and 1,4-addition.[1518] Triple bonds add bromine, although generally more slowly than double bonds (see p. 1015). Molecules that contain both double and triple bonds are preferentially attacked at the double bond. Addition of 2 equivalents of bromine to triple bonds gives tetrabromo products. There is evidence that the addition of the first mole of bromine to a triple bond may take place by a nucleophilic mechanism.[1549] Molecular diiodine on Al_2O_3 adds to triple bonds to give good yields of 1,2-diiodoalkenes.[1550] Interestingly, 1,1-diiodo alkenes are prepared from an alkynyltin compound, via initial treatment with $Cp_2Zr(H)Cl$, and then 2.15 equivalents of iodine.[1551] A mixture of

[1537]For a review of ICl, see McCleland, C.W., in Pizey, J.S. *Synthetic Reagents*, Vol. 5, Wiley, NY, ***1983***, pp. 85–164.

[1538]White, E.P.; Robertson, P.W. *J. Chem. Soc.* ***1939***, 1509.

[1539]Buckles, R.E.; Forrester, J.L.; Burham, R.L.; McGee, T.W. *J. Org. Chem.* ***1960***, *25*, 24.

[1540]Negoro, T.; Ikeda, Y. *Bull. Chem. Soc. Jpn.* ***1986***, *59*, 3519.

[1541]Zefirov, N.S.; Sereda, G.A.; Sosounk, S.E.; Zyk, N.V.; Likhomanova, T.I. *Synthesis* ***1995***, 1359.

[1542]For a review of mixed halogenations where one side is fluorine, see Sharts, C.M.; Sheppard, W.A. *Org. React.* ***1974***, *21*, 125, see pp. 137–157. For a review of halogen fluorides in organic synthesis, see Boguslavskaya, L.S. *Russ. Chem. Rev.* ***1984***, *53*, 1178.

[1543]Evans, R.D.; Schauble, J.H. *Synthesis* ***1987***, 551; Kuroboshi, M.; Hiyama, T. *Synlett* ***1991***, 185.

[1544]Pattison, F.L.M.; Peters, D.A.V.; Dean, F.H. *Can. J. Chem.* ***1965***, *43*, 1689. For other methods, see Boguslavskaya, L.S.; Chuvatkin, N.N.; Kartashov, A.V.; Ternovskoi, L.A. *J. Org. Chem. USSR* ***1987***, *23*, 230; Shimizu, M.; Nakahara, Y.; Yoshioka, H. *J. Chem. Soc., Chem. Commun.* ***1989***, 1881.

[1545]Olah, G.A.; Nojima, M.; Kerekes, I. *Synthesis* ***1973***, 780; Olah, G.A.; Welch, J.T.; Vankar, Y.D.; Nojima, M.; Kerekes, I.; Olah, J.A. *J. Org. Chem.* ***1979***, *44*, 3872. For other halofluorination methods, see Rozen, S.; Brand, M. *J. Org. Chem.* ***1985***, *50*, 3342; ***1986***, *51*, 222; Alvernhe, G.; Laurent, A.; Haufe, G. *Synthesis* ***1987***, 562; Camps, F.; Chamorro, E.; Gasol, V.; Guerrero, A. *J. Org. Chem.* ***1989***, *54*, 4294; Ichihara, J.; Funabiki, K.; Hanafusa, T. *Tetrahedron Lett.* ***1990***, *31*, 3167.

[1546]Barluenga, J.; González, J.M.; Campos, P.J.; Asensio, G. *Angew. Chem. Int. Ed.* ***1985***, *24*, 319.

[1547]Barluenga, J.; Rodríguez, M.A.; González, J.M.; Campos, P.J.; Asensio, G. *Tetrahedron Lett.* ***1986***, *27*, 3303.

[1548]Kobayashi, S.; Sawaguchi, M.; Ayuba, S.; Fukuhara, T.; Hara, S. *Synlett* ***2001***, 1938.

[1549]Sinn, H.; Hopperdietzel, S.; Sauermann, D. *Monatsh. Chem.* ***1965***, *96*, 1036.

[1550]Hondrogiannis, G.; Lee, L.C.; Kabalka, G.W.; Pagni, R.M. *Tetrahedron Lett.* ***1989***, *30*, 2069.

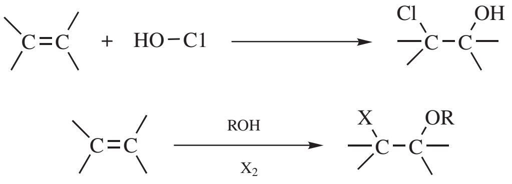
[1551]Dabdoub, M.J.; Dabdoub, V.B.; Baroni, A.C.M. *J. Am. Chem. Soc.* ***2001***, *123*, 9694.

$NaBO_3$ and NaBr adds two bromine atoms across a triple bond.[1552] With allenes it is easy to stop the reaction after only 1 equivalent has added, to give X—C—CX=C.[1553] Addition of halogen to ketenes gives α-halo acyl halides, but the yields are not good.

OS **I**, 205, 521; **II**, 171, 177, 270, 408; **III**, 105, 123, 127, 209, 350, 526, 531, 731, 785; **IV**, 130, 195, 748, 851, 969; **V**, 136, 370, 403, 467; **VI**, 210, 422, 675, 862, 954; **IX**, 117; **76**, 159.

15-40 Addition of Hypohalous Acids and Hypohalites (Addition of Halogen, Oxygen)

Hydroxy-chloro-addition, and so on.[1554]
Alkoxy-chloro-addition, and so on.



Hypohalous acids (HOCl, HOBr, and HOI) can be added to alkenes[1555] to produce halohydrins.[1556] Both HOBr and HOCl are often generated *in situ* by the reaction between water and Br_2 or Cl_2, respectively. HOI, generated from I_2 and H_2O, also adds to double bonds, if the reaction is carried out in tetramethylene sulfone-$CHCl_3$[1557] or if an oxidizing agent, such as HIO_3 is present.[1558] Iodine and cerium sulfate in aqueous acetonitrile generates iodohydrins,[1559] as does iodine and ammonium acetate in acetic acid,[1560] or $NaIO_4$ with sodium bisulfite.[1561] The HOBr can also be conveniently added by the use of a reagent consisting of an *N*-bromo amide

[1552]Kabalka, G.W.; Yang, K. *Synth. Commun.* ***1998***, *28*, 3807; Kabalka, G.W.; Yang, K.; Reddy, N.K.; Narayana, A. *Synth. Commun.* ***1998***, *28*, 925.

[1553]For a review of additions of halogens to allenes, see Jacobs, T.L., in Landor, S.R. *The Chemistry of Allenes*, Vol. 2, Academic Press, NY, ***1982***, pp. 466–483.

[1554]Addends are listed in order of priority in the Cahn–Ingold–Prelog system (p. 155).

[1555]For a list of reagents used to accomplish these additions, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 638–642.

[1556]For a review, see Boguslavskaya, L.S. *Russ. Chem. Rev.* ***1972***, *41*, 740.

[1557]Cambie, R.C.; Noall, W.I.; Potter, G.J.; Rutledge, P.S.; Woodgate, P.D. *J. Chem. Soc. Perkin Trans. 1* ***1977***, 266.

[1558]See, for example, Cornforth, J.W.; Green, D.T. *J. Chem. Soc. C* ***1970***, 846; Furrow, S.D. *Int. J. Chem. Kinet.* ***1982***, *14*, 927; Antonioletti, R.; D'Auria, M.; De Mico, A.; Piancatelli, G.; Scettri, A. *Tetrahedron* ***1983***, *39*, 1765.

[1559]Horiuchi, C.A.; Ikeda, A.; Kanamori, M.; Hosokawa, H.; Sugiyama, T.; Takahashi, T.T. *J. Chem. Res. (S)* ***1997***, 60.

[1560]Myint, Y.Y.; Pasha, M.A. *Synth. Commun.* ***2004***, *34*, 4477.

[1561]Masuda, H.; Takase, K.; Nishio, M.; Hasegawa, A.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.* ***1994***, *59*, 5550.

(e.g., NBS or *N*-bromoacetamide) and a small amount of water in a solvent, such as DMSO or dioxane.[1562] *N*-Iodosuccinimide (NIS) in aqueous dimethoxyethane leads to the iodohydrin.[1563] An especially powerful reagent for HOCl addition is *tert*-butyl hydroperoxide (or di-*tert*-butyl peroxide) along with $TiCl_4$. This reaction is generally complete within 15 min at −78°C.[1564] Chlorohydrins can be conveniently prepared by treatment of the alkene with Chloramine T ($TsNCl^-$ Na^+)[1565] in acetone–water.[1566] The compound HOI can be added by treatment of alkenes with periodic acid and $NaHSO_3$.[1567] The reaction of an alkene with polymeric $(SnO)_n$, and then HCl with $Me_3SiOOSiMe_3$ leads to the chlorohydrin.[1568] Hypervalent iodine compounds react with an alkene and iodine in aqueous media to give the iodohydrin.[1569]

The compound HOF has also been added, but this reagent is difficult to prepare in a pure state and *explosions have occurred.*[1570]

The mechanism of HOX addition is electrophilic, with initial attack by the positive halogen end of the HOX dipole. Following Markovnikov's rule, the positive halogen goes to the side of the double bond that has more hydrogens (forming a more stable carbocation). This carbocation (or bromonium or iodonium ion in the absence of an aqueous solvent) reacts with ^-OH or H_2O to give the product. If the substrate is treated with Br_2 or Cl_2 (or another source of positive halogen such as NBS) in an alcohol or a carboxylic acid solvent, it is possible to obtain, directly $X-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-OR$ or $X-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-OCOR$, respectively (see also, **15-48**).[1571] Even the weak nucleophile $CF_3SO_2O^-$ can participate in the second step: The addition of Cl_2 or Br_2 to alkenes in the presence of this ion resulted in the formation of some β-haloalkyl triflates.[1572] There is evidence that the mechanism with Cl_2 and H_2O is different from that with HOCl.[1573] HOCl and HOBr can be added to triple bonds to give dihalo carbonyl compounds —CX_2—CO—.

[1562]For examples, see Dalton, D.R.; Hendrickson, J.B.; Jones, D. *Chem. Commun.* ***1966***, 591; Dalton, D.R.; Dutta, V.P. *J. Chem. Soc. B* ***1971***, 85; Sisti, A.J. *J. Org. Chem.* ***1970***, *35*, 2670.

[1563]Smietana, M.; Gouverneur, V.; Mioskowski, C. *Tetahedron Lett.* ***2000***, *41*, 193.

[1564]Klunder, J.M.; Caron M.; Uchiyama, M.; Sharpless, K.B. *J. Org. Chem.* ***1985***, *50*, 912.

[1565]For reviews of this reagent, see Bremner, D.H., in Pizey, J.S. *Synthetic Reagents*, Vol. 6, Wiley, NY, ***1985***, pp. 9–59; Campbell, M.M.; Johnson, G. *Chem. Rev.* ***1978***, *78*, 65.

[1566]Damin, B.; Garapon, J.; Sillion, B. *Synthesis* ***1981***, 362.

[1567]Ohta, M.; Sakata, Y.; Takeuchi, T.; Ishii, Y. *Chem. Lett.* ***1990***, 733.

[1568]Sakurada, I.; Yamasaki, S.; Göttlich, R.; Iida, T.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* ***2000***, *122*, 1245.

[1569]DeCorso, A.R.; Panunzi, B.; Tingoli, M. *Tetrahedron Lett.* ***2001***, *42*, 7245.

[1570]Migliorese, K.G.; Appelman, E.H.; Tsangaris, M.N. *J. Org. Chem.* ***1979***, *44*, 1711.

[1571]For a list of reagents that accomplish alkoxy-halo-addition, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 642–643.

[1572]Zefirov, N.S.; Koz'min, A.S.; Sorokin, V.D.; Zhdankin, V.V. *J. Org. Chem. USSR* ***1982***, *18*, 1546. For reviews of this and related reactions, see Zefirov, N.S.; Koz'min, A.S. *Acc. Chem. Res.* ***1985***, *18*, 154; *Sov. Sci. Rev. Sect. B* ***1985***, *7*, 297.

[1573]Buss, E.; Rockstuhl, A.; Schnurpfeil, D. *J. Prakt. Chem.* ***1982***, *324*, 197.

Alcohols and halogens react with alkenes to form halo ethers. When a homoallylic alcohol is treated with bromine, cyclization occurs to give a 3-bromotetrahydrofuran derivative.[1574] *tert*-Butyl hypochlorite (Me_3COCl), hypobromite, and hypoiodite[1575] add to double bonds to give halogenated *tert*-butyl ethers, X—C—C—$OCMe_3$. This is a convenient method for the preparation of tertiary ethers. Iodine and ethanol convert some alkenes to iodo-ethers.[1576] Iodine, alcohol and a $Ce(OTf)_2$ catalyst also generates the iodo-ether.[1577] When Me_3COCl or Me_3COBr is added to alkenes in the presence of excess ROH, the ether produced is $X-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-OR$.[1578] Vinylic ethers give β-halo acetals.[1579] A mixture of Cl_2 and SO_3 at −78°C converts alkenes to 2-chloro chlorosulfates $ClCHRCHROSO_2Cl$, which are stable compounds.[1580] Chlorine acetate [solutions of which are prepared by treating Cl_2 with $Hg(OAc)_2$ in an appropriate solvent] adds to alkenes to give acetoxy chlorides.[1581] Acetoxy fluorides have been obtained by treatment of alkenes with CH_3COOF.[1582]

For a method of iodoacetyl addition, see **15-48**.

An oxidative variation of this reaction treats a vinyl chloride with NaOCl and acetic acid, generating an α-chloro ketone.[1583]

OS **I**, 158; **IV**, 130, 157; **VI**, 184, 361, 560; **VII**, 164; **VIII**, 5, 9.

15-41 Halolactonization and Halolactamization

Halo-alkoxylation

Halo esters can be formed by addition of halogen atoms and ester groups to an alkene. Alkene carboxylic acids give a tandem reaction of formation of a halonium ion followed by intramolecular displacement of the carboxylic group to give a halo lactone. This tandem addition of X and OCOR is called

[1574]Chirskaya, M.V.; Vasil'ev, A.A.; Sergovskaya, N.L.; Shovshinev, S.V.; Sviridov, S.I. *Tetrahedron Lett.* ***2004***, *45*, 8811.

[1575]Glover, S.A.; Goosen, A. *Tetrahedron Lett.* ***1980***, *21*, 2005.

[1576]Sanseverino, A.M.; de Mattos, M.C.S. *Synthesis* ***1998***, 1584. See Horiuchi, C.A.; Hosokawa, H.; Kanamori, M.; Muramatsu, Y.; Ochiai, K.; Takahashi, E. *Chem. Lett.* ***1995***, 13 for an example using I_2/MeOH/ceric ammonium nitrate.

[1577]Iranpoor, N.; Shekarriz, M. *Tetahedron* ***2000***, *56*, 5209.

[1578]Bresson, A.; Dauphin, G.; Geneste, J.; Kergomard, A.; Lacourt, A. *Bull. Soc. Chim. Fr.* ***1970***, 2432; ***1971***, 1080.

[1579]Weissermel, K.; Lederer, M. *Chem. Ber.* ***1963***, *96*, 77.

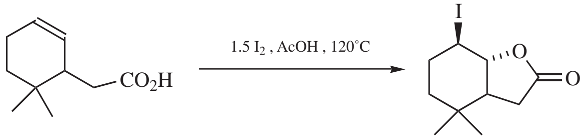
[1580]Zefirov, N.S.; Koz'min, A.S.; Sorokin, V.D. *J. Org. Chem.* ***1984***, *49*, 4086.

[1581]de la Mare, P.B.D.; O'Connor, C.J.; Wilson, M.A. *J. Chem. Soc. Perkin Trans. 2*, ***1975***, 1150. For the addition of bromine acetate, see Wilson, M.A.; Woodgate, P.D. *J. Chem. Soc. Perkin Trans. 2*, ***1976***, 141. For a list of reagents that accomplish acyloxy-halo-addition, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 643–644.

[1582]Rozen, S.; Lerman, O.; Kol, M.; Hebel, D. *J. Org. Chem.* ***1985***, *50*, 4753.

[1583]Van Brunt, M.P.; Ambenge, R.O.; Weinreb, S.M. *J. Org. Chem.* ***2003***, *68*, 3323.

halolactonization.[1584]

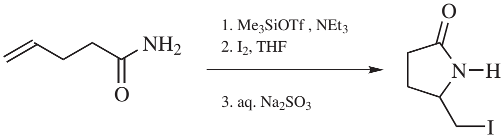


163 **164**

The most common version of this reaction is known as *iodolactonization*,[1585] and a typical example is the conversion of **163** to **164**.[1586] Bromo lactones and, to a lesser extent, chloro lactones have also been prepared. In general, addition of the halogen to an alkenyl acid, as shown, leads to the halo-lactone. Other reagents include $I^+(collidine)_2PF_6^-$,[1587] KI/sodium persulfate.[1588] Thallium reagents, along with the halogen, have also been used.[1589] When done in the presence of a chiral titanium reagent, I_2, and CuO, lactones are formed with good enantioselectivity.[1590] ICl has been used, with formation of a quaternary center at the oxygen-bearing carbon of the lactone.[1591]

In the case of γ,δ-unsaturated acids, 5-membered rings (γ-lactones) are predominantly formed (as shown above; note that Markovnikov's rule is followed), but 6-membered and even 4-membered lactones have also been made by this procedure. There is a gem-dimethyl effect that favors formation of 7–11-membered ring lactones by this procedure.[1592]

Formation of halo-lactams (**15-43**) by a similar procedure is difficult, but the problems have been overcome. Formation of a triflate followed by treatment with iodine leads to the iodo-lactam, **165**.[1593]



165

[1584]For reviews, see Cardillo, G.; Orena, M. *Tetrahedron* ***1990***, *46*, 3321; Dowle, M.D.; Davies, D.I. *Chem. Soc. Rev.* ***1979***, *8*, 171. For a list of reagents that accomplish this, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1870–1876. For a review with respect to the stereochemistry of the reaction, see Bartlett, P.A., in Morrison, J.D. *Organic Synthesis*, Vol. 3, Wiley, NY, ***1984***, pp. 411–454, 416–425.

[1585]Klein, J. *J. Am. Chem. Soc.* ***1959***, *81*, 3611; van Tamelen, E.E.; Shamma, M. *J. Am. Chem. Soc.* ***1954***, *76*, 2315; House, H.O.; Carlson, R.G.; Babad, H. *J. Org. Chem.* ***1963***, *28*, 3359; Corey, E.J.; Albonico, S.M.; Koelliker, V.; Schaaf, T.K.; Varma, R.K. *J. Am. Chem. Soc.* ***1971***, *93*, 1491.

[1586]Yaguchi, Y.; Akiba, M.; Harada, M.; Kato, T. *Heterocycles* ***1996***, *43*, 601.

[1587]Homsi, F.; Rousseau, G. *J. Org. Chem.* ***1998***, *63*, 5255; Simonet, B.; Rousseau, G. *J. Org. Chem.* ***1993***, *58*, 4.

[1588]Royer, A.C.; Mebane, R.C.; Swafford, A.M. *Synlett* ***1993***, 899.

[1589]See Cambie, R.C.; Rutledge, P.S.; Somerville, R.F.; Woodgate, P.D. *Synthesis* ***1988***, 1009, and references cited therein.

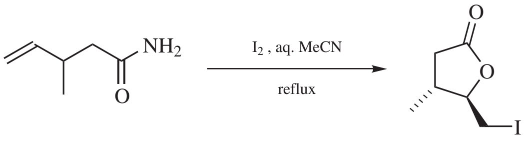
[1590]Inoue, T.; Kitagawa, O.; Kurumizawa, S.; Ochiai, O.; Taguchi, T. *Tetrahedron Lett.* ***1995***, *36*, 1479.

[1591]Haas, J.; Piguel, S.; Wirth, T. *Org. Lett.* ***2002***, *4*, 297.

[1592]Simonot, B.; Rousseau, G. *Tetrahedron Lett.* ***1993***, *34*, 4527.

[1593]Knapp, S.; Rodriques, K.E. *Tetrahedron Lett.* ***1985***, *26*, 1803.

A related cyclization of *N*-sulfonyl-amino-alkenes and NBS gave the bromo-lactam,[1594] and a dichloro-*N,N*-bis(allylamide) was converted to a dichloro-lactam with $FeCl_2$.[1595] It is noted that lactone formation is possible from unsaturated amides. The reaction of 3-methyl *N,N*-dimethylpent-4-ene amide with iodine in aqueous acetonitrile, for example, gave iodolactone **166**.[1596]

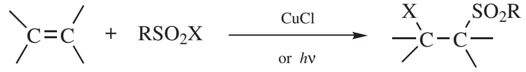


166

OS IX, 516.

15-42 Addition of Sulfur Compounds (Addition of Halogen, Sulfur)

Alkylsulfonyl-chloro-addition, and so on.[1597]



Sulfonyl halides add to double bonds, to give β-halo sulfones, in the presence of free-radical initiators or UV light. A particularly good catalyst is cuprous chloride.[1598] A combination of the anion $ArSO_2Na$, NaI, and ceric ammonium nitrate converts alkenes to vinyl sulfones.[1599] Triple bonds behave similarly, to give β-halo-α,β-unsaturated sulfones.[1600] In a similar reaction, sulfenyl chlorides, RSCl, give β-halo thioethers.[1601] The latter may be free-radical or electrophilic additions, depending on conditions. The addition of MeS and Cl has also been accomplished by treating the alkene with Me_3SiCl and Me_2SO.[1602] The use of Me_3SiBr and Me_2SO does not give this result; dibromides (**15-39**) are formed instead. β-Iodo

[1594]Tamaru, Y.; Kawamura, S.; Tanaka, K.; Yoshida, Z. *Tetrahedron Lett.* ***1984***, *25*, 1063.

[1595]Tseng, C.K.; Teach, E.G.; Simons, R.W. *Synth. Commun.* ***1984***, *14*, 1027.

[1596]Ha, H.-J.; Lee, S.-Y.; Park, Y.-S. *Synth. Commun.* ***2000***, *30*, 3645.

[1597]When a general group (e.g., halo) is used, its priority is that of the lowest member of its group (see Ref. 1555). Thus the general name for this transformation is halo-alkylsulfonyl-addition because “halo” has the same priority as “fluoro,” its lowest member.

[1598]Asscher, M.; Vofsi, D. *J. Chem. Soc.* ***1964***, 4962; Truce, W.E.; Goralski, C.T.; Christensen, L.W.; Bavry, R.H. *J. Org. Chem.* ***1970***, *35*, 4217; Sinnreich, J.; Asscher, M. *J. Chem. Soc. Perkin Trans. 1*, ***1972***, 1543.

[1599]Nair, V.; Augustine, A.; George, T.G.; Nair, L.G. *Tetrahedron Lett.* ***2001***, *42*, 6763.

[1600]Truce, W.E.; Wolf, G.C. *J. Org. Chem.* ***1971***, *36*, 1727; Amiel, Y. *J. Org. Chem.* ***1974***, *39*, 3867; Zakharkin, L.I.; Zhigareva, G.G. *J. Org. Chem. USSR* ***1973***, *9*, 918; Okuyama, T.; Izawa, K.; Fueno, T. *J. Org. Chem.* ***1974***, *39*, 351.

[1601]For reviews, see Rasteikiene, L.; Greiciute, D.; Lin’kova, M.G.; Knunyants, I.L. *Russ. Chem. Rev.* ***1977***, *46*, 548; Kühle, E. *Synthesis* ***1971***, 563.

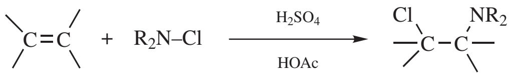
[1602]Bellesia, F.; Ghelfi, F.; Pagnoni, U.M.; Pinetti, A. *J. Chem. Res. (S)* ***1987***, 238. See also, Liu, H.; Nyangulu, J.M. *Tetrahedron Lett.* ***1988***, *29*, 5467.

thiocyanates can be prepared from alkenes by treatment with I_2 and isothiocyanatotributylstannane Bu_3SnNCS.[1603] Bromothiocyanation can be accomplished with Br_2 and thallium(I) thiocyanate.[1604] Lead (II) thiocyanate reacts with terminal alkynes in the presence of $PhICl_2$ to give the bis(thiocyanato) alkene, ArC(SCN)—CHSCN.[1605] Such compounds were also prepared from alkenes using KSCN and $FeCl_3$.[1606] β-Halo disulfides, formed by addition of arenethiosulfenyl chlorides to double-bond compounds, are easily converted to thiiranes by treatment with sodium amide or sodium sulfide.[1607]

OS **VIII**, 212. See also OS **VII**, 251.

15-43 Addition of Halogen and an Amino Group (Addition of Halogen, Nitrogen)

Dialkylamino-chloro-addition



The groups R_2N and Cl can be added directly to alkenes, allenes, conjugated dienes, and alkynes, by treatment with dialkyl-*N*-chloroamines and acids.[1608] The reaction of $TsNCl_2$ and a $ZnCl_2$ catalyst gave the chloro tosylamine.[1609] These are free-radical additions, with initial attack by the $R_2NH^{\bullet +}$ radical ion.[1610] *N*-Halo amides RCONHX add RCONH and X to double bonds under the influence of uv light or chromous chloride.[1611] Amines add to allenes in the presence of a palladium catalyst.[1612] A mixture of *N*-(2-nosyl)NCl_2 and sodium *N*-(2-nosyl)NH^- with a CuOTf catalyst reacted with conjugated esters to give the *vicinal* (*E*)-3-chloro-2-amino ester.[1613] A variation of this latter reaction was done in an ionic liquid.[1614]

[1603]Woodgate, P.D.; Janssen, S.J.; Rutledge, P.S.; Woodgate, S.D.; Cambie, R.C. *Synthesis* ***1984***, 1017, and references cited therein. See also, Watanabe, N.; Uemura, S.; Okano, M. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 2458.

[1604]Cambie, R.C.; Larsen, D.S.; Rutledge, P.S.; Woodgate, P.D. *J. Chem. Soc. Perkin Trans. 1*, ***1981***, 58.

[1605]Prakash, O.; Sharma, V.; Batra, H.; Moriarty, R.M. *Tetrahedron Lett.* ***2001***, *42*, 553.

[1606]Yadav, J.S.; Reddy, B.V.S.; Gupta, M.K. *Synthesis* ***2004***, 1983.

[1607]Fujisawa, T.; Kobori, T. *Chem. Lett.* ***1972***, 935. For another method of alkene-thiirane conversion, see Capozzi, F.; Capozzi, G.; Menichetti, S. *Tetrahedron Lett.* ***1988***, *29*, 4177.

[1608]For reviews see Mirskova, A.N.; Drozdova, T.I.; Levkovskaya, G.G.; Voronkov, M.G. *Russ. Chem. Rev.* ***1989***, *58*, 250; Neale, R.S. *Synthesis* ***1971***, 1; Sosnovsky, G.; Rawlinson, D.J. *Adv. Free-Radical Chem.* ***1972***, *4*, 203, see pp. 238–249.

[1609]Li, G.; Wei, H.-X.; Kim, S.H.; Neighbors, M. *Org. Lett.* ***1999***, *1*, 395; Wei, H.-X.; Ki, S.H.; Li, G. *Tetrahedron* ***2001***, *57*, 3869.

[1610]For a review of these species, see Chow, Y.L.; Danen, W.C.; Nelson, S.F.; Rosenblatt, D.H. *Chem. Rev.* ***1978***, *78*, 243.

[1611]Tuaillon, J.; Couture, Y.; Lessard, J. *Can. J. Chem.* ***1987***, *65*, 2194, and other papers in this series. For a review, see Labeish, N.N.; Petrov, A.A. *Russ. Chem. Rev.* ***1989***, *58*, 1048.

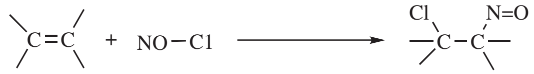
[1612]Besson, L.; Goré, J.; Cazes, B. *Tetrahedron Lett.* ***1995***, *36*, 3857.

[1613]Li, G.; Wei, H.-X.; Kim, S.H. *Org. Lett.* ***2000***, *2*, 2249; Li, G.; Wei, H.-X.; Kim, S.H. *Tetrahedron* ***2001***, *57*, 8407.

[1614]In bmim BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate: Xu, X.; Kotti, S.R.S.S.; Liu, J.; Cannon, J.F.; Headley, A.D.; Li, G. *Org. Lett.* ***2004***, *6*, 4881.

15-44 Addition of NOX and NO_2X (Addition of Halogen, Nitrogen)

Nitroso-chloro-addition



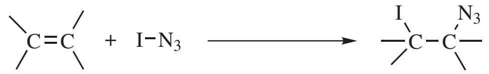
There are three possible products when NOCl is added to alkenes, a β-halo nitroso compound, an oxime, or a β-halo nitro compound.[1615] The initial product is always the β-halo nitroso compound,[1616] but these are stable only if the carbon bearing the nitrogen has no hydrogen. If it has, the nitroso compound tautomerizes to the oxime, H—C–N=O → C=N–OH. With some alkenes, the initial β-halo nitroso compound is oxidized by the NOCl to a β-halo nitro compound.[1617] Many functional groups can be present without interference (e.g., COOH, COOR, CN, OR). The mechanism in most cases is probably simple electrophilic addition, and the addition is usually anti, although syn addition has been reported in some cases.[1618] Markovnikov's rule is followed, the positive NO going to the carbon that has more hydrogens.

Nitryl chloride NO_2Cl also adds to alkenes, to give β-halo nitro compounds, but this is a free-radical process. The NO_2 goes to the less-substituted carbon.[1619] Nitryl chloride also adds to triple bonds to give the expected 1-nitro-2-chloro alkenes.[1620] The compound FNO_2 can be added to alkenes[1621] by treatment with HF in HNO_3[1622] or by addition of the alkene to a solution of nitronium tetrafluoroborate (NO_2^+ BF_4^-) (see **11-2**) in 70% polyhydrogen fluoride–pyridine solution[1623] (see also **15-37**).

OS **IV**, 711; **V**, 266, 863.

15-45 Addition of XN_3 (Addition of Halogen, Nitrogen)

Azido-iodo-addition



[1615]For a review, see Kadzyauskas, P.P.; Zefirov, N.S. *Russ. Chem. Rev.* ***1968***, *37*, 543.

[1616]For a review of preparations of *C*-nitroso compounds, see Gowenlock, B.G.; Richter-Addo, G.B. *Chem. Rev.* ***2004***, *104*, 3315.

[1617]For a review of the preparation of halo nitro compounds, see Shvekhgeimer, G.A.; Smirnyagin, V.A.; Sadykov, R.A.; Novikov, S.S. *Russ. Chem. Rev.* ***1968***, *37*, 351.

[1618]For example, see Meinwald, J.; Meinwald, Y.C.; Baker III, T.N. *J. Am. Chem. Soc.* ***1964***, *86*, 4074.

[1619]Shechter, H. *Rec. Chem. Prog.* ***1964***, *25*, 55–76.

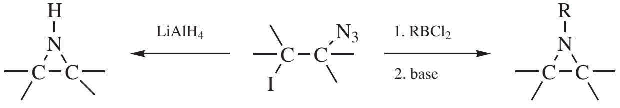
[1620]Schlubach, H.H.; Braun, A. *Liebigs Ann. Chem.* ***1959***, *627*, 28.

[1621]For a review, see Sharts, C.M.; Sheppard, W.A. *Org. React.* ***1974***, *21*, 125–406, see pp. 236–243.

[1622]Knunyants, I.L.; German, L.S.; Rozhkov, I.N. *Bull Acad. Sci. USSR Div. Chem. Sci.* ***1963***, 1794.

[1623]Olah, G.A.; Nojima, M. *Synthesis* ***1973***, 785.

The addition of iodine azide to double bonds gives β-iodo azides.[1624] The reagent can be prepared *in situ* from KI—NaN_3 in the presence of Oxone®-wet alumina.[1625] The addition is stereospecific and anti, suggesting that the mechanism involves a cyclic iodonium ion intermediate.[1626] The reaction has been performed on many double-bond compounds, including allenes[1627] and α,β-unsaturated ketones. Similar reactions can be performed with BrN_3[1628] and ClN_3. 1,4-Addition has been found with acyclic conjugated dienes.[1629] In the case of BrN_3, both electrophilic and free-radical mechanisms are important,[1630] while with ClN_3 the additions are chiefly free radical.[1631] The compound IN_3 also adds to triple bonds to give β-iodo-α,β-unsaturated azides.[1632]



167 **168**

β-Iodo azides can be reduced to aziridines (**167**) with $LiAlH_4$[1633] or converted to *N*-alkyl- or *N*-arylaziridines (**168**) by treatment with an alkyl- or aryldichloroborane followed by a base.[1634] In both cases, the azide is first reduced to the corresponding amine (primary or secondary, respectively) and ring closure (**10-31**) follows. With Chloramine T ($TsNCl^-$ Na^+) and 10% of pyridinium bromide perbromide, however, the reaction with alkenes give an *N*-tosyl aziridine directly.[1635]

OS **VI**, 893.

15-46 Addition of Alkyl Halides (Addition of Halogen, Carbon)

Alkyl-halo-addition[1062]

[1624]For reviews, see Dehnicke, K. *Angew. Chem. Int. Ed.* ***1979***, *18*, 507; Hassner, A. *Acc. Chem. Res.* ***1971***, *4*, 9; Biffin, M.E.C.; Miller, J.; Paul, D.B., in Patai, S. *The Chemistry of the Azido Group*, Wiley, NY, ***1971***, pp. 136–147. See Nair, V.; George, T.G.; Sheeba, V.; Augustine, A.; Balagopal, L.; Nair, L.G. *Synlett* ***2000***, 1597.

[1625]Curini, M.; Epifano, F.; Marcotullio, M.C.; Rosati, O. *Tetrahedron Lett.* ***2002***, *43*, 1201.

[1626]See, however, Cambie, R.C.; Hayward, R.C.; Rutledge, P.S.; Smith-Palmer, T.; Swedlund, B.E.; Woodgate, P.D. *J. Chem. Soc. Perkin Trans. 1*, ***1979***, 180.

[1627]Hassner, A.; Keogh, J. *J. Org. Chem.* ***1986***, *51*, 2767.

[1628]Azido-bromo-addition has also been done with another reagent: Olah, G.A.; Wang, Q.; Li, X.; Prakash, G.K.S. *Synlett* ***1990***, 487.

[1629]Hassner, A.; Keogh, J. *Tetrahedron Lett.* ***1975***, 1575.

[1630]Hassner, A.; Teeter, J.S. *J. Org. Chem.* ***1971***, *36*, 2176.

[1631]Even IN_3 can be induced to add by a free-radical mechanism [see, e.g., Cambie, R.C.; Jurlina, J.L.; Rutledge, P.S.; Swedlund, B.E.; Woodgate, P.D. *J. Chem. Soc. Perkin Trans. 1*, ***1982***, 327]. For a review of free-radical additions of XN_3, see Hassner, A. *Intra-Sci. Chem. Rep.* ***1970***, *4*, 109.

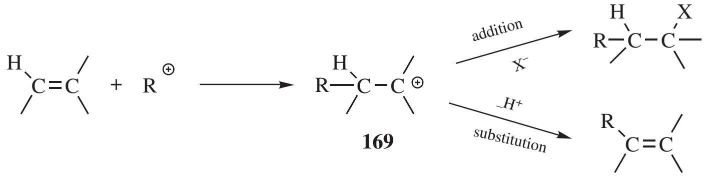
[1632]Hassner, A.; Isbister, R.J.; Friederang, A. *Tetrahedron Lett.* ***1969***, 2939.

[1633]Hassner, A.; Matthews, G.J.; Fowler, F.W. *J. Am. Chem. Soc.* ***1969***, *91*, 5046.

[1634]Levy, A.B.; Brown, H.C. *J. Am. Chem. Soc.* ***1973***, *95*, 4067.

[1635]Ali, S.I.; Nikalje, M.D.; Sudalai, A. *Org. Lett.* ***1999***, *1*, 705.

Alkyl halides can be added to alkenes in the presence of a Friedel–Crafts catalyst, most often $AlCl_3$.[1636] The yields are best for tertiary R. Secondary R can also be used, but primary R give rearrangement products (as with **11-11**). Methyl and ethyl halides, which cannot rearrange to a more stable secondary or tertiary carbocation, give no reaction at all. The attacking species is the carbocation formed from the alkyl halide and the catalyst (see **11-11**).[1637] The addition therefore follows Markovnikov's rule, with the cation going to the carbon with more hydrogens. Substitution is a side reaction, arising from loss of hydrogen from the carbocation formed when an additional molecule of alkene attacks the initially formed carbocation (**169**). Conjugated dienes can add 1,4.[1638] Triple bonds also undergo the reaction, to give vinylic halides.[1639]



169

Simple polyhalo alkanes, such as CCl_4, $BrCCl_3$, ICF_3 and related molecules, add to alkenes in good yield.[1640] These are free-radical additions and require initiation, for example,[1641] by peroxides, metal halides (e.g., $FeCl_2$, CuCl),[1642] ruthenium catalysts,[1643] or UV light. The initial attack is by the carbon, and it goes to the carbon with more hydrogens, as in most free-radical attack:

$$RHC{=}CH_2 + \bullet CX_3 \longrightarrow R\dot{H}C{-}CH_2CX_3 \xrightarrow{CX_4} RH\overset{X}{\overset{|}{C}}{-}CH_2CX_3 + \bullet CX_3$$

[1636]For a review, see Schmerling, L., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 2, Wiley, NY, ***1964***, pp. 1133–1174. See also, Mayr, H.; Schade, C.; Rubow, M.; Schneider, R. *Angew. Chem. Int. Ed.* ***1987***, *26*, 1029.

[1637]For a discussion of the mechanism, see Pock, R.; Mayr, H.; Rubow, M.; Wilhelm, E. *J. Am. Chem. Soc.* ***1986***, *108*, 7767.

[1638]Kolyaskina, Z.N.; Petrov, A.A. *J. Gen. Chem. USSR* ***1962***, *32*, 1067.

[1639]See, for example, Maroni, R.; Melloni, G.; Modena, G. *J. Chem. Soc. Perkin Trans. 1*, ***1973***, 2491; ***1974***, 353.

[1640]For reviews, see Freidlina, R.Kh.; Velichko, F.K. *Synthesis* ***1977***, 145; Freidlina, R.Kh.; Chukovskaya, E.C. *Synthesis* ***1974***, 477.

[1641]For other initiators, see Matsumoto, H.; Nakano, T.; Takasu, K.; Nagai, Y. *J. Org. Chem.* ***1978***, *43*, 1734; Tsuji, J.; Sato, K.; Nagashima, H. *Tetrahedron* ***1985***, *41*, 393; Bland, W.J.; Davis, R.; Durrant, J.L.A. *J. Organomet. Chem.* ***1985***, *280*, 397; Phelps, J.C.; Bergbreiter, D.E.; Lee, G.M.; Villani, R.; Weinreb, S.M. *Tetrahedron Lett.* ***1989***, *30*, 3915.

[1642]For example, see Asscher, M.; Vofsi, D. *J. Chem. Soc.* ***1963***, 1887, 3921; *J. Chem. Soc. B* ***1968***, 947; Murai, S.; Tsutsumi, S. *J. Org. Chem.* ***1966***, *31*, 3000; Martin, P.; Steiner, E.; Streith, J.; Winkler, T.; Bellus, D. *Tetrahedron* ***1985***, *41*, 4057. For the addition of CH_2Cl_2 and PhBr, see Mitani, M.; Nakayama, M.; Koyama, K. *Tetrahedron Lett.* ***1980***, *21*, 4457.

[1643]Simal, F.; Wlodarczak, L.; Demonceau, A.; Noels, A.F. *Eur. J. Org. Chem.* ***2001***, 2689.

This type of polyhalo alkane adds to halogenated alkenes in the presence of $AlCl_3$ by an electrophilic mechanism. This is called the *Prins reaction* (not to be confused with the other Prins reaction, **16-54**).[1644]

α-Iodolactones add to alkenes in the presence of BEt_3/O_2 to give the addition product.[1645] Other α-iodoesters add under similar conditions to give the lactone.[1646] Iodoesters also add to alkenes in the presence of BEt_3 to give iodo-esters that have not cyclized.[1647]

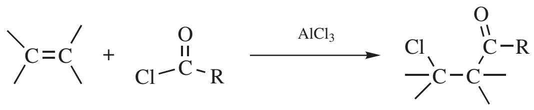
A variant of the free-radical addition method has been used for ring closure (see **15-30**).

For another method of adding R and I to a triple bond (see **15-23**).

OS **II**, 312; **IV**, 727; **V**, 1076; **VI**, 21; **VII**, 290.

15-47 Addition of Acyl Halides (Addition of Halogen, Carbon)

Acyl-halo-addition



Acyl halides have been added to many alkenes, in the presence of Friedel–Crafts catalysts, although polymerization is a problem. The reaction has been applied to straight-chain, branched, and cyclic alkenes, but to very few containing functional groups, other than halogen.[1648] The mechanism is similar to that of **15-46**, and, as in that case, substitution competes (**12-16**). Increasing temperature favors substitution,[1649] and good yields of addition products can be achieved if the temperature is kept under 0°C. The reaction usually fails with conjugated dienes, since polymerization predominates.[1650] Iodo acetates have been formed from alkenes using iodine, $Pb(OAc)_2$ in acetic acid.[1651] The reaction can be performed on triple-bond compounds, producing compounds of the form RCO−C=C−Cl.[1652] A *formyl* group and a halogen can be added to triple bonds by treatment with *N,N*-disubstituted formamides

[1644]For a review with respect to fluoroalkenes, see Paleta, O. *Fluorine Chem. Rev.* ***1977***, *8*, 39.

[1645]Nakamura, T.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Synlett* ***1998***, 1351.

[1646]Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* ***1998***, *63*, 8604.

[1647]Baciocchi, E.; Muraglia, E. *Tetrahedron Lett.* ***1994***, *35*, 2763.

[1648]For reviews, see Groves, J.K. *Chem. Soc. Rev.* ***1972***, *1*, 73; House, H.O. *Modern Synthetic Reaction*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 786–797; Nenitzescu, C.D.; Balaban, A.T., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 1033–1152.

[1649]Jones, N.; Taylor, H.T.; Rudd, E. *J. Chem. Soc.* ***1961***, 1342.

[1650]For examples of 1,4-addition at low temperatures, see Melikyan, G.G.; Babayan, E.V.; Atanesyan, K.A.; Badanyan, Sh.O. *J. Org. Chem. USSR* ***1984***, *20*, 1884.

[1651]Bedekar, A.V.; Nair, K.B.; Soman, R. *Synth. Commun.* ***1994***, *24*, 2299.

[1652]For example, see Nifant'ev, E.Ye.; Grachev, M.A.; Bakinovskii, L.V.; Kara-Murza, C.G.; Kochetkov, N.K. *J. Appl. Chem. USSR* ***1963***, *36*, 646; Savenkov, N.F.; Khokhlov, P.S.; Nazarova, T.A.; Mochalkin, A.I. *J. Org. Chem. USSR* ***1973***, *9*, 914; Martens, H.; Janssens, F.; Hoornaert, G. *Tetrahedron* ***1975***, *31*, 177; Brownstein, S.; Morrison, A.; Tan, L.K. *J. Org. Chem.* ***1985***, *50*, 2796.

and $POCl_3$ (Vilsmeier conditions, see **11-18**).[1653] Chloroformates add to allenes in the presence of a rhodium catalyst go give a β-chloro, β,γ-unsaturated ester.[1654]

OS **IV**, 186; **VI**, 883; **VIII**, 254.

B. Oxygen, Nitrogen, or Sulfur on One or Both Sides

15-48 Hydroxylation (Addition of Oxygen, Oxygen)

Dihydroxy-addition

There are many reagents that add two OH groups to a double bond.[1655] The most common are OsO_4[1656] and alkaline $KMnO_4$,[1657] which give syn addition from the less-hindered side of the double bond. Less substituted double bonds are oxidized more rapidly than more substituted alkenes.[1658] Permanganate adds to alkenes to form an intermediate manganate ester (**171**), which is decomposed under alkaline conditions. Bases catalyze the decomposition of **171** by coordinating with the ester. Osmium tetroxide adds rather slowly but almost quantitatively to form a cyclic ester, such as **170**, as an intermediate, which can be isolated,[1659] but is usually decomposed solution, with sodium sulfite in ethanol or other reagents. The chief drawback to the use of OsO_4 is expensive and highly toxic, but the reaction is made catalytic in OsO_4 by using *N*-methylmorpholine-*N*-oxide (NMO),[1660] *tert*-butyl hydroperoxide in alkaline solution,[1661] H_2O_2,[1662] peroxyacid,[1663] flavin and

[1653]Yen, V.Q. *Ann. Chim. (Paris)* ***1962***, *[13] 7*, 785.

[1654]Hua, R.; Tanaka, M. *Tetrahedron Lett.* ***2004***, *45*, 2367.

[1655]For reviews, see Hudlický, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, ***1990***, pp. 67–73; Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Academic Press, NY, ***1985***, pp. 73–98, 278–294; Sheldon, R.A.; Kochi, J.K. *Metal-Catalyzed Oxidations of Organic Compounds*, Academic Press, NY, ***1981***, pp. 162–171, 294–296. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 996–1003.

[1656]For a review, see Schröder, M. *Chem. Rev.* ***1980***, *80*, 187. OsO_4 was first used for this purpose by Criegee, R. *Liebigs Ann. Chem.* ***1936***, *522*, 75. Also see, Norrby, P.-O.; Gable, K.P. *J. Chem. Soc. Perkin Trans. 2*, ***1996***, 171; Lohray, B.B.; Bhushan, V. *Tetrahedron Lett.* ***1992***, *33*, 5113.

[1657]For a review, see Fatiadi, A.J. *Synthesis* ***1987***, 85, 86. See Nelson, D.J.; Henley, R.L. *Tetrahedron Lett.* ***1995***, *36*, 6375 for rate of oxidation of alkenes.

[1658]Crispino, G.A.; Jeong, K.-S.; Kolb, H.C.; Wang, Z.-M.; Xu, D.; Sharpless, K.B. *J. Org. Chem.* ***1993***, *58*, 3785.

[1659]For a molecular-orbital study of the formation of **170**, see Jørgensen, K.A.; Hoffmann, R. *J. Am. Chem. Soc.* ***1986***, *108*, 1867.

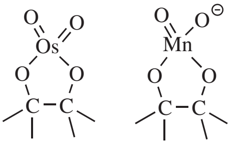
[1660]VanRheenen, V.; Kelly, R.C.; Cha, D.Y. *Tetrahedron Lett.* ***1976***, 1973; Iwasawa, N.; Kato, T.; Narasaka, K. *Chem. Lett.* ***1988***, 1721. See also, Ray, R.; Matteson, D.S. *Tetrahedron Lett.* ***1980***, 449.

[1661]Akashi, K.; Palermo, R.E.; Sharpless, K.B. *J. Org. Chem.* ***1978***, *43*, 2063.

[1662]For a review, see Rylander, P.N. *Organic Syntheses withy Noble Metal Catalysts*, Academic Press, NY, ***1973***, pp. 121–133. See Venturello, C.; Gambaro, M. *Synthesis* ***1989***, 295; Usui, Y.; Sato, K.; Tanaka, M. *Angew. Chem. Int. Ed.* ***2003***, *42*, 5623.

[1663]Bergstad, K.; Piet, J.J.N.; Bäckvall, J.-E. *J. Org. Chem.* ***1999***, *64*, 2545.

TEAA,[1664] $K_3Fe(CN)_6$[1665] and non-heme iron catalysts.[1666] Polymer-bound OsO_4,[1667] and encapsulated OsO_4 have been shown to give the diol in the presence of NMO,[1668] as well as OsO_4^{-2} on an ion exchange resin.[1669] Dihydroxylation has also been reported in ionic liquids,[1670] and with fluorous osmium tetroxide.[1671] A catalytic amount of K_2OsO_4 with a Cinchona alkaloid on a ordered inorganic support, in the presence of $K_3Fe(CN)_6$, gives the cis-diol.[1672] Oxidation of pent-4-en-1-ol to valerolactone was accomplished with Oxone® and a catalytic amount of OsO_4 in DMF.[1673]



170 **171**

The end-product of the reaction of either potassium permanganate or osmium tetroxide under the conditions described above is a 1,2-diol. Potassium permanganate is a strong oxidizing agent and can oxidize the glycol product[1674] (see **19-7** and **19-10**). In acid and neutral solution it always does so; hence glycols must be prepared with alkaline[1675] permanganate, but the conditions must be mild. Even so, yields are seldom >50%, although they can be improved with phase-transfer catalysis[1676] or increased stirring.[1677] The use of ultrasound with permanganate

[1664]Jonsson, S.Y.; Färnegårdh, K.; Bäckvall, J.-E. *J. Am. Chem. Soc.* ***2001***, *123*, 1365.

[1665]Minato, M.; Yamamoto, K.; Tsuji, J. *J. Org. Chem.* ***1990***, *55*, 766; Torii, S.; Liu, P.; Tanaka, H. *Chem. Lett.* ***1995***, 319; Soderquist, J.A.; Rane, A.M.; López, C.J. *Tetrahedron Lett.* ***1993***, *34*, 1893. See Corey, E.J.; Noe, M.C.; Grogan, M.J. *Tetrahedron Lett.* ***1994***, *35*, 6427; Imada, Y.; Saito, T.; Kawakami, T.; Murahashi, S.-I. *Tetrahedron Lett.* ***1992***, *33*, 5081 for oxidation using an asymmetric ligand.

[1666]Chen, K.; Costas, M.; Kim, J.; Tipton, A.K.; Que, Jr., L. *J. Am. Chem. Soc.* ***2002***, *124*, 3026.

[1667]Cainelli, G.; Contento, M.; Manescalchi, F.; Plessi, L. *Synthesis* ***1989***, 45; Ley, S.V.; Ramarao, C.; Lee, A.-L.; Østergaard, N.; Smith, S.C.; Shirley, I.M. *Org. Lett.* ***2003***, *5*, 185.

[1668]Nagayama, S.; Endo, M.; Kobayashi, S. *J. Org. Chem.* ***1998***, *63*, 6094.

[1669]Choudary, B.M.; Chowdari, N.S.; Jyothi, K.; Kantam, M.L. *J. Am. Chem. Soc.* ***2002***, *124*, 5341.

[1670]In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Yao, Q. *Org. Lett.* ***2002***, *4*, 2197; Closson, A.; Johansson, M.; Bäckvall, J.-E. *Chem. Commun.* ***2004***, 1494. In emim BF_4, 1-ethyl-3-methylimidazolium tetrafluoroborate: Yanada, R.; Takemoto, Y. *Tetrahedron Lett.* ***2002***, *43*, 6849.

[1671]Huang, Y.; Meng, W.-D.; Qing, F.L. *Tetrahedron Lett.* ***2004***, *45*, 1965.

[1672]Motorina, I.; Crudden, C.M. *Org. Lett.* ***2001***, *3*, 2325.

[1673]Schomaker, J.M.; Travis, B.R.; Borhan, B. *Org. Lett.* ***2003***, *5*, 3089.

[1674]Or give more highly oxidized products, such as α-hydroxy ketones without going through the glycols. See, for example, Wolfe, S.; Ingold, C.F.; Lemieux, R.U. *J. Am. Chem. Soc.* ***1981***, *103*, 938; Wolfe, S.; Ingold, C.F. *J. Am. Chem. Soc.* ***1981***, *103*, 940. Also see, Lohray, B.B.; Bhushan, V.; Kumar, R.K. *J. Org. Chem.* ***1994***, *59*, 1375.

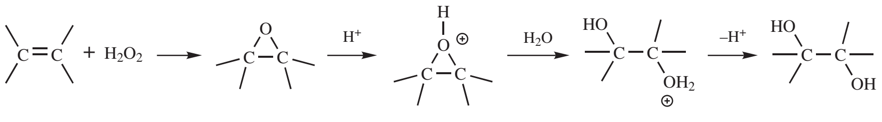
[1675]The role of the base seems merely to be to inhibit acid-promoted oxidations. The base does not appear to play any part in the mechanism: Taylor, J.E.; Green, R. *Can. J. Chem.* ***1985***, *63*, 2777.

[1676]See, for example, Weber, W.P.; Shepherd, J.P. *Tetrahedron Lett.* ***1972***, 4907; Ogino, T.; Mochizuki, K. *Chem. Lett.* ***1979***, 443.

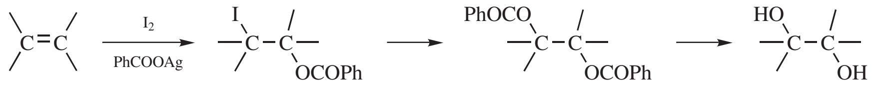
[1677]Taylor, J.E.; Williams, D.; Edwards, K.; Otonnaa, D.; Samanich, D. *Can. J. Chem.* ***1984***, *62*, 11; Taylor, J.E. *Can. J. Chem.* ***1984***, *62*, 2641.

dihydroxylation has resulted in good yields of the diol.[1678] There is evidence that cyclic esters (**171**) are intermediates for OsO_4 dihydroxylation.[1679] This reaction is the basis of the *Baeyer test* for the presence of double bonds. The oxidation is compatible with a number of functional groups, including trichloroacetamides.[1680]

Anti hydroxylation can be achieved by treatment with H_2O_2 and formic acid. In this case, epoxidation (**15-50**) occurs first, followed by an S_N2 reaction, which results in overall anti addition:



The same result can be achieved in one step with *m*-chloroperoxybenzoic acid and water.[1681] Overall anti addition can also be achieved by the method of Prévost (the *Prévost reaction*). In this method, the alkene is treated with iodine and silver benzoate in a 1:2 molar ratio. The initial addition is anti and results in a β-halo benzoate (**172**). These can be isolated, and this represents a method of addition of IOCOPh. However, under the normal reaction conditions, the iodine is replaced by a second PhCOO group. This is a nucleophilic substitution reaction, and it operates by the neighboring-group mechanism (p. 446), so the groups are still anti:



172

Hydrolysis of the ester does not change the configuration. The *Woodward modification* of the Prévost reaction is similar, but results in overall syn hydroxylation.[1682] The alkene is treated with iodine and silver acetate in a 1:1 molar ratio in acetic acid containing water. Here again, the initial product is a β-halo ester; the addition is anti and a nucleophilic replacement of the iodine occurs. However, in the presence of water, neighboring-group participation is prevented or greatly decreased by solvation of the ester function, and the mechanism is the normal S_N2 process,[1683]

[1678]Varma, R.S.; Naicker, K.P. *Tetrahedron Lett.* ***1998***, *39*, 7463.

[1679]For some recent evidence, see Lee, D.G.; Chen, T. *J. Am. Chem. Soc.* ***1989***, *111*, 7534; Ogino, T.; Hasegawa, K.; Hoshino, E. *J. Org. Chem.* ***1990***, *55*, 2653. See, however, Freeman, F.; Chang, L.Y.; Kappos, J.C.; Sumarta, L. *J. Org. Chem.* ***1987***, *52*, 1461; Freeman, F.; Kappos, J.C. *J. Org. Chem.* ***1989***, *54*, 2730, and other papers in this series; Perez-Benito, J.F.; Lee, D.G. *Can. J. Chem.* ***1985***, *63*, 3545.

[1680]Donohoe, T.J.; Blades, K.; Moore, P.R.; Waring, M.J.; Winter, J.J.G.; Helliwell, M.; Newcombe, N.J.; Stemp, G. *J. Org. Chem.* ***2002***, *67*, 7946.

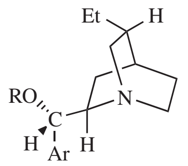
[1681]Fringuelli, F.; Germani, R.; Pizzo, F.; Savelli, G. *Synth. Commun.* ***1989***, *19*, 1939.

[1682]See Brimble, M.A.; Nairn, M.R. *J. Org. Chem.* ***1996***, *61*, 4801.

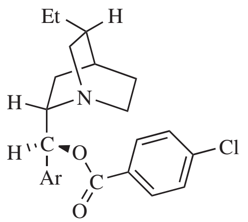
[1683]For another possible mechanism that accounts for the stereochemical result of the Woodward method, see Woodward, R.B.; Brutcher, Jr., F.V. *J. Am. Chem. Soc.* ***1958***, *80*, 209.

so the monoacetate is syn and hydrolysis gives the glycol that is the product of overall syn addition. Although the Woodward method results in overall syn addition, the product may be different from that with OsO_4 or $KMnO_4$, since the overall syn process is from the more-hindered side of the alkene.[1684] Both the Prévost and the Woodward methods[1685] have also been carried out in high yields with thallium(I) acetate and thallium(I) benzoate instead of the silver carboxylates.[1686] Note that cyclic sulfates can be prepared from alkenes by reaction with PhIO and SO_3•DMF.[1687]

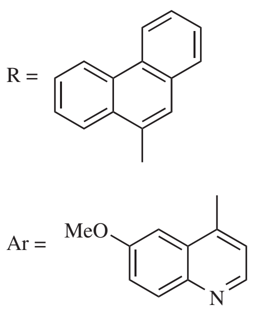
With suitable substrates, addition of two OH groups creates one new stereogenic center from a terminal alkene and two new stereogenic centers from internal alkenes. Addition to alkenes of the form $RCH{=}CH_2$ has been made enantioselective, and addition to $RCH{=}CHR'$ both diastereoselective[1688] and enantioselective,[1689] by using chiral additives or chiral catalysts,[1690] such as **173**, **174** (derivatives of the



173
9′-Phenanthryl ether of dihydroquinidine



174
Dihydroquinine *p*-chlorobenzoate



[1684]For another method of syn hydroxylation, which can be applied to either face, see Corey, E.J.; Das, J. *Tetrahedron Lett.* ***1982***, *23*, 4217.

[1685]For some related methods, see Jasserand, D.; Girard, J.P.; Rossi, J.C.; Granger, R. *Tetrahedron Lett.* ***1976***, 1581; Ogata, Y.; Aoki, K. *J. Org. Chem.* ***1966***, *31*, 1625; Mangoni, L.; Adinolfi, M.; Barone, G.; Parrilli, M. *Tetrahedron Lett.* ***1973***, 4485; *Gazz. Chim. Ital.* ***1975***, *105*, 377; Horiuchi, C.A.; Satoh, J.Y. *Chem. Lett.* ***1988***, 1209; Campi, E.M.; Deacon, G.B.; Edwards, G.L.; Fitzroy, M.D.; Giunta, N.; Jackson, W.R.; Trainor, R. *J. Chem. Soc., Chem. Commun.* ***1989***, 407.

[1686]Cambie, R.C.; Hayward, R.C.; Roberts, J.L.; Rutledge, P.S. *J. Chem. Soc. Perkin Trans. 1*, ***1974***, 1858, 1864; Cambie, R.C.; Rutledge, P.S. *Org. Synth.* ***VI***, 348.

[1687]Robinson, R.I.; Woodward, S. *Tetrahedron Lett.* ***2003***, *44*, 1655.

[1688]For diastereoselective, but not enantioselective, addition of OsO_4, see Cha, J.K.; Christ, W.J.; Kishi, Y. *Tetrahedron* ***1984***, *40*, 2247; Stork, G.; Kahn, M. *Tetrahedron Lett.* ***1983***, *24*, 3951; Vedejs, E.; McClure, C.K. *J. Am. Chem. Soc.* ***1986***, *108*, 1094; Evans, D.A.; Kaldor, S.W. *J. Org. Chem.* ***1990***, *55*, 1698.

[1689]Lohray, B.B. *Tetrahedron Asymmetry* ***1992***, *3*, 1317.

[1690]For a review of enantioselective oxidation methodologies, see Bonini, C.; Righi, G. *Tetrahedron* ***2002***, *58*, 4981. For a study using triazines as a new class of ligand, see McNamara, C.A.; King, F.; Bradley, M. *Tetrahedron Lett.* ***2004***, *45*, 8527. See also, Kuang, Y.-Q.; Zhang, S.-Y.; Jiang, R.; Wei, L.-L. *Tetrahedron Lett.* ***2002***, *43*, 3669; Jiang, R.; Kuang, Y.; Sun, X.; Zhang, S. *Tetrahedron Asymmetry* ***2004***, *15*, 743.

naturally occurring quinine and quinuclidine),[1691] along with OsO_4, in what is called *Sharpless asymmetric dihydroxylation*.[1692] Other chiral ligands[1693] have also been used, as well as polymer[1694] and silica-bound[1695] *Cinchona* alkaloids. These amines bind to the OsO_4 *in situ* as chiral ligands, causing it to add asymmetrically.[1696] This has been done both with the stoichiometric and with the catalytic method.[1697] The catalytic method has been extended to conjugated dienes, which give tetrahydroxy products diastereoselectively,[1698] and to conjugated ketones.[1699] Asymmetric dihydroxylation has also been reported with chiral alkenes.[1700] Ligands **173** and **174** not only cause enantioselective addition, but also accelerate the reaction, so that they may be useful even where enantioselective addition is not required.[1701] Although **173** and **174** are not enantiomers, they give enantioselective addition to a given alkene in the opposite sense; for example, styrene predominantly gave the (*R*)-diol with **173**, and the

[1691]Wai, J.S.M.; Marko, I.; Svendsen, J.S.; Finn, M.G.; Jacobsen, E.N.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1989***, *111*, 1123; Kwong, H.; Sorato, C.; Ogina, Y.; Chen, H.; Sharpless, K.B. *Tetrahedron Lett.* ***1990***, *31*, 2999; Shibata, T.; Gilheany, D.C.; Blackburn, B.K.; Sharpless, K.B. *Tetrahedron Lett.* ***1990***, *31*, 3817; Sharpless, K.B.; Amberg, W.; Beller, M.; Chens, H.; Hartung, J.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* ***1991***, *56*, 4585.

[1692]Kolb, H.C.; Van Nieuwenhze, M.S.; Sharpless, K.B. *Chem. Rev.* ***1994***, *94*, 2483. Also see, Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY, ***2001***, pp. 248–254.

[1693]Wang, L.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1992***, *114*, 7568; Xu, D.; Crispino, G.A.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1992***, *114*, 7570; Corey, E.J.; Jardine, P.D.; Virgil, S.; Yuen, P.; Connell, R.D. *J. Am. Chem. Soc.* ***1989***, *111*, 9243; Corey, E.J.; Lotto, G.I. *Tetrahedron Lett.* ***1990***, *31*, 2665; Tomioka, K.; Nakajima, M.; Koga, K. *J. Am. Chem. Soc.* ***1987***, *109*, 6213; *Tetrahedron Lett.* ***1990***, *31*, 1741; Rosini, C.; Tanturli, R.; Pertici, P.; Salvadori, P. *Tetrahedron Asymmetry* ***1996***, *7*, 2971; Sharpless, K.B.; Amberg, W.; Bennani, Y.L.; Crispino, G.A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* ***1992***, *57*, 2768.

[1694]Bolm, C.; Gerlach, A. *Eur. J. Org. Chem.* ***1998***, 21; Lohray, B.B.; Nandanan, E.; Bhushan, V. *Tetrahedron Asymmetry* ***1996***, *7*, 2805; Lohray, B.B.; Thomas, A.; Chittari, P.; Ahuja, J.; Dhal, P.K. *Tetrahedron Lett.* ***1992***, *33*, 5453. For a review, see Karjalainen, J.K.; Hormi, O.E.O.; Sherrington, D.C. *Tetrahedron Asymmetry* ***1998***, *9*, 1563.

[1695]Song, C.E.; Yang, J.W.; Ha, H.-J. *Tetrahedron Asymmetry* ***1997***, *8*, 841.

[1696]For discussions of the mechanism of the enantioselectivity, see Corey, E.J.; Noe, M.C. *J. Am. Chem. Soc.* ***1996***, *118*, 319; Norrby, P.-O.; Kolb, H.C.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1994***, *116*, 8470; Veldkamp, A.; Frenking, G. *J. Am. Chem. Soc.* ***1994***, *116*, 4937; Wu, Y.-D.; Wang, Y.; Houk, K.N. *J. Org. Chem.* ***1992***, *57*, 1362; Jørgensen, K.A. *Tetrahedron Lett.* ***1990***, *31*, 6417. See Nelson, D.W.; Gypser, A.; Ho, P.T.; Kolb, H.C.; Kondo, T.; Kwong, H.-L.; McGrath, D.V.; Rubin, A.E.; Norrby, P.-O.; Gable, K.P.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1997***, *119*, 1840 for a discussion of electronic effects and Kolb, H.C.; Andersson, P.G.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1994***, *116*, 1278 for a kinetic study.

[1697]For other examples of asymmetric dihydroxylation, see Yamada, T.; Narasaka, K. *Chem. Lett.* ***1986***, 131; Tokles, M.; Snyder, J.K. *Tetrahedron Lett.* ***1986***, *27*, 3951; Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L.; Stefanelli, S. *Tetrahedron Lett.* ***1987***, *28*, 3139; Hirama, M.; Oishi, T.; Itô, S. *J. Chem. Soc., Chem. Commun.* ***1989***, 665.

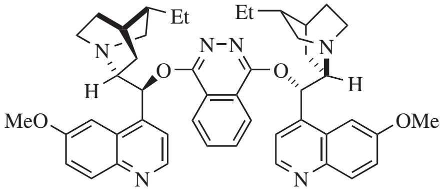
[1698]Park, C.Y.; Kim, B.M.; Sharpless, K.B. *Tetrahedron Lett.* ***1991***, *32*, 1003.

[1699]Walsh, P.J.; Sharpless, K.B. *Synlett* ***1993***, 605.

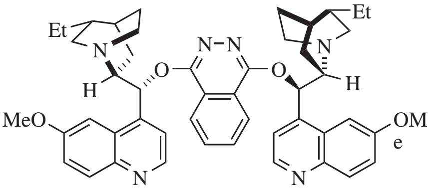
[1700]Oishi, T.; Iida, K.; Hirama, M. *Tetrahedron Lett.* ***1993***, *34*, 3573.

[1701]See Jacobsen, E.N.; Marko, I.; France, M.B.; Svendsen, J.S.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1989***, *111*, 737.

(*S*)-diol with **174**.[1702] Note that ionic liquids have been used in asymmetric dihydroxylation.[1703]



175



176

Two phthalazine derivatives,[1704] $(DHQD)_2$PHAL (**175**) and $(DHQ)_2$PHAL (**176**) used in conjunction with an osmium reagent improve the efficiency and ease of use, and are commercial available as AD-mix-β™ (using **175**) and AD-mix-α™ (using **176**). Catalyst **175** is prepared from dihydroquinidine (DHQD) and 1,4-dichlorophthalazine (PHAL), and **176** is prepared from dihydroquinine (DHQ) and PHAL. The actual oxidation labeled AD-mix α- or β-uses **176** or **175**, respectively, mixed with potassium osmate $[K_2OsO_2(OH)_4]$, powdered $K_3Fe(CN)_6$, and powdered K_2CO_3 in an aqueous solvent mixture.[1705] These additives have been used in conjunction with microencapsulated OsO_4,[1705] and polymer bound **175** has been used.[1706] A catalytic amount of flavin has been used.[1707] Both **175**[1708] and **176**[1709] have been used to generate diols with high enantioselectivity. Oxidation of a terminal alkene with AD-mix and then oxidation with TEMPO/NaOCl/$NaOCl_2$ leads to α-hydroxyl carboxylic acids with high enantioselectivity.[1710]

Enantioselective and diastereoselective addition have also been achieved by using preformed derivatives of OsO_4, already containing chiral ligands,[1711] and by the use of OsO_4 on alkenes that have a chiral group elsewhere in the molecule.[1712]

[1702]Jacobsen, E.N.; Marko, I.; Mungall, W.S.; Schröder, G.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1988***, *110*, 1968.

[1703]See Branco, L.C.; Afonso, C.A.M. *J. Org. Chem.* ***2004***, *69*, 4381; Branco, L.C.; Afonso, C.A.M. *Chem. Commun.* ***2002***, 3036.

[1704]Sharpless, K.B.; Amberg, W.; Bennani, Y.L.; Crispino, G.A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* ***1992***, *57*, 2768.

[1705]Kobayashi, S.; Ishida, T.; Akiyama, R. *Org. Lett.* ***2001***, *3*, 2649.

[1706]Kuang, Y.-Q.; Zhang, S.-Y.; Wei, L.-L. *Tetrahedron Lett.* ***2001***, *42*, 5925.

[1707]Jonsson, S.Y.; Adolfsson, H.; Bäckvall, J.-E. *Org. Lett.* ***2001***, *3*, 3463.

[1708]Krief, A.; Colaux-Castillo, C. *Tetrahedron Lett.* ***1999***, *40*, 4189.

[1709]Junttila, M.H.; Hormi, O.E.O. *J. Org. Chem.* ***2004***, *69*, 4816.

[1710]Aladro, F.J.; Guerra, I.M.; Moreno-Dorado, F.J.; Bustamante, J.M.; Jorge, Z.D.; Massanet, G.M. *Tetrahedron Lett.* ***2000***, *41*, 3209.

[1711]Kokubo, T.; Sugimoto, T.; Uchida, T.; Tanimoto, S.; Okano, M. *J. Chem. Soc., Chem. Commun.* ***1983***, 769.

[1712]Hauser, F.M.; Ellenberger, S.R.; Clardy, J.C.; Bass, L.S. *J. Am. Chem. Soc.* ***1984***, *106*, 2458; Johnson, C.R.; Barbachyn, M.R. *J. Am. Chem. Soc.* ***1984***, *106*, 2459.

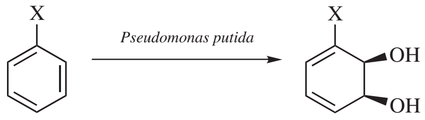
Alkenes can also be oxidized with metallic acetates such as lead tetraacetate[1713] or thallium(III) acetate[1714] to give bis(acetates) of glycols.[1715] Oxidizing agents, such as benzoquinone, MnO_2, or O_2, along with palladium acetate, have been used to convert conjugated dienes to 1,4-diacetoxy-2-alkenes (1,4-addition).[1716] Sodium periodate and sulfuric acid in aqueous media converts conjugated esters to dihydroxy esters.[1717] Diols are also produced by the reaction of a terminal alkyne with Bu_3SnH, followed by ozonolysis, followed by reduction with $BH_3•SMe_2$.[1718] 1,2-Diols are also generated from terminal alkynes by two sequential reactions with a platinum catalyst, and then a palladium catalyst, both with $HSiCl_3$, and a final oxidation with H_2O_2—KF.[1719]

1,2-Dithiols can be prepared from alkenes.[1720]

OS **II**, 307; **III**, 217; **IV**, 317; **V**, 647; **VI**, 196, 342, 348; **IX**, 251, 383.

15-49 Dihydroxylation of Aromatic Rings

Dihydroxy-addition



One π-bond of an aromatic ring can be converted to a cyclohexadiene 1,2-diol by reaction with enzymes associated with *Pseudomonas putida*.[1721] A variety of substituted aromatic compounds can be oxidized, including bromobenzene, chlorobenzene,[1722] and toluene.[1723] In these latter cases, introduction of the hydroxyl

[1713]For a review, see Moriarty, R.M. *Sel Org. Transform.* ***1972***, *2*, 183–237.

[1714]See, for example, Uemura, S.; Miyoshi, H.; Tabata, A.; Okano, M. *Tetrahedron* ***1981***, *37*, 291. For a review of the reactions of thallium (III) compounds with alkenes, see Uemura, S., in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 473–538, 497–513. For a review of thallium (III) acetate and trifluoroacetate, see Uemura, S., in Pizey, J.S. *Synthetic Reagents*, Vol. 5, Wiley, NY, ***1983***, pp. 165–187.

[1715]For another method, see Fristad, W.E.; Peterson, J.R. *Tetrahedron* ***1984***, *40*, 1469.

[1716]See Bäckvall, J.E.; Awasthi, A.K.; Renko, Z.D. *J. Am. Chem. Soc.* ***1987***, *109*, 4750, and references cited therein. For articles on this and related reactions, see Bäckvall, J.E. *Bull. Soc. Chim. Fr.* ***1987***, 665; *New. J. Chem.* ***1990***, *14*, 447. For another method, see Uemura, S.; Fukuzawa, S.; Patil, S.R.; Okano, M. *J. Chem. Soc. Perkin Trans. 1*, ***1985***, 499.

[1717]Plietker, B.; Niggemann, M. *Org. Lett.* ***2003***, *5*, 3353.

[1718]Gómez, A.M.; Company, M.D.; Valverde, S.; López, J.C. *Org. Lett.* ***2002***, *4*, 383.

[1719]Shimada, T.; Mukaide, K.; Shinohara, A.; Han, J.W.; Hayashi, T. *J. Am. Chem. Soc.* ***2004***, *124*, 1584.

[1720]Elgemeie, G.H.; Sayed, S.H. *Synthesis* ***2001***, 1747.

[1721]Gibson, D.T.; Koch, J.R.; Kallio, R.E. *Biochemistry* ***1968***, *7*, 2653; Brown, S.M., in Hudlicky, T. *Organic Synthesis: Theory and Practice*, JAI Press, Greenwich, CT., ***1993***, Vol. 2, p. 113; Carless, H.A.J. *Tetrahedron Asymmetry* ***1992***, *3*, 795; Widdowson, D.A.; Ribbons, D.A.; Thomas, S.D. *Janssenchimica Acta* ***1990***, *8*, 3.

[1722]Gibson, D.T.; Koch, J.R.; Schuld, C.L.; Kallio, R.E. *Biochemistry* ***1968***, *7*, 3795; Hudlicky, T.; Price, J.D. *Synlett.* ***1990***, 159.

[1723]Gibson, D.T.; Hensley, M.; Yoshioka, H.; Mabry, T.J. *Biochemsitry* ***1970***, *9*, 1626.

groups generates a chiral molecule that can be used as a template for asymmetric syntheses.[1724]

OS **X**, 217.

15-50 Epoxidation (Addition of Oxygen, Oxygen)

***epi*-Oxy-addition**

Alkenes can be epoxidized with many peroxyacids,[1725] of which *m*-chloroperoxybenzoic has been the most often used. The reaction, called the *Prilezhaev reaction*, has wide utility.[1726] Alkyl, aryl, hydroxyl, ester, and other groups may be present, although not amino groups, since these are affected by the reagent. Electron-donating groups increase the rate, and the reaction is particularly rapid with tetraalkyl alkenes. Conditions are mild and yields are high. Other peroxyacids, especially peroxyacetic and peroxybenzoic, are also used; trifluoroperoxyacetic acid[1727] and 3,5-dinitroperoxybenzoic acid[1728] are particularly reactive ones. Transition metal catalysts can facilitate epoxidation of alkenes at low temperatures or with alkenes that may otherwise react sluggishly.[1729] Magnesium monoperoxyphthalate (MMPP)[1730] is commercially available, and has been

[1724]Hudlicky, T.; Gonzalez, D.; Gibson, D.T. *Aldrichimica Acta* ***1999***, *32*, 35; Hudlicky, T.; Luna, H.; Barbieri, G.; Kwart, L.D. *J. Am. Chem. Soc.* ***1988***, *110*, 4735; Hudlicky, T.; Seoane, G.; Pettus, T. *J. Org. Chem.* ***1989***, *54*, 4239; Ley, S.V.; Redgrave, A.J. *Synlett* ***1990***, 393; Ley, S.V.; Sternfeld, F.; Taylor, S. *Tetrahedron Lett.* ***1987***, *28*, 225; Hudlicky, T.; Olivo, H.F. *Tetrahedron Lett.* ***1991***, *32*, 6077; Hudlicky, T.; Luna, H.; Price, J.D.; Rulin, F. *J. Org. Chem.* ***1990***, *55*, 4683; Hudlicky, T.; Olivo, H.F. *J. Am. Chem. Soc.* ***1992***, *114*, 9694. Also see, Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY, ***2001***, pp. 256–258.

[1725]For a list of reagents, including peracids and others, used for epoxidation, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 915–927.

[1726]For reviews, see Hudlický, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, pp. 60–64; Haines, A.H. *Methods for the Oxidation of Organic Compunds*, Academic Press, NY, ***1985***, pp. 98–117, 295–303; Dryuk, V.G. *Russ. Chem. Rev.* ***1985***, *54*, 986; Plesničar, B., in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. C, Academic Press, NY, ***1978***, pp. 211–252; Swern, D., in Swern, D. *Organic Peroxides*, Vol. 2, Wiley, NY, ***1971***, pp. 355–533; Metelitsa, D.I. *Russ. Chem. Rev.* ***1972***, *41*, 807; Hiatt, R., in Augustine, R.L.; Trecker, D.J. *Oxidation*, Vol. 2, Marcel Dekker, NY, ***1971***; pp. 113–140; House, H.O. *Modern Synthetic Reaction*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 292–321. For a review pertaining to the stereochemistry of the reaction, see Berti, G. *Top Stereochem.* ***1973***, *7*, 93, p. 95.

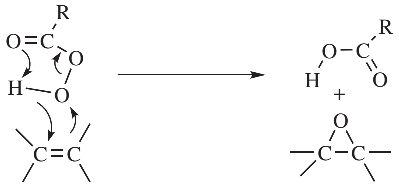
[1727]Emmons, W.D.; Pagano, A.S. *J. Am. Chem. Soc.* ***1955***, *77*, 89.

[1728]Rastetter, W.H.; Richard, T.J.; Lewis, M.D. *J. Org. Chem.* ***1978***, *43*, 3163.

[1729]Cu catalysts: Andrus, M.B.; Poehlein, B.W. *Tetrahedron Lett.* ***2000***, *41*, 1013. Fe catalysts: Dubois, G.; Murphy, A.; Stack, T.D.P. *Org. Lett.* ***2003***, *5*, 2469. Mn catalysts: Murphy, A.; Pace, A.; Stack, T.D.P. *Org. Lett.* ***2004***, *6*, 3119; Murphy, A.; Dubois, G.; Stack, T.D.P. *J. Am. Chem. Soc.* ***2003***, *125*, 5250.

[1730]Brougham, P.; Cooper, M.S.; Cummerson, D.A.; Heaney, H.; Thompson, N. *Synthesis* ***1987***, 1015; Querci, C.; Ricci, M. *J. Chem. Soc., Chem. Commun.* ***1989***, 889. For a reaction using moist MMPP, see Foti, C.J.; Fields, J.D.; Kropp, P.J. *Org. Lett.* ***1999***, *1*, 903.

shown to be a good substitute for *m*-chloroperoxybenzoic acid in a number of reactions.[1731]



177

The one-step mechanism involving a transition state, such as **177**,[1731] was proposed by Bartlett:[1732] Evidence for this concerted mechanism is as follows:[1733] (*1*) The reaction is second order. If ionization were the rate-determining step, it would be first order in peroxyacid. (*2*) The reaction readily takes place in nonpolar solvents, where formation of ions is inhibited.[1734] (*3*) Measurements of the effect on the reaction rate of changes in the substrate structure show that there is no carbocation character in the transition state.[1735] (*4*) The addition is stereospecific (i.e., a trans-alkene gives a trans-epoxide and a cis-alkene a cis-epoxide) even in cases where electron-donating substituents would stabilize a hypothetical carbocation intermediate.[1736] However, where there is an OH group in the allylic or homoallylic position, the stereospecificity diminishes or disappears, with both cis and trans isomers giving predominantly or exclusively the product where the incoming oxygen is syn to the OH group. This probably indicates a transition state in which there is hydrogen bonding between the OH group and the peroxy acid.[1737]

[1731]For discussions of the mechanism, see Dryuk, V.G. *Tetrahedron* ***1976***, *32*, 2855; Finn, M.G.; Sharpless, K.B., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 5, Wiley, NY, ***1985***, pp. 247–308; Bach, R.D.; Canepa, C.; Winter, J.E.; Blanchette, P.E. *J. Org. Chem.* ***1997***, *62*, 5191. For a review of polar mechanisms involving peroxides, see Plesnicar, B., in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, ***1983***, pp. 521–584. See Freccero, M.; Gandolfi, R.; Sarzi-Amadè, M.; Rastelli, A. *J. Org. Chem.* ***2002***, *67*, 8519. For a discussion of arene–arene interactions as related to selectivity, see Kishikawa, K.; Naruse, M.; Kohmoto, S.; Yamamoto, M.; Yamaguchi, K. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 462.

[1732]Bartlett, P.D. *Rec. Chem. Prog.* ***1957***, *18*, 111. For other proposed mechanisms, see Kwart, H.; Hoffman, D.M. *J. Org. Chem.* ***1966***, *31*, 419; Hanzlik, R.P.; Shearer, G.O. *J. Am. Chem. Soc.* ***1975***, *97*, 5231.

[1733]Ogata, Y.; Tabushi, I. *J. Am. Chem. Soc.* ***1961***, *83*, 3440; Freccero, M.; Gandolfi, R.; Sarzi-Amadè, M.; Rastelli, A. *J. Org. Chem.* ***2004***, *69*, 7479. See also, Woods, K.W.; Beak, P. *J. Am. Chem. Soc.* ***1991***, *113*, 6281. Also see, Vedejs, E.; Dent III, W.H.; Kendall, J.T.; Oliver, P.A. *J. Am. Chem. Soc.* ***1996***, *118*, 3556.

[1734]See Gisdakis, P.; Rösch, N. *Eur. J. Org. Chem.* ***2001***, 719.

[1735]Khalil, M.M.; Pritzkow, W. *J. Prakt. Chem.* ***1973***, *315*, 58; Schneider, H.; Becker, N.; Philippi, K. *Chem. Ber.* ***1981***, *114*, 1562; Batog, A.E.; Savenko, T.V.; Batrak, T.A.; Kucher, R.V. *J. Org. Chem. USSR* ***1981***, *17*, 1860.

[1736]For a computational study of facial selectivity, see Freccero, M.; Gandolfi, R.; Sarzi-Amadè, M.; Rastelli, A. *J. Org. Chem.* ***2000***, *65*, 8948.

[1737]See Berti, G. *Top. Stereochem.* ***1973***, *7*, 93, 130–162; Houk, K.N.; Liu, J.; DeMello, N.C.; Condroski, K.R. *J. Am. Chem. Soc.* ***1997***, *119*, 10147.

In general, peroxides (HOOH and ROOH) are poor regents for epoxidation of simple alkenes since OH and OR are poor leaving groups in the concerted mechanism shown above.[1738] Aqueous hydrogen peroxide epoxidizes alkenes in the presence of fluorous compounds, such as CF_3CH_2OH[1739] or hexafluoroacetone.[1740] Transition-metal catalysts[1741] have been used with alkyl hydroperoxides.[1742] In the presence of other reagents,[1743] peroxides give good yields of the epoxide. These coreagents include dicyclohexylcarbodiimide,[1744] magnesium aluminates,[1745] metalloporphyrins,[1746] hydrotalcite[1747] with microwave irradiation,[1748] fluorous aryl selenides,[1749] and arsines in fluorous solvents.[1750] The catalyst $MeReO_3$[1751] has been used for epoxidation with sodium percarbonate and pyrazole,[1752] with hydrogen peroxide,[1753] and with urea—H_2O_2.[1754] Epoxidation occurs with $FeSO_4$/silica,[1755] and with N_2O and a zinc catalyst.[1756] Epoxidation occurs when alkenes

[1738]See Deubel, D.V.; Frenking, G.; Gisdakis, P.; Herrmann, W.A.; Rösch, N.; Sundermeyer, J. *Acc. Chem. Res.* ***2004***, *37*, 645.

[1739]Neimann, K.; Neumann, R. *Org. Lett.* ***2000***, *2*, 2861; van Vliet, M.C.A.; Arends, I.W.C.E.; Sheldon, R.A. *Synlett* ***2001***, 248.

[1740]Shu, L.; Shi, Y. *J. Org. Chem.* ***2000***, *65*, 8807.

[1741]**V**: Sharpless, K.B.; Verhoeven, T.R. *Aldrichimica Acta* ***1979***, *12*, 63; Hoshino, Y.; Yamamoto, H. *J. Am. Chem. Soc.* ***2000***, *122*, 10452; Lattanzi, A.; Leadbeater, N.E. *Org. Lett.* ***2002***, *4*, 1519; Torres, G.; Torres, W.; Prieto, J.A. *Tetrahedron* ***2004***, *60*, 10245. **Mn**: Lane, B.S.; Vogt, M.; De Rose, V.T.; Burgess, K. *J. Am. Chem. Soc.* ***2002***, *124*, 11946. **Ti**: Della Sala, G.D.; Giordano, L.; Lattanzi, A.; Proto, A.; Screttri, A. *Tetrahedron* ***2000***, *56*, 3567; Lattanzi, A.; Iannece, P.; Screttri, A. *Tetrahedron Lett.* ***2002***, *43*, 5629. **Pd**: Yu, J.-Q.; Corey, E.J. *Org. Lett.* ***2002***, *4*, 2727. **Ru**: Adam, W.; Alsters, P.L.; Neumann, R.; Saha-Möller, C.; Sloboda-Rozner, D.; Zhang, R. *Synlett* ***2002***, 2011. **La**: Nemoto, T.; Ohshima, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* ***2001***, *123*, 2725; Chen, R.; Qian, C.; de Vries, J.G. *Tetrahedron* ***2001***, *57*, 9837; Nemoto, T.; Kakei, H.; Gnanadesikan, V.; Tosaki, S.-y.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* ***2002***, *124*, 14544.

[1742]For a table containing several common catalysts, see Hiatt, R., in Augustine, R.L.; Trecker, D.J. *Oxidation*, Vol. 2, Marcel Dekker, NY, ***1971***, p. 124.

[1743]For other methods of converting alkenes to epoxides, see Bruice, T.C. *Aldrichimica Acta* ***1988***, *21*, 87; Adam, W.; Curci, R.; Edwards, J.O. *Acc. Chem. Res.* ***1989***, *22*, 205.

[1744]Majetich, G.; Hicks, R.; Sun, G.-r.; McGill, P. *J. Org. Chem.* ***1998***, *63*, 2564; Murray, R.W.; Iyanar, K. *J. Org. Chem.* ***1998***, *63*, 1730.

[1745]Yamaguchi, K.; Ebitani, K.; Kaneda, K. *J. Org. Chem.* ***1999***, *64*, 2966.

[1746]Chan, W.-K.; Liu, P.; Yu, W.-Y.; Wong, M.-K.; Che, C.-M. *Org. Lett.* ***2004***, *6*, 1597.

[1747]For an example without microwave irradiation, see Pillai, U.R.; Sahle-Demessie, E.; Varma, R.S. *Synth. Commun.* ***2003***, *33*, 2017.

[1748]Pillai, U.R.; Sahle-Demessie, E.; Varma, R.S. *Tetrahedron Lett.* ***2002***, *43*, 2909.

[1749]Betzemeier, B.; Lhermitte, F.; Knochel, P. *Synlett* ***1999***, 489.

[1750]Van Vliet, M.C.A.; Arends, I.W.C.E.; Sheldon, R.A. *Tetrahedron Lett.* ***1999***, *40*, 5239.

[1751]For a polymer-supported $MeReO_3$ reagent, see Saladino, R.; Neri, V.; Pelliccia, A.R.; Caminiti, R.; Sadun, C. *J. Org. Chem.* ***2002***, *67*, 1323.

[1752]Vaino, A.R. *J. Org. Chem.* ***2000***, *65*, 4210.

[1753]van Vliet, M.C.A.; Arends, I.W.C.E.; Sheldon, R.A. *Chem. Commun.* ***1999***, 821; Adolfsson, H.; Copéret, C.; Chiang, J.P.; Yudin, A.K. *J. Org. Chem.* ***2000***, *65*, 8651; Iskra, J.; Bonnet-Delpon, D.; Bégué, J.-P. *Tetrahedron Lett.* ***2002***, *43*, 1001.

[1754]Owens, G.S.; Abu-Omar, M.M. *Chem. Commun.* ***2000***, 1165.

[1755]Monfared, H.H.; Ghorbani, M. *Monat. Chem.* ***2001***, *132*, 989.

[1756]Ben-Daniel, R.; Weiner, L.; Neumann, R. *J. Am. Chem. Soc.* ***2002***, *124*, 8788.

are treated with oxygen gas, *N*-hydroxyphthalimide, and a mixture of cobalt and molybdenum catalyst.[1757]

Other epoxidation methods are available. Enzymatic epoxidation[1758] and epoxidation with catalytic antibodies[1759] have been reported. Chromyl chloride (CrO_2Cl_2) reacts with alkenes, even at −78°C to give an epoxide and numerous side products including chlorohydrins and dichlorides.[1760] Several mechanisms have been proposed.[1761] Epoxidation has been done in ionic liquids using 10% H_2O_2 with $MnSO_4$[1762] or an iron catalyst.[1763] Hypervalent iodine compounds, such as $PhI(OAc)_2$, in conjunction with a ruthenium catalyst in aqueous media, converts alkenes to epoxides.[1764] This reagent has been used in an ionic liquid with a manganese catalyst.[1765]

Dioxiranes,[1766] such as dimethyl dioxirane (**178**),[1767] either isolated or generated *in situ*,[1768] are important epoxidation reagents. With dimethyloxirane, C—H insertion reactions can occur preferentially.[1769] The reaction with alkenes is rapid, mild, safe, and a variety methods have been developed using an oxidant as a coreagent. The most commonly used coreagent is probably potassium peroxomonosulfate ($KHSO_5$). Oxone® (2 $KHSO_5$•$KHSO_4$•K_2SO_4) is a common source of $KHSO_5$. Oxone® reacts with ketones[1770] and sodium bicarbonate to convert an alkene

[1757]Iwahama, T.; Hatta, G.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* ***2000***, 163.

[1758]**Haloperoxidases**: Hu, S.; Hager, L.P. *Tetrahedron Lett.* ***1999***, *40*, 1641; Dembitsky, V.M. *Tetrahedron* ***2003***, *59*, 4701. ***E. coli JM109(pTAB19)***: Bernasconi, S.; Orsini, F.; Sello, G.; Colmegna, A.; Galli, E.; Bestetti, G. *Tetrahedron Lett.* ***2000***, *41*, 9157. **Cyclohexanone monooxygenase**: Colonna, S.; Gaggero, N.; Carrea, G.; Ottolina, G.; Pasta, P.; Zambianchi, F. *Tetrahedron Lett.* ***2002***, *43*, 1797.

[1759]Chen, Y.; Reymond, J.-L. *Synthesis* ***2001***, 934.

[1760]Sharpless, K.B.; Teranishi, A.Y.; Bäckvall, J.-E. *J. Am. Chem. Soc.* ***1977***, *99*, 3120.

[1761]For leading references, see Rappe, A.K.; Li, S. *J. Am. Chem. Soc.* ***2003***, *125*, 11188.

[1762]In bmim BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate: Tong, K.-H.; Wong, K.-Y.; Chan, T.H. *Org. Lett.* ***2003***, *5*, 3423.

[1763]In bmim Br, 1-butyl-3-methylimidazolium bromide: Srinivas, K.A.; Kumar, A.; Chauhan, S.M.S. *Chem. Commun.* ***2002***, 2456.

[1764]Tse, M.K.; Bhor, S.; Klawonn, M.; Döbler, C.; Beller, M. *Tetrahedron Lett.* ***2003***, *44*, 7479.

[1765]In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Li, Z.; Xia, C.-G. *Tetrahedron Lett.* ***2003***, *44*, 2069.

[1766]For general leading references, see Murray, R.W. *Chem. Rev.* ***1989***, *89*, 1187; Adam, W.; Curci, R.; Edwards, J.O. *Acc. Chem. Res.* ***1989***, *22*, 205; Curci, R.; Dinoi, A.; Rubino, M.E. *Pure Appl. Chem.* ***1995***, *67*, 811; Clennan, E.L. *Trends in Organic Chemistry,* ***1995***, *5*, 231; Adam, W.; Smerz, A.K. *Bull Soc. Chim. Belg.* ***1996***, *105*, 581; Denmark, S.E.; Wu, Z. *Synlett* ***1999***, 847.

[1767]Frohn, M.; Wang, Z.-X.; Shi, Y. *J. Org. Chem.* ***1998***, *63*, 6425. See Angelis, Y.; Zhang, X.; Organopoulos, M. *Tetrahedron Lett.* ***1996***, *37*, 5991 for a discussion of the mechanism of this oxidation.

[1768]See Curci, R.; Fiorentino, M.; Troisi, L.; Edwards, J.O.; Pater, R.H. *J. Org. Chem.* ***1980***, *45*, 4758; Gallopo, A.R.; Edwards, J.O. *J. Org. Chem.* ***1981***, *46*, 1684; Corey, P.E; Ward, F.E. *J. Org. Chem.* ***1986***, *51*, 1925; Adam, W.; Hadjiarapoglou, L.; Smerz, A. *Chem. Ber.* ***1991***, *124*, 227; Yang, D.; Wong, M.K.; Yip, Y.C. *J. Org. Chem.* ***1995***, *60*, 3887; Denmark, S.E.; Wu, Z. *J. Org. Chem.* ***1998***, *63*, 2810, and references cited therein; Frohn, M.; Wang, Z.-X.; Shi, Y. *J. Org. Chem.* ***1998***, *63*, 6425; Yang, D.; Yip, Y.-C.; Tang, M.-W.; Wong, M.-K.; Cheung, K.-K. *J. Org. Chem.* ***1998***, *63*, 9888, and references cited therein.

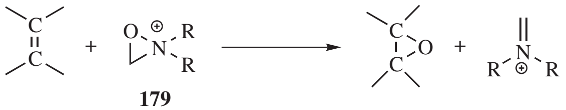
[1769]Adam, W.; Prechtl, F.; Richter, M.J.; Smerz, A.K. *Tetrahedron Lett.* ***1993***, *34*, 8427.

[1770]Ferraz, H.M.C.; Muzzi, R.M.; de O.Viera, T.; Viertler, H. *Tetrahedron Lett.* ***2000***, *41*, 5021; Legros, J.; Crousse, B.; Bourdon, J.; Bonnet-Delpon, D.; Bégué, J.-P. *Tetrahedron Lett.* ***2001***, *42*, 4463. For a reaction with a ketone immobilized on silica, see Sartori, G.; Armstrong, A.; Maggi, R.; Mazzacani, A.; Sartorio, R.; Bigi, F.; Dominguez-Fernandez, B. *J. Org. Chem.* ***2003***, *68*, 3232.

to an epoxide. Oxone® also converts alkenes to epoxides in the presence of certain additives, such as *N,N*-dialkylalloxans.[1771] Oxone, usually with hydrogen peroxide or another similar oxidant, can be used with chiral ketones[1772] or aldehydes to convert alkenes to chiral, nonracemic epoxides.[1773] Chiral dioxiranes have reportedly given nonracemic epoxides.[1774] Hydrogen peroxide, in the presence of chiral ketones in acetonitrile (or other nitrile solvents), probably converts alkenes to epoxides with good enantioselectivity by *in situ* generation of dioxirane.[1775] Epoxidation does not occur in good yields with these reagents in most other solvents, and it is suggested that the active agent that generates dioxirane is peroxyimidic acid MeC(=NH)OOH.[1776] Note that benzaldehyde with Chloramine-M[1777] will convert alkenes to epoxides.[1778] Amines, including chiral amines can be similarly used with aldehydes with aqueous sodium bicarbonate.[1779]

178

oxirene



179

Oxone® oxidizes iminium salts to an oxaziridinium intermediate **179**, which can transfer oxygen to an alkene to form an epoxide and regenerate the iminium salt.[1780]

[1771]Carnell, A.J.; Johnstone, R.A.W.; Parsy, C.C.; Sanderson, W.R. *Tetrahedron Lett.* ***1999***, *40*, 8029.

[1772]For reviews, see Shi, Y. *Acc. Chem. Res.* ***2004***, *37*, 488; Yang, D. *Acc. Chem. Res.* ***2004***, *37*, 497.

[1773]For leading references, see: Denmark, S.E.; Wu, Z.; Crudden, C.M.; Matsuhashi, H. *J. Org. Chem.* ***1997***, *62*, 8288; Yang, D.; Yip, Y.-C.; Chen, J.; Cheung, K.-K. *J. Am. Chem. Soc.* ***1998***, *120*, 7659; Daly, A.M.; Renehan, M.F.; Gilheany, D.G. *Org. Lett.* ***2001***, *3*, 663; Tian, H.; She, X.; Yu, H.; Shu, L.; Shi, Y. *J. Org. Chem.* ***2002***, *67*, 2435; Denmark, S.E.; Matsuhashi, H. *J. Org. Chem.* ***2002***, *67*, 3479; Arsmtrong, A.; Ahmed, G.; Dominguez-Fernandez, B.; Hayter, B.R.; Wailes, J.S. *J. Org. Chem.* ***2002***, *67*, 8610; Wu, X.-Y.; She, X.; Shi, Y. *J. Am. Chem. Soc.* ***2002***, *124*, 8792; Matsumoto, K.; Tomioka, K. *Tetrahedron Lett.* ***2002***, *43*, 631; Bez, G.; Zhao, C.-G. *Tetrahedron Lett.* ***2003***, *44*, 7403. For a carbonyl derivative bound to cyclodextrin, see Chan, W.-K.; Yu, W.-y.; Che, C.-M.; Wong, M.-K. *J. Org. Chem.* ***2003***, *68*, 6576.

[1774]Tian, H.; She, X.; Shu, L.; Yu, H.; Shi, Y. *J. Am. Chem. Soc.* ***2000***, *122*, 11551.

[1775]Shu, L.; Shi, Y. *Tetrahedron Lett.* ***1999***, *40*, 8721.

[1776]Payne, G.B.; Deming, P.H.; Williams, P.H. *J. Org. Chem.* ***1961***, *26*, 659; Payne, G.B. *Tetrahedron* ***1962***, *18*, 763; McIsaac, Jr., J.E.; Ball, R.E.; Behrman, E.J. *J. Org. Chem.* ***1971***, *36*, 3048; Bach, R.D.; Knight, J.W. *Org. Synth.* ***1981***, *60*, 63; Arias, L.A.; Adkins, S.; Nagel, C.J.; Bach, R.D. *J. Org. Chem.* ***1983***, *48*, 888.

[1777]For the preparation of Chloramine-M, see Rudolph, J.; Sennhenn, P.C.; Vlaar, C.P.; Sharpless, K.B. *Angew. Chem. Int. Ed.* ***1996***, *35*, 2810.

[1778]Yang, D.; Zhang, C.; Wang, X.-C. *J. Am. Chem. Soc.* ***2000***, *122*, 4039.

[1779]Wong, M.-K.; Ho, L.-M.; Zheng, Y.-S.; Ho, C.-Y.; Yang, D. *Org. Lett.* ***2001***, *3*, 2587.

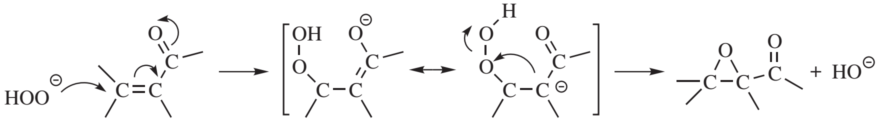
[1780]See Lusinchi, X.; Hanquet, G. *Tetrahedron* ***1997***, *53*, 13727; Hanquet, G.; Lusinchi, X.; Milliet, P. *Tetrahedron Lett.* ***1988***, *29*, 3941; Bohé, L.; Kammoun, M. *Tetrahedron Lett.* ***2002***, *43*, 803; Bohé, L.; Kammoun, M. *Tetrahedron Lett.* ***2004***, *45*, 747.

This variation has been applied to asymmetric[1781] epoxidations using chiral iminium salt precursors.[1782]

Although cis–trans isomerization of epoxides is not formally associated with this section, it is clearly a potential problem in the conversion of an alkene to an epoxide. There are several catalysts for this process.[1783]

It would be useful if triple bonds could be similarly epoxidized to give oxirenes, but they are not stable compounds.[1784] Two of them have been trapped in solid argon matrices at very low temperatures, but they decayed on warming to 35 K.[1785] Oxirenes probably form in the reaction,[1786] but react further before they can be isolated. Note that oxirenes bear the same relationship to cyclobutadiene that furan does to benzene and may therefore be expected to be antiaromatic (see p. 38).

Conjugated dienes can be epoxidized (1,2-addition), although the reaction is slower than for corresponding alkenes, but α,β-unsaturated ketones do not generally give epoxides when treated with peroxyacids.[1787] The epoxidation of α,β-unsaturated ketones with hydrogen peroxide under basic conditions is known as the *Waits–Scheffer epoxidation*, discovered in 1921.[1788] This fundamental reaction has been extended to α,β-unsaturated ketones (including quinones), aldehydes, and sulfones.[1789] This is a nucleophilic addition by a Michael-type mechanism, involving attack by HO_2^-:[1790] This reaction is another example of 1,4-addition of a heteroatom containing species as discussed in **15-31**.



[1781]For a discussion of the origins of selectivity in these reactions, see Washington, I.; Houk, K. N. *J. Am. Chem. Soc.* ***2000***, *122*, 2948.

[1782]See Jacobson, E.N., in Ojima, I. *Catalytic Asymmetric Synthesis*, VCH, NY, ***1993***, pp. 159–203; Armstrong, A.; Ahmed, G.; Garnett, I.; Goacolou, K.; Wailes, J.S. *Tetrahedron* ***1999***, *55*, 2341; Minakata, S.; Takemiya, A.; Nakamura, K.; Ryu, I.; Komatsu, M. *Synlett* ***2000***, 1810; Page, P.C.B.; Rassias, G.A.; Barros, D.; Ardakani, A.; Buckley, B.; Bethell, D.; Smith, T.A.D.; Slawin, A.M.Z. *J. Org. Chem.* ***2001***, *66*, 6926; Page, P.C.B.; Barros, D.; Buckley, B.R.; Ardakani, A.; Marples, B.A. *J. Org. Chem.* ***2004***, *69*, 3595; Page, P.C.B.; Buckley, B.R.; Blacker, A.J. *Org. Lett.* ***2004***, *6*, 1543; Page, P.C.B.; Rassias, G.A.; Barros, D.; Ardakani, A.; Bethell, D.; Merrifield, E. *Synlett* ***2002***, 580.

[1783]Lo, C.-Y.; Pal, S.; Odedra, A.; Liu, R.-S. *Tetrahedron Lett.* ***2003***, *44*, 3143.

[1784]For a review of oxirenes, see Lewars, E.G. *Chem. Rev.* ***1983***, *83*, 519.

[1785]Torres, M.; Bourdelande, J.L.; Clement, A.; Strausz, O.P. *J. Am. Chem. Soc.* ***1983***, *105*, 1698. See also, Laganis, E.D.; Janik, D.S.; Curphey, T.J.; Lemal, D.M. *J. Am. Chem. Soc.* ***1983***, *105*, 7457.

[1786]McDonald, R.N.; Schwab, P.A. *J. Am. Chem. Soc.* ***1964***, *86*, 4866; Ibne-Rasa, K.M.; Pater, R.H.; Ciabattoni, J.; Edwards, J.O. *J. Am. Chem. Soc.* ***1973***, *95*, 7894; Ogata, Y.; Sawaki, Y.; Inoue, H. *J. Org. Chem.* ***1973***, *38*, 1044.

[1787]A few exceptions are known. For example, see Hart, H.; Verma, M.; Wang, I. *J. Org. Chem.* ***1973***, *38*, 3418.

[1788]Weitz, E.; Scheffer, A. *Ber. Dtsch. Chem. Ges.* ***1921***, *54*, 2327.

[1789]For example, see Payne, G.B.; Williams, P.H. *J. Org. Chem.* ***1961***, *26*, 651; Zwanenburg, B.; ter Wiel, J. *Tetrahedron Lett.* ***1970***, 935.

[1790]Bunton, C.A.; Minkoff, G.J. *J. Chem. Soc.* ***1949***, 665; Temple, R.D. *J. Org. Chem.* ***1970***, *35*, 1275; Apeloig, Y.; Karni, M.; Rappoport, Z. *J. Am. Chem. Soc.* ***1983***, *105*, 2784. For a review, see Patai, S.; Rappoport, Z., in Patai, S. *The Chemistry of Alkenes*, pt. 1, Wiley, NY, ***1964***, pp. 512–517.

α,β-Unsaturated compounds can be epoxidized alkyl hydroperoxides and a base,[1791] or with H_2O_2 and a base or heteropoly acids.[1792] The reaction has been done in D_2O using sodium bicarbonate with hydrogen peroxide.[1793] The reaction has been done with LiOH and polymer-bound quaternary ammonium salts.[1794] Epoxides can also be prepared by treating alkenes with oxygen or with an alkyl peroxide[1795] catalyzed by a complex of a transition metal such as V, Mo, Ti, La,[1796] or Co.[1797] The reaction with oxygen, which can also be carried out without a catalyst, is probably a free-radical process.[1798] Conjugated ketones are oxidized to epoxy-ketones with $NaBO_3$ and tetrahexylammonium hydrogen sulfate,[1799] KF-Al_2O_3/*tert*-butyl hydroperoxide.[1800] α,β-Unsaturated esters react normally to give glycidic esters.[1801] When a carbonyl group is elsewhere in the molecule but not conjugated with the double bond, the Baeyer–Villiger reaction (**18-19**) may compete. Allenes[1802] are converted by peroxyacids to allene oxides[1803] or spiro dioxides, both of which species can in certain cases be isolated[1804] but more often are unstable under the reaction conditions and react further to give other products.[1805]

Asymmetric Weitz–Scheffer epoxidation is commonly used for the epoxidation of electron-poor alkenes. Cinchona-derived phase-transfer catalysts, initially used

[1791]**Organolithium reagents**: Bailey, P.L.; Clegg, W.; Jackson, R.F.W.; Meth-Cohn, O. *J. Chem. Soc. Perkin Trans. 1*, ***1990***, 200. **KOH**: Adam, W.; Rao, P.B.; Degen, H.-G.; Saha-Möller, C.R. *J. Am. Chem. Soc.* ***2000***, *122*, 5654. **LiOH**: Arai, S.; Tsuge, H.; Oku, M.; Miura, M.; Shioiri, T. *Tetrahedron* ***2002***, *58*, 1623. **1,5,7-Triazabicyclo[4.4.0]dec-5-ene derivatives**: Genski, T.; Macdonald, G.; Wei, X.; Lewis, N.; Taylor, R.J.K. *Synlett* ***1999***, 795. **DBU**: Yadav, V.K.; Kapoor, K.K. *Tetrahedron* ***1995***, *51*, 8573. **$NaHCO_3$**: Bortolini, O.; Fogagnolo, M.; Fantin, G.; Maietti, S.; Medici, A. *Tetrahedron Asymmetry* ***2001***, *12*, 1113. **Hydrotalcites**: Honma, T.; Nakajo, M.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Tetrahedron Lett.* ***2002***, *43*, 6229.

[1792]Oguchi, T.; Sakata, Y.; Takeuchi, N.; Kaneda, K.; Ishii, Y.; Ogawa, M. *Chem. Lett.* ***1989***, 2053.

[1793]Yao, H.; Richardson, D.E. *J. Am. Chem. Soc.* ***2000***, *122*, 3220.

[1794]Anand, R.V.; Singh, V.K. *Synlett* ***2000***, 807.

[1795]For example, see Gould, E.S.; Hiatt, R.R.; Irwin, K.C. *J. Am. Chem. Soc.* ***1968***, *90*, 4573; Sharpless, K.B.; Michaelson, R.C. *J. Am. Chem. Soc.* ***1973***, *95*, 6136; Kochi, J.K. *Organometallic Mechanisms and Catalysis*; Academic Press, NY, ***1978***, pp. 69–73; Ledon, H.J.; Durbut, P.; Varescon, F. *J. Am. Chem. Soc.* ***1981***, *103*, 3601; Mimoun, H.; Mignard, M.; Brechot, P.; Saussine, L. *J. Am. Chem. Soc.* ***1986***, *108*, 3711; Laszlo, P.; Levart, M.; Singh, G.P. *Tetrahedron Lett.* ***1991***, *32*, 3167.

[1796]Nemoto, T.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* ***2001***, *123*, 9474.

[1797]For a review, see Jørgensen, K.A. *Chem. Rev.* ***1989***, *89*, 431.

[1798]For reviews, see Van Santen, R.A.; Kuipers, H.P.C.E. *Adv. Catal.* ***1987***, *35*, 265; Filippova, T.V.; Blyumberg, E.A. *Russ. Chem. Rev.* ***1982***, *51*, 582.

[1799]Straub, T.S. *Tetrahedron Lett.* ***1995***, *36*, 663.

[1800]Yadav, V.K.; Kapoor, K.K. *Tetrahedron Lett.* ***1994***, *35*, 9481.

[1801]MacPeek, D.L.; Starcher, P.S.; Phillips, B. *J. Am. Chem. Soc.* ***1959***, *81*, 680.

[1802]For a review of epoxidation of allenes, see Jacobs, T.L., in Landor, S.R. *The Chemistry of Allenes*, Vol. 2, Academic Press, NY, ***1982***, pp. 417–510, 483–491.

[1803]For a review of allene oxides, see Chan, T.H.; Ong, B.S. *Tetrahedron* ***1980***, *36*, 2269.

[1804]Camp, R.L.; Greene, F.D. *J. Am. Chem. Soc.* ***1968***, *90*, 7349; Crandall, J.K.; Conover, W.W.; Komin, J.B.; Machleder, W.H. *J. Org. Chem.* ***1974***, *39*, 1723; Crandall, J.K.; Batal, D.J. *J. Org. Chem.* ***1988***, *53*, 1338.

[1805]For example, see Crandall, J.K.; Machleder, W.H.; Sojka, S.A. *J. Org. Chem.* ***1973***, *38*, 1149; Crandall, J.K.; Rambo, E. *J. Org. Chem.* ***1990***, *55*, 5929.

by Wynberg, are now common.[1806] Enantioselectivities can be significantly improved by changes of the catalyst structure as well as the type of oxidant.[1807] A Yb-BINOL complex, with *t*-BuOOH led to epoxidation of conjugated ketones with high asymmetric induction,[1808] as did a mixture of NaOCl and a *Cinchona* alkaloid.[1809] Other enantioselective methods include treatment with diethylzinc, O_2, in the presence of a chiral amino-alcohol, to give the epoxy-ketone.[1810] Similarly, treatment with aqueous NaOCl[1811] or with an alkyl hydroperoxide[1812] and a chiral phase-transfer agent leads to chiral nonracemic epoxy-ketones.

Another important asymmetric epoxidation of a conjugated systems is the reaction of alkenes with polyleucine, DBU and urea—H_2O_2, giving an epoxy-carbonyl compound with good enantioselectivity.[1813] The hydroperoxide anion epoxidation of conjugated carbonyl compounds with a polyamino acid, such as poly-L-alanine or poly-L-leucine is known as the *Juliá–Colonna epoxidation.*[1814] Epoxidation of conjugated ketones to give nonracemic epoxy-ketones was done with aq. NaOCl and a Cinchona alkaloid derivative as catalyst.[1815] A triphasic phase-transfer catalysis protocol has also been developed.[1816] β-Peptides have been used as catalysts in this reaction.[1817]

Allylic alcohols can be converted to epoxy-alcohols with *tert*-butylhydroperoxide on molecular sieves,[1818] or with peroxy acids.[1819] The addition of an appropriate chiral ligand to the metal-catalyzed hydroperoxide epoxidation of allylic alcohols leads to high enantioselectivity. This important modification is

[1806]Helder, R.; Hummelen, J.C.; Laane, R.W.P.M.; Wiering, J.S.; Wynberg, H. *Tetrahedron Lett.* ***1976***, *17*, 1831; Wynberg, H.; Greijdanus, B. *J. Chem. Soc., Chem. Commun.* ***1978***, 427; Wynberg, H.; Marsman, B. *J. Org. Chem.* ***1980***, *45*, 158; Pluim, H.; Wynberg, H. *J. Org. Chem.* ***1980***, *45*, 2498.

[1807]Arai, S.; Tsuge, H.; Shioiri, T. *Tetrahedron Lett.* ***1998***, *39*, 7563; Arai, S.; Shirai, Y.; Ishida, T.; Shioiri, T. *Tetrahedron* ***1999***, *55*, 6375; Corey, E.J.; Zhang, F.-Y. *Org. Lett.* ***1999***, *1*, 1287; Lygo, B.; Wainwright, P.G. *Tetrahedron* ***1999***, *55*, 6289. See Adam, W.; Rao, P.B.; Degen, H.-G.; Levai, A.; Patonay, T.; Saha-Moller, C.R. *J. Org. Chem.* ***2002***, *67*, 259.

[1808]Watanabe, S.; Arai, T.; Sasai, H.; Bougauchi, M.; Shibasaki, M. *J. Org. Chem.* ***1998***, *63*, 8090.

[1809]Lygo, B.; Wainwright, P.G. *Tetrahedron Lett.* ***1998***, *39*, 1599.

[1810]Enders, D.; Zhu, J.; Kramps, L. *Liebigs Ann. Chem.* ***1997***, 1101; Enders, D.; Zhu, J.; Raabe, G. *Angew. Chem. Int. Ed.* ***1996***, *35*, 1725.

[1811]Lygo, B.; To, D.C.M. *Tetrahedron Lett.* ***2001***, *42*, 1343.

[1812]Adam, W.; Rao, P.B.; Degen, H.-G.; Saha-Möller, C.R. *Tetrahedron Asymmetry* ***2001***, *12*, 121.

[1813]Allen, J.V.; Drauz, K.-H.; Flood, R.W.; Roberts, S.M.; Skidmore, J. *Tetrahedron Lett.* ***1999***, *40*, 5417; Geller, T.; Roberts, S.M. *J. Chem. Soc., Perkin Trans. 1*, ***1999***, 1397; Bentley, P.A.; Bickley, J.F.; Roberts, S.M.; Steiner, A. *Tetrahedron Lett.* ***2001***, *42*, 3741.

[1814]Banfi, S.; Colonna, S.; Molinari, H.; Juliá, S.; Guixer, J. *Tetrahedron* ***1984***, *40*, 5207. For reviews, see Lin, P. *Tetrahedron: Asymmetry* ***1998***, *9*, 1457; Ebrahim, S.; Wills, M. *Tetrahedron; Asymmetry* ***1997***, *8*, 3163.

[1815]Lygo, B.; Wainwright, P.G. *Tetrahedron* ***1999***, *55*, 6289.

[1816]Geller, T.; Krüger, C.M.; Militzer, H.-C. *Tetrahedron Lett.* ***2004***, *45*, 5069.

[1817]Coffey, P.E.; Drauz-K.-H.; Roberts, S.M.; Skidmore, J.; Smith, J.A. *Chem. Commun.* ***2001***, 2330.

[1818]Antonioletti, R.; Bonadies, F.; Locati, L.; Scettri, A. *Tetrahedron Lett.* ***1992***, *33*, 3205.

[1819]Fringuelli, F.; Germani, R.; Pizzo, F.; Santinelli, F.; Savelli, G. *J. Org. Chem.* ***1992***, *57*, 1198.

known as the *Sharpless asymmetric epoxidation*,[1820] where allylic alcohols are converted to optically active epoxides with excellent enantioselectivity by treatment with *t*-BuOOH, titanium tetraisopropoxide and optically active diethyl tartrate.[1821] The $Ti(OCHMe_2)_4$ and diethyl tartrate can be present in catalytic amounts (15–10 mol%) if molecular sieves are present.[1822] Polymer-supported catalysts have also been reported.[1823] Both (+) and (−) diethyl tartrate are readily available, so either enantiomer of the product can be prepared. The method has been successful for a wide range of primary allylic alcohols, including substrates where the double bond is mono-, di-, tri-, and tetrasubstituted,[1824] and is highly useful in natural product synthesis. The mechanism of the Sharpless epoxidation is believed to involve attack on the substrate by a compound[1825] formed from the titanium alkoxide and the diethyl tartrate to produce a complex that also contains the substrate and the *t*-BuOOH.[1826]

Ordinary alkenes (without an allylic OH group) do not give optically active alcohols by the Sharpless protocol because binding to the catalyst is necessary for enantioselectivity. Simples alkenes can be epoxidized enantioselectively with sodium hypochlorite (NaOCl, commercial bleach) and an optically active manganese-complex catalyst.[1827] An important variation of this oxidation uses a manganese–salen complex[1828] with various oxidizing agents, in what is called

[1820]For reviews, see Pfenninger, A. *Synthesis* ***1986***, 89; Rossiter, B.E., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 5, Academic Press, NY, ***1985***, pp. 193–246. For histories of its discovery, see Sharpless, K.B. *Chem. Br.* ***1986***, 38; *CHEMTECH* ***1985***, 692. Also see, Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY, ***2001***, pp. 239–245.

[1821]Sharpless, K.B.; Woodard, S.S.; Finn, M.G. *Pure Appl. Chem.* ***1983***, *55*, 1823, and references cited therein.

[1822]Gao, Y.; Hanson, R.M.; Klunder, J.M.; Ko, S.Y.; Masamune, H.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1987***, *109*, 5765. See Massa, A.; D'Ambrosi, A.; Proto, A.; Screttri, A. *Tetrahedron Lett.* ***2001***, *42*, 1995. For another improvement, see Wang, Z.; Zhou, W. *Tetrahedron* ***1987***, *43*, 2935.

[1823]Canali, L.; Karjalainen, J.K.; Sherrington, D.C.; Hormi, O. *Chem. Commun.* ***1997***, 123.

[1824]See the table, in Finn, M.G.; Sharpless, K.B., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 5, Academic Press, NY, ***1985***, pp. 249–250. See also, Schweiter, M.J.; Sharpless, K.B. *Tetrahedron Lett.* ***1985***, *26*, 2543.

[1825]Very similar compounds have been prepared and isolated as solids whose structures have been determined by X-ray crystallography: Williams, I.D.; Pedersen, S.F.; Sharpless, K.B.; Lippard, S.J. *J. Am. Chem. Soc.* ***1984***, *106*, 6430.

[1826]For a review of the mechanism, see Finn, M.G.; Sharpless, K.B., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 5, Academic Press, NY, ***1985***, p. 247. For other mechanistic studies, see Jørgensen, K.A.; Wheeler, R.A.; Hoffmann, R. *J. Am. Chem. Soc.* ***1987***, *109*, 3240; Carlier, P.R.; Sharpless, K.B. *J. Org. Chem.* ***1989***, *54*, 4016; Corey, E.J. *J. Org. Chem.* ***1990***, *55*, 1693; Woodard, S.S.; Finn, M.G.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1991***, *113*, 106; Finn, M.G.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1991***, *113*, 113; Takano, S.; Iwebuchi, Y.; Ogasawara, K. *J. Am. Chem. Soc.* ***1991***, *113*, 2786. See Cui, M.; Adam, W.; Shen, J.H.; Luo, X.M.; Tan, X.J.; Chen, K.X.; Ji, R.Y.; Jiang, H.L. *J. Org. Chem.* ***2002***, *67*, 1427.

[1827]Jacobsen, E.N.; Zhang, W.; Muci, A.R.; Ecker, J.R.; Deng, L. *J. Am. Chem. Soc.* ***1991***, *113*, 7063. See also, Irie, R.; Noda, K.; Ito, Y.; Katsuki, T. *Tetrahedron Lett.* ***1991***, *32*, 1055; Halterman, R.L.; Jan, S. *J. Org. Chem.* ***1991***, *56*, 5253.

[1828]These complexes have been characterized. See Adam, W.; Mock-Knoblauch, C.; Saha-Moller, C.R.; Herderich, M. *J. Am. Chem. Soc.* ***2000***, *122*, 9685.

the *Jacobsen–Katsuki reaction*.[1829] Apart from the commonly used NaOCl, urea—H_2O_2 has been used.[1830] With this reaction, simple alkenes can be epoxidized with high enantioselectivity.[1831] The mechanism of this reaction has been examined.[1832] Radical intermediates have been suggested for this reaction,[1833] A polymer-bound $Mn^{(III)}$–salen complex, in conjunction with NaOCl, has been used for asymmetric epoxidation.[1834] Chromium–salen complexes[1835] and ruthenium–salen complexes[1836] have been used for epoxidation. Manganese porphyrin complexes have also been used.[1837] Cobalt complexes give similar results.[1838] A related epoxidation reaction used an iron complex with molecular oxygen and isopropanal.[1839] Nonracemic epoxides can be prepared from racemic epoxides with salen–cobalt(II) catalysts following a modified procedure for kinetic resolution.[1840]

In a different type of reaction, alkenes are photooxygenated (with singlet O_2, see **14-7**) in the presence of a Ti, V, or Mo complex to give epoxy alcohols, such as **180**, formally derived from allylic hydroxylation followed by epoxidation.[1841] In other cases, modification of the procedure gives simple epoxidation.[1842] Alkenes react with aldehydes and oxygen, with palladium-on-silica[1843] or a ruthenium catalyst,[1844]

[1829]Hosoya, N.; Hatayama, A.; Irie, R.; Sasaki, H.; Katsuki, T. *Tetrahedron* ***1994***, *50*, 4311, and references cited therein; Brandes, B.D.; Jacobsen, E.N. *J. Org. Chem.* ***1994***, *59*, 4378; Sasaki, H.; Irie, R.; Hamada, T.; Suzuki, K.; Katsuki, T. *Tetrahedron* ***1994***, *50*, 11827; Brandes, B.D.; Jacobsen, E.N. *Tetrahedron Lett.* ***1995***, *36*, 5123; Nishikori, H.; Ohta, C.; Katsuki, T. *Synlett* ***2000***, 1557; Tangestaninejad, S.; Habibi, M.H.; Mirkhani, V.; Moghadam, M. *Synth. Commun.* ***2002***, *32*, 3331.

[1830]Kureshy, R.I.; Khan, N.H.; Abdi, S.H.R.; Patel, S.T.; Jasra, R.V. *Tetrahedron Asymmetry* ***2001***, *12*, 433.

[1831]For a discussion of stereocontrol factors, see Nishida, T.; Miyafuji, A.; Ito, Y.N.; Katsuki, T. *Tetrahedron Lett.* ***2000***, *41*, 7053.

[1832]See Linker, T. *Angew. Chem., Int. Ed.* ***1997***, *36*, 2060. See Adam, W.; Roschmann, K.J.; Saha-Möller, C.R. *Eur. J. Org. Chem.* ***2000***, 3519. For the importance of electronic effects, see Cavallo, L.; Jacobsen, H. *J. Org. Chem.* ***2003***, *68*, 6202.

[1833]Cavallo, L.; Jacobsen, H. *Angew. Chem. Int. Ed.* ***2000***, *39*, 589.

[1834]Song, C.E.; Roh, E.J.; Yu, B.M.; Chi, D.Y.; Kim, S.C.; Lee, K.J. *Chem. Commun.* ***2000***, 615; Ahn, K.-H.; Park, S.W.; Choi, S.; Kim, H.-J.; Moon, C.J. *Tetrahedron Lett.* ***2001***, *42*, 2485.

[1835]Daly, A.M.; Renehan, M.F.; Gilheany, D.G. *Org. Lett.* ***2001***, *3*, 663; O'Mahony, C.P.; McGarrigle, E.M.; Renehan, M.F.; Ryan, K.M.; Kerrigan, N.J.; Bousquet, C.; Gilheany, D.G. *Org. Lett.* ***2001***, *3*, 3435. See the references cited therein.

[1836]Nakata, K.; Takeda, T.; Mihara, J.; Hamada, T.; Irie, R.; Katsuki, T. *Chem. Eur. J.* ***2001***, *7*, 3776.

[1837]Konishi, K.; Oda, K.; Nishida, K.; Aida, T.; Inoue, S. *J. Am. Chem. Soc.* ***1992***, *114*, 1313.

[1838]Takai, T.; Hata, E.; Yorozu, K.; Mukaiyama, T. *Chem. Lett.* ***1992***, 2077.

[1839]Saalfrank, R.W.; Reihs, S.; Hug, M. *Tetrahedron Lett.* ***1993***, *34*, 6033.

[1840]Savle, P.S.; Lamoreaux, M.J.; Berry, J.F.; Gandour, R.D. *Tetrahedron Asymmetry* ***1998***, *9*, 1843.

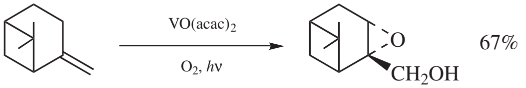
[1841]Adam, W.; Braun, M.; Griesbeck, A.; Lucchini, V.; Staab, E.; Will, B. *J. Am. Chem. Soc.* ***1989***, *111*, 203.

[1842]See Iwahama, T.; Hatta, G.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* ***2000***, 163.

[1843]Gao, H.; Angelici, R.J. *Synth. Commun.* ***2000***, *30*, 1239; Chen, W.; Yamada, J.; Matsumoto, K. *Synth. Commun.* ***2002***, *32*, 17; Ragagnin, G.; Knochel, P. *Synlett* ***2004***, 951.

[1844]Srikanth, A.; Nagendrappa, G.; Chandrasekaran, S. *Tetrahedron* ***2003***, *59*, 7761; Qi, J.Y.; Qiu, L.Q.; Lam, K.H.; Yip, C.W.; Zhou, Z.Y.; Chan, A.S.C. *Chem. Commun.* ***2003***, 1058.

to give the epoxide.



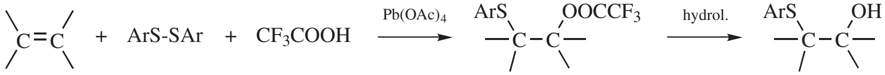
180

Thiiranes can be prepared directly from alkenes using specialized reagents.[1845] Thiourea with a tin catalyst gives the thiirane, for example.[1846] Interestingly, internal alkynes were converted to 1,2-dichorothiiranes by reaction with S_2Cl_2 (sulfur monochloride).[1847] It is noted that epoxides are converted to thiiranes with ammonium thiocyanate and a cerium complex.[1848] A trans-thiiration reaction occurs with a molybdenum catalyst, in which an alkene reacts with styrene thiirane to give the new thiirane.[1849]

OS **I**, 494; **IV**, 552, 860; **V**, 191, 414, 467, 1007; **VI**, 39, 320, 679, 862; **VII**, 121, 126, 461; **VIII**, 546; **IX**, 288; **X**, 29; **80**, 9.

15-51 Hydroxysulfenylation (Addition of Oxygen, Sulfur)

Hydroxy-arylthio-addition (overall transformation)



A hydroxy and an arylthio group can be added to a double bond by treatment with an aryl disulfide and lead tetraacetate in the presence of trifluoroacetic acid.[1850] Manganese and copper acetates have been used instead of $Pb(OAc)_4$.[1851] Addition of the groups OH and RSO has been achieved by treatment of alkenes with O_2 and a thiol RSH.[1852] Two RS groups were added, to give *vic*-dithiols, by treatment of the alkene with a disulfide RSSR and BF_3-etherate.[1853] This reaction

[1845]Capozzi, G.; Menichetti, S.; Neri, S.; Skowronska, A. *Synlett* ***1994***, 267; Adam, W.; Bargon, R.M. *Eur. J. Org. Chem.* ***2001***, 1959; Adam, W.; Bargon, R.M. *Chem. Commun.* ***2001***, 1910.

[1846]Tangestaninejad, S.; Mirkhani, V. *Synth. Commun.* ***1999***, *29*, 2079.

[1847]Nakayama, J.; Takahashi, K.; Watanabe, T.; Sugihara, Y.; Ishii, A. *Tetrahedron Lett.* ***2000***, *41*, 8349.

[1848]Iranpoor, N.; Tamami, B.; Shekarriz, M. *Synth. Commun.* ***1999***, *29*, 3313.

[1849]Adam, W.; Bargon, R.M.; Schenk, W.A. *J. Am. Chem. Soc.* ***2003***, *125*, 3871.

[1850]Trost, B.M.; Ochiai, M.; McDougal, P.G. *J. Am. Chem. Soc.* ***1978***, *100*, 7103. For a related reaction, see Zefirov, N.S.; Zyk, N.V.; Kutateladze, A.G.; Kolbasenko, S.I.; Lapin, Yu.A. *J. Org. Chem. USSR* ***1986***, *22*, 190.

[1851]Bewick, A.; Mellor, J.M.; Owton, W.M. *J. Chem. Soc. Perkin Trans. 1*, ***1985***, 1039; Bewick, A.; Mellor, J.M.; Milano, D.; Owton, W.M. *J. Chem. Soc. Perkin Trans. 1*, ***1985***, 1045; Samii, Z.K.M.A.E.; Ashmawy, M.I.A.; Mellor, J.M. *Tetrahedron Lett.* ***1986***, *27*, 5289.

[1852]Chung, M.; D'Souza, V.T.; Szmant, H.H. *J. Org. Chem.* ***1987***, *52*, 1741, and other papers in this series.

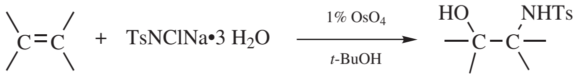
[1853]Caserio, M.C.; Fisher, C.L.; Kim, J.K. *J. Org. Chem.* ***1985***, *50*, 4390; Inoue, H.; Murata, S. *Heterocycles* ***1997***, *45*, 847.

has been carried out internally.[1854] In a similar manner, reaction of alkenes with ceric ammonium nitrate, diphenyl diselenide in methanol leads to vicinally substituted phenylselenyl methyl ethers.[1855] Dimethyl diselenide adds to alkenes to form vicinal bis-methylselenyl compounds, in the presence of tin tetrachloride.[1856]

Halo-ethers can be formed by the reaction of alkenyl alcohols with various reagents. Hept-6-en-1-ol reacts with $(\text{collidine})_2\text{I}^+\text{PF}_6^-$, for example, to form 2-iodomethyl-1-oxacycloheptane.[1857]

15-52 Oxyamination (Addition of Oxygen, Nitrogen)

Tosylamino-hydroxy-addition



N-Tosylated β-hydroxy alkylamines (which can be easily hydrolyzed to β-hydroxyamines[1858]) can be prepared[1859] by treatment of alkenes with the trihydrate of Chloramine-T (*N*-chloro-*p*-toluenesulfonamide sodium salt)[1566] and a catalytic amount of OsO_4.[1860] In some cases, yields can be improved by the use of phase-transfer catalysis.[1861] The reaction has been carried out enantioselectively.[1862] Alkenes can be converted to amido alcohols enantioselectivity by modification of this basic scheme. The *Sharpless asymmetric aminohydroxylation* employs a catalyst consisting of *Cinchona* alkaloid derived ligands and an osmium species in combination with a stoichiometric nitrogen source that also functions as the oxidant.[1863] The reaction of a carbamate with $(\text{DHQ})_2$PHAL (**176**) and the osmium compound, with NaOH and *tert*-butyl hypochlorite, leads to a diastereomeric mixture of amido alcohols **181** and **182**, each formed with high enantioselectivity.[1864] In general, the nitrogen adds to the less sterically hindered carbon of the alkene to give the major product. *N*-Bromoamides, in the presence of a catalytic amount of $(\text{DHQ})_2$PHAL

[1854]Tuladhar, S.M.; Fallis, A.G. *Tetrahedron Lett.* ***1987***, *28*, 523. For a list of other examples, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 905–908.

[1855]Bosman, C.; D'Annibale, A.; Resta, S.; Trogolo, C. *Tetrahedron Lett.* ***1994***, *35*, 6525. See Ogawa, A.; Tanaka, H.; Yokoyama, H.; Obayashi, R.; Yokoyama, K.; Sonoda, N. *J. Org. Chem.* ***1992***, *57*, 111 for formation of mixed PhS—PhSe- compounds from alkenes.

[1856]Hermans, B.; Colard, N.; Hevesi, L. *Tetrahedron Lett.* ***1992***, *33*, 4629.

[1857]Brunel, Y.; Rousseau, G. *Synlett* ***1995***, 323.

[1858]For some reactions of the oxyamination products, see Bäckvall, J.E.; Oshima, K.; Palermo, R.E.; Sharpless, K.B. *J. Org. Chem.* ***1979***, *44*, 1953.

[1859]Sharpless, K.B.; Chong, A.O.; Oshima, K. *J. Org. Chem.* ***1976***, *41*, 177. See Rudolph, J.; Sennhenn, P.C.; Vlaar, C.P.; Sharpless, K.B. *Angew. Chem. Int. Ed.* ***1996***, *35*, 2810 for a discussion of the influence of substituents on nitrogen in this reaction.

[1860]See Fokin, V.V.; Sharpless, K.B. *Angew. Chem. Int. Ed.* ***2001***, *40*, 3455.

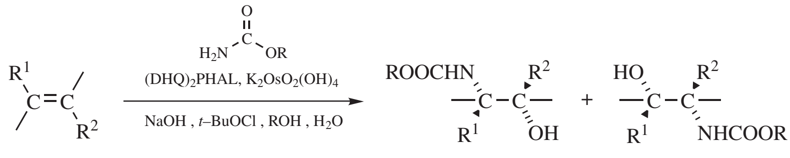
[1861]Herranz, E.; Sharpless, K.B. *J. Org. Chem.* ***1978***, *43*, 2544.

[1862]Hassine, B.B.; Gorsane, M.; Pecher, J.; Martin, R.H. *Bull. Soc. Chim. Belg.* ***1985***, *94*, 759.

[1863]For a review, see Bodkin, J.A.; McLeod, M.D. *J. Chem. Soc., Perkin Trans. 1* ***2002***, 2733.

[1864]Li, G.; Chang, H.-T.; Sharpless, K.B. *Angew. Chem., Int. Ed.* ***1996***, *35*, 451.

and LiOH converts conjugated esters to β-amido-α-hydroxy esters with good enantioselectivity.[1865] In another procedure, certain β-hydroxy secondary alkylamines can be prepared by treatment of alkenes with the osmium compound *t*-Bu—N=OsO_3, followed by reductive cleavage with $LiAlH_4$ of the initially formed osmic esters.[1866] It is presumed that Ts—N=OsO_3 is an intermediate in the Chloramine-T reaction. Another oxyamination reaction involves treatment of a palladium complex of the alkene with a secondary or primary amine, followed by lead tetraacetate or another oxidant.[1867]



181 **182**

The organolanthanide-catalyzed alkene hydroamination has been reported.[1868] With this approach, amino alkenes (not enamines) can be cyclized to form cyclic amines,[1869] and amino alkynes lead to cyclic imine.[1870] The use of synthesized *C*-1[1871] and *C*-2 symmetric[1872] chiral organolanthanide complexes give the amino alcohol with good enantioselectivity.

β-Amino alcohols can be prepared by treatment of an alkene with a reagent prepared from HgO and HBF_4 along with aniline to give an aminomercurial compound PhHN—C—C—$HgBF_4$ (aminomercuration; see **15-7**) which is hydrolyzed

[1865]Demko, Z.P.; Bartsch, M.; Sharpless, K.B. *Org. Lett.* ***2000***, *2*, 2221.

[1866]Hentges, S.G.; Sharpless, K.B. *J. Org. Chem.* ***1980***, *45*, 2257. Also see, Rubinstein, H.; Svendsen, J.S. *Acta Chem. Scand. B* ***1994***, *48*, 439. For another method, in which the NH in the product is connected to an easily removable protecting group, see Herranz, E.; Sharpless, K.B. *J. Org. Chem.* ***1980***, *45*, 2710.

[1867]Bäckvall, J.E.; Björkman, E.E. *Acta Chem. Scand. Ser. B* ***1984***, *38*, 91; Bäckvall, J.E.; Bystrom, S.E. *J. Org. Chem.* ***1982***, *47*, 1126.

[1868]Ryu, J.-S.; Li, G.Y.; Marks, T.J. *J. Am. Chem. Soc.* ***2003***, *125*, 12584; Li, Y.; Marks, T.J. *Organometallics* ***1996***, *15*, 3770; Gagné, M.R.; Stern, C.L.; Marks, T.J. *J. Am Chem. Soc.* ***1992***, *114*, 275; Gagné, M.R.; Marks, T.J. *J. Am Chem. Soc.* ***1989***, *111*, 4108. For a review, see Hong, S.; Marks, T.J. *Acc. Chem. Res.* ***2004***, *37*, 673.

[1869]Gagné, M.R.; Stern, C.L.; Marks, T.J. *J. Am Chem. Soc.* ***1992***, *114*, 275; Gagné, M.R.; Marks, T.J. *J. Am Chem. Soc.* ***1989***, *111*, 4108.

[1870]Li, Y.; Marks, T.J. *J. Am. Chem. Soc.* ***1996***, *118*, 9295; Li, Y.; Fu, P.-F.; Marks, T.J. *Organometallics* ***1994***, *13*, 439; Li, Y.; Marks, T.J. *J. Am. Chem. Soc.* ***1998***, *120*, 1757; Li, Y.; Marks, T.J. *J. Am. Chem. Soc.* ***1996***, *118*, 707.

[1871]Douglass, M.R.; Ogasawara, M.; Hong, S.; Metz, M.V.; Marks, T.J. *Organometallics* ***2002***, *21*, 283; Giardello, M.A.; Conticello, V.P.; Brard, L.; Gagné, M.R.; Marks, T.J. *J. Am. Chem. Soc.* ***1994***, *116*, 10241; Giardello, M.A.; Conticello, V.P.; Brard, L.; Sabat, M.; Rheingold, A.L.; Stern, C.L.; Marks, T.J. *J. Am. Chem. Soc.* ***1994***, *116*, 10212; Gagné, M.R.; Brard, L.; Conticello, V.P.; Giardello, M.A.; Stern, C.L.; Marks, T.J. *Organometallics* ***1992***, *11*, 2003.

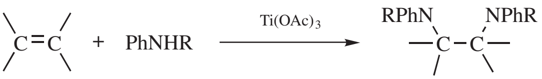
[1872]Hong, S.; Tian, S.; Metz, M.V.; Marks, T.J. *J. Am. Chem. Soc.* ***2003***, *125*, 14768.

to PhHN–C–C–OH.[1873] The use of an alcohol instead of water gives the corresponding amino ether. β-Azido alcohols are prepared by the reaction of an alkene with $Me_3SiOOSiMe_3$, Me_3SiN_3, and 20% $(Cl_2SnO)_n$, followed by treatment with aqueous acetic acid.[1874]

OS **VII**, 223, 375.

15-53 Diamination (Addition of Nitrogen, Nitrogen)

Di(alkylarylamino)-addition



Primary (R = H) and secondary aromatic amines react with alkenes in the presence of thallium(III) acetate to give *vic*-diamines in good yields.[1875] The reaction is not successful for primary aliphatic amines. In another procedure, alkenes can be diaminated by treatment with the osmium compounds R_3NOsO (R = *t*-Bu) and R_2NOsO_2,[1876] analogous to the osmium compound mentioned at **15-52**.[1877] The palladium-promoted method of **15-52** has also been extended to diamination.[1878] Alkenes can also be diaminated[1879] indirectly by treatment of the aminomercurial compound mentioned in **15-52** with a primary or secondary aromatic amine.[1880] The reaction of an alkene with *N*-arylsulfonyl dichloroamines, $ArSO_2NCl_2$, followed by reaction with aqueous Na_2SO_3, gives the *anti-vic*-diacetamde.[1881]

Two azido groups can be added to double bonds by treatment with sodium azide and iodosobenzene in acetic acid, C=C + NaN_3 + PhIO → N_3—C—C —N_3.[1882]

[1873]Barluenga, J.; Alonso-Cires, L.; Asensio, G. *Synthesis* ***1981***, 376.

[1874]Sakurada, I.; Yamasaki, S.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* ***2000***, *41*, 2415.

[1875]Gómez Aranda, V.; Barluenga, J.; Aznar, F. *Synthesis* ***1974***, 504.

[1876]Chong, A.O.; Oshima, K.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1977***, *99*, 3420. See also, Sharpless, K.B.; Singer, S.P. *J. Org. Chem.* ***1976***, *41*, 2504.

[1877]For a X-ray structure of the osmium intermediate, see Muñiz, K.; Iesato, A.; Nieger, M. *Chem. Eur. J.* ***2003***, *9*, 5581.

[1878]Bäckvall, J. *Tetrahedron Lett.* ***1978***, 163.

[1879]For other diamination methods, see Michejda, C.J.; Campbell, D.H. *J. Am. Chem. Soc.* ***1979***, *101*, 7687; Becker, P.N.; White, M.A.; Bergman, R.G. *J. Am. Chem. Soc.* ***1980***, *102*, 5676; Becker, P.N.; Bergman, R.G. *Organometallics* ***1983***, *2*, 787; Jung, S.; Kohn, H. *Tetrahedron Lett.* ***1984***, *25*, 399; *J. Am. Chem. Soc.* ***1985***, *107*, 2931; Osowska-Pacewicka, K.; Zwierzak, A. *Synthesis* ***1990***, 505.

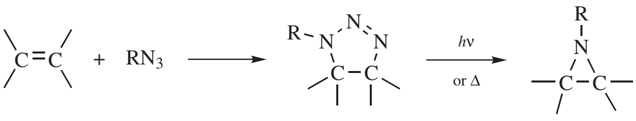
[1880]Barluenga, J.; Alonso-Cires, L.; Asensio, G. *Synthesis* ***1979***, 962.

[1881]Li, G.; Kim, S.H.; Wei, H.-X. *Tetrahedron Lett.* ***2000***, *41*, 8699.

[1882]Moriarty, R.M.; Khosrowshahi, J.S. *Tetrahedron Lett.* ***1986***, *27*, 2809. For other methods, see Minisci, F.; Galli, R. *Tetrahedron Lett.* ***1962***, 533; Fristad, W.E.; Brandvold, T.A.; Peterson, J.R.; Thompson, S.R. *J. Org. Chem.* ***1985***, *50*, 3647.

15-54 Formation of Aziridines (Addition of Nitrogen, Nitrogen)

***epi*-Arylimino-addition**, and so on.



Triazoline

Aziridines can be prepared directly from double-bond compounds by photolysis or thermolysis of a mixture of the substrate and an azide.[1883] The reaction has been carried out with R = aryl, cyano, EtOOC, and RSO_2, as well as other groups. The reaction can take place by at least two pathways.

In one pathway a 1,3-dipolar addition (**15-58**) takes place to give a triazoline (which can be isolated), followed thermal by extrusion of nitrogen (**17-34**). Evidence for the nitrene pathway is most compelling for R = acyl groups. In the other, the azide is converted to a nitrene, which adds to the double bond in a manner analogous to that of carbene addition (**15-64**). Sulfonyloxy amines, such as $ArSO_2ONHCO_2Et$, form an aziridine when treated with CaO in the presence of a conjugated carbonyl compound.[1884] In the presence of copper,[1885] cobalt,[1886] or rhodium complexes,[1887] ethyl diazoacetate adds to imines to give aziridines. Diazirines (p. 288) with *n*-butyllithium converted conjugated amides to the α,β-aziridino amide.[1888] Calcium oxide has also been used to generate the nitrene,[1889] including nitrene precursors that have an attached chiral ester.[1890] Other specialized reagents have also been used.[1891] As discussed on p. 293, singlet nitrenes add stereospecifically while triplet nitrenes do not. Diphenyl sulfimide (Ph_2SNH) converts

[1883]For reviews, see Dermer, O.C.; Ham, G.E. *Ethylenimine and Other Aziridines*, Academic Press, NY, ***1969***, pp. 68–79; Muller, L.L.; Hamer, J. *1,2-Cycloaddition Reactions*, Wiley, NY, ***1967***.

[1884]Fioravanti, S.; Pellacani, L.; Tabanella, S.; Tardella, P.A. *Tetrahedron* ***1998***, *54*, 14105; Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P.A. *Synthesis* ***2001***, 1975. For an enantioselective version of this reaction using a chiral ester auxiliary, see Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P.A. *J. Org. Chem.* ***2002***, *67*, 4972.

[1885]Li, Z.; Zheng, Z.; Chen, H. *Tetrahedron Asymmetry* ***2000***, *11*, 1157; Wong, H.L.; Tian, Y.; Chan, K.S. *Tetrahedron Lett.* ***2000***, *41*, 7723; Sanders, C.J.; Gillespie, K.M.; Scott, P. *Tetrahedron Asymmetry* ***2001***, *12*, 1055; Ma, J.-A.; Wang, L.-X.; Zhang, W.; Zhou, W.; Zhou, Q.-L. *Tetrahedron Asymmetry* ***2001***, *12*, 2801.

[1886]Ikeno, T.; Nishizuka, A.; Sato, M.; Yamada, T. *Synlett* ***2001***, 406.

[1887]Mohan, J.M.; Uphade, T.S.S.; Choudhary, V.R.; Ravindranathan, T.; Sudalai, A. *Chem. Commun.* ***1997***, 1429; Moran, M.; Bernardinelli, G.; Müller, P. *Helv. Chim. Acta* ***1995***, *78*, 2048.

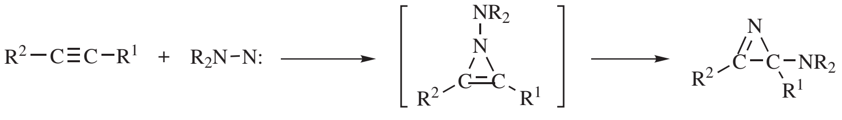
[1888]Hori, K.; Sugihara, H.; Ito, Y.N.; Katsuki, T. *Tetrahedron Lett.* ***1999***, *40*, 5207; Ishihara, H.; Ito, Y.N.; Katsuki, T. *Chem. Lett.* ***2001***, 984.

[1889]Carducci, M.; Fioravanti, S.; Loreta, M.A.; Pellacani, L.; Tardella, P.A. *Tetrahedron Lett.* ***1996***, *37*, 3777.

[1890]Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P.A. *Tetrahedron Lett.* ***2003***, *44*, 3031.

[1891]Aires-de-Sousa, J.; Labo, A.M.; Prabhakar, S. *Tetrahedron Lett.* ***1996***, *37*, 3183.

Michael-type substrates to the corresponding aziridines.[1892] Aminonitrenes (R_2NN:) have been shown to add to alkenes[1893] to give *N*-substituted aziridines and to triple bonds to give 1-azirines, which arise from rearrangement of the initially formed 2-azirines.[1894] Like oxirenes (see **15-50**), 2-azirines are unstable, probably because of anti-aromaticity. 1-Azirines can be reduced to give chiral aziridines.[1895]



2-Azirine 1-Azirine

An alternative preparation of aziridines reacts an alkene with iodine and chloramine-T, generating the corresponding *N*-tosyl aziridine.[1896] Chloramine T and NBS also gives the *N*-tosyl aziridine,[1897] and bromamine-T ($TsNBr^-Na^+$) has been used in a similar manner,[1898] and also TsNIK.[1899] Diazoalkanes react with imines to give aziridines.[1900] Another useful reagent is NsN=IPh, which reacts with alkenes in the presence of rhodium compounds[1901] or $Cu(OTf)_2$[1902] to give *N*-Ns aziridines. Other sulfonamide reagents can be used,[1903] including PhI=NTs.[1904] Enantioselective aziridination is possible using this reaction with

[1892]Furukawa, N.; Yoshimura, T.; Ohtsu, M.; Akasaka, T.; Oae, S. *Tetrahedron* ***1980***, *36*, 73. For other methods, see Groves, J.T.; Takahashi, T. *J. Am. Chem. Soc.* ***1983***, *105*, 2073; Mahy, J.; Bedi, G.; Battioni, P.; Mansuy, D. *J. Chem. Soc. Perkin Trans. 2*, ***1988***, 1517; Atkinson, R.S.; Kelly, B.J. *J. Chem. Soc. Perkin Trans. 1*, ***1989***, 1515.

[1893]Siu, T.; Yudin, A.K. *J. Am. Chem. Soc.* ***2002***, *124*, 530.

[1894]Anderson, D.J.; Gilchrist, T.L.; Rees, C.W. *Chem. Commun.* ***1969***, 147.

[1895]Roth, P.; Andersson, P.G.; Somfai, P. *Chem. Commun.* ***2002***, 1752.

[1896]Ando, T.; Kano, D.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron* ***1998***, *54*, 13485. For the use of $TsNCl_2$, see Chen, D.; Timmons, C.; Guo, L.; Xu, X.; Li, G. *Synthesis* ***2004***, 2479.

[1897]Thakur, V.V.; Sudalai, A. *Tetrahedron Lett.* ***2003***, *44*, 989.

[1898]Vyas, R.; Chanda, B.M.; Bedekar, A.V. *Tetrahedron Lett.* ***1998***, *39*, 4715; Hayer, M.F.; Hossain, M.M. *J. Org. Chem.* ***1998***, *63*, 6839. This reaction was catalyzed by $CuCl_2$ with microwave irradiation, see Chanda, B.M.; Vyas, R.; Bedekar, A.V. *J. Org. Chem.* ***2001***, *66*, 30. Iron catalysts have been used, see Vyas, R.; Gao, G.-Y.; Hardin, J.D.; Zhang, X.P. *Org. Lett.* ***2003***, *6*, 1907.

[1899]Jain, S.L.; Sain, B. *Tetrahedron Lett.* ***2003***, *44*, 575.

[1900]Casarrubios, L.; Pérez, J.A.; Brookhart, M.; Templeton, J.L. *J. Org. Chem.* ***1996***, *61*, 8358.

[1901]Müller, P.; Baud, C.; Jacquier, Y. *Tetrahedron* ***1996***, *52*, 1543. Also see, Södergren, M.J.; Alonso, D.A.; Bedekar, A.V.; Andersson, P.G. *Tetrahedron Lett.* ***1997***, *38*, 6897.

[1902]Knight, J.G.; Muldowney, M.P. *Synlett* ***1995***, 949. See also, Dauben, P.; Sanière, L.; Tarrade, A.; Dodd, R.H. *J. Am. Chem. Soc.* ***2001***, *123*, 7707; Shi, M.; Wang, C.-J.; Chan, A.S.C. *Tetrahedron Asymmetry* ***2001***, *12*, 3105.

[1903]$PhI{=}NSO_2CH_2CCl_3$: GuthiKonda, K.; Du Bois, J. *J. Am. Chem. Soc.* ***2002***, *124*, 13672. See also, Di Chenna, P.H.; Robert-Peillard, F.; Dauban, P.; Dodd, R.H. *Org. Lett.* ***2004***, *6*, 4503; Kwong, H.-L.; Liu, D.; Chan, K.-Y.; Lee, C.-S.; Huang, K.-H.; Che, C.-M. *Tetrahedron Lett.* ***2004***, *45*, 3965.

[1904]Vedernikov, A.N.; Caulton, K.G. *Org. Lett.* ***2003***, *5*, 2591; Cui, Y.; He, C. *J. Am. Chem. Soc.* ***2003***, *125*, 16202. $PhI{=}NSO_2CH_2CH_2SiMe_3$: Dauban, P.; Dodd, R.H. *J. Org. Chem.* ***1999***, *64*, 5304, and see Nishimura, M.; Minakata, S.; Takahashi, T.; Oderaotoshi, Y.; Komatsu, M. *J. Org. Chem.* ***2002***, *67*, 2101.

chiral ligands.[1905] This reagent has been used in ionic liquids with a copper catalyst.[1906] Such reactions are catalyzed by palladium[1907] and methyl trioxorhenium ($MeReO_3$) can be used in these reactions.[1908] Manganese–salen catalysts have also been used with this reagent.[1909] A nitrido manganese–salen complex was also used with ditosyl anhydride, converting a conjugated diene to an allylic *N*-tosylaziridine.[1910]

Nitrenes can also add to aromatic rings to give ring-expansion products analogous to those mentioned in **15-62**.[1911]

OS **VI**, 56.

15-55 Aminosulfenylation (Addition of Nitrogen, Sulfur)

Arylamino-arylthio-addition

An amino and an arylthio group can be added to a double bond by treatment with a sulfenanilide PhSNHAr in the presence of BF_3-etherate.[1912] The addition is anti, and the mechanism probably involves a thiiranium ion.[1913] In another aminosulfenylation procedure, the substrate is treated with dimethyl(methylthio)sulfonium fluoroborate ($MeSSMe_2\ BF_4^-$) and ammonia or an amine,[1914] the latter acting as a nucleophile. This reaction was extended to other nucleophiles:[1915] N_3^-,[1916]

[1905]See Gillespie, K.M.; Sanders, C.J.; O'Shaughnessy, P.; Westmoreland, I.; Thickitt, C.P.; Cott, P. *J. Org. Chem.* ***2002***, *67*, 3450.

[1906]In bmim BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate: Kantam, M.L.; Neeraja, V.; Kavita, B.; Haritha, Y. *Synlett* ***2004***, 525.

[1907]Antunes, A.M.M.; Marto, S.J.L.; Branco, P.S.; Prabhakar, S.; Lobo, A.M. *Chem. Commun.* ***2001***, 405.

[1908]Jean, H.-J.; Nguyen, S.B.T. *Chem. Commun.* ***2001***, 235.

[1909]O'Connor, K.J.; Wey, S.-J.; Burrows, C.J. *Tetrahedron Lett.* ***1992***, *33*, 1001; Nishikori, H.; Katsuki, T. *Tetrahedron Lett.* ***1996***, *37*, 9245; Noda, K.; Hosoya, N.; Irie, R.; Ito, Y.; Katsuki, T. *Synlett* ***1993***, 469.

[1910]Nishimura, M.; Minakata, S.; Thonchant, S.; Ryu, I.; Komatsu, M. *Tetrahedron Lett.* ***2000***, *41*, 7089.

[1911]For example, see Hafner, K.; König, C. *Angew. Chem. Int. Ed.* ***1963***, *2*, 96; Lwowski, W.; Johnson, R.L. *Tetrahedron Lett.* ***1967***, 891.

[1912]Benati, L.; Montavecchi, P.C.; Spagnolo, P. *Tetrahedron Lett.* ***1984***, *25*, 2039. See also, Brownbridge, P. *Tetrahedron Lett.* ***1984***, *25*, 3759.

[1913]See Ref. 21.

[1914]Trost, B.M.; Shibata, T. *J. Am. Chem. Soc.* ***1982***, *104*, 3225; Caserio, M.C.; Kim., J.K. *J. Am. Chem. Soc.* ***1982***, *104*, 3231.

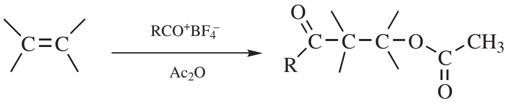
[1915]Trost, B.M.; Shibata, T.; Martin, S.J. *J. Am. Chem. Soc.* ***1982***, *104*, 3228; Trost, B.M.; Shibata, T. *J. Am. Chem. Soc.* ***1982***, *104*, 3225. For an extension that allows A to be C≡CR, see Trost, B.M.; Martin, S.J. *J. Am. Chem. Soc.* ***1984***, *106*, 4263.

[1916]Sreekumar, R.; Padmakumar, R.; Rugmini, P. *Chem. Commun.* ***1997***, 1133.

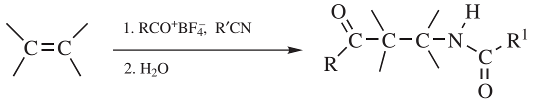
NO_2^- CN^-, ^-OH, and ^-OAc to give MeS–C–C–A, where A = N_3, NO_2, CN, OH, and OAc, respectively. An RS (R = alkyl or aryl) and an NHCOMe group have been added in an electrochemical procedure.[1917]

15-56 Acylacyloxylation and Acylamidation (Addition of Oxygen, Carbon, or Nitrogen, Carbon)

Acyl-acyloxy-addition

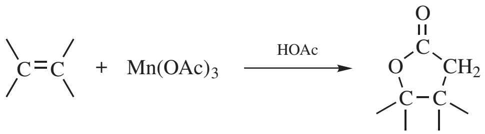


An acyl and an acyloxy group can be added to a double bond by treatment with an acyl fluoroborate and acetic anhydride.[1918] As expected, the addition follows Markovnikov's rule, with the electrophile Ac^+ going to the carbon with more hydrogens. In an analogous reaction, an acyl and an amido group can be added to give **183**, if a nitrile is used in place of the anhydride. Similarly, halo acetoxylation is known.[1919] This reaction has also been carried out on triple bonds, to give the unsaturated analogs of **183** (syn addition).[1920]



183

15-57 The Conversion of Alkenes to γ-Lactones (Addition of Oxygen, Carbon)



This reaction is clearly related to forming esters and lactones by reaction of carboxylic acids with alkenes (**15-6**), but the manganese reagent leads to

[1917]Bewick, A.; Coe, D.E.; Mellor, J.M.; Owton, M.W. *J. Chem. Soc. Perkin Trans. 1*, ***1985***, 1033.
[1918]Shastin, A.V.; Balenkova, E.S. *J. Org. Chem. USSR* ***1984***, *20*, 870.
[1919]Hashem, Md.A.; Jung, A.; Ries, M.; Kirschning, A. *Synlett* ***1998***, 195.
[1920]Gridnev, I.D.; Balenkova, E.S. *J. Org. Chem. USSR* ***1988***, *24*, 1447.

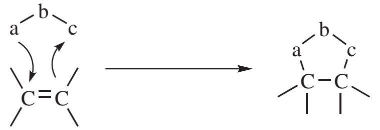
differences. Alkenes react with manganese(III) acetate to give γ-lactones.[1921] The mechanism is probably free radical, involving addition of •CH_2COOH to the double bond. Ultrasound improves the efficiency of the reaction.[1922] In a related reaction, cyclohexene reacted with $MeO_2CCH_2CO_2K$ and $Mn(OAc)_3$ to give an α-carbomethoxy bicyclic lactone.[1923] The use of dimethyl malonate and ultrasound in this reaction gave the same type of product.[1924] Lactone formation has also been accomplished by treatment of alkenes with α-bromo carboxylic acids in the presence of benzoyl peroxide as catalyst,[1925] and with alkylidene chromium pentacarbonyl complexes.[1926] Alkenes can also be converted to γ- lactones by indirect routes.[1927] Chromium–carbene complexes add to alkenes to give β-lactones using ultrasound.[1928]

An intramolecular variation of this reaction is known, involving amides, which generates a lactam.[1929]

OS **VII**, 400.

For addition of aldehydes and ketones, see the Prins reaction (**16-54**), and reactions **16-95** and **16-96**.

15-58 1,3-Dipolar Addition (Addition of Oxygen, Nitrogen, Carbon)



184

There are a large group of reactions ([3 + 2]-cycloadditions) in which five-membered heterocyclic compounds are prepared by addition of 1,3-dipolar compounds to double bonds. This reaction is quite useful in the synthesis of alkaloids,[1930] including asymmetric syntheses.[1931] These dipolar compounds have a

[1921]Bush Jr., J.B.; Finkbeiner, H. *J. Am. Chem. Soc.* ***1968***, *90*, 5903; Heiba, E.I.; Dessau, R.M.; Koehl, Jr., W.J. *J. Am. Chem. Soc.* ***1968***, *90*, 5905; Heiba, E.I.; Dessau, R.M.; Rodewald, P.G. *J. Am. Chem. Soc.* ***1974***, *96*, 7977; Midgley, G.; Thomas, C.B. *J. Chem. Soc. Perkin Trans. 2*, ***1984***, 1537; Ernst, A.B.; Fristad, W.E. *Tetrahedron Lett.* ***1985***, *26*, 3761; Shundo, R.; Nishiguchi, I.; Matsubara, Y.; Hirashima, T. *Tetrahedron* ***1991***, *47*, 831. See also, Corey, E.J.; Gross, A.W. *Tetrahedron Lett.* ***1985***, *26*, 4291.

[1922]D'Annibale, A.; Trogolo, C. *Tetrahdron Lett.* ***1994***, *35*, 2083.

[1923]Lamarque, L.; Méou, A.; Brun, P. *Tetrahedron* ***1998***, *54*, 6497.

[1924]Allegretti, M.; D'Annibale, A.; Trogolo, C. *Tetrahedron* ***1993***, *49*, 10705.

[1925]Nakano, T.; Kayama, M.; Nagai, Y. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 1049. See also, Kraus, G.A.; Landgrebe, K. *Tetrahedron Lett.* ***1984***, *25*, 3939.

[1926]Wang, S.L.B.; Su, J.; Wulff, W.D. *J. Am. Chem. Soc.* ***1992***, *114*, 10665.

[1927]See, for example, Boldt, P.; Thielecke, W.; Etzemüller, J. *Chem. Ber.* ***1969***, *102*, 4157; Das Gupta, T.K.; Felix, D.; Kempe, U.M.; Eschenmoser, A. *Helv. Chim. Acta* ***1972***, *55*, 2198; Bäuml, E.; Tscheschlok, K.; Pock, R.; Mayr, H. *Tetrahedron Lett.* ***1988***, *29*, 6925.

[1928]Caldwell, J.J.; Harrity, J.P.A.; Heron, N.M.; Kerr, W.J.; McKendry, S.; Middlemiss, D. *Tetrahedron Lett.* ***1999***, *40*, 3481; Caldwell, J.J.; Kerr, W.J.; McKendry, S. *Tetrahedron Lett.* ***1999***, *40*, 3485.

[1929]Davies, D.T.; Kapur, N.; Parsons, A.F. *Tetrahedron Lett.* ***1998***, *39*, 4397.

[1930]See Broggini, G.; Zecchi, G. *Synthesis* ***1999***, 905.

[1931]Karlsson, S.; Högberg, H.-E. *Org. Prep. Proceed. Int.* ***2001***, *33*, 103.

sequence of three atoms *a–b–c*, of which *a* has a sextet of electrons in the outer shell and *c* an octet with at least one unshared pair (see Table 15.3).[1932] The reaction can then be formulated as shown to generate **184**. Note that the initial reaction of potassium permanganate (**15-48**) occurs by [3 + 2]-cycloaddition to give a manganate ester (**171**).[1933] [3+2]-Cycloadditions occur with other metal oxides.[1934] Hydrazones have also been reported to give [3 + 2]-cycloadditions.[1935]

1,3-Dipoles of the type shown in Table 15.3 have an atom with six electrons in the outer shell, which is usually unstable, and such compounds will delocalize the change to alleviate this electronic arrangement (they are resonance stabilized). 1,3-Dipolar compounds can be divided into two main types:

1. Those in which the dipolar canonical form has a double bond on the sextet atom and the other canonical form has a triple bond on that atom:

$$\overset{\ominus}{a}-b=\overset{\oplus}{c}- \quad \longleftrightarrow \quad \overset{\ominus}{a}-b\equiv\overset{\oplus}{c}-$$

[1932]For a treatise, see Padwa, A. *1,3-Dipolar Cycloaddition Chemistry* 2 vols., Wiley, NY, ***1984***. For general reviews, see Carruthers, W. *Cycloaddition reactins in Organic Synthesis*, Pergamon, Elmsford, NY, ***1990***; Drygina, O.V.; Garnovskii, A.D. *Russ. Chem. Rev.* ***1986***, *55*, 851; Samuilov, Ya.D.; Konovalov, A.I. *Russ. Chem. Rev.* ***1984***, *53*, 332; Beltrame, P., in Bamford, C.H.; Tipper, C.F.H. *Comprhensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 117–131; Huisgen, R.; Grashey, R.; Sauer, J., in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, ***1964***, pp. 806–878; Huisgen, R. *Helv. Chim. Acta* ***1967***, *50*, 2421; *Bull. Soc. Chim. Fr.* ***1965***, 3431; *Angew. Chem. Int. Ed.* ***1963***, *2*, 565, 633. For specific monographs and reviews, see Torssell, K.B.G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH, NY, ***1988***; Scriven, E.F.V. *Azides and Nitrenes*; Academic Press, NY, ***1984***; Stanovnik, B. *Tetrahedron* ***1991***, *47*, 2925 (diazoalkanes); Kanemasa, S.; Tsuge, O. *Heterocycles* ***1990***, *30*, 719 (nitrile oxides); Paton, R.M. *Chem. Soc. Rev.* ***1989***, *18*, 33 (nitrile sulfides); Terao, Y.; Aono, M.; Achiwa, K. *Heterocycles* ***1988***, *27*, 981 (azomethine ylids); Vedejs, E. *Adv. Cycloaddit.* ***1988***, *1*, 33 (azomethine ylids); DeShong, P.; Lander, Jr., S.W.; Leginus, J.M.; Dicken, C.M. *Adv. Cycloaddit.* ***1988***, *1*, 87 (nitrones); Balasubramanian, N. *Org. Prep. Proced. Int.* ***1985***, *17*, 23 (nitrones); Confalone, P.N.; Huie, E.M. *Org. React.* ***1988***, *36*, 1 (nitrones); Padwa, A., in Horspool, W.M. *Synthetic Organic Photochemistry*, Plenum, NY, ***1984***, pp. 313–374 (nitrile ylids); Bianchi, G.; Gandolfi, R.; Grünanger, P., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 1, Wley, NY, ***1983***, pp. 752–784 (nitrile oxides); Black, D.S.; Crozier, R.F.; Davis, V.C. *Synthesis* ***1975***, 205 (nitrones); Stuckwisch, C.G. *Synthesis* ***1973***, 469 (azomethine ylids, azomethine imines). For reviews of intramolecular 1,3-dipolar additions, see Padwa, A., in Padwa, A. treatise cited above, Vol. 2, pp. 277–406; Padwa, A.; Schoffstall, A.M. *Adv. Cycloaddit.* ***1990***, *2*, 1; Tsuge, O.; Hatta, T.; Hisano, T., in Patai, S. *Supplement A: The Chemistry of Double-bonded Functional Groups*, Vol. 2, pt. 1, Wiley, NY, ***1989***, pp. 345–475; Padwa, A. *Angew. Chem. Int. Ed.* ***1976***, *15*, 123. For a review of azomethine ylids, see Tsuge, O.; Kanemasa, S. *Adv. Heterocycl. Chem.* ***1989***, *45*, 231. For reviews of 1,3-dipolar cycloreversions, see Bianchi, G.; Gandolfi, R. in Padwa, A. treatise cited above, Vol. 2, pp. 451–542; Bianchi, G.; De Micheli, C.; Gandolfi, R. *Angew. Chem. Int. Ed.* ***1979***, *18*, 721. For a related review, see Petrov, M.L.; Petrov, A.A. *Russ. Chem. Rev.* ***1987***, *56*, 152. For the use of this reaction to synthesize natural products, see papers in *Tetrahedron* ***1985***, *41*, 3447.

[1933]Houk, K.N.; Strassner, T. *J. Org. Chem.* ***1999***, *64*, 800.

[1934]See Gisdakis, P.; Rösch, N. *J. Am. Chem. Soc.* ***2001***, *123*, 697.

[1935]Kobayashi, S.; Hirabayashi, R.; Shimizu, H.; Ishitani, H.; Yamashita, Y. *Tetrahedron Lett.* ***2003***, *44*, 3351.

TABLE 15.3. Some Common 1,3-Dipolar Compounds

Type 1		
	Azide	$R-\overset{\ominus}{N}-N=\overset{\oplus}{N} \longleftrightarrow R-\overset{\ominus}{N}-\overset{\oplus}{N}\equiv N$
	Diazoalkane[1936]	$R_2\overset{\ominus}{C}-N=\overset{\oplus}{N} \longleftrightarrow R_2\overset{\ominus}{C}-\overset{\oplus}{N}\equiv N$
	Nitrous oxide	$\overset{\ominus}{O}-N=\overset{\oplus}{N} \longleftrightarrow \overset{\ominus}{O}-\overset{\oplus}{N}\equiv N$
	Nitrile imine[1937]	$R-\overset{\ominus}{N}-N=\overset{\oplus}{C}R' \longleftrightarrow R-\overset{\ominus}{N}-\overset{\oplus}{N}\equiv CR'$
	Nitrile ylid[1938]	$R_2\overset{\ominus}{C}-N=\overset{\oplus}{C}R' \longleftrightarrow R_2\overset{\ominus}{C}-\overset{\oplus}{N}\equiv CR'$
	Nitrile oxide[1939]	$\overset{\ominus}{O}-N=\overset{\oplus}{C}R \longleftrightarrow \overset{\ominus}{O}-\overset{\oplus}{N}\equiv CR$
Type 2		
	Azomethine imine	$R_2\overset{\ominus}{C}-\underset{R^2}{N}-\overset{\oplus}{N}R' \longleftrightarrow R_2\overset{\ominus}{C}-\underset{R^2}{\overset{\oplus}{N}}=NR'$
	Azoxy compound	$\overset{\ominus}{O}-\underset{R}{N}-\overset{\oplus}{N}R' \longleftrightarrow \overset{\ominus}{O}-\underset{R}{\overset{\oplus}{N}}=NR'$
	Azomethine ylid[1940]	$R_2\overset{\ominus}{C}-\underset{R^2}{N}-\overset{\oplus}{C}R'_2 \longleftrightarrow R_2\overset{\ominus}{C}-\underset{R^2}{\overset{\oplus}{N}}=CR'_2$
	Nitrone	$\overset{\ominus}{O}-\underset{R'}{N}-\overset{\oplus}{C}R_2 \longleftrightarrow \overset{\ominus}{O}-\underset{R'}{\overset{\oplus}{N}}=CR_2$
	Carbonyl oxide[1941]	$\overset{\ominus}{O}-O-\overset{\oplus}{C}R_2 \longleftrightarrow \overset{\ominus}{O}-\overset{\oplus}{O}=CR_2$
	Ozone	$\overset{\ominus}{O}-O-\overset{\oplus}{O} \longleftrightarrow \overset{\ominus}{O}-\overset{\oplus}{O}=O$

If we limit ourselves to the first row of the periodic table, *b* can only be nitrogen, *c* can be carbon or nitrogen, and *a* can be carbon, oxygen, or

[1936]See Baskaran, S.; Vasu, J.; Prasad, R.; Kodukulla, K.; Trivedi, G.K. *Tetrahedron* ***1996***, *52*, 4515.

[1937]Foti, F.; Grassi, G.; Risitano, F. *Tetrahedron Lett.* ***1999***, *40*, 2605.

[1938]Raposo, C.; Wilcox, C.S. *Tetrahedron Lett.* ***1999***, *40*, 1285.

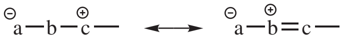
[1939]See Nishiwaki, N.; Uehara, T.; Asaka, N.; Tohda, Y.; Ariga, M.; Kanemasa, S. *Tetrahedron Lett.* ***1998***, *39*, 4851; Jung, M.E.; Vu, B.T. *Tetrahedron Lett.* ***1996***, *37*, 451; Weidner-Wells, M.A.; Fraga, S.A.; Demers, J.P. *Tetrahedron Lett.* ***1994***, *35*, 6473; Easton, C.J.; Hughes, C.M.; Tiekink, E.R.T.; Lubin, C.E.; Savage, G.P.; Simpson, G.W. *Tetrahedron Lett.* ***1994***, *35*, 3589; Brown, F.K.; Raimondi, L.; Wu, Y.-D.; Houk, K.N. *Tetrahedron Lett.* ***1992***, *33*, 4405; Raimondi, L.; Wu, Y.-D.; Brown, F.K.; Houk, K.N. *Tetrahedron Lett.* ***1992***, *33*, 4409. For a synthesis of nitrile oxides, see Muri, D.; Bode, J.W.; Carreira, E.M. *Org. Lett.* ***2000***, *2*, 539. Nitrolic acids are precursors, see Matt, C.; Gissot, A.; Wagner, A.; Mioskowski, C. *Tetrahedron Lett.* ***2000***, *41*, 1191.

[1940]For a review, see Pearson, W.H.; Stoy, P. *Synlett* ***2003***, 903. For chloroiminium salts as precursors, see Anderson, R.J.; Batsanov, A.S.; Belskaia, N.; Groundwater, P.W.; Meth-Cohn, O.; Zaytsev, A. *Tetrahedron Lett.* ***2004***, *45*, 943.

[1941]See Iesce, M.R.; Cermola, F.; Giordano, F.; Scarpati, R.; Graziano, M.L. *J. Chem. Soc. Perkin Trans. 1*, ***1994***, 3295; MuCullough, K.J.; Sugimoto, T.; Tanaka, S.; Kusabayashi, S.; Nojima, M. *J. Chem. Soc. Perkin Trans. 1*, ***1994***, 643.

nitrogen; hence there are six types. Among these are azides ($a = b = c =$ N) and diazoalkanes.

2. Those in which the dipolar canonical form has a single bond on the sextet atom and the other form has a double bond:



Here *b* can be nitrogen or oxygen, and *a* and *c* can be nitrogen, oxygen, or carbon, but there are only 12 types, since, for example, N–N–C is only another form of C–N–N. Examples are shown in Table 15.3.

Of the 18 systems, some of which are unstable and must be generated *in situ*,[1942] the reaction has been accomplished for at least 15, but not in all cases with a carbon–carbon double bond (the reaction also can be carried out with other double bonds[1943]). Not all alkenes undergo 1,3-dipolar addition equally well. The reaction is most successful for those that are good dienophiles in the Diels–Alder reaction (**15-60**). The addition is stereospecific and syn, and the mechanism is probably a one-step concerted process,[1944] as illustrated above,[1945] largely controlled by Frontier Molecular Orbital considerations.[1946] In-plane aromaticity has been invoked for these dipolar cycloadditions.[1947] As expected for this type of mechanism, the rates do not vary much with changes in solvent,[1948] although rate acceleration has been observed in ionic liquids.[1949] Nitrile oxide cycloadditions have also been done in supercritical carbon dioxide.[1950] There are no simple rules

[1942]For a review of some aspects of this, see Grigg, R. *Chem. Soc. Rev.* ***1987***, *16*, 89.

[1943]For a review of 1,3-dipolar addition to other double bonds, see Bianchi, G.; De Micheli, C.; Gandolfi, R., in Patai, S. *Supplement A: The Chemistry of Double-Bonded Functional Groups*, pt. 1, Wiley, NY, ***1977***, pp. 369–532. For a review of such addition to the C=S bond, see Dunn, A.D.; Rudorf, W. *Carbon Disulfide in Organic Chemistry*, Wiley, NY, ***1989***, pp. 97–119.

[1944]Di Valentin, C.; Freccero, M.; Gandolfi, R.; Rastelli, A. *J. Org. Chem.* ***2000***, *65*, 6112. For a theoretical study of transition states, see Lu, X.; Xu, X.; Wang, N.; Zhang, Q. *J. Org. Chem.* ***2002***, *67*, 515. For a theoretical study of stepwise vs. concerted reactions, see DiValentin, C.; Freccero, M.; Gandolfi, R.; Rastelli, A. *J. Org. Chem.* ***2000***, *65*, 6112. For a discussion of loss of concertedness in reactions of azomethine ylids, see Vivanco, S.; Lecea, B.; Arrieta, A.; Prieto, P.; Morao, I.; Linden, A.; Cossío, F.P. *J. Am. Chem. Soc.* ***2000***, *122*, 6078.

[1945]For a review, see Huisgen, R. *Adv. Cycloaddit.* ***1988***, *1*, 1. For discussions, see Huisgen, R. *J. Org. Chem.* ***1976***, *41*, 403; Firestone, R.A. *Tetrahedron* ***1977***, *33*, 3009; Harcourt, R.D. *Tetrahedron* ***1978***, *34*, 3125; Haque, M.S. *J. Chem. Educ.* ***1984***, *61*, 490; Al-Sader, B.H.; Kadri, M. *Tetrahedron Lett.* ***1985***, *26*, 4661; Houk, K.N.; Firestone, R.A.; Munchausen, L.L.; Mueller, P.H.; Arison, B.H.; Garcia, L.A. *J. Am. Chem. Soc.* ***1985***, *107*, 7227; Majchrzak, M.W.; Warkentin, J. *J. Phys. Org. Chem.* ***1990***, *3*, 339.

[1946]Caramella, P.; Gandour, R.W.; Hall, J.A.; Deville, C.G.; Houk, K.N. *J. Am. Chem. Soc.* ***1977***, *99*, 385, and references cited therein.

[1947]Morao, I.; Lecea, B.; Cossío, F.P. *J. Org. Chem.* ***1997***, *62*, 7033; Cossío, F.P.; Marao, I.; Jiao, H.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1999***, *121*, 6737.

[1948]For a review of the role of solvents in this reaction, see Kadaba, P.K. *Synthesis* ***1973***, 71.

[1949]Dubreuil, J.F.; Bazureau, J.P. *Tetrahedron Lett.* ***2000***, *41*, 7351.

[1950]Lee, C.K.Y; Holmes, A.B.; Al-Duri, B.; Leeke, G.A.; Santos, R.C.D.; Seville, J.P.K. *Chem. Commun.* ***2004***, 2622.

covering orientation in 1,3-dipolar additions. The regioselectivity has been explained by molecular-orbital treatments,[1951] where overlap of the largest orbital coefficients of the atoms forming the new bonds leads to the major regioisomer. When the 1,3-dipolar compound is a thiocarbonyl ylid ($R_2C{=}S^+{-}CH_2^-$) the addition has been shown to be nonstereospecific with certain substrates but stereospecific with others, indicating a nonsynchronous mechanism in these cases, and in fact, a diionic intermediate (see mechanism *c* on p. 1224) has been trapped in one such case.[1952] In a theoretical study of the 1,3-dipolar cycloadditions (diazomethane and ethene; fulminic acid [H—C≡N—O] and ethyne),[1953] calculations based on valence bond descriptions suggest that many concerted 1,3-dipolar cycloaddition reactions follow an electronic heterolytic mechanism where the movement of well-identifiable orbital pairs are retained along the entire reaction path from reactants to product.[1954]

An antibody-catalyzed [3 + 2]-cycloaddition has been reported.[1955] Metal assisted dipolar additions are also known.[1956]

Many of the cycloadducts formed from the dipoles in Table 15.3 are unstable, leading to other products. The reaction of alkyl azides with alkenes generates triazolines (**15-54**), which extrude nitrogen (N≡N) upon heating or photolysis to give an aziridine.

[3 + 2]-Cycloaddition reactions occur intramolecularly to generate bicyclic and polycyclic compounds.[1957] The intramolecular cycloaddition of azomethine imines give bicyclic pyrrazolidines for example.[1958] When diazoalkanes, including diazo acetates such as N_2CHCO_2Et react with an alkene and a chromium catalyst the initially formed product is a five-membered ring, a pyrazoline. Pyrazolines are generally unstable and extrusion of nitrogen leads to a cyclopropane.[1959]

There are many cases where the [3 + 2]-cycloaddition leads to cycloadducts with high enantioselectivity.[1960] Cycloaddition of diazo esters with a cobalt catalyst having a chiral ligand leads to cyclopropane derivatives with good enantioselectivity.[1961]

[1951]For a review, see Houk, K.N.; Yamaguchi, K., in Padwa, A. *1,3-Dipolar Cycloaddition Chemistry* Vol. 2, Wiley, NY, ***1984***, pp. 407–450. See also, Burdisso, M.; Gandolfi, R.; Quartieri, S.; Rastelli, A. *Tetrahedron* ***1987***, *43*, 159.

[1952]Huisgen, R.; Mloston, G.; Langhals, E. *J. Am. Chem. Soc.* ***1986***, *108*, 6401; *J. Org. Chem.* ***1986***, *51*, 4085; Mloston, G.; Langhals, E.; Huisgen, R. *Tetrahedron Lett.* ***1989***, *30*, 5373; Huisgen, R.; Mloston, G. *Tetrahedron Lett.* ***1989***, *30*, 7041.

[1953]Karadakov, P.B.; Cooper, D.L.; Gerratt, J. *Theor. Chem. Acc.* ***1998***, *100*, 222.

[1954]Blavins, J.J.; Karadakov, P.B.; Cooper, D.L. *J. Org. Chem.* ***2001***, *66*, 4285.

[1955]Toker, J.D.; Wentworth Jr., P.; Hu, Y.; Houk, K.N.; Janda, K.D. *J. Am. Chem. Soc.* ***2000***, *122*, 3244.

[1956]Kanemasa, S. *Synlett* ***2002***, 1371.

[1957]For reviews, see Padwa, A. *Angew. Chem. Int. Ed.* ***1976***, *15*, 123; Oppolzer, W. *Angew. Chem. Int. Ed.* ***1977***, *16*, 10 (see pp. 18–22).

[1958]Dolle, R.E.; Barden, M.C.; Brennan, P.E.; Ahmed, G.; Tran, V.; Ho, D.M. *Tetrahedron Lett.* ***1999***, *40*, 2907.

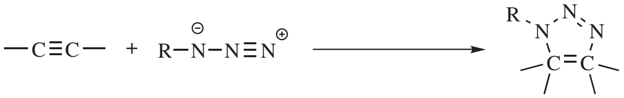
[1959]Jan, D.; Simal, F.; Demonceau, A.; Noels, A.F.; Rufanov, K.A.; Ustynyuk, N.A.; Gourevitch, D.N. *Tetrahedron Lett.* ***1999***, *40*, 5695.

[1960]Gothelf, K.V.; Jørgensen, K.A. *Chem. Rev.* ***1998***, *98*, 863.

[1961]Niimi, T.; Uchida, T.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* ***2000***, *41*, 3647.

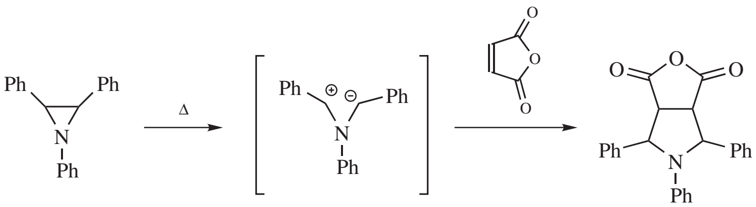
Cycloaddition of nitrones and pyrazolinones with a copper catalyst and a chiral ligand leads to pyrrolidine derivatives with good enantioselectivity.[1962]

Conjugated dienes generally give exclusive 1,2-addition, although 1,4 addition (a [3 + 4]-cycloaddition) has been reported.[1963] Carbon–carbon triple bonds can also undergo 1,3-dipolar addition.[1964] For example, azides react to give triazoles, **185**.



185

The 1,3-dipolar reagent can in some cases be generated by the *in situ* opening of a suitable three-membered ring system. For example, aziridines open to give a zwitterion, such as **186**, which can add to activated double bonds to give pyrrolidines.[1965]



186

Aziridines also add to C≡C triple bonds as well as to other unsaturated linkages, including C=O, C=N, and C≡N.[1966] In some of these reactions it is a C–N bond of the aziridine that opens rather than the C–C bond.

For other [3 + 2]-cycloadditions, see **15-59**.

OS **V**, 957, 1124; **VI**, 592, 670; **VIII**, 231. Also see, OS **IV**, 380.

C. Carbon on Both Sides

Reactions **15-58–15-64** are cycloaddition reactions.[1967]

[1962]Sibi, M.P.; Ma, Z.; Jasperse, C.P. *J. Am. Chem. Soc.* ***2004***, *126*, 718.

[1963]Baran, J.; Mayr, H. *J. Am. Chem. Soc.* ***1987***, *109*, 6519.

[1964]For reviews, see Bastide, J.; Hamelin, J.; Texier, F.; Quang, Y.V. *Bull. Soc. Chim. Fr.* ***1973***, 2555; 2871; Fuks, R.; Viehe, H.G., in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 460–477.

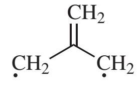
[1965]For a review, see Lown, J.W., in Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*, Vol 1. Wiley, NY, ***1984***, pp. 683–732.

[1966]For reviews, see Lown, J.W. *Rec. Chem. Prog.* ***1971***, *32*, 51; Gladysheva, F.N.; Sineokov, A.P.; Etlis, V.S. *Russ. Chem. Rev.* ***1970***, *39*, 118.

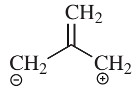
[1967]For a system of classification of cycloaddition reactions, see Huisgen, R. *Angew. Chem. Int. Ed.* ***1968***, *7*, 321. For a review of certain types of cycloadditions leading to 3- to 6-membered rings involving 2, 3, or 4 components, see Posner, G.H. *Chem. Rev.* ***1986***, *86*, 831. See also, the series *Advances in Cycloaddition*.

15-59 All-Carbon [3 + 2]-Cycloadditions[1968]

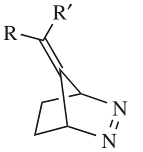
Several methods have been reported for the formation of cyclopentanes by [3 + 2]-cycloadditions.[1969] Heating a conjugated ketones wtih trialkylphosneines genrates an intermdiate that adds to conjugated alkynes.[1970] One type involves reagents that produce intermediates **187** or **188**.[1971] A synthetically useful example[1972] uses 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate (**191**) (which is commercially available) and a palladium or other transition-metal catalyst to generate **187** or **188**, which adds to double bonds, to give, in



187



188



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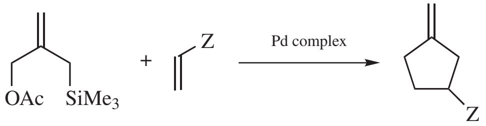
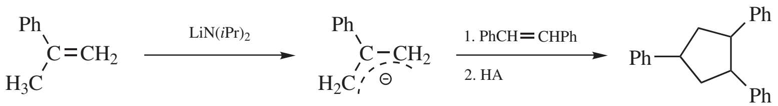
190

good yields, cyclopentanes with an exocyclic double bond. Note that **95** also reacts with *N*-tosyl aziridines, with 20% *n*-butyllithium and 10% of $Pd(OAc)_2$, to give a vinylidene piperidine derivative.[1973] Similar or identical intermediates generated from bicyclic azo compounds **189** (see **17-34**) or methylenecyclopropane **190**[1974] also add to activated double bonds. With suitable substrates the addition can be enantioselective.[1975]



191

In a different type of procedure, [3 + 2]-cycloadditions are performed with allylic anions. Such reactions are called 1,3-anionic cycloadditions.[1976] For example, α-methylstyrene adds to stilbene on treatment with the strong base LDA.[1977]



[1968]See Smith, M.B. *Organic Synthesis, 2nd* ed., McGraw-Hill, NY, ***2001***, pp. 999–1010.

[1969]For a list of methods, with references, see Trost, B.M.; Seoane, P.; Mignani, S.; Acemoglu, M. *J. Am. Chem. Soc.* ***1989***, *111*, 7487.

[1970]Wang, J.-C.; Ng, S.-S.; Krische, M.J. *J. Am. Chem. Soc.* ***2003***, *125*, 3682.

[1971]For reviews, see Trost, B.M. *Pure Appl. Chem.* ***1988***, *60*, 1615; *Angew. Chem. Int. Ed.* ***1986***, *25*, 1.

[1972]See, for example, Trost, B.M.; Lynch, J.; Renaut,P.; Steinman, D.H. *J. Am. Chem. Soc.* ***1986***, *108*, 284.

[1973]Hedley, S.J.; Moran, W.J.; Price, D.A.; Harrity, J.P.A. *J. Org. Chem.* ***2003***, *68*, 4286.

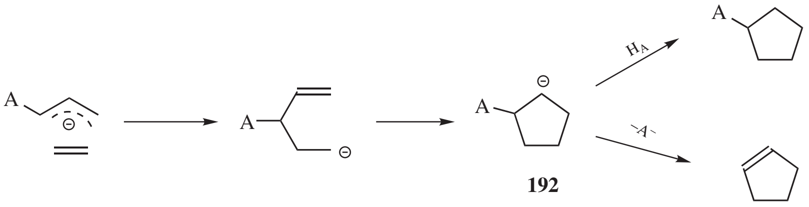
[1974]See Yamago, S.; Nakamura, E. *J. Am. Chem. Soc.* ***1989***, *111*, 7285.

[1975]See Binger, P.; Schäfer, B. *Tetrahedron Lett.* ***1988***, *29*, 529; Chaigne, F.; Gotteland, J.; Malacria, M. *Tetrahedron Lett.* ***1989***, *30*, 1803.

[1976]For reviews, see Kauffmann, T. *Top. Curr. Chem.* ***1980***, *92*, 109, pp. 111–116; *Angew. Chem. Int. Ed.* ***1974***, *13*, 627.

[1977]Eidenschink, R.; Kauffmann, T. *Angew. Chem. Int. Ed.* ***1972***, *11*, 292.

The mechanism can be outlined as



192

In the case above, **192** is protonated in the last step by the acid HA, but if the acid is omitted and a suitable nucleofuge is present, it may leave, resulting in a cyclopentene.[1978] In these cases the reagent is an allylic anion, but similar [3 + 2]-cycloadditions involving allylic cations have also been reported.[1979]

OS **VIII**,173, 347.

15-60 The Diels–Alder Reaction

(4 + 2)*cyclo*-Ethylene-1/4/addition or **(4 + 2)*cyclo*-[Bu*t*-2-ene-1,4-diyl]-1/2/ addition**, and so on.

In the prototype *Diels–Alder reaction* the double bond of an alkene adds 1,4 to a conjugated diene (a [4 + 2]-cycloaddition),[1980] so the product is always a cyclohexene. The cycloaddition is not limited to alkenes or to dienes (see **15-61**), but the substrate that reacts with the diene is called a *dienophile*. The reaction is of

[1978]See, for example, Padwa, A.; Yeske, P.E. *J. Am. Chem. Soc.* ***1988***, *110*, 1617; Beak, P.; Burg, D.A. *J. Org. Chem.* ***1989***, *54*, 1647.

[1979]For example, see Hoffmann, H.M.R.; Vathke-Ernst, H. *Chem. Ber.* ***1981***, *114*, 2208, 2898; Klein, H.; Mayr, H. *Angew. Chem. Int. Ed.* ***1981***, *20*, 1027; Noyori, R.; Hayakawa, Y. *Tetrahedron* ***1985***, *41*, 5879.

[1980]For a monograph, see Wasserman, A. *Diels-Alder Reactions*, Elsevier, NY, ***1965***. For reviews, see Fleming, I. *Pericyclic Reactions*, Oxford University Press, Oxford, ***1999***, pp. 7–30; Roush, W.R. *Adv. Cycloaddit.* ***1990***, *2*, 91; Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*, Pergamon, Elmsford, NY, ***1990***; Brieger, G.; Bennett, J.N. *Chem. Rev.* ***1980***, *80*, 63; Oppolzer, W. *Angew. Chem. Int. Ed.* ***1977***, *16*, 10; Beltrame, P., in Bamford, C.H.; Tipper, C.F.H *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 94–117; Huisgen, R.; Grashey, R.; Sauer, J., in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, ***1964***, pp. 878–929; Carruthers, W. *Some Modern Methods of Organic Synthesis*, 3rd. ed., Cambridge University Press, Cambridge, ***1986***, pp. 183–244; Sauer, J. *Angew. Chem. Int. Ed.* ***1966***, *5*, 211; ***1967***, *6*, 16. For a monograph on intramolecular Diels–Alder reactions, see Taber, D.F. *Intramolecular Diels–Alder and Alder Ene Reactions*, Springer, NY, ***1984***. For reviews, see Deslongchamps, P. *Aldrichimica Acta* ***1991***, *24*, 43; Craig, D. *Chem. Soc. Rev.* ***1987***, *16*, 187; Salakhov, M.S.; Ismailov, S.A. *Russ. Chem. Rev.* ***1986***, *55*, 1145; Fallis, A.G. *Can. J. Chem.* ***1984***, *62*, 183. For a long list of references to various aspects of the Diels–Alder reaction, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 523–544.

very broad scope[1981] and reactivity of dienes and dienophiles can be predicted based on analysis of the HOMOs[1982] and LUMOs of these species (frontier molecular orbital theory).[1983] Ethylene and simple alkenes make poor dienophiles, unless high temperatures and/or pressures are used. Most dienophiles are of the form —C=C—Z or Z—C=C—Z′, where Z and Z′ are electron-withdrawing groups,[1984] such as CHO, COR,[1985] COOH, COOR, COCl, COAr, CN,[1986] NO_2,[1987] Ar, CH_2OH, CH_2Cl, CH_2NH_2, CH_2CN, CH_2COOH, halogen, $PO(OEt)_2$,[1988] or C=C. In the last case, the dienophile is itself a diene.[1989] Particularly common dienophiles are maleic anhydride[1990] and quinones.[1991] Triple bond compounds (–C≡C–Z or Z–C≡C– Z′)

193

may be dienophiles,[1992] generating nonconjugated cyclohexadienes (**193**), and this reaction can be catalyzed by transition-metal compounds.[1993] Allenes react as dienophiles, but without activating groups are very poor dienophiles.[1994]

[1981]For a review of reactivity in the Diels–Alder reaction, see Konovalov, A.I. *Russ. Chem. Rev.* ***1983***, *52*, 1064.

[1982]For a correlation of ionization potential and HOMO correlation with alkene reactions, see Nelson, D.J.; Li, R.; Brammer, C. *J. Org. Chem.* ***2001***, *66*, 2422.

[1983]For a discussion of Frontier Orbital interactions, see Spino, C.; Rezaei, H.; Dory, Y.L. *J. Org. Chem.* ***2004***, *69*, 757. For tables of experimentally determined HOMOs and LUMOs for dienes and dienophiles, see Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY, ***2001***, pp. 917–940.

[1984]For a density-Functional theory analysis see Domingo, L.R. *Eur. J. Org. Chem.* ***2004***, 4788.

[1985]For a review of Diels–Alder reactions with cyclic enones, see Fringuelli, F.; Taticchi, A.; Wenkert, E. *Org. Prep. Proced. Int.* ***1990***, *22*, 131.

[1986]For a review of the Diels–Alder reaction with acrylonitrile, see Butskus, P.F. *Russ. Chem. Rev.* ***1962***, *31*, 283. For a review of tetracyanoethylene as a dienophile, see Ciganek, E.; Linn, W.J.; Webster, O.W., in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 449–453.

[1987]For a review of the Diels–Alder reaction with nitro compounds, see Novikov, S.S.; Shuekhgeimer, G.A.; Dudinskaya, A.A. *Russ. Chem. Rev.* ***1960***, *29*, 79.

[1988]McClure, C.K.; Herzog, K.J.; Bruch, M.D. *Tetrahedron Lett.* ***1996***, *37*, 2153.

[1989]Johnstone, R.A.W.; Quan, P.M. *J. Chem. Soc.* ***1963***, 935.

[1990]For a review of Diels–Alder reactions with maleic anhydride see Kloetzel, M.C. *Org. React.* ***1948***, *4*, 1.

[1991]For reviews of Diels–Alder reactions with quinones, see Finley, K.T., in Patai, S *The Chemistry of the Quinoid Compounds*, Vol. 1, pt. 2, Wiley, NY, ***1988***, pp. 986–1018; Patai, S.; Rapaport, Z. Vol. 2, pt. 1 ***1988***, 537–717, 614–645. For a review of the synthesis of quinones using Diels–Alder reactions, see Naruta, Y.; Maruyama, K. in the same treatise, Vol. 2, pt. 1, pp. 241–402, 277–303.

[1992]For reviews of triple bonds in cycloaddition reactions, see Bastide, J.; Henri-Rousseau, O., in Patai, S. *The Chemistry of the Carbon-Carbon Triple Bond*, pt. 1, Wiley, NY, ***1978***, pp. 447–522, Fuks, R.; Viehe, H.G., in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 477–508.

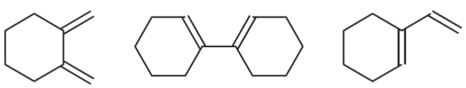
[1993]See Paik, S.-J.; Son, S.U.; Chung, Y.K. *Org. Lett.* ***1999***, *1*, 2045.

[1994]For a review of allenes as dienes or dienophiles, see Hopf, H., in Landor, S.R. *The Chemistry of Allenes*, Vol. 2, Academic Press, NY, ***1982***, pp. 563–577. See Nendel, M.; Tolbert, L.M.; Herring, L.E.; Islam, Md.N.; Houk, K.N. *J. Org. Chem.* ***1999***, *64*, 976.

Ketenes, however, do not undergo Diels–Alder reactions.[1995] Benzynes, although not isolable, act as dienophiles and can be trapped with dienes,[1996] for example,

194

The low reactivity of simple alkenes can be overcome by incorporating an electron-withdrawing group to facilitate the cycloaddition, but a group that can be removed after the cycloaddition. An example is phenyl vinyl sulfone $PhSO_2CH{=}CH_2$.[1997] The $PhSO_2$ group can be easily removed with Na–Hg after the ring-closure reaction. Similarly, phenyl vinyl sulfoxide ($PhSOCH{=}CH_2$) can be used as a synthon for acetylene.[1998] In this case PhSOH is lost from the sulfoxide product (**17-12**).



195 **196** **197**

Electron-donating substituents in the diene accelerate the reaction; electron-withdrawing groups retard it.[1999] For the dienophile it is just the reverse: donating groups decrease the rate, and withdrawing groups increase it. The cisoid conformation is required for the cycloaddition,[2000] and acyclic dienes are conformationally mobile so the cisoid conformation will be available. Cyclic dienes, in which the cisoid conformation is built in, usually react faster than the corresponding open-chain compounds, which have to achieve the cisoid conformation by rotation.[2001] Dienes can be open-chain, inner-ring (e.g., **194**), outer-ring[2002] (e.g., **195**), across

[1995]Ketenes react with conjugated dienes to give 1,2-addition (see **15-49**).

[1996]For a review of benzynes as dienophiles, see Hoffmann, R.W. *Dehydrobenzene and Cycloalkynes*; Academic Press, NY, ***1967***, pp. 200–239. For a review of the reactions of benzynes with heterocyclic compounds see Bryce, M.R.; Vernon, J.M. *Adv. Heterocycl. Chem.* ***1981***, *28*, 183–229.

[1997]Carr, R.V.C.; Williams, R.V.; Paquette, L.A. *J. Org. Chem.* ***1983***, *48*, 4976; Kinney, W.A.; Crouse, G.D.; Paquette, L.A. *J. Org. Chem.* ***1983***, *48*, 4986.

[1998]Paquette, L.A.; Moerck, R.E.; Harirchian, B.; Magnus, P.D. *J. Am. Chem. Soc.* ***1978***, *100*, 1597. For other acetylene synthons see De Lucchi, O.; Lucchini, V.; Pasquato, L.; Modena, G. *J. Org. Chem.* ***1984***, *49*, 596; Hermeling, D.; Schäfer, H.J. *Angew. Chem. Int. Ed.* ***1984***, *23*, 233. For a review, see De Lucchi, O.; Modena, G. *Tetrahedron* ***1984***, *40*, 2585. For a review of [2+2]- and [2+4]-cycloadditions of vinylic sulfides, sulfoxides, and sulfones, see De Lucchi, O.; Pasquato, L. *Tetrahedron* ***1988***, *44*, 6755.

[1999]For a discussion of the electrophilicity power of dienes and dienophiles, see Domingo, L.R.; Aurell, M.J.; Pérez, P.; Contreras, R. *Tetrahedron* ***2002***, *58*, 4417.

[2000]For a discussion of ground state conformations, see Bur, S.K.; Lynch, S.M.; Padwa, A. *Org. Lett.* ***2002***, *4*, 473.

[2001]Sauer, J.; Lang, D.; Mielert, A. *Angew. Chem. Int. Ed.* ***1962***, *1*, 268; Sauer, J.; Wiest, H. *Angew. Chem. Int. Ed.* ***1962***, *1*, 269. See, however, Scharf, H.; Plum, H.; Fleischhauer, J.; Schleker, W. *Chem. Ber.* ***1979***, *112*, 862.

[2002]For reviews of Diels-Alder reactions of some of these compounds, see Charlton, J.L.; Alauddin, M.M. *Tetrahedron* ***1987***, *43*, 2873; Oppolzer, W. *Synthesis* ***1978***, 793.

rings (e.g., **196**), or inner-outer (e.g., **197**), except that they may not be frozen into a transoid conformation (see p. 1201). They need no special activating groups, and nearly all conjugated dienes undergo the reaction with suitable dienophiles.[2003]

In most Diels–Alder reactions, no catalyst is needed, but Lewis acids are effective catalysts in many cases,[2004] particularly those in which Z in the dienophile is a C=O or C=N group. A Lewis acid catalyst usually increases both the regioselectivity of the reaction (in the sense given above) and the extent of endo addition,[2005] and, in the case of enantioselective reactions, the extent of enantioselectivity. It has been shown that $InCl_3$ is an effective catalyst for aqueous Diels–Alder reactions,[2006] which is suitable for ionic Diels–Alder reactions,[2007] and there are other Lewis acid catalysts that are effective in water.[2008] Brønsted acids have also been used to accelerate the rate of the Diels–Alder reaction.[2009] Lanthanum triflate [$La(OTf)_3$] has been reported as a reusable catalyst[2010] and Me_3SiNTf_2 has been used as a green Lewis acid catalyst.[2011] Cationic Diels–Alder catalysts have been developed, particularly oxazaborolidine catalysts.[2012] Some Diels–Alder reactions can also be catalyzed by the addition of a stable cation radical,[2013] for

[2003]For a monograph on dienes, with tables showing > 800 types, see Fringuelli, F.; Taticchi, A. *Dienes in the Diels–Alder Reaction*, Wiley, NY, ***1990***. For a review of Diels–Alder reactions with 2-pyrones, see Shusherina, N.P. *Russ. Chem. Rev.* ***1974***, *43*, 851. For reviews of dienes with hetero substituents, see Danishefsky, S. *Chemtracts: Org. Chem.* ***1989***, *2*, 273; Petrzilka, M.; Grayson, J.I. *Synthesis* ***1981***, 753. For dienes containing a 1-$CONR_2$ group, see Smith, M.B. *Org. Prep. Proced. Int.* ***1990***, *22*, 315; Robiette, R.; Cheboub-Benchaba, K.; Peeters, D.; Marchand-Brynaert, J. *J. Org. Chem.* ***2003***, *68*, 9809. For dienes containing a 1-$NRCO_2R$ group, see Huang, Y.; Iwama, T.; Rawal, V.H. *J. Am. Chem. Soc.* ***2002***, *122*, 5950.

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[2005]For discussions see Houk, K.N.; Strozier, R.W. *J. Am. Chem. Soc.* ***1973***, *95*, 4094; Alston, P.V.; Ottenbrite, R.M. *J. Org. Chem.* ***1975***, *40*, 1111.

[2006]Loh, T.-P.; Pei, J.; Lin, M. *Chem. Commun.* ***1996***, 2315. For a review of Lewis acid catalysis in aqueous media, see Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *Eur. J. Org. Chem.* ***2001***, 439.

[2007]Reddy, B.G.; Kumareswaran, R.; Vankar, Y.D. *Tetrahedron Lett.* ***2000***, *41*, 10333. Iodine is a catalyst for ionic Diels–Alder reactions, see Chavan, S.P.; Sharma, P.; Krishna, G.R.; Thakkar, M. *Tetrahedron Lett.* ***2003***, *44*, 3001.

[2008]Otto, S.; Engberts, J.B.F.N. *Tetrahedron Lett.* ***1995***, *36*, 2645; Ward, D.E.; Gai, Y. *Tetrahedron Lett.* ***1992***, *33*, 1851.

[2009]Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc*, ***1996***, *118*, 3049.

[2010]Kobayashi, S.; Hachiya, I.; Takahori, T.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* ***1992***, *33*, 6815.

[2011]Mathieu, B.; Ghosez, L. *Tetrahedron* ***2002***, *58*, 8219.

[2012]See Sprott, K.T.; Corey, E.J. *Org. Lett.* ***2003***, *5*, 2465; Corey, E.J.; Shibata, T.; Lee, T.W. *J. Am. Chem. Soc.* ***2002***, *124*, 3808; Ryu, D.H.; Lee, T.W.; Corey, E.J. *J. Am. Chem. Soc.* ***2002***, *124*, 9992.

[2013]Gao, D.; Bauld, N.L. *J. Org. Chem.* ***2000***, *65*, 6276. See Saettel, N.J.; Oxgaard, J.; Wiest, O. *Eur. J. Org. Chem.* ***2001***, 1429.

example, tris(4-bromophenyl)aminium hexachloroantimonate $Ar_3N^{\bullet+}$ $SbCl_6^-$.[2014] Carbazoles are dienophiles for cation radical Diels–Alder reactions.[2015] Zirconocene-catalyzed cationic Diels–Alder reactions are known.[2016] Certain antibodies have been developed that catalyze Diels–Alder reactions.[2017] Photochemically induced Diels–Alder reactions are also known.[2018] Cyclodextrins exhibit noncovalent catalysis of Diels–Alder reactions.[2019] There are cases of hydrogen-bonding acceleration.[2020]

A number of other methods have been reported for the acceleration of Diels–Alder reactions,[2021] including the use of microwave irradiation,[2022] ultrasound,[2023] absorption of the reactants on chromatographic absorbents,[2024] via encapsulation techniques,[2025] and the use of an ultracentrifuge[2026] (one of several ways to achieve reaction at high pressures).[2027] Solid-state Diels–Alder reactions are known.[2028] One of the most common methods is to use water as a solvent or a cosolvent (a hydrophobic effect).[2029] The influence of hydrophobicity of reactants

[2014]For a review, see Bauld, N.L. *Tetrahedron* ***1989***, *45*, 5307.

[2015]Gao, D.; Bauld, N.L. *Tetrahedron Lett.* ***2000***, *41*, 5997.

[2016]Wipf, P.; Xu, W. *Tetrahedron* ***1995***, *51*, 4551.

[2017]Meekel, A.A.P.; Resmini, M.; Pandit, U.K. *J. Chem. Soc., Chem. Commun.* ***1995***, 571; Zhang, X.; Deng, Q.; Yoo, S.H.; Houk, K.N. *J. Org. Chem.* ***2002***, *67*, 9043.

[2018]Pandey, B.; Dalvi, P.V. *Angew. Chem. Int. Ed.* ***1993***, *32*, 1612.

[2019]Kim, S.P.; Leach, A.G.; Houk, K.N. *J. Org. Chem.* ***2002***, *67*, 4250. For a discussion of micellar catalysis see Rispens, T.; Engberts, J.B.F.N. *J. Org. Chem.* ***2002***, *67*, 7369.

[2020]Pearson, R.J.; Kassianidis, E.; Philip, D. *Tetrahedron Lett.* ***2004***, *45*, 4777.

[2021]See Smith, M.B. *Organic Synthesis, 2nd* ed., McGraw-Hill, NY, ***2001***, pp. 944–953.

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[2023]Raj. C.P.; Dhas, N.A.; Cherkinski, M.; Gedanken, A.; Braverman, S. *Tetrahedron Lett.* ***1998***, *39*, 5413.

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[2025]Kang, J.; Hilmersson, G.; Sartamaría, J.; Rebek Jr., J. *J. Am. Chem. Soc.* ***1998***, *120*, 3650. For a discussion of the Diels–Alder reaction with aqueous surfactants see Diego-Castro, M.J.; Hailes, H.C. *Tetrahedron Lett.* ***1998***, *39*, 2211.

[2026]Dolata, D.P.; Bergman, R. *Tetrahedron Lett.* ***1987***, *28*, 707.

[2027]For reviews, see Isaacs, N.S.; George, A.V. *Chem. Br.* ***1987***, 47–54; Asano, T.; le Noble, W.J. *Chem. Rev.* ***1978***, *78*, 407. See also, Firestone, R.A.; Smith, G.M. *Chem. Ber.* ***1989***, *122*, 1089.

[2028]Kim, J.H.; Hubig, S.M.; Lindeman, S.V.; Kochi, J.K. *J. Am. Chem. Soc.* ***2001***, *123*, 87.

[2029]Rideout, D.C.; Breslow, R. *J. Am. Chem. Soc.* ***1980***, *102*, 7816. For a review, see Breslow, R. *Acc. Chem. Res.* ***1991***, *24*, 159; Furlani, T.R.; Gao, J. *J. Org. Chem.* ***1996***, *61*, 5492. See also, Grieco, P.A.; Garner, P.; He, Z. *Tetrahedron Lett.* ***1983***, 1897; Blokzijl, W.; Blandamer, M.J.; Engberts, J.B.F.N. *J. Am. Chem. Soc.* ***1991***, *113*, 4241; Breslow, R.; Rizzo, C.J. *J. Am. Chem. Soc.* ***1991***, *113*, 4340; Engberts, J.B.F.N. *Pure Appl. Chem.* ***1995***, *67*, 823; Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* ***1993***, *93*, 741; Otto, S.; Blokzijl, W.; Engberts, J.B.F.N. *J. Org. Chem.* ***1994***, *59*, 5372; Otto, S.; Egberts, J.B.F.N. *Pure. Appl. Chem.* ***2000***, *72*, 1365.

on the reaction has been examined[2030] as has micellular effects.[2031] Another alternative reaction medium is the use of 5 *M* $LiClO_4$ in Et_2O as solvent,[2032] An alternative to lithium perchlorate in ether is lithium triflate in acetonitrile.[2033] The addition of HPO_4^-– to an aqueous ethanol solution has also been shown to give an small rate enhancement.[2034] This appears to be the only case where an anion is responsible for a rate enhancement. The *retro*-Diels–Alder reaction has also been done in water.[2035]

It is noted that the Diels–Alder reaction has been done with supercritical CO_2[2036] and with supercritical water[2037] as solvents. Diels–Alder reactions on solid supports have also been reported,[2038] and zeolites have been used in conjunction with catalytic agents.[2039] Alumina has been used to promote Diels–Alder reactions.[2040] Diels–Alder reactions can be done in ionic liquids,[2041] including asymmetric Diels–Alder reactions.[2042]

When an unsymmetrical diene adds to an unsymmetrical dienophile, regioisomeric products (not counting stereoisomers) are possible. Rearrangements have been encountered in some cases.[2043] In simple cases, 1-substituted dienes give cyclohexenes with a 1,2- and a 1,3- substitution pattern. 2-Substituted dienes

[2030]Meijer, A.; Otto, S.; Engberts, J.B.F.N. *J. Org. Chem.* ***1998***, *63*, 8989; Rizzo, C.J. *J. Org. Chem.* ***1992***, *57*, 6382.

[2031]Jaeger, D.A.; Wang, J. *Tetrahedron Lett.* ***1992***, *33*, 6415.

[2032]Grieco, P.A.; Nunes, J.J.; Gaul, M.D. *J. Am. Chem. Soc.* ***1990***, *112*, 4595. See also, Braun, R.; Sauer, J. *Chem. Ber.* ***1986***, *119*, 1269; Grieco, P.A.; Handy, S.T.; Beck, J.P. *Tetrahedron Lett.* ***1994***, *35*, 2663. For the possibility of migration of terminal dienes prior to cycloaddition see Grieco, P.A.; Beck, J.P.; Handy, S.T.; Saito, N.; Daeuble, J.F. *Tetrahedron Lett.* ***1994***, *35*, 6783. An alternative to this catalyst is $LiNTf_2$ in ether, see Handy, S.T.; Grieco, P.A.; Mineur, C.; Ghosez, L. *Synlett* ***1995***, 565.

[2033]Augé, J.; Gil, R.; Kalsey, S.; Lubin-Germain, N. *Synlett* ***2000***, 877.

[2034]Pai, C.K.; Smith, M.B. *J. Org. Chem.* ***1995***, *60*, 3731; Smith, M.B.; Fay, J.N.; Son, Y.C. *Chem. Lett.* ***1992***, 2451.

[2035]Wijnen, J.W.; Engberts, J.B.F.N. *J. Org. Chem.* ***1997***, *62*, 2039.

[2036]Renslo, A.R.; Weinstein, R.D.; Tester, J.W.; Danheiser, R.L. *J. Org. Chem.* ***1997***, *62*, 4530; Oakes, R.S.; Heppenstall, T.J.; Shezad, N.; Clifford, A.A.; Rayner, C.M. *Chem. Commun.* ***1999***, 1459. For an asymmetric cycloaddition, see Fukuzawa, S.-i.; Metoki, K.; Esumi, S.-i. *Tetrahedron* ***2003***, *59*, 10445.

[2037]Harano, Y.; Sato, H.; Hirata, F. *J. Am. Chem. Soc.* ***2000***, *122*, 2289.

[2038]For a review, see Yli-Kauhaluoma, J. *Tetrahedron* ***2001***, *57*, 7053. For silica and alumina-modified Lewis acid catalysts, see Cativiela, C.; Figueras, F.; García, J.I.; Mayoral, J.A.; Pires, E.; Royo, A.J. *Tetrahedron Asymmetry* ***1993***, *4*, 621.

[2039]Eklund, L.; Axelsson, A.-K.; Nordahl, Å.; Carlson, R. *Acta Chem. Scand.* ***1993***, *47*, 581.

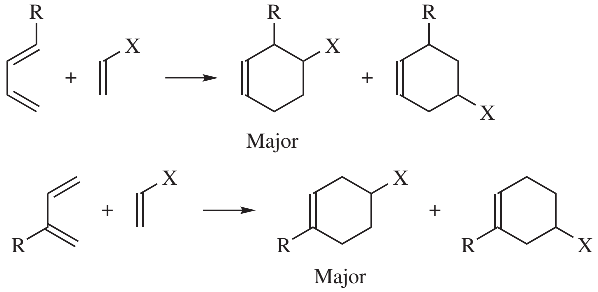
[2040]Pagni, R.M.; Kabalka, G.W.; Hondrogiannis, G.; Bains, S.; Anosike, P.; Kurt, R. *Tetrahedron* ***1993***, *49*, 6743.

[2041]In **bmim** BF_4 and ClO_4: 1-butyl-3-methylimidazolium tetrafluoroborate and perchlorate: Fischer, T.; Sethi, A.; Welton, T.; Woolf, J. *Tetrahedron Lett.* ***1999***, *40*, 793. In **chloroaluminates**: Lee, C.W. *Tetrahedron Lett.* ***1999***, *40*, 2461. In **phosphonium tosylates**: Ludley, P.; Karodia, N. *Tetrahedron Lett.* ***2001***, *42*, 2011. In **pyridinium salts**: Xiao, Y.; Malhotra, S.V. *Tetrahedron Lett.* ***2004***, *45*, 8339. In **HBuIm**, hydrogenbutylimidazolium tetrafluoroborate and **DiBuIm**, 1,3-dibutylimidazolium, tetrafluoroborate: Jaegar, D. A.; Tucker, C. E. *Tetrahedron Lett.* ***1989***, *30*, 1785.

[2042]Meracz, I.; Oh, T. *Tetrahedron Lett.* ***2003***, *44*, 6465.

[2043]Murali, R.; Scheeren, H.W. *Tetrahedron Lett.* ***1999***, *40*, 3029.

lead to 1,4- and 1,3-disubstituted products.



Although mixtures are often obtained, usually one predominates, the one indicated above, but selectivity depends on the nature of the substituents on both diene and alkene. This regioselectivity, in which the "ortho" or "para" product is favored over the "meta," has been explained by molecular-orbital considerations.[2044] When $X = NO_2$, regioselectivity to give the "ortho" or "para" product was very high at room temperature, and this method, combined with subsequent removal of the NO_2 (see **19-67**) has been used to perform regioselective Diels–Alder reactions.[2045]

The stereochemistry of the Diels–Alder reaction can be considered from several aspects:[2046]

1. With respect to the dienophile, the addition is stereospecifically syn, with very few exceptions.[2047] This means that groups that are cis in the alkene will be cis in the cyclohexene ring, (A—B and C—D) and groups that are trans in the alkene will be trans in the cyclohexene ring (A—D and C—B).

2. With respect to 1,4-disubstituted dienes, fewer cases have been investigated, but here too the reaction is stereospecific and syn. Thus, *trans*, *trans*-1,4-diphenylbutadiene gives *cis*-1,4-diphenylcyclohexene derivatives. This

[2044]Feuer, J.; Herndon, W.C.; Hall, L.H. *Tetrahedron* ***1968***, *24*, 2575; Inukai, T.; Sato, H.; Kojima, T. *Bull. Chem. Soc. Jpn.* ***1972***, *45*, 891; Epiotis, N.D. *J. Am. Chem. Soc.* ***1973***, *95*, 5624; Sustmann, R. *Pure Appl. Chem.* ***1974***, *40*, 569; Trost, B.M.; Vladuchick, W.C.; Bridges, A.J. *J. Am. Chem. Soc.* ***1980***, *102*, 3554; Alston, P.V.; Gordon, M.D.; Ottenbrite, R.M.; Cohen, T. *J. Org. Chem.* ***1983***, *48*, 5051; Kahn, S.D.; Pau, C.F.; Overman, L.E.; Hehre, W.J. *J. Am. Chem. Soc.* ***1986***, *108*, 7381.

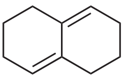
[2045]Danishefsky, S.; Hershenson, F.M. *J. Org. Chem.* ***1979***, *44*, 1180; Ono, N.; Miyake, H.; Kamimura, A.; Kaji, A. *J. Chem. Soc. Perkin Trans. 1*, ***1987***, 1929. For another method of controlling regioselectivity, see Kraus, G.A.; Liras, S. *Tetrahedron Lett.* ***1989***, *30*, 1907.

[2046]See Smith, M.B. *Organic Synthesis, 2nd* ed., McGraw-Hill, NY, ***2001***, pp. 933–940, 968–977; Bakalova, S.M.; Santos, A.G. *J. Org. Chem.* ***2004***, *69*, 8475.

[2047]For an exception, see Meier, H.; Eckes, H.; Niedermann, H.; Kolshorn, H. *Angew. Chem. Int. Ed.* ***1987***, *26*, 1046.

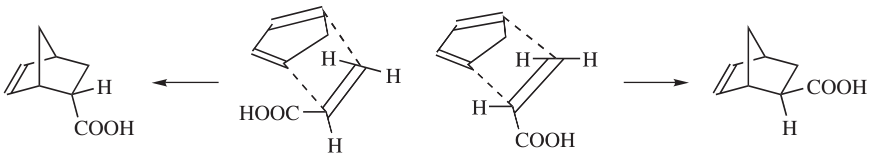
selectivity is predicted by disrotatory motion of the substituent in the transition state[2048] of the reaction (see **18-27**).

3. The diene must be in the cisoid conformation. If it is frozen into the transoid conformation, as in **198**, the reaction does not take place. The diene either must be frozen into the cisoid conformation or must be able to achieve it during the reaction.



198

4. When the diene is cyclic, there are two possible ways in which addition can occur if the dienophile is not symmetrical. The larger side of the dienophile may be under the ring (*endo addition*), or it may be the smaller side (*exo addition*):



Most of the time, the addition is predominantly endo; that is, the more bulky side of the alkene is under the ring, and this is probably true for open-chain dienes also.[2049] However, exceptions are known, and in many cases mixtures of exo and endo addition products are found.[2050] An imidazolidone catalyst was used to give a 1:1.3 mixture favoring the exo isomer in a reaction of conjugated aldehydes and cyclopentadiene.[2051] It has been argued that facial selectivity is not due to torsional angle decompression.[2052] Secondary orbital interactions.[2053] have been invoked, but this approach has been called into question.[2054] There has been a direct evaluation of such interactions, however.[2055] The endo/exo ratio can be influenced by the nature of the solvent.[2056]

[2048]Robiette, R.; Marchand-Brynaert, J.; Peeters, D. *J. Org. Chem.* ***2002***, *67*, 6823.

[2049]See, for example, Baldwin, J.E.; Reddy, V.P. *J. Org. Chem.* ***1989***, *54*, 5264. For a theoretical study for endo selectivity, see Imade, M.; Hirao, H.; Omoto, K.; Fujimoto, H. *J. Org. Chem.* ***1999***, *64*, 6697.

[2050]See, for example, Alder, K.; Günzl, W. *Chem. Ber.* ***1960***, *93*, 809; Stockmann, H. *J. Org. Chem.* ***1961***, *26*, 2025; Jones, D.W.; Wife, R.L. *J. Chem. Soc., Chem. Commun.* ***1973***, 421; Lindsay Smith, J.R.; Norman, R.O.C.; Stillings, M.R. *Tetrahedron* ***1978***, *34*, 1381; Mülle, P.; Bernardinelli, G.; Rodriguez, D.; Pfyffer, J.; Schaller, J. *Chimia* ***1987***, *41*, 244.

[2051]Ahrendt, K.A.; Borths, C.J.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2000***, *122*, 4243.

[2052]Hickey, E.R.; Paquette, L.A. *Tetrahedron Lett.* ***1994***, *35*, 2309, 2313.

[2053]Hoffmann, R.; Woodward, R.B. *J. Am. Chem. Soc.* ***1965***, *87*, 4388, 4389.

[2054]García, J.I.; Mayoral, J.A.; Salvatella, L. *Acc. Chem. Res.* ***2000***, *33*, 658.

[2055]Arrieta, A.; Cossío, F.P.; Lecea, B. *J. Org. Chem.* ***2001***, *66*, 6178.

[2056]Cainelli, G.; Galletti, P.; Giacomini, D.; Quintavalla, A. *Tetrahedron Lett.* ***2003***, *44*, 93.

5. As we have seen, the Diels–Alder reaction can be both stereoselective and regioselective.[2057] In some cases, the Diels–Alder reaction can be made enantioselective[2058] Solvent effects are important in such reactions.[2059] The role of reactant polarity on the course of the reaction has been examined.[2060] Most enantioselective Diels–Alder reactions have used a chiral dienophile (e.g., **199**) and an achiral diene,[2061] along with a Lewis acid catalyst (see below). In such cases, addition of the diene to the two faces[2062] of **199** takes place at different rates, and **200** and **201** are formed in different amounts.[2063] An achiral compound A can be converted to a chiral compound by a chemical reaction with a compound B that is enantiopure. After the reaction, the resulting diastereomers can be separated, providing enantiopure compounds, each with a bond between molecule A and chiral compound B (a chiral auxiliary). Common chiral auxiliaries include chiral carboxylic acids, alcohols, or sultams. In the case illustrated, hydrolysis of the product removes the chiral R group, making it a chiral auxiliary in this reaction. Asymmetric Diels–Alder reactions have also been carried out with achiral dienes and dienophiles, but with an optically active catalyst.[2064] Many chiral catalysts

[2057]Domingo, L.R.; Picher, M.T.; Andrés, J.; Safont, V.S. *J. Org. Chem.* ***1997***, *62*, 1775. Also see, Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY, ***2001***, pp. 933–940, 968–977. See Ujaque, G.; Norton, J.E.; Houk, K.N. *J. Org. Chem.* **2002**, *67*, 7179.

[2058]See Corey, E.J.; Sarshar, S.; Lee, D.-H. *J. Am. Chem. Soc.* ***1994***, *116*, 12089. For reviews, see Taschner, M.J. *Org. Synth: Theory Appl.* ***1989***, *1*, 1; Helmchen, G.; Karge, R.; Weetman, J. *Mod. Synth. Methods* ***1986***, *4*, 261; Paquette, L.A. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 3, Academic Press, NY, ***1983***, pp. 455–501; Oppolzer, W. *Angew. Chem. Int. Ed.* ***1984***, *23*, 876. See also, the list of references in Macaulay, J.B.; Fallis, A.G. *J. Am. Chem. Soc.* ***1990***, *112*, 1136.

[2059]Ruiz-López, M.F.; Assfeld, X.; García, J.I.; Mayoral, J.A.; Salvatella, L. *J. Am. Chem. Soc.* ***1993***, *115*, 8780.

[2060]Sustmann, R.; Sicking, W. *J. Am. Chem. Soc.* ***1996***, *118*, 12562.

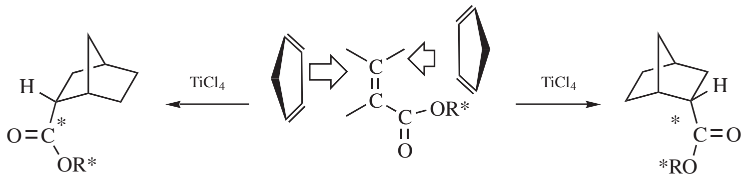
[2061]For the use of chiral dienes, see Fisher, M.J.; Hehre, W.J.; Kahn, S.D.; Overman, L.E. *J. Am. Chem. Soc.* ***1988***, *110*, 4625; Menezes, R.F.; Zezza, C.A.; Sheu, J.; Smith, M.B. *Tetrahedron Lett.* ***1989***, *30*, 3295; Charlton, J.L.; Plourde, G.L.; Penner, G.H. *Can. J. Chem.* ***1989***, *67*, 1010; Tripathy, R.; Carroll, P.J.; Thornton, E.R. *J. Am. Chem. Soc.* ***1990***, *112*, 6743; ***1991***, *113*, 7630; Rieger, R.; Breitmaier, E. *Synthesis* ***1990***, 697.

[2062]For a discussion of facial selectivity, see Xidos, J.D.; Poirier, R.A.; Pye, C.C.; Burnell, D.J. *J. Org. Chem.* ***1998***, *63*, 105.

[2063]Oppolzer, W.; Kurth, M.; Reichlin, D.; Moffatt, F.*Tetrahedron Lett.* ***1981***, *22*, 2545. See also, Walborsky, H.M.; Barash, L.; Davis, T.C. *Tetrahedron* ***1963***, *19*, 2333; Furuta, K.; Iwanaga, K.; Yamamoto, H. *Tetrahedron Lett.* ***1986***, *27*, 4507; Evans, D.A.; Chapman, K.T.; Bisaha, J. *J. Am. Chem. Soc.* ***1988***, *110*, 1238; Mattay, J.; Mertes, J.; Maas, G. *Chem. Ber.* ***1989***, *122*, 327; Alonso, I.; Carretero, J.C.; Garcia Ruano, J.L. *Tetrahedron Lett.* ***1989***, *30*, 3853; Tomioka, K.; Hamada, N.; Suenaga, T.; Koga, K. *J. Chem. Soc. Perkin Trans. 1*, ***1990***, 426; Cativiela, C.; López, P.; Mayoral, J.A. *Tetrahedron: Asymmetry* ***1990***, *1*, 61.

[2064]For a review, see Narasaka, K. *Synthesis* ***1991***, 1. For some recent examples, see Bir, G.; Kaufmann, D. *J. Organomet. Chem.* ***1990***, *390*, 1; Rebiere, F.; Riant, O.; Kagan, H.B. *Tetrahedron: Asymmetry* ***1990***, *1*, 199; Terada, M.; Mikami, K.; Nakai, T. *Tetrahedron Lett.* ***1991***, *32*, 935; Corey, E.J.; Imai, N.; Zhang, H. *J. Am. Chem. Soc.* ***1991***, *113*, 728; Narasaka, K.; Tanaka, H.; Kanai, F. *Bull. Chem. Soc. Jpn.* ***1991***, *64*, 387; Hawkins, J.M.; Loren, S. *J. Am. Chem. Soc.* ***1991***, *113*, 7794; Evans, D.A.; Barnes, D.M.; Johnson, J.S.; Lectka, T.; von Matt, P.; Miller, S.J.; Murry, J.A.; Norcross, R.D.; Shaughnessy, E.A.; Campos, K.R. *J. Am. Chem. Soc.* ***1999***, *121*, 7582.

have been developed.[2065] In many cases, asymmetric Lewis acids form a chiral complex with the dienophile.[2066]



200 199 201

R = (+) or (–) phenylmenthyl

Many interesting compounds can be prepared by the Diels–Alder reaction,[2067] some of which would be hard to make in any other way. Azelines react with dienes to form cyclohexene derivatives fused to a four-membered ring amine (azetidine).[2068] The C_{60}-Fullerenes undergo Diels–Alder reactions,[2069] and the reaction is reversible.[2070] Bicyclic sultams can be prepared by an intramolecular Diels–Alder reaction.[2071] Polycyclic lactones can be prepared.[2072]Aromatic compounds can behave as dienes,[2073] but benzene is very unreactive toward dienophiles,[2074] and very few dienophiles (one of them is benzyne) have been reported to give Diels–Alder adducts with it.[2075] Naphthalene and phenanthrene are also quite resistant, although naphthalene has given Diels–Alder addition at high pressures.[2076] However, anthracene and other compounds with at least three linear benzene rings give Diels–Alder reactions readily. The interesting compound triptycene can be prepared by a Diels–Alder

[2065]For a review, see Corey, E.J. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1651. See also, Doyle, M.P.; Phillips, I.M.; Hu, W. *J. Am. Chem. Soc.* ***2001***, *123*, 5366; Owens, T.D.; Hollander, F.J.; Oliver A.G.; Ellman, J.A. *J. Am. Chem. Soc.* ***2001***, *123*, 1539; Faller, J.W.; Grimmond, B.J.; D'Alliessi, D.G. *J. Am. Chem. Soc.* ***2001***, *123*, 2525; Bolm, C.; Simić, O. *J. Am. Chem. Soc.* ***2001***, *123*, 3830; Fukuzawa, S.; Komuro, Y.; Nakano, N.; Obara, S. *Tetrahedron Lett.* ***2003***, *44*, 3671.

[2066]Hawkins, J.M.; Loren, S.; Nambu, M. *J. Am. Chem Soc.* ***1994***, *116*, 1657. See Sibi, M.P.; Venkatraman, L.; Liu, M.; Jaspersé, C.P. *J. Am. Chem. Soc.* ***2001***, *123*, 8444.

[2067]For a review of this reaction in synthesis, see Nicolaou, K.C.; Snyder, S.A.; Montagnon, T.; Vassilkogiannakis, G. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1669.

[2068]Dave, P.R.; Duddu, R.; Surapaneni, R.; Gilardi, R. *Tetrahedron Lett.* ***1999***, *40*, 443.

[2069]Murata, Y.; Kato, N.; Fujiwara, K.; Komatsu, K. *J. Org. Chem.* ***1999***, *64*, 3483.

[2070]Wang, G.-W.; Saunders, M.; Cross, R.J. *J. Am. Chem. Soc.* ***2001***, *123*, 256.

[2071]Greig, I.R.; Tozer, M.J.; Wright, P.T. *Org. Lett.* ***2001***, *3*, 369.

[2072]Vlaar, M.J.M.; Lor, M.H.; Ehlers, A.W.; Schakel, M.; Lutz, M.; Spek, A.L.; Lammertsma, K. *J. Org. Chem.* ***2002***, *67*, 2485.

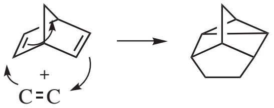
[2073]For a review, see Wagner-Jauregg, T. *Synthesis* ***1980***, 165, 769. See also, Balaban, A.T.; Biermann, D.; Schmidt, W. *Nouv. J. Chim.* ***1985***, *9*, 443.

[2074]However, see Chordia, M.D.; Smith, P.L.; Meiere, S.H.; Sabat, M.; Harman, W.D. *J. Am. Chem. Soc.* ***2001***, *123*, 10756.

[2075]Miller, R.G.; Stiles, M. *J. Am. Chem. Soc.* ***1963***, *85*, 1798; Meyerson, S.; Fields, E.K. *Chem. Ind. (London)* ***1966***, 1230; Ciganek, E. *Tetrahedron Lett.* ***1967***, 3321; Friedman, L. *J. Am. Chem. Soc.* ***1967***, *89*, 3071; Liu, R.S.H.; Krespan, C.G. *J. Org. Chem.* ***1969***, *34*, 1271.

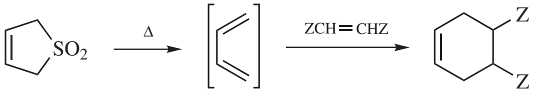
[2076]Plieninger, H.; Wild, D.; Westphal, J. *Tetrahedron* ***1969***, *25*, 5561.

reaction between benzyne and anthracene:[2077] For both all-carbon and hetero systems, the "diene" can be a conjugated enyne. If the geometry of the molecule is suitable, the diene can even be nonconjugated, for example,[2078]



This last reaction is known as the *homo–Diels–Alder reaction*. A similar reaction has been reported with alkynes, using a mixture of a cobalt complex, ZnI_2 and tetrabutylammonium borohydride as catalysts.[2079]

Competing reactions are polymerization of the diene or dienophile, or both, and [1,2]-cycloaddition (**15-63**). Intramolecular versions of the Diels–Alder reaction are well-known, and this is a powerful method for the synthesis of mono- and polycyclic compounds.[2080] There are many examples and variations. Internal Diels–Alder reactions can be viewed as linking the diene and alkene by a tether, usually of carbon atoms. If the tether is replaced by functional groups that allow the selectivity inherent to the intramolecular cycloaddition, but can be cleaved afterward, a powerful modification is available. Indeed, such tethered cycloaddition reactions are increasingly common. After cycloaddition, the tether can be cleaved to give a functionalized cyclohexene derivative. Such tethered reactions allow enhancement of stereoselectivity[2081] and sometimes reactivity, relative to an untethered reaction, giving an indirect method for enhancing those parameters. Tethers or linkages include C—O—SiR_2—C[2082] or a C—O—SiR_2—O—C,[2083] or hydroxamides.[2084] Transient tethers can be used, as in the reaction of a diene having an allylic alcohol unit in a reaction is allyl alcohol, with $AlMe_3$, to give the cycloadduct with good selectivity.[2085]



3-Sulfolene

[2077]Wittig, G.; Niethammer, K. *Chem. Ber.* ***1960***, *93*, 944; Wittig, G.; Härle, H.; Knauss, E.; Niethammer, K. *Chem. Ber.* ***1960***, *93*, 951. For a review of triptycene, see Skvarchenko, V.R.; Shalaev, V.K.; Klabunovskii, E.I. *Russ. Chem. Rev.* ***1974***, *43*, 951.

[2078]See, for example, Fickes, G.N.; Metz, T.E. *J. Org. Chem.* ***1978***, *43*, 4057; Paquette, L.A.; Kesselmayer, M.A.; Künzer, H. *J. Org. Chem.* ***1988***, *53*, 5183.

[2079]Hilt, G.; du Mesnil, F.-X. *Tetrahedron Lett.* ***2000***, *41*, 6757.

[2080]Carlson, R.G. *Ann. Rep. Med. Chem.* ***1974***, *9*, 270; Oppolzer, W. *Angew. Chem. Int. Ed.* ***1977***, *16*, 10 (see pp. 10–18); Brieger, G.; Bennett, J.N. *Chem. Rev.* ***1980***, *80*, 63 (see p. 67); Fallis, A.G. *Can. J. Chem.* ***1984***, *62*, 183; Smith, M.B. *Org. Prep. Proceed. Int.* ***1990***, *22*, 315.

[2081]For a discussion of the origins of stereoselectivity in intramolecular tethered reactions, see Tantillo, D.J.; Houk, K.N.; Jung, M.E. *J. Org. Chem.* ***2001***, *66*, 1938.

[2082]Stork, G.; Chan, T.Y.; Breault, G.A. *J. Am. Chem. Soc.* ***1992***, *114*, 7578.

[2083]Craig, D.; Reader, J.C. *Tetrahedron Lett.* ***1992***, *33*, 6165.

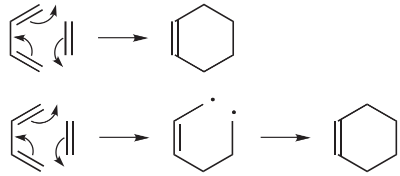
[2084]Ishikawa, T.; Senzaki, M.; Kadoya, R.; Morimoto, T.; Miyake, N.; Izawa, M.; Saito, S. Kobayashi, H. *J. Am. Chem. Soc.* ***2001***, *123*, 4607.

[2085]Bertozzi, F.; Olsson, R.; Frejd, T. *Org. Lett.* ***2000***, *2*, 1283.

The Diels–Alder reaction is usually reversible, although the retro reaction typically occurs at significantly higher temperatures than the forward reaction. However, the reversibility of the reaction and has been used to protect double bonds.[2086] A convenient substitute for butadiene in the Diels–Alder reaction is the compound 3-sulfolene since the latter is a solid which is easy to handle while the former is gas.[2087] Butadiene is generated *in situ* by a reverse Diels–Alder reaction (see **17-20**).

Mechanism *a*

Mechanism *b*



There are, broadly speaking, three possible mechanisms that have been considered for the uncatalyzed Diels-Alder reaction.[2088] In mechanism *a* there is a cyclic six-centered transition state and no intermediate. The reaction is concerted and occurs in one step. In mechanism *b*, one end of the diene fastens to one end of the dienophile first to give a diradical, and then, in a second step, the other ends become fastened.[2089] A diradical formed in this manner must be a singlet; that is, the two unpaired electrons must have opposite spins, by an argument similar to that outlined on p. 277. The third mechanism (*c*, not shown) is similar to mechanism *b*, but the initial bond and the subsequent bond are formed by movements of electron pairs and the intermediate is a diion. There have been many mechanistic investigations of the Diels–Alder reaction. The bulk of the evidence suggests that most Diels–Alder reactions take place by the one-step cyclic mechanism *a*,[2090] although it is possible

[2086]For reviews of the reverse Diels–Alder reaction, see Ichihara, A. *Synthesis* ***1987***, 207; Lasne, M.; Ripoll, J.L. *Synthesis* ***1985***, 121; Ripoll, J.L.; Rouessac, A.; Rouessac, F. *Tetrahedron* ***1978***, *34*, 19; Brown, R.F.C. *Pyrolytic Methods in Organic Chemistry*, Academic Press, NY, ***1980***, pp. 259–281; Kwart, H.; King, K. *Chem. Rev.* ***1968***, *68*, 415.

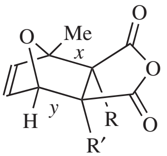
[2087]Sample Jr., T.E.; Hatch, L.F. *Org. Synth.* ***VI***, 454. For a review, see Chou, T.; Tso, H. *Org. Prep. Proced. Int.* ***1989***, *21*, 257.

[2088]For reviews, see Sauer, J.; Sustmann, R. *Angew. Chem. Int. Ed.* ***1980***, *19*, 779; Houk, K.N. *Top. Curr. Chem.* ***1979***, *79*, 1; Seltzer, S. *Adv. Alicyclic Chem.* ***1968***, *2*, 1; Ref. 1981. For a review of the application of quantum-chemical methods to the study of this reaction, see Babichev, S.S.; Kovtunenko, V.A.; Voitenko, Z.V.; Tyltin, A.K. *Russ. Chem. Rev.* ***1988***, *57*, 397. For a discussion of synchronous versus nonsynchronous mechanisms, see Beno, B.R.; Houk, K.N.; Singleton, D.A. *J. Am. Chem. Soc.* ***1996***, *118*, 9984; Singleton, D.A.; Schulmeier, B.E.; Hang, C.; Thomas, A.A.; Leung, S.-W.; Merrigan, S.R. *Tetrahedron* ***2001***, *57*, 5149. Also see, Li, Y.; Houk, K.N. *J. Am. Chem. Soc.* ***1993***, *115*, 7478 for the dimerization mechanism of 1,3-butadiene.

[2089]For a discussion of a diradical stepwise versus concerted mechanism for reactions with chalcogens, see Orlova, G.; Goddard, J.D. *J. Org. Chem.* ***2001***, *66*, 4026.

[2090]For a contrary view, see Dewar, M.J.S.; Olivella, S.; Stewart, J.J.P. *J. Am. Chem. Soc.* ***1986***, *108*, 5771. For arguments against this view, see Houk, K.N.; Lin, Y.; Brown, F.K. *J. Am. Chem. Soc.* ***1986***, *108*, 554; Hancock, R.A.; Wood, Jr., B.F. *J. Chem. Soc., Chem. Commun.* ***1988***, 351; Gajewski, J.J.; Peterson, K.B.; Kagel, J.R.; Huang, Y.C.J. *J. Am. Chem. Soc.* ***1989***, *111*, 9078.

that a diradical[2091] or even a diion[2092] mechanism may be taking place in some cases. Radical cation Diels–Alder reactions have been considered.[2093] The main evidence in support of mechanism *a* is as follows: (*1*) The reaction is stereospecific in both the diene and dienophile. A completely free diradical or diion probably would not be able to retain its configuration. (*2*) In general, the rates of Diels–Alder reactions depend very little on the nature of the solvent. This would rule out a diion intermediate because polar solvents increase the rates of reactions that develop charges in the transition state. (*3*) It was shown that, in the decomposition of **202**, the isotope effect k_I/k_{II} was equal to 1.00 within experimental error.[2094] If bond *x* were to break before bond *y*, there



I: R = H, R′ = D

II: R = D, R′ = H

202

should surely be a secondary isotope effect. This result strongly indicates that the bond breaking of *x* and *y* is simultaneous. This is the reverse of a Diels–Alder reaction, and by the principle of microscopic reversibility, the mechanism of the forward reaction should involve simultaneous formation of bonds *x* and *y*. Subsequently, a similar experiment was carried out on the forward reaction[2095] and the result was the same. There is also other evidence for mechanism *a*.[2096] However, the fact that the mechanism is concerted does not necessarily mean that it is synchronous.[2097] In the transition state of a synchronous reaction both new σ bonds would be formed to the same extent, but a Diels–Alder reaction with non-symmetrical components might very well be non-synchronous;[2098] that is, it could have a transition state in which one

[2091]See, for example, Bartlett, P.D.; Mallet, J.J. *J. Am. Chem. Soc.* ***1976***, *98*, 143; Jenner, G.; Rimmelin, J. *Tetrahedron Lett.* ***1980***, *21*, 3039; Van Mele, B.; Huybrechts, G. *Int. J. Chem. Kinet.* ***1987***, *19*, 363; ***1989***, *21*, 967.

[2092]For a reported example, see Gassman, P.G.; Gorman, D.B. *J. Am. Chem. Soc.* ***1990***, *112*, 8624.

[2093]Haberl, U.; Wiest, O.; Steckhan, E. *J. Am. Chem. Soc.* ***1999***, *121*, 6730.

[2094]Seltzer, S. *J. Am. Chem. Soc.* ***1963***, *85*, 1360; ***1965***, *87*, 1534. For a review of isotope effect studies of Diels–Alder and other pericyclic reactions, see Gajewski, J.J. *Isot. Org. Chem.* ***1987***, *7*, 115–176.

[2095]Van Sickle, D.E.; Rodin, J.O. *J. Am. Chem. Soc.* ***1964***, *86*, 3091.

[2096]See, for example, Dewar, M.J.S.; Pyron R.S. *J. Am. Chem. Soc.* ***1970***, *92*, 3098; Brun, C.; Jenner, G. *Tetrahedron* ***1972***, *28*, 3113; Doering, W. von E.; Franck-Neumann, M.; Hasselmann, D.; Kaye, R.L. *J. Am. Chem. Soc.* ***1972***, *94*, 3833; McCabe, J.R.; Eckert, C.A. *Acc. Chem. Res.* ***1974***, *7*, 251; Berson, J.A.; Dervan, P.B.; Malherbe, R.; Jenkins, J.A. *J. Am. Chem. Soc.* ***1976***, *98*, 5937; Rücker, C.; Lang, D.; Sauer, J.; Friege, H.; Sustmann, R. *Chem. Ber.* ***1980***, *113*, 1663; Tolbert, L.M.; Ali, M.B. *J. Am. Chem. Soc.* ***1981***, *103*, 2104.

[2097]For an example of a study of a reaction that is concerted but asynchronous, see Avalos, M.; Babiano, R.; Clemente, F.R.; Cintas, P.; Gordillo, R.; Jiménez, J.L.; Palacios, J.C. *J. Org. Chem.* ***2000***, *65*, 8251

[2098]Woodward, R.B.; Katz, T.J. *Tetrahedron* ***1959***, *5*, 70; Liu, M.T.H.; Schmidt, C. *Tetrahedron* ***1971***, *27*, 5289; Dewar, M.J.S.; Pyron R.S. *J. Am. Chem. Soc.* ***1970***, *92*, 3098; Papadopoulos, M.; Jenner, G. *Tetrahedron Lett.* ***1982***, *23*, 1889; Houk, K.N.; Loncharich, R.J.; Blake, J.F.; Jorgensen, W.L. *J. Am. Chem. Soc.* ***1989***, *111*, 9172; Lehd, M.; Jensen, F. *J. Org. Chem.* ***1990***, *55*, 1034.

bond has been formed to a greater degree than the other.[2099] A biradical mechanism has been proposed for some Diels–Alder reactions.[2100]

In another aspect of the mechanism, the effects of electron-donating and electron-withdrawing substituents (p. 1196) indicate that the diene is behaving as a nucleophile and the dienophile as an electrophile. However, this can be reversed. Perchlorocyclopentadiene reacts better with cyclopentene than with maleic anhydride and not at all with tetracyanoethylene, although the latter is normally the most reactive dienophile known. It is apparent, then, that this diene is the electrophile in its Diels–Alder reactions.[2101] Reactions of this type are said to proceed with *inverse electron demand*.[2102]

We have emphasized that the Diels–Alder reaction generally takes place rapidly and conveniently. In sharp contrast, the apparently similar dimerization of alkenes to cyclobutanes (**15-63**) gives very poor results in most cases, except when photochemically induced. Woodward and Hoffmann, and Fukui have shown that these contrasting results can be explained by the *principle of conservation of orbital symmetry*,[2103] which predicts that certain reactions are allowed and others forbidden. The orbital-symmetry rules (also called the Woodward–Hoffmann rules)[2104] apply *only to concerted reactions*, for example, mechanism *a*, and are based on the principle that reactions take place in such a way as to maintain maximum bonding throughout the course of the reaction. There are several ways of applying the orbital-symmetry principle to cycloaddition reactions, three

[2099]For a theoretical investigation of the ionic Diels–Alder reaction, see dePascual-Teresa, B.; Houk, K.N. *Tetrahedron Lett.* ***1996***, *37*, 1759. For a discussion of the origin of synchronicity in the transition state of polar Diels–Alder reactions, see Domingo, L.R.; Aurell, M.J.; Pérez, P.; Contreras, R. *J. Org. Chem.* ***2003***, *68*, 3884.

[2100]de Echagüen, C.O.; Ortuño, R.M. *Tetrahedron Lett.* ***1995***, *36*, 749. See Li, Y.; Padias, A.B.; Hall Jr., H.K. *J. Org. Chem.* ***1993***, *58*, 7049 for a discussion of diradicals in concerted Diels–Alder reactions.

[2101]Sauer, J.; Wiest, H. *Angew. Chem. Int. Ed.* ***1962***, *1*, 269.

[2102]For a review, see Boger, D.L.; Patel, M. *Prog. Heterocycl. Chem.* ***1989***, *1*, 30. Also see, Pugnaud, S.; Masure, D.; Hallé, J.-C.; Chaquin, P. *J. Org. Chem,.* ***1997***, *62*, 8687; Wan, Z.-K.; Snyder, J.K. *Tetrahedron Lett.* ***1998***, *39*, 2487; Markó, I.E.; Evans, G.R. *Tetrahedron Lett.* ***1994***, *35*, 2767, 2771.

[2103]For monographs, see Fleming, I. *Pericyclic Reactions*, Oxford University Press, Oxford, ***1999***, pp. 31–56; Gilchrist, T.L.; Storr, R.C. *Organic Reactions and Orbital Symmetry*, 2nd ed., Cambridge University Press, Cambridge, ***1979***; Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*, Wiley, NY, ***1976***; Woodward, R.B.; Hoffmann, R. *The Conservation of Orbital Symmetry*, Academic Press, NY, ***1970*** [the text of this book also appears in *Angew. Chem. Int. Ed.* ***1969***, *8*, 781; Lehr, R.E.; Marchand, A.P. *Orbital Symmetry*, Academic Press, NY, ***1972***. For reviews, see Pearson, R.G. *J. Chem. Educ.* ***1981***, *58*, 753; in Klopman, G. *Chemical Reactivity and Reaction Paths*, Wiley, NY, ***1974***, the articles by Fujimoto, H.; Fukui, K. pp. 23–54, Klopman, G. pp. 55–165, Herndon, W.C.; Feuer, J.; Giles, W.B.; Otteson, D.; Silber, E. pp. 275–299; Michl, J. pp. 301–338; Simonetta, M. *Top. Curr. Chem.* ***1973***, *42*, 1; Houk, K.N. *Surv. Prog. Chem.* ***1973***, *6*, 113; Vollmer, J.J.; Servis, K.L. *J. Chem. Educ.* ***1970***, *47*, 491; Gill, G.B. *Essays Chem.* ***1970***, *1*, 43; *Q. Rev. Chem. Soc.* ***1968***, *22*, 338; Seebach, D. *Fortschr. Chem. Forsch.* ***1969***, *11*, 177; Miller, S.I. *Adv. Phys. Org. Chem.* ***1968***, *6*, 185; Miller, S.I. *Bull. Soc. Chim. Fr.* ***1966***, 4031. For a review of applications to inorganic chemistry, see Pearson, R.G. *Top Curr. Chem.* ***1973***, *41*, 75.

[2104]Chattaraj, P.K.; Fuentealba, P.; Gómez, B.; Contreras, R. *J. Am. Chem. Soc.* ***2000***, *122*, 348.

of which are used more frequently than others.[2105] Of these three, we will discuss two: the frontier-orbital method and the Möbius–Hückel method. The third, called the correlation diagram method,[2106] is less convenient to apply than the other two.

The Frontier Orbital Method[2107]

As applied to cycloaddition reactions the rule is that *reactions are allowed only when all overlaps between the highest occupied molecular orbital* (HOMO) *of one reactant and the lowest unoccupied molecular orbital* (LUMO) *of the other are such that a positive lobe overlaps only with another positive lobe and a negative lobe only with another negative lobe*. We may recall that monoalkenes have two π molecular orbitals (p. 10) and that conjugated dienes have four (p. 38), as shown in Fig. 15.2. A concerted cyclization of two monoalkenes (a [2 + 2]-reaction) is not allowed because it would require that a positive lobe overlap with a negative lobe (Fig. 15.3). On the other hand, the Diels–Alder reaction (a [4 + 2]-reaction) is allowed, whether considered from either direction (Fig. 15.4).

These considerations are reversed when the ring closures are photochemically induced since in such cases an electron is promoted to a vacant orbital before the reaction occurs. Obviously, the [2 + 2] reaction is now allowed (Fig. 15.5) and the [4 + 2]-reaction disallowed. The reverse reactions follow the same rules, by the principle of microscopic reversibility. In fact, Diels–Alder adducts are usually cleaved quite readily, while cyclobutanes, despite the additional strain, require more strenuous conditions.

[2105]For other approaches, see Epiotis, N.D. *Theory of Organic Reactions*, Springer, NY, ***1978***; Epiotis, N.D.; Shaik, S. *J. Am. Chem. Soc.* ***1978***, *100*, 1, 9; Halevi, E.A. *Angew. Chem. Int. Ed.* ***1976***, *15*, 593; Shen, K. *J. Chem. Educ.* ***1973***, *50*, 238; Salem, L. *J. Am. Chem. Soc.* ***1968***, *90*, 543, 553; Trindle, C. *J. Am. Chem. Soc.* ***1970***, *92*, 3251, 3255; Mulder, J.J.C.; Oosterhoff, L.J. *Chem. Commun.* ***1970***, 305, 307; Goddard III, W.A. *J. Am. Chem. Soc.* ***1970***, *92*, 7520; ***1972***, *94*, 793; Herndon, W.C. *Chem. Rev.* ***1972***, *72*, 157; Perrin, C.L. *Chem. Br.* ***1972***, *8*, 163; Langlet, J.; Malrieu, J. *J. Am. Chem. Soc.* ***1972***, *94*, 7254; Pearson, R.G. *J. Am. Chem. Soc.* ***1972***, *94*, 8287; Mathieu, J. *Bull. Soc. Chim. Fr.* ***1973***, 807; Silver, D.M.; Karplus, M. *J. Am. Chem. Soc.* ***1975***, *97*, 2645; Day, A.C. *J. Am. Chem. Soc.* ***1975***, *97*, 2431; Mok, K.; Nye, M.J. *J. Chem. Soc. Perkin Trans. 2*, ***1975***, 1810; Ponec, R. *Collect. Czech. Chem. Commun.* ***1984***, *49*, 455; ***1985***, *50*, 1121; Hua-ming, Z.; De-xiang, W. *Tetrahedron* ***1986***, *42*, 515; Bernardi, F.; Olivucci, M.; Robb, M.A. *Res. Chem. Intermed.* ***1989***, *12*, 217; *Acc. Chem. Res.* ***1990***, *23*, 405.

[2106]For excellent discussions of this method, see Woodward, R.B.; Hoffmann, R. *The Conservation of Orbital Symmetry*, Academic Press, NY, ***1970***; *Angew. Chem. Int. Ed.* ***1969***, *8*, 781; Jones, R.A.Y. *Physical and Mechanistic Organic Chemistry* 2nd ed., Cambridge University Press, Cambridge, ***1984***, pp. 352–366; Klumpp, G.W. *Reactivity in Organic Chemistry*, Wiley, NY, ***1982***, pp. 378–389; Yates, K. *Hückel Molecular Orbital Theory*, Academic Press, NY, ***1978***, pp. 263–276.

[2107]Fukui, K.; Fujimoto, H. *Bull. Chem. Soc. Jpn.* ***1967***, *40*, 2018; ***1969***, *42*, 3399; Fukui, K. *Fortschr. Chem. Forsch.* ***1970***, *15*, 1; *Acc. Chem. Res.* ***1971***, *4*, 57; Houk, K.N. *Acc. Chem. Res.* ***1975***, *8*, 361. See also, Chu, S. *Tetrahedron* ***1978***, *34*, 645. For a monograph on Frontier Orbitals see Fleming, I. *Pericyclic Reactions*, Oxford University Press, Oxford, **1999**. For reviews, see Fukui, K. *Angew. Chem. Int. Ed.* ***1982***, *21*, 801; Houk, K.N., in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 2; Academic Press, NY, ***1977***, pp. 181–271.

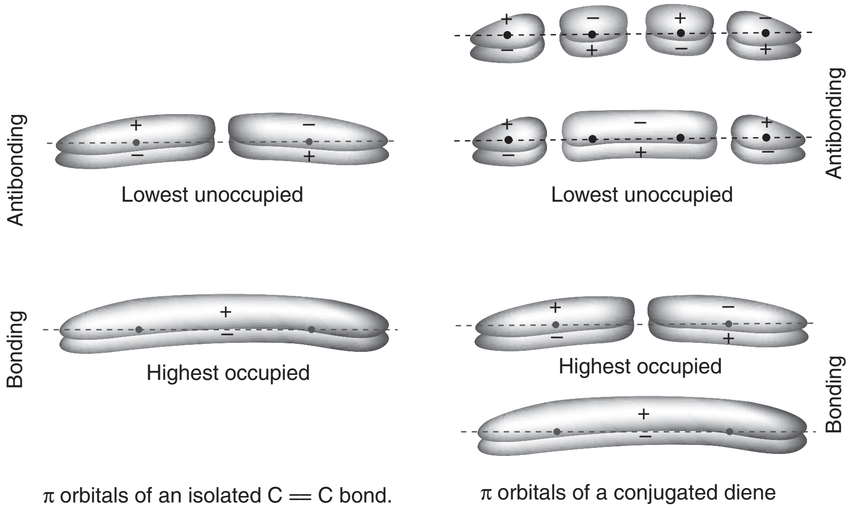


Fig. 15.2. Schematic drawings of the π-orbitals of an isolated C=C bnd and a conjugated diene.

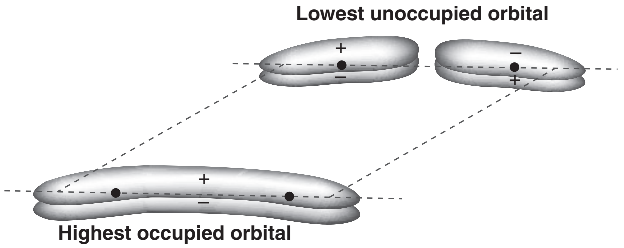


Fig. 15.3. Overlap of orbitals in a thermal [2 + 2]-cycloaddition.

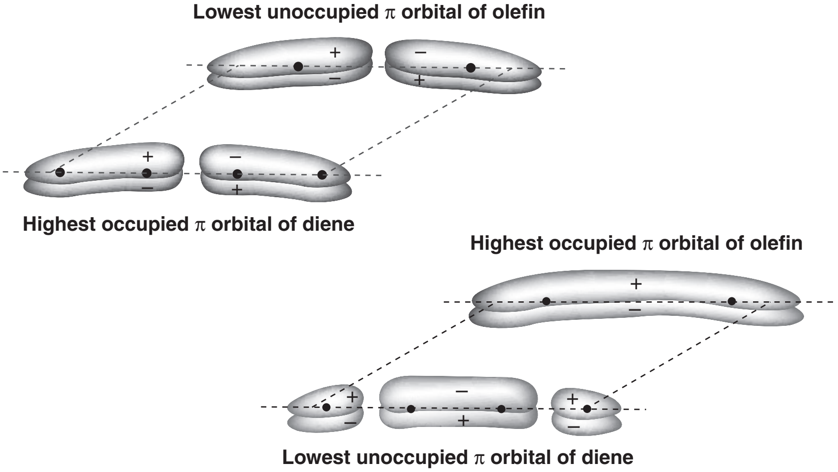


Fig. 15.4. Two ways for orbitals to overlap in a thermal [4 + 2]-cycloaddition.

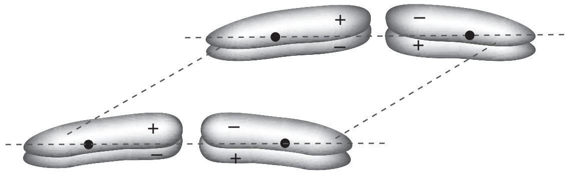


Fig. 15.5. Overlap of orbitals in a photochemical [2 + 2]-cycloaddition.

The Möbius–Hückel Method[2108]

In this method, the orbital symmetry rules are related to the Hückel aromaticity rule discussed in Chapter 2.[2109] Hückel's rule, which states that a cyclic system of electrons is aromatic (hence, stable) when it consists of $4n + 2$ electrons, applies of course to molecules in their ground states. In applying the orbital symmetry principle we are not concerned with ground states, but with transition states. In the present method, we do not examine the molecular orbitals themselves, but rather the *p* orbitals before they overlap to form the molecular orbitals. Such a set of *p* orbitals is called a *basis set* (Fig. 15.6). In investigating the possibility of a concerted reaction, we put the basis sets into the position they would occupy in the transition state. Figure 15.7 shows this for both the [2 + 2] and the [4 + 2] ring closures. What we look for are *sign inversions*. In Fig. 15.7, we can see that there are no sign inversions in either case. That is, the dashed line connects only lobes with a minus sign. Systems with *zero or an even number* of sign inversions are called *Hückel systems*. Because they have no sign inversions, both of these systems are Hückel systems. Systems with *an odd number* of sign

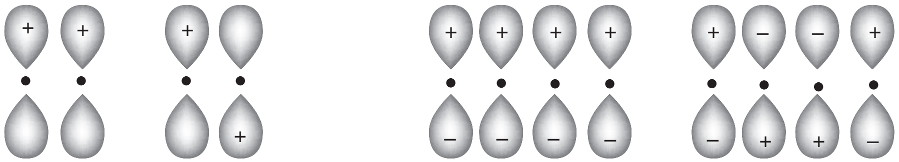


Fig. 15.6. Some basis sets.

[2108]Zimmerman, H.E., in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, ***1977***, pp. 53–107; *Acc. Chem. Res.* ***1971***, *4*, 272; *J. Am. Chem. Soc.* ***1966***, *88*, 1564, 1566; Dewar, M.J.S. *Angew. Chem. Int. Ed.* ***1971***, *10*, 761; Jefford, C.W.; Burger, U. *Chimia*, ***1971***, *25*, 297; Herndon, W.C. *J. Chem. Educ.* ***1981***, *58*, 371.

[2109]See Morao, I.; Cossío, F.P. *J. Org. Chem.* ***1999***, *64*, 1868.

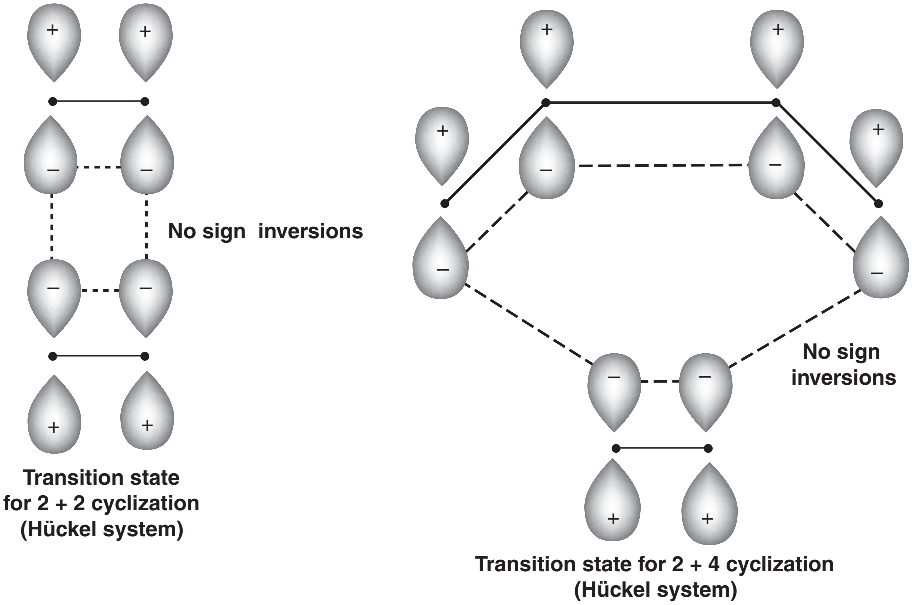


Fig. 15.7. Transition states illustrating Hückel–Möbius rules for cycloaddition reactions.

inversions are called *Möbius systems* (because of the similarity to the Möbius strip, which is a mathematical surface, shown in Fig. 15.8). Möbius systems do not enter into either of these reactions, but an example of such a system is shown on p. $$$.

The rule may then be stated: *A thermal pericyclic reaction involving a Hückel system is allowed only if the total number of electrons is* $4n + 2$. *A thermal pericyclic reaction involving a Möbius system is allowed only if the total number of electrons is* $4n$. For photochemical reactions these rules are reversed. Since both the [4 + 2]- and [2 + 2]-cycloadditions are Hückel systems, the Möbius–Hückel method predicts that the [4 + 2]-reaction, with 6 electrons, is thermally allowed,

Fig. 15.8. A Möbius strip. Such a strip is easily constructed by twisting a thin strip of paper 180° and fastening the ends together.

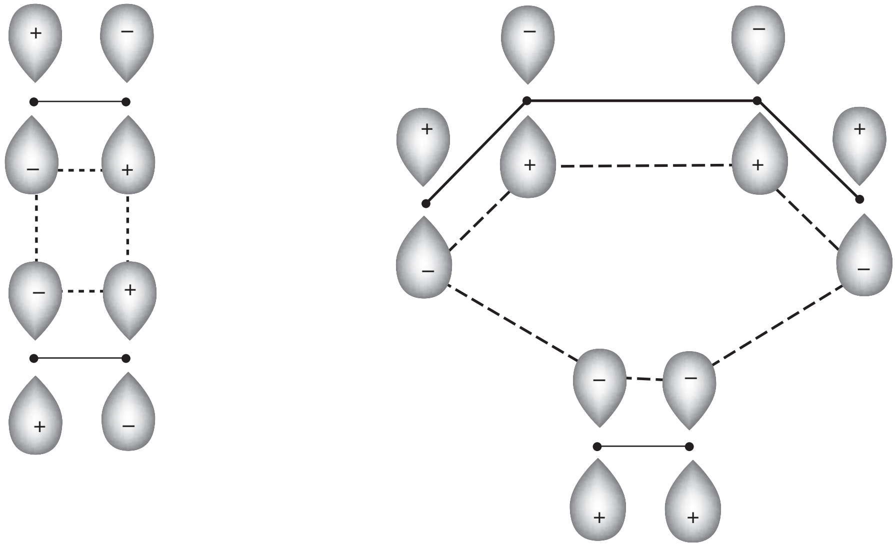


Fig. 15.9. Transition states of [2 + 2]- and [4 + 2]-cyclizations involing other basis sets.

but the [2 + 2]-reaction is not. One the other hand, the [2 + 2]-reaction is allowed photochemically, while the [4 + 2]-reaction is forbidden.

Note that both the [2 + 2] and [4 + 2] transition states are Hückel systems no matter what basis sets we chose. For example, Fig. 15.9 shows other basis sets we might have chosen. In every case there will be zero or an even number of sign inversions.

Thus, the frontier orbital and Hückel–Möbius methods (and the correlation-diagram method as well) lead to the same conclusions: thermal [4 + 2]-cycloadditions and photochemical [2 + 2]-cycloadditions (and the reverse ring openings) are allowed, while photochemical [4 + 2] and thermal [2 + 2] ring closings (and openings) are forbidden.

Application of the same procedures to other ring closures shows that [4 + 4] and [2 + 6] ring closures and openings require photochemical induction while the [4 + 6]- and [2 + 8]-reactions can take place only thermally (see **15-53**). In general, cycloaddition reactions allowed thermally are those with $4n + 2$ electrons, while those allowed photochemically have $4n$ electrons.

It must be emphasized once again that the rules apply only to cycloaddition reactions that take place by cyclic mechanisms, that is, where two σ bonds are formed (or broken) at about the same time.[2110] The rule does not apply to cases where one bond is clearly formed (or broken) before the other. It must further be emphasized that the fact that the thermal Diels–Alder reaction (mechanism *a*) is allowed by the principle of conservation of orbital symmetry does not constitute

[2110]For a discussion of concertedness in these reactions see Lehr, R.E.; Marchand, A.P., in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 1, Academic Press, NY, ***1977***, pp. 1–51.

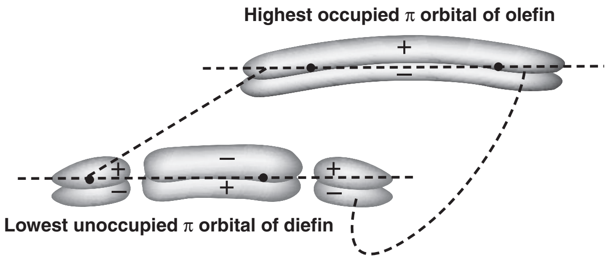


Fig. 15.10. Overlap of orbitals in an antarafacial thermal [4 + 2]-cycloaddition.

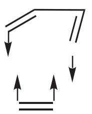
proof that any given Diels–Alder reaction proceeds by this mechanism. The principle merely says the mechanism is allowed, not that it must go by this pathway. However, the principle does say that thermal [2 + 2]-cycloadditions in which the molecules assume a face-to-face geometry cannot[2111] take place by a cyclic mechanism because their activation energies would be too high (however, see below). As we will see (**15-62**), such reactions largely occur by two-step mechanisms. Similarly, [4 + 2]-photochemical cycloadditions are also known, but the fact that they are not stereospecific indicates that they also take place by the two-step diradical mechanism (mechanism *b*).[2112]

In all of the above discussion we have assumed that a given molecule forms both the new σ bonds from the same face of the π system. This manner of bond formation, called *suprafacial*, is certainly most reasonable and almost always takes place. The subscript s is used to designate this geometry, and a normal Diels–Alder reaction would be called a $[_{\pi}2_s + {}_{\pi}4_s]$-cycloaddition (the subscript π indicates that π electrons are involved in the cycloaddition). However, we can conceive of another approach in which the newly forming bonds of the diene lie on *opposite* faces of the π system, that is, they point in opposite directions. This type of orientation of the newly formed bonds is called *antarafacial*, and the reaction would be a $[_{\pi}2_s + {}_{\pi}4_a]$-cycloaddition (a stands for antarafacial). We can easily show by the frontier-orbital method that this reaction (and consequently the reverse ring-opening reactions) are thermally forbidden and photochemically allowed. Thus in order for a $[_{\pi}2_s + {}_{\pi}4_a]$-reaction to proceed, overlap between the highest occupied π orbital of the alkene and the lowest unoccupied π orbital of the diene would have to occur as shown in Fig. 15.10, with a + lobe

[2111]The possibility has been raised that some disallowed reactions may nevertheless proceed by concerted mechanisms: see Schmidt, W. *Helv. Chim. Acta* ***1971***, *54*, 862; *Tetrahedron Lett.* ***1972***, 581; Muszkat, K.A.; Schmidt, W. *Helv. Chim. Acta* ***1971***, *54*, 1195; Baldwin, J.E.; Andrist, A.H.; Pinschmidt Jr., R.K. *Acc. Chem. Res.* ***1972***, *5*, 402; Berson, J.A. *Acc. Chem. Res.* ***1972***, *5*, 406; Baldwin, J.E., in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, ***1977***, pp. 273–302.

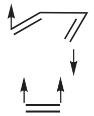
[2112]For example, see Sieber, W.; Heimgartner, H.; Hansen, H.; Schmid, H. *Helv. Chim. Acta* ***1972***, *55*, 3005. For discussions see Bartlett, P.D.; Helgeson, R.; Wersel, O.A. *Pure Appl. Chem.* ***1968***, *16*, 187; Seeley, D.A. *J. Am. Chem. Soc.* ***1972***, *94*, 4378; Kaupp, G. *Angew. Chem. Int. Ed.* ***1972***, *11*, 313, 718.

overlapping a – lobe. Since like signs are no longer overlapping, the thermal reaction is now forbidden. Similarly, thermal [$_{\pi}4_s + _{\pi}2_a$]- and



Normal Diels–Adler reaction

[$4_s + 2_s$]



Twisted Diels–Adler reaction

[$4_a + 2_s$]

[$_{\pi}2_a + _{\pi}2_a$]-cyclizations are forbidden, while thermal [$_{\pi}4_a + _{\pi}2_a$]- and [$_{\pi}2_s + _{\pi}2_a$]-cyclizations are allowed, and these considerations are reversed for the corresponding photochemical processes. Of course, an antarafacial approach is highly unlikely in a [4 + 2]-cyclization,[2113] but larger ring closures could take place by such a pathway, and [2 + 2]-thermal cyclizations, where the [$_{\pi}2_s + _{\pi}2_s$] pathway is forbidden, can also do so in certain cases (see **15-63**). We therefore see that whether a given cycloaddition is allowed or forbidden depends on the geometry of approach of the two molecules involved.

Symmetry considerations have also been advanced to explain predominant endo addition.[2114] In the case of [4 + 2] addition of butadiene to itself, the approach can be exo or endo. It can be seen (Fig. 15.11) that whether the HOMO of the diene overlaps with the LUMO of the alkene or vice versa, the endo orientation is stabilized by additional secondary overlap of orbitals[2115] of like sign (dashed lines between heavy dots). Addition from the exo direction has no such stabilization. Evidence for secondary orbital overlap as the cause of predominant endo orientation, at least in some cases, is that [4 + 6]-cycloaddition is predicted by similar considerations to proceed with predominant exo orientation, and that is what is found.[2116] However, this explanation does not account for endo orientation in cases where the dienophile does not possess additional π orbitals, and a number of alternative explanations have been offered.[2117]

[2113]A possible photochemical [$_{\pi}2a + _{\pi}4_s$]-cycloaddition has been reported: Hart, H.; Miyashi, T.; Buchanan, D.N.; Sasson, S. *J. Am. Chem. Soc.* ***1974***, *96*, 4857.

[2114]Hoffmann, R.; Woodward, R.B. *J. Am. Chem. Soc.* ***1965***, *87*, 4388.

[2115]For reviews of secondary orbital interactions, see Ginsburg, D. *Tetrahedron* ***1983***, *39*, 2095; Gleiter, R.; Paquette, L.A. *Acc. Chem. Res.* ***1983***, *16*, 328. For a new secondary orbital interaction see Singleton, D.A. *J. Am. Chem. Soc.* ***1992***, *114*, 6563.

[2116]See, for example, Cookson, R.C.; Drake, B.V.; Hudec, J.; Morrison, A. *Chem. Commun.* ***1966***, 15; Itô, S.; Fujise, Y.; Okuda, T.; Inoue, Y. *Bull. Chem. Soc. Jpn.* ***1966***, *39*, 1351; Paquette, L.A.; Barrett, J.H.; Kuhla, D.E. *J. Am. Chem. Soc.* ***1969***, *91*, 3616; Houk, K.N.; Woodward, R.B. *J. Am. Chem. Soc.* ***1970***, *92*, 4143, 4145; Jones, D.W.; Kneen, G. *J. Chem. Soc., Chem. Commun.* ***1973***, 420. Also see Apeloig, Y.; Matzner, E. *J. Am. Chem. Soc.* ***1995***, *117*, 5375.

[2117]See, for example, Houk, K.N.; Luskus, L.J. *J. Am. Chem. Soc.* ***1971***, *93*, 4606; Kobuke, Y.; Sugimoto, T.; Furukawa, J.; Fueno, T. *J. Am. Chem. Soc.* ***1972***, *94*, 3633; Jacobson, B.M. *J. Am. Chem. Soc.* ***1973***, *95*, 2579; Mellor, J.M.; Webb, C.F. *J. Chem. Soc. Perkin Trans. 2*, ***1974***, 17, 26; Fox, M.A.; Cardona, R.; Kiwiet, N.J. *J. Org. Chem.* ***1987***, *52*, 1469.

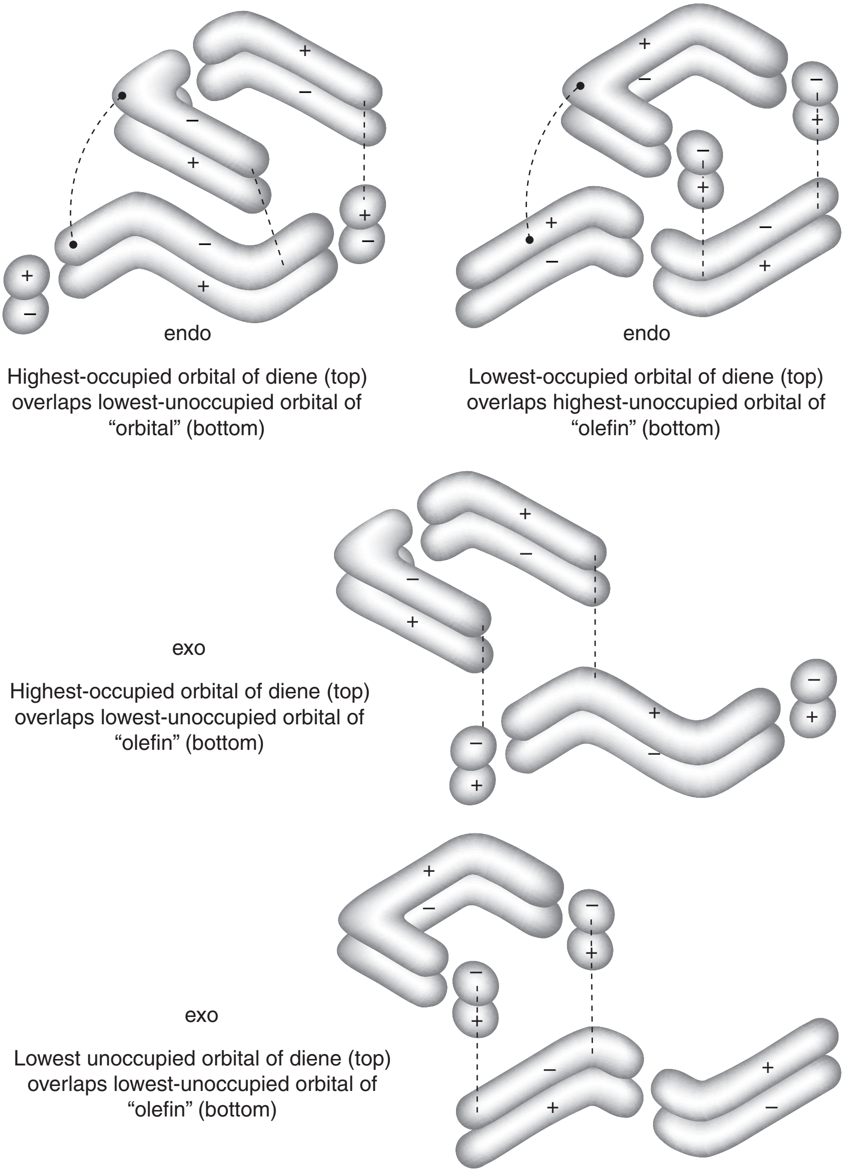
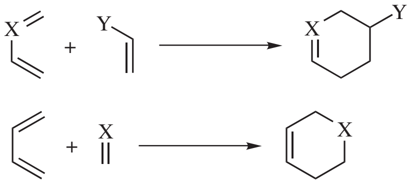


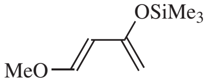
Fig. 15.11. Overlap of orbitals in [4 + 2]-cycloaddition of dienes.

OS **II**, 102; **III**, 310, 807; **IV**, 238, 738, 890, 964; **V**, 414, 424, 604, 985, 1037; **VI**, 82, 196, 422, 427, 445, 454; **VII**, 4, 312, 485; **VIII**, 31, 38, 298, 353, 444, 597; **IX**, 186, 722; **75**, 201; **81**, 171. For a reverse Diels–Alder reaction, see OS **VII**, 339.

15-61 Heteroatom Diels–Alder Reactions



Carbon–carbon multiple bonds are not the only units that can participate in Diels–Alder reactions. Other double- and triple-bond compounds can be dienophiles and they give rise to heterocyclic compounds.[2118] Among these are N≡C—, —N=C—,[2119] iminium salts,[2120] —N=N—, O=N—,[2121] and —C=O compounds[2122] and even molecular oxygen (**15-62**). It is noted that in the presence of a $YbCl_3$ catalyst, azirines reaction with dienes to give a 1-azabicyclo[4.1.0] heptene.[2123] Several catalysts can be used, depending on the nature of the heteroatoms incorporated into the alkene or diene.[2124] Intramolecular cycloaddition with a diene–imine substrate leads to pyrrolidines.[2125]



203

Aldehydes react with suitably functionalized dienes, such as **203**, known as *Danishefsky's diene*,[2126] and the reaction usually requires a Lewis acid catalyst

[2118]For transition structures for selected hetero Diels–Alder reactions, see McCarrick, M.A.; Wu, Y.-D.; Houk, K.N. *J. Org. Chem.* ***1993***, *58*, 3330.

[2119]Nogue, D.; Paugam, R.; Wartski, L. *Tetrahedron Lett.* ***1992***, *33*, 1265; Collin, J.; Jaber, N.; Lannou, M.I. *Tetrahedron Lett.* ***2001***, *42*, 7405; Hedberg, C.; Pinho, P.; Roth, P.; Andersson, P.G. *J. Org. Chem.* ***2000***, *65*, 2810. For a review see Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* ***2001***, *57*, 6099; Anniyappan, M.; Muralidharan, D.; Perumal, P.T. *Tetrahedron Lett.* ***2003***, *44*, 3653.

[2120]Domingo, L.R. *J. Org. Chem.* ***2001***, *66*, 3211; Chou, S.-S.P.; Hung, C.-C. *Synth. Commun.* ***2001***, *31*, 1097.

[2121]Martin, S.F.; Hartmann, M.; Josey, J.A. *Tetrahedron Lett.* ***1992***, *33*, 3583.

[2122]For monographs on dienes and dienophiles with heteroatoms, see Boger, D.L.; Weinreb, S.M. *Hetero Diels–Alder Methodology in Organic Synthesis*, Academic Press, NY, ***1987***; Hamer, J. *1,4-Cycloaddition Reactions*, Academic Press, NY, ***1967***. For reviews, see Weinreb, S.M.; Scola, P.M. *Chem. Rev.* ***1989***, *89*, 1525; Boger, D.L., in Lindberg, T. *Strategies and Tactics in Organic Synthesis*, Vol. 2, Academic Press, NY, ***1989***, pp. 1–56; Kametani, T.; Hibino, S. *Adv. Heterocycl. Chem.* ***1987***, *42*, 245; Boger, D.L. *Tetrahedron* ***1983***, *39*, 2869; Weinreb, S.M.; Staib, R.R. *Tetrahedron* ***1982***, *38*, 3087; Weinreb, S.M.; Levin, J.I. *Heterocycles* ***1979***, *12*, 949; Desimoni, G.; Tacconi, G. *Chem. Rev.* ***1975***, *75*, 651; Kresze, G.; Firl, J. *Fortschr. Chem. Forsch.* ***1969***, *11*, 245. See also, Katritzky, A.R.; Dennis, N. *Chem. Rev.* ***1989***, *89*, 827; Schmidt, R.R. *Acc. Chem. Res.* ***1986***, *19*, 250; Boger, D.L. *Chem. Rev.* ***1986***, *86*, 781.

[2123]Ray, C.A.; Risberg, E.; Somfai, P. *Tetrahedron Lett.* ***2001***, *42*, 9289.

[2124]See Molander, G.A.; Rzasa, R.M. *J. Org. Chem.* ***2000***, *65*, 1215.

[2125]Amos, D.T.; Renslo, A.R.; Danhesier, R.L. *J. Am. Chem. Soc.* ***2003***, *125*, 4970.

[2126]Danishefsky, S.; Kitahara, T.; Schuda, P.F.; Etheredge, S.J. *J. Am. Chem. Soc.* ***1976***, *98*, 3028; Danishefsky, S.; Kitahara, T.; McKee, R.; Schuda, P.F. *J. Am. Chem. Soc.* ***1976***, *98*, 6715; Danishefsky, S.; Schuda, P.F.; Kitahara, T. Etheredge, S.J. *J. Am. Chem. Soc.* ***1977***, *99*, 6066.

such as lanthanide compounds. Aldehydes react using a chiral titanium[2127] or a zirconium[2128] catalyst to give the dihydropyran with good enantioselectivity. Note that the reaction of Danishefsky's diene with an imine, formed *in situ* by reaction of an aryl aldehyde and an aniline derivative, proceeds without a Lewis acid.[2129] Such reactions of aldehydes can be catalyzed with Lewis acids and transition-metal catalysts. The Diels–Alder reaction of aldehydes with dienes can be catalyzed by many transition-metal compounds, including cobalt[2130] and indium[2131] catalyst. Ketones also react with suitably functionalized dienes.[2132]

Azadienes undergo Diels–Alder reactions to form pyridine, dihydro- and tetrahydropyridine derivatives.[2133] Aza-Diels–Alder reactions have been done in ionic liquids.[2134] Similarly, acyl iminium salts C=N(R)—C=O react with alkenes via cycloaddition.[2135] *N*-Vinyl lactim ethers undergo Diels–Alder reactions with a limited set of dienophiles.[2136] Thioketones react with dienes to give Diels–Alder cycloadducts.[2137] The carbonyl group of lactams have also been shown to be a dienophile.[2138] Certain heterocyclic aromatic rings (among them furans)[2139] can also behave as dienes in the Diels–Alder reaction. Some hetero dienes that give the reaction are —C=C—C=O, O=C—C=O, and N=C—C=N.[1999] Nitroso compounds of the type *t*-BuO_2C—N=O react with dienes to give the corresponding 2-azadihydropyran.[2140]

Catalysts, such as $Fe(BuEtCHCO_2)_3$, have been developed that are effective for the heteroatom Diels–Alder reaction.[2141] Indium trichloride ($InCl_3$) is a good catalyst for imino-Diels–Alder reactions.[2142] Hetero-Diels–Alder reactions involving carbonyls have been done in water.[2143] Ultrasound has been used to promote the Diels–Alder reactions of 1-azadienes.[2144] Polymer-supported dienes have been used.[2145]

[2127]Wang, B.; Feng, X.; Huang, Y.; Liu, H.; Cui, X.; Jiang, Y. *J. Org. Chem.* ***2002***, *67*, 2175.

[2128]Yamashita, Y.; Saito, S.; Ishitani, H.; Kobayashi, S. *J. Am. Chem. Soc.* ***2003***, *125*, 3793.

[2129]Yuan, Y.; Li, X.; Ding, K. *Org. Lett.* ***2002***, *4*, 3309.

[2130]Kezuka, S.; Mita, T.; Ohtsuki, N.; Ikeno, T.; Yamada, T. *Bull. Chem. Soc. Jpn.* ***2001***, *74*, 1333.

[2131]Ali, T.; Chauhan, K.K.; Frost, C.G. *Tetrahedron Lett.* ***1999***, *40*, 5621.

[2132]Huang, Y.; Rawal, V.H.; *J. Am. Chem. Soc.* ***2002***, *124*, 9662; Jørgensen, K.A. *Eur. J. Org. Chem.* ***2004***, 2093.

[2133]Gilchrist, T.L.; Gonsalves, A.M. d'A.R.; Pinho e Melo, T.M.V.D. *Pure Appl. Chem.* ***1996***, *68*, 859; Jayakumar, S.; Ishar, M.P.S.; Mahajan, M.P. *Tetrahedron* ***2002***, *58*, 379.

[2134]Yadav, J.S.; Reddy, B.V.S.; Reddy, J.S.S.; Rao, R.S. *Tetrahedron* ***2003***, *59*, 1599.

[2135]Suga, S.; Nagaki, A.; Tsutsui, Y.; Yoshida, J.-i. *Org. Lett.* ***2003***, *5*, 945.

[2136]Sheu, J.; Smith, M.B.; Matsumoto, K. *Synth. Commun*, ***1993***, *23*, 253.

[2137]Schatz, J.; Sauer, J. *Tetrahedron Lett.* ***1994***, *35*, 4767.

[2138]Degnan, A.P.; Kim, C.S.; Stout, C.W.; Kalivretenos, A.G. *J. Org. Chem.* ***1995***, *60*, 7724.

[2139]For reviews, see Katritzky, A.R.; Dennis, N. *Chem. Rev.* ***1989***, *89*, 827; Schmidt, R.R. *Acc. Chem. Res.* ***1986***, *19*, 250; Boger, D.L. *Chem. Rev.* ***1986***, *86*, 781. See Hayashi, Y.; Nakamura, M.; Nakao, S.; Inoue, T.; Shoji, M. *Angew. Chem. Int. Ed.* ***2002***, *41*, 4079.

[2140]Bach, P.; Bols, M. *Tetrahedron Lett.* ***1999***, *40*, 3461.

[2141]Gorman, D.B.; Tomlinson, I.A. *Chem. Commun.* ***1998***, 25.

[2142]Babu, G.; Perumal, P.T. *Tetrahedron* ***1998***, *54*, 1627.

[2143]Lubineau, A.; Augé, J.; Grand, E.; Lubin, N. *Tetrahedron* ***1994***, *50*, 10265.

[2144]Villacampa, M.; Pérez, J.M.; Avendaño, C.; Menéndez, J.C. *Tetrahedron* ***1994***, *50*, 10047.

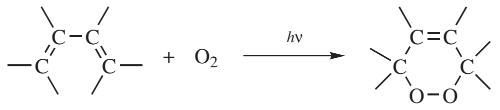
[2145]Pierres, C.; George, P.; van Hijfte, L.; Ducep, J.-B.; Hibert, M.; Mann, A. *Tetrahedron Lett.* ***2003***, *44*, 3645.

Hetero- Diels–Alder reactions that proceed with good to excellent asymmetric induction are well known.[2146] Chiral 1-aza-dienes have been developed as substrates, for example.[2147] Chiral catalysts have been developed.[2148] Conjugated aldehydes react with vinyl ethers, with a chiral chromium catalyst, in an inverse electron demand cycloaddition that give a dihydropyran with good enantioselectivity.[2149] Vinyl sulfilimines have been used in chiral Diels–Alder reactions.[2150]

OS **IV**, 311; **V**, 60, 96; **80**, 133. See also OS **VII**, 326.

15-62 Photooxidation of Dienes (Addition of Oxygen, Oxygen)

[4 + 2] *OC*,*OC-cyclo*-Peroxy-1/4/addition



204

Conjugated dienes react with oxygen under the influence of light to give cyclic peroxides **204**.[2151] The reaction has mostly[2152] been applied to cyclic dienes.[2153] Cycloaddition of furan has been reported using singlet oxygen.[2154] The scope extends to certain aromatic compounds such as phenanthrene.[2155] Besides those dienes and aromatic rings that can be photooxidized directly, there is a larger group that give the reaction in the presence of a photosensitizer such as eosin (see p. 340).

[2146]Yao, S.; Johannsen, M.; Audrain, H.; Hazell, R.G.; Jørgensen, K.A. *J. Am. Chem. Soc.* ***1998***, *120*, 8599; Pouilhès, A.; Langlois, Y.; Nshimyumkiza, P.; Mbiya, K.; Ghosez, L. *Bull. Soc. Chim. Fr.* ***1993***, *130*, 304.

[2147]Beaudegnies, R.; Ghosez, L. *Tetrahedron Asymmetry* ***1994***, *5*, 557.

[2148]Du, H.; Long, J.; Hu, J.; Li, X.; Ding, K. *Org. Lett.* ***2002***, *4*, 4349; Du, H.; Ding, K. *Org. Lett.* ***2003***, *5*, 1091; Macheño, O.G.; Arrayás, R.G.; Carretero, J.C. *J. Am. Chem. Soc.* ***2004***, *126*, 456.

[2149]Gademann, K.; Chavez, D.E.; Jacobsen, E.N. *Angew. Chem. Int. Ed.* ***2002***, *41*, 3059.

[2150]Ruano, J.L.G.; Clemente, F.R.; Gutiérrez, L.G.; Gordillo, R.; Castro, A.M.M.; Ramos, J.H.R. *J. Org. Chem.* ***2002***, *67*, 2926.

[2151]For reviews, see Clennan, E.L. *Tetrahedron* ***1991***, *47*, 1343; *Adv. Oxygenated Processes* ***1988***, *1*, 85; Wasserman, H.H.; Ives, J.L. *Tetrahedron* ***1981***, *37*, 1825; Denny, R.W.; Nickon, A. *Org. React.* ***1973***, *20*, 133; Adams, W.R. in Augustine, R.L.; Trecker, D.J. *Oxidation*, Vol. 2, Marcel Dekker, NY, ***1971***, pp. 65–112; Gollnick, K. *Adv. Photochem.* ***1968***, *6*, 1; Schönberg, A. *Preparative Organic Photochemistry*, Springer, NY, ***1968***, pp. 382–397; Gollnick, K.; Schenck, G.O., in Hamer, T. *1,4-Cycloaddition Reactions*, Academic Press, NY, ***1967***, pp. 255–344; Arbuzov, Yu.A. *Russ. Chem. Rev.* ***1965***, *34*, 558.

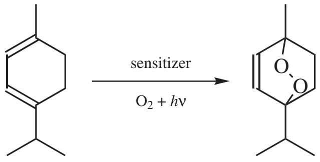
[2152]For many examples with acyclic dienes, see Matsumoto, M.; Dobashi, S.; Kuroda, K.; Kondo, K. *Tetrahedron* ***1985***, *41*, 2147.

[2153]For reviews of cyclic peroxides, see Saito, I.; Nittala, S.S., in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, ***1983***, pp. 311–374; Balci, M. *Chem. Rev.* ***1981***, *81*, 91; Adam, W.; Bloodworth, A.J. *Top. Curr. Chem.* ***1981***, *97*, 121.

[2154]Onitsuka, S.; Nishino, H.; Kurosawa, K. *Tetrahedron* ***2001***, *57*, 6003.

[2155]For reviews, see in Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*; Academic Press, NY, ***1979***, the articles by Wasserman, H.H.; Lipshutz, B.H. pp. 429–509; Saito, I.; Matsuura, T. pp. 511–574; Rigaudy, J. *Pure Appl. Chem.* ***1968***, *16*, 169.

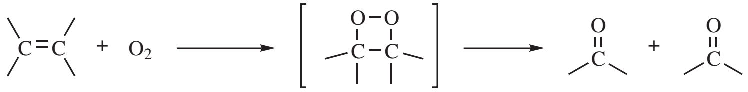
Among these is α-terpinene, which is converted to ascaridole:



As in **14-7**, it is not the ground-state oxygen (the triplet), that reacts, but the excited singlet state,[2156,2157] so the reaction is actually a Diels–Alder reaction (see **15-60**) with singlet oxygen as dienophile:[2158]

Like **15-60**, this reaction is reversible.

We have previously discussed the reaction of singlet oxygen with double-bond compounds to give



205

hydroperoxides (**14-7**), but singlet oxygen can also react with double bonds in another way to give a dioxetane intermediate[2159] (**205**), which usually cleaves to

[2156]For books on singlet oxygen, see Frimer, A.A. *Singlet O_2*, 4 vols., CRC Press, Boca Raton, FL, ***1985***; Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, ***1979***. For reviews, see Frimer, A.A. in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, ***1983***, pp. 201–234; Gorman, A.A.; Rodgers, M.A.J. *Chem. Soc. Rev.* ***1981***, *10*, 205; Shinkarenko, N.V.; Aleskovskii, V.B. *Russ. Chem. Rev.* ***1981***, *50*, 220; Shlyapintokh, V.Ya.; Ivanov, V.B. *Russ. Chem. Rev.* ***1976***, *45*, 99; Ohloff, G. *Pure Appl. Chem.* ***1975***, *43*, 481; Kearns, D.R. *Chem. Rev.* ***1971***, *71*, 395; Wayne, R.P. *Adv. Photochem.* ***1969***, *7*, 311.

[2157]For reviews, see Turro, N.J.; Ramamurthy, V., in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, ***1980***, pp. 1–23; Murray, R.W., in Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, ***1979***, pp. 59–114. For a general monograph, see Adam, W.; Cilento, G. *Chemical and Biological Generation of Excited States*, Academic Press, NY, ***1982***.

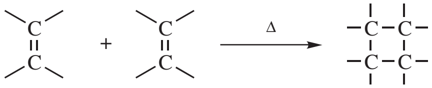
[2158]Corey, E.J.; Taylor, W.C. *J. Am. Chem. Soc.* ***1964***, *86*, 3881; Foote, C.S.; Wexler, S.; Ando, W. *Tetrahedron Lett.* ***1965***, 4111; Monroe, B.M. *J. Am. Chem. Soc.* ***1981***, *103*, 7253. See also, Hathaway, S.J.; Paquette, L.A. *Tetrahedron Lett.* ***1985***, *41*, 2037; O'Shea, K.E.; Foote, C.S. *J. Am. Chem. Soc.* ***1988***, *110*, 7167.

[2159]For reviews, see Adam, W.; Cilento, G. *Angew. Chem. Int. Ed.* ***1983***, *22*, 529; Schaap, A.; Zaklika, K.A. in Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, ***1979***, pp. 173–242; Bartlett, P.D. *Chem. Soc. Rev.* ***1976***, *5*, 149. For discussions of the mechanisms see Frimer, A.A. *Chem. Rev.* ***1979***, *79*, 359; Clennan, E.L.; Nagraba, K. *J. Am. Chem. Soc.* ***1988***, *110*, 4312.

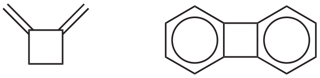
aldehydes or ketones,[2160] but has been isolated.[2161] Both the six-membered cyclic peroxides[2162] and the four-membered **205**[2163] have been formed from oxygenation reactions that do not involve singlet oxygen. If cyclic peroxides, such as **205**, are desired, better reagents[2164] are triphenyl phosphite ozonide $(PhO)_3PO_3$ and triethylsilyl hydrotrioxide ($Et_3SiOOOH$), but yields are not high.[2165]

15-63 [2 + 2]-Cycloadditions

[2 + 2]*cyclo*-Ethylene-1/2/addition



The thermal reaction between two molecules of alkene to give cyclobutane derivatives (a [2 + 2]-cycloaddition) can be carried out where the alkenes are the same or different, but the reaction is not a general one for alkenes.[2166] The cycloaddition can be catalyzed by certain transition-metal complexes.[2167] Dimerization of like alkenes occurs with the following compounds: $F_2C{=}CX_2$ ($X = F$ or Cl) and certain other



206 Biphenylene

[2160]For discussions see Kearns, D.R. *Chem. Rev.* ***1971***, *71*, 395, 422–424; Foote, C.S. *Pure Appl. Chem.* ***1971***, *27*, 635.

[2161]For reviews of 1,2-dioxetanes see Adam, W., in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, ***1983***, pp. 829–920; Bartlett, P.D.; Landis, M.E., in Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, ***1979***, pp. 243–286; Adam, W. *Adv. Heterocycl. Chem.* ***1977***, *21*, 437. See also, Inoue, Y.; Hakushi, T.; Turro, N.J. *Kokagaku Toronkai Koen Yoshishu* ***1979***, 150 [*C.A.* *92*, 214798q]; Adam, W.; Encarnación, L.A.A. *Chem. Ber.* ***1982***, *115*, 2592; Adam, W.; Baader, W.J. *Angew. Chem. Int. Ed.* ***1984***, *23*, 166.

[2162]See Nelson, S.F.; Teasley, M.F.; Kapp, D.L. *J. Am. Chem. Soc.* ***1986***, *108*, 5503.

[2163]For a review, see Nelson, S.F. *Acc. Chem. Res.* ***1987***, *20*, 269.

[2164]For another reagent, see Curci, R.; Lopez, L.; Troisi, L.; Rashid, S.M.K.; Schaap, A.P. *Tetrahedron Lett.* ***1987***, *28*, 5319.

[2165]Posner, G.H.; Weitzberg, M.; Nelson, W.M.; Murr, B.L.; Seliger, H.H. *J. Am. Chem. Soc.* ***1987***, *109*, 278.

[2166]For reviews, see Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*, Pergamon, Elmsford, NY, ***1990***; Reinhoudt, D.N. *Adv. Heterocycl. Chem.* ***1977***, *21*, 253; Roberts, J.D.; Sharts, C.M. *Org. React.* ***1962***, *12*, 1; Gilchrist, T.L.; Storr, R.C. *Organic Reactions and Orbital Symmetry* 2nd ed., Cambridge University Press, Cambridge, ***1979***, pp. 173–212; Beltrame, P., in Bamford, C.H.; Tipper, C.F.H. Ref. 1, Vol. 9, pp. 131–152; Huisgen, R.; Grashey, R.; Sauer, J., in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, ***1964***, pp. 779–802. For a review of the use of [2 + 2]-cycloadditions in polymerization reactions, see Dilling, W.L. *Chem. Rev.* ***1983***, *83*, 1. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 546–647, 1341–1344.

[2167]For an example using $EtAlCl_2$ see Takasu, K.; Ueno, M.; Inanaga, K.; Ihara, M. *J. Org. Chem.* ***2004***, *69*, 517.

fluorinated alkenes (although not $F_2C{=}CH_2$), allenes (to give derivatives of **206**),[2168] benzynes (to give biphenylene derivatives),[2169] activated alkenes (e.g., styrene, acrylonitrile, butadiene), and certain methylenecyclopropanes.[2170] Dimerization of allenes lead to bis(alkylidene) cyclobutanes.[2171] Substituted ketenes can dimerize to give cyclobutenone derivatives, although ketene itself dimerizes in a different manner, to give an unsaturated β-lactone (**16-95**).[2172] Alkenes react with activated alkynes, with a ruthenium catalyst, to give cyclobutenes.[2173]

Intramolecular [2 + 2]-cycloadditions are common in which a diene is converted to a bicyclic compound with a four-membered ring fused to another ring. Heating *N*-vinyl imines, where the vinyl moiety is a silyl enol, gives β-lactams.[2174] Apart from photochemical initiation of such reactions, intramolecular cycloaddition of two conjugated ketone units, in the presence of $PhMeSiH_2$ and catalyzed by cobalt compounds, leads to the bicyclic compound with two ketone substituents.[2175] In a variation of this reaction, a diyne was treated with $Ti(O\textit{i}Pr)_4$/2 *i*-PrMgCl to generate a bicyclic cyclobutene with two vinylidene units.[2176]

Ketenes react with many alkenes to give cyclobutanone derivatives[2177] and intermolecular cycloadditions are well known.[2178] typical reaction is that of dimethylketene and ethene to give 2,2-dimethylcyclobutanone.[2179] Ketenes react with imines via [2 + 2]-cycloaddition to produce β-lactams.[2180] Cycloaddition of an imine with a conjugated ester in the presence of Et_2MeSiH and an iridium

[2168]For a review, see Fischer, H., in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, ***1964***, pp. 1064–1067.

[2169]For cycloaddition with a pyridyne, see Mariet, N.; Ibrahim-Ouali, M.; Santelli, M. *Tetrahedron Lett.* ***2002***, *43*, 5789.

[2170]Dolbier, Jr., W.R.; Lomas, D.; Garza, T.; Harmon, C.; Tarrant, P. *Tetrahedron* ***1972***, *28*, 3185.

[2171]Saito, S.; Hirayama, K.; Kabuto, C.; Yamamoto, Y. *J. Am. Chem. Soc.* ***2000***, *122*, 10776.

[2172]Farnum, D.G.; Johnson, J.R.; Hess, R.E.; Marshall, T.B.; Webster, B. *J. Am. Chem. Soc.* ***1965***, *87*, 5191; Dehmlow, E.V.; Pickardt, J.; Slopianka, M.; Fastabend, U.; Drechsler, K.; Soufi, J. *Liebigs Ann. Chem.* ***1987***, 377.

[2173]Jordan, R.W.; Tam, W. *Org. Lett.* ***2000***, *2*, 3031.

[2174]Bandin, E.; Favi, G.; Martelli, G.; Panunzio, M.; Piersanti, G. *Org. Lett.* ***2000***, *2*, 1077.

[2175]Baik, T.-G.; Luis, A.L.; Wang, L.-C.; Krische, M.J. *J. Am. Chem. Soc.* ***2001***, *123*, 6716.

[2176]Delas, C.; Urabe, H.; Sato, F. *Tetrahedron Lett.* ***2001***, *42*, 4147.

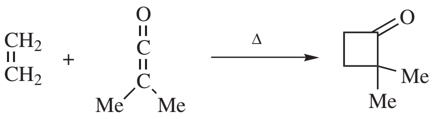
[2177]An example is de Faria, A.R.; Matos, C.R.; Correia, C.R.D. *Tetrahedron Lett.* ***1993***, *34*, 27.

[2178]Krepski, L.R.; Hassner, A. *J. Org. Chem.* ***1978***, *43*, 2879; Bak, D.A.; Brady, W.T. *J. Org. Chem.* ***1979***, *44*, 107; Martin, P.; Greuter, H.; Belluš, D. *Helv. Chim. Acta.*, ***1984***, *64*, 64; Brady, W.T. *Synthesis* ***1971***, 415.

[2179]Sustmann, R.; Ansmann, A.; Vahrenholt, F. *J. Am. Chem. Soc.* ***1972***, *94*, 8099; Desimoni, G.; Tacconi, G.; Barco, A.; Pollini, G.P. *Natural Product Synthesis Through Pericyclic Reactions*, American Chemical Society, Washington, DC, ***1983***, pp. 119–254, 39.

[2180]For reviews of the formation of β-lactams, see Brown, M.J. *Heterocycles* ***1989***, *29*, 2225; Isaacs, N.S. *Chem. Soc. Rev.* ***1976***, *5*, 181; Mukerjee, A.K.; Srivastava, R.C. *Synthesis* ***1973***, 327. For a review of cycloaddition reactions of imines, see Sandhu, J.S.; Sain, B. *Heterocycles* ***1987***, *26*, 777. For a new catalyst, see Wack, H.; France, S.; Hafez, A.M.; Drury, III, W.J.; Weatherwax, A.; Lectka, T. *J. Org. Chem.* ***2004***, *69*, 4531.

catalyst also gives a β-lactam.[2181]



Different alkenes combine as follows:

1. $F_2C{=}CX_2$ (X = F or Cl), especially $F_2C{=}CF_2$, form cyclobutanes with many alkenes. Compounds of this type even react with conjugated dienes to give four-membered rings rather than undergoing normal Diels–Alder reactions.[2182]
2. Allenes[2183] and ketenes[2184] react with activated alkenes and alkynes. Ketenes give 1,2-addition, even with conjugated dienes.[2185] Ketenes also add to unactivated alkenes if sufficiently long reaction times are used.[2186] Allenes and ketenes also add to each other.[2187]
3. Enamines[2188] form four-membered rings with Michael-type alkenes[2189] and ketenes.[2190] In both cases, only enamines from aldehydes give stable

[2181]Townes, J.A.; Evans, M.A.; Queffelec, J.; Taylor, S.J.; Morken, J.P. *Org. Lett.* ***2002***, *4*, 2537.

[2182]Bartlett, P.D.; Montgomery, L.K.; Seidel, B. *J. Am. Chem. Soc.* ***1964***, *86*, 616; De Cock, C.; Piettre. S.; Lahousse, F.; Janousek, Z.; Merényi, R.; Viehe, H.G. *Tetrahedron* ***1985***, *41*, 4183.

[2183]For reviews of [2 + 2]-cycloadditions of allenes, see Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis*, Wiley, NY, ***1984***, pp. 286–317; Hopf, H., in Landor, S.R.I. *The Chemistry of Allenes*, Vol. 2, Academic Press, NY, ***1982***, pp. 525–562; Ghosez, L.; O'Donnell, M.J., in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, ***1977***, pp. 79–140; Baldwin, J.E.; Fleming, R.H. *Fortschr. Chem. Forsch.* ***1970***, *15*, 281.

[2184]For reviews of cycloadditions of ketenes, see Ghosez, L.; O'Donnell, M.J. in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, ***1977***; Brady, W.T. *Synthesis* ***1971***, 415; Luknitskii, F.I.; Vovsi, B.A. *Russ. Chem. Rev.* ***1969***, *38*, 487; Ulrich, H. *Cycloaddition Reactions of Heterocumulenes*, Academic Press, NY, ***1967***, pp. 38–121; Holder, R.W. *J. Chem. Educ.* ***1976***, *53*, 81. For a review of intramolecular cycloadditions of ketenes to alkenes, see Snider, B.B. *Chem. Rev.* ***1988***, *88*, 793.

[2185]See, for example, Martin, J.C.; Gott, P.G.; Goodlett, V.W.; Hasek, R.H. *J. Org. Chem.* ***1965***, *30*, 4175; Brady, W.T.; O'Neal, H.R. *J. Org. Chem.* ***1967***, *32*, 2704; Huisgen, R.; Feiler, L.A.; Otto, P. *Tetrahedron Lett.* ***1968***, 4491; *Chem. Ber.* ***1969***, *102*, 3475. For indirect methods of the 1,4-addition of the elements of ketene to a diene, see Freeman, P.K.; Balls, D.M.; Brown, D.J. *J. Org. Chem.* ***1968***, *33*, 2211; Corey, E.J.; Ravindranathan, T.; Terashima, S. *J. Am. Chem. Soc.* ***1971***, *93*, 4326. For a review of ketene equivalents, see Ranganathan, S.; Ranganathan, D.; Mehrotra, A.K. *Synthesis* ***1977***, 289.

[2186]Huisgen, R.; Feiler, L.A. *Chem. Ber.* ***1969***, *102*, 3391; Bak, D.A.; Brady, W.T. *J. Org. Chem.* ***1979***, *44*, 107.

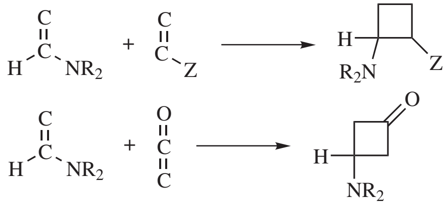
[2187]Bampfield, H.A.; Brook, P.R.; McDonald, W.S. *J. Chem. Soc., Chem. Commun.* ***1975***, 132; Gras, J.; Bertrand, M. *Nouv. J. Chim.* ***1981***, *5*, 521.

[2188]For a review of cycloaddition reactions of enamines, see Cook, A.G., in Cook, A.G. *Enamines*, 2nd ed.; Marcel Dekker, NY, ***1988***, pp. 347–440.

[2189]Brannock, K.C.; Bell, A.; Goodlett, V.W.; Thweatt, J.G. *J. Org. Chem.* ***1964***, *29*, 813.

[2190]Berchtold, G.A.; Harvey, G.R.; Wilson, G.E. *J. Org. Chem.* ***1961***, *26*, 4776; Opitz, G.; Kleeman, M. *Liebigs Ann. Chem.* ***1963***, *665*, 114; Hasek, R.H.; Gott, P.G.; Martin, J.C. *J. Org. Chem.* ***1966***, *31*, 1931.

four-membered rings:



The reaction of enamines with ketenes can be conveniently carried out by generating the ketene *in situ* from an acyl halide and a tertiary amine.

4. Alkenes with electron-withdrawing groups may form cyclobutanes with alkenes containing electron-donating groups. The enamine reactions, mentioned above, are examples of this, but it has also been accomplished with tetracyanoethylene and similar molecules, which give substituted cyclobutanes when treated with alkenes of the form C=C—A, where A may be OR,[2191] SR (enol and thioenol ethers),[2192] cyclopropyl,[2193] or certain aryl groups.[2194]

Solvents are not necessary for [2 + 2]-cycloadditions. They are usually carried out at 100–225°C under pressure, although the reactions in Group 4 (IVB) occur under milder conditions.

It has been found that certain [2 + 2]-cycloadditions, which do not occur thermally can be made to take place without photochemical initiation by the use of certain catalysts, usually transition-metal compounds.[2195] Photochemical[2196] [$_\pi 2 + {}_s 2$]-cycloadditions have also been reported. Among the catalysts used are Lewis acids[2197] and phosphine–nickel complexes.[2198] Certain of the reverse cyclobutane ring openings can also be catalytically induced (**18-38**). The role of the catalyst is not certain and may be different in each case. One possibility is that the

[2191]For a review with ketene acetals $R_2C{=}C(OR')_2$, see Scheeren, J.W. *Recl. Trav. Chim. Pays-Bas* ***1986***, *105*, 71–84.

[2192]Williams, J.K., Wiley, D.W.; McKusick, B.C. *J. Am. Chem. Soc.* ***1962***, *84*, 2210.

[2193]Nishida, S.; Moritani, I.; Teraji, T. *J. Org. Chem.* ***1973***, *38*, 1878.

[2194]Nagata, J.; Shirota, Y.; Nogami, T.; Mikawa, H. *Chem. Lett.* ***1973***, 1087; Shirota, Y.; Yoshida, K.; Nogami, T.; Mikawa, H. *Chem. Lett.* ***1973***, 1271.

[2195]For reviews, see Dzhemilev, U.M.; Khusnutdinov, R.I.; Tolstikov, G.A. *Russ. Chem. Rev.* ***1987***, *56*, 36; Kricka, L.J.; Ledwith, A. *Synthesis* ***1974***, 539.

[2196]Freeman, P.K.; Balls, D.M. *J. Org. Chem.* ***1967***, *32*, 2354; Wiskott, E.; Schleyer, P.v.R. *Angew. Chem. Int. Ed.* ***1967***, *6*, 694; Prinzbach, H.; Eberbach, W. *Chem. Ber.* ***1968***, *101*, 4083; Prinzbach, H.; Sedelmeier, G.; Martin, H. *Angew. Chem. Int. Ed.* ***1977***, *16*, 103.

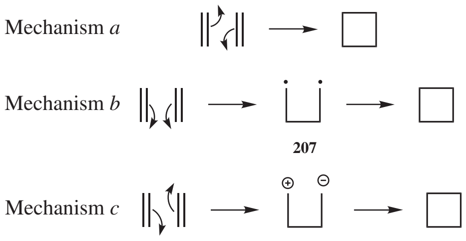
[2197]Yamazaki, S.; Fujitsuka, H.; Yamabe, S.; Tamura, H. *J. Org. Chem.* ***1992***, *57*, 5610. West, R.; Kwitowski, P.T. *J. Am. Chem. Soc.* ***1968***, *90*, 4697; Lukas, J.H.; Baardman, F.; Kouwenhoven, A.P. *Angew. Chem. Int. Ed.* ***1976***, *15*, 369.

[2198]See, for example, Hoover, F.W.; Lindsey Jr., R.V. *J. Org. Chem.* ***1969***, *34*, 3051; Noyori, R.; Ishigami, T.; Hayashi, N.; Takaya, H. *J. Am. Chem. Soc.* ***1973***, *95*, 1674; Yoshikawa, S.; Aoki, K.; Kiji, J.; Furukawa, J. *Tetrahedron* ***1974***, *30*, 405.

presence of the catalyst causes a forbidden reaction to become allowed, through coordination of the catalyst to the π or s bonds of the substrate.[2199] In such a case, the reaction would of course be a concerted $[2_s + 2_s]$-process. [2200] However, the available evidence is more consistent with nonconcerted mechanisms involving metal–carbon σ-bonded intermediates, at least in most cases.[2201] For example, such an intermediate was isolated in the dimerization of norbornadiene, catalyzed by iridium complexes.[2202]

Thermal cycloadditions leading to four-membered rings can also take place between a cyclopropane ring and an alkene or alkyne[2203] bearing electron-withdrawing groups.[2204] These reactions are $[{}_{\pi}2 + {}_{s}2]$-cycloadditions. Ordinary cyclopropanes do not undergo the reaction, but it has been accomplished with strained systems such as bicyclo[1.1.0]butanes[2205] and bicyclo[2.1.0]pentanes. For example, bicyclo[2.1.0]pentane reacts with maleonitrile (or fumaronitrile) to give all three isomers of 2,3-dicyanonorbornane, as well as four other products.[2206] The lack of stereospecificity and the negligible effect of solvent on the rate indicate a diradical mechanism.

The reaction is similar to the Diels–Alder (in action, not in scope), and if dienes are involved, the latter reaction may compete, although most alkenes react with a diene either entirely by 1,2 or entirely by 1,4 addition. Three mechanisms can be proposed[2207] analogous to those proposed for the Diels–Alder reaction. Mechanism *a* is a



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208

[2199]For discussions, see Labunskaya, V.I.; Shebaldova, A.D.; Khidekel, M.L. *Russ. Chem. Rev.* ***1974***, *43*, 1; Mango, F.D. *Top. Curr. Chem.* ***1974***, *45*, 39; *Tetrahedron Lett.* ***1973***, 1509; *Intra-Sci. Chem. Rep.* ***1972***, *6 (3)*, 171; *CHEMTECH* ***1971***, *1*, 758; *Adv. Catal.* ***1969***, *20*, 291; Mango, F.D.; Schachtschneider, J.H. *J. Am. Chem. Soc.* ***1971***, *93*, 1123; ***1969***, *91*, 2484; van der Lugt, W.T.A.M. *Tetrahedron Lett.* ***1970***, 2281; Wristers, J.; Brener, L.; Pettit, R. *J. Am. Chem. Soc.* ***1970***, *92*, 7499.

[2200]See Bachrach, S.M.; Gilbert, J.C. *J. Org. Chem.* ***2004***, *69*, 6357; Ozkan, I.; Kinal, A. *J. Org. Chem.* ***2004***, *69*, 5390.

[2201]See, for example, Cassar, L.; Halpern, J. *Chem. Commun.* ***1970***, 1082; Doyle, M.J.; McMeeking, J.; Binger, P. *J. Chem. Soc., Chem. Commun.* ***1976***, 376; Grubbs, R.H.; Miyashita, A.; Liu, M.M.; Burk, P.L. *J. Am. Chem. Soc.* ***1977***, *99*, 3863.

[2202]Fraser, A.R.; Bird, P.H.; Bezman, S.A.; Shapley, J.R.; White, R.; Osborn, J.A. *J. Am. Chem. Soc.* ***1973***, *95*, 597.

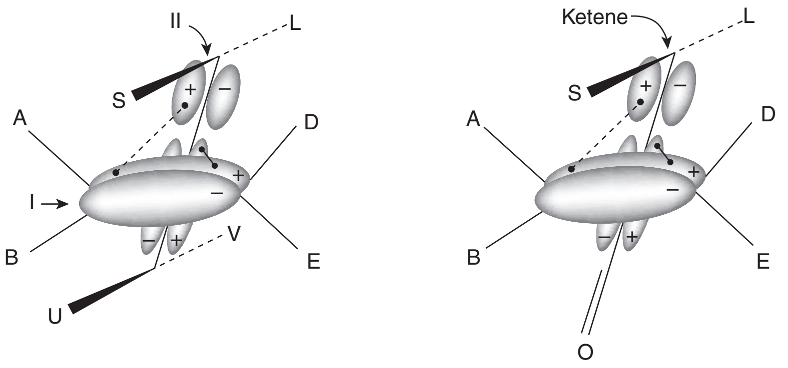
[2203]Gassman, P.G.; Mansfield, K.T. *J. Am. Chem. Soc.* ***1968***, *90*, 1517, 1524.

[2204]For a review, see Gassman, P.G. *Acc. Chem. Res.* ***1971***, *4*, 128.

[2205]Cairncross, A.; Blanchard, E.P. *J. Am. Chem. Soc.* ***1966***, *88*, 496.

[2206]Gassman, P.G.; Mansfield, K.T.; Murphy, T.J. *J. Am. Chem. Soc.* ***1969***, *91*, 1684.

[2207]For a review, see Bartlett, P.D. *Q. Rev. Chem. Soc.* ***1970***, *24*, 473.



(a) (b)

Fig. 15.12. Orbital overlap in $[_{\pi}2_s + {}_{\pi}2_s]$-cycloaddition between (*a*) two alkene molecules and (*b*) a ketene and an alkene. S and L stand for small and large

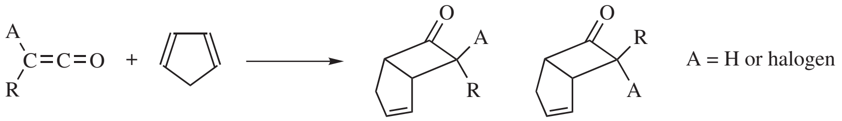
concerted pericyclic process, and mechanisms *b* and *c* are two-step reactions involving, respectively, a diradical (**207**) and a diion (**208**) intermediate. As in **15-60**, a diradical intermediate must be a singlet. In searching for ways to tell which mechanism is operating in a given case, we would expect mechanism *c* to be sensitive to changes in solvent polarity, while mechanisms *a* and *b* should be insensitive. We would also expect mechanism *a* to be stereospecific, while mechanisms *b* and *c* probably would not be stereospecific, although if the second step of these processes takes place very rapidly, before **207** or **208** has a chance to rotate about the newly formed single bond, stereospecificity might be observed. Because of entropy considerations such rapid ring closure might be more likely here than in a [4 + 2]-cycloaddition.

There is evidence that the reactions can take place by all three mechanisms, depending on the structure of the reactants. A thermal $[_{\pi}2_s + {}_{\pi}2_s]$ mechanism is ruled out for most of these substrates by the orbital symmetry rules, but a $[_{\pi}2_s + {}_{\pi}2_a]$ mechanism is allowed (p. 1212), and there is much evidence that ketenes and certain other linear molecules[2208] in which the steric hindrance to such an approach is minimal can and often do react by this mechanism. In a $[_{\pi}2_s + {}_{\pi}2_a]$-cycloaddition the molecules must approach each other in such a way (Fig. 15.12*a*) that the + lobe of the HOMO of one molecule (I) overlaps with both + lobes of the LUMO of the other (II), even although these lobes are on opposite sides of the nodal plane of II. The geometry of this approach requires that the groups S and U of molecule II project *into* the plane of molecule I. This has not been found to happen for ordinary alkenes,[2209] but if

[2208]There is evidence that a cyclopentyne (generated *in situ*) also adds to a double bond by an antarafacial process: Gilbert, J.C.; Baze, M.E. *J. Am. Chem. Soc.* ***1984***, *106*, 1885.

[2209]See, for example, Padwa, A.; Koehn, W.; Masaracchia, J.; Osborn, C.L.; Trecker, D.J. *J. Am. Chem. Soc.* ***1971***, *93*, 3633; Bartlett, P.D.; Cohen, G.M.; Elliott, S.P.; Hummel, K.; Minns, R.A.; Sharts, C.M.; Fukunaga, J.Y. *J. Am. Chem. Soc.* ***1972***, *94*, 2899.

molecule II is a ketene (Fig. 15.12*b*), the group marked U is not present and the $[_{\pi}2_s + _{\pi}2_a]$-reaction can take place. Among the evidence[2210] for this mechanism[2211] is the following: (*1*) The reactions are stereospecific.[2212] (*2*) The isomer that forms is the *more-hindered one*. Thus methylketene plus cyclopentadiene gave only the endo product (**209**, A = H, R = CH_3).[2213] Even more remarkably, when



endo **209** endo **210**

haloalkyl ketenes RXC=C=O were treated with cyclopentadiene, the endo/exo ratio of the product (**209**, **210**, A = halogen) actually *increased* substantially when R was changed from Me to *i*-Pr to *t*-Bu![2214] One would expect preferential formation of the exo products (**210**) from $[_{\pi}2_s + _{\pi}2_s]$-cycloadditions where the molecules approach each other face-to-face, but a $[_{\pi}2_s + _{\pi}2_a]$ process leads to endo products because the ketene molecule (which for steric reasons would approach with its smaller group directed toward the alkene) must twist as shown in Fig. 15.13 (L = larger; S = smaller group) in order for the + lobes to interact and this swings the larger group into the endo position.[2215] The experimental results in which the amount of endo isomer increases with the increasing size of the R group would seem to be contrary to what would be expected from

[2210]For other evidence, see Baldwin, J.E.; Kapecki, J.A. *J. Am. Chem. Soc.* ***1970***, *92*, 4874; Brook, P.R.; Griffiths, J.G. *Chem. Commun.* ***1970***, 1344; Egger, K.W. *Int. J. Chem. Kinet.* ***1973***, *5*, 285; Moon, S.; Kolesar, T.F. *J. Org. Chem.* ***1974***, *39*, 995; Isaacs, N.S.; Hatcher, B.G. *J. Chem. Soc., Chem. Commun.* ***1974***, 593; Hassner, A.; Cory, R.M.; Sartoris, N. *J. Am. Chem. Soc.* ***1976***, *98*, 7698; Gheorghiu, M.D.; Pârvulescu, L.; Drâghici, C.; Elian, M. *Tetrahedron* ***1981***, *37 Suppl.*, 143. See, however, Holder, R.W.; Graf, N.A.; Duesler, E.; Moss, J.C. *J. Am. Chem. Soc.* ***1983***, *105*, 2929.

[2211]On the other hand, molecular-orbital calculations predict that the cycloaddition of ketenes to alkenes does not take place by a $[_{\pi}2_s + _{\pi}2_a]$ mechanism: Wang, X.; Houk, K.N. *J. Am. Chem. Soc.* ***1990***, *112*, 1754; Bernardi, F.; Bottoni, A.; Robb, M.A.; Venturini, A. *J. Am. Chem. Soc.* ***1990***, *112*, 2106; Valentí, E.; Pericàs, M.A.; Moyano, A. *J. Org. Chem.* ***1990***, *55*, 3582.

[2212]Huisgen, R.; Feiler, L.A.; Binsch, G. *Angew. Chem. Int. Ed.* ***1964***, *3*, 753; *Chem. Ber.* ***1969***, *102*, 3460; Martin, J.C.; Goodlett, V.W.; Burpitt, R.D. *J. Org. Chem.* ***1965***, *30*, 4309; Montaigne, R.; Ghosez, L. *Angew. Chem. Int. Ed.* ***1968***, *7*, 221 Bertrand, M.; Gras, J.L.; Goré, J. *Tetrahedron* ***1975***, *31*, 857; Marchand-Brynaert, J.; Ghosez, L. *J. Am. Chem. Soc.* ***1972***, *94*, 2870; Huisgen, R.; Mayr, H. *Tetrahedron Lett.* ***1975***, 2965, 2969.

[2213]Brady, W.T.; Hoff, E.F.; Roe, Jr., R.; Parry III, F.H. *J. Am. Chem. Soc.* ***1969***, *91*, 5679; Rey, M.; Roberts, S.; Dieffenbacher, A.; Dreiding, A.S. *Helv. Chim. Acta* ***1970***, *53*, 417. See also, Brady, W.T.; Parry III, F.H.; Stockton, J.D. *J. Org. Chem.* ***1971***, *36*, 1486; DoMinh, T.; Strausz, O.P. *J. Am. Chem. Soc.* ***1970***, *92*, 1766; Isaacs, N.S.; Stanbury, P. *Chem. Commun.* ***1970***, 1061; Brook, P.R.; Harrison, J.M.; Duke, A.J. *Chem. Commun.* ***1970***, 589; Dehmlow, E.V. *Tetrahedron Lett.* ***1973***, 2573; Rey, M.; Roberts, S.M.; Dreiding, A.S.; Roussel, A.; Vanlierde, H.; Toppet, S.; Ghosez, L. *Helv. Chim. Acta* ***1982***, *65*, 703.

[2214]Brady, W.T.; Roe Jr., R. *J. Am. Chem. Soc.* ***1970***, *92*, 4618.

[2215]Brook, P.R.; Harrison, J.M.; Duke, A.J. *Chem. Commun.* ***1970***, 589

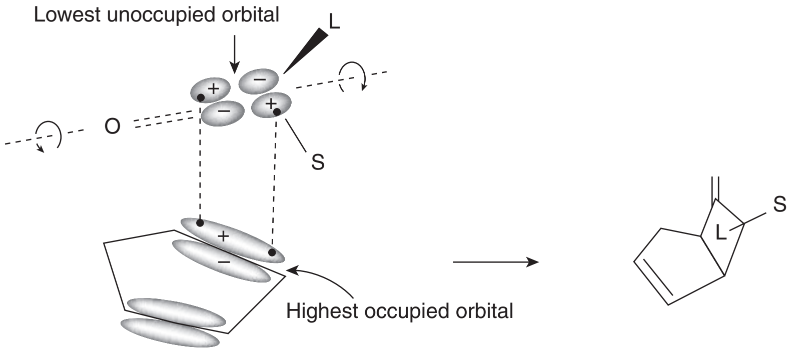


Fig. 15.13. Orbital overlap in the reaction of a ketene with cyclopentadiene. S and L stand for small and large.

considerations of steric hindrance (we may call them *masochistic steric effects*), but they are just what is predicted for a $[_{\pi}2_s + {_{\pi}2_a}]$-reaction. (*3*) There is only moderate polar solvent acceleration.[2216] (*4*) The rate of the reaction is not very sensitive to the presence of electron-withdrawing or electron-donating substituents.[2217] Because cycloadditions involving allenes are often stereospecific, it has been suggested that these also take place by the $[_{\pi}2_s + {_{\pi}2_a}]$ mechanism,[2218] but the evidence in these cases is more consistent with the diradical mechanism *b*.[2219]

The diradical mechanism *b* is most prominent in the reactions involving fluorinated alkenes.[2220] These reactions are generally not stereospecific[2221] and are insensitive to solvent effects. Further evidence that a diion is not involved is that head-to-head coupling is found when an unsymmetrical molecule is dimerized. Thus dimerization of $F_2C{=}CFCl$ gives **211**, not **212**. If one pair of electrons moved before the other, the positive end of one molecule would be expected to attack the

[2216]Brady, W.T.; O'Neal, H.R. *J. Org. Chem.* ***1967***, *32*, 612; Huisgen, R.; Feiler, L.A.; Otto, P. *Tetrahedron Lett.* ***1968***, 4485, *Chem. Ber.* ***1969***, *102*, 3444; Sterk, H. *Z. NaturForsch. Teil B* ***1972***, *27*, 143.

[2217]Baldwin, J.E.; Kapecki, J.A. *J. Am. Chem. Soc.* ***1970***, *92*, 4868; Isaacs, N.S.; Stanbury, P. *J. Chem. Soc. Perkin Trans. 2*, ***1973***, 166.

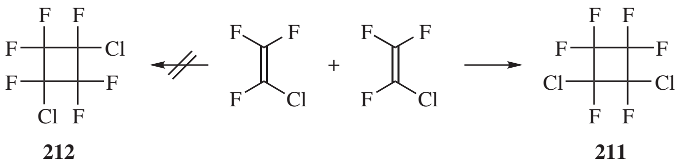
[2218]For example, see Kiefer, E.F.; Okamura, M.Y. *J. Am. Chem. Soc.* ***1968***, *90*, 4187; Baldwin, J.E.; Roy, U.V. *Chem. Commun.* ***1969***, 1225; Moore, W.R.; Bach, R.D.; Ozretich, T.M. *J. Am. Chem. Soc.* ***1969***, *91*, 5918.

[2219]Muscio Jr., O.J.; Jacobs, T.L. *Tetrahedron Lett.* ***1969***, 2867; Taylor, D.R.; Warburton, M.R.; Wright, D.B. *J. Chem. Soc. C* ***1971***, 385; Dai, S.; Dolbier Jr., W.R. *J. Am. Chem. Soc.* ***1972***, *94*, 3946; Duncan, W.G.; Weyler Jr., W.; Moore, H.W. *Tetrahedron Lett.* ***1973***, 4391; Grimme, W.; Rother, H. *Angew. Chem. Int. Ed.* ***1973***, *12*, 505; Levek, T.J.; Kiefer, E.F. *J. Am. Chem. Soc.* ***1976***, *98*, 1875; Pasto, D.J.; Yang, S.H. *J. Org. Chem.* ***1986***, *51*, 1676; Dolbier, D.W.; Seabury, M. *Tetrahedron Lett.* ***1987***, *28*, 1491; *J. Am. Chem. Soc.* ***1987***, *109*, 4393; Dolbier Jr., W.R.; Weaver, S.L. *J. Org. Chem.* ***1990***, *55*, 711; Becker, D.; Denekamp, C.; Haddad, N. *Tetrahedron Lett.* ***1992***, *33*, 827.

[2220]It has been argued that the mechanism here is not the diradical mechanism, but the $[_{\pi}2_s + {_{\pi}2_a}]$ mechanism: Roberts, D.W. *Tetrahedron* ***1985***, *41*, 5529.

[2221]Bartlett, P.D.; Hummel, K.; Elliott, S.P.; Minns, R.A. *J. Am. Chem. Soc.* ***1972***, *94*, 2898.

negative end of the other.[2222]



The diion mechanism[2223] *c* has been reported for at least some of the reactions[2224] in categories 3 and 4,[2225] as well as some ketene dimerizations.[2226] For example, the rate of the reaction between 1,2-bis(trifluoromethyl)-1,2-dicyanoethene and ethyl vinyl ether was strongly influenced by changes in solvent polarity.[2227] Some of these reactions are nonstereospecific, but others are stereospecific.[2228] As previously indicated, it is likely that in the latter cases the diionic intermediate closes before rotation can take place. Such rapid ring closure is more likely for a diion than for a diradical because of the attraction between the opposite charges. Other evidence for the diion mechanism in these cases is that reaction rates are greatly dependent on the presence of electron-donating and electron-withdrawing groups and that it is possible to trap the diionic intermediates.

Whether a given alkene reacts by the diradical or diion mechanism depends, among other things, on the groups attached to it. For example, phenyl and vinyl groups at the α positions of **207** or **208** help to stabilize a diradical, while donors, such as oxygen and nitrogen, favor a diion (they stabilize the positively charged end).[2229] A table on p. 451 of Ref. 2230 shows which mechanism is more likely for [2 + 2]-cycloadditions of various pairs of alkenes.

Thermal cleavage of cyclobutanes[2230] to give two alkene molecules (*cycloreversion*,[2231] the reverse of [2 + 2]-cycloaddition) operates by the diradical mechanism,

[2222]For additional evidence based on radical stabilities, see Silversmith, E.F.; Kitahara, Y.; Caserio, M.C.; Roberts, J.D. *J. Am. Chem. Soc.* ***1958***, *80*, 5840; Bartlett, P.D.; Montgomery, L.K.; Seidel, B. *J. Am. Chem. Soc.* ***1964***, *86*, 616; De Cock, C.; Piettre. S.; Lahousse, F.; Janousek, Z.; Merényi, R.; Viehe, H.G. *Tetrahedron* ***1985***, *41*, 4183; Doering, W. von E.; Guyton, C.A. *J. Am. Chem. Soc.* ***1978***, *100*, 3229.

[2223]For reviews of this mechanism, see Huisgen, R. *Acc. Chem. Res.* ***1977***, *10*, 117, 199; Huisgen, R.; Schug, R.; Steiner, G. *Bull. Soc. Chim. Fr.* ***1976***, 1813.

[2224]For a review of cycloadditions with polar intermediates, see Gompper, R. *Angew. Chem. Int. Ed.* ***1969***, *8*, 312.

[2225]The reactions of ketenes with enamines are apparently not concerted, but take place by the diionic mechanism: Otto, P.; Feiler, L.A.; Huisgen, R. *Angew. Chem. Int. Ed.* ***1968***, *7*, 737.

[2226]See Moore, H.W.; Wilbur, D.S. *J. Am. Chem. Soc.* ***1978***, *100*, 6523.

[2227]Proskow, S.; Simmons, H.E.; Cairns, T.L. *J. Am. Chem. Soc.* ***1966***, *88*, 5254. See also, Huisgen, R. *Pure Appl. Chem.* ***1980***, *52*, 2283.

[2228]Proskow, S.; Simmons, H.E.; Cairns, T.L. *J. Am. Chem. Soc.* ***1966***, *88*, 5254; Huisgen, R.; Steiner, G. *J. Am. Chem. Soc.* ***1973***, *95*, 5054, 5055.

[2229]Hall, Jr., H.K. *Angew. Chem. Int. Ed.* ***1983***, *22*, 440.

[2230]See Frey, H.M. *Adv. Phys. Org. Chem.* ***1966***, *4*, 147, see pp. 170–175, 180–183.

[2231]For reviews of [2 + 2]-cycloreversions, see Schaumann, E.; Ketcham, R. *Angew. Chem. Int. Ed.* ***1982***, *21*, 225; Brown, R.F.C. *Pyrolytic Methods in Organic Chemistry*, Academic Press, NY, **1980**, pp. 247–259. See also, Reddy, G.D.; Wiest, O.; Hudlický, T.; Schapiro, V.; Gonzalez, D. *J. Org. Chem.* ***1999***, *64*, 2860.

and the $[_{\sigma}2_s + _{\sigma}2_a]$ pathway has not been found[2232] (the subscripts σ indicate that σ bonds are involved in this reaction).

In some cases, double bonds add to triple bonds to give cyclobutenes, apparently at about the same rate that they add to double bonds. The addition of triple bonds to triple bonds would give cyclobutadienes, and this has not been observed, except where these rearrange before they can be isolated (see **15-65**)[2233] or in the presence of a suitable coordination compound, so that the cyclobutadiene is produced in the form of a complex (p. 76).[2234]

Although thermal [2 + 2]-cycloaddition reactions are essentially limited to the cases described above, many (although by no means all) double-bond compounds undergo such reactions *when photochemically excited* (either directly or by a photosensitizer, see p. 340), even if they are not in the above categories.[2235] Simple alkenes absorb in the far UV (p. 332), which is difficult to reach experimentally, although this problem can sometimes be overcome by the use of suitable photosensitizers. The reaction has been applied to simple alkenes[2236] (especially to strained compounds, such as cyclopropenes and cyclobutenes), but more often the double-bond compounds involved are conjugated dienes,[2237] α,β-unsaturated ketones,[2238]

[2232]See, for example, Cocks, A.T.; Frey, H.M.; Stevens, I.D.R. *Chem. Commun.* ***1969***, 458; Srinivasan, R.; Hsu, J.N.C. *J. Chem. Soc., Chem. Commun.* ***1972***, 1213; Paquette, L.A.; Carmody, M.J. *J. Am. Chem. Soc.* ***1976***, *98*, 8175. See however Cant, P.A.E.; Coxon, J.M.; Hartshorn, M.P. *Aust. J. Chem.* ***1975***, *28*, 391; Doering, W. von E.; Roth, W.R.; Breuckmann, R.; Figge, L.; Lennartz, H.; Fessner, W.; Prinzbach, H. *Chem. Ber.* ***1988***, *121*, 1.

[2233]For a review of these cases, and of cycloadditions of triple to double bonds, see Fuks, R.; Viehe, H.G., in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 435–442.

[2234]D'Angelo, J.; Ficini, J.; Martinon, S.; Riche, C.; Sevin, A. *J. Organomet. Chem.* ***1979***, *177*, 265. For a review, see Hogeveen, H.; Kok, D.M., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 2, Wiley, NY, ***1983***, pp. 981–1013.

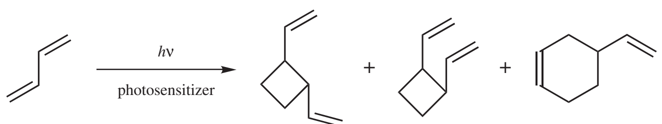
[2235]For reviews, see Demuth, M.; Mikhail, G. *Synthesis* ***1989***, 145; Ninomiya, I.; Naito, T. *Photochemical Synthesis*, Academic Press, NY, ***1989***, pp. 58–109; Ramamurthy, V.; Venkatesan, K. *Chem. Rev.* ***1987***, *87*, 433; Lewis, F.D. *Adv. Photochem.* ***1986***, *13*, 165; Wender, P.A., in Coyle, J.D. *Photochemistry in Organic Synthesis*, Royal Society of Chemistry, London, ***1986***, pp. 163–188; Schreiber, S.L. *Science*, ***1985***, *227*, 857; Neckers, D.C.; Tinnemans, A.H.A., in Horspool, W.M. *Synthetic Organic Photochemistry*, Plenum, NY, ***1984***, pp. 285–311; Baldwin, S.W. *Org. Photochem.* ***1981***, *5*, 123; Turro, N.J. *Modern Molecular Photochemistry*, W.A. Benjamin, NY, ***1978***, pp. 417–425, 458–465; Kricka, L.J.; Ledwith, A. *Synthesis* ***1974***, 539; Herndon, W.C. *Top. Curr. Chem.* ***1974***, *46*, 141; Sammes, P.G. *Q. Rev. Chem. Soc.* ***1970***, *24*, 37, 46–55; Crowley, K.J.; Mazzocchi, P.H., in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, ***1970***, 297–316; Turro, N.J.; Dalton, J.C.; Weiss, D.S. *Org. Photochem.* ***1969***, *2*, 1; Trecker, D.J. *Org. Photochem.* ***1969***, *2*, 63; Scharf, H. *Fortschr. Chem. Forsch.* ***1969***, *11*, 216; Steinmetz, R. *Fortschr. Chem. Forsch.* ***1967***, *7*, 445; Fonken, G.J. *Org. Photochem.* ***1967***, *1*, 197; Chapman, O.L.; Lenz, G. *Org. Photochem.* ***1967***, *1*, 283; Schönberg, A. *Preparative Organic Photochemistry*, Springer, NY, ***1968***, pp. 70–96, 109–117; Warrener, R.N.; Bremner, J.B. *Rev. Pure Appl. Chem.* ***1966***, *16*, 117, 122–128.

[2236]For examples of nonphotosensitized dimerization of simple alkenes, see Arnold, D.R.; Abraitys, V.Y. *Chem. Commun.* ***1967***, 1053; Yamazaki, H.; Cvetanović, R.J. *J. Am. Chem. Soc.* ***1969***, *91*, 520.

[2237]For a review, see Dilling, W.L. *Chem. Rev.* ***1969***, *69*, 845.

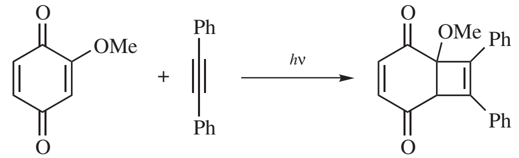
[2238]For reviews of various aspects of this subject, see Cossy, J.; Carrupt, P.; Vogel, P., in Patai, S. *Supplement A: The Chemistry of Double-Bonded Functional Groups*, Vol. 2, pt. 2, Wiley, NY, ***1989***, pp. 1369–1565; Kemernitskii, A.V.; Ignatov, V.N.; Levina, I.S. *Russ. Chem. Rev.* ***1988***, *57*, 270; Weedon, A.C., in Horspool, W.M. *Synthetic Organic Photochemistry*, Plenum, NY, ***1984***, pp. 61–143; Lenz, G.R. *Rev. Chem. Intermed.* ***1981***, *4*, 369; Margaretha, P. *Chimia*, ***1975***, *29*, 203; Bauslaugh, P.G. *Synthesis* ***1970***, 287; Eaton, P.E. *Acc. Chem. Res.* ***1968***, *1*, 50; Schuster, D.I.; Lem, G.; Kaprinidis, N.A. *Chem. Rev.* ***1993***, *93*, 3; Erickson, J.A.; Kahn, S.D. *Tetrahedron* ***1993***, *49*, 9699.

acids, or acid derivatives, or quinones, since these compounds, because they are conjugated, absorb at longer wavelengths (p. 332). Both dimerizations and mixed additions are common, some examples being (see also, the example on p. 347):



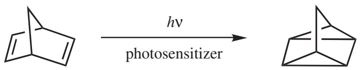
Diels–Alder product

Ref. [2239]



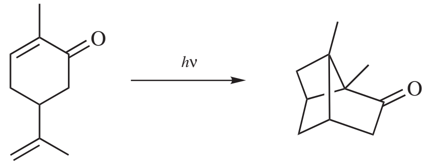
Ref. [2240]

Photochemical $[2+2]$-cycloadditions can also take place intramolecularly if a molecule has two double bonds that are properly oriented.[2241] The cyclization of the quinone dimer shown above is one example. Other examples are



Quadricyclane

Ref. [2242]



Carvone Carvonecamphor

Ref. [2243]

It is obvious that many molecules can be constructed in this way that would be difficult to make by other procedures. However, attempted cyclizations of this kind are not always successful. In many cases, polymeric or other side products are

[2239]Liu, R.S.H.; Turro, N.J.; Hammond, G.S. *J. Am. Chem. Soc.* ***1965***, *87*, 3406; Cundall, R.B.; Griffiths, P.A. *Trans. Faraday Soc.* ***1965***, *61*, 1968; DeBoer, C.D.; Turro, N.J.; Hammond, G.S. *Org. Synth.* ***V***, 528.

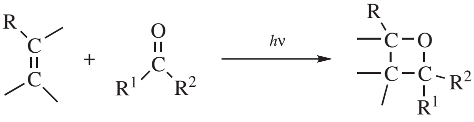
[2240]Pappas, S.P.; Pappas, B.C. *Tetrahedron Lett.* ***1967***, 1597.

[2241]For reviews, see Becker, D.; Haddad, N. *Org. Photochem.* ***1989***, *10*, 1–162; Crimmins, M.T. *Chem. Rev.* ***1988***, *88*, 1453; Oppolzer, W. *Acc. Chem. Res.* ***1982***, *15*, 135; Prinzbach, H. *Pure Appl. Chem.* ***1968***, *16*, 17; Dilling, W.L. *Chem. Rev.* ***1966***, *66*, 373.

[2242]Hammond, G.S.; Turro, N.J.; Fischer, A. *J. Am. Chem. Soc.* ***1961***, *83*, 4674; Dauben, W.G.; Cargill, R.L. *Tetrahedron* ***1961***, *15*, 197. See also, Cristol, S.J.; Snell, R.L. *J. Am. Chem. Soc.* ***1958***, *80*, 1950.

[2243]Ciamician, G.; Silber, P. *Ber.* ***1908***, *41*, 1928; Büchi, G.; Goldman, I.M. *J. Am. Chem. Soc.* ***1957***, *79*, 4741.

obtained instead of the desired product.



213

The photochemical cycloaddition of a carbonyl, generally from an aldehyde or ketone, and an alkene is called the *Paternò–Büchi reaction*.[2244] This [2 + 2]-cycloaddition gives an oxetane (**213**) and the reaction is believed to proceed via a diradical intermediate. Silyl enol ethers react with aldehydes under nonphotochemical conditions using $ZnCl_2$ at 25°C or $SnCl_4$ at −78°C.[2245]

It is possible that some of these photochemical cycloadditions take place by a $[_{\pi}2_s + _{\pi}2_s]$ mechanism (which is of course allowed by orbital symmetry); when and if they do, one of the molecules must be in the excited singlet state (S_1) and the other in the ground state.[2246] The nonphotosensitized dimerizations of *cis*- and *trans*-2-butene are stereospecific,[2247] making it likely that the $[_{\pi}2_s + _{\pi}2_s]$ mechanism is operating in these reactions. However, in most cases it is a triplet excited state that reacts with the ground-state molecule; in these cases the diradical (or in certain cases, the diionic) mechanism is taking place.[2248] In one intramolecular case, the intermediate diradical has been trapped.[2249] Photosensitized [2π + 2π]-cycloadditions almost always involve the triplet state, and hence a diradical (or diionic) mechanism.

The photochemical diradical mechanism is not quite the same as the thermal diradical mechanism. In the thermal mechanism the initially formed diradical must be a singlet, but in the photochemical process a triplet excited state is adding to a ground state (which is of course a singlet). Thus, in order to conserve spin,[2250] the initially formed diradical must be a triplet; that is, the two electrons must have the same spin. Consequently, the second, or ring-closing, step of the mechanism cannot take place at once, because a new bond cannot form from a combination of two electrons with the same spin, and the diradical has a reasonably long lifetime before collisions with molecules in the environment allow a spin inversion to take

[2244]Paternò, E.; Chieffi, C. *Gazz. Chim. Ital.* ***1909***, *39*, 341; Büchi, G.; Inman, C.G.; Lipinsky, E.S. *J. Am. Chem. Soc.* ***1954***, *76*, 4327. See García-Expósito, E.; Bearpark, M.J.; Ortuño, R.M.; Robb, M.A.; Branchadell, V. *J. Org. Chem.* ***2002***, *67*, 6070.

[2245]Wang, Y.; Zhao, C.; Romo, D. *Org. Lett.* ***1999***, *1*, 1197.

[2246]We have previously seen (p. $$$) that reactions between two excited molecules are extremely rare.

[2247]Yamazaki, H.; Cvetanović, R.J. *J. Am. Chem. Soc.* ***1969***, *91*, 520; Yamazaki, H.; Cvetanović, R.J.; Irwin, R.S. *J. Am. Chem. Soc.* ***1976***, *98*, 2198. For other likely examples, see Lewis, F.D.; Hoyle, C.E.; Johnson, D.E. *J. Am. Chem. Soc.* ***1975***, *97*, 3267; Lewis, F.D.; Kojima, M. *J. Am. Chem. Soc.* ***1988***, *110*, 8660.

[2248]Maradyn, D.J.; Weedon, A.C. *Tetrahedron Lett.* ***1994***, *35*, 8107.

[2249]Becker, D.; Haddad, N.; Sahali, Y. *Tetrahedron Lett.* ***1989***, *30*, 2661.

[2250]This is an example of the Wigner spin conservation rule (p. 340). Note that spin conservation is something entirely different from symmetry conservation.

place and the diradical to cyclize. We would therefore predict nonstereospecificity, and that is what is found.[2251] It has been believed that at least some [2 + 2]-photocycloadditions take place by way of exciplex intermediates[2252] [an *exciplex*[2253] is an excited EDA complex (p. 342) that is dissociated in the ground state; in this case one double bond is the donor and the other the acceptor], but there is evidence against this.[2254]

In **15-60**, we used the principle of conservation of orbital symmetry to explain why certain reactions take place readily and others do not. The orbital-symmetry principle can also explain why certain molecules are stable although highly strained. For example, quadricyclane and hexamethylprismane[2255] are thermodynamically much less stable (because much more strained) than their corresponding isomeric dienes, norbornadiene and

214

Quadricyclane Norbornadiene Hexamethylprismane (A Dewar benzene)

hexamethylbicyclo[2.2.0]hexadiene (**214**).[2256] Yet the former two compounds can be kept indefinitely at room temperature, although in the absence of orbital-symmetry considerations it is not easy to understand why the electrons simply do not move over to give the more stable diene isomers. The reason is that both these reactions involve the conversion of a cyclobutane ring to a pair of double bonds (a $_s2 + {}_s2$ process) and, as we have seen, a thermal process of this sort is forbidden by the Woodward–Hoffmann rules. The process is allowed photochemically, and we are not surprised to find that both quadricyclane and hexamethylprismane are photochemically converted to the respective dienes at room temperature or below.[2257] It is also possible to conceive of simple

[2251]See, for example, Liu, R.S.H.; Hammond, G.S. *J. Am. Chem. Soc.* ***1967***, *89*, 4936; Kramer, B.D.; Bartlett, P.D. *J. Am. Chem. Soc.* ***1972***, *94*, 3934.

[2252]See, for example, Farid, S.; Doty, J.C.; Williams, J.L.R. *J. Chem. Soc., Chem. Commun.* ***1972***, 711; Mizuno, K.; Pac, C.; Sakurai, H. *J. Am. Chem. Soc.* ***1974***, *96*, 2993; Caldwell, R.A.; Creed, D. *Acc. Chem. Res.* ***1980***, *13*, 45; Mattes, S.L.; Farid, S. *Acc. Chem. Res.* ***1982***, *15*, 80; Swapna, G.V.T.; Lakshmi, A.B.; Rao, J.M.; Kunwar, A.C. *Tetrahedron* ***1989***, *45*, 1777.

[2253]For a review of exciplexes, see Davidson, R.S. *Adv. Phys. Org. Chem.* ***1983***, *19*, 1–130.

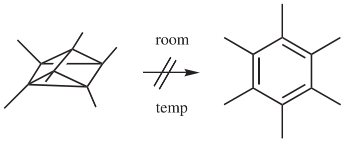
[2254]Schuster, D.I.; Heibel, G.E.; Brown, P.B.; Turro, N.J.; Kumar, C.V. *J. Am. Chem. Soc.* ***1988***, *110*, 8261.

[2255]This compound can be prepared by photolysis of **210**, another example of an intramolecular photochemical [2 + 2]-cycloaddition: Lemal, D.M.; Lokensgard, J.P. *J. Am. Chem. Soc.* ***1966***, *88*, 5934; Schäfer, W.; Criegee, R.; Askani, R.; Grüner, H. *Angew. Chem. Int. Ed.* ***1967***, *6*, 78.

[2256]For a review of this compound, see Schäfer, W.; Hellmann, H. *Angew. Chem. Int. Ed.* ***1967***, *6*, 518.

[2257]These conversions can also be carried out by the use of transition-metal catalysts: Hogeveen, H.; Volger, H.C. *Chem. Commun.* ***1967***, 1133; *J. Am. Chem. Soc.* ***1967***, *89*, 2486; Kaiser, K.L.; Childs, R.F.; Maitlis, P.M. *J. Am. Chem. Soc.* ***1971***, *93*, 1270; Landis, M.E.; Gremaud, D.; Patrick, T.B. *Tetrahedron Lett.* ***1982***, *23*, 375; Maruyama, K.; Tamiaki, H. *Chem. Lett.* ***1987***, 683.

bond rearrangements whereby hexamethylprismane is converted to hexamethylbenzene, which



of course is far more stable than either hexamethylprismane or **214**. It has been calculated that hexamethylbenzene is at least 90 kcal mol^{-1} (380 kJ mol^{-1}) more stable than hexamethylprismane. The fact that hexamethylprismane does not spontaneously undergo this reaction has prompted the observation[2258] that the prismane has "the aspect of an angry tiger unable to break out of a paper cage." However, a correlation diagram for this reaction[2259] discloses that it too is a symmetry-forbidden process. All three of these "forbidden" reactions do take place when the compounds are heated, but the diradical mechanism is likely under these conditions.[2259]

Bicyclo[2.2.0]hexadienes and prismanes are *valence isomers* of benzenes.[2260] These compounds actually have the structures that were proposed for benzenes in the nineteenth century. Prismanes have the Ladenburg formula, and bicyclo[2.2.0]hexadienes have the Dewar formula. Because of this bicyclo[2.2.0]hexadiene is often called Dewar benzene. On p. 32, it was mentioned that Dewar formulas are canonical forms (although not very important) of benzenes. Yet they also exist as separate compounds in which the positions of the nuclei are different from those of benzenes.

OS **V**, 54, 235, 277, 297, 370, 393, 424, 459, 528; **VI**, 378, 571, 962, 1002, 1024, 1037; **VII**, 177, 256, 315; **VIII**, 82, 116, 306, 377; **IX**, 28, 275; **80**, 160. For the reverse reaction, see OS **V**, 734.

15-64 The Addition of Carbenes and Carbenoids to Double and Triple Bonds

***epi*-Methylene-addition**

[2258]Woodward, R.B.; Hoffmann, R. *The Conservation of Orbital Symmetry* Acaademic Press, NY, ***1970***, pp. 107–112.

[2259]See, for example, Oth, J.F.M. *Recl. Trav. Chim. Pays-Bas* ***1968***, *87*, 1185.

[2260]For reviews of valence isomers of benzene, see Kobayashi, Y.; Kumadaki, I. *Adv. Heterocycl. Chem.* ***1982***, *31*, 169; *Acc. Chem. Res.* ***1981***, *14*, 76; van Tamelen, E.E. *Acc. Chem. Res.* ***1972***, *5*, 186; *Angew. Chem. Int. Ed.* ***1965***, *4*, 738; Bolesov, I.G. *Russ. Chem. Rev.* ***1968***, *37*, 666; Viehe, H.G. *Angew. Chem. Int. Ed.* ***1965***, *4*, 746; Schäfer, W.; Hellmann, H. *Angew. Chem. Int. Ed.* ***1967***, *6*, 518.

Carbenes and substituted carbenes add to double bonds to give cyclopropane derivatives by what can be considered as a formal [1 + 2]-cycloaddition.[2261] Many carbene derivatives, for example, PhCH, ROCH,[2262] $Me_2C{=}C$, $C(CN)_2$, have been added to double bonds, but the reaction is often performed with CH_2 itself, with halo and dihalocarbenes,[2263] and with carbalkoxycarbenes[2264] (generated from diazoacetic esters). Alkylcarbenes HCR have been added to alkenes,[2265] but more often these rearrange to give alkenes (p. 291). The carbene can be generated in any of the ways normally used (p. 287). However, most reactions in which a cyclopropane is formed by treatment of an alkene with a carbene "precursor" do not actually involve free carbene intermediates. In some cases, it is certain that free carbenes are not involved, and in other cases there is doubt. Because of this, the term *carbene transfer* is often used to cover all reactions in which a double bond is converted to a cyclopropane, whether a carbene or a carbenoid (p. 288) is actually involved.

Carbene itself ($:CH_2$) is extremely reactive and gives many side reactions, especially insertion reactions (**12-21**), which greatly reduce yields. This competition is also true with rhodium-catalyzed diazoalkane cyclopropanations[2266] (see below). When it is desired to add $:CH_2$ for preparative purposes, free carbene is not used, but the Simmons–Smith procedure (p. 1241) or some other method that does not involve free carbenes is employed instead. Halocarbenes are less active than carbenes, and this reaction proceeds quite well, since insertion reactions do not interfere.[2267] The absolute rate constant for addition of selected alkoxychlorocarbene to butenes has been measured to range from 330 to $1 \times 10^4 M^{-1}$ s^{-1}.[2268] A few of the many ways[2269] in which halocarbenes or carbenoids are generated for

[2261]For reviews, see, in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, Wiley, NY, ***1987***, the reviews by Tsuji, T.; Nishida, S., pt. 1, pp. 307–373; Verhé, R.; De Kimpe, N. pt. 1, pp. 445–564; Marchand, A.P., in Patai, S. *Supplement A: The Chemistry of Double-Bonded Functional Groups*, pt. 1, Wiley, NY, ***1977***, pp. 534–607, 625–635; Bethell, D., in McManus, S.P. *Organic Reactive Intermediates*; Academic Press, NY, ***1973***, pp. 101–113; in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, ***1964***, the articles by Cadogan, J.I.G.; Perkins, M.J. pp. 633–671; Huisgen, R.; Grashey, R.; Sauer, J. pp. 755–776; Kirmse, W. *Carbene Chemistry* 2nd ed.; Academic Press, NY, ***1971***, pp. 85–122, 267–406. For a review of certain intramolecular additions, see Burke, S.D.; Grieco, P.A. *Org. React.* ***1979***, *26*, 361. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 135–153.

[2262]For a review, see Schöllkopf, U. *Angew. Chem. Int. Ed.* ***1968***, *7*, 588.

[2263]For a review of the addition of halocarbenes, see Parham, W.E.; Schweizer, E.E. *Org. React.* ***1963***, *13*, 55.

[2264]For a review, see Dave, V.; Warnhoff, E.W. *Org. React.* ***1970***, *18*, 217.

[2265]For example see Frey, H.M. *J. Chem. Soc.* ***1962***, 2293.

[2266]Doyle, M.P.; Phillips, I.M. *Tetrahedron Lett.* ***2001***, *42*, 3155. For a review, see Merlic, C.A.; Zechman, A.L. *Synthesis* ***2003***, 1137.

[2267]For reviews of carbene selectivity in this reaction, see Moss, R.A. *Acc. Chem. Res.* ***1989***, *22*, 15; ***1980***, *13*, 58. For a review with respect to halocarbenes, see Kostikov, R.R.; Molchanov, A.P.; Khlebnikov, A.F. *Russ. Chem. Rev.* ***1989***, *58*, 654.

[2268]Moss, R.A.; Ge, C.-S.; Wostowska, J.; Jang, E.G.; Jefferson, E.A.; Fan, H. *Tetrahedron Lett.* ***1995***, *36*, 3083.

[2269]Much of the work in this field has been carried out by Seyferth, D. and co-workers; see, for example, Seyferth, D.; Haas, C.K. *J. Org. Chem.* ***1975***, *40*, 1620; Seyferth, D.; Haas, C.K.; Dagani, D. *J. Organomet. Chem.* ***1976***, *104*, 9.

this reaction are the following,[2270] most of which involve formal elimination (the first two steps of the S_N1cB mechanism, p. 521):

$$CH_2Cl_2 + RLi \longrightarrow CHCl$$

$$N_2CHBr \xrightarrow{h\nu} CHBr$$

$$CHCl_3 + {}^{-}OH \longrightarrow CCl_2$$

$$PhHgCCl_2Br \xrightarrow{\Delta} CCl_2 \quad \text{Ref. }^{2271}$$

$$Me_3SnCF_3 + NaI \longrightarrow CF_2 \quad \text{Ref. }^{2272}$$

$$Me_2CBr_2 \xrightarrow{\text{electrolysis}} Me_2C\!: \quad \text{Ref. }^{2273}$$

The reaction between $CHCl_3$ and HO– is often carried out under phase transfer conditions.[2274] It has been shown that the reaction between $PhCHCl_2$ and *t*-BuOK produces a carbenoid, but when the reaction is run in the presence of a crown ether, the free Ph(Cl)C: is formed instead.[2275] The reaction of iodoform and $CrCl_2$ leads to iodocyclopropanes upon reaction with alkenes.[2276] Dihalocyclopropanes are very useful compounds[2277] that can be reduced to cyclopropanes, treated with magnesium or sodium to give allenes (**18-3**), or converted to a number of other products.

Alkenes of all types can be converted to cyclopropane derivatives by this reaction, but difficulty may be encountered with sterically hindered ones.[2278]

[2270]A much longer list, with references, is given, in Kirmse, W. *Carbene Chemistry Carbene Chemistry* 2nd ed., Academic Press, NY, ***1971***, pp. 313–319. See also, Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 135–143.

[2271]For a review of the use of phenyl(trihalomethyl)mercury compounds as dihalocarbene or dihalocarbenoid precursors, see Seyferth, D. *Acc. Chem. Res.* ***1972***, *5*, 65. For a review of the synthesis of cyclopropanes with the use of organomercury reagents, see Larock, R.C. *Organomercurcury Compounds in Organic Synthesis*, Springer, NY, ***1985***, pp. 341–380.

[2272]For reviews of flourinated carbenes, see Seyferth, D., in Moss, R.A.; Jones, Jr., M. *Carbenes*, Vol. 2, Wiley, NY, ***1975***, pp. 101–158; Sheppard, W.A.; Sharts, C.M. *Organic Fluorine Chemistry*, W. A. Benjamin, NY, ***1969***, pp. 237–270.

[2273]Léonel, E.; Paugam, J.P.; Condon-Gueugnot, S.; Nédélec, Y.-Y. *Tetrahedron* ***1998***, *54*, 3207.

[2274]For reviews of the use of phase-transfer catalysis in the addition of dihalocarbenes to C=C bonds, see Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Academic Press, NY, ***1978***, pp. 224–268; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, ***1977***, pp. 18–43, 58–62. For a discussion of the mechanism, see Gol'dberg, Yu.Sh.; Shimanskaya, M.V. *J. Org. Chem. USSR* ***1984***, *20*, 1212.

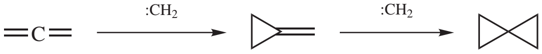
[2275]Moss, R.A.; Pilkiewicz, F.G. *J. Am. Chem. Soc.* ***1974***, *96*, 5632; Moss, R.A.; Lawrynowicz, W. *J. Org. Chem.* ***1984***, *49*, 3828.

[2276]Takai, K.; Toshikawa, S.; Inoue, A.; Kokumai, R. *J. Am. Chem. Soc.* ***2003***, *125*, 12990.

[2277]For reviews of dihalocyclopropanes, see Banwell, M.G.; Reum, M.E. *Adv. Strain Org. Chem.* ***1991***, *1*, 19–64; Kostikov, R.R.; Molchanov, A.P.; Hopf, H. *Top. Curr. Chem.* ***1990***, *155*, 41–80; Barlet, R.; Vo-Quang, Y. *Bull. Soc. Chim. Fr.* ***1969***, 3729–3760.

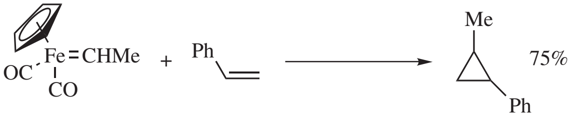
[2278]Dehmlow, E.V.; Eulenberger, A. *Liebigs Ann. Chem.* ***1979***, 1112.

Even tetracyanoethylene, which responds very poorly to electrophilic attack, gives cyclopropane derivatives with carbenes.[2279] Conjugated dienes give 1,2-addition to give a vinylcyclopropane.[2280] Addition of a second mole gives bicyclopropyl derivatives.[2281] 1,4-Addition is rare but has been reported in certain cases.[2282] Carbene adds to ketene to give cyclopropanone.[2283] Allenes react with carbenes to give cyclopropanes with exocyclic unsaturation:[2284]



A second equivalent gives spiropentanes. In fact, any size ring with an exocyclic double bond can be converted by a carbene to a spiro compound.[2285]

Free carbenes can also be avoided by using transition-metal–carbene complexes $L_nM{=}CRR'$ (L = a ligand, M = a metal),[2286] which add the group CRR′ to double bonds.[2287] An example is the reaction of iron carbene **215**.[2288]



215

These complexes can be isolated in some cases; in others they are generated *in situ* from appropriate precursors, of which diazo compounds are among the

[2279]Cairns, T.L.; McKusick, B.C. *Angew. Chem.* ***1961***, *73*, 520.

[2280]Woodworth, R.C.; Skell, P.S. *J. Am. Chem. Soc.* ***1957***, *79*, 2542.

[2281]Orchin, M.; Herrick, E.C. *J. Org. Chem.* ***1959***, *24*, 139; Nakhapetyan, L.A.; Safonova, I.L.; Kazanskii, B.A. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1962***, 840; Skattebøl, L. *J. Org. Chem.* ***1964***, *29*, 2951.

[2282]Anastassiou, A.G.; Cellura, R.P.; Ciganek, E. *Tetrahedron Lett.* ***1970***, 5267; Jefford, C.W.; Mareda, J.; Gehret, J-C.E.; Kabengele, T.; Graham, W.D.; Burger, U. *J. Am. Chem. Soc.* ***1976***, *98*, 2585; Mayr, H.; Heigl, U.W. *Angew. Chem. Int. Ed.* ***1985***, *24*, 579; Le, N.A.; Jones, Jr., M.; Bickelhaupt, F.; de Wolf, W.H. *J. Am. Chem. Soc.* ***1989***, *111*, 8491; Kraakman, P.A.; de Wolf, W.H.; Bickelhaupt, F. *J. Am. Chem. Soc.* ***1989***, *111*, 8534; Hudlický, T.; Seoane, G.; Price, J.D.; Gadamasetti, K.G. *Synlett* ***1990***, 433; Lambert, J.B.; Ziemnicka-Merchant, B.T. *J. Org. Chem.* ***1990***, *55*, 3460.

[2283]Turro, N.J.; Hammond, W.B. *Tetrahedron* ***1968***, *24*, 6017; Rothgery, E.F.; Holt, R.J.; McGee, Jr., H.A. *J. Am. Chem. Soc.* ***1975***, *97*, 4971. For a review of cyclopropanones, see Wasserman, H.H.; Berdahl, D.R.; Lu, T., in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, Wiley, NY, ***1987***, pt. 2, pp. 1455–1532.

[2284]For reviews of the addition of carbenes and carbenoids to allenes, see Landor, S.R., in Landor, S.R. *The Chemistry of Allenes,* Vol. 2, Academic Press, NY, ***1982***, pp. 351–360; Bertrand, M. *Bull. Soc. Chim. Fr.* ***1968***, 3044–3054. For a review of the synthetic uses of methylenecyclopropanes and cyclopropenes, see Binger, P.; Büch, H.M. *Top. Curr. Chem.* ***1987***, *135*, 77.

[2285]For a review of the preparation of spiro compounds by this reaction, see Krapcho, A.P. *Synthesis* ***1978***, 77–126.

[2286]Doyle, M.P.; McKervey, M.A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley, NY, ***1998***.

[2287]For reviews, see Helquist, P. *Adv. Met.-Org. Chem.* ***1991***, *2*, 143; Brookhart, M.; Studabaker, W.B. *Chem. Rev.* ***1987***, *87*, 411; Syatkovskii, A.I.; Babitskii, B.D. *Russ. Chem. Rev.* ***1984***, *53*, 672.

[2288]Brookhart, M.; Tucker, J.R.; Husk, G.R. *J. Am. Chem. Soc.* ***1983***, *105*, 258.

most important. Chromium complexes have been used for the cyclopropanation of alkenes.[2289]

Polymer-supported benzenesulfonyl azides have been developed as a safe diazo-transfer reagent.[2290] These compounds, including CH_2N_2 and other diazoalkanes, react with metals or metal salts (copper, palladium,[2291] and rhodium are most commonly used) to give the carbene complexes that add: CRR′ to double bonds.[2292] Diazoketones and diazoesters with alkenes to give the cyclopropane derivative, usually with a transition-metal catalyst, such as a copper complex.[2293] The ruthenium catalyst reaction of diazoesters with an alkyne give a cyclopropene.[2294] An X-ray structure of an osmium catalyst intermediate has been determined.[2295] Electron-rich alkenes react faster than simple alkenes.[2296]

Optically active complexes have been used for enantioselective cyclopropane synthesis.[2297] Decomposition of diazoalkanes in the presence of chiral rhodium[2298] copper,[2299] or ruthenium[2300] complexes leads to optically active cyclopropanes.

[2289]Barluenga, J.; Aznar, F.; Gutiérrez, I.; García-Granda, S. Llorca-Baragaño, M.A. *Org. Lett.* ***2002***, *4*, 4233.

[2290]Green, G.M.; Peet, N.P.; Metz, W.A. *J. Org. Chem.* ***2001***, *66*, 2509.

[2291]For a discussion of the mechanism of the palladium-catalyzed reaction, see Rodríguez-García, C.; Oliva, A.; Ortuño, R.M.; Branchadell, V. *J. Am. Chem. Soc.* ***2001***, *123*, 6157.

[2292]For reviews, see Adams, J.; Spero, D.M. *Tetrahedron* ***1991***, *47*, 1765; Collman, J.P., Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry* University Science Books, Mill Valley, CA ***1987***, pp. 800–806; Maas, G. *Top. Curr. Chem.* ***1987***, *137*, 75; Doyle, M.P. *Chem. Rev.* ***1986***, *86*, 919; *Acc. Chem. Res.* ***1986***, *19*, 348; Heck, R.F. *Palladium Reagents in Organic Synthesis*, Academic Press, NY, ***1985***, pp. 401–407; Wulfman, D.S.; Poling, B. *React. Intermed. (Plenum)* ***1980***, *1*, 321; Müller, E.; Kessler, H.; Zeeh, B. *Fortschr. Chem. Forsch.* ***1966***, *7*, 128.

[2293]Díaz-Requejo, M.M.; Belderraín, T.R.; Trofimenko, S.; Pérez, P.J. *J. Am. Chem. Soc.* ***2001***, *123*, 3167. For a discussion of the mechanism and selectivity, see Bühl, M.; Terstegen, F.; Löffler, F.; Meynhardt, B.; Kierse, S.; Müller, M.; Näther, C.; Lüning, U. *Eur. J. Org. Chem.* ***2001***, 2151.

[2294]Lou, Y.; Horikawa, M.; Kloster, R.A.; Hawryluk, N.A.; Corey, E.J. *J. Am. Chem. Soc.* ***2004***, *126*, 8916.

[2295]Li, Y.; Huang, J.-S.; Zhou, Z.-Y.; Che, C.-M. *J. Am. Chem. Soc.* ***2001***, *123*, 4843.

[2296]See Davies, H.M.L.; Xiang, B.; Kong, N.; Stafford, D.G. *J. Am. Chem. Soc.* ***2001***, *123*, 7461.

[2297]Brookhart, M.; Liu, Y.; Goldman, E.W.; Timmers, D.A.; Williams, G.D. *J. Am. Chem. Soc.* ***1991***, *113*, 927; Lowenthal, R.E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* ***1990***, *31*, 6005; Evans, D.A.; Woerpel, K.A.; Hinman, M.M.; Faul, M.M. *J. Am. Chem. Soc.* ***1991***, *113*, 726; Ito, K.; Katsuki, T. *Tetrahedron Lett.* ***1993***, *34*, 2661. For a review of enantioselective cyclopropanation using carbenoid chemistry see Singh, V.K.; DattaGupta, A.; Sekar, G. *Synthesis* ***1997***, 137. For the effect of diazoalkane structure of stereoselectivity, see Davies, H.M.L.; Bruzinski, P.R.; Fall, M.J. *Tetrahedron Lett.* ***1996***, *37*, 4133.

[2298]Davies, H.M.L.; Rusiniak, L. *Tetrahedron Lett.* ***1998***, *39*, 8811; Haddad, N.; Galili, N. *Tetrahedron Asymmetry* ***1997***, *8*, 3367; Ichiyanagi, T.; Shimizu, M.; Fujisawa, T. *Tetrahedron* ***1997***, *53*, 9599; Fukuda, T.; Katsuki, T. *Tetrahedron* ***1997***, *53*, 7201; Frauenkron M.; Berkessel, A. *Tetrahedron Lett.* ***1997***, *38*, 7175; Doyle, M.P.; Zhou, Q.-L.; Charnsangavej, C.; Longoria, M.A.; McKervey, M.A.; Garcia, C.F. *Tetrahedron Lett.* ***1996***, *37*, 4129.

[2299]Díaz-Requejo, M.M.; Caballero, A.; Belderraín, T.R.; Nicasio, M.C.; Trofimenko, S.; Pérez, P.J. *J. Am. Chem. Soc.* ***2002***, *124*, 978.

[2300]Uchida, T.; Irie, R.; Katsuki, T. *Synlett* ***1999***, 1163; Uchida, T.; Irie, R.; Katsuki, T. *Synlett* ***1999***, 1793; Iwasa, S.; Takezawa, F.; Tuchiya, Y.; Nishiyama, H. *Chem. Commun.* ***2001***, 59. For a discussion of the mechanism, see Oxgaard, J.; Goddard II, W.A. *J. Am. Chem. Soc.* ***2004***, *126*, 442.

The use of chiral additives with a rhodium complex also leads to cyclopropanes enantioselectively.[2301] An important chiral rhodium species is Rh_2(*S*-DOSP)$_4$,[2302] which leads to cyclopropanes with excellent enantioselectivity in carbene cyclopropanation reactions.[2303] Asymmetric, intramolecular cyclopropanation reactions have been reported.[2304] The copper catalyzed diazoester cyclopropanation was reported in an ionic liquid.[2305] It is noted that the reaction of a diazoester with a chiral dirhodium catalyst leads to β-lactones with modest enantioselectivity.[2306] Phosphonate esters have been incorporated into the diazo compound.[2307]

Triple-bond compounds[2308] react with carbenes to give cyclopropenes, except that in the case of acetylene itself, the cyclopropenes first formed cannot be isolated because they rearrange to allenes.[2309] Cyclopropenones (p. 73) are obtained by hydrolysis of dihalocyclopropenes.[2310]

Most carbenes are electrophilic, and, in accord with this, electron-donating substituents on the alkene increase the rate of the reaction, and electron-withdrawing groups decrease it,[2311] although the range of relative rates is not very great.[2312] As discussed on p. 284, carbenes in the singlet state (which is the most common state) react stereospecifically and syn,[2313] probably by a one-step mechanism,[2314] similar

[2301]Aggarwal, V.K.; Smith, H.W.; Hynd, G. ; Jones, R.V.H.; Fieldhouse, R.; Spey, S.E. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 3267; Yao, X.; Qiu, M.; Lü, W.; Chen, H.; Zheng, Z. *Tetrahedron Asymmetry* ***2001***, *12*, 197.

[2302]Doyle, M.P. *Pure Appl. Chem.* ***1998***, *70* 1123; Doyle, M.P.; Protopopova, M.N. *Tetrahedron* ***1998***, *54*, 7919; Martin, S.F.; Spaller, M.R.; Liras, L.; Hartman, B. *J. Am. Chem. Soc.* ***1994***, *116*, 4493; Davies, H.M.L.; Hansen, T.; Churchill, M.R. *J. Am. Chem. Soc.* ***2000***, *122*, 3063; Davies, H.M.L.; Hansen, T. *J. Am. Chem. Soc.* ***1997***, *119*, 9075. See also, Davies, H.M.L. *Aldrichimica Acta* ***1997***, *30*, 107. For related chiral ligands see Nagashima, T.; Davies, H.M.L. *Org. Lett.* ***2002***, *4*, 1989; Davies, H.M.L.; Lee, G.H. *Org. Lett.* ***2004***, *6*, 2117.

[2303]Davies, H.M.L.; Townsend, R.J. *J. Org. Chem.* ***2001***, *66*, 6595; Davies, H.M.; Boebel, T.A. *Tetrahedron Lett.* ***2000***, *41*, 8189.

[2304]Piqué, C.; Fähndrich, B.; Pfaltz, A. *Synlett* ***1995***, 491; Barberis, M.; Pérez-Prieto, J.; Stiriba, S.-E.; Lahuerta, P. *Org. Lett.* ***2001***, *3*, 3317; Saha, B.; Uchida, T.; Katsuki, T. *Synlett* ***2001***, 114; Honma, M.; Sawada, T.; Fujisawa, Y.; Utsugi, M.; Watanabe, H.; Umino, A.; Matsumura, T.; Hagihara, T.; Takano, M.; Nakada, M. *J. Am. Chem. Soc.* ***2003***, *125*, 2860.

[2305]In emim NTf_2, 1-ethyl-3-methylimidazolium triflimide: Fraile, J.M.; García, J.I.; Herrerías, C.I.; Mayoral, J.A.; Carrié, D.; Vaultier, M. *Tetrahedron Asymmetry* ***2001***, *12*, 1891.

[2306]Doyle, M.P.; May, E.J. *Synlett* ***2001***, 967.

[2307]Ferrand, Y.; Le Maux, P.; Simonneaux, G. *Org. Lett.* ***2004***, *6*, 3211.

[2308]For reviews, see Fuks, R.; Viehe, H.G., in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 427–434; Closs, G.L. *Adv. Alicyclic Chem.* ***1966***, *1*, 53–127, see pp. 58–65.

[2309]Frey, H.M. *Chem. Ind. (London)* ***1960***, 1266.

[2310]Vol'pin, M.E.; Koreshkov, Yu.D.; Kursanov, D.N. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1959***, 535.

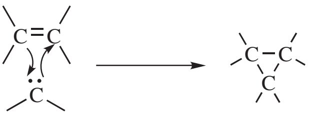
[2311]Skell, P.S.; Garner, A.Y. *J. Am. Chem. Soc.* ***1956***, *78*, 5430; Doering, W. von E.; Henderson, Jr., W.A. *J. Am. Chem. Soc.* ***1958***, *80*, 5274; Mitsch, R.A.; Rodgers, A.S. *Int. J. Chem. Kinet.* ***1969***, *1*, 439.

[2312]For a review of reactivity in this reaction, with many comprehensive tables of data, see Moss, R.A., in Jones, Jr. M.; Moss, R.A. *Carbenes*, Vol. 1, Wiley, NY, ***1973***, pp. 153–304. See also, Cox, D.P.; Gould, I.R.; Hacker, N.P.; Moss, R.A.; Turro, N.J. *Tetrahedron Lett.* ***1983***, *24*, 5313.

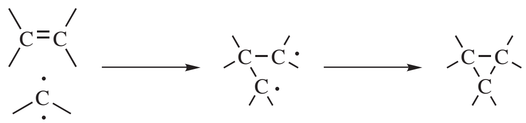
[2313]Woodworth, R.C.; Skell, P.S. *J. Am. Chem. Soc.* ***1959***, *81*, 3383; Jones Jr., M.; Ando, W.; Hendrick, M.E.; Kulczycki Jr., A.; Howley, P.M.; Hummel, K.F.; Malament, D.S. *J. Am. Chem. Soc.* ***1972***, *94*, 7469.

[2314]For evidence that at least some singlet carbenes add by a two-step mechanism, see Giese, B.; Lee, W.; Neumann, C. *Angew. Chem. Int. Ed.* ***1982***, *21*, 310.

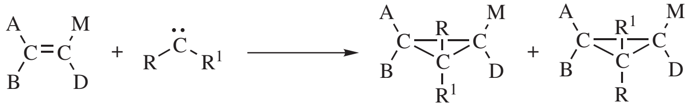
to mechanism *a* of **15-60** and **15-63**:



Infrared spectra of a carbene and the cyclopropane product have been observed in an argon matrix at 12–45 K.[2315] Carbenes in the triplet state react nonstereospecifically,[2316] probably by a diradical mechanism, similar to mechanism *b* of **15-49** and **15-63**:

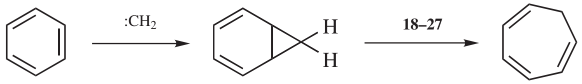


For carbenes or carbenoids of the type R—C—R′ there is another aspect of stereochemistry.[2317] When these species are added to all but symmetrical alkenes, two isomers are possible, even if the four groups originally on the double–bond carbons maintain their configurations:



Which isomer is predominantly formed depends on R, R′, and on the method by which the carbene or carbenoid is generated. Most studies have been carried out on monosubstituted species (R′ = H), and in these studies it is found that aryl groups generally prefer the more substituted side (syn addition) while carbethoxy groups usually show anti stereoselectivity. When R = halogen, free halocarbenes show little or no stereochemical preference, while halocarbenoids exhibit a preference for syn addition. Beyond this, it is difficult to make simple generalizations.

Carbenes are so reactive that they add to the "double bonds" of aromatic rings.[2318] The products are usually unstable and rearrange to give ring expansion. Carbene reacts with benzene to give cycloheptatriene (**216**),[2319]



Norcaradiene **216**

[2315]Nefedov, O.M.; Zuev, P.S.; Maltsev, A.K.; Tomilov, Y.V. *Tetrahedron Lett.* ***1989***, *30*, 763.

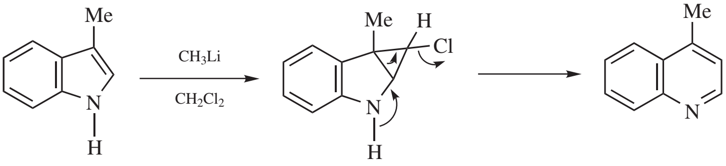
[2316]Skell, P.S.; Klebe, J. *J. Am. Chem. Soc.* ***1960***, *82*, 247. See also, Jones, Jr., M.; Tortorelli, V.J.; Gaspar, P.P.; Lambert, J.B. *Tetrahedron Lett.* ***1978***, 4257.

[2317]For reviews of the stereochemistry of carbene and carbenoid addition to double bonds, see Moss, R.A. *Sel. Org. Transform.*, ***1970***, *1*, 35–88; Closs, G.L. *Top Stereochem.* ***1968***, *3*, 193–235. For a discussion of enantioselectivity in this reaction, see Nakamura, A. *Pure Appl. Chem.* ***1978***, *50*, 37.

[2318]See Giese, C.M.; Hadad, C.M. *J. Org. Chem.* ***2002***, *67*, 2532.

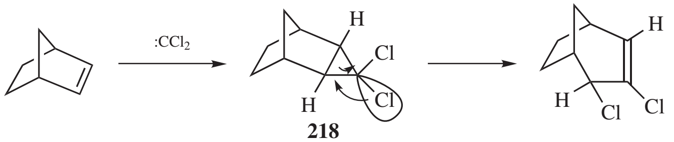
[2319]Doering, W. von E.; Knox, L.H. *J. Am. Chem. Soc.* ***1951***, *75*, 297.

but not all carbenes are reactive enough to add to benzene. The norcaradiene intermediate cannot be isolated in this case[2320] (it undergoes an electrocyclic rearrangement, **18-27**), although certain substituted norcaradienes, for example, the product of addition of: $C(CN)_2$ to benzene,[2321] have been isolated.[2322] With: CH_2, insertion is a major side reaction, and, for example, benzene gives toluene as well as cycloheptatriene. A method of adding: CH_2 to benzene rings without the use of free carbene is the catalytic decomposition of diazomethane (CH_2N_2) in the aromatic compound as solvent with CuCl or CuBr.[2323] By this method better yields of cycloheptatrienes are obtained without insertion side products. Picosecond optical grating calorimetry has been used to investigate the photochemical decomposition of diazomethane in benzene, and it appears that a transient is formed that is consistent with a weak complex between singlet methylene and benzene.[2324] Chlorocarbene, :CHCl, is active enough to add to benzene, but dihalocarbenes do not add to benzene or toluene, only to rings with greater electron density. Pyrroles and indoles can be expanded, respectively, to pyridines and quinolines by treatment with halocarbenes[2325] via the initially formed adduct **217** in the case of the indole.



217

In such cases, a side reaction that sometimes occurs is expansion of the *six-membered* ring. Ring expansion can occur even with non–aromatic compounds, when the driving force is supplied by relief of strain (see **218**).[2326]



218

[2320]It has been detected by uv spectroscopy: Rubin, M.B. *J. Am. Chem. Soc.* ***1981***, *103*, 7791.

[2321]Ciganek, E. *J. Am. Chem. Soc.* ***1967***, *89*, 1454.

[2322]See, for example, Mukai, T.; Kubota, H.; Toda, T. *Tetrahedron Lett.* ***1967***, 3581; Maier, G.; Heep, U. *Chem. Ber.* ***1968***, *101*, 1371; Ciganek, E. *J. Am. Chem. Soc.* ***1971***, *93*, 2207; Dürr, H.; Kober, H. *Tetrahedron Lett.* ***1972***, 1255, 1259; Vogel, E.; Wiedemann, W.; Roth, H.D.; Eimer, J.; Günther, H. *Liebigs Ann. Chem.* ***1972***, *759*, 1; Bannerman, C.G.F.; Cadogan, J.I.G.; Gosney, I.; Wilson, N.H. *J. Chem. Soc., Chem. Commun.* ***1975***, 618; Takeuchi, K.; Kitagawa, T.; Senzaki, Y.; Okamoto, K. *Chem. Lett.* ***1983***, 73; Kawase, T.; Iyoda, M.; Oda, M. *Angew. Chem. Int. Ed.* ***1987***, *26*, 559.

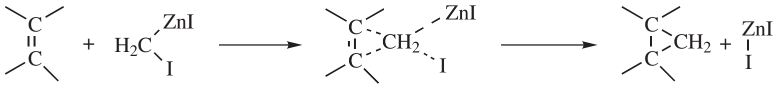
[2323]Wittig, G.; Schwarzenbach, K. *Liebigs Ann. Chem.* ***1961***, *650*, 1; Müller, E.; Fricke, H. *Liebigs Ann. Chem.* ***1963***, *661*, 38; Müller, E.; Kessler, H.; Fricke, H.; Kiedaisch, W. *Liebigs Ann. Chem.* ***1961***, *675*, 63.

[2324]Khan, M.I.; Goodman, J.L. *J. Am. Chem. Soc.* ***1995***, *117*, 6635.

[2325]For a review of the reactions of heterocyclic compounds with carbenes, see Rees, C.W.; Smithen, C.E. *Adv. Heterocycl. Chem.* ***1964***, *3*, 57–78.

[2326]Jefford, C.W.; Gunsher, J.; Hill, D.T.; Brun, P.; Le Gras, J.; Waegell, B. *Org. Synth.* ***VI***, 142. For a review of the addition of halocarbenes to bridged bicyclic alkenes see Jefford, C.W. *Chimia*, ***1970***, *24*, 357–363.

As previously mentioned, free carbene is not very useful for additions to double bonds since it gives too many side products. The *Simmons–Smith procedure* accomplishes the same result without a free carbene intermediate and without insertion side products.[2327] This procedure involves treatment of the double-bond compound with CH_2I_2 and a Zn–Cu couple and leads to cyclopropane derivatives in good yields.[2328] The Zn–Cu couple can be prepared in several ways,[2329] of which heating Zn dust with CuCl in ether under nitrogen[2330] is particularly convenient. The reaction has also been done with unactivated zinc and ultrasound.[2331] When $TiCl_4$ is used along with Zn and CuCl, CH_2I_2 can be replaced by the cheaper CH_2Br_2.[2332] The actual attacking species is an organozinc intermediate, probably $(ICH_2)_2Zn{\bullet}ZnI_2$, which is stable enough for isolable solutions.[2333] An X-ray crystallographic investigation of the intermediate, complexed with a diether, has been reported.[2334] The addition is stereospecifically syn, and a concerted mechanism[2335] is likely, perhaps[2336]



Asymmetric induction is possible when chiral additives are used.[2337] With the Simmons–Smith procedure, as with free carbenes, conjugated dienes give 1,2-addition,[2338] and allenes give methylenecyclopropanes or spiropentanes.[2339]

An alternative way of carrying out the Simmons–Smith reaction is by treatment of the substrate with CH_2I_2 or another dihalomethane and Et_2Zn in ether.[2340] This method can be adapted to the introduction of RCH and ArCH by the use of $RCHI_2$

[2327]For reviews, see Simmons, H.E.; Cairns, T.L.; Vladuchick, S.A.; Hoiness, C.M. *Org. React.* ***1973***, *20*, 1–131; Furukawa, J.; Kawabata, N. *Adv. Organomet. Chem.* ***1974***, *12*, 83–134, see pp. 84–103.

[2328]Simmons, H.E.; Smith, R.D. *J. Am. Chem. Soc.* ***1959***, *81*, 4256.

[2329]Shank, R.S.; Shechter, H. *J. Org. Chem.* ***1959***, *24*, 1525; LeGoff, E. *J. Org. Chem.* ***1964***, *29*, 2048. For the use of a Zn—Ag couple, see Denis, J.M.; Girard, C.; Conia, J.M. *Synthesis* ***1972***, 549.

[2330]Rawson, R.J.; Harrison, I.T. *J. Org. Chem.* ***1970***, *35*, 2057.

[2331]Repič; O.; Lee, P.G.; Giger, U. *Org. Prep. Proced. Int.* ***1984***, *16*, 25.

[2332]Friedrich, E.C.; Lunetta, S.E.; Lewis, E.J. *J. Org. Chem.* ***1989***, *54*, 2388.

[2333]Blanchard, E.P.; Simmons, H.E. *J. Am. Chem. Soc.* ***1964***, *86*, 1337. For an analysis of the reaction by density functional theory, see Fang, W.-H.; Phillips, D.L.; Wang, D.-q.; Li, Y.-L. *J. Org. Chem.* ***2002***, *67*, 154.

[2334]Denmark, S.E.; Edwards, J.P.; Wilson, S.R. *J. Am. Chem. Soc.* ***1991***, *113*, 723.

[2335]Dargel, T.K.; Koch, W. *J. Chem. Soc. Perkin Trans. 2*, ***1996***, 877.

[2336]Simmons, H.E.; Blanchard, E.P.; Smith, R.D. *J. Am. Chem. Soc.* ***1964***, *86*, 1347. For a discussion of the transition state and intermediate in this reaction, see Bernardi, F.; Bottoni, A.; Miscione, G.P. *J. Am. Chem. Soc.* ***1997***, *119*, 12300.

[2337]Charette, A.B.; Juteau, H.; Lebel, H.; Molinaro, C. *J. Am. Chem. Soc.* ***1998***, *120*, 11943; Kitajima, H.; Ito, K.; Aoki, Y.; Katsuki, T. *Bull. Chem. Soc. Jpn.* ***1997***, *70*, 207; Imai, N.; Sakamoto, K.; Maeda, M.; Kouge, K.; Yoshizane, K.; Nokami, J. *Tetrahedron Lett*, ***1997***, *38*, 1423; Denmark, S.E.; Edwards, J.P. *Synlett* ***1992***, 229; Balsells, J.; Walsh, P.J. *J. Org. Chem.* ***2000***, *65*, 5005.

[2338]Overberger, C.G.; Halek, G.W. *J. Org. Chem.* ***1963***, *28*, 867.

[2339]Charette, A.B.; Jolicoeur, E.; Bydlinski, G.A.S. *Org. Lett.* ***2001***, *3*, 3293.

[2340]See Charette, A.B.; Beauchemin, A.; Marcoux, J.-F. *Tetrahedron Lett.* ***1999***, *40*, 33; Zhao, C.; Wang, D.; Phillips, D.L. *J. Am. Chem. Soc.* ***2002***, *124*, 12903.

or $ArCHI_2$ instead of the dihalomethane.[2341] The reaction is compatible with other functionality in the carbenoid complex. The reaction of RCO_2CH_2I with diethyl zinc and an alkene under photolysis conditions give a cyclopropane.[2342] Chiral additives lead to enantioselectivity in the cyclopropanation reaction.[2343] In another method, CH_2I_2 or $MeCHI_2$ is used along with an alane R_3Al to transfer CH_2 or CHMe.[2344] Titanium complexes have been used similarly.[2345] Samarium and CH_2I_2 has been used for the cyclopropanation of conjugated amides.[2346] For the conversion of enolates to cyclopropanols, CH_2I_2 has been used along with SmI_2.[2347]

Other cyclopropanation techniques have been developed. Treatment of an alkene with $ArCH(SnBu_3)OCO_2Me$ and $BF_3{\bullet}OEt_2$ leads to the cyclopropane with high cis-selectivity.[2348] Diodomethane in the presence of isopropylmagnesium chloride has been used to cyclopropanate allyl alcohols.[2349]

The Simmons–Smith reaction is the basis of a method for the indirect α methylation of a ketone.[2350] The ketone (illustrated for cyclohexanone) is first converted to an enol ether, an enamine (**16-13**) or silyl enol ether[2351] (**12-17**) and cyclopropanation via the Simmons–Smith reaction is followed by hydrolysis to give the α methylated ketone. A related procedure using diethylzinc and diiodomethane allows ketones to be chain-extended by one carbon.[2352] In another variation, phenols can be ortho-methylated in one laboratory step, by treatment with Et_2Zn and CH_2I_2.[2353]

Diazoesters react with amines with a rhodium catalyst to give α-amino esters.[2354] Diazoesters also react with aldehydes and a rhodium catalyst, and the product is an α,β-epoxy ester.[2355] Diazoalkanes react similarly with aldehydes to give an alkene ($Me_3SiCH{=}N_2 + ArCHO \rightarrow ArCH{=}CHOSiMe_3$).[2356]

OS **V**, 306, 855, 859, 874; **VI**, 87, 142, 187, 327, 731, 913, 974; **VII**, 12, 200, 203; **VIII**, 124, 196, 321, 467; **IX**, 422; **76**, 86.

[2341]Nishimura, J.; Kawabata, N.; Furukawa, J. *Tetrahedron* ***1969***, *25*, 2647; Miyano, S.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* ***1973***, *46*, 892; Friedrich, E.C.; Biresaw, G. *J. Org. Chem.* ***1982***, *47*, 1615.

[2342]Charette, A.B.; Beauchemin, A.; Fraancoeur, S. *J. Am. Chem. Soc.* ***2001***, *123*, 8139.

[2343]Long, J.; Yuan, Y.; Shi, Y. *J. Am. Chem. Soc.* ***2003***, *125*, 13632.

[2344]Maruoka, K.; Fukutani, Y.; Yamamoto, H. *J. Org. Chem.* ***1985***, *50*, 4412; *Org. Synth., 67*, 176.

[2345]Charette, A.B.; Molinaro, C.; Brochu, C. *J. Am. Chem. Soc.* ***2001***, *123*, 12168.

[2346]Concellón, J.M.; Rodríguez-Solla, H.; Gómez, C. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1917.

[2347]Imamoto, T.; Takiyama, N. *Tetrahedron Lett.* ***1987***, *28*, 1307. See also, Molander, G.A.; Harring, L.S. *J. Org. Chem.* ***1989***, *54*, 3525.

[2348]Sugawara, M.; Yoshida, J. *J. Am. Chem. Soc.* ***1997***, *119*, 11986.

[2349]Bolm, C.; Pupowicz, D. *Tetrahedron Lett.* ***197***, *38*, 7349.

[2350]See Wenkert, E.; Mueller, R.A.; Reardon Jr., E.J.; Sathe, S.S.; Scharf, D.J.; Tosi, G. *J. Am. Chem. Soc.* ***1970***, *92*, 7428 for the enol ether procedure; Kuehne, M.E.; King, J.C. *J. Org. Chem.* ***1973***, *38*, 304 for the enamine procedure; Conia, J.M. *Pure Appl. Chem.* ***1975***, *43*, 317–326 for the silyl ether procedure.

[2351]In the case of silyl enol ethers, the inner bond can be cleaved with $FeCl_3$, giving a ring-enlarged β-chloro ketone: Ito, Y.; Fujii, S.; Saegusa, T. *J. Org. Chem.* ***1976***, *41*, 2073; *Org. Synth.* ***VI***, 327.

[2352]Brogan, J.B.; Zercher, C.K. *J. Org. Chem.* ***1997***, *62*, 6444.

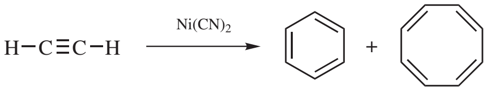
[2353]Lehnert, E.K.; Sawyer, J.S.; Macdonald, T.L. *Tetrahedron Lett.* ***1989***, *30*, 5215.

[2354]Yang, M.; Wang, X.; Li, H.; Livant, P. *J. Org. Chem.* ***2001***, *66*, 6729.

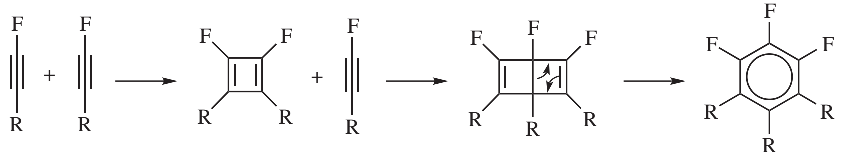
[2355]Doyle, M.P.; Hu, W.; Timmons, D.J. *Org. Lett.* ***2001***, *3*, 933.

[2356]Dias, E.L.; Brookhart, M.; White, P.S. *J. Am. Chem. Soc.* ***2001***, *123*, 2442.

15-65 Trimerization and Tetramerization of Alkynes



Aromatic compounds can be prepared by cyclotrimerization of alkynes[2357] or triynes. Cyclotrimerization is possible by heating to 450–600°C with no catalyst.[2358] The *spontaneous* (no catalyst) trimerization of *t*-BuC≡CF gave 1,2,3-tri-*tert*-butyl-4,5,6-trifluorobenzene (**220**), the first time three adjacent *tert*-butyl groups had been put onto a benzene ring.[2359] The fact that this is a head-to-head joining allows formation of **220** from two alkynes. The fact that **219** (a Dewar benzene) was also isolated lends support to this scheme.[2360] Three equivalents of 3-hexyne trimerized to hexaethylbenzene at 200°C in the presence of Si_2Cl_6.[2361]



R = *tert*-butyl **219** **220**

When acetylene is heated with nickel cyanide, other Ni(II) or Ni(0) compounds, or similar catalysts, it gives benzene and cyclooctatetraene.[2362] It is possible to get more of either product by a proper choice of catalyst. Substituted acetylenes give substituted benzenes.[2363] This reaction has been used to prepare very crowded

[2357]For a review, see Rubin, M.; Sromek, A.W.; Gevorgyan, V. *Synlett* ***2003***, 2265.

[2358]Kociolek, M.G.; Johnson, R.P. *Tetrahedron Lett.* ***1999***, *40*, 4141.

[2359]Viehe, H.G.; Merényi, R.; Oth, J.F.M.; Valange, P. *Angew. Chem. Int. Ed.* ***1964***, *3*, 746; Viehe, H.G.; Merényi, R.; Oth, J.F.M.; Senders, J.R.; Valange, P. *Angew. Chem. Int. Ed.* ***1964***, *3*, 755.

[2360]For other reactions between cyclobutadienes and triple bonds to give Dewar benzenes, see Wingert, H.; Regitz, M. *Chem. Ber.* ***1986***, *119*, 244.

[2361]Yang, J.; Verkade, J.G. *J. Am. Chem. Soc.* ***1998***, *120*, 6834.

[2362]For reviews, see Winter, M.J., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 3, Wiley, NY, ***1985***, pp. 259–294; Vollhardt, K.P.C. *Angew. Chem. Int. Ed.* ***1984***, *23*, 539; *Acc. Chem. Res.* ***1977***, *10*, 1; Maitlis, P.M. *J. Organomet. Chem.* ***1980***, *200*, 161; *Acc. Chem. Res.* ***1976***, *9*, 93; *Pure Appl. Chem.* ***1972***, *30*, 427; Yur'eva, L.P. *Russ. Chem. Rev.* ***1974***, *43*, 48; Khan, M.M.T.; Martell, A.E. *Homogeneous Catalysis by Metal Complexes*, Vol. 2, Academic Press, NY, **1974**, pp. 163–168; Reppe, W.; Kutepow, N.V.; Magin, A. *Angew. Chem. Int. Ed.* ***1969***, *8*, 727; Fuks, R.; Viehe, H.G. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 450–460; Hoogzand, C.; Hübel, W., in Wender, I.; Pino, P. *Organic Syntheses Via Metal Carbonyls*, Vol. 1, Wiley, NY, ***1968***, pp. 343–371; Reikhsfel'd, V.O.; Makovetskii, K.L. *Russ. Chem. Rev.* ***1966***, *35*, 510. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 198–201. For a review of metal-catalyzed cycloadditions of alkynes to give rings of all sizes, see Schore, N.E. *Chem. Rev.* ***1988***, *88*, 1081.

[2363]Sigman, M.S.; Fatland, A.W.; Eaton, B.E. *J. Am. Chem. Soc.* ***1998***, *120*, 5130; Gevorgyan, V.; Takeda, A.; Yamamoto, Y. *J. Am. Chem. Soc.* ***1997***, *119*, 11313; Takeda, A.; Ohno, A.; Kadota, I.; Gevorgyan, V.; Yamamoto, Y. *J. Am. Chem. Soc.* ***1997***, *119*, 4547; Larock, R.C.; Tian, Q. *J. Org. Chem.* ***1998***, *63*, 2002; Sato, Y.; Nishimata, T.; Mori, M. *J. Org. Chem.* ***1994***, *59*, 6133; Grissom, J.W.; Calkins, T.L. *Tetrahedron Lett.* ***1992***, *33*, 2315.

molecules. Diisopropylacetylene was trimerized over $CO_2(CO)_8$[2364] and over $Hg[Co(CO)_4]_2$ to hexaisopropylbenzene.[2365] The six isopropyl groups are not free to rotate but are lined up perpendicular to the plane of the benzene ring. Highly substituted benzene derivatives have also been prepared using a rhodium,[2366] nickel,[2367] titanium,[2368] molybdenum,[2369] ruthenium,[2370] cobalt,[2371] or a palladium[2372] catalyst. Alkynes react with allenes and a nickel catalyst go give highly substituted benzene derivatives.[2373] Conjugated ketones react with internal alkynes with Me_3Al and a nickel catalyst[2374] leads to an aromatic ring fused to a cyclic ketone after reaction with DBU and air.[2375] *N*-Aryl chloroimines react with alkynes and a rhodium catalyst to give quinolines,[2376] as do *N*-aryl alkynyl imines with a tungsten complex.[2377]

An intramolecular cyclotrimerization has been reported by condensation of a diyne[2378] with an alkyne in the presence of a palladium,[2379] molybdenum,[2380] nickel,[2381] rhodium,[2382] iridium,[2383] or ruthenium catalyst.[2384] Triynes have been

[2364]See Yong, L.; Butenschön, H. *Chem. Commun.* ***2002***, 2852. For a modification that gives a phenol from 3,3-dimethyl-1-butyne, see Marchueta, I.; Olivella, S.; Solà, L.; Moyano, A.; Pericàs, M.A.; Riera, A. *Org. Lett.* ***2001***, *3*, 3197.

[2365]Arnett, E.M.; Bollinger, J.M. *J. Am. Chem. Soc.* ***1964***, *86*, 4729; Hopff, H.; Gati, A. *Helv. Chim. Acta* ***1965***, *48*, 509.

[2366]Taber, D.F.; Rahimizadeh, M. *Tetrahedron Lett.* ***1994***, *35*, 9139; Tanaka, K.; Shirasaka, K. *Org. Lett.* ***2003***, *5*, 4697.

[2367]Mori, N.; Ikeda, S.-i.; Odashima, K. *Chem. Commun.* ***2001***, 181.

[2368]Tanaka, R.; Nakano, Y.; Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* ***2002***, *124*, 9682.

[2369]Nishida, M.; Shiga, H.; Mori, M. *J. Org. Chem.* ***1998***, *63*, 8606.

[2370]Yamamoto, Y.; Ishii, J.-i.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* ***2004***, *126*, 3712.

[2371]Sugihara, T.; Wakabayashi, A.; Nagai, Y.; Takao, H.; Imagawa, H.; Nishizawa, M. *Chem. Commun.* ***2002***, 576.

[2372]Gevorgyan, V.; Takeda, A.; Homma, M.; Sadayori, N.; Radhakrishnan, U.; Yamamoto, Y. *J. Am. Chem. Soc.* ***1999***, *121*, 6391; Gevorgyan, V.; Quan, L.G.; Yamamoto, Y. *J. Org. Chem.* ***2000***, *65*, 568. For a reaction in conjunction with silver carbonate, see Kawasaki, S.; Satoh, T.; Miura, M.; Nomura, M. *J. Org. Chem.* ***2003***, *68*, 6836; In conjunction with $CuCl_2$, see Li, J.-H.; Xie, Y.-X. *Synth. Commun.* ***2004***, *34*, 1737.

[2373]Shanmugasundaram, M.; Wu, M.-S.; Cheng, C.-H. *Org. Lett.* ***2001***, *3*, 4233.

[2374]Ikeda, S.; Kondo, H.; Arii, T.; Odashima, K. *Chem. Commun.* ***2002***, 2422.

[2375]Mori, N.; Ikeda, S.-i.; Sato, Y. *J. Am. Chem. Soc.* ***1999***, *121*, 2722.

[2376]Amii, H.; Kishikawa, Y.; Uneyama, K. *Org. Lett.* ***2001***, *3*, 1109.

[2377]Sangu, K.; Fuchibe, K.; Akiyama, T. *Org. Lett.* ***2004***, *6*, 353.

[2378]See Kawathar, S.P.; Schreiner, P.R. *Org. Lett.* ***2002***, *4*, 3643.

[2379]Yamamoto, Y.; Nagata, A.; Itoh, K. *Tetrahedron Lett.* ***1999***, *40*, 5035; Gevorgyan, V.; Radhakrishnan, U.; Takeda, A.; Rubina, M.; Rubin, M.; Yamamoto, Y. *J. Org. Chem.* ***2001***, *66*, 2835. See also, Tsukada, N.; Sugawara, S.; Nakaoka, K.; Inoue, Y. *J. Org. Chem.* ***2003***, *68*, 5961.

[2380]Hara, R.; Guo, Q.; Takahashi, T. *Chem. Lett.* ***2000***, 140.

[2381]Jeevanandam, A.; Korivi, R.P.; Huang, I.-w.; Cheng, C.-H. *Org. Lett.* ***2002***, *4*, 807.

[2382]Witulski, B.; Zimmermann, A. *Synlett* ***2002***, 1855.

[2383]Takeuchi, R.; Tanaka, S.; Nakaya, Y. *Tetrahedron Lett.* ***2001***, *42*, 2991; Shibata, T.; Fujimoto, T.; Yokota, K.; Takagi, K. *J. Am. Chem. Soc.* ***2004***, *126*, 8382.

[2384]Yamamoto, Y.; Ogawa, R.; Itoh, K. *Chem. Commun.* ***2000***, 549; Witulski, B.; Stengel, T.; Fernández-Hernandez, J.M. *Chem. Commun.* ***2000***, 1965.

similarly condensed with a rhodium catalyst.[2385] The internal cyclotrimerization of a triyne, utilizing a siloxy tether and a cobalt catalyst has been reported.[2386] Fused ring aromatic compounds are prepared by this method. Similar results were obtained from diynes and allenes with a nickel catalyst.[2387] bis(Enynes) are cyclized to bicyclic arenes using a palladium catalyst.[2388] Diynes with nitriles and a ruthenium catalyst lead to isoquinolines.[2389] Pyridines fused to carboxylic rings can be prepared by similar methodology using a cyanoamine and a cobalt catalyst.[2390] In the presence of $PhMe_2SiH$, CO and a rhodium catalyst, a nonconjugated triyne leads to a tricyclic compound in which a benzene ring is fused to two carbocyclic rings.[2391] Internal cyclotrimerization of an aryl alkynyl ketone where the aryl group has an *ortho* trimethylsiylalkyne substituent gives a tetracyclic naphthalene derivative with a fused cyclopentanone unit.[2392] An isocyanate (Ar—N=C=O) reacts with a diyne and a ruthenium catalyst to give a bicyclic pyridone.[2393] Benzene derivatives with ortho alkyne units can be converted to naphthalene derivatives in aqueous NaOH with hydrazine, Te, $NaBH_4$ and sonication.[2394] Benzene derivatives having ortho imine and alkyne substituents give an isoquinoline when treated with iodine[2395] or with a palladium catalyst.[2396] Imino and iodo substituents with a silyl alkyne and a palladium catalyst leads to an isoquinoline.[2397] Vinyl and alkyne substituents with a ruthenium catalyst lead to naphthalene derivatives.[2398] Ortho alkynyl and epoxy substituents leads to β-naphthols using a ruthenium catalyst.[2399] Cyclotrimerization occurs with alkynyl boronic esters.[2400]

In contrast to the spontaneous reaction, the catalyzed process seldom gives the 1,2,3-trisubstituted benzene isomer from an acetylene RC≡CH. The chief product is usually the 1,2,4-isomer,[2401] with lesser amounts of the 1,3,15-isomer also generally obtained, but little if any of the 1,2,3-isomer. The mechanism of

[2385]Kinoshita, H.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* ***2003***, *125*, 7784.

[2386]Chouraqui, G.; Petit, M.; Aubert, C.; Malacria, M. *Org. Lett.* ***2004***, *6*, 1519.

[2387]Shanmugasundaram, M.; Wu, M.-S.; Jeganmohan, M.; Huang, C.-W.; Cheng, C.-H. *J. Org. Chem.* ***2002***, *67*, 7724.

[2388]Kawasaki, T.; Saito, S.; Yamamoto, Y. *J. Org. Chem.* ***2002***, *67*, 2653.

[2389]Yamamoto, Y.; Okuda, S.; Itoh, K. *Chem. Commun.* ***2001***, 1102; Varela, J.A.; Castedo, L.; Saá, C. *J. Org. Chem.* ***2003***, *68*, 8595.

[2390]Boñaga, L.V.R.; Zhang, H.-C.; Maryanoff, B.E. *Chem. Commun.* ***2004***, 2394.

[2391]Ojima, I.; Vu, A.T.; McCullagh, J.V.; Kinoshita, A. *J. Am. Chem. Soc.* ***1999***, *121*, 3230.

[2392]Atienza, C.; Mateo, C.; de Frutos, Ó.; Echavarren, A.M. *Org. Lett.* ***2001***, *3*, 153.

[2393]Yamamoto, Y.; Takagishi, H.; Itoh, K. *Org. Lett.* ***2001***, *3*, 2117.

[2394]Landis, C.A.; Payne, M.M.; Eaton, D.L.; Anthony, J.E. *J. Am. Chem. Soc.* ***2004***, *126*, 1338.

[2395]Huang, Q.; Hunter, J.A.; Larock, R.C. *Org. Lett.* ***2001***, *3*, 2973.

[2396]Dai, G.; Larock, R.C. *Org. Lett.* ***2001***, *3*, 4035; Dai, G.; Larock, R.C. *J. Org. Chem.* ***2003***, *68*, 920; Dai, G.; Larock, R.C. *Org. Lett.* ***2002***, *4*, 193.

[2397]Roesch, K.R.; Larock, R.C. *J. Org. Chem.* ***2002***, *67*, 86.

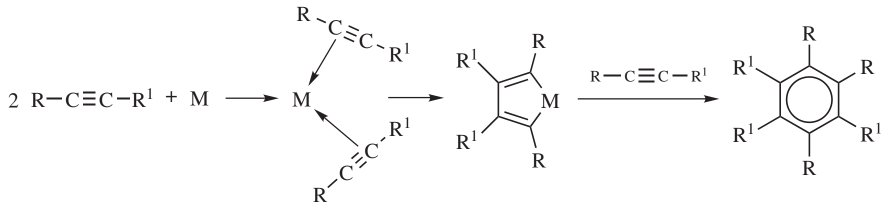
[2398]Klumpp, D.A.; Beauchamp, P.S.; Sanchez, Jr., G.V.; Aguirre, S.; de Leon, S. *Tetrahedron Lett.* ***2001***, *42*, 5821.

[2399]Madhusaw, R.J.; Lin, M.-Y.; Shoel, S.Md.A.; Liu, R.-S. *J. Am. Chem. Soc.* ***2004***, *126*, 6895.

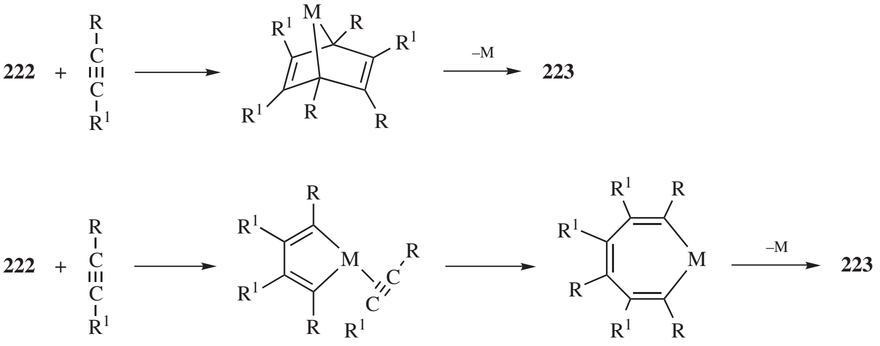
[2400]Gandon, V.; Leca, D.; Aechtner, T.; Vollhardt, K.P.C.; Malacria, M.; Aubert, C. *Org. Lett.* ***2004***, *6*, 3405.

[2401]See Saito, S.; Kawasaki, T.; Tsuboya, N.; Yamamoto, Y. *J. Org. Chem.* ***2001***, *66*, 796.

the catalyzed



reaction to form benzenes[2402] is believed to go through a species **221** in which two molecules of alkyne coordinate with the metal, and another species **222**, a five-membered heterocyclic intermediate.[2403] Such intermediates (where M = Rh, Ir, Zr,[2404] or Ni) have been isolated and shown to give benzenes (**223**) when treated with alkynes.[2405] Note that this pathway accounts for the predominant formation of the 1,2,4-isomer. Two possibilities for the last step are a Diels–Alder reaction, and a ring expansion, each followed by extrusion of the metal:[2406]



[2402]For studies of the mechanism of the reaction that produces cyclooctatetraenes, see Diercks, R.; Stamp, L.; Kopf, J.; Tom Dieck, H. *Angew. Chem. Int. Ed.* ***1984***, *23*, 893; Colborn, R.E.; Vollhardt, K.P.C. *J. Am. Chem. Soc.* ***1986***, *108*, 5470; Lawrie, C.J.; Gable, K.P.; Carpenter, B.K. *Organometallics* ***1989***, *8*, 2274.

[2403]See, for example, Colborn, R.E.; Vollhardt, K.P.C. *J. Am. Chem. Soc.* ***1981***, *103*, 6259; Kochi, J.K. *Organometallic Mechanisms and Catalysis*, Academic Press, NY, ***1978***, pp. 428–432; Collman, J.P., Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, CA ***1987***, pp. 870–877; Eisch, J.J.; Sexsmith, S.R. *Res. Chem. Intermed.* ***1990***, *13*, 149–192.

[2404]Takahahsi, T.; Ishikawa, M.; Huo, S. *J. Am. Chem. Soc.* ***2002***, *124*, 388.

[2405]See, for example, Collman, J.P. *Acc. Chem. Res.* ***1968***, *1*, 136; Yamazaki, H.; Hagihara, N. *J. Organomet. Chem.* ***1967***, *7*, P22; Wakatsuki, Y.; Kuramitsu, T.; Yamazaki, H. *Tetrahedron Lett.* ***1974***, 4549; Moseley, K.; Maitlis, P.M. *J. Chem. Soc. Dalton Trans.* ***1974***, 169; Müller, E. *Synthesis* ***1974***, 761; Eisch, J.J.; Galle, J.E. *J. Organomet. Chem.* ***1975***, *96*, C23; McAlister, D.R.; Bercaw, J.E.; Bergman, R.G. *J. Am. Chem. Soc.* ***1977***, *99*, 1666.

[2406]There is evidence that the mechanism of the last step more likely resembles the Diels–Alder pathway than the ring expansion pathway: Bianchini, C.; Caulton, K.G.; Chardon, C.; Eisenstein, O.; Folting, K.; Johnson, T.J.; Meli, A.; Peruzzini, M.; Raucher, D.J.; Streib, W.E.; Vizza, F. *J. Am. Chem. Soc.* ***1991***, *113*, 5127.

In at least one case the mechanism is different, going through a cyclobutadiene–nickel complex (see p. 76), which has been isolated.[2407] Similar results were obtained with a titanium complex.[2408] Using a mixture of $PdCl_2$ and $CuCl_2$, however, aliphatic alkynes are converted to the 1,3,5-trialkyl benzene derivative.[2409]

Alkoxy chromium carbenes (Fischer carbene complexes) react with phenylalkynes to give naphthalene derivatives.[2410] These chromium carbenes react with alkynyl boronates, cerium(IV) compounds, and then PhBr and a palladium catalyst to give a naphthoquinone.[2411] Diynes react to give cyclotrimerization.[2412] It is noted that vinyl chromium carbenes react directly with alkynes to give spirocyclic compounds (spiro[4.4]nona-1,3,6-trienes).[2413] Benzofurans can be prepared using methoxy carbenes.[2414] Amino-substituted chromium carbenes react with alkynes and then silica to give substituted benzene derivatives that have an aminoalkyl ($-NR_2$) substituent.[2415] Imino-substituted chromium carbenes react with alkynes to give pyrrole derivatives.[2416] Fischer carbene complexes react with alkynes to give the *Dötz benzannulation*,[2417] giving *p*-alkoxylphenol derivatives. Modification of this basic technique can lead to eight-membered ring carbocycles (see **15-66**).[2418]

When benzene, in the gas phase, was adsorbed onto a surface of 10% rhodium-on-alumina, the reverse reaction took place, and acetylene was formed.[2419]

In a related reaction, heating ketones in the presence of $TlCl_3OTf$ leads to 1,3,5-trisubstituted arenes.[2420] Heating acetophenone with $TiCl_4$ gives 1,3,5-triphenylbenzene.[2421] Nitriles react with 2 mol of acetylene, in the presence of a cobalt catalyst, to give 2-substituted pyridines.[2422] Propargyl amines react with cyclohexanone derivatives and a gold complex give tetrahydroquinolines.[2423] Treatment of alkynes with Cp_2ZrEt_2 followed by reaction with acetonitrile and then a second alkyne with a nickel catalyst gives a highly substituted pyridine.[2424] This reaction can be done intramolecularly using a photochemically induced reaction with a

[2407]Mauret, P.; Alphonse, P. *J. Organomet. Chem.* ***1984***, *276*, 249. See also, Pepermans, H.; Willem, R.; Gielen, M.; Hoogzand, C. *Bull. Soc. Chim. Belg.* ***1988***, *97*, 115.

[2408]Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* ***2001***, *123*, 7925.

[2409]Li, J.; Jiang, H.; Chen, M. *J. Org. Chem.* ***2001***, *66*, 3627.

[2410]Pulley, S.R.; Sen, S.; Vorogushin, A.; Swanson, E. *Org. Lett.* ***1999***, *1*, 1721; Jackson, T.J.; Herndon, J.W. *Tetrahedron* ***2001***, *57*, 3859.

[2411]Davies, M.W.; Johnson, C.N.; Harrity, J.P.A. *J. Org. Chem.* ***2001***, *66*, 3525.

[2412]Jiang, M.X.-W.; Rawat, M.; Wulff, W.D. *J. Am. Chem. Soc.* ***2004***, *126*, 5970.

[2413]Schirmer, H.; Flynn, B.L.; de Meijere, A. *Tetrahedron* ***2000***, *56*, 4977.

[2414]Herndon, J.W.; Zhang, Y.; Wang, H.; Wang, K. *Tetrahedron Lett.* ***2000***, *41*, 8687.

[2415]Barluenga, J.; López, L.A.; Martínez, S.; Tomás, M. *Tetrahedron* ***2000***, *56*, 4967.

[2416]Campos, P.J.; Sampedro, D.; Rodríquez, M.A. *J. Org. Chem.* ***2003***, *68*, 4674.

[2417]Dötz, K.H. *Angew. Chem. Int. Ed.* ***1975***, *14*, 644.

[2418]Barluenga, J.; Aznar, F.; Palomero, M.A. *Angew. Chem. Int. Ed.* ***2000***, *39*, 4346.

[2419]Parker, W.L.; Hexter, R.M.; Siedle, A.R. *J. Am. Chem. Soc.* ***1985***, *107*, 4584.

[2420]Iranpoor, N.; Zeynizaded, B. *Synlett* ***1998***, 1079.

[2421]Li, Z.; Sun, W.-H.; Jin, X.; Shao, C. *Synlett* ***2001***, 1947.

[2422]Heller, B.; Oehme, G. *J. Chem. Soc., Chem. Commun.* ***1995***, 179.

[2423]Abbiati, G.; Arcadi, A.; Bianchi, G.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *J. Org. Chem.* ***2003***, *68*, 6959.

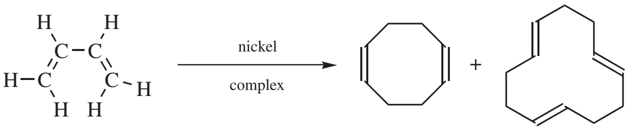
[2424]Takahashi, T.; Tsai, F.Y.; Kotora, M. *J. Am. Chem. Soc.* ***2000***, *122*, 4994.

cobalt catalyst and *p*-TolCN to give pyridines incorporated into macrocycles.[2425] Alkynyl esters react with enamino esters with a $ZnBr_2$ catalyst to give substituted pyridines.[2426] α-Halo oxime ethers react with alkynes and Grignard reagents, with a mixture of palladium and copper catalysts, to give pyrimidines.[2427] Triketones fix nitrogen gas in the presence of $TiCl_4$ and lithium metal to form bicyclic pyrrole derivatives.[2428]

OS **VII**, 256; **IX**, 1; **80**, 93.

15-66 Other Cycloaddition Reactions

***cyclo*-[But-2-en-1,4-diyl]-1/4/addition**, and so on



Cycloaddition reactions other than [4 + 2], [3 + 2], or [2 + 2] are possible, often providing synthetically useful routes to cyclic compounds. Conjugated dienes can be dimerized or trimerized at their 1,4 positions (formally, [4 + 4] and [4 + 4 + 4]-cycloadditions) by treatment with certain complexes or other transition-metal compounds.[2429] Thus butadiene gives 1,5-cyclooctadiene and 1,5,9-cyclododecatriene.[2430] The relative amount of each product can be controlled by use of the proper catalyst. For example, $Ni{:}P(OC_6H_4\text{—}o\text{—}Ph)_3$ gives predominant dimerization, while Ni(cyclooctadiene)$_2$ gives mostly trimerization. The products arise, not by direct 1,4 to 1,4 attack, but by stepwise mechanisms involving metal–alkene complexes.[2431] The rhodium catalyzed intramolecular cycloaddition of a furan with a conjugated diazoester gives a [3 + 4]-cycloadduct.[2432] The suprafacial thermal addition of an allylic cation to a diene (a [4 + 3]-cycloaddition) is allowed by the Woodward–Hoffmann rules (this reaction would

[2425] Moretto, A.F.; Zhang, H.-C.; Maryanoff, B.E. *J. Am. Chem. Soc.* ***2001***, *123*, 3157.

[2426] Bagley, M.C.; Dale, J.W.; Hughes, D.D.; Ohnesorge, M.; Philips, N.G.; Bower, J. *Synlett* ***2001***, 1523.

[2427] Kikiya, H.; Yagi, K.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* ***2002***, *124*, 9032.

[2428] Mori, M.; Hori, M.; Sato, Y. *J. Org. Chem.* ***1998***, *63*, 4832; Mori, M.; Hori, K.; Akashi, M.; Hori, M.; Sato, Y.; Nishida, M. *Angew. Chem. Int. Ed.* ***1998***, *37*, 636.

[2429] For reviews, see Wilke, G. *Angew. Chem. Int. Ed.* ***1988***, *27*, 186; Tolstikov, G.A.; Dzhemilev, U.M. *Sov. Sci. Rev. Sect. B* ***1985***, *7*, 237, 278–290; Heimbach, P.; Schenkluhn, H. *Top Curr. Chem.* ***1980***, *92*, 45; Baker, R. *Chem. Rev.* ***1973***, *73*, 487, see pp. 489–512; Semmelhack, M.F. *Org. React.* ***1972***, *19*, 115, pp. 128–143; Khan, M.M.T.; Martell, A.E. *Homogeneous Catalysis by Metal Complexes*, Vol. 2, Academic Press, NY, ***1974***, pp. 159–163; Heck, R.F. *Organotransition Metal Chemistry*, Academic Press, NY, ***1974***, pp. 157–164.

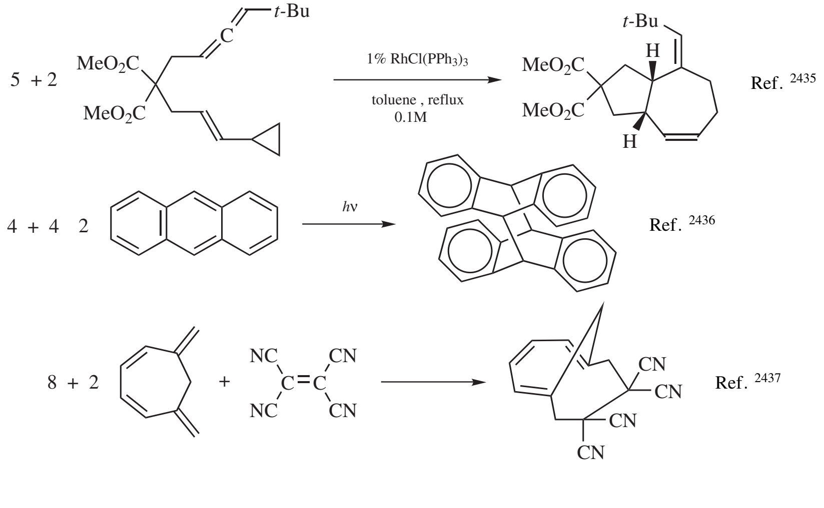
[2430] For a review of the 1,5,9-cyclododecatrienes (there are four stereoisomers, of which the *ttt* is shown above), see Rona, P. *Intra-Sci. Chem. Rep.* ***1971***, *5*, 105.

[2431] For example, see Heimbach, P.; Wilke, G. *Liebigs Ann. Chem.* ***1969***, *727*, 183; Barnett, B.; Büssemeier, B.; Heimbach, P.; Jolly, P.W.; Krüger, C.; Tkatchenko, I.; Wilke, G. *Tetrahedron Lett.* ***1972***, 1457; Barker, G.K.; Green, M.; Howard, J.A.K.; Spencer, J.L.; Stone, F.G.A. *J. Am. Chem. Soc.* ***1976***, *98*, 3373; Graham, G.R.; Stephenson, L.M. *J. Am. Chem. Soc.* ***1977***, *99*, 7098.

[2432] Davies, H.M.L.; Calvo, R.L.; Townsend, R.-J.; Ren, P.; Churchill, R.M. *J. Org. Chem.* ***2000***, *65*, 4261. For reviews of [3 + 4]-cycloadditions see Mann, J. *Tetrahedron* ***1986***, *42*, 4611; Hoffmann, H.M.R. *Angew. Chem. Int. Ed.* ***1984***, *23*, 1; ***1973***, *12*, 819; Noyori, R. *Acc. Chem. Res.* ***1979***, *12*, 61.

be expected to follow the same rules as the Diels–Alder reaction[2433]). Chiral cations have been used in [4 + 3]-cycloadditions.[2434]

As we saw in **15-60**, the Woodward–Hoffmann rules allow suprafacial concerted cycloadditions to take place thermally if the total number of electrons is 4*n*+2 and photochemically if the number is 4*n*. Furthermore, forbidden reactions become allowed if one molecule reacts antarafacially. It would thus seem that syntheses of many large rings could easily be achieved. However, when the newly formed ring is eight-membered or greater, concerted mechanisms, although allowed by orbital symmetry for the cases stated, become difficult to achieve because of the entropy factor (the two ends of one system must simultaneously encounter the two ends of the other), unless one or both components are cyclic, in which case the molecule has many fewer possible conformations. There have been a number of reports of cycloaddition reactions leading to eight-membered and larger rings, some thermally and some photochemically induced, but (apart from the dimerization and trimerization of butadienes mentioned above, which are known not to involve direct [4 + 4]- or [4 + 4 + 4]-cycloaddition) in most cases evidence is lacking to indicate whether they are concerted or stepwise processes. Some examples are



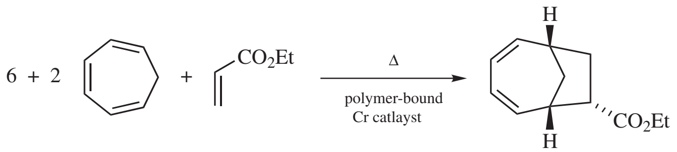
[2433]Garst, M.E.; Roberts, V.A.; Houk, K.N.; Rondan, N.G. *J. Am. Chem. Soc.* ***1984***, *106*, 3882.

[2434]Harmata, M; Jones, D.E.; Kahraman, M.; Sharma, U.; Barnes, C.L. *Tetrahedron Lett.* ***1999***, *40*, 1831.

[2435]Wender, P.A.; Glorius, F.; Husfeld, C.O.; Langkopf, E.; Love, J.A. *J. Am. Chem. Soc.* ***1999***, *121*, 5348. For another example, see Trost, B.M.; Toste, F.D.; Shen, H. *J. Am. Chem. Soc.* ***2000***, *122*, 2379. See also, Wender, P.A.; Gamber, G.G.; Scanio, M.J.C. *Angew. Chem. Int. Ed.* ***2001***, *40*, 3895; Wender, P.A.; Pedersen, T.M.; Scanio, M.J.C. *J. Am. Chem. Soc.* ***2002***, *124*, 15154; Wender, P.A.; Love, J.A.; Williams, T.J. *Synlett* ***2003***, 1295.

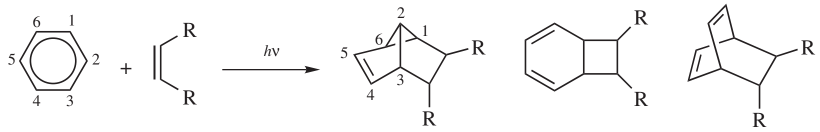
[2436]Shönberg, A. *Preparative Organic Photochemistry*, Springer, NY, ***1968***, pp. 97–99. For other examples see Sieburth, S.Mc.N.; McGee, Jr., K.F.; Al-Tel, T.H. *Tetrahedron Lett.* ***1999***, *40*, 4007; Sieburth, S.Mc.N.; Lin, C.H.; Rucando, D. *J. Org. Chem.* ***1999***, *64*, 950, 954; Zhu, M.; Qiu, Z.; Hiel, G.P.; Sieburth, S.Mc.N. *J. Org. Chem.* ***2002***, *67*, 3487.

[2437]Farrant, G.C.; Feldmann, R. *Tetrahedron Lett.* ***1970***, 4979.



Ref. [2438]

Benzene rings can undergo photochemical cycloaddition with alkenes.[2439] The major product is usually the 1,3-addition product **224** (in which a three-membered ring has also been formed), although some of the 1,2 product **225**



224 **225** **226**

(**15-63**) is sometimes formed as well. (**225** is usually the main product where the alkene bears electron-withdrawing groups and the aromatic compound electron-donating groups, or vice versa.) The 1,4 product **226** is rarely formed. The reaction has also been run with benzenes substituted with alkyl, halo, OR, CN, and other groups, and with acyclic and cyclic alkenes bearing various groups.[2440]

A [2 + 2 + 2]-cycloaddition reaction is also known, facilitated by $Ni(cod)_2$[2441] or a cobalt catalyst.[2442] [2 + 2 + 1]-Cycloaddition is known.[2443] A cobalt catalyst is used for a [4 + 2 + 2]-cycloaddition of 1,3-butadiene and bicyclo[2.2.2]octa-2,5-diene.[2444] Eight-membered rings are products by a rhodium catalyzed [4 + 2 + 2]-cycloaddition.[2445] Chromium catalysts are available for [6 + 4]-cycloadditions.[2446]

OS **VI**, 512; **VII**, 485; **X**, 1, 336.

[2438] Rigby, J.H.; Kondratenko, M.A.; Fiedler, C. *Org. Lett.* ***2000***, *2*, 3917; Rigby, J.H.; Mann, L.W.; Myers, B.J. *Tetrahedron Lett.* ***2001***, *42*, 8773. See Rigby, J.H.; Ateeq, H.S.; Charles, N.R.; Henshilwood, J.A.; Short, K.M.; Sugathapala, P.M. *Tetrahedron* ***1993***, *49*, 5495.

[2439] For reviews, see Wender, P.A.; Ternansky, R.; deLong, M.; Singh, S.; Olivero, A.; Rice, K. *Pure Appl. Chem.* ***1990***, *62*, 1597; Gilbert, A., in Horspool, W.M. *Synthetic Organic Photochemistry*, Plenum, NY, ***1984***, pp. 1–60. For a review of this and related reactions, see McCullough, J.J. *Chem. Rev.* ***1987***, *87*, 811.

[2440] See the table, in Wender, P.A.; Siggel, L.; Nuss, J.M. *Org. Photochem.* ***1989***, *10*, 357, pp. 384–415.

[2441] Lautens, M.; Edwards, L.G.; Tam, W.; Lough, A.J. *J. Am. Chem. Soc.* ***1995***, *117*, 10276; Louie, J.; Gibby, J.E.; Farnsworth, M.V.; Tekavec, T.N. *J. Am. Chem. Soc.* ***2002***, *124*, 15188.

[2442] Slowinski, F.; Aubert, C.; Malacria, M. *Tetrahedron Lett.* ***1999***, *40*, 5849.

[2443] Knölker, H.-J.; Braier, A.; Bröcher, D.J.; Jones, P.G.; Piotrowski, H. *Tetrahedron Lett.* ***1999***, *40*, 8075; Chatani, N.; Tobisu, M.; Asaumi, T.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* ***1999***, *121*, 7160.

[2444] Kiattansakul, R.; Snyder, J.K. *Tetrahedron Lett.* ***1999***, *40*, 1079.

[2445] Gilbertson, S. R.; DeBoef, B.*J. Am. Chem. Soc.* ***2002***, *124*, 8784.

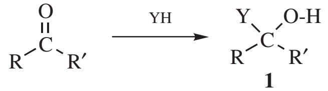
[2446] Kündig, E.P.; Robvieux, F.; Kondratenko, M. *Synthesis* ***2002***, 2053.

CHAPTER 16

Addition to Carbon–Hetero Multiple Bonds

MECHANISM AND REACTIVITY

The reactions considered in this chapter involve addition to the carbon–oxygen, carbon–nitrogen, and carbon–sulfur double bonds, and the carbon–nitrogen triple bond. The mechanistic study of these reactions is much simpler than that of the additions to carbon–carbon multiple bonds considered in Chapter 15.[1] Most of the questions that concerned us there either do not arise here or can be answered very simply. Since C=O, C=N, and C≡N bonds are strongly polar, with the carbon always the positive end (except for isocyanides, see p. 1466), there is never any doubt about the *orientation* of unsymmetrical addition to these bonds. Nucleophilic attacking species always go to the carbon and electrophilic species to the oxygen or nitrogen. Additions to C=S bonds are much less common,[2] but in these cases the addition can be in the other direction.[3] For example, thiobenzophenone ($Ph_2C{=}S$), when treated with phenyllithium gives, after hydrolysis, benzhydryl phenyl sulfide (Ph_2CHSPh).[4]



1

[1]For a discussion, see Jencks, W.P. *Prog. Phys. Org. Chem.* ***1964***, *2*, 63.

[2]For reviews of thioketones and other compounds with C=S bonds, see Schaumann, E., in Patai, S. *Supplement A: The Chemistry of Double-Bonded Functional Groups*, Vol. 2, pt. 2, Wiley, NY, ***1989***, pp. 1269–1367; Ohno, A. in Oae, S. *Organic Chemistry of Sulfur*, Plenum, NY, ***1977***, pp. 189–229; Mayer, R., in Janssen, M.J. *Organosulfur Chemistry*, Wiley, NY, ***1967***, pp. 219–240; Campaigne, E., in Patai, S. *The Chemistry of the Carbonyl Group*, pt. 1, Wiley, NY, ***1966***, pp. 917–959.

[3]For a review of additions of organometallic compounds to C=S bonds, both to the sulfur (*thiophilic addition*) and to the carbon (*carbophilic addition*), see Wardell, J.L.; Paterson, E.S., in Hartley, F.P.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 2, Wiley, NY, ***1985***, pp. 219–338, 261–267.

[4]Beak, P.; Worley, J.W. *J. Am. Chem. Soc.* ***1972***, *94*, 597. For some other examples, see Schaumann, E.; Walter, W. *Chem. Ber.* ***1974***, *107*, 3562; Metzner, P.; Vialle, J.; Vibet, A. *Tetrahedron* ***1978***, *34*, 2289.

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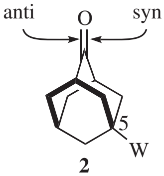
In addition of YH to a ketone to give **1** the product has a stereogenic carbon, but unless there is chirality in R or R′ or YH is optically active, the product must be a racemic mixture because there is no facial bias about the carbonyl. The same holds true for C=N and C=S bonds, since in none of these cases can chirality be present at the heteroatom. The stereochemistry of addition of a single YH to the carbon–nitrogen triple bond could be investigated, since the product can exist in (*E*) and (*Z*) forms (p. 183), but these reactions generally give imine products that undergo further reaction. Of course, if R or R′ *is* chiral, a racemic mixture will not always arise and the stereochemistry of addition can be studied in such cases. Cram's rule (p. 168) allows us to predict the direction of attack of Y in many cases.[5] However, even in this type of study, the relative directions of attack of Y and H are not determined, but only the direction of attack of Y with respect to the rest of the substrate molecule.



2

On p. 1023, it was mentioned that electronic effects can play a part in determining which face of a carbon–carbon double bond is attacked. The same applies to additions to carbonyl groups. For example, in 5-substituted adamantanones (**2**) electron-withdrawing (*-I*) groups W cause the attack to come from the syn face, while electron-donating groups cause it to come from the anti face.[6] In 5,6-disubstituted norborn-2-en-7-one systems, the carbonyl appears to tilt away from the π-bond, with reduction occurring from the more hindered face.[7] An *ab initio* study of nucleophilic addition to 4-*tert*-butylcyclohexanones attempted to predict π-facial selectivity in that system.[8]

The mechanistic picture is further simplified by the fact that free-radical additions to carbon–heteroatom double bonds are not as prevalent.[9] In most cases, it

[5]For a discussion of such rules, see Eliel, E.L. *The Stereochemistry of Carbon Compounds*, McGraw-Hill, NY, ***1962***, pp. 68–74. For reviews of the stereochemistry of addition to carbonyl compounds, see Bartlett, P.A. *Tetrahedron* ***1980***, *36*, 2, 22; Ashby, E.C.; Laemmle, J.T. *Chem. Rev.* ***1975***, *75*, 521; Goller, E.J. *J. Chem. Educ.* ***1974***, *51*, 182; Toromanoff, E. *Top. Stereochem.* ***1967***, *2*, 157.

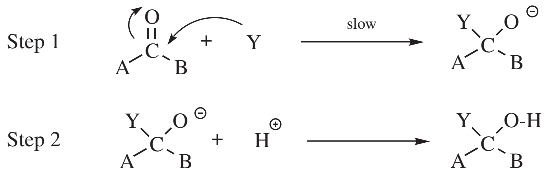
[6]Cheung, C.K.; Tseng, L.T.; Lin, M.; Srivastava, S.; le Noble, W.J. *J. Am. Chem. Soc.* ***1986***, *108*, 1598; Laube, T.; Stilz, H.U. *J. Am. Chem. Soc.* ***1987***, *109*, 5876.

[7]Kumar, V.A.; Venkatesan, K.; Ganguly, B.; Chandrasekhar, J.; Khan, F.A.; Mehta, G. *Tetrahedron Lett.* ***1992***, *33*, 3069.

[8]Yadav, V.K.; Jeyaraj, D.A. *J. Org. Chem.* ***1998***, *63*, 3474. For a discussion of models, see Priyakumar, U.D.; Sastry, G.N.; Mehta, G. *Tetrahedron* ***2004***, *60*, 3465.

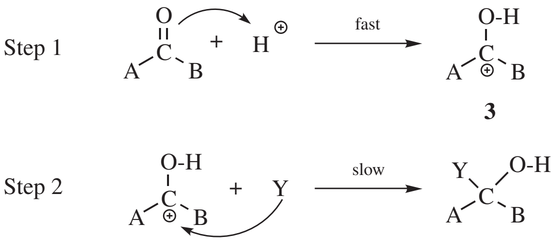
[9]An example is found in **16-31**. For other examples, see Kaplan, L. *J. Am. Chem. Soc.* ***1966***, *88*, 1833; Drew, R.M.; Kerr, J.A. *Int. J. Chem. Kinet.* ***1983***, *15*, 281; Fraser-Reid, B.; Vite, G.D.; Yeung, B.A.; Tsang, R. *Tetrahedron Lett.* ***1988***, *29*, 1645; Beckwith, A.L.J.; Hay, B.P. *J. Am. Chem. Soc.* ***1989***, *111*, 2674; Clerici, A.; Porta, O. *J. Org. Chem.* ***1989***, *54*, 3872; Cossy, J.; Pete, J.P.; Portella, C. *Tetrahedron Lett.* ***1989***, *30*, 7361.

is the nucleophile that forms the first new bond to carbon, and these reactions are regarded as *nucleophilic additions*, which can be represented thus (for the C=O bond, analogously for the others):



The electrophile shown in step 2 is the proton. In almost all the reactions considered in this chapter, the electrophilic atom is either hydrogen or carbon. Note that step 1 is exactly the same as step 1 of the tetrahedral mechanism of nucleophilic substitution at a carbonyl carbon (p. 1255), but carbon groups (A, B = H, alkyl aryl, etc.) are poor leaving groups so that substitution does not compete with addition. For carboxylic acids and their derivatives (B = OH, OR, NH_2, etc.) much better leaving groups are available and acyl substitution predominates (p. 1254). It is thus the nature of A and B that determines whether a nucleophilic attack at a carbon–heteroatom multiple bond will lead to substitution or addition.

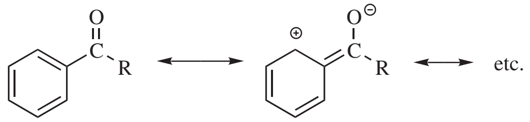
It is also possible for the heteroatom (oxygen in a carbonyl) to react as a base, attacking the electrophilic species. This species is most often a proton and the mechanism is



Whether the nucleophile attacks the carbon or the heteroatom attacks the electrophilic species, the rate-determining step is usually the one involving nucleophilic attack. It may be observed that many of these reactions can be catalyzed by both acids and bases.[10] Bases catalyze the reaction by converting a reagent of the form YH to the more powerful nucleophile Y^- (see p. 490). Acids catalyze it by converting the substrate to an heteroatom-stabilized cation (formation of **3**), thus making it more attractive to nucleophilic attack. Similar catalysis can also be found with metallic ions (e.g., Ag^+) which act here as Lewis acids.[11] We have mentioned before (p. 242) that ions of type **3** are comparatively stable carbocations because the positive charge is spread by resonance.

[10]For a discussion of acid and base catalysis in these reactions, see Jencks, W.P.; Gilbert, H.F. *Pure Appl. Chem.* ***1977***, *49*, 1021.
[11]Toromanoff, E. *Bull. Soc. Chim. Fr.* ***1962***, 1190.

Reactivity factors in additions to carbon–heteroatom multiple bonds are similar to those for the tetrahedral mechanism of nucleophilic substitution.[12] If A and/or B are electron-donating groups, rates are decreased. Electron-attracting substituents increase rates. This means that aldehydes are more reactive than ketones. Aryl groups are somewhat deactivating compared to alkyl, because of resonance that stabilizes the substrate molecule, but is lost on going to the intermediate:



Double bonds in conjugation with the carbon–heteroatom multiple bond also lower addition rates, for similar reasons but, more important, may provide competition from 1,4-addition (p. 1008). Steric factors are also quite important and contribute to the decreased reactivity of ketones compared with aldehydes. Highly hindered ketones like hexamethylacetone and dineopentyl ketone either do not undergo many of these reactions or require extreme conditions.

Nucleophilic Substitution at an Aliphatic Trigonal Carbon: The Tetrahedral Mechanism

All the mechanisms so far discussed take place at a saturated carbon atom. Nucleophilic substitution is also important at trigonal carbons, especially when the carbon is double bonded to an oxygen, a sulfur, or a nitrogen. Substitution at a carbonyl group (or the corresponding nitrogen and sulfur analogs) most often proceeds by a second-order mechanism, which in this book is called the *tetrahedral*[13] *mechanism.*[14] The IUPAC designation is $A_N + D_N$. The S_N1 mechanisms, involving carbocations, are sometimes found with these substrates, especially with essentially ionic substrates such as RCO^+ BF_4^-; there is evidence that in certain cases simple S_N2 mechanisms can take place, especially with a very good leaving group such as Cl^-;[15]

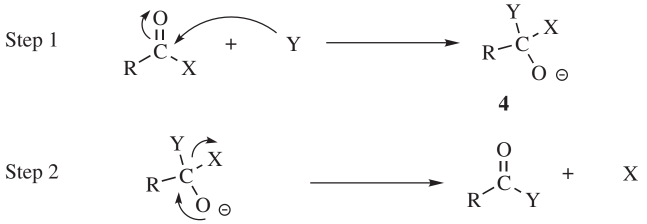
[12]For a review of the reactivity of nitriles, see Schaefer, F.C., in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 239–305.

[13]This mechanism has also been called the "additionelimination mechanism," but in this book we limit this term to the type of mechanism shown on p. $$$.

[14]For reviews of this mechanism, see Talbot, R.J.E., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 10, Elsevier, NY, ***1972***, pp. 209–223; Jencks, W.P. *Catalysis in Chemistry and Enzymology*, McGraw-Hill, NY, ***1969***, pp. 463–554; Satchell, D.P.N.; Satchell, R.S., in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 375–452; Johnson, S.L. *Adv. Phys. Org. Chem.* ***1967***, *5*, 237.

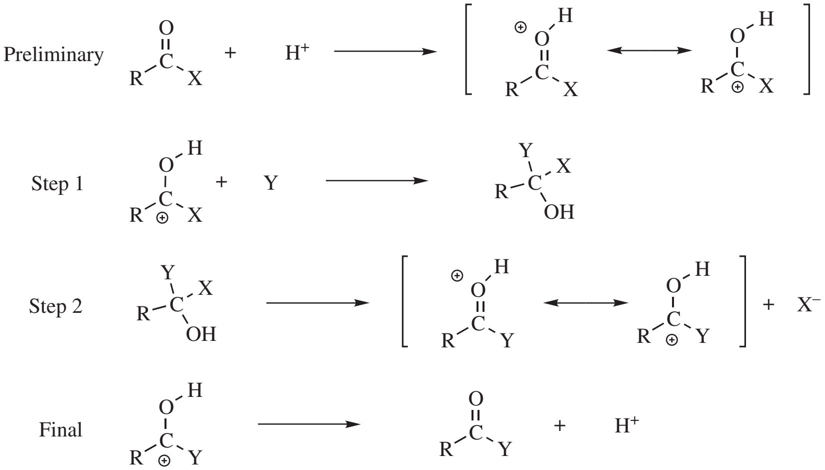
[15]For a review, see Williams, A. *Acc. Chem. Res.* ***1989***, *22*, 387. For examples, see Kevill, D.N.; Foss, F.D. *J. Am. Chem. Soc.* ***1969***, *91*, 5054; Haberfield, P.; Trattner, R.B. *Chem. Commun.* ***1971***, 1481; De Tar, D.F. *J. Am. Chem. Soc.* ***1982***, *104*, 7205; Shpan'ko, I.V.; Goncharov, A.N. *J. Org. Chem. USSR* ***1987***, *23*, 2287; Guthrie, J.P.; Pike, D.C. *Can. J. Chem.* ***1987***, *65*, 1951; Kevill, D.N.; Kim, C. *Bull. Soc. Chim. Fr.* ***1988***, 383, *J. Chem. Soc. Perkin Trans. 2* ***1988***, 1353; Bentley, T.W.; Koo, I.S. *J. Chem. Soc. Perkin Trans. 2* ***1989***, 1385. See, however, Buncel, E.; Um, I.H.; Hoz, S. *J. Am. Chem. Soc.* ***1989***, *111*, 971.

and an SET mechanism has also been reported.[16] However, the tetrahedral mechanism is by far the most prevalent. Although this mechanism displays second-order kinetics, it is not the same as the S_N2 mechanism previously discussed. In the tetrahedral mechanism, first Y attacks to give an intermediate containing both X and Y (**4**), and then X leaves. This sequence, impossible at a saturated carbon, is possible at an unsaturated one because the central carbon can release a pair of electrons to the oxygen and so preserve its octet:



4

When reactions are carried out in acid solution, there may also be a preliminary and a final step:



The hydrogen ion is a catalyst. The reaction rate is increased because it is easier for the nucleophile to attack the carbon when the electron density of the latter has been decreased.[17]

Evidence for the existence of the tetrahedral mechanism is as follows:[18]

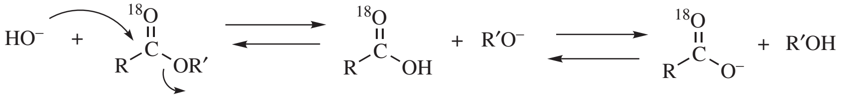
1. The kinetics are first order each in the substrate and in the nucleophile, as predicted by the mechanism.

[16]Bacaloglu, R.; Blaskó, A.; Bunton, C.A.; Ortega, F. *J. Am. Chem. Soc.* ***1990***, *112*, 9336.

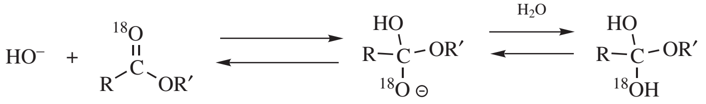
[17]For discussions of general acid and base catalysis of reactions at a carbonyl group, see Jencks, W.P. *Acc. Chem. Res.* ***1976***, *9*, 425; *Chem. Rev.* ***1972***, *72*, 705.

[18]For additional evidence, see Guthrie, J.P. *J. Am. Chem. Soc.* ***1978***, *100*, 5892; Kluger, R.; Chin, J. *J. Am. Chem. Soc.* ***1978***, *100*, 7382; O'Leary, M.H.; Marlier, J.F. *J. Am. Chem. Soc.* ***1979***, *101*, 3300.

2. There is other kinetic evidence in accord with a tetrahedral intermediate. For example, the rate "constant" for the reaction between acetamide and hydroxylamine is not constant, but decreases with increasing hydroxylamine concentration.[19] This is not a smooth decrease; there is a break in the curve. A straight line is followed at low hydroxylamine concentration and another straight line at high concentration. This means that the identity of the rate-determining step is changing. Obviously, this cannot happen if there is only one step: there must be two steps, and hence an intermediate. Similar kinetic behavior has been found in other cases as well,[20] in particular, plots of rate against pH are often bell shaped.
3. Basic hydrolysis has been carried out on carboxylic esters labeled with ^{18}O in the carbonyl group.[21] If this reaction proceeded by the normal S_N2 mechanism, all the ^{18}O would remain in the carbonyl group, even if, in an equilibrium process, some of the carboxylic acid formed went back to the starting material:

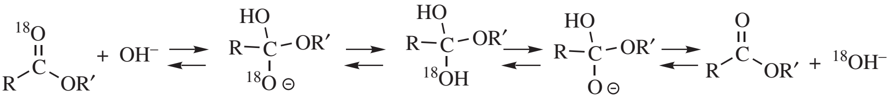


On the other hand, if the tetrahedral mechanism operates



5

then the intermediate **5**, by gaining a proton, becomes converted to the symmetrical intermediate **6**. In this intermediate the OH groups are equivalent, and (except for the small $^{18}O/^{16}O$ isotope effect) either one can lose a proton with equal facility:



5 6 7

The intermediates **5** and **7** can now lose OR′ to give the acid (not shown in the equations given), or they can lose OH to regenerate the carboxylic ester. If **5** goes back to ester, the ester will still be labeled, but if **7** reverts to ester, the

[19]Jencks, W.P.; Gilchrist, M. *J. Am. Chem. Soc.* ***1964***, *86*, 5616.

[20]Hand, E.S.; Jencks, W.P. *J. Am. Chem. Soc.* ***1962***, *84*, 3505; Johnson, S.L. *J. Am. Chem. Soc.* ***1964***, *86*, 3819; Fedor, L.R.; Bruice, T.C. *J. Am. Chem. Soc.* ***1964***, *86*, 5697; ***1965***, *87*, 4138; Kevill, D.N.; Johnson, S.L. *J. Am. Chem. Soc.* ***1965***, *87*, 928; Leinhard, G.E.; Jencks, W.P. *J. Am. Chem. Soc.* ***1965***, *87*, 3855; Schowen, R.L.; Jayaraman, H.; Kershner, L.D. *J. Am. Chem. Soc.* ***1966***, *88*, 3373.

[21]Bender, M.L. *J. Am. Chem. Soc.* ***1951***, *73*, 1626; Bender, M.L.; Thomas, R.J. *J. Am. Chem. Soc.* ***1961***, *83*, 4183, 4189.

^{18}O will be lost. A test of the two possible mechanisms is to stop the reaction before completion and to analyze the recovered ester for ^{18}O. This is just what was done by Bender, who found that in alkaline hydrolysis of methyl, ethyl, and isopropyl benzoates, the esters had lost ^{18}O. A similar experiment carried out for acid-catalyzed hydrolysis of ethyl benzoate showed that here too the ester lost ^{18}O. However, alkaline hydrolysis of substituted benzyl benzoates showed *no* ^{18}O loss.[22] This result does not necessarily mean that no tetrahedral intermediate is involved in this case. If **5** and **7** do not revert to ester, but go entirely to acid, no ^{18}O loss will be found even with a tetrahedral intermediate. In the case of benzyl benzoates, this may very well be happening, because formation of the acid relieves steric strain. Another possibility is that **5** loses OR′ before it can become protonated to **6**.[23] Even the experiments that *do* show ^{18}O loss do not *prove* the existence of the tetrahedral intermediate, since it is possible that ^{18}O is lost by some independent process not leading to ester hydrolysis. To deal with this possibility, Bender and Heck[24] measured the rate of ^{18}O loss in the hydrolysis of ethyl trifluorothioloacetate-^{18}O:

This reaction had previously been shown[25] to involve an intermediate by the kinetic methods mentioned on p. 1256. Bender and Heck showed that the rate of ^{18}O loss and the value of the partitioning ratio k_2/k_3 as determined by the oxygen exchange technique were exactly in accord with these values as previously determined by kinetic methods. Thus the original ^{18}O-exchange measurements showed that there is a tetrahedral species present, though not necessarily on the reaction path, while the kinetic experiments showed that there is some intermediate present, though not necessarily tetrahedral. Bender and Heck's results demonstrate that there is a tetrahedral intermediate and that it lies on the reaction pathway.

4. In some cases, tetrahedral intermediates have been isolated[26] or detected spectrally.[27]

[22]Bender, M.L.; Matsui, H.; Thomas, R.J.; Tobey, S.W. *J. Am. Chem. Soc.* ***1961***, *83*, 4193. See also, Shain, S.A.; Kirsch, J.F. *J. Am. Chem. Soc.* ***1968***, *90*, 5848.

[23]For evidence for this possibility, see McClelland, R.A. *J. Am. Chem. Soc.* ***1984***, *106*, 7579.

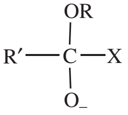
[24]Bender, M.L.; Heck, H. d'A. *J. Am. Chem. Soc.* ***1967***, *89*, 1211.

[25]Fedor, L.R.; Bruice, T.C. *J. Am. Chem. Soc.* ***1965***, *87*, 4138.

[26]Rogers, G.A.; Bruice, T.C. *J. Am. Chem. Soc.* ***1974***, *96*, 2481; Khouri, F.F.; Kaloustian, M.K. *J. Am. Chem. Soc.* ***1986***, *108*, 6683.

[27]For reviews, see Capon, B.; Dosunmu, M.I.; Sanchez, M. de N de M. *Adv. Phys. Org. Chem.* ***1985***, *21*, 37; McClelland, R.A.; Santry, L.J. *Acc. Chem. Res.* ***1983***, *16*, 394; Capon, B.; Ghosh, A.K.; Grieve, D.M.A. *Acc. Chem. Res.* ***1981***, *14*, 306. See also, Lobo, A.M.; Marques, M.M.; Prabhakar, S.; Rzepa, H.S. *J. Chem. Soc., Chem. Commun.* ***1985***, 1113; van der Wel, H.; Nibbering, N.M.M. *Recl. Trav. Chim. Pays-Bas* ***1988***, *107*, 479, 491.

Several studies have been made of the directionality of approach by the nucleophile.[28] Menger has proposed for reactions in general, and specifically for those that proceed by the tetrahedral mechanism, that there is no single definable preferred transition state, but rather a "cone" of trajectories. All approaches within this cone lead to reaction at comparable rates; it is only when the approach comes outside of the cone that the rate falls.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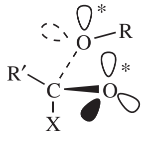
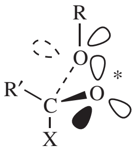

A


B

Directionality has also been studied for the second step. Once the tetrahedral intermediate (**4**) is formed, it loses Y (giving the product) or X (reverting to the starting compound). Deslongchamps has proposed that one of the factors affecting this choice is the conformation of the intermediate; more specifically, the positions of the lone pairs. In this view, a leaving group X or Y can depart only if the other two atoms on the carbon both have an orbital antiperiplanar to the C—X or C—Y bond. For example, consider an intermediate **8** formed by attack of $^{-}$OR on a substrate R′COX. Cleavage of the C—X bond with loss of X can take place from conformation **A**, because the two lone-pair orbitals marked * are antiperiplanar to the C—X bond, but not from **B** because only the O^{-} has such an orbital. If the intermediate is in conformation **B**, the OR may leave (if X has a lone-pair orbital in the proper position) rather than X. This factor is called *stereoelectronic control*.[29] Of course, there is free rotation in acyclic intermediates, and many conformations are possible, but some are preferred, and cleavage reactions may take place faster than rotation, so stereoelectronic control can be a factor in some situations. Much evidence has been presented for this concept.[30] More generally, the term *stereoelectronic effects* refers to any case in which orbital

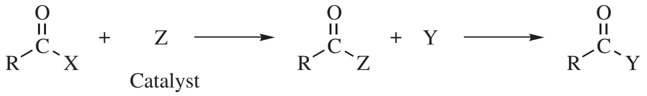
[28]For discussions, see Menger, F.M. *Tetrahedron* ***1983***, *39*, 1013; Liotta, C.L.; Burgess, E.M.; Eberhardt, W.H. *J. Am. Chem. Soc.* ***1984***, *106*, 4849.

[29]It has also been called the "antiperiplanar lone pair hypothesis (ALPH)." For a reinterpretation of this factor in terms of the principle of least nuclear motion (see **15-10**), see Hosie, L.; Marshall, P.J.; Sinnott, M.L. *J. Chem. Soc. Perkin Trans. 2* ***1984***, 1121; Sinnott, M.L. *Adv. Phys. Org. Chem.* ***1988***, *24*, 113.

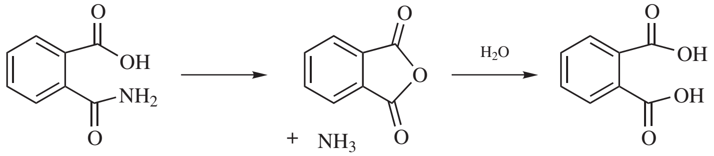
[30]For monographs, see Kirby, A.J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer, NY, ***1983***; Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*, Pergamon, NY, ***1983***. For lengthy treatments, see Sinnott, M.L. *Adv. Phys. Org. Chem.* ***1988***, *24*, 113; Gorenstein, D.G. *Chem. Rev.* ***1987***, *87*, 1047; Deslongchamps, P. *Heterocycles* ***1977***, *7*, 1271; *Tetrahedron* ***1975***, *31*, 2463. For additional evidence, see Perrin, C.L.; Arrhenius, G.M.L. *J. Am. Chem. Soc.* ***1982***, *104*, 2839; Briggs, A.J.; Evans, C.M.; Glenn, R.; Kirby, A.J. *J. Chem. Soc. Perkin Trans. 2* ***1983***, 1637; Ndibwami, A.; Deslongchamps, P.*Can. J. Chem.* ***1986***, *64*, 1788; Hegarty, A.F.; Mullane, M. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 995. For evidence against the theory, see Perrin, C.L.; Nuñez, O. *J. Am. Chem. Soc.* ***1986***, *108*, 5997; ***1987***, *109*, 522.

position requirements affect the course of a reaction. The backside attack in the S_N2 mechanism is an example of a stereoelectronic effect.

Some nucleophilic substitutions at a carbonyl carbon are *catalyzed* by nucleophiles.[31] There occur, in effect, two tetrahedral mechanisms:



(For an example, see **16-58**). When this happens internally, we have an example of a neighboring-group mechanism at a carbonyl carbon.[32] For example, the hydrolysis of phthalamic acid (**9**) takes place as follows:



9

Evidence comes from comparative rate studies.[33] Thus **9** was hydrolyzed ~10^5 times faster than benzamide ($PhCONH_2$) at about the same concentration of hydrogen ions. That this enhancement of rate was not caused by the resonance or field effects of COOH (an electron-withdrawing group) was shown by the fact both *o*-nitrobenzamide and terephthalamic acid (the para isomer of **9**) were hydrolyzed more slowly than benzamide. Many other examples of neighboring-group participation at a carbonyl carbon have been reported.[34] It is likely that nucleophilic catalysis is involved in enzyme catalysis of ester hydrolysis.

The attack of a nucleophile on a carbonyl group can result in substitution or addition, though the first step of each mechanism is the same. The main factor that determines the product is the identity of the group X in RCOX. When X is alkyl or hydrogen, addition usually takes place. When X is halogen, OH, OCOR, NH_2, and so on, the usual reaction is substitution.

In both the S_N1 and S_N2 mechanisms, the leaving group departs during the rate-determining step and so directly affects the rate. In the tetrahedral mechanism at a carbonyl carbon, the bond between the substrate and leaving group is still intact during the slow step. Nevertheless, the nature of the leaving group still affects the reactivity in two ways: (*1*) By altering the

[31]For reviews of nucleophilic catalysis, see Bender, M.L. *Mechanisms of Homogeneous Catalysis from Protons to Proteins*, Wiley, NY, ***1971***, pp. 147–179; Jencks, W.P. *Catalysis in Chemistry and Enzymology*, McGraw-Hill, NY, ***1969***, pp. 67–77; Johnson, S.L. *Adv. Phys. Org. Chem.* ***1967***, *5*, p. 271. For a review where Z = a tertiary amine (the most common case), see Cherkasova, E.M.; Bogatkov, S.V.; Golovina, Z.P. *Russ. Chem. Rev.* ***1977***, *46*, 246.

[32]For reviews, see Kirby, A.J.; Fersht, A.R. *Prog. Bioorg. Chem.* ***1971***, *1*, 1; Capon, B. *Essays Chem.* ***1972***, *3*, 127.

[33]Bender, M.L.; Chow, Y.; Chloupek, F.J. *J. Am. Chem. Soc.* ***1958***, *80*, 5380.

[34]For examples, see Bruice, T.C.; Pandit, U.K. *J. Am. Chem. Soc.* ***1960***, *82*, 5858; Kluger, R.; Lam, C. *J. Am. Chem. Soc.* ***1978***, *100*, 2191; Page, M.I.; Render, D.; Bernáth, G. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 867.

TABLE 16.1. The More Important Synthetic Reactions that Take Place by the Tetrahedral Mechanism[a]

Reaction Number	Reaction
16-57	$RCOX + H_2O \longrightarrow RCOOH$
16-58	$RCOOCOR' + H_2O \longrightarrow RCOOH + R'COOH$
16-59	$RCO_2R' + H_2O \longrightarrow RCOOH + R'OH$
16-59	$RCONR'_2 + H_2O \longrightarrow RCOOH + R_2NH$ (R′ = H, alkyl, aryl)
16-61	$RCOX + R'OH \longrightarrow RCO_2R'$
16-62	$RCOOCOR + R'OH \longrightarrow RCO_2R'$
16-63	$RCOOH + R'OH \longrightarrow RCO_2R'$
16-64	$RCO_2R' + R''OH \longrightarrow RCO_2R'' + R'OH$
16-66	$RCOX + R'COO^- \longrightarrow RCOOCOR'$
10-21	$RCOX + H_2O_2 \longrightarrow RCO_3H$
16-69	$RCOX + R'SH \longrightarrow RCOSR'$
16-72	$RCOX + NHR'_2 \longrightarrow RCONR'_2$ (R′ = H, alkyl, aryl)
16-73	$RCOOCOR + NHR'_2 \longrightarrow RCONR'_2$ (R′ = H, alkyl, aryl)
16-74	$RCOOH + NHR'_2 \xrightarrow[\text{agent}]{\text{coupling}} RCONR'_2$ (R′ = H, alkyl, aryl)
16-75	$RCO_2R' + NHR^2 \longrightarrow RCONR^2$ (R^2 = H, alkyl, aryl)
16-79	$RCOOH + SOCl_2 \longrightarrow RCOCl$
19-39	$RCOX + LiAlH(O\text{—}t\text{-Bu})_3 \longrightarrow RCHO$
19-41	$RCONR'_2 + LiAlH_4 \longrightarrow RCHO$
16-81	$RCOX + R_{2'}CuLi \longrightarrow RCOR'$
16-85	$2RCH_2CO_2R' \longrightarrow RCH_2COCHRCO_2R'$

[a]Catalysts are not shown.

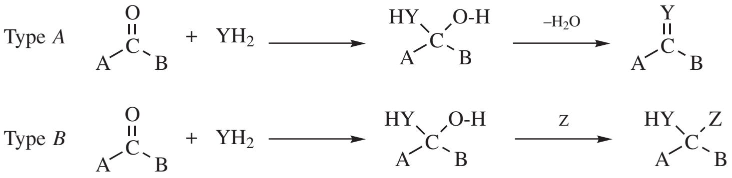
electron density at the carbonyl carbon, the rate of the reaction is affected. The greater the electron-withdrawing character of X, the greater the partial positive charge on C and the more rapid the attack by a nucleophile. (*2*) The nature of the leaving group affects the *position of equilibrium*. In the intermediate **4** (p. 1255), there is competition between X and Y as to which group leaves. If X is a poorer leaving group than Y, then Y will preferentially leave and **4** will revert to the starting compounds. Thus there is a partitioning factor between **4** going on to product (loss of X) or back to starting compound (loss of Y). The sum of these two factors causes the sequence of reactivity to be $RCOCl > RCOOCOR' > RCOOAr > RCOOR' > RCONH_2 > RCONR'_2 > RCOO^-$.[35] Note that this order is approximately the order of decreasing stability of the leaving-group anion. If the leaving group is bulky, it may exert a steric effect and retard the rate for this reason.

For a list of some of the more important reactions that operate by the tetrahedral mechanism, see Table 16.1, which shows the main reactions that proceed by the tetrahedral mechanism.

[35]RCOOH would belong in this sequence just after RCOOAr, but it fails to undergo many reactions for a special reason. Many nucleophiles, instead of attacking the C=O group, are basic enough to take a proton from the acid, converting it to the unreactive $RCOO^-$.

REACTIONS

Many of the reactions in this chapter are simple additions to carbon–hetero multiple bonds, with the reaction ending when the two groups have been added. But in many other cases subsequent reactions take place. We will meet a number of such reactions, but most are of two types:



In type *A*, the initially formed adduct loses water (or, in the case of addition to C=NH, ammonia, etc.), and the net result of the reaction is the substitution of C=Y for C=O (or C=NH, etc.). In type *B*, there is a rapid substitution, and the OH (or NH_2, etc.) is replaced by another group Z, which is often another YH moiety. This substitution is in most cases nucleophilic, since Y usually has an unshared pair and S_N1 reactions occur very well on this type of compound (see p. 482), even when the leaving group is as poor as OH or NH_2. In this chapter, we will classify reactions according to what is initially adding to the carbon–hetero multiple bond, even if subsequent reactions take place so rapidly that it is not possible to isolate the initial adduct.

Most of the reactions considered in this chapter can be reversed. In many cases, we will consider the reverse reactions with the forward ones, in the same section. The reverse of some of the other reactions are considered in other chapters. In still other cases, one of the reactions in this chapter is the reverse of another (e.g., **16-2** and **16-13**). For reactions that are reversible, the principle of microscopic reversibility (p. 309) applies.

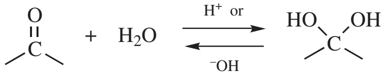
First, we will discuss reactions in which hydrogen or a metallic ion (or in one case phosphorus or sulfur) adds to the heteroatom and second reactions in which carbon adds to the heteroatom. Within each group, the reactions are classified by the nature of the nucleophile. Additions to isocyanides, which are different in character, follow. Acyl substitution reactions that proceed by the tetrahedral mechanism, which mostly involve derivatives of carboxylic acids, are treated at the end.

REACTIONS IN WHICH HYDROGEN OR A METALLIC ION ADDS TO THE HETEROATOM

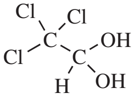
A. Attack by OH (Addition of H_2O)

16-1 The Addition of Water to Aldehydes and Ketones: Formation of Hydrates

O-Hydro-*C*-hydroxy-addition



The adduct formed upon addition of water to an aldehyde or ketone is called a hydrate or *gem*-diol.[36] These compounds are usually stable only in water solution and decompose on distillation; that is, the equilibrium shifts back toward the carbonyl compound. The position of the equilibrium is greatly dependent on the structure of the hydrate. Thus, formaldehyde in water at 20°C exists 99.99% in the hydrated form, while for acetaldehyde this figure is 58%, and for acetone the hydrate concentration is negligible.[37] It has been found, by exchange with ^{18}O, that the reaction with acetone is quite rapid when catalyzed by acid or base, but the equilibrium lies on the side of acetone and water.[38] Since methyl, a +*I* group, inhibits hydrate formation, it may be expected that electron-attracting groups would have the opposite effect, and this is indeed the case. The hydrate of chloral (trichloroacetaldehyde)[39] is a stable crystalline substance. In order for it to revert to chloral, ^-OH or H_2O must leave; this is made difficult by the electron-withdrawing character of the Cl_3C group. Some other[40] polychlorinated and polyfluorinated



Chloral hydrate

Hydrate of cyclopropanone

aldehydes and ketones[41] and α-keto aldehydes also form stable hydrates, as do cyclopropanones.[42] In the last case,[43] formation of the hydrate relieves some of the *I* strain (p. 399) of the parent ketone.

[36]For reviews, see Bell, R.P. *The Proton in Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, ***1973***, pp. 183–187; *Adv. Phys. Org. Chem.* ***1966***, *4*, 1; Le Hénaff, P. *Bull. Soc. Chim. Fr.* ***1968***, 4687.

[37]Bell, R.P.; Clunie, J.C. *Trans. Faraday Soc.* ***1952***, *48*, 439. See also, Bell, R.P.; McDougall, A.O. *Trans. Faraday Soc.* ***1960***, *56*, 1281.

[38]Cohn, M.; Urey, H.C. *J. Am. Chem. Soc.* ***1938***, *60*, 679.

[39]For a review of chloral, see Luknitskii, F.I. *Chem. Rev.* ***1975***, *75*, 259.

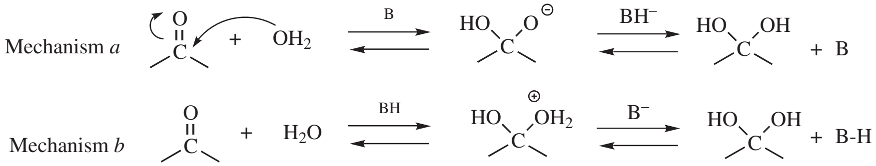
[40]For a discussion, see Schulman, E.M.; Bonner, O.D.; Schulman, D.R.; Laskovics, F.M. *J. Am. Chem. Soc.* ***1976***, *98*, 3793.

[41]For a review of addition to fluorinated ketones, see Gambaryan, N.P.; Rokhlin, E.M.; Zeifman, Yu.V.; Ching-Yun, C.; Knunyants, I.L. *Angew. Chem. Int. Ed.* ***1966***, *5*, 947.

[42]For other examples, see Krois, D.; Lehner, H. *Monatsh. Chem.* ***1982***, *113*, 1019.

[43]Turro, N.J.; Hammond, W.B. *J. Am. Chem. Soc.* ***1967***, *89*, 1028; Schaafsma, S.E.; Steinberg, H.; de Boer, T.J. *Recl. Trav. Chim. Pays-Bas* ***1967***, *86*, 651. For a review of cyclopropanone chemistry, see Wasserman, H.H.; Clark, G.M.; Turley, P.C. *Top. Curr. Chem.* ***1974***, *47*, 73.

The reaction is subject to both general-acid and general-base catalysis; the following mechanisms can be written for basic (B) and acidic (BH) catalysis, respectively:[44]



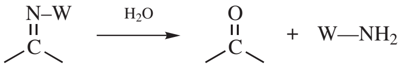
In mechanism *a*, as the H_2O attacks, the base pulls off a proton, and the net result is addition of ^{-}OH. This can happen because the base is already hydrogen bonded to the H_2O molecule before the attack. In mechanism *b*, because HB is already hydrogen bonded to the oxygen of the carbonyl group, it gives up a proton to the oxygen as the water attacks. In this way, B and HB accelerate the reaction even beyond the extent that they form ^{-}OH or H_3O^+ by reaction with water. Reactions in which the catalyst donates a proton to the electrophilic reagent (in this case the aldehyde or ketone) in one direction and removes it in the other are called class e reactions. Reactions in which the catalyst does the same to the nucleophilic reagent are called class n reactions.[45] Thus the acid-catalyzed process here is a class e reaction, while the base catalyzed process is a class n reaction.

For the reaction between ketones and H_2O_2, see **17-37**.

There are no OS references, but see OS **VIII**, 597, for the reverse reaction.

16-2 Hydrolysis of the Carbon-Nitrogen Double Bond[46]

Oxo-de-alkylimino-bisubstitution, and so on



Compounds containing carbon–nitrogen double bonds can be hydrolyzed to the corresponding aldehydes or ketones.[47] For imines (W = R or H) the hydrolysis is easy and can be carried out with water. When W = H, the imine is seldom stable enough for isolation, and in aqueous media hydrolysis usually occurs *in situ*, without isolation. The hydrolysis of Schiff bases (W = Ar) is more difficult and requires

[44]Bell, R.P.; Rand, M.H.; Wynne-Jones, K.M.A. *Trans. Faraday Soc.* ***1956***, *52*, 1093; Pocker, Y. *Proc. Chem. Soc.* ***1960***, 17; Sørensen, P.E.; Jencks, W.P. *J. Am. Chem. Soc.* ***1987***, *109*, 4675. For a comprehensive treatment, see Lowry, T.H.; Richardson, K.S. *Mechanism and Theory in Organic Chemistry*, 3rd ed., Harper and Row, NY, ***1987***, pp. 662–680. For a theoretical treatment see Wolfe, S.; Kim, C.-K.; Yang, K.; Weinberg, N.; Shi, Z. *J. Am. Chem. Soc.* ***1995***, *117*, 4240.

[45]Jencks, W.P. *Acc. Chem. Res.* ***1976***, *9*, 425.

[46]For a review, see Khoee, S.; Ruoho, A.E. *Org. Prep. Proceed. Int.* ***2003***, *35*, 527.

[47]The proton affinities of imines have been determined, see Hammerum, S.; Sølling, T.I. *J. Am. Chem. Soc.* ***1999***, *121*, 6002.

acid or base catalysis. Oximes (W = OH), arylhydrazones (W = NHAr), and, most easily, semicarbazones (W = $NHCONH_2$) can also be hydrolyzed. Often a reactive aldehyde (e.g., formaldehyde) is added to combine with the liberated amine.

A number of other reagents[48] have been used to cleave C=N bonds, especially those not easily hydrolyzable with acidic or basic catalysts or that contain other functional groups that are attacked under these conditions. Oximes have been converted to the corresponding aldehyde or ketone[49] by treatment with, among other reagents, NBS in water,[50] glyoxylic acid (HCOCOOH),[51] Chloramine-T[52] Caro's acid on SiO_2,[53] HCOOH on SiO_2 with microwave irradiation,[54] bromosulfonamides,[55] $SiBr_4$ on wet silica,[56] and $KMnO_4$ on Al_2O_3[57] or on zeolite.[58] Chromate oxidizing agents can be quite effective, including tetraethylammonium permanganate,[59] tetraalkylammonium dichromate with microwave irradiation,[60] pyridinium fluorochromate,[61] quinolinium fluorochromate[62] or dichromate.[63] Alkaline H_2O_2,[64] iodine in acetonitrile,[65] singlet oxygen with NaOMe/MeOH[66] and with an ionic liquids on SiO_2[67] have also been used. Transition-metal compounds have been used, including $SbCl_5$,[68] $Co_2(CO)_8$[69] $Hg(NO_3)_2/SiO_2$,[70] or $BiBr_3$—$Bi(OTf)_3$ in aqueous media,[71] $Bi(NO_3)_3/SiO_2$,[72] a nickel(II) complex

[48]For a list of reagents, with references, see Ranu, B.C.; Sarkar, D.C. *J. Org. Chem.* ***1988***, *53*, 878.

[49]For a review, see Corsaro, A.; Chiacchio, U.; Pistarà, V. *Synthesis* ***2001***, 1903.

[50]Bandgar, B.P.; Makone, S.S. *Org. Prep. Proceed. Int.* ***2000***, *32*, 391.

[51]Chavan, S.P.; Soni, P. *Tetrahedron Lett.* ***2004***, *45*, 3161.

[52]Padmavathi, V.; Reddy, K.V.; Padmaja, A.; Venugopalan, P. *J. Org. Chem.* **2003**, *68*, 1567.

[53]Movassagh, B.; Lakouraj, M.M.; Ghodrati, K. *Synth. Commun.* ***2000***, *30*, 4501.

[54]A solvent-free reaction. See Zhou, J.-F.; Tu, S.-J.; Feng, J.-C. *Synth.Commun.* ***2002***, *32*, 959.

[55]Khazaei, A.; Vaghei, R.G.; Tajbakhsh, M. *Tetrahedron Lett.* ***2001***, *42*, 5099.

[56]De, S.K. *Tetrahedron Lett.* ***2003***, *44*, 9055.

[57]Chrisman, W.; Blankinship, M.J.; Taylor, B.; Harris, C.E. *Tetrahedron Lett.* ***2003***, *33*, 4775; Imanzadeh, G.H.; Hajipour, A.R.; Mallakpour, S.E. *Synth. Commun.* ***2003***, *33*, 735.

[58]Jadhav, V.K.; Wadgaonkar, P.P.; Joshi, P.L.; Salunkhe, M.M. *Synth. Commun.* ***1999***, *29*, 1989.

[59]Bigdeli, M.A.; Nikje, M.M.A.; Heravi, M.M. *J. Chem. Res. (S)* ***2001***, 496.

[60]Hajipour, A.R.; Mallakpour, S.E.; Khoee, E. *Synth. Commun.* ***2002***, *32*, 9.

[61]Ganguly, N.C.; De, P.; Sukai, A.K.; De, S. *Synth. Commun.* ***2002***, *32*, 1.

[62]Bose, D.S.; Narasaiah, A.V. *Synth. Commun.* ***2000***, *30*, 1153. See also, Ganguly, N.C.; Sukai, A.K.; De, S.; De, P. *Synth. Commun.* ***2001***, *31*, 1607.

[63]Sadeghi, M.M.; Mohammadpoor-Baltork, I.; Azarm, M.; Mazidi, M.R. *Synth. Commun.* ***2001***, *31*, 435. See also, Hajipour, A.R.; Mallakpour, S.E.; Mohammadpoor-Baltork, I.; Khoee, S. *Synth. Commun.* ***2001***, *31*, 1187; Tajbakhsh, M.; Heravi, M.M.; Mohanazadeh, F.; Sarabi, S.; Ghassemzadeh, M. *Monat. Chem.* ***2001***, *132*, 1229; Zhang, G.-S.; Yang, D.-H.; Chen. M.-F. *Org. Prep. Proceed. Int.* ***1998***, *30*, 713.

[64]Ho, T. *Synth. Commun.* ***1980***, *10*, 465.

[65]Yadav, J.S.; Sasmal, P.K.; Chand, P.K. *Synth. Commun.* ***1999***, *29*, 3667.

[66]Öcal, N.; Erden, I. *Tetrahedron Lett.* ***2001***, *42*, 4765.

[67]BAcIm BF_4, 3-butyl-1-(CH_2COOH)imidazolium tetrafluoroborate: Li, D.; Shi, F.; Guo, S.; Deng, Y. *Tetrahedron Lett.* ***2004***, *45*, 265. In Dmim BF_4, 1-decyl-3-methyl imidazolium tetrafluoroborate: Li, D.; Shi, F.; Deng, Y. *Tetrahedron Lett.* ***2004***, *45*, 6791.

[68]Narsaiah, A.V.; Nagaiah, K. *Synthesis* ***2003***, 1881.

[69]Mukai, C.; Nomura, I.; Kataoka, O.; Hanaoka, M. *Synthesis* ***1999***, 1872.

[70]De, S.K. *Synth. Commun.* 2004, *34*, 2289.

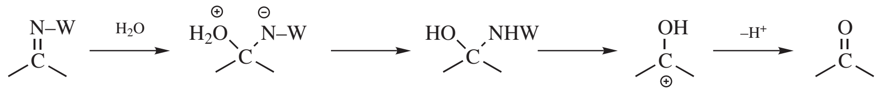
[71]Arnold, J.N.; Hayes, P.D.; Kohaus, R.L.; Mohan, R.S. *Tetrahedron Lett.* ***2003***, *44*, 9173.

[72]Samajdar, S.; Basu, M.K.; Becker, F.F.; Banik, B.K. *Synth. Commun.* ***2002***, *32*, 1917.

with trimethylacetaldehyde,[73] CuCl on Kieselguhr with oxygen,[74] $Bi(NO_3)_3$/$Cu(OAc)_2$ on Montmorillonite K10,[75] CrO_3-SiO_2,[76] and In addition, peroxomonosulfate-SiO_2,[77] $Cu(NO_3)_2$–SiO_2,[78] $Zn(NO_3)_2$-SiO_2,[79] and clay (Clayan)[80] have all been used with microwave irradiation. Phenylhydrazones can be converted to a ketone using Oxone® and $KHCO_3$,[81] polymer-bound iodonium salts,[82] or $KMnO_4$ on wet SiO_2.[83] Dimethylhydrazones have been converted to ketones by heating with potassium carbonate in dimethyl sulfate,[84] with $MeReO_3/H_2O_2$ in acetic acid-acetonitrile,[85] with $Pd(OAc)_2/SnCl_2$ in aq. DMF,[86] $FeSO_4$•7 H_2O in chloroform,[87] Me_3SiCl/NaI in acetonitrile with 1% water,[88] $[Ni(en)_3]_2S_2O_3$, where en = ethylenediamine, in chloroform,[89] or $CeCl_3$•7 H_2O–SiO_2 with microwave irradiation.[90]

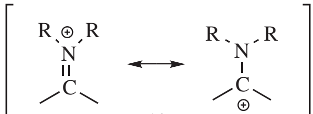
Hydrazones, such as RAMP or SAMP (see p. 633) can be hydrolyzed with aq. $CuCl_2$.[91] Tosylhydrazones can be hydrolyzed to the corresponding ketones with aq. acetone and BF_3–etherate,[92] as well as with other reagents.[93] Semicarbazones have been cleaved with ammonium chlorochromates on alumina[94] $(Bu_4N)_2S_2O_8$,[95] $Mg(HSO_4)_2$ on wet silica,[96] or by $SbCl_3$ with microwave irradiation.[97]

The hydrolysis of carbon–nitrogen double bonds involves initial addition of water and elimination of a nitrogen moiety:



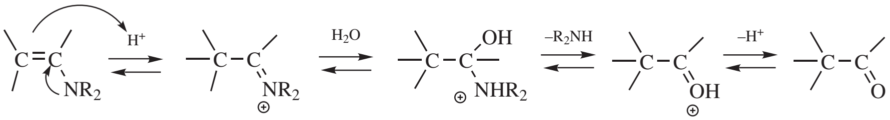
[73]Blay, G.; Benach, E.; Fernández, I.; Galletero, S.; Pedro, J.R.; Ruiz, R. *Synthesis* ***2000***, 403.
[74]Hashemi, M.M.; Beni, Y.A. *Synth. Commun.* ***2001***, *31*, 295.
[75]Nattier, B.A.; Eash, K.J.; Mohan, R.S. *Synthesis* ***2001***, 1010.
[76]Bendale, P.M.; Khadilkar, B.M. *Synth. Commun.* ***2000***, *30*, 665.
[77]Bose, D.S.; Narsaiah, A.V.; Lakshminarayana, V. *Synth. Commun.* ***2000***, *30*, 3121.
[78]Ghiaci, M.; Asghari, J. *Synth. Commun.* ***2000***, *30*, 3865.
[79]Tamami, B.; Kiasat, A.R. *Synth. Commun.* ***2000***, *30*, 4129.
[80]Meshram, H.M.; Srinivas, D.; Reddy, G.S.; Yadav, J.S. *Synth. Commun.* ***1998***, *28*, 4401; 2593.
[81]Hajipour, A.R.; Mahboubghah, N. *Org. Prep Proceed. Int.* ***1999***, *31*, 112.
[82]Chen, D.-J.; Cheng, D.-P.; Chen, Z.-C. *Synth. Commun.* ***2001***, *31*, 3847.
[83]Hajipour, A.R.; Adibi, H.; Ruoho, A.E. *J. Org. Chem.* ***2003***, *68*, 4553.
[84]Kamal, A.; Arifuddin, M.; Rao, N.V. *Synth. Commun.* ***1998***, *28*, 3927.
[85]Stanković, S.; Espenson, J.H. *J. Org. Chem.* ***2000***, *65*, 2218.
[86]Mino, C.; Hirota, T.; Fujita, N.; Yamashita, M. *Synthesis* ***1999***, 2024.
[87]Nasreen, A.; Adapa, S.R. *Org. Prep. Proceed. Int.* ***1999***, *31*, 573.
[88]Kamal, A.; Ramana, K.V.; Arifuddin, M. *Chem. Lett.* ***1999***, 827.
[89]Kamal, A.; Arifuddin, M.; Rao, M.V. *Synlett* ***2000***, 1482.
[90]Yadav, J.S.; Subba Reddy, B.V.; Reddy, M.S.K.; Sabitha, G. *Synlett* ***2001***, 1134.
[91]Enders, D.; Hundertmark, T.; Lazny, R. *Synth. Commun.* ***1999***, *29*, 27.
[92]Sacks, C.E.; Fuchs, P.L. *Synthesis* ***1976***, 456.
[93]DDQ with dichloromethane/water: Chandrasekhar, S.; Reddy, Ch.R.; Reddy, M.V. *Chem. Lett.* ***2000***, 430. For references, see Jiricny, J.; Orere, D.M.; Reese, C.B. *Synthesis* ***1970***, 919.
[94]Zhang, G.-S.; Gong, H.; Yang, D.-H.; Chen, M.-F. *Synth. Commun.* ***1999***, *29*, 1165; Gong, H.; Zhang, G.-S. *Synth. Commun.* ***1999***, *29*, 2591.
[95]Chen, F.-E.; Liu, J.-P.; Fu, H.; Peng, Z.-Z.; Shao, L.-Y. *Synth. Commun.* ***2000***, *30*, 2295.
[96]Shirini, F.; Zolfigol, M.A.; Mallakpour, B.; Mallakpour, S.E.; Hajipour, A.R.; Baltork, I.M. *Tetrahedron Lett.* ***2002***, *43*, 1555.
[97]Mitra, A.K.; De, A.; Karchaudhuri, N. *Synth. Commun.* ***2000***, *30*, 1651.

It is thus an example of reaction type *A* (p. 1261). The sequence shown is generalized.[98] In specific cases, there are variations in the sequence of the steps, depending on acid or basic catalysis or other conditions.[99] Which step is rate determining also depends on acidity and on the nature of W and of the groups connected to the carbonyl.[100]



10

Iminium ions (**10**)[101] would be expected to undergo hydrolysis quite readily, since there is a contributing form with a positive charge on the carbon. Indeed, they react with water at room temperature.[102] Acid-catalyzed hydrolysis of enamines (the last step of the Stork reaction, **10-69** involves conversion to iminium ions:[103]



The mechanism of enamine hydrolysis is thus similar to that of vinyl ether hydrolysis (**10-6**).

OS **I**, 217, 298, 318, 381; **II**, 49, 223, 234, 284, 310, 333, 395, 519, 522; **III**, 20, 172, 626, 818; **IV**, 120; **V**, 139, 277, 736, 758; **VI**, 1, 358, 640, 751, 901, 932; **VII**, 8; **65**, 108, 183; **67**, 33; **76**, 23.

Related to this process is the hydrolysis of isocyanates or isothiocyanates[104] where addition of water to the carbon–nitrogen double bond would give an *N*-substituted carbamic acid (**11**). Such compounds are unstable and break down to

[98]For reviews of the mechanism, see Bruylants, A.; Feytmants-de Medicis, E., in Patai, S. *The Chemistry of the Carbon–Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 465–504; Salomaa, P., in Patai, S. *The Chemistry of the Carbonyl Group* pt. 1, Wiley, NY, ***1966***, pp. 199–205.

[99]For example, see Reeves, R.L. *J. Am. Chem. Soc.* ***1962***, *82*, 3332; Sayer, J.M.; Conlon, E.H. *J. Am. Chem. Soc.* ***1980***, *102*, 3592.

[100]Cordes, E.H.; Jencks, W.P. *J. Am. Chem. Soc.* ***1963***, *85*, 2843.'

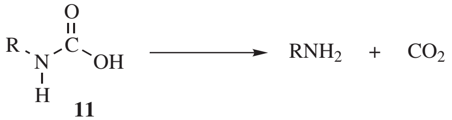
[101]For a review of iminium ions, see Böhme, H.; Haake, M. *Adv. Org. Chem.* ***1976***, *9*, pt. 1, 107.

[102]Hauser, C.R.; Lednicer, D. *J. Org. Chem.* ***1959***, *24*, 46. For a study of the mechanism, see Gopalakrishnan, G.; Hogg, J.L. *J. Org. Chem.* ***1989***, *54*, 768.

[103]Maas, W.; Janssen, M.J.; Stamhuis, E.J.; Wynberg, H. *J. Org. Chem.* ***1967***, *32*, 1111; Sollenberger, P.Y.; Martin, R.B. *J. Am. Chem. Soc.* ***1970***, *92*, 4261. For a review of enamine hydrolysis, see Stamhuis, E.J.; Cook, A.G., in Cook *Enamines*, 2nd ed.; Marcel Dekker, NY, ***1988***, pp. 165–180.

[104]For a study of the mechanism, see Castro, E.A.; Moodie, R.B.; Sansom, P.J. *J. Chem. Soc. Perkin Trans. 2* ***1985***, 737. For a review of the mechanisms of reactions of isocyanates with various nucleophiles, see Satchell, D.P.N.; Satchell, R.S. *Chem. Soc. Rev.* ***1975***, *4*, 231.

carbon dioxide (or COS in the case of isothiocyanates) and the amine:

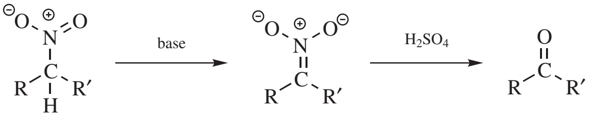


11

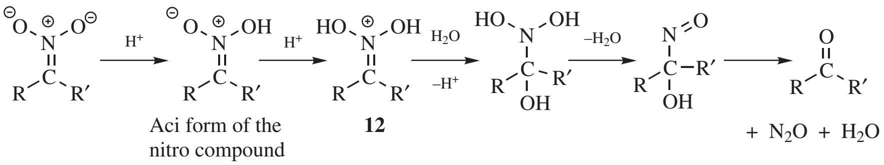
OS **II**, 24; **IV**, 819; **V**, 273; **VI**, 910.

16-3 Hydrolysis of Aliphatic Nitro Compounds

Oxo-de-hydro,nitro-bisubstitution



Primary or secondary aliphatic nitro compounds can be hydrolyzed, respectively, to aldehydes or ketones, by treatment of their conjugate bases with sulfuric acid. This is called the *Nef reaction*.[105] Tertiary aliphatic nitro compounds do not give the reaction because they cannot be converted to their conjugate bases. Like **16-2**, this reaction involves hydrolysis of a C=N double bond. A possible mechanism is[106]



Intermediates of type **12** have been isolated in some cases.[107]

The conversion of nitro compounds to aldehydes or ketones has been carried out with better yields and fewer side reactions by several alternative methods.[108] Among these are treatment of the nitro compound with tin complexes and $NaHSO_3$,[109] activated dry silica gel,[110] or 30% H_2O_2—K_2CO_3,[111] *t*-BuOOH and a catalyst,[112]

[105]For reviews, see Pinnick, H.W. *Org. React.* ***1990***, *38*, 655; Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Academic Press, NY, ***1988***, pp. 220–231, 416–419.

[106]Hawthorne, M.F. *J. Am. Chem. Soc.* ***1957***, *79*, 2510. A similar mechanism, but with some slight differences, was suggested earlier by van Tamelen, E.E.; Thiede, R.J. *J. Am. Chem. Soc.* ***1952***, *74*, 2615. See also, Sun, S.F.; Folliard, J.T. *Tetrahedron* ***1971***, *27*, 323.

[107]Feuer, H.; Spinicelli, L.F. *J. Org. Chem.* ***1977***, *42*, 2091.

[108]For a review, see Ballini, R.; Petrini, M. *Tetrhaedron* ***2004***, *60*, 1017.

[109]Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* ***1990***, *31*, 7499.

[110]Keinan, E.; Mazur, Y. *J. Am. Chem. Soc.* ***1977***, *99*, 3861.

[111]Olah, G.A.; Arvanaghi, M.; Vankar, Y.D.; Prakash, G.K.S. *Synthesis* ***1980***, 662.

[112]Bartlett, P.A.; Green III, F.R.; Webb, T.R. *Tetrahedron Lett.* ***1977***, 331.

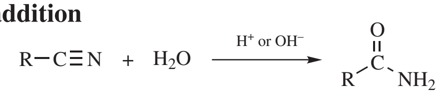
DBU in acetonitrile,[113] NaH and $Me_3SiOOSiMe_3$,[114] $NaNO_2$ in aq. DMSO,[115] or ceric ammonium nitrate (CAN).[116] The reaction of Al—$NiCl_2$•6 H_2O in THF converted α,β-unsaturated nitro compounds to the corresponding aldehyde, $PhCH{=}CHNO_2 \rightarrow PhCH_2CHO$.[117]

When *primary* nitro compounds are treated with sulfuric acid without previous conversion to the conjugate bases, they give carboxylic acids. Hydroxamic acids are intermediates and can be isolated, so that this is also a method for preparing them.[118] Both the Nef reaction and the hydroxamic acid process involve the aci form; the difference in products arises from higher acidity, for example, a difference in sulfuric acid concentration from 2 to 15.5 *M* changes the product from the aldehyde to the hydroxamic acid.[119] The mechanism of the hydroxamic acid reaction is not known with certainty, but if higher acidity is required, it may be that the protonated aci form of the nitro compound is further protonated.

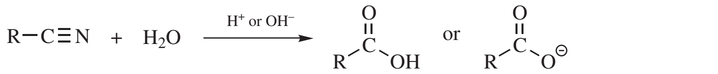
OS **VI**, 648; **VII**, 414. See also OS **IV**, 573.

16-4 Hydrolysis of Nitriles

***NN*-Dihydro-*C-oxo*-biaddition**



Hydroxy,oxo-de-nitrilo-tersubstitution



Nitriles can be hydrolyzed to give either amides or carboxylic acids.[120] The amide is formed initially, but since amides are also hydrolyzed with acid or basic treatment, the carboxylic acid is readily formed. When the acid is desired,[121] the reagent of choice is aq. NaOH containing ~6–12% H_2O_2, though acid-catalyzed hydrolysis is also frequently carried out. A "dry" hydrolysis of nitriles has been reported.[122] The hydrolysis of nitriles to carboxylic acids is one of the best methods for the preparation of these compounds. Nearly all nitriles give the reaction, with either acidic or basic catalysts. Hydrolysis of cyanohydrins, RCH(OH)CN, is usually carried out under acidic conditions, because basic solutions cause competing

[113]Ballini, R.; Bosica, G.; Fiorini, D.; Petrini, M. *Tetahedron Lett.* ***2002***, *43*, 5233.

[114]Shahi, S.P.; Vankar, Y.D. *Synth. Commun.* ***1999***, *29*, 4321.

[115]Gissot, A.; N'Gouela, S.; Matt, C.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* ***2004***, *69*, 8997.

[116]Olah, G.A.; Gupta, B.G.B. *Synthesis* ***1980***, 44.

[117]Bezbarua, M.S.; Bez, G.; Barua, N.C. *Chem. Lett.* ***1999***, 325.

[118]Hydroxamic acids can also be prepared from primary nitro compounds with SeO_2 and Et3N: Sosnovsky, G.; Krogh, J.A. *Synthesis* ***1980***, 654.

[119]Kornblum, N.; Brown, R.A. *J. Am. Chem. Soc.* ***1965***, *87*, 1742. See also, Cundall, R.B.; Locke, A.W. *J. Chem. Soc. B* ***1968***, 98; Edward, J.T.; Tremaine, P.H. *Can J. Chem.* ***1971***, *49*, 3483, 3489, 3493.

[120]For reviews, see Zil'berman, E.N. *Russ. Chem. Rev.* ***1984***, *53*, 900; Compagnon, P.L.; Miocque, M. *Ann. Chim. (Paris)* ***1970***, *[14] 5*, 11, 23.

[121]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1986–1987.

[122]Chemat, F.; Poux, M.; Berlan, J. *J. Chem. Soc. Perkin Trans. 2* ***1996***, 1781; ***1994***, 2597.

reversion of the cyanohydrin to the aldehyde and CN^-. However, cyanohydrins have been hydrolyzed under basic conditions with borax or alkaline borates.[123] Enzymatic hydrolysis with *Rhodococcus* sp AJ270 has also been reported.[124] In methanol with BF_3•OEt_2, benzonitrile is converted to methyl benzoate.[125]

There are a number of procedures for stopping at the amide stage,[126] among them the use of concentrated H_2SO_4; 2 equivalents of chlorotrimethylsilane followed by H_2O,[127] aq. NaOH with PEG-400 and microwave irradiation,[128] $NaBO_3$ with 4 equivalents of water and microwave irradiation,[129] heating on neutral alumina,[130] Oxone®,[131] and dry HCl followed by H_2O. The same result can also be obtained by use of water and certain metal ions or complexes;[132] a ruthenium catalyst on alumina with water,[133] MnO_2/SiO_2 with microwave irradiation,[134] $Hg(OAc)_2$ in HOAc;[135] or 2-mercaptoethanol in a phosphate buffer.[136] Nitriles can be hydrolyzed to the carboxylic acids without disturbing carboxylic ester functions also present, by the use of tetrachloro- or tetrafluorophthalic acid.[137] Nitriles are converted to thioamides $ArC(=S)NH_2$ with ammonium sulfide $(NH_4)_2S$ in methanol, with microwave irradiation.[138]

Thiocyanates are converted to thiocarbamates in a similar reaction:[139] $R{-}S{-}C{\equiv}N + H_2O \rightarrow R{-}S{-}C{-}O\ NH_2$. Hydrolysis of cyanamides gives amines, produced by the breakdown of the unstable carbamic acid intermediates: $R_2NCN \rightarrow [R_2NCOOH] \rightarrow R_2NH$.

OS **I**, 21, 131, 201, 289, 298, 321, 336, 406, 436, 451; **II**, 29, 44, 292, 376, 512, 586 (see, however, **V**, 1054), 588; III; 34, 66, 84, 88, 114, 221, 557, 560, 615, 851; **IV**, 58, 93, 496, 506, 664, 760, 790; **V**, 239; **VI**, 932; **76**, 169. Also see, OS **III**, 609; **IV**, 359, 502; **66**, 142.

[123]Jammot, J.; Pascal, R.; Commeyras, A. *Tetrahedron Lett.* ***1989***, *30*, 563.

[124]Wang, M.-X.; Lin, S.-J. *J. Org. Chem.* ***2002***, *67*, 6542.

[125]Jayachitra, G.; Yasmeen, N..; Rao, K.S.; Ralte, S.L.; Srinivasan, R.; Singh, A.K. *Synth. Commun.* ***2003***, *33*, 3461.

[126]For a discussion, see Beckwith, A.L.J., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 119–125. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1988–1990.

[127]Basu, M.K.; Luo, F.-T. *Tetrahedron Lett.* ***1998***, *39*, 3005.

[128]Bendale, P.M.; Khadilkar, B.M. *Synth. Commun.* ***2000***, *30*, 1713.

[129]Sharifi, A.; Mohsenzadeh, F.; Mohtihedi, M.M.; Saidi, M.R.; Balalaie, S. *Synth. Commun.* ***2001***, *31*, 431.

[130]Wligus, C.P.; Downing, S.; Molitor, E.; Bains, S.; Pagni, R.M.; Kabalka, G.W. *Tetrahedron Lett.* ***1995***, *36*, 3469.

[131]Bose, D.S.; Baquer, S.M. *Synth. Commun.* ***1997***, *27*, 3119.

[132]For example, see Bennett, M.A.; Yoshida, T. *J. Am. Chem. Soc.* ***1973***, *95*, 3030; Paraskewas, S. *Synthesis* ***1974***, 574; McKenzie, C.J.; Robson, R. *J. Chem. Soc., Chem. Commun.* ***1988***, 112.

[133]Yamaguchi, K.; Matsushita, M.; Mizuno, N. *Angew. Chem. Int. Ed.* ***2004***, *43*, 1576.

[134]A solvent-free reaction. See Khadilkar, B.M.; Madyar, V.R. *Synth. Commun.* ***2002***, *32*, 1731.

[135]Plummer, B.F.; Menendez, M.; Songster, M. *J. Org. Chem.* ***1989***, *54*, 718.

[136]Lee, Y.B.; Goo, Y.M.; Lee,Y.Y.; Lee, J.K. *Tetrahedron Lett.* ***1989***, *30*, 7439.

[137]Rounds, W.D.; Eaton, J.T.; Urbanowicz, J.H.; Gribble, G.W. *Tetrahedron Lett.* ***1988***, *29*, 6557.

[138]Bagley, M.C.; Chapaneri, K.; Glover, C.; Merritt, E.A. *Synlett* ***2004*** 2615.

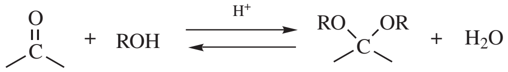
[139]Zil'berman, E.N.; Lazaris, A.Ya. *J. Gen. Chem. USSR* ***1963***, *33*, 1012.

B. Attack by OR or SR (Addition of ROH; RSH)

16-5 The Addition of Alcohols to Aldehydes and Ketones

Dialkoxy-de-oxo-bisubstitution

Dithioalkyl-de-oxo-bisubstitution



Acetals and ketals are formed by treatment of aldehydes and ketones, respectively, with alcohols in the presence of acid catalysts.[140] Lewis acids such as $TiCl_4$[141] $RuCl_3$,[142] or $CoCl_2$[143] can be used in conjunction with alcohols. Dioxolanes have been prepared in ethylene glycol using microwave irradiation and *p*-toluenesulfonic acid as a catalyst.[144] This reaction is reversible, and acetals and ketals can be hydrolyzed by treatment with acid.[145] With small unbranched aldehydes the equilibrium lies to the right. If ketals or acetals of larger molecules must be prepared the equilibrium must be shifted, usually by removal of water. This can be done by azeotropic distillation, ordinary distillation, or the use of a drying agent such as Al_2O_3 or a molecular sieve.[146] The reaction is not catalyzed in either direction by bases, so most acetals and ketals are quite stable to bases, though they are easily hydrolyzed by acids. This reaction is therefore a useful method of protection of aldehyde or ketone functions from attack by bases. The reaction is of wide scope. Most aldehydes are easily converted to acetals.[147] With ketones the process is more difficult, presumably for steric reasons, and the reaction often fails, though many ketals, especially from cyclic ketones, have been made in this manner.[148] Many functional groups may be present without being affected. 1,2-Glycols and 1,3-glycols form cyclic acetals and ketals (1,3-dioxolanes[149]

[140]For reviews, see Meskens, F.A.J. *Synthesis* ***1981***, 501; Schmitz, E.; Eichhorn, I., in Patai, S. *The Chemistry of the Ether Linkage*, Wiley, NY, ***1967***, pp. 309–351.

[141]Clerici, A.; Pastori, N.; Porta, O. *Tetrahedron* ***2001***, *57*, 217.

[142]De, S.K.; Gibbs, R.A. *Tetrahedron Lett.* ***2004***, *45*, 8141.

[143]Velusamy, S.; Punniyamurthy, T. *Tetrahedron Lett.* ***2004***, *45*, 4917.

[144]Pério, B.; Dozias, M.-J.; Jacquault, P.; Hamelin, J. *Tetrahdron Lett.* ***1997***, *38*, 7867; Moghaddam, F.M.; Sharifi, A. *Synth. Commun.* ***1995***, *25*, 2457.

[145]See Heravi, M.M.; Tajbakhsh, M.; Habibzadeh, S.; Ghassemzadeh, M. *Monat. Chem.* ***2001***, *132*, 985.

[146]For many examples of each of these methods, see Meskens, F.A.J. *Synthesis* ***1981***, 501, pp. 502–505.

[147]For other methods, see Caputo, R.; Ferreri, C.; Palumbo, G. *Synthesis* ***1987***, 386; Ott, J.; Tombo, G.M.R.; Schmid, B.; Venanzi, L.M.; Wang, G.; Ward, T.R. *Tetrahedron Lett.* ***1989***, *30*, 6151, Liao, Y.; Huang, Y.; Zhu, F. *J. Chem. Soc., Chem. Commun.* ***1990***, 493; Chan, T.H.; Brook, M.A.; Chaly, T. *Synthesis* ***1983***, 203.

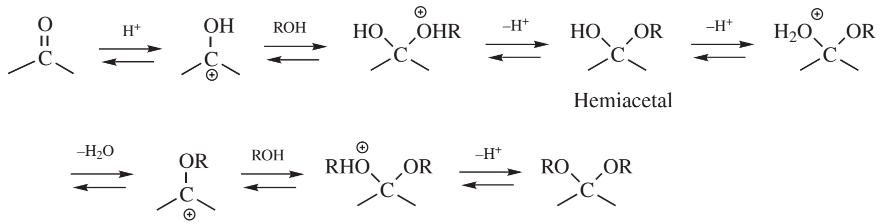
[148]High pressure has been used to improve the results with ketones: Dauben, W.G.; Gerdes, J.M.; Look, G.C. *J. Org. Chem.* ***1986***, *51*, 4964. For other methods, see Otera, J.; Mizutani, T.; Nozaki, H. *Organometallics*, ***1989***, *8*, 2063; Thurkauf, A.; Jacobson, A.E.; Rice, K.C. *Synthesis* ***1988***, 233.

[149]See Yadav, J.S.; Reddy, B.V.S.; Srinivas, R.; Ramalingam, T. *Synlett* ***2000***, 701; Laskar, D.D.; Prajapati, D.; Sandhu, J.S. *Chem. Lett.* ***1999***, 1283; Curini, M.; Epifano, F.; Marcotullio, M.C.; Rosati, O. *Synlett* ***2001***, 1182; Kawabata, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Tetrahedron Lett.* ***2001***, *42*, 8329; Reddy, B.M.; Reddy, V.R.; Giridhar, D. *Synth. Commun.* ***2001***, *31*, 1819; Gopinath, R.; Haque, Sk.J.; Patel, B.K. *J. Org. Chem.* ***2002***, *67*, 5842.

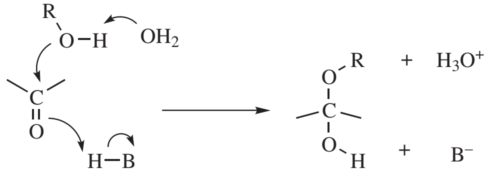
and 1,3-dioxanes,[150] respectively), and these are often used to protect aldehydes and ketones. Chiral dioxolanes have been prepared from chiral diols.[151] Dioxolanes have been prepared from ketones in ionic liquids.[152] Ketones are converted with dimethyl ketals by electrolysis with NaBr in methanol.[153]

Intramolecular reactions are possible in which a keto diol or an aldehyde diol generates a bicyclic ketal or acetal. Fused ring [2.2.0] ketals have been prepared in this manner.[154]

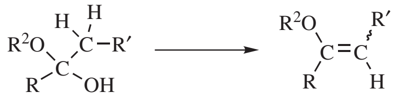
The mechanism, which involves initial formation of a *hemiacetal*,[155] is the reverse of that given for acetal hydrolysis:



In a study of the acid-catalyzed formation of the hemiacetal, Grunwald showed[156] that the data best fit a mechanism in which the three steps shown here are actually all concerted; that is, the reaction is simultaneously catalyzed by acid and base, with water acting as the base:[157]



If the original aldehyde or ketone has an α hydrogen, it is possible for water to split out in that way and enol ethers can be prepared in this manner:



[150]Wu, H.-H.; Yang, F.; Cui, P.; Tang, J.; He, M.-Y. *Tetrahedron Lett.* ***2004***, *45*, 4963; Ishihara, K.; Hasegawa, A.; Yamamoto, H. *Synlett* ***2002***, 1296.

[151]Kurihara, M.; Hakamata, W. *J. Org. Chem.* ***2003***, *68*, 3413.

[152]In AmBIm Cl,: Li, D.; Shi, F.; Peng, J.; Guo, S.; Deng, Y. *J. Org. Chem.* ***2004***, *69*, 3582.

[153]Elinson, M.N.; Feducovich, S.K.; Dmitriev, D.E.; Dorofeev, A.S.; Vereshchagin, A.N.; Nikishin, G.I. *Tetrahedron Lett.* ***2001***, *42*, 5557.

[154]Wang, G.; Wang, Y.; Arcari, A.R.; Rheingold, A.L.; Concolino, T. *Tetrahedron Lett.* ***1999***, *40*, 7051.

[155]For a review of hemiacetals, see Hurd, C.D. *J. Chem. Educ.* ***1966***, *43*, 527.

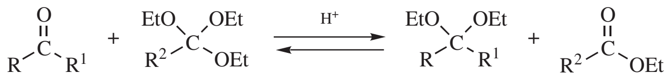
[156]Grunwald, E. *J. Am. Chem. Soc.* ***1985***, *107*, 4715.

[157]Grunwald also studied the mechanism of the base-catalyzed formation of the hemiacetal, and found it to be the same as that of base-catalyzed hydration (**16-1**, mechanism *a*): Grunwald, E. *J. Am. Chem. Soc.* ***1985***, *107*, 4710. See also, Sørensen, P.E.; Pedersen, K.J.; Pedersen, P.R.; Kanagasabapathy, V.M.; McClelland, R.A. *J. Am. Chem. Soc.* ***1988***, *110*, 5118; Leussing, D.L. *J. Org. Chem.* ***1990***, *55*, 666.

Similarly, treatment with an anhydride and a catalyst can give an enol ester (see **16-6**).[158]

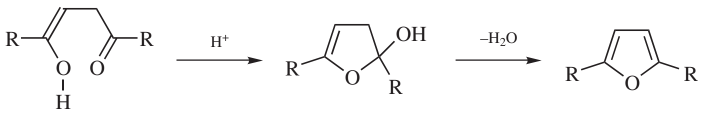
Hemiacetals themselves are no more stable than the corresponding hydrates (**16-1**). As with hydrates, hemiacetals of cyclopropanones[159] and of polychloro and polyfluoro aldehydes and ketones may be quite stable.

When acetals or ketals are treated with an alcohol of higher molecular weight than the one already there, it is possible to get a transacetalation (see **10-13**). In another type of transacetalation, aldehydes or ketones can be converted to acetals or ketals by treatment with another acetal or ketal or with an ortho ester,[160] in the presence of an acid catalyst (shown for an ortho ester):



This method is especially useful for the conversion of ketones to ketals, since the direct reaction of a ketone with an alcohol often gives poor results. In another method, the substrate is treated with an alkoxysilane $ROSiMe_3$ in the presence of trimethylsilyl trifluoromethanesulfonate.[161]

1,4-Diketones give furans when treated with acids. This is actually an example of an intramolecular addition of an alcohol to a ketone, since it is the enol form that adds:



Similarly, 1,5-diketones give pyrans. Conjugated 1,4-diketones, such as 1,4-diphenylbut-2-en-1,4-dione is converted to 2,5-diphenylfuran with formic acid, 5% Pd/C, PEG-200, and a sulfuric acid catalyst with microwave irradiation.[162] Formic acid reacts with alcohols to give orthoformates. Note that alkynyl ketones are converted to furans with palladium (II) acetate.[163]

[158]For a list of catalysts, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1484–1485.

[159]For a review, see Salaun, J. *Chem. Rev.* ***1983***, *83*, 619.

[160]For a review with respect to ortho esters, see DeWolfe, R.H. *Carboxylic Ortho Ester Derivatives*; Academic Press, NY, ***1970***, pp. 154–164. See Karimi, B.; Ebrahimian, G.R.; Seradj, H. *Org. Lett.* ***1999***, *1*, 1737; Karimi, B.; Ashtiani, A.M. *Chem. Lett.* ***1999***, 1199; Firouzabadi, H.; Iranpoor, N.; Karimi, B. *Synlett* ***1999***, 321; Firouzabadi, H.; Iranpoor, N,; Karimi, B. *Synth. Commun.* ***1999***, *29*, 2255; Leonard, N.M.; Oswald, M.C.; Freiberg, D.A.; Nattier, B.A.; Smith, R.C.; Mohan, R.S. *J. Org. Chem.* ***2002***, *67*, 5202.

[161]Tsunoda, T.; Suzuki, M.; Noyori, R.*Tetrahedron Lett.* ***1980***, *21*, 1357; Kato, J.; Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* ***1985***, 743. See also, Torii, S.; Takagishi, S.; Inokuchi, T.; Okumoto, H. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 775.

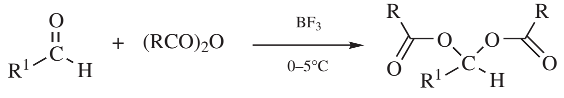
[162]Rao, H.S.P.; Jothilingam, S. *J. Org. Chem.* ***2003***, *68*, 5392.

[163]Jeevanandam, A.; Narkunan, K.; Ling, Y.-C. *J. Org. Chem.* ***2001***, *66*, 6014. See Arcadi, A.; Cerichelli, G.; Chiarini, M.; Di Giuseppe, S. Marinelli, F. *Tetrahedron Lett.* ***2000***, *41*, 9195.

OS **I**, 1, 298, 364, 381; **II**, 137; **III**, 123, 387, 502, 536, 644, 731, 800; **IV**, 21, 479, 679; **V**, 5, 292, 303, 450, 539; **VI**, 567, 666, 954; **VII**, 59, 149, 168, 177, 241, 271, 297; **VIII**, 357. Also see OS **IV**, 558, 588; **V**, 25; **VIII**, 415.

16-6 Acylation of Aldehydes and Ketones

***O*-Acyl-*C*-acyloxy-addition**

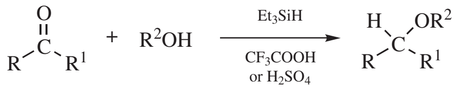


Aldehydes can be converted to *acylals* by treatment with an anhydride in the presence of BF_3, proton acids,[164] PCl_3,[165] NBS,[166] $LiBF_4$,[167] $FeCl_3$,[168] $InCl_3$,[169] $InBr_3$,[170] $Cu(OTf)_2$,[171] $Bi(OTf)_3$,[172] $BiCl_3$,[173] $Bi(NO_3)_3$,[174] WCl_6,[175] $ZrCl_4$,[176] ceric ammonium nitrate,[177] With Envirocat EPZ10 and microwave irradiation, acetic anhydride react with aldehydes to give the acylal.[178] Conjugated aldehydes are converted to the corresponding acylal by reaction with acetic anhydride and a $FeCl_3$ catalyst.[179] The reaction cannot normally be applied to ketones, though an exception has been reported when the reagent is trichloroacetic anhydride, which gives acylals with ketones without a catalyst.[180]

OS **IV**, 489.

16-7 Reductive Alkylation of Alcohols

***C*-Hydro-*O*-alkyl-addition**



[164]For example, see Olah, G.A.; Mehrotra, A.K. *Synthesis* ***1982***, 962.

[165]See Michie, J.K.; Miller, J.A. *Synthesis* ***1981***, 824.

[166]Karimi, B.; Seradj, H.; Ebrahimian, G.R. *Synlett* ***2000***, 623

[167]Sumida, N.; Nishioka, K.; Sato, T. *Synlett* ***2001***, 1921; Yadav, J.S.; Reddy, B.V.S.; Venugapal, C.; Ramalingam, V.T. *Synlett* ***2002***, 604.

[168]Li, Y.-Q. *Synth. Commun.* ***2000***, *30*, 3913; Trost, B.M.; Lee, C.B. *J. Am. Chem. Soc.* ***2001***, *123*, 3671; Wang, C.; Li, M. *Synth. Commun.* ***2002***, *32*, 3469.

[169]Yadav, J.S.; Reddy, B.V.S.; Srinivas, Ch. *Synth. Commun.* ***2002***, *32*, 1175, 2169.

[170]Yin, L.; Zhang, Z.H.; Wang, Y.-M. ; Pang, M.-L. *Synlett* ***2004***, 1727.

[171]Chandra, K.L.; Saravanan, P.; Singh, V.K. *Synlett* ***2000***, 359.

[172]Carrigan, M.D.; Eash, K.J.; Oswald, M.C.; Mohan, R.S. *Tetrahedron Lett.* ***2001***, *42*, 8133.

[173]Mohammadpoor-Baltork, I.; Aliyan, H. *Synth. Commun.* ***1999***, *29*, 2741.

[174]Aggen, D.H.; Arnold, J.N.; Hayes, P.D.; Smoter, N.J.; Mohan, R.S. *Tetrahedron* ***2004***, *60*, 3675.

[175]A solvent-free reaction. See Karimi, B.; Ebrahimian, G.-R.; Seradj, H. *Synth. Commun.* ***2002***, *32*, 669.

[176]Smitha, G.; Reddy, Ch.S. *Tetrahedron* ***2003***, *59*, 9571.

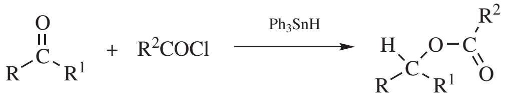
[177]Roy, S.C.; Banerjee, B. *Synlett* ***2002***, 1677.

[178]Bandgar, B.P.; Makone, S.S.; Kulkarni, S.R. *Monat. Chem.* ***2000***, *131*, 417.

[179]Trost, B.M.; Lee, C.B. *J. Am. Chem. Soc.* ***2001***, *123*, 3671.

[180]Libman, J.; Sprecher, M.; Mazur, Y. *Tetrahedron* ***1969***, *25*, 1679.

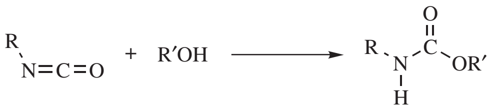
Aldehydes and ketones can be converted to ethers by treatment with an alcohol and triethylsilane in the presence of a strong acid[181] or by hydrogenation in alcoholic acid in the presence of platinum oxide.[182] The process can formally be regarded as addition of ROH to give a hemiacetal, RR′C(OH)OR^2, followed by reduction of the OH. In this respect, it is similar to **16-17**. The reaction of an aldehyde with $BuOSiHMe_2$ and a Me_3SiI catalyst gives the corresponding butyl alkyl ether.[183] In a similar reaction, ketones can be converted to carboxylic esters (reductive acylation of ketones) by treatment with an acyl chloride and triphenyltin hydride.[184]



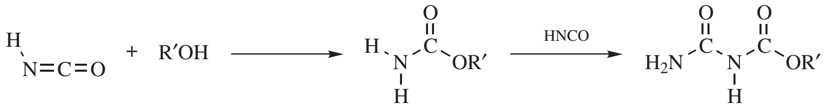
Ethers have also been prepared by the reductive dimerization of two molecules of an aldehyde or ketone (e.g., cyclohexanone → dicyclohexyl ether). This was accomplished by treatment of the substrate with a trialkylsilane and a catalyst.[185]

16-8 The Addition of Alcohols to Isocyanates

N-Hydro-*C*-alkoxy-addition



Carbamates (substituted urethanes) are prepared when isocyanates are treated with alcohols. This is an excellent reaction, of wide scope, and gives good yields. Isocyanic acid HNCO gives unsubstituted carbamates. Addition of a second equivalent of HNCO gives *allophanates*.



Allophanate

The isocyanate can be generated *in situ* by the reaction of an amine and oxalyl chloride, and subsequent reaction with HCl and then an alcohol gives the carbamate.[186] Polyurethanes are made by combining compounds with two NCO groups with

[181]Doyle, M.P.; DeBruyn, D.J.; Kooistra, D.A. *J. Am. Chem. Soc.* ***1972***, *94*, 3659.

[182]Verzele, M.; Acke, M.; Anteunis, M. *J. Chem. Soc.* ***1963***, 5598. For still another method, see Loim, L.M.; Parnes, Z.N.; Vasil'eva, S.P.; Kursanov, D.N. *J. Org. Chem. USSR* ***1972***, *8*, 902.

[183]Miura, K.; Ootsuka, K.; Suda, S.; Nishikori, H.; Hosomi, A. *Synlett* ***2002***, 313.

[184]Kaplan, L. *J. Am. Chem. Soc.* ***1966***, *88*, 4970.

[185]Sassaman, M.B.; Kotian, K.D.; Prakash, G.K.S.; Olah, G.A. *J. Org. Chem.* ***1987***, *52*, 4314. See also, Kikugawa, Y. *Chem. Lett.* ***1979***, 415.

[186]Oh, L.M.; Spoors, P.G.; Goodman, R.M. *Tetrahedron Lett.* ***2004***, *45*, 4769.

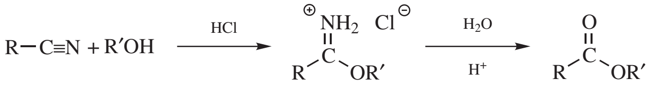
compounds containing two OH groups. Cyclic carbamates, such as 1,3-oxazine-2-ones, are generated by the reaction of an isocyanate with an oxetane, in the presence of a palladium catalyst.[187] Isothiocyanates similarly give thiocarbamates[188] RNHCSOR′, though they react slower than the corresponding isocyanates. Isocyanates react with LiAlHSeH and then iodomethane to give the corresponding selenocarbonate (RNHCOSeMe).[189]

The details of the mechanism are poorly understood,[190] though the oxygen of the alcohol is certainly attacking the carbon of the isocyanate. Hydrogen bonding complicates the kinetic picture.[191] The addition of ROH to isocyanates can also be catalyzed by metallic compounds,[192] by light,[193] or, for tertiary ROH, by lithium alkoxides[194] or *n*-butyllithium.[195]

OS **I**, 140; **V**, 162; **VI**, 95, 226, 788, 795.

16-9 Alcoholysis of Nitriles

Alkoxy,oxo-de-nitrilo-tersubstitution



The addition of dry HCl to a mixture of a nitrile and an alcohol in the absence of water leads to the hydrochloride salt of an imino ester (imino esters are also called imidates and imino ethers). This reaction is called the *Pinner synthesis*.[196] The salt can be converted to the free imino ester by treatment with a weak base such as sodium bicarbonate, or it can be hydrolyzed with water and an acid catalyst to the corresponding carboxylic ester. If the latter is desired, water may be present from the beginning, in which case aq. HCl can be used and the need for gaseous HCl is eliminated. Imino esters can also be prepared from nitriles with basic catalysts.[197]

[187]Larksarp, C.; Alper, H. *J. Org. Chem.* ***1999***, *64*, 4152.

[188]For a review of thiocarbamates, see Walter, W.; Bode, K. *Angew. Chem. Int. Ed.* ***1967***, *6*, 281. See also, Wynne, J.H.; Jensen, S.D.; Snow, A.W. *J. Org. Chem.* ***2003***, *68*, 3733.

[189]Koketsu, M.; Ishida, M.; Takakura, N.; Ishihara, H. *J. Org. Chem.* ***2002***, *67*, 486.

[190]For reviews, see Satchell, D.P.N.; Satchell, R.S.*Chem. Soc. Rev.* ***1975***, *4*, 231; Entelis, S.G.; Nesterov, O.V. *Russ. Chem. Rev.* ***1966***, *35*, 917.

[191]See for example, Robertson, W.G.P.; Stutchbury, J.E. *J. Chem. Soc.* ***1964***, 4000; Donohoe, G.; Satchell, D.P.N.; Satchell, R.S. *J. Chem. Soc. Perkin Trans. 2* ***1990***, 1671 and references cited therein. See also, Sivakamasundari, S.; Ganesan, R. *J. Org. Chem.* ***1984***, *49*, 720.

[192]For example, see Kim, Y.H.; Park, H.S. *Synlett* ***1998***, 261; Hazzard, G.; Lammiman, S.A.; Poon, N.L.; Satchell, D.P.N.; Satchell, R.S. *J. Chem. Soc. Perkin Trans. 2* ***1985***, 1029; Duggan, M.E.; Imagire, J.S. *Synthesis* ***1989***, 131.

[193]McManus, S.P.; Bruner, H.S.; Coble, H.D.; Ortiz, M. *J. Org. Chem.* ***1977***, *42*, 1428.

[194]Bailey, W.J.; Griffith, J.R. *J. Org. Chem.* ***1978***, *43*, 2690.

[195]Nikoforov, A.; Jirovetz, L.; Buchbauer, G. *Liebigs Ann. Chem.* ***1989***, 489.

[196]For a review, see Compagnon, P.L.; Miocque, M. *Ann. Chim. (Paris)* ***1970***, *[14] 5*, 23, see pp. 24–26. For a review of imino esters, see Neilson, D.G., in Patai, S. *The Chemistry of Amidines and Imidates*, Wiley, NY, ***1975***, pp. 385–489.

[197]Schaefer, F.C.; Peters, G.A. *J. Org. Chem.* ***1961***, *26*, 412.

This reaction is of broad scope and is good for aliphatic, aromatic, and heterocyclic R and for nitriles with oxygen-containing functional groups. The application of the reaction to nitriles containing a carboxyl group constitutes a good method for the synthesis of mono esters of dicarboxylic acids with the desired group esterified and with no diester or diacid present.

Cyanogen chloride reacts with alcohols in the presence of an acid catalyst, such as dry HCl or $AlCl_3$, to give carbamates:[198]

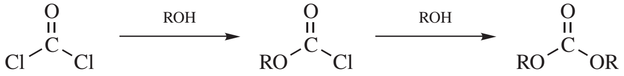
$$ClCN \quad + \quad 2\,ROH \xrightarrow[\text{or}\ AlCl_3]{HCl} ROCONH_2 \quad + \quad RCl$$

ROH can also be added to nitriles in another manner (**16-91**).

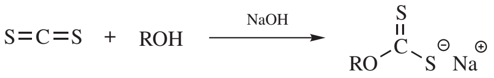
OS **I**, 5, 270; **II**, 284, 310; **IV**, 645; **VI**, 507; **VIII**, 415.

16-10 The Formation of Carbonates and Xanthates

Di-*C*-alkoxy-addition; *S*-Metallo-*C*-alkoxy-addition



The reaction of phosgene with an alcohol generates a haloformic esters, and reaction with a second equivalent of alcohol gives a carbonate. This reaction is related to the acyl addition reactions of acyl chlorides in Reaction **16-98**. An important example is the preparation of carbobenzoxy chloride ($PhCH_2OCOCl$) from phosgene and benzyl alcohol. This compound is widely used for protection of amino groups during peptide synthesis. When an alcohol reacts with certain alkyl halides (e.g., benzyl chloride) and carbon dioxide, in the presence of Cs_2CO_3 and tetrabutylammonium iodide, a mixed carbonate is formed.[199]



The addition of alcohols to carbon disulfide in the presence of a base produces xanthates.[200] The base is often HO^-, but in some cases better results can be obtained by using methylsulfinyl carbanion $MeSOCH_2^-$.[201] If an alkyl halide RX is present, the xanthate ester ROCSSR′ can be produced directly. In a similar manner, alkoxide ions add to CO_2 to give carbonate ester salts ($ROCOO^-$).

OS **V**, 439; **VI**, 207, 418; **VII**, 139.

[198]Bodrikov, I.V.; Danova, B.V. *J. Org. Chem. USSR* ***1968***, *4*, 1611; ***1969***, *5*, 1558; Fuks, R.; Hartemink, M.A. *Bull. Soc. Chim. Belg.* ***1973***, *82*, 23.

[199]Kim, S.i.; Chu, F.; Dueno, E.E.; Jung, K.W. *J. Org. Chem.* ***1999***, *64*, 4578.

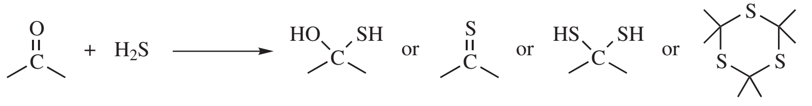
[200]For a review of the formation and reactions of xanthates, see Dunn, A.D.; Rudorf, W. *Carbon Disulphide in Organic Chemistry*; Ellis Horwood: Chichester, ***1989***, pp. 316–367.

[201]Meurling, P.; Sjöberg, B.; Sjöberg, K. *Acta Chem. Scand.* ***1972***, *26*, 279.

C. Sulfur Nucleophiles

16-11 The Addition of H_2S and Thiols to Carbonyl Compounds

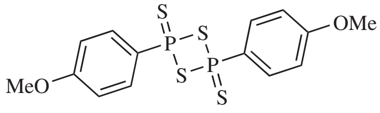
O-Hydro-*C*-mercapto-addition[202]



13 14 15 16

The addition of H_2S to an aldehyde or ketone can result in a variety of products. The most usual product is the trithiane **16**.[203] *gem*-Dithiols (**15**) are much more stable than the corresponding hydrates or α-hydroxy thiols.[204] They have been prepared by the treatment of ketones with H_2S under pressure[205] and under mild conditions with HCl as a catalyst.[206] Thiols add to aldehydes and ketones to give hemimercaptals, CH(OH)SR and dithioacetals, $CH(SR)_2$ (**16-5**). α-Hydroxy thiols (**13**) can be prepared from polychloro and polyfluoro aldehydes and ketones.[207] Apparently **13** are stable only when prepared from these compounds, and not even for all of them.

Thioketones[2] (**14**) can be prepared from certain ketones, such as diaryl ketones, by treatment with H_2S and an acid catalyst, usually HCl. They are often unstable and usually trimerize (to **16**) or react with air. Thioaldehydes[208] are even less stable and simple ones[209] apparently have never been isolated, though *t*-BuCHS has been prepared in



17

[202]This name applies to formation of **13**. Names for formation of **14**–**16**, are, respectively, thioxo-de-oxo-bisubstitution, dimercapto-de-oxo-bisubstitution, and carbonyl–trithiane transformation.

[203]Campaigne, E.; Edwards, B.E. *J. Org. Chem.* ***1962***, *27*, 3760.

[204]For a review of the preparation of *gem*-dithiols, see Mayer, R.; Hiller, G.; Nitzschke, M.; Jentzsch, J. *Angew. Chem. Int. Ed.* ***1963***, *2*, 370.

[205]Cairns, T.L.; Evans, G.L.; Larchar, A.W.; McKusick, B.C. *J. Am. Chem. Soc.* ***1952***, *74*, 3982.

[206]Campaigne, E.; Edwards, B.E. *J. Org. Chem.* ***1962***, *27*, 3760; Demuynck, M.; Vialle, J. *Bull. Soc. Chim. Fr.* ***1967***, 1213.

[207]Harris Jr., J.F. *J. Org. Chem.* ***1960***, *25*, 2259.

[208]For a review of thioaldehydes, see Usov, V.A.; Timokhina, L.V.; Voronkov, M.G. *Russ. Chem. Rev.* ***1990***, *59*, 378.

[209]For the preparation and reactions of certain substituted thioaldehydes, see Hofstra, G.; Kamphuis, J.; Bos, H.J.T. *Tetrahedron Lett.* ***1984***, *25*, 873; Okazaki, R.; Ishii, A.; Inamoto, N. *J. Am. Chem. Soc.* ***1987***, *109*, 279; Adelaere, B.; Guemas, J.; Quiniou, H. *Bull. Soc. Chim. Fr.* ***1987***, 517; Muraoka, M.; Yamamoto, T.; Enomoto, K.; Takeshima, T. *J. Chem. Soc. Perkin Trans. 1* ***1989***, 1241, and references cited in these papers.

solution, where it exists for several hours at 20°C.[210] A high-yield synthesis of thioketones involves treatment of acyclic[211] ketones with 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide **9**[212] (known as *Lawesson's reagent*)[213]. Thioketones can also be prepared by treatment of ketones with P_4S_{10},[214] P_4S_{10} and hexamethyldisiloxane,[215] P_4S_{10} on alumina,[216] or $CF_3SO_3SiMe_3/S(SiMe_3)_2$,[217] and from oximes or various types of hydrazone (overall conversion $C{=}N^{-} \rightarrow C{=}S$).[218] Reagent **17** converts the C=O groups of amides and carboxylic esters[219] to C=S groups.[220] Similarly, $POCl_3$ followed by $S(TMS)_2$ converts lactams to thiolactams[221] and treatment with triflic anhydride, and then H_2S converts amides to thioamides.[222] The reaction of an amide with triflic anhydride, and then aq. $S(NH_4)_2$ gives the corresponding thioamide.[223] The $H_2S{-}Me_3SiCl{-}(i\text{Pr})_2NLi$ complex converts carboxylic esters to thiono esters.[224] Lactones react with **9** in the presence of hexamethyldisiloxane an microwave irradiation to give the thiolactone.[225] Carboxylic acids (RCOOH) can be converted directly to dithiocarboxylic esters (RCSSR′)[226] in moderate yield, with P_4S_{10} and a primary alcohol (R′OH).[227]

Thiols add to aldehydes and ketones to give hemimercaptals and dithioacetals. Hemimercaptals are ordinarily unstable,[228] though they are more stable than the corresponding hemiacetals and can be isolated in certain cases.[229] Dithioacetals,

[210]Vedejs, E.; Perry, D.A. *J. Am. Chem. Soc.* ***1983***, *105*, 1683. See also, Baldwin, J.E.; Lopez, R.C.G. *J. Chem. Soc., Chem. Commun.* ***1982***, 1029.

[211]Cyclopentanone and cyclohexanone gave different products: Scheibye, S.; Shabana, R.; Lawesson, S.; Rømming, C. *Tetrahedron* ***1982***, *38*, 993.

[212]See Thomsen, I.; Clausen, K.; Scheibye, S.; Lawesson, S. *Org. Synth.* ***VII***, 372.

[213]For reviews of this and related reagents, see Cava, M.P.; Levinson, M.I.*Tetrahedron* ***1985***, *41*, 5061; Cherkasov, R.A.; Kutyrev, G.A.; Pudovik, A.N. *Tetrahedron* ***1985***, *41*, 2567; Jesberger, M.; Davis, T.P.; Barner, L. *Synthesis* ***2003***, 1929. For a study of the mechanism, see Rauchfuss, T.B.; Zank, G.A. *Tetrahedron Lett.* ***1986***, *27*, 3445.

[214]See, for example, Scheeren, J.W.; Ooms, P.H.J.; Nivard, R.J.F. *Synthesis* ***1973***, 149.

[215]Curphey, T.J. *J. Org. Chem.* ***2002***, *67*, 6461.

[216]Polshettiwar, V.; Kaushik, M.P. *Tetrahedron Lett.* ***2004***, *45*, 6255.

[217]Degl'Innocenti, A.; Capperucci, A.; Mordini, A.; Reginato, G.; Ricci, A.; Cerreta, F. *Tetrahedron Lett.* ***1993***, *34*, 873.

[218]See for example, Kimura, K.; Niwa, H.; Motoki, S. *Bull. Chem. Soc. Jpn.* ***1977***, *50*, 2751; de Mayo, P.; Petrainas, G.L.R.; Weedon, A.C. *Tetrahedron Lett.* ***1978***, 4621; Okazaki, R.; Inoue, K.; Inamoto, N. *Tetrahedron Lett.* ***1979***, 3673.

[219]For a review of thiono esters RC(=S)OR′, see Jones, B.A.; Bradshaw, J.S. *Chem. Rev.* ***1984***, *84*, 17.

[220]Ghattas, A.A.G.; El-Khrisy, E.A.M.; Lawesson, S. *Sulfur Lett.* ***1982***, *1*, 69; Yde, B.; Yousif, N.M.; Pedersen, U.S.; Thomsen, I.; Lawesson, S.-O. *Tetrahedron* ***1984***, *40*, 2047; Thomsen, I.; Clausen, K.; Scheibye, S.; Lawesson, S. *Org. Synth.* ***VII***, 372.

[221]Smith, D.C.; Lee, S.W.; Fuchs, P.L. *J. Org. Chem.* ***1994***, *59*, 348.

[222]Charette, A.B.; Chua, P. *Tetrahedron Lett.* ***1998***, *39*, 245.

[223]Charette, A.B.; Grenon, M. *J. Org. Chem.* ***2003***, *68*, 5792.

[224]Corey, E.J.; Wright, S.W. *Tetrahedron Lett.* ***1984***, *25*, 2639.

[225]Filippi, J.-J.; Fernandez, X.; Lizzani-Cuvelier, L.; Loiseau, A.-M. *Tetrahedron Lett.* ***2003***, *44*, 6647.

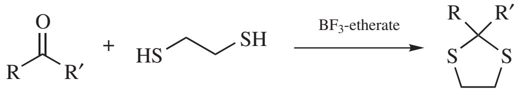
[226]For a review of dithiocarboxylic esters, see Kato, S.; Ishida, M. *Sulfur Rep.*, ***1988***, *8*, 155.

[227]Davy, H.; Metzner, P. *Chem. Ind. (London)* ***1985***, 824.

[228]See, for example, Fournier, L.; Lamaty, G.; Nata, A.; Roque, J.P. *Tetrahedron* ***1975***, *31*, 809.

[229]For example, see Field, L.; Sweetman, B.J. *J. Org. Chem.* ***1969***, *34*, 1799.

like acetals, are stable in the presence of bases, except that a strong base can remove the aldehyde proton, if there is one[230] (see **10-71**).



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The reaction of aldehydes or ketones with thiols, usually with a Lewis acid catalyst, leads to dithioacetals[231] or dithioketals. The most common catalyst used is probably boron trifluoride etherate (BF_3•OEt_2).[232] Similarly reactions that use 1,2-ethanedithiol or 1,3-propanedithiol lead to 1,3-dithiolanes, such as **18**[233] or 1,3-dithianes.[234] Dithioacetals can also be prepared from aldehydes or ketones by treatment with thiols in the presence of $TiCl_4$,[235] $SiCl_4$,[236] $LiBF_4$,[237] $Al(OTf)_3$,[238] with a disulfide RSSR (R = alkyl or aryl),[239] or with methylthiotrimethylsilane ($MeSSiMe_3$).[240]

Dithioacetals and dithioketals are used as protecting groups for aldehydes and ketones, and after subsequent reactions involving the R or R′ group, the protecting group can then be removed.[241] There are a variety of reagents that convert these compounds back to the carbonyl.[242] Simple hydrolysis is the most common method for converting thiocarbonyls to carbonyls. Stirring thioketones with 4-nitrobenzaldehyde and a catalytic amount of TMSOTf gives the ketone.[243] The reaction of a thioketone and Clayfen with microwave irradiation give the ketone.[244] Thioamides

[230]Truce, W.E.; Roberts, F.E. *J. Org. Chem.* ***1963***, *28*, 961.

[231]See Samajdar, S.; Basu, M.K.; Becker, F.F.; Banik, N.K. *Tetrahedron Lett.* ***2001***, *42*, 4425.

[232]Fujita, E.; Nagao, Y.; Kaneko, K. *Chem. Pharm. Bull.* 1978, *26*, 3743; Corey, E.J.; Bock, M.G. *Tetrahedron Lett.* ***1975***, 2643.

[233]See Anand, R.V.; Saravanan, P.; Singh, V.K. *Synlett* ***1999***, 415; Ceschi, M.A.; Felix, L.de A.; Peppe, C. *Tetrahedron Lett.* ***2000***, *41*, 9695; Muthusamy, S.; Babu, S.A.; Gunanathan, C. *Tetrahedron Lett.* ***2001***, *42*, 359; Yadav, J.S.; Reddy, B.V.S.; Pandey, S.K. *Synlett* ***2001***, 238; Ballini, R.; Barboni, L.; Maggi, R.; Sartori, G. *Synth. Commun.* ***1999***, *29*, 767; Jin, T.-S.; Sun, X.; Ma, Y.-R.; Li, T.-S. *Synth. Commun.* ***2001***, *31*, 1669; Deka, N.; Sarma, J.C. *Chem. Lett.* ***2001***, 794; Kamal, A.; Chouhan, G. *Synlett* ***2002***, 474. For a review, see Olsen, R.K.; Currie, Jr., J.O., in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, ***1974***, pp. 521–532.

[234]See Firouzabadi, H.; Karimi, B.; Eslami, S. *Tetrahedron Lett.* ***1999***, *40*, 4055; Firouzabadi, H.; Iranpoor, N.; Karimi, B. *Synthesis* ***1999***, 58; Tietze, L.F.; Weigand, B.; Wulff, C. *Synthesis* ***2000***, 69; Graham, A.E. *Synth. Commun.* ***1999***, *29*, 697; Firouzabadi, H.; Eslami, S.; Karimi, B. *Bull. Chem. Soc. Jpn.* ***2001***, *74*, 2401; Laskar, D.D.; Prajapati, D.; Sandhu, J.S. *J. Chem. Res. (S)* ***2001***, 313; De, S.K. *Tetrahedron Lett.* ***2004***, *45*, 1035, 2339.

[235]Kumar, V.; Dev, S. *Tetrahedron Lett.* ***1983***, *24*, 1289.

[236]Ku, B.; Oh, D.Y. *Synth. Commun.* ***1989***, 433.

[237]This reaction is done neat, see Kazaraya, K.; Tsuji, S.; Sato, T. *Synlett* ***2004***, 1640.

[238]This is a solvent-free reaction. See Firouzabadi, H.; Iranpoor, N.; Kohmarch, G. *Synth. Commun.* ***2003***, *33*, 167.

[239]Tazaki, M.; Takagi, M. *Chem. Lett.* ***1979***, 767.

[240]Evans, D.A.; Grimm, K.G.; Truesdale, L.K. *J. Am. Chem. Soc.* ***1975***, *97*, 3229.

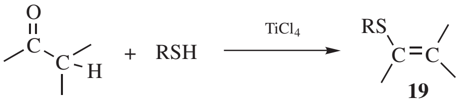
[241]For example, see Ganguly, N.C.; Datta, M. *Synlett* ***2004***, 659.

[242]Corsaro, A.; Pistarà, V. *Tetrahedron* ***1998***, *54*, 15027.

[243]Ravindrananthan, T.; Chavan, S.P.; Awachat, M.M.; Kelkar, S.V. *Tetrahedron Lett.* ***1995***, *36*, 2277.

[244]Varma, R.S.; Kumar, D. *Synth. Commun.* ***1999***, *29*, 1333.

are converted to amides with Caro's acid on SiO_2.[245] Lewis acids, such as aluminum chloride ($AlCl_3$) and mercuric salts, are common reagents and their use is referred to as the Corey–Seebach procedure.[246] Other reagents include BF_3•OEt_2 in aq. THF containing mercuric oxide (HgO),[247] NBS,[248] iodine in DMSO,[249] ceric ammonium nitrate, $Ce(NH_4)_2(NO_3)_6$,[250] iodomethane in aqueous media,[251] Clayfen with microwave irradiation,[252] $PhI(OAc)_2$ in aqueous acetone,[253] and NCS with silver nitrate in aqueous acetonitrile.[254] When aldehydes and ketones react with mercapto-alcohols, mixed acetals or ketals are formed. The use of 2-mercaptoethanol ($HSCH_2CH_2OH$), for example, leads to an oxathiolane[255] and 3-mercaptopropanol ($HSCH_2CH_2CH_2OH$) leads to an oxathiane. Alternatively, the dithioketal can be desulfurized with Raney nickel (**14-27**), giving the overall conversion $C{=}O \rightarrow CH_2$.



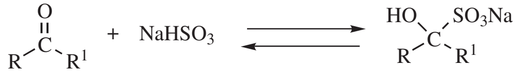
19

If an aldehyde or ketone possesses an α hydrogen, it can be converted to the corresponding enol thioether (**19**) by treatment with a thiol in the presence of $TiCl_4$.[256] Aldehydes and ketones have been converted to sulfides by treatment with thiols and pyridine–borane, $RCOR' + R^2SH \rightarrow RR'CHSR^2$,[257] in a reductive alkylation reaction, analogous to **16-7**.

OS **II**, 610; **IV**, 927; **VI**, 109; **VII**, 124, 372. Also see OS **III**, 332; **IV**, 967; **V**, 780; **VI**, 556; **VIII**, 302.

16-12 Formation of Bisulfite Addition Products

***O*-Hydro-*C*-sulfonato-addition**



[245]Movassagh, B.; Lakouraj, M.M.; Ghodrati, K. *Synth. Commun.* ***2000***, *30*, 2353.

[246]Seebach, D.; Corey, E.J. J. *Org. Chem.* ***1975***, *40*, 231; Seebach, D. *Synthesis* ***1969***, 17; Vedejs, E.; Fuchs, P.L. *J. Org. Chem.* ***1971***, *36*, 366.

[247]Vedejs, E.; Fuchs, P.L. *J. Org. Chem.* ***1971***, *36*, 366.

[248]Cain, E.N.; Welling, L.L. *Tetrahedron Lett.* ***1975***, 1353; Corey, E.J.; Erickson, B.W. *J. Org. Chem.* ***1971***, *36*, 3553.

[249]Chattopadhyaya, J.B.; Rama Rao, A.V. *Tetrahedron Lett.* ***1973***, 3735.

[250]Ho, T.-L.; Ho, H.C.; Wong, C.M. *J. Chem. Soc., Chem. Commun.* ***1972***, 791a.

[251]Fétizon, M.; Jurion, M. *J. Chem. Soc., Chem. Commun.* ***1972***, 382; Takano, S.; Hatakeyama, S.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* ***1977***, 68.

[252]Meshram, H.M.; Reddy, G.S.; Sumitra, G.; Yadav, J.S. *Synth. Commun.* ***1999***, *29*, 1113.

[253]Shi, X.-X.; Wu, Q.-Q. *Synth. Commun.* ***2000***, *30*, 4081.

[254]Corey, E.J.; Erickson, B.W. *J. Org. Chem.* ***1971***, *36*, 3553.

[255]See Karimi, B.; Seradj, H. *Synlett* ***2000***, 805; Ballini, R.; Bosica, G.; Maggi, R. ; Mazzacani, A.; Righi, P.; Sartori, G. *Synthesis* ***2001***,1826; Mondal, E.; Sahu, P.R.; Khan, A.T. *Synlett* ***2002***, 463.

[256]Mukaiyama, T.; Saigo, K. *Chem. Lett.* ***1973***, 479.

[257]Kikugawa, Y. *Chem. Lett.* ***1981***, 1157.

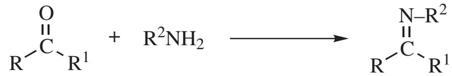
Bisulfite addition products are formed from aldehydes, methyl ketones, cyclic ketones (generally seven-membered and smaller rings), α-keto esters, and isocyanates, upon treatment with sodium bisulfite. Most other ketones do not undergo the reaction, probably for steric reasons. The reaction is reversible (by treatment of the addition product with either acid or base[258])[259] and is useful for the purification of the starting compounds, since the addition products are soluble in water and many of the impurities are not.[260]

OS **I**, 241, 336; **III**, 438; **IV**, 903; **V**, 437.

D. Attack by NH_2, NHR, or NR_2 (Addition of NH_3, RNH_2, R_2NH)

16-13 The Addition of Amines to Aldehydes and Ketones

Alkylimino-de-oxo-bisubstitution



The addition of ammonia[261] to aldehydes or ketones does not generally give useful products. According to the pattern followed by analogous nucleophiles, the initial products would be expected to be *hemiaminals*,[262] but these compounds are generally unstable. Most imines with a hydrogen on the nitrogen spontaneously polymerize.[263] In the presence of an oxidizing agent, such a MnO_2 (see **19-3**), primary alcohols can be converted to imines.[264]

In contrast to ammonia, primary, secondary, and tertiary amines can add to aldehydes[265] and ketones to give different kinds of products. Primary amines give imines[266] and secondary amines gives enamines (**10-69**). This section will focus on imines. Reduction of ω-azido ketones leads to the amino-ketones, which cyclizes to form a 2-substituted pyrroline.[267] Reduction of nitro-ketones in the presence

[258]For cleavage with ion-exchange resins, see Khusid, A.Kh.; Chizhova, N.V. *J. Org. Chem. USSR* ***1985***, *21*, 37.

[259]For a discussion of the mechanism, see Young, P.R.; Jencks, W.P. *J. Am. Chem. Soc.* ***1978***, *100*, 1228.

[260]The reaction has also been used to protect an aldehyde group in the presence of a keto group: Chihara, T.; Wakabayashi, T.; Taya, K. *Chem. Lett.* ***1981***, 1657.

[261]For a review of this reagent in organic synthesis, see Jeyaraman, R., in Pizey, J.S. *Synthetic Reagents*, Vol. 5, Wiley, NY, ***1983***, pp. 9–83.

[262]These compounds have been detected by ^{13}C NMR: Chudek, J.A.; Foster, R.; Young, D. *J. Chem. Soc. Perkin Trans. 2* ***1985***, 1285.

[263]Methanimine $CH_2{=}NH$ is stable in solution for several hours at −95°C, but rapidly decomposes at −80°C: Braillon, B.; Lasne, M.C.; Ripoll, J.L.; Denis, J.M. *Nouv. J. Chim.*, ***1982***, *6*, 121. See also, Bock, H.; Dammel, R. *Chem. Ber.* ***1987***, *120*, 1961.

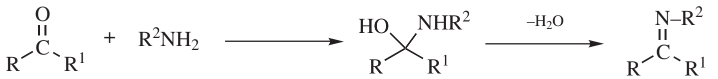
[264]Kanno, H.; Taylor, R.J.K. *Synlett* ***2002***, 1287.

[265]For a review of the reactions between amines and formaldehyde, see Farrar, W.V. *Rec. Chem. Prog.*, ***1968***, *29*, 85.

[266]For reviews of reactions of carbonyl compounds leading to the formation of C=N bonds, see Dayagi, S.; Degani, Y. in Patai, S. *The Chemistry of the Carbon–Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 64–83; Reeves, R.L., in Patai, S. *The Chemistry of the Carbonyl Group*, pt. 1, Wiley, NY, ***1966***, pp. 600–614.

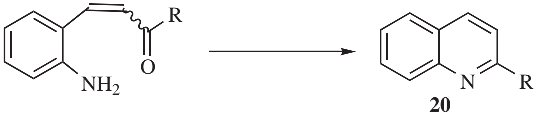
[267]Prabhu, K.P.; Sivanand, P.S.; Chandrasekaran, S. *Synlett* ***1998***, 47.

of ruthenium compounds and CO also leads to 1-substituted pyrrolines.[268] In contrast to imines in which the nitrogen is attached to a hydrogen, these imines are stable enough for isolation. However, in some cases, especially with simple R groups, they rapidly decompose or polymerize unless there is at least one aryl group on the nitrogen or the carbon. When there is an aryl group, the compounds are quite stable. They are usually called *Schiff bases*, and this reaction is the best way to prepare them.[269] The reaction is straightforward and proceeds in high yields. Even sterically hindered imines can be prepared.[270] Both imines and enamines (see below) have been prepared on clay with microwave irradiation.[271] The initial *N*-substituted hemiaminals[272] lose water to give the stable Schiff bases:



In general, ketones react more slowly than aldehydes, and higher temperatures and longer reaction times are often required.[273] In addition, the equilibrium must often be shifted, usually by removal of the water, either azeotropically by distillation, or with a drying agent, such as $TiCl_4$,[274] or with a molecular sieve.[275] Imines have been formed from aldehydes and amines in an ionic liquid.[276]

The reaction is often used to effect ring closure.[277] The *Friedländer quinoline synthesis*[278] is an example where ortho alkenyl aniline derivatives give the quinoline, **20**.[279] The alkene derivative can be prepared *in situ* from an aldehyde and a suitably functionalized ylid.[280]

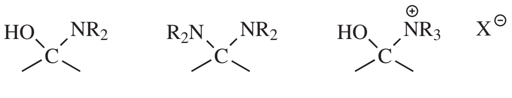


20

[268]Watanabe, Y.; Yamamoto, J.; Akazome, M.; Kondo, T.; Mitsudo, T. *J. Org. Chem.* ***1995***, *60*, 8328.
[269]See Lai, J.T. *Tetrahedron Lett.* ***2002***, *43*, 1965.
[270]Love, B.E.; Ren, J. *J. Org. Chem.* ***1993***, *58*, 5556.
[271]Varma, R.S.; Dahiya, R.; Kumar, S. *Tetrahedron Lett.* ***1997***, *38*, 2039.
[272]Some of these have been observed spectrally; see Forlani, L.; Marianucci, E.; Todesco, P.E. *J. Chem. Res. (S)* ***1984***, 126.
[273]For improved methods, see Morimoto, T.; Sekiya, M. *Chem. Lett.* ***1985***, 1371; Eisch, J.J.; Sanchez, R. *J. Org. Chem.* ***1986***, *51*, 1848.
[274]Weingarten, H.; Chupp, J.P.; White, W.A. *J. Org. Chem.* ***1967***, *32*, 3246.
[275]Bonnett, R.; Emerson, T.R. *J. Chem. Soc.* ***1965***, 4508; Roelofsen, D.P.; van Bekkum, H. *Recl. Trav. Chim. Pays-Bas* ***1972***, *91*, 605.
[276]Andrade, C.K.Z.; Takada, S.C.S.; Alves, L.M.; Rodrigues, J.P.; Suarez, P.A.Z.; Brand, R.F.; Soares, V.C.D. *Synlett* ***2004***, 2135.
[277]For a review of such ring closures, see Katritzky, A.R.; Ostercamp, D.L.; Yousaf, T.I. *Tetrahedron* ***1987***, *43*, 5171.
[278]For a review, see Cheng, C.; Yan, S. *Org. React.* ***1982***, *28*, 37.
[279]See Arcadi, A.; Chiarini, M.; Di Giuseppe, S.; Marinelli, F. *Synlett* ***2003***, 203; Yadav, J.S.; Reddy, B.V.S.; Premalatha, K. *Synlett* ***2004***, 963.
[280]Hsiao, Y.; Rivera, N.R.; Yasuda, N.; Hughes, D.L.; Reider, P.J. *Org. Lett.* ***2001***, *3*, 1101.

Pyrylium ions react with ammonia or primary amines to give pyridinium ions[281] (see p. 498). Primary amines react with 1,4-diketones, with microwave irradiation, to give *N*-substituted pyrroles.[282] Similar reactions in the presence of Montmorillonite KSF[283] or by simply heating the components with tosic acid[284] have been reported.

As mentioned, the reaction of secondary amines with ketones leads to enamines (**10-69**). When secondary amines are added to aldehydes or ketones, the initially formed *N,N*-disubstituted hemiaminals (**21**) cannot lose water in the same way, and in some cases it is possible to isolate them.[285] However, they are generally unstable, and under the reaction conditions usually react further. If no α hydrogen is present, **10** is converted to



21 **22** (aminal) **23**

the more stable *aminal* (**22**).[286] However, if an α hydrogen is present, water (from **21**) or RNH_2 (from **22**) can be lost in that direction to give an enamine, **24**.[287] This is the most common method[288] for the preparation of enamines and usually takes place when an aldehyde or ketone containing an α hydrogen is treated with a secondary amine. The water is usually removed azeotropically or with a drying agent,[289] but molecular sieves can also be used.[290] Silyl carbamates, such as $Me_2NCO_2SiMe_3$, have been used to convert ketones to enamines.[291] Stable primary enamines have also been prepared.[292] Enamino-ketones have been prepared from diketones and secondary amines using low molecular weight amines in water,[293] or using microwave irradiation on silica gel.[294] Secondary amine perchlorates react

[281]For a review, see Zvezdina, E.A.; Zhadonva, M.P.; Dorofeenko, G.N. *Russ. Chem. Rev.* ***1982***, *51*, 469.

[282]Danks, T.N. *Tetrahedron Lett.* ***1999***, *40*, 3957.

[283]Banik, B.K.; Samajdar, S.; Banik, I. *J. Org. Chem.* ***2004***, *69*, 213.

[284]Klappa, J.J.; Rich, A.E.; McNeill, K. *Org. Lett.* ***2002***, *4*, 435.

[285]For example, see Duhamel, P.; Cantacuzène, J. *Bull. Soc. Chim. Fr.* ***1962***, 1843.

[286]For a review of aminals, see Duhamel, P., in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 2, Wiley, NY, ***1982***, pp. 849–907.

[287]For reviews of the preparation of enamines, see Haynes, L.W.; Cook, A.G., in Cook, A.G. *Enamines*, 2nd. ed., Marcel Dekker, NY, ***1988***, pp. 103–163; Pitacco, G.; Valentin, E., in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 1, Wiley, NY, ***1982***, pp. 623–714.

[288]For another method, see Katritzky, A.R.; Long, Q.; Lue, P.; Jozwiak, A. *Tetrahedron* ***1990***, *46*, 8153.

[289]For example, $TiCl_4$: White, W.A.; Weingarten, H. *J. Org. Chem.* ***1967***, *32*, 213; Kuo, S.C.; Daly, W.H. *J. Org. Chem.* ***1970***, *35*, 1861; Nilsson, A.; Carlson, R. *Acta Chem. Scand. Ser. B* ***1984***, *38*, 523.

[290]Brannock, K.C.; Bell, A.; Burpitt, R.D.; Kelly, C.A. *J. Org. Chem.* ***1964***, *29*, 801; Taguchi, K.; Westheimer, F.H. *J. Org. Chem.* ***1971***, *36*, 1570; Roelofsen, D.P.; van Bekkum, H. *Recl. Trav. Chim. Pays-Bas* ***1972***, *91*, 605; Carlson, R.; Nilsson, A.; Strömqvist, M. *Acta Chem. Scand. Ser. B* ***1983***, *37*, 7.

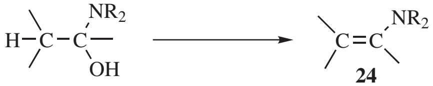
[291]Kardon, F.; Mörtl, M.; Knausz, D. *Tetrahedron Lett.* ***2000***, *41*, 8937.

[292]Erker, G.; Riedel, M.; Koch, S.; Jödicke, T.; Würthwein, E.-U. *J. Org. Chem.* ***1995***, *60*, 5284.

[293]Stefani, H.A.; Costa, I.M.; Silva, D. de O. *Synthesis* ***2000***, 1526.

[294]Rechsteiner, B.; Texier-Boullet, F.; Hamelin, J. *Tetrahedron Lett.* ***1993***, *34*, 5071.

with aldehydes and ketones to give iminium salts (**10**, p. $$$).[295] Tertiary amines can only give salts (**23**). Enamines have been prepared by the reaction of an aldehyde, a secondary amine and a terminal alkyne in the presence of AgI at 100°C,[296] AgI in an ionic liquid,[297] CuI with microwave irradiation,[298] or a gold catalyst.[299]



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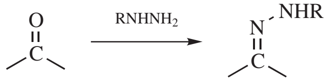
OS **I**, 80, 355, 381; **II**, 31, 49, 65, 202, 231, 422; **III**, 95, 328, 329, 332, 358, 374, 513, 753, 827; **IV**, 210, 605, 638, 824; **V**, 191, 277, 533, 567, 627, 703, 716, 736, 758, 808, 941, 1070; **VI**, 5, 448, 474, 496, 520, 526, 592, 601, 818, 901, 1014; **VII**, 8, 135, 144, 473; **VIII**, 31, 132, 403, 451, 456, 493, 586, 597. Also see OS **IV**, 283, 464; **VII**, 197; **VIII**, 104, 112, 241.

16-14 The Addition of Hydrazine Derivatives to Carbonyl Compounds

Hydrazono-de-oxo-bisubstitution



The product of condensation of a hydrazine and an aldehyde or ketone is called a *hydrazone*. Hydrazine itself gives hydrazones only with aryl ketones. With other aldehydes and ketones, either no useful product can be isolated, or the remaining NH_2 group condenses with a second equivalent of carbonyl compound to give an *azine*. This type of product is especially important for aromatic aldehydes:

$$ArCH{=}N{-}NH_2 \quad + \quad ArCHO \longrightarrow ArCH{=}N{-}N{=}CHAr$$ An azine

However, in some cases azines can be converted to hydrazones by treatment with excess hydrazine and NaOH.[300] Arylhydrazines, especially phenyl, *p*-nitrophenyl, and 2,4-dinitrophenyl,[301] are used much more often and give the corresponding hydrazones with most aldehydes and ketones.[302] Since these are usually solids, they make excellent derivatives and are commonly employed for this purpose. Cyclic hydrazones are also known,[303] as are conjugated hydrazones.[304] Azides react

[295]Leonard, N.J.; Paukstelis, J.V. *J. Org. Chem.* ***1964***, *28*, 3021.

[296]Wei, C.; Li, Z.; Li, C.-J. *Org. Lett.* ***2003***, *5*, 4473.

[297]In bmim BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate: Li, Z.; Wei, C.; Chen, L.; Varma, R.S.; Li, C.-J. *Tetrahedron Lett.* ***2004***, *45*, 2443.

[298]Shi, L.; Tu, Y.-Q.; Wang, M.; Zhang, F.-M.; Fan, C.-A. *Org. Lett.* ***2004***, *6*, 1001.

[299]Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* ***2003***, *125*, 9584.

[300]For example, see Day, A.C.; Whiting, M.C. *Org. Synth.* ***VI***, 10.

[301]For an improved procedure for the preparation of 2,4-dinitrophenylhydrazones, see Behforouz, M.; Bolan, J.L.; Flynt, M.S. *J. Org. Chem.* ***1985***, *50*, 1186.

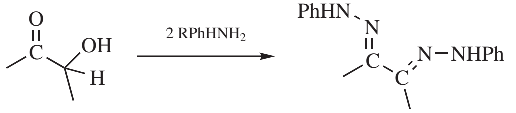
[302]For a review of arylhydrazones, see Buckingham, J. *Q. Rev. Chem. Soc.* ***1969***, *23*, 37.

[303]Nakamura, E.; Sakata, G.; Kubota, K. *Tetrahedron Lett.* ***1998***, *39*, 2157.

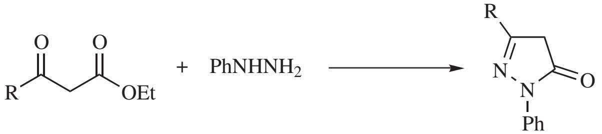
[304]Palacios, F.; Aparicio, D.; de los Santos, J.M. *Tetrahedron Lett.* ***1993***, *34*, 3481.

with *N,N*-dimethylhydrazine and ferric chloride to give the *N,N*-dimethylhydrazone.[305] Alkenes react with CO/H_2, phenylhydrazine and a diphosphine catalyst to give a regioisomeric mixture of phenylhydrazones that favored "anti-Markovnikov" addition.[306] Oximes are converted to hydrazones with water and hydrazine in refluxing ethanol.[307]

α-Hydroxy aldehydes and ketones and α-dicarbonyl compounds give *osazones*, in which two adjacent carbons have carbon–nitrogen double bonds:



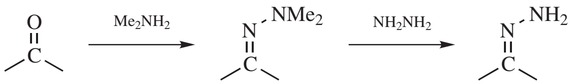
Osazones are particularly important in carbohydrate chemistry. In contrast to this behavior, β-diketones and β-keto esters give *pyrazoles* and *pyrazolones*, respectively (illustrated for β-keto esters):



Other hydrazine derivatives frequently used to prepare the corresponding hydrazone are semicarbazide $NH_2NHCONH_2$, in which case the hydrazone is called a semicarbazone, and *Girard's reagents T and P*, in which case the hydrazone is water soluble because of the ionic group. Girard's reagents are often used for purification of carbonyl compounds.[308]

Girard's reagent T Girard's reagent P

Simple *N*-unsubstituted hydrazones can be obtained by an exchange reaction. The *N,N*-dimethylhydrazone is prepared first, and then treated with hydrazine:[309]



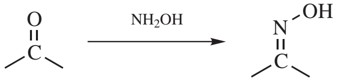
No azines are formed under these conditions.

[305]Barrett, I.C.; Langille, J.D.; Kerr, M.A. *J. Org. Chem.* ***2000***, *65*, 6268.
[306]Ahmed, M.; Jackstell, R.; Seayad, A.M.; Klein, H.; Beller, M. *Tetrahedron Lett.* ***2004***, *45*, 869.
[307]Pasha, M.A.; Nanjundaswamy, H.M. *Synth. Commun.* ***2004***, *34*, 3827.
[308]For a study of the mechanism with Girard's reagent T, see Stachissini, A.S.; do Amaral, L. *J. Org. Chem.* ***1991***, *56*, 1419.
[309]Newkome, G.R.; Fishel, D.L. *J. Org. Chem.* ***1966***, *31*, 677.

OS **II**, 395; **III**, 96, 351; **IV**, 351, 377, 536, 884; **V**, 27, 258, 747, 929; **VI**, 10, 12, 62, 242, 293, 679, 791; **VII**, 77, 438. Also see OS **III**, 708; **VI**, 161; **VIII**, 597.

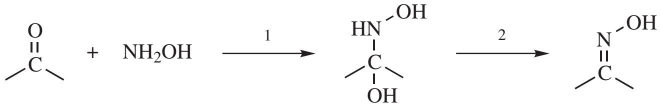
16-15 The Formation of Oximes

Hydroxyimino-de-oxo-bisubstitution



In a reaction very much like **16-14**, oximes can be prepared by the addition of hydroxylamine to aldehydes or ketones. Derivatives of hydroxylamine [e.g., H_2NOSO_3H and $HON(SO_3Na)_2$] have also been used. For hindered ketones, such as hexamethylacetone, high pressures (as high as 10,000 atm) may be necessary.[310] The reaction of hydroxylamine with unsymmetrical ketones or with aldehydes leads to a mixture of (*E*)- and (*Z*)-isomers. For aromatic aldehydes, heating with K_2CO_3 led to the (*E*)- isomer whereas heating with $CuSO_4$ gave the (*Z*)-hydroxylamine.[311] Hydroxylamines react with ketones in ionic liquids[312] and on silica gel.[313]

It has been shown[314] that the rate of formation of oximes is at a maximum at a pH that depends on the substrate but is usually ~4, and that the rate decreases as the pH is either raised or lowered from this point. We have previously seen (p. 1256) that bell-shaped curves like this are often caused by changes in the rate-determining step. In this case, at low pH values step 2 is rapid (because it is acid-catalyzed), and step 1



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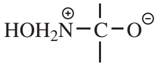
is slow (and rate-determining), because under these acidic conditions most of the NH_2OH molecules have been converted to the conjugate NH_3OH^+ ions, which cannot attack the substrate. As the pH is slowly increased, the fraction of free NH_2OH molecules increases and consequently so does the reaction rate, until the maximum rate is reached at ~pH 4. As the rising pH has been causing an increase in the rate of step 1, it has also been causing a *decrease* in the rate of the acid-catalyzed step 2, although this latter process has not affected the overall rate since step 2 was still faster than step 1. However, when the pH goes above ~4, step 2 becomes rate-determining, and although the rate of step 1 is still increasing (as it will until essentially all the NH_2OH is unprotonated), it is now

[310]Jones, W.H.; Tristram, E.W.; Benning, W.F. *J. Am. Chem. Soc.* ***1959***, *81*, 2151.
[311]Sharghi, H.; Sarvari, M.H. *Synlett* ***2001***, 99.
[312]In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Ren, R.X.; Ou, W. *Tetrahedron Lett.* ***2001***, *42*, 8445.
[313]Hajipour, A.R.; Mohammadpoor-Baltork, I.; Nikbaghat, K.; Imanzadeh, G. *Synth. Commun.* ***1999***, *29*, 1697.
[314]Jencks, W.P. *J. Am. Chem. Soc.* ***1959***, *81*, 475; *Prog. Phys. Org. Chem.* ***1964***, *2*, 63.

step 2 that determines the rate, and this step is slowed by the decrease in acid concentration. Thus the overall rate decreases as the pH rises beyond ~4. It is likely that similar considerations apply to the reaction of aldehydes and ketones with amines, hydrazines, and other nitrogen nucleophiles.[315] There is evidence that when the nucleophile is 2-methylthiosemicarbazide, there is a second change in the rate-determining step: above pH ~10 *basic* catalysis of step 2 has increased the rate of this step to the point where step 1 is again rate determining.[316] Still a third change in the rate-determining step has been found at about pH 1, showing that at least in some cases step 1 actually consists of two steps: formation of a zwitterion, for example,



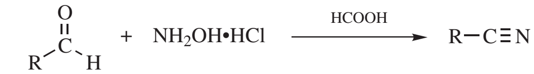
in the case shown above, and conversion of this to **25**.[317] The intermediate **25** has been detected by nmr in the reaction between NH_2OH and acetaldehyde.[318]

In another type of process, oximes can be obtained by passing a mixture of ketone vapor, NH_3, and O_2 over a silica-gel catalyst.[319] Ketones can also be converted to oximes by treatment with other oximes, in a transoximation reaction.[320]

OS **I**, 318, 327; **II**, 70, 204, 313, 622; **III**, 690, **IV**, 229; **V**, 139, 1031; **VII**, 149. See also, OS **VI**, 670.

16-16 The Conversion of Aldehydes to Nitriles

Nitrilo-de-hydro,oxo-tersubstitution



Aldehydes can be converted to nitriles in one step by treatment with hydroxylamine hydrochloride and either formic acid,[321] $NaHSO_4$•SiO_2 with microwave irradiation,[322] or $(Bu_4N)_2S_2O_8$ with $Cu(HCO_2)$•$Ni(COOH)_2$ and aq. KOH.[323] Heating in NMP is also effective with aryl aldehydes[324] and heating on dry alumina with

[315]For reviews of the mechanism of such reactions, see Cockerill, A.F.; Harrison, R.G., in Patai, S. *The Chemistry of Functional Groups: Supplement A*, pt. 1, Wiley, NY, ***1977***, pp. 288–299; Sollenberger, P.Y.; Martin, R.B., in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, pp. 367–392. For isotope effect studies, see Rossi, M.H.; Stachissini, A.S.; do Amaral, L. *J. Org. Chem.* ***1990***, *55*, 1300.

[316]Sayer, J.M.; Jencks, W.P. *J. Am. Chem. Soc.* ***1972***, *94*, 3262.

[317]Sayer, J.M.; Edman, C. *J. Am. Chem. Soc.* ***1979***, *101*, 3010.

[318]Cocivera, M.; Fyfe, C.A.; Effio, A.; Vaish, S.P.; Chen, H.E. *J. Am. Chem. Soc.* ***1976***, *98*, 1573; Cocivera, M.; Effio, A. *J. Am. Chem. Soc.* ***1976***, *98*, 7371.

[319]Armor, J.N. *J. Am. Chem. Soc.* ***1980***, *102*, 1453.

[320]For example, see Block Jr., P.; Newman, M.S. *Org. Synth. V*, 1031.

[321]Olah, G.A.; Keumi, T. *Synthesis* ***1979***, 112.

[322]Das, B.; Ramesh, C.; Madhusudhan, P. *Synlett* ***2000***, 1599.

[323]Chen, F.-E.; Fu, H.; Meng, G.; Cheng, Y.; Lü, Y.-X. *Synthesis* ***2000***, 1519.

[324]Kumar, H.M.S.; Reddy, B.V.S.; Reddy, P.T.; Yadav, J.S. *Synthesis* ***1999***, 586; Chakraborti, A.K.; Kaur, G. *Tetrahedron* ***1999***, *55*, 13265.

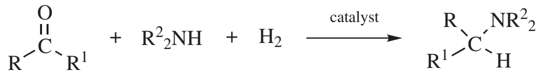
aliphatic aldehyde.[325] The reaction is a combination of **16-15** and **17-29**. Direct nitrile formation has also been accomplished with certain derivatives of NH_2OH, notably, NH_2OSO_2OH.[326] Treatment with hydroxylamine and NaI[327] or certain carbonates[328] also converts aldehydes to the nitrile. Another method involves treatment with hydrazoic acid, though the Schmidt reaction (**18-16**) may compete.[329] Aromatic aldehydes have been converted to nitriles in good yield with $NH_2OH/HCOOH$ on silica gel.[330] Microwave irradiation has been used with NH_2OH•HCl and another reagent, which includes phthalic anhydride,[331] Bu_2SnO•Al_2O_3,[332] or H—Y zeolite.[333] Other reagents include *N*-phenylurea with tosic acid,[334] MnO_2 and ammonia,[335] I_2 with aqueous ammonia,[336] dimethylhydrazine followed by dimethyl sulfoxide,[337] trimethylsilyl azide,[338] and with hydroxylamine hydrochloride, $MgSO_4$, and TsOH.[339] The reaction of a conjugated aldehyde with ammonia, CuCl and 50% H_2O_2 gave the conjugated nitrile.[340] Benzylic alcohols can be oxidized in the presence of ammonia to give the nitrile.[341] Trichloroisocyanuric acid with a catalytic amount of TEMPO (p. 274) converts aldehydes to nitriles at 0°C in dichloromethane.[342]

On treatment with 2 equivalents of dimethylaluminum amide Me_2AlNH_2, carboxylic esters can be converted to nitriles: $RCOOR' \rightarrow RCN$.[343] This is very likely a combination of **16-75** and **17-30**. See also, **19-5**.

OS **V**, 656.

16-17 Reductive Alkylation of Ammonia or Amines

Hydro,dialkylamino-de-oxo-bisubstitution



[325]Sharghi, H.; Sarvari, M.H. *Tetrahedron* ***2002***, *58*, 10323. With wet alumina followed by $MeSO_2Cl$ the product is an amide.

[326]Streith, J.; Fizet, C.; Fritz, H. *Helv. Chim. Acta* ***1976***, *59*, 2786.

[327]Ballini, R.; Fiorini, D.; Palmieri, A. *Synlett* ***2003***, 1841.

[328]Bose, D.S.; Goud, P.R. *Synth. Commun.* ***2002***, *32*, 3621.

[329]For additional methods, see Gelas-Mialhe, Y.; Vessière, R. *Synthesis* ***1980***, 1005; Arques, A.; Molina, P.; Soler, A. *Synthesis* ***1980***, 702; Sato, R.; Itoh, K.; Itoh, K.; Nishina, H.; Goto, T.; Saito, M. *Chem. Lett.* ***1984***, 1913; Reddy, P.S.N.; Reddy, P.P. *Synth. Commun.* ***1988***, *18*, 2179; Neunhoeffer, H.; Diehl, W.; Karafiat, U. *Liebigs Ann. Chem.* ***1989***, 105.

[330]Kabalka, G.W.; Yang, K. *Synth. Commun.* ***1998***, *28*, 3807.

[331]Veverková, E.; Toma, Š. *Synth. Commun.* ***2000***, *30*, 3109.

[332]Yadav, J.S.; Reddy, B.V.S.; Madan, Ch. *J. Chem. Res. (S)* ***2001***, 190.

[333]Srinivas, K.V.N.S.; Reddy, E.B.; Das, B. *Synlett* ***2002***, 625.

[334]Cokun, N.; Arikan, N. *Tetrahedron* ***1999***, *55*, 11943.

[335]Lai, G.; Bhamare, N.K.; Anderson, W.K. *Synlett* ***2001***, 230.

[336]Talukdar, S.; Hsu, J.-L.; Chou, T.-C.; Fang, J.-M. *Tetrahedron Lett.* ***2001***, *42*, 1103.

[337]Kamal, A.; Arifuddin, M.; Rao, N.V. *Synth. Commun.* ***1998***, *28*, 4507.

[338]Nishiyama, K.; Oba, M.; Watanabe, A. *Tetrahedron* ***1987***, *43*, 693.

[339]Ganboa, I.; Palomo, C. *Synth. Commun.* ***1983***, *13*, 219.

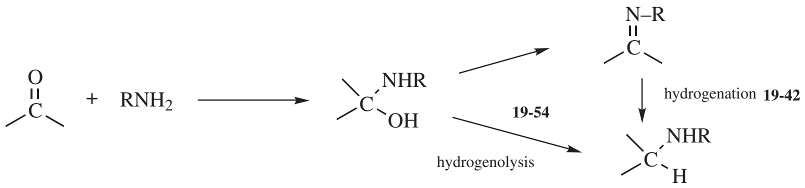
[340]Erman, M.B.; Snow, J.W.; Williams, M.J. *Tetrahedron Lett.* ***2000***, *41*, 6749.

[341]See Baxendale, I.R.; Ley, S.V.; Sneddon, H.F. *Synlett* ***2002***, 775; McAllister, G.D.; Wilfred, C.D.; Taylor, R.J.K. *Synlett* ***2002***, 1291.

[342]Chen, F.-E.; Kuang, Y.-Y.; Dai, H.-F.; Lu, L.; Huo, M. *Synthesis* ***2003***, 2629.

[343]Wood, J.L.; Khatri, N.A.; Weinreb, S.M. *Tetrahedron Lett.* ***1979***, 4907.

When an aldehyde or a ketone is treated with ammonia or a primary or secondary amine in the presence of hydrogen and a hydrogenation catalyst (heterogeneous or homogeneous),[344] *reductive alkylation* of ammonia or the amine (or *reductive amination* of the carbonyl compound) takes place.[345] The reaction can formally be regarded as occurring in the following manner (shown for a primary amine), which probably does correspond to the actual sequence of steps:[346] In this regard, the reaction of an aldehyde with an amine to give an iminium salt (**16-31**) can be followed in a second chemical step of reduction of the C=N unit (**19-42**) using $NaBH_4$ or a variety of other reagents.[347]



Primary amines have been prepared from many aldehydes with at least five carbons and from many ketones by treatment with ammonia and a reducing agent. Smaller aldehydes are usually too reactive to permit isolation of the primary amine. Secondary amines have been prepared by both possible procedures: 2 equivalents of ammonia and 1 equivalent of aldehyde or ketone, and 1 equivalent of primary amine and 1 equivalent of carbonyl compound, the latter method being better for all but aromatic aldehydes. Tertiary amines can be prepared in three ways, but the method is seldom carried out with 3 equivalents of ammonia and 1 equivalent of carbonyl compound. Much more often they are prepared from primary or secondary amines.[348] When the reagent is ammonia, it is possible for the initial product to react again and for this product to react again, so that secondary and tertiary amines are usually obtained as side products. Similarly, primary amines give tertiary as well as secondary amines. In order to minimize this, the aldehyde or ketone is treated with an excess of ammonia or primary amine (unless of course the higher amine is desired).

For ammonia and primary amines there are two possible pathways, but when secondary amines are involved, only the hydrogenolysis pathway is possible. The reaction is compatible with amino acids, giving the *N*-alkylated amino acid.[349]

[344]**Rh**: Kadyrov, R.; Riermeier, T.H.; Dingerdissen, U.; Tararov, V.; Börner, A. *J. Org. Chem.* ***2003***, *68*, 4067; Gross, T.; Seayad, A.M.; Ahmad, M.; Beller, M. *Org. Lett.* ***2002***, *4*, 2055. **Ir**: Chi, Y.; Zhou, Y.-G.; Zhang, X. *J. Org. Chem.* ***2003***, *68*, 4120.

[345]For reviews, see Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, ***1985***, pp. 82–93; Klyuev, M.V.; Khidekel, M.L. *Russ. Chem. Rev.* ***1980***, *49*, 14; Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, ***1967***, pp. 291–303.

[346]See, for example, Le Bris, A.; Lefebvre, G.; Coussemant, F. *Bull. Soc. Chim. Fr.* ***1964***, 1366, 1374, 1584, 1594.

[347]For a simple example see, Bhattacharyya, S. *Synth. Commun.* ***2000***, *30*, 2001.

[348]For a review of the preparation of tertiary amines by reductive alkylation, see Spialter, L.; Pappalardo, J.A. *The Acyclic Aliphatic Tertiary Amines*, Macmillan, NY, ***1965***, pp. 44–52.

[349]Song, Y.; Sercel, A.D.; Johnson, D.R.; Colbry, N.L.; Sun, K.-L.; Roth, B.D. *Tetrahedron Lett.* ***2000***, *41*, 8225.

Other reducing agents[350] can be used instead of hydrogen and a catalyst, among them zinc and HCl, $B_{10}H_{14}$[351] or $B_{10}H_{14}$ with Pd/C,[352] a picolinyl borane complex in acetic acid–methanol,[353] $PhSiH_3$ with 2% Bu_2SnCl_2,[354] and polymethylhydrosiloxane.[355] Several hydride reducing agents can be used, including $NaBH_4$[356] sodium borohydride with $Ti(OiPr)_4$[357] or $NiCl_2$,[358] $NaBH_4/H_3BO_4$,[359] borohydride-exchange resin,[360] sodium cyanoborohydride ($NaBH_3CN$),[361] sodium triacetoxyborohydride,[362] or a polymer-bound triethylammonium acetoxyborohydride.[363] A Hantzsch dihydropyridine in conjunction with a scandium catalyst has been used.[364] An interesting variation uses a benzylic alcohol in a reaction with a primary amine, and a mixture of MnO_2 and $NaBH_4$, giving *in situ* oxidation to the aldehyde and reductive amination to give the amine as the final product.[365]

Formic acid is commonly used for reductive amination[366] in what is called the *Wallach reaction*. Secondary amines react with formaldehyde and NaH_2PO_3 to give the *N*-methylated tertiary amine[367] and microwave irradiation has also been used.[368] Conjugated aldehydes are converted to alkenyl-amines with the amine/silica gel followed by reduction with zinc borohydride.[369] In the particular case where primary or secondary amines are reductively methylated with formaldehyde and formic acid, the method is called the *Eschweiler–Clarke procedure*. Heating with paraformaldehyde and oxalyl chloride has been used to give the same result.[370] It is

[350]For a list of many of these, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 835–840.

[351]Bae, J.W.; Lee, S.H.; Cho, Y.J.; Yoon, C.M. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 145.

[352]Jung, Y.J.; Bae, J.W.; Park, E.S.; Chang, Y.M.; Yoon, C.M. *Tetrahedron* ***2003***, *59*, 10331.

[353]Sato, S.; Sakamoto, T.; Miyazawa, E.; Kitugawa, Y. *Tetrahedron* ***2004***, *60*, 7899.

[354]Apodaca, R.; Xiao, W. *Org. Lett.* ***2001***, *3*, 1745.

[355]Chandrasekhar, S.; Reddy, Ch.R.; Ahmed, M. *Synlett* ***2000***, 1655.

[356]Sondengam, B.L.; Hentchoya Hémo, J.; Charles, G. *Tetrahedron Lett.* ***1973***, 261; Schellenberg, K.A. *J. Org. Chem.* ***1963***, *28*, 3259; Gribble, G.W.; Nutaitis, C.F. *Synthesis* ***1987***, 709.

[357]Neidigh, K.A.; Avery, M.A.; Williamson, J.S.; Bhattacharyya, S. *J. Chem. Soc. Perkin Trans. 1* ***1998***, 2527; Bhattacharyya, S. *J. Org. Chem.* ***1995***, *60*, 4928.

[358]Saxena, I.; Borah, R.; Sarma, J.C. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 503.

[359]This is a solvent-free reaction. See Cho, B.T.; Kang, S.K. *Synlett* ***2004***, 1484.

[360]Yoon, N.M.; Kim, E.G.; Son, H.S.; Choi, J. *Synth. Commun.* ***1993***, *23*, 1595.

[361]Borch, R.F.; Bernstein, M.D.; Durst, H.D. *J. Am. Chem. Soc.* ***1971***, *93*, 2897; Mattson, R.J.; Pham, K.M.; Leuck, D.J.; Cowen, K.A. *J. Org. Chem.* ***1990***, *55*, 2552. See also, Barney, C.L.; Huber, E.W.; McCarthy, J.R. *Tetrahedron Lett.* ***1990***, *31*, 5547. For reviews of $NaBH_3CN$, see Hutchins, R.O.; Natale, N.R. *Org. Prep. Proced. Int.* ***1979***, *11*, 201; Lane, C.F. *Synthesis* ***1975***, 135.

[362]Abdel-Magid, A.F.; Maryanoff, C.A.; Carson, K.G. *Tetrahedron Lett.* ***1990***, *31*, 5595; Abdel-Magid, A.F.; Carson, K.G.; Harris, B.D.; Maryanoff, C.A.; Shah, R.D. *J. Org. Chem.* ***1996***, *61*, 3849.

[363]Bhattacharyya, S.; Rana, S.; Gooding, O.W.; Labadie, J. *Tetrahedron Lett.* ***2003***, *44*, 4957.

[364]Itoh, T.; Nagata, K.; Kurihara, A.; Miyazaki, M.; Ohsawa, A. *Tetrahedron lett.* ***2002***, *43*, 3105; Itoh, T.; Nagata, K.; Miyazaki, M.; Ishikawa, H.; Kurihara, A.; Ohsawa, A. *Tetrahedron* ***2004***, *60*, 6649.

[365]Kanno, H.; Taylor, R.J.K. *Tetrahedron Lett.* ***2002***, *43*, 7337.

[366]For a microwave induced reaction see Torchy, S.; Barbry, D. *J. Chem. Res. (S)* ***2001***, 292.

[367]Davis, B.A.; Durden, D.A. *Synth. Commun.* ***2000***, *30*, 3353.

[368]Barbry, D.; Torchy, S. *Synth. Commun.* ***1996***, *26*, 3919.

[369]Ranu, B.C.; Majee, A.; Sarkar, A. *J. Org. Chem.* ***1998***, *63*, 370.

[370]Rosenau, T.; Potthast, A.; Röhrling, J.; Hofinger, A.; Sixxa, H.; Kosma, P. *Synth. Commun.* ***2002***, *32*, 457.

possible to use ammonium (or amine) salts of formic acid,[371] or formamides, as a substitute for the Wallach conditions. This method is called the *Leuckart reaction*,[372] and in this case the products obtained are often the *N*-formyl derivatives of the amines instead of the free amines. A transition-metal catalyzed variation has been reported.[373] Primary and secondary amines can be *N*-ethylated (e.g., ArNHR → ArNREt) by treatment with $NaBH_4$ in acetic acid.[374] Aldehydes react with aniline in the presence of Montmorillonite K10 clay and microwaves to give the amine.[375] Tributyltin hydride is used with an ammonium salt,[376] or Bu_2SnClH•HMPA with an aromatic amine,[377] in the presence of a ketone to give the corresponding amine. Allylic silanes react with aldehydes and carbamates, in the presence of bismuth catalysts,[378] or BF_3•OEt_2[379] to give the corresponding allylic *N*-carbamoyl derivative, and trityl perchlorate has been used for the same purpose when *N*-trimethylsilyl carbamates are employed.[380] The reaction can be done with aromatic amines in the presence of vinyl ethers and a copper complex to give β-amino ketones.[381] Reductive amination of an aryl amine and an aryl aldehyde that contains a ortho conjugated ketone substituents gives the amine, which adds 1,4- (**15-AA**) to the α,β-unsaturated ketone unit to give a bicyclic amine.[382] Alternative methods of reductive alkylation have been developed. Alkylation of an imine formed *in situ* is also possible.[383]

Reductive alkylation has also been carried out on nitro, nitroso, azo, and other compounds that are reduced *in situ* to primary or secondary amines. Azo compounds react with aldehydes, in the presence of proline, and subsequent reduction with $NaBH_4$ gives the chiral hydrazine derivative.[384]

[371]For a review of ammonium formate in organic synthesis, see Ram, S.; Ehrenkaufer, R.E. *Synthesis* ***1988***, 91.

[372]For a review, see Moore, M.L. *Org. React.* ***1949***, *5*, 301. For discussions of the mechanism, see Awachie, P.I.; Agwada, V.C. *Tetrahedron* ***1990***, *46*, 1899, and references cited therein. For a microwave-induced variation, see Loupy, A.; Monteux, D.; Petit, A.; Aizpurua, J.M.; Domínguez, E.; Palomo, C. *Tetrahedron Lett.* ***1996***, *37*, 8177. For the effects of added formamide, see Lejon, T.; Helland, I. *Acta Chem. Scand.* ***1999***, *53*, 76.

[373]Using a rhodium catalyst, see Kitamura, M.; Lee, D.; Hayashi, S.; Tanaka, S.; Yoshimura, M. *J. Org. Chem.* ***2002***, *67*, 8685. For a review of this reaction, see Riermeier, T.H.; Dingerdissen, U.; Börner, A. *Org. Prep. Proceed. Int.* ***2004***, *36*, 99.

[374]For a review, see Gribble, G.W.; Nutaitis, C.F. *Org. Prep. Proced. Int.* ***1985***, *17*, 317, pp. 336–350.

[375]Varma, R.S.; Dahiya, R. *Tetrahedron* ***1998***, *54*, 6293.

[376]Suwa, T.; Sugiyama, E.; Shibata, I.; Baba, A. *Synlett* ***2000***, 556.

[377]Suwa, T.; Sugiyama, E.; Shibata, I.; Baba, A. *Synthesis* ***2000***, 556.

[378]Ollevier, T.; Ba, T. *Tetrahedron Lett.* ***2003***, *44*, 9003.

[379]Billet, M.; Klotz, P.; Mann, A. *Tetrahedron lett.* ***2001***, *42*, 631.

[380]Niimi, L.; Serita, K.-i.; Hiraoka, S.; Yokozawa, T. *Tetrahedron Lett.* ***2000***, *41*, 7075.

[381]Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H.; Kim, H.-S.; Wataya, Y. *J. Org. Chem.* ***1999***, *64*, 6833.

[382]Suwa, T.; Shibata, I.; Nishino, K.; Baba, A. *Org. Lett.* ***1999***, *1*, 1579.

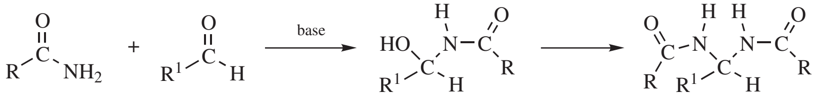
[383]See Choudary, B.M.; Jyothi, K.; Madhi, S.; Kantam, M.L. *Synlett* ***2004***, 231. For an example in the ionic liquid bmim BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate, see Yadav, J.S.; Reddy, B.V.S.; Raju, A.K. *Synthesis* ***2003***, 883.

[384]List, B. *J. Am. Chem. Soc.* ***2002***, *124*, 5656; Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bøgevig, A.; Jørgensen, K.A. *J. Am. Chem. Soc.* ***2002***, *124*, 6254.

OS **I**, 347, 528, 531; **II**, 503; **III**, 328, 501, 717, 723; **IV**, 603; **V**, 552; **VI**, 499; **VII**, 27.

16-18 Addition of Amides to Aldehydes

Alkylamido-de-oxo-bisubstitution

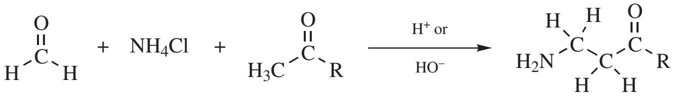


Amides can add to aldehydes in the presence of bases (so the nucleophile is actually $RCONH^-$) or acids to give acylated amino alcohols, which often react further to give alkylidene or arylidene bisamides.[385] If the R′ group contains an α hydrogen, water may split out.

Sulfonamides add to aldehydes to give the *N*-sulfonyl imine. Benzaldehyde reacts with $TsNH_2$, for example, at 160°C in the presence of $Si(OEt)_4$,[386] with trifluoroacetic anhydride (TFAA) in refluxing dichloromethane,[387] or with $TiCl_4$ in refluxing dichloroethane,[388] to give the *N*-tosylimine, Ts—N=CHPh. In a similar manner, the reaction of $TolSO_2Na + PhSO_2Na$ with an aldehyde in aqueous formic acid gives the *N*-phenylsulfonyl imine.[389] The reaction of an aldehyde with $Ph_3P{=}NTs$ and a ruthenium catalyst gives the *N*-tosyl imine.[390] Reaction of aldehydes with $LiAl(NHBn)_4$ also give the corresponding *N*-benzylimine.[391]

16-19 The Mannich Reaction

Acyl,amino-de-oxo-bisubstitution, and so on



In the *Mannich reaction*, formaldehyde (or sometimes another aldehyde) is condensed with ammonia, in the form of its salt, and a compound containing an active hydrogen.[392] This can formally be considered as an addition of ammonia to give

[385]For reviews, see Challis, B.C.; Challis, J.A. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 754–759; Zaugg, H.E.; Martin, W.B. *Org. React.* ***1965***, *14*, 52, 91–95, 104–112. For a discussion, see Gilbert, E.E. *Synthesis* ***1972***, 30.

[386]Love, B.E.; Raje, P.S.; Williams II, T.C. *Synlett* ***1994***, 493.

[387]Lee, K.Y.; Lee, C.G.; Kim, J.N. *Tetrahedron Lett.* ***2003***, *44*, 1231.

[388]Ram, R.N.; Khan, A.A. *Synth. Commun.* ***2001***, *31*, 841.

[389]Chemla, F.; Hebbe, V.; Normant, J.-F. *Synthesis* ***2000***, 75.

[390]Jain, S.L.; Sharma, V.B.; Sain, B. *Tetrahedron Lett.* ***2004***, *45*, 4341.

[391]Solladié-Cavallo, A.; Benchegroun, M.; Bonne, F. *Synth. Commun.* ***1993***, *23*, 1683.

[392]For reviews, see Tramontini, M.; Angiolini, L. *Tetrahedron* ***1990***, *46*, 1791; Gevorgyan, G.A.; Agababyan, A.G.; Mndzhoyan, O.L. *Russ. Chem. Rev.* ***1984***, *53*, 561; Tramontini, M. *Synthesis* ***1973***, 703; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 654–660. For reviews on the reactions of Mannich Bases, see Tramontini, M.; Angeloni, L. cited above; Gevorgyan, G.A.; Agababyan, A.G.; Mndzhoyan, O.L. *Russ. Chem. Rev.* ***1985***, *54*, 495.

H_2NCH_2OH, followed by a nucleophilic substitution. Instead of ammonia, the reaction can be carried out with salts of primary or secondary amines,[393] or with amides,[394] in which cases the product is substituted on the nitrogen with R, R_2, and RCO, respectively. The imine can be generated *in situ*, and the reaction of a ketone, formaldehyde, and diethylamine with microwave irradiation gave the Mannich product, a β-amino ketone.[395] Arylamines do not normally give the reaction. Hydrazines can be used.[396] The product is referred to as a *Mannich base*. Many active hydrogen compounds give the reaction, including ketones and aldehydes, esters, nitroalkanes,[397] and nitriles as well as ortho-carbons of phenols, the carbon of terminal alkynes, the oxygen of alcohols and the sulfur of thiols.[398] Vinylogous Mannich reactions are known.[399]

The Mannich base can react further in three ways. If it is a primary or secondary amine, it may condense with one or two additional molecules of aldehyde and active compound, for example,

$$H_2NCH_2CH_2COR \xrightarrow[CH_3COR]{HCHO} HN(CH_2CH_2COR)_2 \xrightarrow[CH_3COR]{HCHO} N(CH_2CH_2COR)_3$$

If the active hydrogen compound has two or three active hydrogens, the Mannich base may condense with one or two additional molecules of aldehyde and ammonia or amine, for example,

$$H_2NCH_2CH_2COR \xrightarrow[NH_3]{HCHO} (H_2NCH_2)_2CHCOR \xrightarrow[NH_3]{HCHO} (H_2NCH_2)_3CHCOR$$

Another further reaction consists of condensation of the Mannich base with excess formaldehyde:

$$H_2NCH_2CH_2COR + HCHO \longrightarrow H_2C{=}NCH_2CH_2COR$$

Sometimes it is possible to obtain these products of further condensation as the main products of the reaction. At other times they are side products.

When the Mannich base contains an amino group β to a carbonyl (and it usually does), ammonia is easily eliminated. This is a route to α,β-unsaturated aldehydes, ketones, esters, and so on.

[393]For a review where the amine component is an amino acid, see Agababyan, A.G.; Gevorgyan, G.A.; Mndzhoyan, O.L. *Russ. Chem. Rev.* ***1982***, *51*, 387.

[394]Hellmann, H. *Angew. Chem.* ***1957***, *69*, 463; *Newer Methods Prep. Org. Chem.* ***1963***, *2*, 277.

[395]Gadhwal, S.; Baruah, M.; Prajapati, D.; Sandhu, J.S. *Synlett* ***2000***, 341.

[396]El Kaim, L.; Grimaud, L.; Perroux, Y.; Tirla, C. *J. Org. Chem.* ***2003***, *68*, 8733.

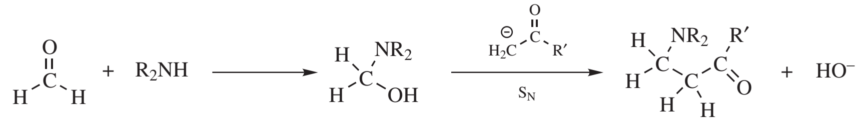
[397]Qian, C.; Gao, F.; Chen, R. *Tetrahedron Lett.* ***2001***, *42*, 4673. See Baer, H.H.; Urbas, L., in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, Wiley, NY, ***1970***, pp. 117–130.

[398]see Massy, D.J.R. *Synthesis* ***1987***, 589; Dronov, V.I.; Nikitin, Yu.E. *Russ. Chem. Rev.* ***1985***, *54*, 554

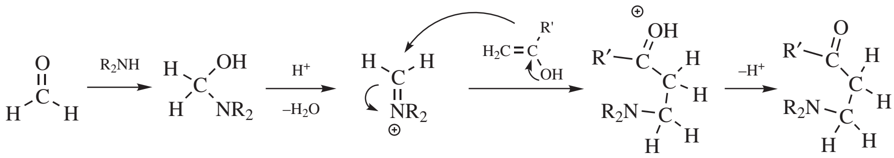
[399]Bur, S.; Martin, S.F. *Tetrahedron* ***2001***, *57*, 3221. For a review, see Martin, S.F. *Acc. Chem. Res.* ***2002***, *35*, 895.

Studies of the reaction kinetics have led to the following proposals for the mechanism of the Mannich reaction.[400]

The base-catalyzed reaction:



The acid-catalyzed reaction:



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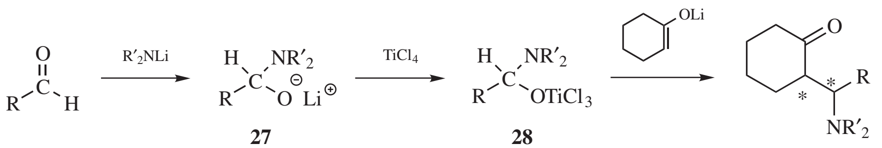
According to this mechanism, it is the free amine, not the salt that reacts, even in acid solution; and the active-hydrogen compound (in the acid-catalyzed process) reacts as the enol when that is possible. This latter step is similar to what happens in **12-4**. There is kinetic evidence for the intermediacy of the iminium ion (**26**).[401]

When an unsymmetrical ketone is used as the active-hydrogen component, two products are possible. Regioselectivity has been obtained by treatment of the ketone with pre-formed iminium ions:[402] the use of $Me_2N^+{=}CH_2\ CF_3COO^{\ominus}$ in CF_3COOH gives substitution at the more highly substituted position, while with $(i\text{Pr})_2N{=}CH_2^+\ ClO_4^{\ominus}$ the reaction takes place at the less highly substituted position.[403] The pre-formed iminium compound dimethyl(methylene)ammonium iodide $CH_2{=}N^+Me_2\ I^{\ominus}$, called *Eschenmoser's salt*,[404] has also been used in Mannich reactions.[405] The analogous chloride salt has been condensed with an imine to give and a β,β′-dimethylamino ketone after acid hydrolysis.[406]



27 **28**

[400]Cummings, T.F.; Shelton, J.R. *J. Org. Chem.* ***1960***, *25*, 419.

[401]Benkovic, S.J.; Benkovic, P.A.; Comfort, D.R. *J. Am. Chem. Soc.* ***1969***, *91*, 1860.

[402]For earlier use of pre-formed iminium ions in the Mannich reaction, see Ahond, A.; Cavé, A.; Kan-Fan, C.; Potier, P. *Bull. Soc. Chim. Fr.* ***1970***, 2707; Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem. Int. Ed.* ***1971***, *10*, 330.

[403]Jasor, Y.; Luche, M.; Gaudry, M.; Marquet, A. *J. Chem. Soc., Chem. Commun.* ***1974***, 253; Gaudry, M.; Jasor, Y.; Khac, T.B. *Org. Synth.* ***VI***, 474.

[404]Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem. Int. Ed.* ***1971***, *10*, 330.

[405]See Holy, N.; Fowler, R.; Burnett, E.; Lorenz, R. *Tetrahedron* ***1979***, *35*, 613; Bryson, T.A.; Bonitz, G.H.; Reichel, C.J.; Dardis, R.E. *J. Org. Chem.* ***1980***, *45*, 524, and references cited therein.

[406]Arend, M.; Risch, N. *Tetrahedron Lett.* ***1999***, *40*, 6205.

Another type of pre-formed reagent (**28**) has been used to carry out diastereoselective Mannich reactions. The lithium salts **27** are treated with $TiCl_4$ to give **28**, which is then treated with the enolate of a ketone.[407] The palladium catalyzed Mannich reaction of enol ethers to imines is also known.[408] The reaction of silyl enol ethers and imines is catalyzed by HBF_4 in aqueous methanol.[409] Similarly, silyl enol ethers react with aldehydes and aniline in the presence of $InCl_3$ to give the β-amino ketone.[410] Imines react on Montmorillonite K10 clay and microwave irradiation gives β-amino esters.[411] Enol ethers react similarly in the presence of $Yb(OTf)_3$.[412]

Enantioselective Mannich reactions are known.[413] The most common method uses a chiral catalyst, including proline,[414] proline derivatives or proline analogs.[415] Chiral diamine[416] or phosphine-imine[417] ligands have been used. Chiral auxiliaries on the carbonyl fragment can be used.[418] Chiral imines, in the form of chiral hydrazones have been used with silyl enol ethers and a scandium catalyst.[419] Chiral amine react with aldehydes, with silyl enol ethers and an $InCl_3$ catalyst in ionic liquids, to give the Mannich product with good enantioselectivity.[420]

Also see, **11-22**.

OS **III**, 305; **IV**, 281, 515, 816; **VI**, 474, 981, 987; **VII**, 34. See also, OS **VIII**, 358.

16-20 The Addition of Amines to Isocyanates

N-Hydro-*C*-alkylamino-addition

[407]Seebach, D.; Schiess, M.; Schweizer, W.B. *Chimia* ***1985***, *39*, 272. See also, Heaney, H.; Papageorgiou, G.; Wilkins, R.F. *J. Chem. Soc., Chem. Commun.* ***1988***, 1161; Katritzky, A.R.; Harris, P.A. *Tetrahedron* ***1990***, *46*, 987.

[408]For a discussion of the mechanism, see Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* ***1999***, *121*, 5450.

[409]Akiyama, T.; Takaya, J.; Kagoshima, H. *Synlett* ***1999***, 1045; Akiyama, T.; Takaya, J.; Kagoshima, H. *Tetrahedron Lett.* ***2001***, *42*, 4025.

[410]Loh, T.-P.; Wei, L.L. *Tetrahedron Lett.* ***1998***, *39*, 323.

[411]Texier-Boullet, F.; Latouche, R.; Hamelin, J. *Tetrahedron Lett.* ***1993***, *34*, 2123.

[412]Kobayashi, S.; Ishitani, H. *J. Chem. Soc., Chem. Commun.* ***1995***, 1379.

[413]For a review, see Córdova, A. *Acc. Chem. Res.* ***2004***, *37*, 102.

[414]List, B.; Pojarliev, P.; Biller, W.T.; Martin, H.J. *J. Am. Chem. Soc.* ***2004***, *124*, 827; Ibrahem, I.; Casas, J.; Córdova, A. *Angew. Chem. Int. Ed.* ***2004***, *43*, 6528.

[415]Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G.; Barbas III, C.F. *Tetrahedron Lett.* ***2000***, *42*, 199.

[416]Kobayashi, S.; Hamada, T.; Manabe, K. *J. Am. Chem. Soc.* ***2002***, *124*, 5640; Trost, B.M.; Terrell, C.R. *J. Am. Chem. Soc.* ***2003***, *125*, 338.

[417]Josephsohn, N.S.; Snapper, M.L.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2004***, *126*, 3734.

[418]Hata, S.; Iguchi, M.; Iwasawa, T.; Yamada, K.-i.; Tomioka, K. *Org. Lett.* ***2004***, *6*, 1721.

[419]Jacobsen, M.F.; Ionita, L.; Skrydstrup, T. *J. Org. Chem.* ***2004***, *69*, 4792.

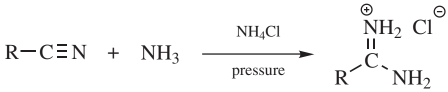
[420]In bmim BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate: Sun, W.; Xia, C.-G.; Wang, H.-W. *Tetrahedron Lett.* ***2003***, *44*, 2409.

Ammonia and primary and secondary amines can be added to isocyanates[421] to give substituted ureas.[422] Isothiocyanates give thioureas.[423] This is an excellent method for the preparation of ureas and thioureas, and these compounds are often used as derivatives for primary and secondary amines. Isocyanic acid (HNCO) also gives the reaction; usually its salts (e.g., NaNCO) are used. Wöhler's famous synthesis of urea involved the addition of ammonia to a salt of this acid.[424]

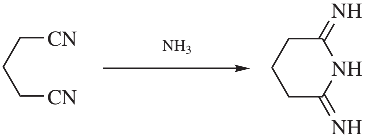
OS **II**, 79; **III**, 76, 617, 735; **IV**, 49, 180, 213, 515, 700; **V**, 555, 801, 802, 967; **VI**, 936, 951; **VIII**, 26.

16-21 The Addition of Ammonia or Amines to Nitriles

N-Hydro-*C*-amino-addition



Unsubstituted amidines (in the form of their salts) can be prepared by addition of ammonia to nitriles.[425] Many amidines have been made in this way. Dinitriles of suitable chain length can give imidines:[426]



Primary and secondary amines can be used instead of ammonia, to give substituted amidines, but only if the nitrile contains electron-withdrawing groups; for example, Cl_3CCN gives the reaction. Ordinary nitriles do not react, and, in fact, acetonitrile is often used as a solvent in this reaction.[427] Ordinary nitriles can be converted to amidines by treatment with an alkylchloroaluminum amide, $MeAl(Cl)NR_2$ (R = H or Me).[428] The addition of ammonia to cyanamide (NH_2CN) gives guanidine, $(NH_2)_2C{=}NH$. Guanidines can also be formed from amines.[429]

[421]For a review of the mechanism, see Satchell, D.P.N.; Satchell, R.S. *Chem. Soc. Rev.* ***1975***, *4*, 231.

[422]For a review of substituted ureas, see Vishnyakova, T.P.; Golubeva, I.A.; Glebova, E.V. *Russ. Chem. Rev.* ***1985***, *54*, 249.

[423]Herr, R.J.; Kuhler, J.L.; Meckler, H.; Opalka, C.J. *Synthesis* ***2000***, 1569.

[424]For a history of the investigation of the mechanism of the Wöhler synthesis, see Shorter, J. *Chem. Soc. Rev.* ***1978***, *7*, 1. See also, Williams, A.; Jencks, W.P. *J. Chem. Soc. Perkin Trans. 2* ***1974***, 1753, 1760; Hall, K.J.; Watts, D.W. *Aust. J. Chem.* ***1977***, *30*, 781, 903.

[425]For reviews of amidines, see Granik, V.G. *Russ. Chem. Rev.* ***1983***, *52*, 377; Gautier, J.; Miocque, M.; Farnoux, C.C., in Patai, S. *The Chemistry of Amidines and Imidates*, Wiley, NY, ***1975***, pp. 283–348.

[426]Elvidge, J.A.; Linstead, R.P.; Salaman, A.M. *J. Chem. Soc.* ***1959***, 208.

[427]Grivas, J.C.; Taurins, A. *Can. J. Chem.* ***1961***, *39*, 761.

[428]Garigipati, R.S. *Tetrahedron Lett.* ***1990***, *31*, 1969.

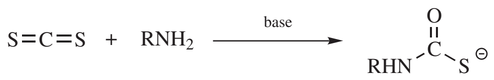
[429]Dräger, G.; Solodenko, W.; Messinger, J.; Schön, U.; Kirschning, A. *Tetrahedron Lett.* ***2002***, *43*, 1401.

If water is present, in the presence of a ruthenium catalyst[430] or a platinum catalyst,[431] the addition of a primary or secondary amine to a nitrile gives an amide: $RCN + R^1NHR^2 + H_2O \rightarrow RCONR^1R^2 + NH_3$ (R^2 may be H). When benzonitrile reacts with $H_2PO_3Se^-$ in aqueous methanol, a selenoamide, PhC=Se)NH_2, is formed after treatment with aq. potassium carbonate.[432]

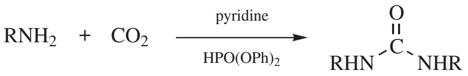
OS **I**, 302 [but also see OS **V**, 589]; **IV**, 245, 247, 515, 566, 769. See also, OS **V**, 39.

16-22 The Addition of Amines to Carbon Disulfide and Carbon Dioxide

***S*-Metallo-*C*-alkylamino-addition**



Salts of dithiocarbamic acid can be prepared by the addition of primary or secondary amines to carbon disulfide.[433] This reaction is similar to **16-10**. Hydrogen sulfide can be eliminated from the product, directly or indirectly, to give isothiocyanates (RNCS). Isothiocyanates can be obtained directly by the reaction of primary amines and CS_2 in pyridine in the presence of dicyclohexylcarbodiimide.[434] Aniline derivatives react with CS_2 and NaOH, and then ethyl chloroformate to give the aryl isothiocyanate.[435] In the presence of diphenyl phosphite and pyridine, primary amines add to CO_2 and to CS_2 to give, respectively, symmetrically substituted ureas and thioureas:[436] Isoselenoureas, $R_2NC(=NR^1)SeR^2$, can also be formed.[437]



OS **I**, 447; **III**, 360, 394, 599, 763; **V**, 223.

[430]Murahashi, S.; Naota, T.; Saito, E. *J. Am. Chem. Soc.* ***1986***, *108*, 7846.

[431]Cobley, C.J.; van den Heuvel, M.; Abbadi, A.; de Vries, J.G. *Tetrahedron Lett.* ***2000***, *41*, 2467.

[432]Kamiñski, R.; Glass, R.S.; Skowroñska, A. *Synthesis* ***2001***, 1308.

[433]For reviews, see Dunn, A.D.; Rudorf, W. *Carbon Disuphide in Organic Chemistry*, Ellis Horwood, Chichester, ***1989***, pp. 226–315; Katritzky, A.R.; Faid-Allah, H.; Marson, C.M. *Heterocycles* ***1987***, *26*, 1657; Yokoyama, M.; Imamoto, T. *Synthesis* ***1984***, 797, see pp. 804–812. For a review of the addition of heterocyclic amines to CO_2 to give, for example, salts of pyrrole-1-carboxylic acids, see Katritzky, A.R.; Marson, C.M.; Faid-Allah, H. *Heterocycles* ***1987***, *26*, 1333.

[434]Jochims, J.C. *Chem. Ber.* ***1968***, *101*, 1746. For other methods, see Sakai, S.; Fujinami, T.; Aizawa, T. *Bull. Chem. Soc. Jpn.* ***1975***, *48*, 2981; Gittos, M.W.; Davies, R.V.; Iddon, B.; Suschitzky, H. *J. Chem. Soc. Perkin Trans. 1* ***1976***, 141; Shibanuma, T.; Shiono, M.; Mukaiyama, T. *Chem. Lett.* ***1977***, 573; Molina, P.; Alajarin, M.; Arques, A. *Synthesis* ***1982***, 596.

[435]Li, Z.; Qian, X.; Liu, Z.; Li, Z.; Song, G. *Org. Prep. Proceed. Int.* ***2000***, *32*, 571.

[436]Yamazaki, N.; Higashi, F.; Iguchi, T. *Tetrahedron Lett.* ***1974***, 1191. For other methods for the conversion of amines and CO_2 to ureas, see Ogura, H.; Takeda, K.; Tokue, R.; Kobayashi, T. *Synthesis* ***1978***, 394; Fournier, J.; Bruneau, C.; Dixneuf, P.H.; Lécolier, S. *J. Org. Chem.* ***1991***, *56*, 4456. See Chiarotto, I.; Feroci, M. *J. Org. Chem.* ***2003***, *68*, 7137; Lemoucheux, L.; Rouden, J.; Ibazizene, M.; Sobrio, F.; Lasne, M.-C. *J. Org. Chem.* ***2003***, *68*, 7289.

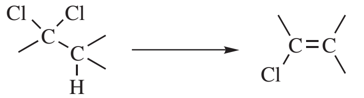
[437]Asanuma, Y.; Fujiwara, S.-i.; Shi-ike, T.; Kambe, N. *J. Org. Chem.* ***2004***, *69*, 4845.

E. Halogen Nucleophiles

16-23 The Formation of *gem*-Dihalides from Aldehydes and Ketones

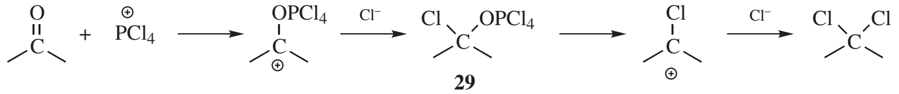
Dihalo-de-oxo-bisubstitution

Aliphatic aldehydes and ketones can be converted to *gem*-dichlorides[438] by treatment with PCl_5. The reaction fails for perhalo ketones.[439] If the aldehyde or ketone has an α hydrogen, elimination of HCl may follow and a vinylic chloride is a frequent side product:[440]



or even the main product.[441] The PBr_5 does not give good yields of *gem*-dibromides,[442] but these can be obtained from aldehydes, by the use of Br_2 and triphenyl phosphite.[443] *gem*-Dichlorides can be prepared by reacting an aldehyde with $BiCl_3$.[444]

The mechanism of *gem*-dichloride formation involves initial attack on PCl_4^+ (which is present in solid PCl_5) at the oxygen, followed by addition of Cl^- to the carbon:[445]



This chloride ion may come from PCl_6^- (which is also present in solid PCl_5). There follows a two-step S_N1 process. Alternatively, **29** can be converted to the product without going through the chlorocarbocation, by an S_Ni process.

This reaction has sometimes been performed on carboxylic esters, though these compounds very seldom undergo any addition to the C=O bond. An example is the conversion of $F_3CCOOPh$ to F_3CCCl_2OPh.[446] However, formates commonly give the reaction.

[438]For a list of reagents that convert aldehydes and ketones to *gem*-dihalides or vinylic halides, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 719–722.

[439]Farah, B.S.; Gilbert, E.E. *J. Org. Chem.* ***1965***, *30*, 1241.

[440]See, for example, Nikolenko, L.N.; Popov, S.I. *J. Gen. Chem. USSR* ***1962***, *32*, 29.

[441]See, for example, Newman, M.S.; Fraenkel, G.; Kirn, W.N. *J. Org. Chem.* ***1963***, *28*, 1851.

[442]For an indirect method of converting ketones to *gem*-dibromides, see Napolitano, E.; Fiaschi, R.; Mastrorilli, E. *Synthesis* ***1986***, 122.

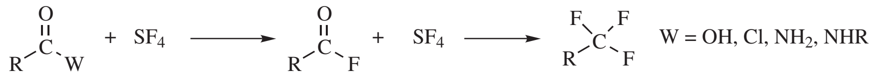
[443]Hoffmann, R.W.; Bovicelli, P. *Synthesis* ***1990***, 657. See also, Lansinger, J.M.; Ronald, R.C. *Synth. Commun.* ***1979***, *9*, 341.

[444]Kabalka, G.W.; Wu, Z. *Tetrahedron Lett.* ***2000***, *41*, 579.

[445]Newman, M.S. *J. Org. Chem.* ***1969***, *34*, 741.

[446]Kirsanov, A.V.; Molosnova, V.P. *J. Gen. Chem. USSR* ***1958***, *28*, 31; Clark, R.F.; Simons, J.H. *J. Org. Chem.* ***1961***, *26*, 5197.

Many aldehydes and ketones have been converted to *gem*-difluoro compounds with sulfur tetrafluoride SF_4,[447] including quinones, which give 1,1,4,4-tetrafluorocyclohexadiene derivatives. With ketones, yields can be raised and the reaction temperature lowered, by the addition of anhydrous HF.[448] Carboxylic acids, acyl chlorides, and amides react with SF_4 to give 1,1,1-trifluorides. In these cases the first product is the acyl fluoride, which then undergoes the *gem*-difluorination reaction:



The acyl fluoride can be isolated. Carboxylic esters also give trifluorides, but more vigorous conditions are required. In this case, the carbonyl group of the ester is attacked first, and RCF_2OR' can be isolated from RCOOR′[449] and then converted to the trifluoride. Anhydrides can react in either manner. Both types of intermediate are isolable under the right conditions and SF_4 even converts carbon dioxide to CF_4. A disadvantage of reactions with SF_4 is that they require a pressure vessel lined with stainless steel. Selenium tetrafluoride SeF_4 gives similar reactions, but atmospheric pressure and ordinary glassware can be used.[450] Another reagent that is often used to convert aldehydes and ketones to *gem*-difluorides is the commercially available diethylaminosulfur trifluoride (DAST, Et_2NSF_3), and CF_2Br_2 in the presence of zinc.[451] The mechanism with SF_4 is probably similar in general nature, if not in specific detail, to that with PCl_5.

Treatment with hydrazine to give the hydrazone, and then $CuBr_2$/*t*-BuOLi, generated the *gem*-dibromide.[452] Oximes gives *gem*-dichlorides upon treatment with chlorine and BF_3•OEt_2, and then HCl.[453] Some dithianes can be converted to *gem*-difluorides with a mixture of fluorine and iodine in acetonitrile.[454] Oximes give *gem*-difluorides with $NO^+BF_4^-$ and pyridinium polyhydrogen fluoride.[455]

In a related process, α-halo ethers can be prepared by treatment of aldehydes and ketones with an alcohol and HX. The reaction is applicable to aliphatic aldehydes and ketones and to primary and secondary alcohols. The addition of HX to an aldehyde or ketone gives α-halo alcohols, which are usually unstable, although exceptions are known, especially with perfluoro and perchloro species.[456]

[447]For reviews, see Wang, C.J. *Org. React.* ***1985***, *34*, 319; Boswell, Jr., G.A.; Ripka, W.C.; Scribner, R.M.; Tullock, C.W. *Org. React.* ***1974***, *21*, 1.

[448]Muratov, N.N.; Mohamed, N.M.; Kunshenko, B.V.; Burmakov, A.I.; Alekseeva, L.A.; Yagupol'skii, L.M. *J. Org. Chem. USSR* ***1985***, *21*, 1292.

[449]For methods of converting RCOOR′ to RCF_2OR', see Boguslavskaya, L.S.; Panteleeva, I.Yu.; Chuvatkin, N.N. *J. Org. Chem. USSR* ***1982***, *18*, 198; Bunnelle, W.H.; McKinnis, B.R.; Narayanan, B.A. *J. Org. Chem.* ***1990***, *55*, 768.

[450]Olah, G.A.; Nojima, M.; Kerekes, I. *J. Am. Chem. Soc.* ***1974***, *96*, 925.

[451]Hu, C.-M.; Qing, F.-L.; Shen, C.-X. *J. Chem. Soc. Perkin Trans. 1* ***1993***, 335.

[452]Takeda, T.; Sasaki, R.; Nakamura, A.; Yamauchi, S.; Fujiwara, T. *Synlett* ***1996***, 273.

[453]Tordeux, M.; Boumizane, K.; Wakselman, C. *J. Org. Chem.* ***1993***, *58*, 1939.

[454]Chambers, R.D.; Sandford, G.; Atherton, M. *J. Chem. Soc., Chem. Commun.* ***1995***, 177.

[455]York, C.; Prakash, G.K.S.; Wang, Q.; Olah, G.A. *Synlett* ***1994***, 425.

[456]For example, see Andreades, S.; England, D.C. *J. Am. Chem. Soc.* ***1961***, *83*, 4670; Clark, D.R.; Emsley, J.; Hibbert, F. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 1107.

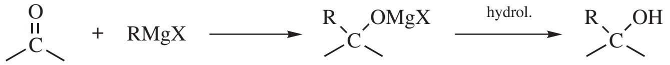
Aromatic aldehydes are converted to benzylic bromides with dibromoboranes, such as c-$C_6H_{11}BBr_2$.[457] Aldehydes are converted directly to benzylic chlorides with $HSiMe_2Cl$ and an $In(OH)_3$ catalyst.[458] The reaction of $BuBCl_2$ and oxygen gives alkylation (**16-25**) and chlorination.[459]

OS **II**, 549; **V**, 365, 396, 1082; **VI**, 505, 845; **VIII**, 247. Also see OS **I**, 506. For α-halo-ethers, see OS **I**, 377; **IV**, 101 (see, however, OS **V**, 218), 748; **VI**, 101.

F. Attack at Carbon by Organometallic Compounds[460]

16-24 The Addition of Grignard Reagents and Organolithium Reagents to Aldehydes and Ketones

O-Hydro-*C*-alkyl-addition



Organomagnesium compounds, commonly known as Grignard reagents (RMgX), are formed by the reaction of alkyl, vinyl, or aryl halides with magnesium metal, usually in ether solvents such as diethyl ether or THF (**12-38**), although the reaction can be done in water[461] under certain conditions. Halogen–magnesium exchange generates a Grignard reagent by reaction of aryl halides with reactive aliphatic Grignard reagents.[462] The addition of Grignard reagents to aldehydes and ketones [463] is known as the *Grignard reaction.*[464] The initial product is a magnesium alkoxide, requiring a hydrolysis step to generate the final alcohol product. Formaldehyde gives primary alcohols; other aldehydes give secondary alcohols; and ketones give tertiary alcohols. The reaction is of very broad scope. In many cases, the hydrolysis step is carried out with dilute HCl or H_2SO_4, but this cannot be done for tertiary alcohols in which at least one R group is alkyl because such alcohols are easily dehydrated under acidic conditions (**17-1**). In such cases (and often for other alcohols as well), an aqueous solution of ammonium chloride is used instead of a strong acid. Grignard reagents have been used in solid phase synthesis.[465]

[457]Kabalka, G.W.; Wu, Z.; Ju, Y. *Tetrahedron Lett.* ***2000***, *41*, 5161.
[458]Onishi, Y.; Ogawa, D.; Yasuda, M.; Baba, A. *J. Am. Chem. Soc.* ***2002***, *124*, 13690.
[459]Kabalka, G.W.; Wu, Z.; Ju, Y. *Tetrahedron Lett.* ***2001***, *42*, 6239.
[460]Discussions of most of the reactions in this section are found, in Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vols. 2–4, Wiley, NY, ***1985–1987***.
[461]Li, C.-J. *Tetrahedron* ***1996***, *52*, 5643.
[462]Song, J.J.; Yee, N.K.; Tan, Z.; Xu, J.; Kapadia, S.R.; Senanayake, C.H. *Org. Lett.* ***2004***, *6*, 4905.
[463]For a discussion of the effect of addends on aggregation and reactivity, see Leung, S.S.-W.; Streitwieser, A. *J. Org. Chem.* ***1999***, *64*, 3390.
[464]For reviews of the addition of organometallic compounds to carbonyl groups, see Eicher, T., in Patai, S. *The Chemistry of the Carbonyl Group*, pt. 1, Wiley, NY, ***1966***, pp. 621–693; Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall: Englewood Cliffs, NJ, ***1954***, pp. 138–528. For a review of reagents that extend carbon chains by three carbons, with some functionality at the new terminus, see Stowell, J.C. *Chem. Rev.* ***1984***, *84*, 409. For a computational study of this reaction, see Yamazaki, S.; Yamabe, S. *J. Org. Chem.* ***2002***, *67*, 9346.
[465]Franzén, R.G. *Tetrahedron* ***2000***, *56*, 685.

Alternative methods to generate the arylmagnesium compound are available, including the reaction of an aryl bromide with Bu_3MgLi in THF.[466] Subsequent addition of an aldehyde leads to addition of the aryl group to form an alcohol. An interesting method to form an alkylmagnesium halide used dibutylmagnesium (Bu_2Mg) and a chiral diamine, and subsequent reaction with an aldehyde led to the alcohol derived from acyl addition of a butyl group with good enantioselectivity.[467]

Organolithium reagents (RLi), prepared from alkyl halides and lithium metal or by exchange of an alkyl halide with a reactive organolithium (**12-38**) react with aldehydes and ketones by acyl addition to give the alcohol,[468] after hydrolysis. Organolithium reagents are more basic than the corresponding Grignard reagent, which leads to problems of deprotonation in some cases. Organolithium regents are generally more nucleophilic, and can add to hindered ketones with relative ease when compared to the analogous Grignard reagent.[469] These reagents tend to form aggregates, which influences the reactivity and selectivity of the addition reaction.[470] Alkyl, vinyl[471] and aryl organolithium reagents can be prepared and undergo this reaction. Structural variations are also possible. A lithio-epoxide was formed by treating an epoxide with *sec*-butyllithium in the presence of sparteine,[472] or with *n*-butyllithium/TMEDA,[473] and subsequent reaction with an aldehyde led to an epoxy alcohol. Treatment of an allenic silyl enol ether ($R_3SiOC{=}C{=}C$) with *tert*-butyllithium and then a ketone leads to acyl addition of a vinyllithium reagents to give a product with a conjugated ketone in which the C=C is allylic to the alcohol, $R_3SiC({=}O)C({=}CH_2){-}C(OH)R_2$.[474] The dilithio compound $LiC{\equiv}CCH_2Li$ reacts with ketones via acyl addition, and an interesting workup with formaldehyde and then aqueous ammonium chloride gave the homopropargyl alcohol, $R_2C(OH)CH_2C{\equiv}CH$.[475] Aryl sulfonamides can be treated with 2 equivalents of *n*-butyllithium to give an ortho aryllithium which can then be added to an aldehyde to give the resulting diaryl carbinol.[476] A very interesting variation of the fundamental acyl addition reaction of organolithium reagents treated an aldehyde with an acyllithio amide, $LiC({=}O)N(Me)CH_2Me$, to give an α-hydroxy amide derivative.[477]

The reaction of aldehydes or ketones with alkyl and aryl Grignard reagents has also been done without preliminary formation of RMgX, by mixing RX the carbonyl compound and magnesium metal in an ether solvent. This approach

[466] Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* ***2001***, *66*, 4333.

[467] Yong, K.H.; Taylor, N.J.; Chong, J.M. *Org. Lett.* ***2002***, *4*, 3553.

[468] For a study of Hammett ρ values for this reaction, see Maclin, K.M.; Richey Jr., H.G. *J. Org. Chem.* ***2002***, *67*, 4370.

[469] Lecomte, V.; Stéphan, E.; Le Bideau, F.; Jaouen, G. *Tetrahedron* ***2003***, *59*, 2169.

[470] See Fressigné, C.; Maddaluno, J.; Marquez, A.; Giessner-Prettre, C. *J. Org. Chem.* ***2000***, *65*, 8899; Granander, J.; Sott, R.; Hilmersson, G. *Tetrahedron* ***2002***, *58*, 4717.

[471] For a discussion of selectivity, see Spino, C.; Granger, M.-C.; Tremblay, M.-C. *Org. Lett.* ***2002***, *4*, 4735.

[472] Hodgson, D.M.; Reynolds, N.J.; Coote, S.J. *Org. Lett.* ***2004***, *6*, 4187.

[473] Florio, S.; Aggarwal, V.; Salomone, A. *Org. Lett.* ***2004***, *6*, 4191.

[474] Stergiades, I.A.; Tius, M.A. *J. Org. Chem.* ***1999***, *64*, 7547.

[475] Cabezas, J.A.; Pereira, A.R.; Amey, A. *Tetrahedron Lett.* ***2001***, *42*, 6819.

[476] Stanetty, P.; Emerschitz, T. *Synth. Commun.* ***2001***, *31*, 961.

[477] Cunico, R.F. *Tetrahedron Lett.* ***2002***, *43*, 355.

preceded Grignard's work, and is now known as the *Barbier reaction*.[478] The organolithium analog of this process is also known.[479] Yields were generally satisfactory. Carboxylic ester, nitrile, and imide groups in the R are not affected by the reaction conditions.[480] Modern versions of the Barbier reaction employ other metals and/or reaction conditions, and will be discussed in **16-25**. A retro-Barbier reaction has been reported in which a cyclic tertiary alcohol was treated to an excess of bromine and potassium carbonate to give 6-bromo-2-hexanone from 1-methylcyclopentanol.[481] This section will focus on variations of the Barbier reaction that employ Mg or Li derivatives. The reaction of allyl iodide, benzaldehyde and Mg/I_2, for example, gave the acyl addition product 1-phenylbut-3-en-1-ol.[482]

The reaction of RMgX or RLi with α,β-unsaturated aldehydes or ketones can proceed via 1,4-addition as well as normal 1,2-addition (see **15-25**).[483] In general, alkyllithium reagents give less 1,4-addition than the corresponding Grignard reagents.[484] Quinones add Grignard reagents on one or both sides or give 1,4-addition. In a compound containing both an aldehyde and a ketone it is possible to add RMgX chemoselectively to the aldehyde without significantly disturbing the carbonyl of the ketone group[485] (see also, p. 1306). In conjunction with $BeCl_2$, organolithium reagents add to conjugated ketones. In THF, 1,4- addition is observed, but in diethyl ether the 1,2-addition product is formed.[486] Organocerium reagents, generated from cerium chloride ($CeCl_3$ and a Grignard reagent or an organolithium reagent) gives an organometallic reagent that adds chemoselectively.[487] Grignard reagents with a catalytic amount of $InCl_3$ to give a mixture of 1,2- and 1,4-addition products with the 1,4-product predominating, but there was an increased 1,2-addition relative to the uncatalyzed reaction.[488]

As with the reduction of aldehydes and ketones (**19-36**), the addition of organometallic compounds to these substrates can be carried out enantioselectively and diastereoselectively.[489] Chiral secondary alcohols have been obtained with high

[478]Barbier, P. *Compt. Rend.*, ***1899***, *128*, 110. For a review, with Mg, Li, and other metals, see Blomberg, C.; Hartog, F.A. *Synthesis* ***1977***, 18. For a discussion of the mechanism, see Molle, G.; Bauer, P. *J. Am. Chem. Soc.* ***1982***, *104*, 3481. For a list of Barbier-type reactions, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1125–1134.

[479]Guijarro, A.; Yus, M. *Tetrahedron Lett.* ***1993***, *34*, 3487; de Souza-Barboza, J.D.; Pétrier, C.; Luche, J. *J. Org. Chem.* ***1988***, *53*, 1212.

[480]Yeh, M.C.P.; Knochel, P.; Santa, L.E. *Tetrahedron Lett.* ***1988***, *29*, 3887.

[481]Zhang, W.-C.; Li, C.-J. *J. Org.Chem.* ***2000***, *65*, 5831.

[482]Zhang, W.-C.; Li, C.-J. *J. Org. Chem.* ***1999***, *64*, 3230.

[483]For a discussion of the mechanism of this reaction, see Holm, T. *Acta Chem. Scand.* ***1992***, *46*, 985.

[484]An example was given on p. $$$.

[485]Vaskan, R.N.; Kovalev, B.G. *J. Org. Chem. USSR* ***1973***, *9*, 501.

[486]Krief, A.; de Vos, M.J.; De Lombart, S.; Bosret, J.; Couty, F. *Tetrahedron Lett.* ***1997***, *38*, 6295.

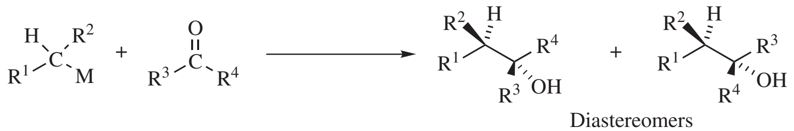
[487]Bartoli, G.; Marcantoni, E.; Petrini, M. *Angew. Chem. Int. Ed.* ***1993***, *32*, 1061; Dimitrov, V.; Bratovanov, S.; Simova, S.; Kostova, K. *Tetrahedron Lett.* ***1994***, *35*, 6713; Greeves, N.; Lyford, L. *Tetrahedron Lett.* ***1992***, *33*, 4759.

[488]Kelly, B.G.; Gilheany; D.G. *Tetrahedron Lett.* ***2002***, *43*, 887.

[489]For reviews, see Solladié, G., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 2, Academic Press, NY, ***1983***, pp. 157–199, 158–183; Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, ***1986***, pp. 160–193; Noyori, R.; Kitamura, M. *Angew. Chem. Int. Ed.* ***1991***, *30*, 49.

enantioselectivity by addition of Grignard and organolithium compounds to aromatic aldehydes, in the presence of optically active amino alcohols as ligands.[490]

Diastereoselective addition[491] has been carried out with achiral reagents and chiral substrates,[492] similar to the reduction shown on p. 1802.[493] Because the attacking atom in this case is carbon, not hydrogen, it is also possible to get diastereoselective addition with an achiral substrate and an optically active reagent.[494] Use of suitable reactants creates, in the most general case, two new stereogenic centers, so the product can exist as two pairs of enantiomers:



Even if the organometallic compound is racemic, it still may be possible to get a diastereoselective reaction; that is, one pair of enantiomers is formed in greater amount than the other.[495]

In some cases, the Grignard reaction can be performed intramolecularly.[496] For example, treatment of 5-bromo-2-pentanone with magnesium and a small amount

[490]Mukaiyama, T.; Soai, K.; Sato, T.; Shimizu, H.; Suzuki, K. *J. Am. Chem. Soc.* ***1979***, *101*, 1455; Mazaleyrat, J.; Cram, D.J. *J. Am. Chem. Soc.* ***1981***, *103*, 4585; Eleveld, M.B.; Hogeveen, H. *Tetrahedron Lett.* ***1984***, *25*, 5187; Schön, M.; Naef, R. *Tetrahedron Asymmetry* ***1999***, *10*, 169; Arvidsson, P.I.; Davidsson, Ö.; Hilmersson, G. *Tetrahedron Asymmetry* ***1999***, *10*, 527.

[491]For a review, see Yamamoto, Y.; Maruyama, K. *Heterocycles* ***1982***, *18*, 357. For a discussion of facial selectivity, see Tomoda, S.; Senju, T. *Tetrahedron* ***1999***, *55*, 3871. See Schulze, V.; Nell, P.G.; Burton, A.; Hoffmann, R.W. *J. Org. Chem.* ***2003***, *68*, 4546.

[492]For a review of cases in which the substrate bears a group that can influence the diastereoselectivity by chelating with the metal, see Reetz, M.T. *Angew. Chem. Int. Ed.* ***1984***, *23*, 556. See also, Keck, G.E.; Castellino, S. *J. Am. Chem. Soc.* ***1986***, *108*, 3847.

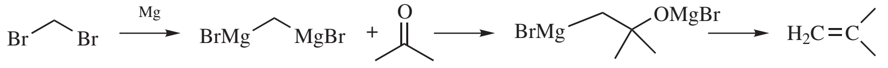
[493]See, for example, Eliel, E.L.; Morris-Natschke, S. *J. Am. Chem. Soc.* ***1984***, *106*, 2937; Reetz, M.T.; Steinbach, R.; Westermann, J.; Peter, R.; Wenderoth, B. *Chem. Ber.* ***1985***, *118*, 1441; Yamamoto, Y.; Matsuoka, K. *J. Chem. Soc., Chem. Commun.* ***1987***, 923; Boireau, G.; Deberly, A.; Abenhaïm, D. *Tetrahedron Lett.* ***1988***, *29*, 2175; Page, P.C.B.; Westwood, D.; Slawin, A.M.Z.; Williams, D.J. *J. Chem. Soc. Perkin Trans. 1* ***1989***, 1158; Soai, K.; Niwa, S.; Hatanaka, T. *Bull. Chem. Soc. Jpn.* ***1990***, *63*, 2129. For examples in which both reactants were chiral, see Roush, W.R.; Halterman, R.L. *J. Am. Chem. Soc.* ***1986***, *108*, 294; Hoffmann, R.W.; Dresely, S.; Hildebrandt, B. *Chem. Ber.* ***1988***, *121*, 2225; Paquette, L.A.; Learn, K.S.; Romine, J.L.; Lin, H. *J. Am. Chem. Soc.* ***1988***, *110*, 879; Brown, H.C.; Bhat, K.S.; Randad, R.S. *J. Org. Chem.* ***1989***, *54*, 1570.

[494]For a review of such reactions with crotylmetallic reagents, see Hoffmann, R.W. *Angew. Chem. Int. Ed.* ***1982***, *21*, 555. For a discussion of the mechanism, see Denmark, S.E.; Weber, E.J. *J. Am. Chem. Soc.* ***1984***, *106*, 7970. For some examples, see Greeves, N.; Pease, J.E. *Tetrahedron Lett.* ***1996***, *37*, 5821; Zweifel, G.; Shoup, T.M. *J. Am. Chem. Soc.* ***1988***, *110*, 5578; Gung, B.W.; Smith, D.T.; Wolf, M.A. *Tetrahedron Lett.* ***1991***, *32*, 13.

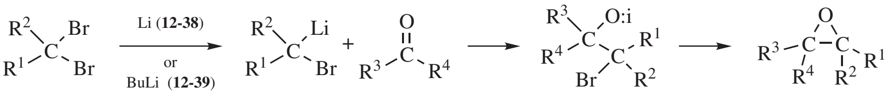
[495]For examples, see Coxon, J.M.; van Eyk, S.J.; Steel, P.J. *Tetrahedron Lett.* ***1985***, *26*, 6121; Mukaiyama, T.; Ohshima, M.; Miyoshi, N. *Chem. Lett.* ***1987***, 1121; Masuyama, Y.; Takahara, J.P.; Kurusu, Y. *Tetrahedron Lett.* ***1989***, *30*, 3437.

[496]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1134–1135.

of mercuric chloride in THF produced 1-methyl-1-cyclobutanol in 60% yield.[497] Other four- and five-membered ring compounds were also prepared by this procedure. Similar closing of five- and six-membered rings was achieved by treatment of a δ- or ε-halocarbonyl compound, not with a metal, but with a dianion derived from nickel tetraphenyporphine.[498]



The *gem*-disubstituted magnesium compounds formed from CH_2Br_2 or CH_2I_2 (**12-38**) react with aldehydes or ketones to give alkenes in moderate-to-good yields.[499] Wittig type reacts also produce alkenes and are discussed in **16-44**. The reaction could not be extended to other *gem*-dihalides. Similar reactions with *gem*-dimetallic compounds prepared with metals other than magnesium have also produced alkenes.[500] An interesting variation is the reaction of methyllithium and CH_2I_2 with an aliphatic aldehyde to give an epoxide,[501] but this reagent reacted with lactones to give a cyclic hemiketal with a pendant iodomethyl unit.[502] Alkylidene oxetanes react with lithium, and then with an aldehyde to give a conjugated ketone.[503] The α,α-dimetallic derivatives of phenyl sulfones ($PhSO_2CM_2R$) (M = Li or Mg) react with aldehydes or ketones $R'COR^2$ to give good yields of the α,β-unsaturated sulfones $PhSO_2CR{=}CR'R^2$,[504] which can be reduced with aluminum amalgam (see **10-67**) or with $LiAlH_4$-$CuCl_2$ to give the alkenes $CHR{=}CR'R^2$.[505] On the other hand, *gem*-dihalides treated with a carbonyl compound and Li or BuLi give epoxides[506] (see also, **16-46**).



[497]Leroux, Y. *Bull. Soc. Chim. Fr.* ***1968***, 359.

[498]Corey, E.J.; Kuwajima, I. *J. Am. Chem. Soc.* ***1970***, *92*, 395. For another method, see Molander, G.A.; McKie, J.A. *J. Org. Chem.* ***1991***, *56*, 4112, and references cited therein.

[499]Bertini, F.; Grasselli, P.; Zubiani, G.; Cainelli, G.*Tetrahedron* ***1970***, *26*, 1281.

[500]For example, see Zweifel, G.; Steele, R.B. *Tetrahedron Lett.* ***1966***, 6021; Cainelli, G.; Bertini, F.; Grasselli, P.; Zubiani, G. *Tetrahedron Lett.* ***1967***, 1581; Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* ***1980***, *53*, 1698; Knochel, P.; Normant, J.F. *Tetrahedron Lett.* ***1986***, *27*, 1039; Barluenga, J.; Fernández-Simón, J.L.; Concellón, J.M.; Yus, M. *J. Chem. Soc., Chem. Commun.* ***1986***, 1665; Okazoe, T.; Takai, K.; Utimoto, K. *J. Am. Chem. Soc.* ***1987***, *109*, 951; Piotrowski, A.M.; Malpass, D.B.; Boleslawski, M.P.; Eisch, J.J. *J. Org. Chem.* ***1988***, *53*, 2829; Tour, J.M.; Bedworth, P.V.; Wu, R. *Tetrahedron Lett.* ***1989***, *30*, 3927; Lombardo, L. *Org. Synth. 65*, 81.

[501]Concellón, J.M.; Cuervo, H.; Fernándex-Fano, R. *Tetrahedron* ***2001***, *57*, 8983.

[502]Bessieres, B.; Morin, C. *Synlett* ***2000***, 1691.

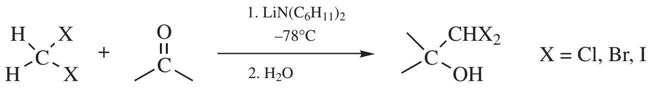
[503]Hashemsadeh, M.; Howell, A.R. *Tetrahedron Lett.* ***2000***, *41*, 1855, 1859.

[504]Pascali, V.; Tangari, N.; Umani-Ronchi, A. *J. Chem. Soc. Perkin Trans. 1* ***1973***, 1166.

[505]Pascali, V.; Umani-Ronchi, A. *J. Chem. Soc., Chem. Commun.* ***1973***, 351.

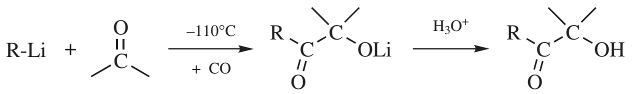
[506]Cainelli, G.; Tangari, N.; Umani-Ronchi, A. *Tetrahedron* ***1972***, *28*, 3009, and references cited therein.

In other uses of *gem*-dihalo compounds, aldehydes and ketones add the CH_2I group [$R_2CO \rightarrow R_2C(OH)CH_2I$] when treated with CH_2I_2 in the presence of SmI_2,[507] and the CHX_2 group when treated with methylene halides and lithium dicyclohexylamide at low temperatures.[508]



A hydroxymethyl group can be added to an aldehyde or ketone with the masked reagent $Me_2((i\text{Pr})O)SiCH_2MgCl$, which with R_2CO gives $R_2C(OH)CH_2$-$Si(O{-}(i\text{Pr}))Me_2$, but with H_2O_2 give 1,2-diols $R_2C(OH)CH_2OH$.[509]

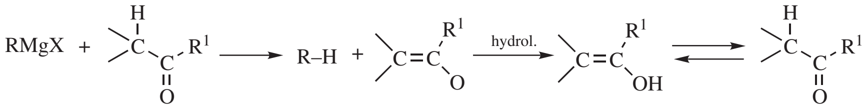
It is possible to add an acyl group to a ketone to give (after hydrolysis) an α-hydroxy ketone.[510] This can be done by adding RLi and CO to the ketone at −110°C:[511]



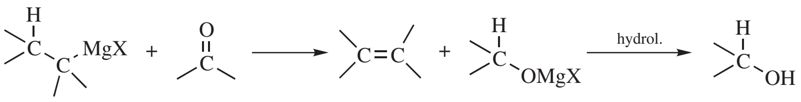
When the same reaction is carried out with carboxylic esters ($R'COOR^2$), α-diketones (RCOCOR′) are obtained.[511]

Most aldehydes and ketones react with most Grignard reagents, but there are several potential side reactions[512] that occur mostly with hindered ketones and with bulky Grignard reagents. The two most important of these are *enolization* and *reduction*. The former requires that the aldehyde or ketone have an α hydrogen, and the latter requires that the Grignard reagent have a β hydrogen:

Enolization



Reduction



[507]Imamoto, T.; Takeyama, T.; Koto, H. *Tetrahedron Lett.* ***1986***, *27*, 3243.

[508]Taguchi, H.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* ***1977***, *50*, 1588.

[509]Tamao, K.; Ishida, N. *Tetrahedron Lett.* ***1984***, *25*, 4245. For another method, see Imamoto, T.; Takeyama, T.; Yokoyama, M. *Tetrahedron Lett.* ***1984***, *25*, 3225.

[510]For a review, see Seyferth, D.; Weinstein, R.M.; Wang, W.; Hui, R.C.; Archer, C.M. *Isr. J. Chem.* ***1984***, *24*, 167.

[511]Seyferth, D.; Weinstein, R.M.; Wang, W. *J. Org. Chem.* ***1983***, *48*, 1144; Seyferth, D.; Weinstein, R.M.; Wang,W.; Hui, R.C. *Tetrahedron Lett.* ***1983***, *24*, 4907.

[512]Lajis, N. Hj.; Khan, M.N.; Hassan, H.A. *Tetrahedron* ***1993***, *49*, 3405.

Enolization is an acid–base reaction (**12-24**) in which a proton is transferred from the α carbon to the Grignard reagent. The carbonyl compound is converted to its enolate anion form, which, on hydrolysis, gives the original ketone or aldehyde. Enolization is important not only for hindered ketones but also for those that have a relatively high percentage of enol form (e.g., β-keto esters). In reduction, the carbonyl compound is reduced to an alcohol (**16-24**) by the Grignard reagent, which itself undergoes elimination to give an alkene. Two other side reactions are condensation (between enolate ion and excess ketone) and Wurtz-type coupling (**10-64**). Such highly hindered tertiary alcohols as triisopropylcarbinol, tri-*tert*-butylcarbinol, and diisopropylneopentylcarbinol cannot be prepared (or can be prepared only in extremely low yields) by the addition of Grignard reagents to ketones, because reduction and/or enolization become prominent.[513] However, these carbinols can be prepared by the use of alkyllithium reagents at $-80°C$[514] because enolization and reduction are much less important.[515] Other methods of increasing the degree of addition at the expense of reduction include complexing the Grignard reagent with $LiClO_4$ or Bu_4N^+ Br^-,[516] or using benzene or toluene instead of ether as solvent.[517] Both reduction and enolization can be avoided by adding $CeCl_3$ to the Grignard reagent (see above).[518]

Another way to avoid complications is to add $(RO)_3TiCl$, $TiCl_4$,[519] $(RO)_3ZrCl$, or $(R_2N)_3TiX$ to the Grignard or lithium reagent. This produces organotitanium or organozirconium compounds that are much more selective than Grignard or organolithium reagents.[520] An important advantage of these reagents is that they do not react with NO_2 or CN functions that may be present in the substrate, as Grignard and organolithium reagents do. The reaction of a β-keto amide with $TiCl_4$, for example, gives a complex that allows selective reaction of the ketone unit with MeMgCl—$CeCl_3$ to give the corresponding alcohol.[521] Premixing an allylic Grignard reagent with $ScCl_3$ prior to reaction with the aldehyde gives direct acyl addition without allylic rearrangement as the major product, favoring the trans-alkene unit.[522]

[513]Whitmore, F.C.; George, R.S. *J. Am. Chem. Soc.* ***1942***, *64*, 1239.

[514]Zook, H.D.; March, J.; Smith, D.F. *J. Am. Chem. Soc.* ***1959***, *81*, 1617; Bartlett, P.D.; Tidwell, T.T. *J. Am. Chem. Soc.* ***1968***, *90*, 4421. See also, Lomas, J.S. *Nouv. J. Chim.*, ***1984***, *8*, 365; Molle, G.; Briand, S.; Bauer, P.; Dubois, J.E. *Tetrahedron* ***1984***, *40*, 5113.

[515]Buhler, J.D. *J. Org. Chem.* ***1973***, *38*, 904.

[516]Chastrette, M.; Amouroux, R. *Chem. Commun.* ***1970***, 470; *Bull. Soc. Chim. Fr.* ***1970***, 4348. See also, Richey Jr., H.G.; DeStephano, J.P. *J. Org. Chem.* ***1990***, *55*, 3281.

[517]Canonne, P.; Foscolos, G.; Caron H.; Lemay, G. *Tetrahedron* ***1982***, *38*, 3563.

[518]Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* ***1989***, *111*, 4392.

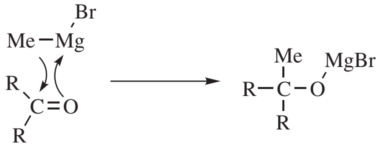
[519]See Reetz, M.T.; Kyung, S.H.; Hüllmann, M. *Tetrahedron* ***1986***, *42*, 2931.

[520]For a monograph, see Reetz, M.T. *Organotitanium Reagents in Organic Synthesis*, Springer, NY, ***1986***. For reviews, see Weidmann, B.; Seebach, D. *Angew. Chem. Int. Ed.* ***1983***, *22*, 31; Reetz, M.T. *Top. Curr. Chem.* ***1982***, *106*, 1.

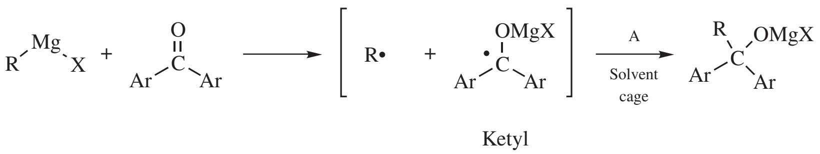
[521]Bartoli, G.; Bosco, M.; Marcantoni, E.; Massaccesi, M.; Rinaldi, S.; Sambri, L. *Tetrahedron Lett.* ***2001***, *42*, 6093.

[522]Matsukawa, S.; Funabashi, Y.; Imamoto, T. *Tetrahedron Lett.* ***2003***, *44*, 1007.

There has been much controversy regarding the mechanism of addition of Grignard reagents to aldehydes and ketones.[523] The reaction is difficult to study because of the variable nature of the species present in the Grignard solution (p. 260) and because the presence of small amounts of impurities in the magnesium seems to have a great effect on the kinetics of the reaction, making reproducible experiments difficult.[524] There seem to be two basic mechanisms, depending on the reactants and the reaction conditions. In one of these, the R group is transferred to the carbonyl carbon with its electron pair. A detailed mechanism of this type has been proposed by Ashby and co-workers,[525] based on the discovery that this reaction proceeds by two paths: one first order in MeMgBr and the other first order in Me_2Mg.[526] According to this proposal, both MeMgBr and Me_2Mg add to the carbonyl carbon, though the exact nature of the step by which MeMgBr or Me_2Mg reacts with the substrate is not certain. One possibility is a four-centered cyclic transition state:[527]



The other type of mechanism is a single electron transfer (SET) process[528] with a ketyl intermediate:[529]



This mechanism, which has been mostly studied with diaryl ketones, is more likely for aromatic and other conjugated aldehydes and ketones than it is for

[523]For reviews, see Holm, T. *Acta Chem. Scand. Ser. B* ***1983***, *37*, 567; Ashby, E.C. *Pure Appl. Chem.* ***1980***, *52*, 545; *Bull. Soc. Chim. Fr.* ***1972***, 2133; *Q. Rev. Chem. Soc.* ***1967***, *21*, 259; Ashby, E.C.; Laemmle, J.; Neumann, H.M. *Acc. Chem. Res.* ***1974***, *7*, 272; Blomberg, C. *Bull. Soc. Chim. Fr.* ***1972***, 2143. For a review of the stereochemistry of the reaction, see Ashby, E.C.; Laemmle, J. *Chem. Rev.* ***1975***, *75*, 521. For a review of the effects of the medium and the cation, see Solv'yanov, A.A.; Beletskaya, I.P. *Russ. Chem. Rev.* ***1987***, *56*, 465.

[524]See, for example, Ashby, E.C.; Neumann, H.M.; Walker, F.W.; Laemmle, J.; Chao, L. *J. Am. Chem. Soc.* ***1973***, *95*, 3330.

[525]Ashby, E.C.; Laemmle, J.; Neumann, H.M. *J. Am. Chem. Soc.* ***1972***, *94*, 5421.

[526]Ashby, E.C.; Laemmle, J.; Neumann, H.M. *J. Am. Chem. Soc.* ***1971***, *93*, 4601; Laemmle, J.; Ashby, E.C.; Neumann, H.M. *J. Am. Chem. Soc.* ***1971***, *93*, 5120.

[527]Tuulmets, A. *Org. React. (USSR)* ***1967***, *4*, 5; House, H.O.; Oliver, J.E. *J. Org. Chem.* ***1968***, *33*, 929; Ashby, E.C.; Yu, S.H.; Roling, P.V. *J. Org. Chem.* ***1972***, *37*, 1918. See also, Billet, J.; Smith, S.G. *J. Am. Chem. Soc.* ***1968***, *90*, 4108; Lasperas, M.; Perez-Rubalcaba, A.; Quiroga-Feijoo, M.L. *Tetrahedron* ***1980***, *36*, 3403.

[528]For a review, see Dagonneau, M. *Bull. Soc. Chim. Fr.* ***1982***, II-269.

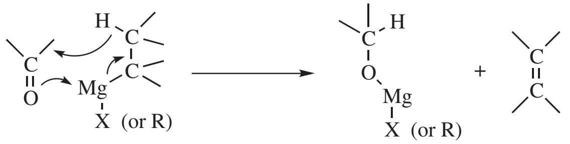
[529]There is kinetic evidence that the solvent cage shown may not be necessary: Walling, C. *J. Am. Chem. Soc.* ***1988***, *110*, 6846.

strictly aliphatic ones. Among the evidence[530] for the SET mechanism are ESR spectra[531] and the fact that

side products are obtained (from dimerization of the ketyl).[532] In the case of addition of RMgX to benzil (PhCOCOPh), esr spectra of two different ketyl radicals were observed, both reported to be quite stable at room temperature.[533] Note that a separate study failed to observe freely defusing radicals in the formation of Grignard reagents.[534] Carbon isotope effect studies with $Ph^{14}COPh$ showed that the rate-determining step with most Grignard reagents is the carbon–carbon bond-forming step (marked *A*), though with allylmagnesium bromide it is the initial electron-transfer step.[535] In the formation of Grignard reagents from bromocyclopropane, diffusing cyclopropyl radical intermediates were found.[536] The concerted versus stepwise mechanism has been probed with chiral Grignard reagents.[537]

Mechanisms for the addition of organolithium reagents have been investigated much less.[538] Addition of a cryptand that binds Li^+ inhibited the normal addition reaction, showing that the lithium is necessary for the reaction to take place.[539]

There is general agreement that the mechanism leading to reduction[540] is usually as follows:



Reduction

[530]For other evidence, see Savin, V.I.; Kitaev, Yu.P. *J. Org. Chem. USSR* ***1975***, *11*, 2622; Ōkubo, M. *Bull. Chem. Soc. Jpn.* ***1977***, *50*, 2379; Ashby, E.C.; Bowers Jr., J.R. *J. Am. Chem. Soc.* ***1981***, *103*, 2242; Holm, T. *Acta Chem. Scand. Ser. B* ***1988***, *42*, 685; Liotta, D.; Saindane, M.; Waykole, L. *J. Am. Chem. Soc.* ***1983***, *105*, 2922; Yamataka, H.; Miyano, N.; Hanafusa, T. *J. Org. Chem.* ***1991***, *56*, 2573.

[531]Fauvarque, J.; Rouget, E. *C. R. Acad. Sci., Ser C*, ***1968***, *267*, 1355; Maruyama, K.; Katagiri, T. *Chem. Lett.* ***1987***, 731, 735; *J. Phys. Org. Chem.* ***1988***, *1*, 21.

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[533]Maruyama, K.; Katagiri, T. *J. Am. Chem. Soc.* ***1986***, *108*, 6263; *J. Phys. Org. Chem.* ***1989***, *2*, 205. See also, Holm, T. *Acta Chem. Scand. Ser. B* ***1987***, *41*, 278; Maruyama, K.; Katagiri, T. *J. Phys. Org. Chem.* ***1991***, *4*, 158.

[534]Walter, R.I. *J. Org. Chem.* ***2000***, *65*, 5014.

[535]Yamataka, H.; Matsuyama, T.; Hanafusa, T. *J. Am. Chem. Soc.* ***1989***, *111*, 4912.

[536]Garst, J.F.; Ungváry, F. *Org. Lett.* ***2001***, *3*, 605.

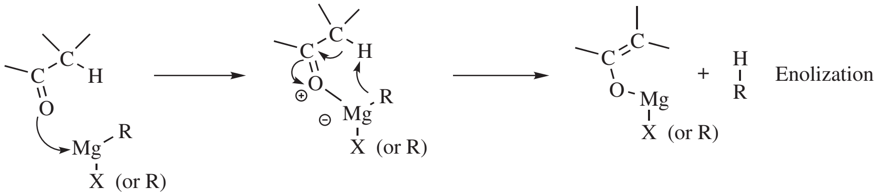
[537]Hoffmann, RW.; Hölzer, B. *Chem. Commun.* ***2001***, 491.

[538]See, for example, Al-Aseer, M.A.; Smith, S.G. *J. Org. Chem.* ***1984***, *49*, 2608; Yamataka, H.; Kawafuji, Y.; Nagareda, K.; Miyano, N.; Hanafusa, T. *J. Org. Chem.* ***1989***, *54*, 4706.

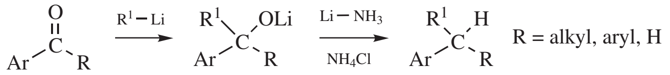
[539]Perraud, R.; Handel, H.; Pierre, J. *Bull. Soc. Chim. Fr.* ***1980***, II-283.

[540]For discussions of the mechanism of reduction, see Singer, M.S.; Salinger, R.M.; Mosher, H.S. *J. Org. Chem.* ***1967***, *32*, 3821; Denise, B.; Fauvarque, J.; Ducom, J. *Tetrahedron Lett.* ***1970***, 335; Cabaret, D.; Welvart, Z. *J. Organomet. Chem.* ***1974***, *80*, 199; Holm, T. *Acta Chem. Scand.* ***1973***, *27*, 1552; Morrison, J.D.; Tomaszewski, J.E.; Mosher, H.S.; Dale, J.; Miller, D.; Elsenbaumer, R.L. *J. Am. Chem. Soc.* ***1977***, *99*, 3167; Okuhara, K. *J. Am. Chem. Soc.* ***1980***, *102*, 244.

There is evidence that the mechanism leading to enolization is also cyclic, but involves prior coordination with magnesium:[541]



Aromatic aldehydes and ketones can be alkylated and reduced in one reaction vessel by treatment with an alkyl- or aryllithium, followed by lithium and ammonia and then by ammonium chloride.[542]

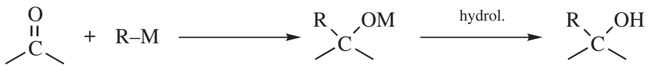


A similar reaction has been carried out with *N,N*-disubstituted amides: $RCONR'_2 \rightarrow RR^2CHNR'_2$.[543]

OS **I**, 188; **II**, 406, 606; **III**, 200, 696, 729, 757; **IV**, 771, 792; **V**, 46, 452, 608, 1058; **VI**, 478, 537, 542, 606, 737, 991, 1033; **VII**, 177, 271, 447; **VIII**, 179, 226, 315, 343, 386, 495, 507, 556; **IX**, 9, 103, 139, 234, 306, 391, 472; **75**, 12; **76**, 214; **X**, 200.

16-25 Addition of Other Organometallics to Aldehydes and Ketones

***O*-Hydro-*C*-alkyl-addition**



A variety of organometallic reagents other than RMgX and RLi add to aldehydes and ketones. A simple example is formation of sodium, or potassium alkyne anions (e.g., RC≡CNa, **16-38**), which undergo acyl addition to ketones or aldehydes to give the propargylic alcohol. For the addition of acetylenic groups, sodium may be the metal used; while vinylic alanes (prepared as in **15-17**) are the reagents of choice for the addition of vinylic groups.[544] A variation includes the use of tetraalkylammonium hydroxide to generate the alkyne anion,[545] and terminal alkynes with CsOH react similarly.[546] A solvent-free reaction was reported that mixed a ketone, a terminal alkyne and potassium *tert*-butoxide.[547] The reagent $Me_3Al/^{-}C{\equiv}CH$

[541]Pinkus, A.G.; Sabesan, A. *J. Chem. Soc. Perkin Trans. 2* ***1981***, 273.

[542]Lipsky, S.D.; Hall, S.S. *Org. Synth.* ***VI***, 537; McEnroe, F.J.; Sha, C.; Hall, S.S. *J. Org. Chem.* ***1976***, *41*, 3465.

[543]Hwang, Y.C.; Chu, M.; Fowler, F.W. *J. Org. Chem.* ***1985***, *50*, 3885.

[544]Newman, H. *Tetrahedron Lett.* ***1971***, 4571. Vinylic groups can also be added with 9-vinylic-9-BBN compounds: Jacob III, P.; Brown, H.C. *J. Org. Chem.* ***1977***, *42*, 579.

[545]Ishikawa, T.; Mizuta, T.; Hagiwara, K.; Aikawa, T.; Kudo, T.; Saito, S. *J. Org. Chem.* ***2003***, *68*, 3702.

[546]Tzalis, D.; Knochel, P. *Angew. Chem. Int. Ed.* ***1999***, *38*, 1463.

[547]Miyamoto, H.; Yasaka, S.; Tanaka, K. *Bull. Chem. Soc. Jpn.* ***2001***, *74*, 185.

Na^+ also adds to aldehydes to give the ethynyl alcohol.[548] Dialkylzinc reagents have been used for the same purpose, and in the presence of a chiral titanium complex the propargylic alcohol was formed with good enantioselectivity.[549] Zinc(II) chloride facilitates the addition of a terminal alkyne to an aldehyde to give a propargylic alcohol.[550] Zinc(II) triflate can also be used for alkyne addition to aldehydes,[551] and in the presence of a chiral ligand leads to good enantioselectivity in the propargyl alcohol product.[552] Terminal alkynes add to aryl aldehydes in the presence of $InBr_3$ and NEt_3[553] or SmI_2.[554] 1-Iodoalkynes react with In metal and an aldehyde to give the propargylic alcohol.[555] Potassium alkynyltrifluoroborates (p. 817) react with aldehydes and a secondary amine, in an ionic liquid, to give a propargylic amine.[556]

Propargylic acetate adds to aldehydes with good anti selectivity in the presence of Et_2Zn and a palladium catalyst.[557] Propargylic bromide add to ketones in the presence of NaI/Dy,[558] In,[559] or Mn/Cr catalyst/TMSCl.[560] Propargylic tin compounds react with aldehydes to give the alcohol, with good antiselectivity.[561]

With other organometallic compounds, active metals, such as alkylzinc reagents,[562] are useful; and compounds such as alkylmercurys do not react. When the reagent is $MeNbCl_4$, ketones (R_2CO) are converted to $R_2C(Cl)Me$.[563]

[548]Joung, M.J.; Ahn, J.H.; Yoon, N.M. *J. Org. Chem.* ***1996***, *61*, 4472.

[549]For a review, see Pu, L. *Tetrahedron* ***2003***, *59*, 9873. For some leading references, see Gao, G.; Moore, D.; Xie, R.-G.; Pu. L. *Org. Lett.*2002, *4*, 4143; Li, Z.-B.; Pu, L. *Org. Lett.* ***2004***, *6*, 1065; Dahmen, S. *Org. Lett.* ***2004***, *6*, 2113; Kamble, R.M.; Singh, V.K. *Tetrahedron Lett.* ***2003***, *44*, 5347; Lu, G.; Li, X.; Chen, G.; Chan, W.L.; Chan, A.S.C. *Tetrahedron Asymmetry* ***2003***, *14*, 449; Kang, Y.-F.; Liu, L.; Wang, R.; Yan, W.-J.; Zhou, Y.-F. *Tetrahedron Asymmetry* ***2004***, *15*, 3155; Lu, G.; Li, X.; Jia, X.; Chan, W.L.; Chan, A.S.C. *Angew. Chem. Int. Ed.* ***2003***, *42*, 5057; Xu, Z.; Wang, R.; Xu, J.; Da, C.-s.; Yan, W.-j.; Chen, C. *Angew. Chem. Int. Ed.* ***2003***, *42*, 5747;.

[550]Jiang, B.; Si, Y.-G. *Tetrahedron Lett.* ***2002***, *43*, 8323

[551]Frantz, D.E.; Fässler, R.; Carreira, E.M. *J. Am. Chem. Soc.* ***2000***, *122*, 1806.

[552]Anand, N.K.; Carreira, E.M. *J. Am. Chem. Soc.* ***2001***, *123*, 9687; Sasaki, H.; Boyall, D.; Carreira, E.M. *Helv. Chim. Acta* ***2001***, *84*, 964; Boyall, D.; Frantz, D.E.; Carreira, E.M. *Org. Lett.* ***2002***, *4*, 2605.; Xu, Z.; Chen, C.; Xu, J.; Miao, M.; Yan, W.; Wang, R. *Org. Lett.* ***2004***, *6*, 1193; Jiang, B.; Chen, Z.; Xiong, W. *Chem. Commun.* ***2002***, 1524. For an example using zinc (II) diflate, see Chen, Z.; Xiong, W.; Jiang, B. *Chem. Commun.* ***2002***, 2098.

[553]Sakai, N.; Hirasawa, M.; Konakahara, T. *Tetrahedron Lett.* ***2003***, *44*, 4171.

[554]Kwon, D.W.; Cho, M.S.; Kim, Y.H. *Synlett* ***2001***, 627.

[555]Augé, J.; Lubin-Germain, N.; Seghrouchni, L. *Tetrahedron Lett.* ***2002***, *43*, 5255.

[556]In bmim BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate: Kabalka, G.W.; Venkataiah, B.; Dong, G. *Tetrahedron Lett.* ***2004***, *45*, 729.

[557]Marshall, J.A.; Adams, N.D. *J. Org. Chem.* ***1999***, *64*, 5201.

[558]Li, Z.; Jia, Y.; Zhou, J. *Synth. Commun.* ***2000***, *30*, 2515.

[559]In the presence of (−)-cinchonidine: Loh, T.-P.; Lin, M.-J.; Tan, K.L. *Tetrahedron Lett.* ***2003***, *44*, 507.

[560]Inoue, M.; Nakada, M. *Org. Lett.* ***2004***, *6*, 2977.

[561]Savall, B.M.; Powell, N.A.; Roush, W.R. *Org. Lett.* ***2001***, *3*, 3057.

[562]For a review with respect to organozinc compounds, see Furukawa, J.; Kawabata, N. *Adv. Organomet. Chem.* ***1974***, *12*, 103. For an example, see Sjöholm, R.; Rairama, R.; Ahonen, M. *J. Chem. Soc., Chem. Commun.* ***1994***, 1217. For a review with respect to organocadmium compounds, see Jones, P.R.; Desio, P.J. *Chem. Rev.* ***1978***, *78*, 491.

[563]Kauffmann, T.; Abel, T.; Neiteler, G.; Schreer, M. *Tetrahedron Lett.* ***1990***, 503.

Furthermore, organotitanium reagents can be made to add chemoselectively to aldehydes in the presence of ketones.[564] Organomanganese compounds are also chemoselective in this way.[565] Aryl halides that have a pendant ketone unit react with a palladium catalyst to give cyclization via acyl addition.[566] Chiral amides react with aldehydes in the presence of $TiCl_4$ to give syn-selective addition products,[567] and titanium-catalyzed enantioselective additions are known.[568] An alkene-ketone, where the alkene is a vinyl bromide, reacted with $CrCl_2/NiCl_2$ to give a vinyl organometallic, which cyclized to generate a cyclic allylic alcohol with the double bond within the ring.[569] Aryl halides react with a nickel complex under electrolytic conditions to add the aryl group to aldehydes.[570] The C-3 position of an indole adds to aldehydes in the presence of a palladium catalyst.[571] The addition of trifluoromethyl to an aldehyde was accomplished photochemically using CF_3I and $(Me_2N)_2C{=}C(NMe_2)_2$.[572] α-Iodo phosphonate esters react with aldehydes and SmI_2 to give a β-hydroxy phosphonate ester.[573]

Dialkylzinc compounds react with aldehydes to give the secondary alcohol, and R_3ZnLi reagents also add R to a carbonyl.[574] Dimethylzinc and diethylzinc are probably the most common reagents. An intramolecular version is possible by reaction an allene-aldehyde with dimethylzinc. Addition to the allene in the presence of a nickel catalyst[575] or a $CeCl_3$ catalyst[576] is followed by addition of the intermediate organometallic to the aldehyde to give the cyclic product. Aryl halides react with Zn–Ni complexes to give acyl addition of the aryl group to an aldehyde.[577] The reaction of an allylic halide and Zn[578] or Zn/TMSCl[579] leads to acyl addition of aldehydes.

[564]Reetz, M.T. *Organotitanium Reagents in Organic Synthesis*, Springer, NY, ***1986*** (monograph), pp. 75–86. See also, Reetz, M.T.; Maus, S. *Tetrahedron* ***1987***, *43*, 101; Kim, S.-H.; Rieke, R.D. *Tetrahedron Lett.* ***1999***, *40*, 4931.

[565]Cahiez, G.; Figadere, B. *Tetrahedron Lett.* ***1986***, *27*, 4445. For other organometallic reagents with high selectivity towards aldehyde functions, see Kauffmann, T.; Hamsen, A.; Beirich, C. *Angew. Chem. Int. Ed.* ***1982***, *21*, 144; Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* ***1983***, *24*, 5281; Soai, K.; Watanabe, M.; Koyano, M. *Bull. Chem. Soc. Jpn.* ***1989***, *62*, 2124.

[566]Quan, L.G.; Lamrani, M.; Yamamoto, Y. *J. Am. Chem. Soc.* ***2000***, *122*, 4827.

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[572]Aït-Mohand, S.; Takechi, N.; Médebielle, M.; Dolbier Jr., W.R. *Org. Lett.* ***2001***, *3*, 4271.

[573]Orsini, F.; Caselli, A. *Tetrahedron Lett.* ***2002***, *43*, 7255.

[574]For a discussion of the electronic and steric effects, see Musser, C.A.; Richey, Jr., H.G. *J. Org. Chem.* ***2000***, *65*, 7750. For a kinetic study of Et3ZnLi and di-*tert*-butyl ketone, see Maclin, K.M.; Richey, Jr., H.G. *J. Org. Chem.* ***2002***, *67*, 4602.

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[576]Fischer, S.; Groth, U.; Jeske, M.; Schütz, T. *Synlett* ***2002***, 1922.

[577]Majumdar, K.K.; Cheng, C.-H. *Org. Lett.* ***2000***, *2*, 2295.

[578]Yavari, I.; Riazi-Kermani, F. *Synth. Commun.* ***1995***, *25*, 2923; Ranu, B.C.; Majee, A.; Das, A.R. *Tetrahedron Lett.* ***1995***, *36*, 4885; Durant, A.; Delplancke, J.-L.; Winand, R.; Reisse, J. *Tetrahedron Lett.* ***1995***, *36*, 4257; Felpin, F.-X.; Bertrand, M.-J.; Lebreton, J. *Tetrahedron* ***2002***, *58*, 7381.

[579]Ito, T.; Ishino, Y.; Mizuno, T.; Ishikawa, A.; Kobyashi, J.-i. *Synlett* ***2002***, 2116.

Lithium dimethylcopper (Me_2CuLi) reacts with aldehydes[580] and with certain ketones[581] to give the expected alcohols. The RCu(CN)ZnI reagents also react with aldehydes, in the presence of BF_3–etherate, to give secondary alcohols. Vinyltellurium compound react with BF_3•OEt_2 and cyano cuprates [R(2-thienyl)CuCN-Li_2] to give a reagent that adds 1,2- to the carbonyl of a conjugated ketone.[582] Vinyl tellurium compounds also react with *n*-butyllithium to give a reagent that adds to nonconjugated ketones.[583]

Many methods have been reported for the addition of allylic groups,[584] including enantioselective reactions.[585] One of the most common methods is the Barbier reaction, employing metals and metal compounds other than Mg or Li, although the method is not limited to allylic compounds. Allyl indium compounds[586] add to aldehydes or ketones in various solvents.[587] Indium metal is used for the acyl addition of allylic halides with a variety of aldehydes and ketones, including aliphatic aldehydes,[588] aryl aldehydes[589] and α-keto esters.[590] Indium reacts with allylic bromides and ketones in water[591] and in aqueous media. Elimination of the homoallylic alcohol to a conjugated diene can accompany the addition in some cases.[592] The reaction of a propargyl halide, In, and an aldehyde in aq. THF leads to an allenic alcohol.[593] The reaction of benzaldehyde with a propargylic bromide, indium metal and water give the alcohol.[594] Allyl bromide reacts with Mn/TMSCl and an In catalyst in water to give the homoallylic

[580]Barreiro, E.; Luche, J.; Zweig, J.S.; Crabbé, P. *Tetrahedron Lett.* ***1975***, 2353; Zweig, J.S.; Luche; Barreiro, E.; Crabbé, P. *Tetrahedron Lett.* ***1975***, 2355; Reetz, M.T.; Rölfing, K.; Griebenow, N. *Tetrahedron Lett.* ***1994***, *35*, 1969.

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[582]Araújo, M.A.; Barrientos-Astigarraga, R.E.; Ellensohn, R.M.; Comasseto, J.V. *Tetrahedron Lett.* ***1999***, *40*, 5115.

[583]Dabdoub, M.J.; Jacob, R.G.; Ferreira, J.T.B.; Dabdoub, V.B.; Marques, F.de.A. *Tetrahedron Lett.* ***1999***, *40*, 7159.

[584]For a list of reagents and references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1156–1170. For a discussion of a deuterium kinetic isotope effect in the addition of allylic reagents to benzaldehyde, see Gajewski, J.J.; Bocian, W.; Brichford, N.L.; Henderson, J.L. *J. Org. Chem.* ***2002***, *67*, 4236.

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[586]For a review, see Cintas, P. *Synlett* ***1995***, 1087.

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[589]Khan, F.A.; Prabhudas, B. *Tetrahedron* ***2000***, *56*, 7595.

[590]Loh, T.-P.; Huang, J.-M.; Xu, K.-C.; Goh, S.-H.; Vittal, J.J. *Tetrahedron Lett.* ***2000***, *41*, 6511; Kumar, S.; Kaur, P.; Chimni, S.S. *Synlett* ***2002***, 573.

[591]Chan, T.H.; Yang, Y. *J. Am. Chem. Soc.* ***1999***, *121*, 3228; Paquette, L.A.; Bennett, G.D.; Isaac, M.B.; Chhatriwalla, A. *J. Org. Chem.* ***1998***, *63*, 1836; Li, X.-R.; Loh, T.-P. *Tetrahedron Asymmetry* ***1996***, *7*, 1535; Isaac, M.B.; Chan, T.-H. *Tetrahedron Lett.* ***1995***, *36*, 8957.

[592]Kumar, V.; Chimni, S.; Kumar, S. *Tetrahedron Lett.* ***2004***, *45*, 3409.

[593]Lin, M.-J.; Loh, T.-P. *J. Am. Chem. Soc.* ***2003***, *125*, 13042.

[594]Lu, W.; Ma, J.; Yang, Y.; Chan, T.H. *Org. Lett.* ***2000***, *2*, 3469.

alcohols from aldehydes.[595] When allyl iodide is mixed with In and TMSCl, reaction with a conjugated ketone proceed by 1,4-addition, but in the presence of 10% CuI, the major product is that of 1,2-addition.[596] The reaction with indium is compatible with the presence of a variety of other functional groups in the molecule, including phosphonate,[597] propargylic sulfides.[598] Ethyl α-bromoacetate reacts with aldehydes using In with ultrasound.[599] Vinyl epoxides can be added to aldehydes using InI and a palladium catalyst,[600] and vinyl acetates react with indium metal to give a reactive intermediate that adds to the carbonyl of aldehydes.[601] A tandem reaction has been reported in which a bis(indium) reagent, $Br_2InC(=CH_2)–C(=CH_2)InBr_2$, reacts with 2 equivalents of an aldehyde in the presence of ZnF_2 to give a 3-hexyne-1,6-diol derivative.[602] Alkyl halides react with Zn/Cu and an InCl catalyst, in the presence of 0.07 *M* $Na_2Cr_2O_7$ to give an intermediate that adds to aldehydes.[603] Analogous to aldehydes, 1,1-diacetates react with In and allyl bromide in aq. THF to give a homoallylic acetate,[604] as do dimethyl ketals.[605] Allylic alcohols react with InI and a nickel catalyst to give acyl addition of an allylic group to an aldehyde, giving the homoallylic alcohol.[606]

Another important metal for Barbier-type reaction is samarium. Allyl bromide reacts with a ketone and Sm to give the homoallylic alcohol.[607] Samarium compounds, such as SmI_2,[608] can also be used with allylic halides.

Allyltin compounds readily add to aldehydes and ketones.[609] Allylic bromides react with tin to generate the organometallic *in situ*, which then adds to aldehydes.[610] Allylic chlorides react with aldehydes in the presence of ditin compounds such as $Me_3Sn–SnMe_3$ and a palladium catalyst.[611] Allyltrialkyltin compounds[612]

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603Keh, C.C.K.; Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* ***2003***, *125*, 4062.

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605Kwon, J.S.; Pae, A.N.; Choi, K.I.; Koh, H.Y.; Kim, Y.; Cho, Y.S. *Tetrahedron Lett.* ***2001***, *42*, 1957.

606Hirashita, T.; Kambe, S.; Tsuji, H.; Omori, H.; Araki, S. *J. Org. Chem.* ***2004***, *69*, 5054.

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and tetraallyltin react with aldehydes or ketones in the presence of BF_3–etherate,[613] $Cu(OTf)_2$,[614] $CeCl_3$ with NaI,[615] $Bi(OTf)_3$,[616] PbI_2,[617] AgOTf,[618] $Cd(ClO_4)_2$,[619] SnX_2,[620] Ti (IV),[621] $NbCl_5$,[622] $Zr(O\textit{t}\text{-}Bu)_4$,[623] or $La(OTf)_3$.[624] Tetraallyltin reacts via 1,2-addition to conjugated ketones in refluxing methanol.[625] Aluminum catalysts, such as MABR, facilitate addition of allyltributyltin to aldehydes.[626] Selectfluor has been used to induce 1,2-addition of the allyl group of allyltributyltin to a conjugated aldehyde.[627] Allyltributyltin reacts with aldehydes in the presence of aqueous trifluoromethanesulfonic acid to give the homoallylic alcohol.[628] Tetraallyltin reacts with aldehydes in ionic liquids[629] and on wet silica,[630] and allyltributyltin adds to aldehydes in ionic liquids with $InCl_3$.[631] Tetraallyltin adds to ketones or aldehydes to give homoallylic alcohols with good enantioselectivity in the presence of a chiral titanium complex.[632] Allylic alcohols and homoallylic alcohols add to aldehydes in the presence of $Sn(OTf)_2$[633] In/$InCl_3$,[634] or with a rhodium catalyst.[635] Vinyltin regents, such as (2-butadiene)tributyltin, react with aldehydes in the presence of $SnCl_4$ and 3 equivalents of DMF to

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give the dienyl alcohol.[636] Allenyl tin compounds ($CH_2{=}C{=}CHSnBu_3$) also react with aldehydes in the presence of $BF_3{\bullet}OEt_2$ to give a 2-dienyl alcohol.[637] The tin compound can be prepared *in situ* using an α-iodo ketone with an aldehyde and Bu_2SnI_2—LiI.[638] A similar addition occurs with $(allyl)_2SnBr_2$ in water.[639] Asymmetric induction has been reported.[640] The use of a chiral rhodium[641] or titanium[642] catalyst leads to enantioselective addition of allyltributyltin to aldehydes. Allyltributyltin reacts with aldehydes in the presence of $SiCl_4$ and a chiral phosphoramide to give the homoallylic alcohol with moderate enantioselectivity.[643] It is noted that tetraallyl germanium adds to aldehydes in a similar manner in the presence of a $Sc(OTf)_3$ catalyst.[644]

A variety of other allylic metal compounds add to aldehydes or ketones.[645] A variety of alkyl and allylic halides add to aldehydes or ketones in the presence of metals or metal compounds; the metal or compounds based on Ti,[646] Mn,[647] Fe,[648] Ga,[649]

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Ge,[650] Zr,[651] Nb,[652] Cd,[653] Sn,[654] Sb,[655] Te,[656] Ba,[657] Ce,[658] Nd,[659] Hg,[660] Bi,[661] and Pb.[662] In addition, $BiCl_3/NaBH_4$,[663] Mg—$BiCl_3$,[664] and $CrCl_2/NiCl_2$,[665] have been used. Allylic alcohols have been converted to organometallic reagents with diethyl zinc and a palladium catalyst[666] or a ruthenium catalyst[667] leading to the homoallylic alcohol upon reaction with an aldehyde. A chiral Cr/Mn complex has been used with allylic bromides in conjunction with trimethylsilyl chloride.[668] Reagents of the type R—Yb have been prepared from RMgX.[669] Vinyl bromides react with $NiBr_2/CrCl_3$/TMSCl to give a reagent that adds to aldehydes to give the allylic alcohol.[670] Vinyl complexes generated from alkynes and SmI_2 add intramolecularly, and eight-membered rings have been formed in this way.[671] Allylic alcohols add to aldehydes in some cases, using $SnCl_2$ and a palladium catalyst.[672] Glyoxal reacted with 2 equivalents of allyl bromide and $SnCl_2$ with KI in water, to give the bis-homoallylic alcohol oct-1,7-diene-4,5-diol.[673] The alkyl group of trialkyl aluminum compounds such as $AlEt_3$ add to aldehydes, enantioselectively in the presence of chiral transition-metal complexes.[674] Certain functional groups (COOEt, $CONMe_2$, CN) can be present in the R group when

[650]Hashimoto, Y.; Kagoshima, H.; Saigo, K. *Tetrahedron Lett.* ***1994***, *35*, 4805.

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[656]For an example using a cyclopropylcarbinyl tosylate and an allyl surrogate, see Avilov, D.V.; Malasare, M.G.; Arslancan, E.; Dittmer, D.L. *Org. Lett.* ***2004***, *6*, 2225.

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[659]Evans, W.J.; Workman, P.S.; Allen, N.T. *Org. Lett.* ***2003***, *5*, 2041.

[660]Chan, T.H.; Yang, Y. *Tetrahedron Lett.* ***1999***, *40*, 3863.

[661]Miyamoto, H.; Daikawa, N.; Tanaka, K. *Tetrahedron Lett.* ***2003***, *44*, 6963; Wada, S.; Hayashi, N.; Suzuki, H. *Org. Biomol. Chem.* ***2003***, *1*, 2160; Smith, K.; Lock, S.; El-Hiti, G.A.; Wada, M.; Miyoshi, N. *Org. Biomol. Chem.* ***2004***, *2*, 935; Xu, X.; Zha, Z.; Miao, Q.; Wang, Z. *Synlett* ***2004***, 1171.

[662]Zhou, J.-Y.; Jia, Y.; Sun, G.-F.; Wu, S.-H. *Synth. Commun.* ***1997***, *27*, 1899.

[663]Ren, P.-D.; Shao, D.; Dong, T.-W. *Synth. Commun.* ***1997***, *27*, 2569.

[664]Wada, M.; Fukuma, T.; Morioka, M.; Takahashi, T.; Miyoshi, N. *Tetrahedron Lett.* ***1997***, *38*, 8045.

[665]Taylor, R.E.; Ciavarri, J.P. *Org. Lett.* ***1999***, *1*, 467.

[666]Kimura, M.; Shimizu, M.; Shibata, K.; Tazoe, M.; Tamaru, Y. *Angew. Chem. Int. Ed.* ***2003***, *42*, 3392.

[667]Wang, M.; Yang, X.-F.; Li, C.-J. *Eur. J. Org. Chem.* ***2003***, 998.

[668]Inoue, M.; Suzuki, T.; Nakada, M. *J. Am. Chem. Soc.* ***2003***, *125*, 1140.

[669]Matsubara, S.; Ikeda, T.; Oshima, K.; Otimoto, K. *Chem. Lett.* ***2001***, 1226.

[670]Kuroboshi, M.; Tanaka, M.; Kishimoto, S.; Goto, K.; Mochizuki, M.; Tanaka, H. *Tetrahedron Lett.* ***2000***, *41*, 81.

[671]Hölemann, A.; Reissig, H.-U. *Synlett* ***2004***, 2732.

[672]Márquez, F.; Llebaria, A.; Delgado, A. *Tetrahedron Asymmetry* ***2001***, *12*, 1625.

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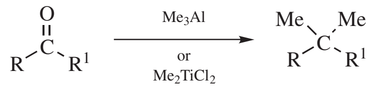
[674]Lu, J.-F.; You, J.-S.; Gau, H.-M. *Tetrahedron Asymmetry* ***2000***, *11*, 2531.

organotin reagents $RSnEt_3$ are added to aldehydes.[675] Trimethylaluminum[676] and dimethyltitanium dichloride[677] exhaustively methylate ketones to give *gem*-dimethyl compounds[678] (see also **10-63**):



The titanium reagent also dimethylates aromatic aldehydes.[679] Triethylaluminum reacts with aldehydes, however, to give the mono-ethyl alcohol, and in the presence of a chiral additive the reaction proceeds with good asymmetric induction.[680] A complex of Me_3Ti•MeLi has been shown to be selective for 1,2-addition with conjugated ketones, in the presence of nonconjugated ketones.[681] In other variations, the organometallic reagent is generated *in situ*. 1,4-Dimethoxybenzene reacts with ethyl glyoxylate (EtO_2C—CHO) in the presence of 5% $Yb(OTf)_3$, to give the alcohol formed by addition of the aryl group to the aldehyde unit.[682]

High ee values have also been obtained with organometallics,[683] including organotitanium compounds (methyl, aryl, allylic) in which an optically active ligand is coordinated to the titanium,[684] allylic boron compounds, and organozinc compounds. As for the organozinc reagents, very high enantioselection was obtained from R_2Zn reagents (R = alkyl)[685] and aromatic[686] aldehydes by the use of a small

[675]Kashin, A.N.; Tulchinsky, M.L.; Beletskaya, I.P. *J. Organomet. Chem.* ***1985***, *292*, 205.

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[677]Reetz, M.T.; Westermann, J.; Kyung, S. *Chem. Ber.* ***1985***, *118*, 1050.

[678]For the *gem*-diallylation of anhydrides, with an indium reagent, see Araki, S.; Katsumura, N.; Ito, H.; Butsugan, Y. *Tetrahedron Lett.* ***1989***, *30*, 1581.

[679]Reetz, M.T.; Kyung, S. *Chem. Ber.* ***1987***, *120*, 123.

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[681]Markó, I.E.; Leung, C.W. *J. Am. Chem. Soc.* ***1994***, *116*, 371.

[682]Zhang, W.; Wang, P.G. *J. Org. Chem.* ***2000***, *65*, 4732.

[683]For examples involving other organometallic compounds, see Abenhaïm, D.; Boireau, G.; Deberly, A. *J. Org. Chem.* ***1985***, *50*, 4045; Minowa, N.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 3697; Takai, Y.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* ***1990***, *55*, 1707.

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[685]For a discussion of transition states in the amino alcohol promoted reaction, see Rasmussen, T.; Norrby, P.-O. *J. Am. Chem. Soc.* ***2001***, *123*, 2464.

[686]For catalysts that are also successful for aliphatic aldehydes, see Takahashi, H.; Kawakita, T.; Yoshioka, M.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* ***1989***, *30*, 7095; Tanaka, K.; Ushio, H.; Suzuki, H. *J. Chem. Soc., Chem. Commun.* ***1989***, 1700; Soai, K.; Yokoyam, S.; Hayasaka, T. *J. Org. Chem.* ***1991***, *56*, 4264.

amount of various catalysts.[687] The enantioselectivity is influenced by additives, such as LiCl.[688] Silica-immobilized chiral ligands[689] can be used in conjunction with dialkylzinc reagents, and polymer-supported ligands have been used.[690]. Chiral dendritic titanium catalysts have been used to give moderate enantioselectivity.[691]

Enantioselective reaction of a carbonyl with a dialkylzinc is possible when other functional groups are present in the molecule. Examples include keto esters.[692] An enzyme-mediated addition of dialkylzinc reagents to aldehydes has also been reported.[693] When benzaldehyde was treated with Et_2Zn in the presence of the optically active catalyst 1-piperidino-3,3-dimethyl-2-butanol, a surprising result was obtained. Although the catalyst had only 10.7% excess of one enantiomer, the

[687]For a review, see Pu, L.; Yu, H.-B. *Chem. Rev.* ***2001***, *101*, 757. See also, Richmond, M.I.; Seto, C.T. *J. Org. Chem.* ***2003***, *68*, 7505; Sprout, C.M.; Seto, C.T. *J. Org. Chem.* ***2003***, *68*, 7788; Nugent, W.A. *Org. Lett.* ***2002***, *4*, 2133; García, C.; Walsh, P.J. *Org. Lett.* ***2003***, *5*, 3641; Kang, S.-W.; Ko, D.-H.; Kim, K.H.; Ha, D.-C. *Org. Lett.* ***2003***, *5*, 4517; Mao, J.; Wan, B.; Wang, R.; Wu, F.; Lu, S. *J. Org. Chem.* ***2004***, *69*, 9123; Superchi, S.; Giorgio, E.; Scafato, P.; Rosini, C. *Tetrahedron Asymmetry* ***2002***, *13*, 1385; Bastin, S.; Ginj, M.; Brocarrd, J.; Pélinski, L.; Novogrocki, G. *Tetrahedron Asymmetry* ***2003***, *14*, 1701; Joshi, S.N.; Malhotra, S.V. *Tetrahedron Asymmetry* ***2003***, *14*, 1763; Prieto, O.; Ramón, D.J.; Yus, M. *Tetrahedron Asymmetry* ***2003***, *14*, 1955; Lesma, G.; Danieli, B.; Passarella, D.; Sacchetti, A.; Silovani, A. *Tetrahedron Asymmetry* ***2003***, *14*, 2453; Danilova, T.I.; Rozenberg, V.I.; Starikova, Z.A.; Bräse, S. *Tetrahedron Asymmetry* ***2004***, *15*, 223; Scarpi, D.; Lo Galbo, F.; Occhiato, E.G.; Guarna, A. *Tetrahedron Asymmetry* ***2004***, *15*, 1319; Funabashi, K.; Jachmann, M.; Kanai, M.; Shibasaki, M. *Angew. Chem. Int. Ed.* ***2003***, *42*, 5489; Lake, F.; Moberg, C. *Eur. J. Org. Chem.* ***2002***, 3179; Reddy, K.S.; Solà, L.; Huang, W.-S.; Pu, L. *J. Org. Chem.* ***1999***, *64*, 4222; Paleo, M.R.; Cabeza, I.; Sardina, F.J. *J. Org. Chem.* ***2000***, *65*, 2108; Yang, L.; Shen, J.; Da, C.; Wang, R.; Choi, M.C.K.; Yang, L.; Wong, K.-y. *Tetrahedron Asymmetry* ***1999***, *10*, 133; Shi, M.; Jiang, J.-K. *Tetrahedron Asymmetry* ***1999***, *10*, 1673; Kawanami, Y.; Mitsuie, T.; Miki, M.; Sakamoto, T.; Nishitani, K. *Tetrahedron* ***2000***, *56*, 175; Hanyu, N.; Aoki, T.; Mino, T.; Sakamoto, M.; Fujita, T. *Tetrahedron Asymmetry* ***2000***, *11*, 2971; Arroyo, N.; Haslinger, U.; Mereiter, K.; Widhalm, M. *Tetrahedron Asymmetry* ***2000***, *11*, 4207; Jimeno, C.; Moyano, A.; Pericàs, M.A.; Riera, A. *Synlett* ***2001***, 1155; Hermsen, P.J.; Cremers, J.G.O.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* ***2001***, *42*, 4243; Xu, Q.; Wang, H.; Pan, X.; Chan, A.S.C.; Yang, T.-k. *Tetrahedron Lett.* ***2001***, *42*, 6171; Yang, X.-w.; Shen, J.-h.; Da, C.-s.; Wang, H.-s.; Su, W.; Liu, D.-x.; Wang, R.; Choi, M.C.K.; Chan, A.S.C. *Tetrahedron Lett.* ***2001***, *42*, 6573; Ohga, T.; Umeda, S.; Kawanami, Y. *Tetrahedron* ***2001***, *57*, 4825; Zhao, G.; Li, X.-G.; Wang, X.-R. *Tetrahedron Asymmetry* ***2001***, *12*, 399; You, J.-S.; Shao, M.-Y.; Gau, H.-M. *Tetrahedron Asymmetry* ***2001***, *12*, 2971; Priego, J.; Mancheño, O.G.; Cabrera, S.; Carretero, J.C. *Chem. Commun.* ***2001***, 2026; Bolm, C.; Kesselgruber, M; Hermanns, N.; Hildebrand, J.P.; Raabe, G. *Angew. Chem. Int. Ed.* ***2001***, *40*, 1488; Wipf, P.; Wang, X. *Org. Lett.* ***2002***, *4*, 1197; Braga, A.L.; Milani, P.; Paixão, M.W.; Zeni, G.; Rodrigues, O.E.D.; Alves, E.F. *Chem. Commun.* ***2004***, 2488; Sibi, M.P.; Stanley, L.M. *Tetrahedron Asymmetry* ***2004***, *15*, 3353; Tseng, S.-L.; Yang, T.-K. *Tetrahedron Asymmetry* ***2004***, *15*, 3375; Harada, T.; Kanda, K.; Hiraoka, Y.; Marutani, Y.; Nakatsugawa, M. *Tetrahedron Asymmetry* ***2004***, *15*, 3879; Casey, M.; Smyth, M.P. *Synlett* ***2003***, 102.

[688]Sosa-Rivadeneyra, M.; Muñoz-Muñiz, O.; de Parrodi, C.A.; Quintero, L.; Juaristi, E. *J. Org. Chem.* ***2003***, *68*, 2369; García, C.; La Rochelle, L.K.; Walsh, P.J. *J. Am. Chem. Soc.* ***2002***, *124*, 10970; Priego, J.; Mancheño, O.G.; Cabrera, S.; Carretero, J.C. *J. Org. Chem.* ***2002***, *67*, 1346.

[689]Fraile, J.M.; Mayoral, J.A.; Servano, J.; Pericàs, M.A.; Solà, L.; Castellnou, D. *Org. Lett.* ***2003***, *5*, 4333.

[690]Sung, D.W.L.; Hodge, P.; Stratford, P.W. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 1463; Lipshutz, B.H.; Shin, Y.-J. *Tetrahedron Lett.* ***2000***, *41*, 9515.

[691]Fan, O.-H.; Liu, G.-H.; Chen, X.-M.; Deng, G.-J.; Chan, A.S.C. *Tetrahedron Asymmetry* ***2001***, *12*, 1559.

[692]DiMauro, E.F.; Kozlowski, M.C. *Org. Lett.* ***2002***, *4*, 3781.

[693]Yang, W.K.; Cho, B.T. *Tetrahedron Asymmetry* ***2000***, *11*, 2947.

product PhCH(OH)Me had an ee of 82%.[694] When the catalyst ee was increased to 20.5%, the product ee rose to 88%. The question is, how could a catalyst produce a product with an ee much higher than itself? One possible explanation[695] is that (*R*) and (*S*) molecules of the catalyst form a complex with each other, and that only the uncomplexed molecules are actually involved in the reaction. Since initially the number of (*R*) and (*S*) molecules was not the same, the (*R/S*) ratio of the uncomplexed molecules must be considerably higher (or lower) than that of the initial mixture.

Although organoboranes do not generally add to aldehydes and ketones,[696] allylic boranes are exceptions.[697] When they add, an allylic rearrangement always takes place. Allylic rearrangements take place with the other reagents as well. The use of a chiral catalyst leads to asymmetric induction[698] and chiral allylic boranes have been prepared.[699] It is noted that chloroboranes (R_2BCl) react with aldehydes via acyl addition of the alkyl group, giving the corresponding alcohol after treatment with water.[700] A variation is the reaction of a diketone, where one carbonyl is conjugated. Treatment with catecholborane gives addition to the conjugated ketone, and subsequent cyclization of the resulting organometallic at the nonconjugated ketone gives a cyclic alcohol with a pendant ketone unit, after treatment with methanol.[701] In the presence of ruthenium complexes, $RB(OH)_2$ and arylboronic acids $ArB(OH)_2$ (p. 815) add to aldehydes to give the corresponding alcohol.[702] Polymer-bound aryl borates add an aryl group to aldehydes in the presence of a rhodium catalyst.[703] An intramolecular version of the phenylboronic acid-induced reaction is known, where a molecule with ketone and conjugated ketone units is converted to a cyclic alcohol using a chiral rhodium catalyst.[704] Allylic boronates add to aldehydes.[705]

[694]Oguni, N.; Matsuda, Y.; Kaneko, T. *J. Am. Chem. Soc.* ***1988***, *110*, 7877.

[695]See Wynberg, H. *Chimia* ***1989***, *43*, 150.

[696]For another exception, involving a vinylic borane, see Satoh, Y.; Tayano, T.; Hara, S.; Suzuki, A. *Tetrahedron Lett.* ***1989***, *30*, 5153.

[697]For reviews, see Hoffmann, R.W.; Niel, G.; Schlapbach, A. *Pure Appl. Chem.* ***1990***, *62*, 1993; Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, pp. 310–318. For a review of allylic boranes, see Bubnov, Yu.N. *Pure Appl. Chem.* ***1987***, *21*, 895. For an example that proceeds with asymmetric induction, see Buynak, J.D.; Geng, B.; Uang, S.; Strickland, J.B. *Tetrahedron Lett.* ***1994***, *35*, 985.

[698]Ishiyama, T.; Ahiko, T.-a.; Miyaura, N. *J. Am. Chem. Soc.* ***2002***, *124*, 12414; Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* ***2004***, *126*, 8910.

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[700]Kabalka, G.W.; Wu, Z.; Ju, Y. *Tetrahedron* ***2001***, *57*, 1663; Kabalka, G.W.; Wu, Z.; Ju, Y. *Tetrahedron* ***2002***, *58*, 3243.

[701]Huddleston, R.R.; Cauble, D.F.; Krische, M.J. *J. Org. Chem.* ***2003***, *68*, 11.

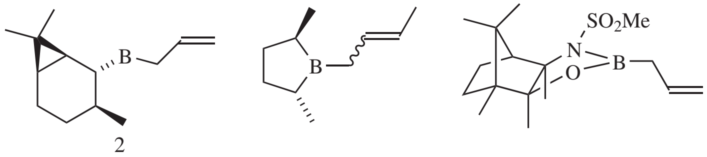
[702]Ueda, M.; Miyaura, N. *J. Org. Chem.* ***2000***, *65*, 4450 and references cited therein.

[703]Pourbaix, C.; Carreaux, F.; Carboni, B. *Org. Lett.* ***2001***, *3*, 803; Rudolph, J.; Schmidt, F.; Bolm, C. *Synthesis* ***2005***, 840.

[704]Cauble, D.F.; Gipson, J.D.; Krische, M.J. *J. Am. Chem. Soc.* ***2003***, *125*, 1110.

[705]For a review of the scandium-catalyzed enantioselective addition, see Gravel, M.; Lachance, H.; Lu, X.; Hall, D.G. *Synthesis* ***2004***, 1290.

A number of optically active allylic boron compounds have been used, including[706] B-allylbis(2-isocaranyl)borane (**30**),[707] (*E*)- and (*Z*)-crotyl-(*R*,*R*)-2,5-dimethylborolanes (**31**),[708] and the borneol



30 **31** **32**

derivative **32**,[709] all of which add an allyl group to aldehydes, with good enantioselectivity. Where the substrate possesses an aryl group or a triple bond, enantioselectivity is enhanced by using a metal carbonyl complex of the substrate.[710]

Alkenes and alkynes add to aldehydes or ketones by conversion to a reactive organometallic. A radical-type addition is possible using alkenes with BEt_3. Benzaldehyde reacted with isoprene in the presence of BEt_3 and $Ni(acac)_2$ to give an anti-Markovnikov-type addition to the carbonyl, C=C—C(Me)=C + PhCHO → $C{=}CCHMeCH_2CH(OH)Ph$.[711] Alkynes add to aldehydes elsewhere in the same molecule in the presence of BEt_3 and a nickel catalyst to give a cyclic allylic alcohol.[712] Alkene aldehydes react similarly using Me_3SiOTf.[713] In a similar manner, dienes add to aldehydes in the presence of a nickel catalyst.[714] Propargylic halides add to aldehydes to give an allenic alcohol using β-SnO$[Rd(cod)Cl]_2$.[715] Allylic acetates react with ketones to give the homoallylic alcohol under electrochemical conditions that include bipyridyl, tetrabutylammonium tetrafluoroborate and $FeBr_2$.[716] Terminal alkynes react with zirconium complexes and Me_2Zn to give an allylic tertiary alcohol.[717] Internal alkynes also give allylic alcohols in the presence of BEt_3 and a nickel catalysts.[718] Reaction of an aldehyde containing a conjugated diene unit with diethylzinc and a nickel catalyst leads to cyclic

[706]For some others, see Hoffmann, R.W. *Pure Appl. Chem.* ***1988***, *60*, 123; Corey, E.J.; Yu, C.; Kim, S.S. *J. Am. Chem. Soc.* ***1989***, *111*, 5495; Roush, W.R.; Ando, K.; Powers, D.B.; Palkowitz, A.D.; Halterman, R.L. *J. Am. Chem. Soc.* ***1990***, *112*, 6339; Brown, H.C.; Randad, R.S. *Tetrahedron Lett.* ***1990***, *31*, 455; Stürmer, R.; Hoffmann, R.W. *Synlett* ***1990***, 759.

[707]Racherla, U.S.; Brown, H.C. *J. Org. Chem.* ***1991***, *56*, 401, and references cited therein.

[708]Garcia, J.; Kim, B.M.; Masamune, S. *J. Org. Chem.* ***1987***, *52*, 4831.

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[710]Roush, W.R.; Park, J.C. *J. Org. Chem.* ***1990***, *55*, 1143.

[711]Kimura, M.; Fujimatsu, H.; Ezoe, A.; Shibata, K.; Shimizu, M.; Matsumoto, S.; Tamaru, Y. *Angew. Chem. Int. Ed.* ***1999***, *38*, 397.

[712]Miller, K.M.; Huang, W.-S.; Jamison, T.F. *J. Am. Chem. Soc.* ***2003***, *125*, 3442; Miller, K.M.; Luanphaisarnnont, T.; Molinaro, C.; Jamison, T.F. *J. Am. Chem. Soc.* ***2004***, *126*, 4130.

[713]Suginome, M.; Iwanami, T.; Yamamoto, A.; Ito, Y. *Synlett* ***2001***, 1042.

[714]Sawaki, R.; Sato, Y.; Mori, M. *Org. Lett.* ***2004***, *6*, 1131.

[715]Banerjee, M.; Roy, S. *Org. Lett.* ***2004***, *6*, 2137.

[716]Durandetti, M.; Meignein, C.; Périchon, J. *J. Org. Chem.* ***2003***, *68*, 3121.

[717]Li, H.; Walsh, P.J. *J. Am. Chem. Soc.* ***2004***, *126*, 6538.

[718]Miller, K.M.; Jamison, T.F. *J. Am. Chem. Soc.* ***2004***, *126*, 15342.

alcohols having a pendant allylic unit.[719] A similar reaction was reported using a copper catalyst.[720] Vinyl iodides also react with Cp_2ZrCl_2 to give a vinylzirconium complex that reacts with aldehydes.[721] The intramolecular addition of an alkene to an aldehyde leads to a saturated cyclic alcohol using $PhSiH_3$ and a cobalt catalyst.[722] Intramolecular addition of a conjugated ester (via the β-carbon) to an aldehyde generates a cyclic ketone.[723] This type of coupling has been called the *Stetter reaction*,[724] which actually involves the addition of aldehydes to activated double bonds (**15-34**), mediated by a catalytic amount of thiazolium salt in the presence of a weak base. The intramolecular addition of the allene moiety to an aldehyde is catalyzed by a palladium complex in the presence of $Me_3SiSnBu_3$.[725] A highly enantio- and diastereoselective intramolecular Stetter reaction has been developed.[726] Alkynyl aldehydes react with silanes such as Et_3SiH and a nickel catalyst to give a cyclic compound having a silyl ether and an exocyclic vinylidene unit.[727] Alkene-aldehydes give cyclic alcohols via intramolecular addition of the C=C unit to the carbonyl under electrolytic conditions using a phase-transfer catalyst.[728] A similar cyclization was reported using $SnCl_4$.[729] Vinylidene cycloalkanes react with aldehydes in the presence of a palladium catalyst to give a homoallylic alcohol where addition occurs at the carbon exocyclic to the ring.[730] Alkenes having an allylic hydrogen react with α-keto aldehydes, with a cobalt catalyst, to give α-hydroxy ketones where the alcohol is homoallylic relative to the C=C unit.[731] Allenes react with benzaldehyde using HCl—$SnCl_2$ with a palladium catalyst.[732] Silyl allenes react with aldehydes in the presence of a chiral scandium catalyst to give homopropargylic alcohols with good enantioselectivity.[733] Intramolecular addition of an allene to aldehyde via addition of phenyl when treated with PhI and a palladium catalyst.[734] Allenes add to ketones

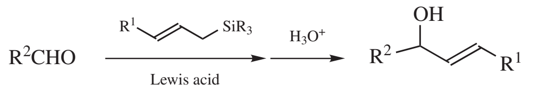
[719]Shibata, K.; Kimura, M.; Shimizu, M.; Tamaru, Y. *Org. Lett.* ***2001***, *3*, 2181.
[720]Agapiou, K.; Cauble, D.F.; Krische, M.J. *J. Am. Chem. Soc.* ***2004***, *126*, 4528.
[721]Namba, K.; Kishi, Y. *Org. Lett.* ***2004***, *6*, 5031.
[722]Baik, T.-G.; Luis, A.L.; Wang, L.-C.; Krische, M.J. *J. Am. Chem. Soc.* ***2001***, *123*, 5112.
[723]Kerr, M.S.; Rovis, T. *J. Am. Chem. Soc.* ***2004***, *126*, 8876.
[724]Stetter, H.; Schreckenberg, M. *Angew. Chem., Int. Ed* ***1973***, *12*, 81; Stetter, H. *Angew. Chem., Int. Ed.* ***1976***, *15*, 639; Stetter, H.; Kuhlmann, H. *Org. React.* ***1991***, *40*,407; Enders, D.; Breuer, K.; Runsink, J.; Teles, J.H. *Helv. Chim. Acta* ***1996***, *79*, 1899; Kerr, M.S.; Rovis, T. *J. Am. Chem. Soc.* ***2004***, *126*, 8876; Pesch, J.; Harms, K.; Bach, T. *Eur. J. Org. Chem.* ***2004***, 2025; Mennen, S.; Blank, J.; Tran-Dube, M.B.; Imbriglio, J.E.; Miller, S.J. *Chem. Commun.* ***2005***, 195. For examples of the Stetter reaction with acyl silanes, see Mattson, A.E.; Bharadwaj, A.R.; Scheidt, K.A. *J. Am. Chem. Soc.* ***2004***, *126*, 2314.
[725]Kang, S.-K.; Ha, Y.-H.; Ko, B.-S.; Lim, Y.; Jung, J. *Angew. Chem. Int. Ed.* ***2002***, *41*, 343.
[726]Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* ***2005***, *127*, 6284; Kerr, M.S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* ***2002***, *124*, 10298.
[727]Tang, X.-Q.; Montgomery, J. *J. Am. Chem. Soc.* ***1999***, *121*, 6098.
[728]Locher, C.; Peerzada, N. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 179.
[729]Alcaide, B.; Pardo, C.; Rodríguez-Ranera, C.; Rodríguez-Vicente, A. *Org. Lett.* ***2001***, *3*, 4205.
[730]Hao, J.; Hatano, M.; Mikami, K. *Org. Lett.* ***2000***, *2*, 4059.
[731]Kezuka, S.; Ikeno, T.; Yamada, T. *Org. Lett.* ***2001***, *3*, 1937.
[732]Chang, H.-M.; Cheng, C.-H. *Org. Lett.* ***2000***, *2*, 3439.
[733]Evans, D.A.; Sweeney, Z.K.; Rovis, T.; Tedrow, J.S. *J. Am. Chem. Soc.* ***2001***, *123*, 12095.
[734]Kang, S.-K.; Lee, S.-W.; Jung, J.; Lim, Y. *J. Org. Chem.* ***2002***, *67*, 4376.

to give homoallylic alcohols in the presence of SmI_2 and HMPA.[735] Allenes add to carbonyl groups in the presence of 2.2 equivalents of SmI_2 and an excess of HMPA.[736] Alkenes have an allylic methyl group add to formaldehyde, in the presence of BF_3•OEt_2, to give a homoallylic alcohol.[737] Conjugated dienes react with aldehyde via acyl addition of a terminal carbon of the diene, in the presence of $Ni(acac)_2$ and Et_2Zn.[738] Aldehydes having an allylic acetate unit elsewhere in the molecule undergo cyclization in CO and a ruthenium catalyst to give a cyclic alcohol with a pendant vinyl group.[739]

Allylic trifluoroborates (p. 817) react with aldehydes to give the homoallylic alcohol. Pivaldehyde reacts with potassium 2-butenyltrifluoroborate and a catalytic amount of tetrabutylammonium iodide to give 2,2,4-trimethylhex-5-en-3-ol.[740] Aliphatic aldehydes react with this reagent, in the presence of BF_3•OEt_2, to give the homoallylic alcohol with allylic rearrangement and a preference for the syn diastereomer,[741] and aryl aldehydes react as well.[742]

16-26 Addition of Trialkylallylsilanes to Aldehydes and Ketones

***O*-Hydro-*C*-alkyl-addition**



Allylic trialkyl, trialkoxy, and trihalosilanes add to aldehydes to give the homoallylic alcohols in the presence of a Lewis acid[743] (including $TaCl_5$[744] and $YbCl_3$[745]), Me_3SiOTf,[746] fluoride ion,[747] proazaphosphatranes,[748] or a catalytic amount of iodine.[749] The mechanism of this reaction has been examined.[750] A ruthenium catalyst has also been used in conjunction with an arylsilane and an aldehyde.[751]

[735]Hölemann, A.; Reissig, H.-U. *Org. Lett.* ***2003***, *5*, 1463.
[736]Hölemann, A.; Reißig, H.-U. *Chem. Eur. J.* ***2004***, *10*, 5493.
[737]Okachi, T.; Fujimoto, K.; Onaka, M. *Org. Lett.* ***2002***, *4*, 1667.
[738]Loh, T.-P.; Song, H.-Y.; Zhou, Y. *Org. Lett.* ***2002***, *4*, 2715.
[739]Yu, C.-M.; Lee, S.; Hong, Y.-T.; Yoon, S.-K. *Tetrahedron Lett.* ***2004***, *45*, 6557.
[740]Thadani, A.N.; Batey, R.A. *Org. Lett.* ***2002***, *4*, 3827.
[741]Batey, R.A.; Thadani, A.N.; Smil, D.V. *Tetrahedron Lett.* ***1999***, *40*, 4289.
[742]Batey, R.A.; Thadani, A.N.; Smil, D.V.; Lough, A.J. *Synthesis* ***2000***, 990.
[743]For reviews, see Fleming, I.; Dunoguès, J.; Smithers, R. *Org. React.* ***1989***, *37*, 57, 113–125, 290–328; Parnes, Z.N.; Bolestova, G.I. *Synthesis* ***1984***, 991, see pp. 997–1000. For studies of the mechanism, see Denmark, S.E.; Weber, E.J.; Wilson, T.; Willson, T.M. *Tetrahedron* ***1989***, *45*, 1053; Keck, G.E.; Andrus, M.B.; Castellino, S. *J. Am. Chem. Soc.* ***1989***, *111*, 8136. For examples, see Aggarwal, V.K.; Vennall, G.P. *Tetrahedron Lett.* ***1996***, *37*, 3745.
[744]Chandrasekhar, S.; Mohanty, P.K.; Raza, A. *Synth. Commun.* ***1999***, *29*, 257.
[745]Fang, X.; Watkin, J.G.; Warner, B.P. *Tetrahedron Lett.* ***2000***, *41*, 447.
[746]Davis, A.P.; Jaspars, M. *Angew. Chem. Int. Ed.* ***1992***, *31*, 470.
[747]See Cossy, J.; Lutz, F.; Alauze, V.; Meyer, C. *Synlett* ***2002***, 45.
[748]Wang, Z.; Kisanga, P.; Verkade, J.G. *J. Org. Chem.* ***1999***, *64*, 6459.
[749]Yadav, J.S.; Chand, P.K.; Anjaneyulu, S. *Tetrahedron Lett.* ***2002***, *43*, 3783.
[750]Bottoni, A.; Costa, A.L.; DiTommaso, D.; Rossi, I.; Tagliavini, E. *J. Am. Chem. Soc.* ***1997***, *119*, 12131.
[751]Fujii, T.; Koike, T.; Mori, A.; Osakada, K. *Synlett* ***2002***, 298.

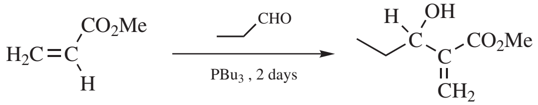
The reaction of an allene aldehyde with Et_3SiH, CO and a rhodium catalyst leads to addition to the alkene followed by intramolecular addition to the aldehyde to give the cyclic alcohol.[752] Allyl(trimethoxy)silane adds an allyl group to aldehydes using a CdF_2[753] catalyst or a chiral AgF complex.[754] Allyltrichlorosilanes have also been used in addition reactions with aldehydes.[755] Hünig's base (*i*Pr_2NEt) and a sulfoxide have also been used to facilitate the addition of an allyl group to an aldehyde from allyltrichlorosilane.[756]

Allyltrichlorosilane reacts with benzaldehyde in the presence of Bu_4NF to give 1-phenylbut-3-en-1ol,[757] and with a chiral additive the reaction proceeds with good enantioselectivity. When chiral titanium complexes are used in the reaction, allylic alcohols are produced with good asymmetric induction.[758] Other chiral additives have been used,[759] as well as chiral catalysts,[760] and chiral complexes of allyl silanes.[761] Chiral allylic silyl derivatives add to aldehydes to give the chiral homoallylic alcohol.[762]

Allylic silanes react with *gem*-diacetates in the presence of $InCl_3$ to give a homoallylic acetate[763] or with dimethyl acetals and TMSOTf in an ionic liquid to give the homoallylic methyl ether.[764] Allylic alcohols can be treated with TMS—Cl and NaI, and then Bi to give an organometallic reagent that adds to aldehydes.[765]

16-27 Addition of Conjugated Alkenes to Aldehydes (the Baylis–Hillman Reaction)[766]

O-Hydro-*C*-alkenyl-addition



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[752]Kang, S.-K.; Hong, Y.-T.; Lee, J.-H.; Kim, W.-Y.; Lee. I.; Yu, C.-M. *Org. Lett.* ***2003***, *5*, 2813.

[753]Aoyama, N.; Hamada, T.; Manabe, K.; Kobayashi, S. *Chem. Commun.* ***2003***, 676.

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[764]In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Zerth, H.M.; Leonard, N.M.; Mohan, R.S. *Org. Lett.* ***2003***, *5*, 55.

[765]Miyoshi, N.; Nishio, M.; Murakami, S.; Fukuma, T.; Wada, M. *Bull. Chem. Soc. Jpn.* ***2000***, *73*, 689.

[766]For a review, see Basavaih, D.; Rao, A.J.; Satyanarayana, T. *Chem. Rev.* ***2003***, *103*, 811.

In the presence of a base,[767] such as 1,4-diazabicyclo[2.2.2]octane (DABCO) or trialkylphosphines, conjugated carbonyl compounds (ketones, esters,[768] thioesters,[769] and amides[770]) add to aldehydes via the α-carbon to give α-alkenyl-β-hydroxy esters or amides. This sequence is called the *Baylis–Hillman reaction*,[771] and a simple example is the formation of **33**.[772] It was observed that methyl vinyl ketone gave other products in the Baylis–Hillman reaction, whereas conjugated esters did not.[773] Methods that are catalytic in base have been developed for the Baylis–Hillman reaction.[774] Both microwave irradiation[775] and ultrasound[776] have been used to induce the reaction. Under certain conditions, rate enhancements have been observed.[777] Rate acceleration occurs with bis-aryl(thio)ureas in a DABCO-promoted reaction.[778] The reaction has been done in ionic liquids[779] and polyethylene glycol (PEG)[780] or sulpholane.[781] Alkynyl carbonyl compounds can be used as partners in the Baylis–Hillman reaction.[782] Transition metal compounds can facilitate the Baylis–Hillman reaction, and BF_3•OEt_2 has been used.[783] With the boron trifluoride

[767]For an example using NaOMe, see Luo, S.; Mi, X.; Xu, H.; Wang, P.G.; Cheng, J.-P. *J. Org. Chem.* ***2004***, *69*, 8413.

[768]For an example with a conjugated lactone, see Karur, S.; Hardin, J.; Headley, A.; Li, G. *Tetrahedron Lett.* ***2003***, *44*, 2991.

[769]Pei, W.; Wei, H.-X.; Li, G. *Chem. Commun.* ***2002***, 1856.

[770]See Yu, C.; Hu, L. *J. Org. Chem.* ***2002***, *67*, 219; Faltin, C.; Fleming, E.M.; Connon, S.J. *J. Org. Chem.* ***2004***, *69*, 6496.

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[772]Rafel, S.; Leahy, J.W. *J. Org. Chem.* ***1997***, *62*, 1521. Also see, Drewes, S.E.; Rohwer, M.B. *Synth. Commun.* ***1997***, *27*, 415.

[773]Shi, M.; Li, C.-Q.; Jiang, J.-K. *Chem. Commun.* ***2001***, 833.

[774]With imidazole: Gatri, R.; El Gaïed, M.M. *Tetrahedron Lett.* ***2002***, *43*, 7835. With azoles: Luo, S.; Mi, X.; Wang, P.G.; Cheng, J.-P. *Tetrahedron Lett.* ***2004***, *45*, 5171. With proazaphosphatranes/$TiCl_4$: You, J.; Xu, J.; Verkade, J.G. *Angew. Chem. Int. Ed.* ***2003***, *42*, 5054. See Leadbeater, N.E.; van der Pol, C. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 2831. For a discussion of pK_a and reactivity, see Aggarwal, V.K.; Emme, I.; Fulford, S.Y. *J. Org. Chem.* ***2003***, *68*, 692.

[775]Kundu, M.K.; Mukherjee, S.B.; Balu, N.; Padmakumar, R.; Bhat, S.V. *Synlett* ***1994***, 444.

[776]Coelho, F.; Almeida, W.P.; Veronese, D.; Mateus, C.R.; Lopes, E.C.S.; Rossi, R.C.; Silveira, G.P.C.; Pavam, C.H. *Tetrahedron* ***2002***, *58*, 7437.

[777]See Rafel, S.; Leahy, J.W. *J. Org. Chem.* ***1997***, *62*, 1521; Lee, W.-D.; Yang, K.-S.; Chen, K. *Chem. Commun.* ***2001***, 1612. For rate acceleration in water or aqueous media, see Augé, J.; Lubin, N.; Lubineau, A. *Tetrahedron Lett.* ***1994***, *35*, 7947; Luo, S.; Wang, P.G.; Cheng, J.-P. *J. Org. Chem.* ***2004***, *69*, 555; Cai, J.; Zhou, Z.; Zhao, G.; Tang, C. *Org. Lett.* ***2002***, *4*, 4723. For rate acceleration in polar solvents, see Aggarwal, V.K.; Dean, D.K.; Mereu, A.; Williams, R. *J. Org. Chem.* ***2002***, *67*, 510. For a discussion of salt effects, see Kumar, A.; Pawar, S.S. *Tetrahedron* ***2003***, *59*, 5019.

[778]Maher, D.J.; Connon, S.J. *Tetrahedron Lett.* ***2004***, *45*, 1301.

[779]Rosa, J.N.; Afonso, C.A.M.; Santos, A.G. *Tetrahedron* ***2001***, *57*, 4189. For an example in a chiral ionic liquid, see Pégot, B.; Vo-Thanh, G.; Gori, D.; Loupy, A. *Tetrahedron Lett.* ***2004***, *45*, 6425.

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induced reaction between an aldehyde and a conjugated ketone, a saturated β-hydroxy ketone was formed with good antiselectivity.[784] The coupling of aldehydes with conjugated ketones was accomplished with $TiCl_4$,[785] dialkylaluminum halides,[786] and with (polymethyl)hydrosiloxane and a copper catalyst.[787] Conjugated esters were coupled to aldehydes with DABCO and a lanthanum catalyst.[788] Aldehydes were coupled to conjugated nitriles with $TiCl_4$.[789] The reaction of a conjugated ester, an aldehyde and $LiClO_4$, with 15% DABCO gave the allylic alcohol product.[790] *N*-Tosyl imines can be used in place of aldehydes, and the reaction of the imine, a conjugated ester and DABCO gave the allylic *N*-tosylimine.[791] Aldehydes are coupled to conjugated esters with a chiral quinuclidine catalyst and a titanium catalyst, and in the presence of tosylamine, the final product was the allylic *N*-tosylamine formed with modest enantioselectivity.[792]

An intramolecular version of the Baylis–Hillman reaction generated cyclopentenone derivatives from alkyne-aldehydes and a rhodium catalyst.[793] Another intramolecular reaction gave cyclopentenols via cyclization of an aldehyde-conjugated thioester upon treatment with DBU and DMAP.[794] Cyclization of a conjugated ester using DABCO, where the "alcohol" group contained an aldehyde unit (an α-hydroxy aldehyde derivative) gave a lactone with an hydroxy unit at C3 relative to the carbonyl and an α-vinylidene.[795] A "double Baylis–Hillman" reaction has also been reported using *N*-tosylimines and conjugated ketones.[796]

Using a chiral auxiliary via an amide[797] or ester[798] leads to asymmetric induction.[799] Aryl aldehydes and conjugated ketones were condensed using proline, leading to modest enantioselectivity.[800] Chiral biaryl catalysts have been used with trialkylphosphines, giving good enantioselectivity.[801] Chiral quinuclidine catalysts lead to

[784]Chandrasekhar, S.; Narsihmulu, Ch.; Reddy, N.R.; Reddy, M.S. *Tetrahedron Lett.* ***2003***, *44*, 2583.

[785]Li, G.; Wei, H.-X.; Gao, J.J.; Caputo, T.D. *Tetrahedron Lett.* ***2000***, *41*, 1; Shi, M.; Jiang, J.-K.; Feng, Y.-S. *Org. Lett.* ***2000***, *2*, 2397.

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[790]Kawamura, M.; Kobayashi, S. *Tetrahedron Lett.* ***1999***, *40*, 1539.

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[792]Balan, D.; Adolfsson, H. *Tetrahedron Lett.* ***2003***, *44*, 2521.

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[795]Krishna, P.R.; Kannan, V.; Sharma, G.V.M. *J. Org. Chem.* ***2004***, *69*, 6467.

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[797]Brzezinski, L.J.; Rafel, S.; Leahy, J.W. *J. Am. Chem. Soc.* ***1997***, *119*, 4317.

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[799]Also see, Markó, I.E.; Giles, P.R.; Hindley, N.J. *Tetrahedron* ***1997***, *53*, 1015.

[800]Imbriglio, J.E.; Vasbinder, M.M.; Miller, S.J. *Org. Lett.* ***2003***, *5*, 3741. See also, Shi, M.; Jiang, J.-K.; L:i, C.-Q. *Tetrahedron Lett.* ***2002***, *43*, 127.

[801]McDougal, N.T.; Schaus, S.E. *J. Am. Chem. Soc.* ***2003***, *125*, 12094.

asymmetric induction.[802] A combination of a chiral sulfinamide, an In catalyst and 3-hydroxyquinuclidine led to the allylic amine derivative with modest enantioselectivity.[803] Sugars have been used as ester auxiliaries, and in reaction with aryl aldehydes and 20% DABCO gave the allylic alcohol with modest enantioselectivity.[804]

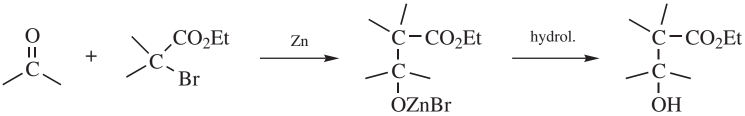
The reaction can be modified to give additional products, as with the reaction of *o*-hydroxybenzaldehyde and methyl vinyl ketone with DABCO, where the initial Baylis–Hillman product cyclized via conjugate addition of the phenolic oxygen to the conjugated ketone (**15-31**).[805] Aldehydes and conjugated esters can be coupled with a sulfonamide to give an allylic amine.[806]

A variant of this reaction couples halides with alkenes. α-Bromomethyl esters react with conjugated ketones and DABCO to give a coupling product, **34**.[807] A similar DBU-induced reaction was reported using α-bromomethyl esters and conjugated nitro compounds.[808]

34

16-28 The Reformatsky Reaction

O-Hydro-*C*-α-ethoxycarbonylalkyl-addition



The *Reformatsky reaction*[809] is very similar to **16-24**. An aldehyde or ketone is treated with zinc and a halide; the halide is usually an α-halo ester or a vinylog of an α-halo ester (e.g., RCHBrCH=CHCOOEt), though α-halo nitriles,[810] α-halo ketones,[811] and α-halo *N,N*-disubstituted amides have also been used. Especially

[802]Shi, M.; Jiang, J.-K. *Tetrahedron Asymmetry* ***2002***, *13*, 1941. See Shi, M.; Xu, Y.-M. *Angew. Chem. Int. Ed.* ***2002***, *41*, 4507.

[803]Aggarwal, V.K.; Castro, A.M.M.; Mereu, A.; Adams, H. *Tetrahedron Lett.* ***2002***, *43*, 1577.

[804]Filho, E.P.S.; Rodrigues, J.A.R.; Moran, P.J.S. *Tetrahedron Asymmetry* ***2001***, *12*, 847.

[805]Kaye, P.T.; Nocanda, X.W. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 1331.

[806]Balan, D.; Adolfsson, H. *J. Org. Chem.* ***2002***, *67*, 2329.

[807]Basavaiah, D.; Sharada, D.S.; Kumaragurubaran, N.; Reddy, R.M. *J. Org. Chem.* ***2002***, *67*, 7135.

[808]Ballini, R.; Barboni, L.; Bosica, G.; Fiorini, D.; Mignini, E.; Palmieri, A. *Tetrahedron* ***2004***, *60*, 4995.

[809]For reviews, see Fürstner, A. *Synthesis* ***1989***, 571; Rathke, M.W. *Org. React.* ***1975***, *22*, 423; Gaudemar, M. *Organomet. Chem. Rev. Sect. A* ***1972***, *8*, 183. For a review of the Reformatsky reaction in synthesis, see Ocampo, R.; Dolbier, Jr., W.R. *Tetrahedron* ***2004***, *60*, 9325.

[810]Vinograd, L.Kh.; Vul'fson, N.S. *J. Gen. Chem. USSR* ***1959***, *29*, 248, 1118, 2656, 2659; Palomo, C.; Aizpurua, J.M.; López, M.C.; Aurrekoetxea, N. *Tetrahedron Lett.* ***1990***, *31*, 2205; Zheng, J.; Yu, Y.; Shen, Y. *Synth. Commun.* ***1990***, *20*, 3277.

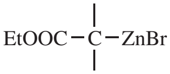
[811]For examples (with R_3Sb and $CrCl_2$, respectively, instead of Zn), see Huang, Y.; Chen, C.; Shen, Y. *J. Chem. Soc. Perkin Trans. 1* ***1988***, 2855; Dubois, J.E.; Axiotis, G.; Bertounesque, E. *Tetrahedron Lett.* ***1985***, *26*, 4371.

high reactivity can be achieved with activated zinc,[812] with zinc/silver-graphite,[813] and with zinc and ultrasound.[814] The reaction is catalytic in zinc in the presence of iodine and ultrasound.[815] Metals other than zinc can be used, including In,[816] Mn,[817] low valent Ti,[818] and metal compounds, such as TiI_4,[819] $TiCl_2$,[820] Cp_2TiCl_2,[821] $(Bu_3Sn)_2/Bu_2SnCl_2$,[822] SmI_2,[823] and $Sc(OTf)_3/PPh_3$.[824] A combination of Zn and an α-bromo ester can be used in conjunction with BF_3•OEt_2, followed by reaction with dibenzoyl peroxide.[825] The aldehyde or ketone can be aliphatic, aromatic, or heterocyclic or contain various functional groups. Solvents used are generally ethers, including Et_2O, THF, and 1,4-dioxane, although the reaction can be done in water[826] using dibenzoyl peroxide and $MgClO_4$.

Dialkylzinc compounds are an alternative source of zinc in the Reformatsky reaction. When an α-bromo ester, an aldehyde, and diethylzinc were reacted in THF with a rhodium catalyst, the β-hydroxy ester was formed.[827]

The use of additives, such as germanium, can lead to highly diastereoselective reactions.[828] Using chiral auxiliaries[829] or chiral additives,[830] good enantioselectivity[831] can be achieved.

Formally, the reaction can be regarded as if it were analogous to the Grignard reaction (**16-24**), with



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[815]Ross, N.A.; Bartsch, R.A. *J. Org. Chem.* ***2003***, *68*, 360.
[816]Araki, S.; Yamada, M.; Butsugan, Y. *Bull. Chem. Soc. Jpn.* ***1994***, *67*, 1126.
[817]Cahiez, G.; Chavant, P. *Tetrahedron Lett.* ***1989***, *30*, 7373; Suh, Y.S.; Rieke, R.D. *Tetrahedron Lett.* ***2004***, *45*, 1807.
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[819]Shimizu, M.; Kobayashi, F.; Hayakawa, R. *Tetrahedron* ***2001***, *57*, 9591.
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[821]Parrish, J.D.; SheHon, D.R.; Little, R.D. *Org. Lett.* ***2003***, *5*, 3615.
[822]Shibata, I.; Kawasaki, M.; Yasuda, M.; Baba, A. *Chem. Lett.* ***1999***, 689.
[823]Utimoto, K.; Matsui, T.; Takai, T.; Matsubara, S. *Chem. Lett.* ***1995***, 197; Arime, T.; Takahashi, H.; Kobayashi, S.; Yamaguchi, S.; Mori, N. *Synth. Commun.* ***1995***, *25*, 389; Park, H.S.; Lee, I.S.; Kim, Y.H. *Tetrahedron Lett.* ***1995***, *36*, 1673; Molander, G.A.; Etter, J.B. *J. Am. Chem. Soc.* ***1987***, *109*, 6556.
[824]Kagoshima, H.; Hashimoto, Y.; Saigo, K. *Tetrahedron Lett.* ***1998***, *39*, 8465.
[825]Chattopadhyay, A.; Salaskar, A. *Synthesis* ***2000***, 561.
[826]Bieber, L.W.; Malvestiti, I.; Storch, E.C. *J. Org. Chem.* ***1997***, *62*, 9061.
[827]Kanai, K.; Wakabyashi, H.; Honda, T. *Org. Lett.* ***2000***, *2*, 2549.
[828]Kagoshima, H.; Hashimoto, Y.; Oguro, D.; Saigo, K. *J. Org. Chem.* ***1998***, *63*, 691.
[829]Fukuzawa, S.-i.; Tatsuzawa, M.; Hirano, K. *Tetrahedron Lett.* ***1998***, *39*, 6899.
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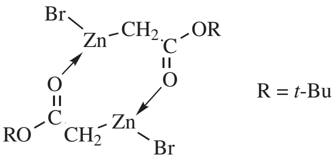
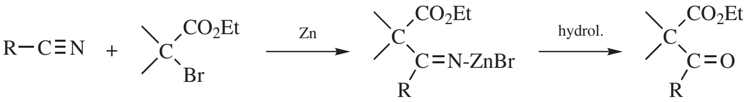
[831]Pini, D.; Uccello-Barretta, G.; Mastantuono, A.; Salvadori, P. *Tetrahedron* ***1997***, *53*, 6065; Andrés, J.M.; Martín, Y.; Pedrosa, R.; Pérez-Encabo, A. *Tetrahedron* ***1997***, *53*, 3787; Mi, A.; Wang, Z.; Zhang, J.; Jiang, Y. *Synth. Commun.* ***1997***, *27*, 1469.; Ribeiro, C.M.R.; de S. Santos, E.; de O. Jardim, A.H.; Maia, M.P.; da Silva, F.C.; Moreira, A.P.D.; Ferreira, V.F. *Tetrahedron Asymmetry* ***2002***, *13*, 1703.

(**35**) as an intermediate analogous to RMgX.[832] There *is* an intermediate derived from zinc and the ester, the structure of which has been shown to be **36**, by X-ray crystallography of the solid intermediate prepared from *t*-$BuOCOCH_2Br$ and Zn.[833] As can be seen, it has some of the characteristics of **35**.

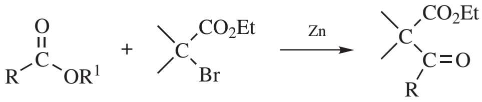


36

After hydrolysis, the alcohol is the usual product, but sometimes (especially with aryl aldehydes) elimination follows directly and the product is an alkene. By the use of Bu_3P along with Zn, the alkene can be made the main product,[834] making this an alternative to the Wittig reaction (**16-44**). The alkene is also the product when $K_2CO_3/NaHCO_3$ is used with 2% PEG–telluride.[835] Since Grignard reagents cannot be formed from α-halo esters, the method is quite useful, though there are competing reactions and yields are sometimes low. A similar reaction (called the *Blaise reaction*) has been carried out on nitriles:[836]



Carboxylic esters have also been used as substrates, but then, as might be expected (p. 1252), the result is substitution and not addition:



The product in this case is the same as with the corresponding nitrile, though the pathways are different. The reaction is compatible with amine substituents, and α-(*N,N*-dibenzyl)amino aldehydes have been used to prepare β-hydroxy-γ-(*N,N*-dibenzylamino) esters with good anti-selectivity.[837]

[832]For a study of transition structures, see Maiz, J.; Arrieta, A.; Lopez, X.; Ugalde, J.M.; Cossio, F.P.; Fakultatea, K.; Unibertsitatea, E.H.; Lecea, B. *Tetrahedron Lett.* ***1993***, *34*, 6111.

[833]Dekker, J.; Budzelaar, P.H.M.; Boersma, J.; van der Kerk, G.J.M.; Spek, A.L. *Organometallics*, ***1984***, *3*, 1403.

[834]Shen, Y.; Xin, Y.; Zhao, J. *Tetrahedron Lett.* ***1988***, *29*, 6119. For another method, see Huang, Y.; Shi, L.; Li, S.; Wen, X. *J. Chem. Soc. Perkin Trans. 1* ***1989***, 2397.

[835]Huang, Z.-Z.; Ye, S.; Xia, W.; Yu, Y.-H.; Tang, Y. *J. Org. Chem.* ***2002***, *67*, 3096.

[836]See Cason, J.; Rinehart Jr., K.L.; Thornton, S.D. *J. Org. Chem.* ***1953***, *18*, 1594; Bellassoued, M.; Gaudemar, M. *J. Organomet. Chem.* ***1974***, *81*, 139; Hannick, S.M.; Kishi, Y. *J. Org. Chem.* ***1983***, *48*, 3833.

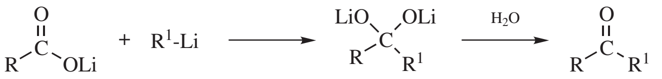
[837]Andrés, J.M.; Pedrosa, R.; Pérez, A.; Pérez-Encabo, A. *Tetrahedron* ***2001***, *57*, 8521.

For an alternative approach involving ester enolates (see **16-36**).

OS **III**, 408; **IV**, 120, 444; **IX**, 275.

16-29 The Conversion of Carboxylic Acid Salts to Ketones with Organometallic Compounds

Alkyl-de-oxido-substitution



Good yields of ketones can often be obtained by treatment of the lithium salt of a carboxylic acid with an alkyllithium reagent, followed by hydrolysis.[838] The R′ group may be aryl or primary, secondary, or tertiary alkyl and R may be alkyl or aryl. The compounds MeLi and PhLi have been employed most often. Tertiary alcohols are side products. Lithium acetate can be used, but generally gives low yields.

A variation of this transformation reacts the acid with lithium naphthalenide in the presence of 1-chlorobutane. The product is the ketone.[839] A related reaction treats the lithium carboxylate with lithium metal and the alkyl halide, with sonication, to give the ketone.[840] Phenylboronic acid (p. 815) reacts with aryl carboxylic acids in the presence of a palladium catalyst and disuccinoyl carbonate to give a diaryl ketone.[841]

OS **V**, 775.

16-30 The Addition of Organometallic Compounds to CO_2 and CS_2

C-Alkyl-*O*-halomagnesio-addition

Grignard reagents add to one C=O bond of CO_2 exactly as they do to an aldehyde or a ketone.[842] Here, of course, the product is the salt of a carboxylic acid. The reaction is usually performed by adding the Grignard reagent to dry ice. Many carboxylic acids have been prepared in this manner, and this constitutes an important way of increasing a carbon chain by one unit. Since labeled CO_2 is commercially

[838]For a review, see Jorgenson, M.J. *Org. React.* ***1970***, *18*, 1. For an improved procedure, see Rubottom, G.M.; Kim, C. *J. Org. Chem.* ***1983***, *48*, 1550.

[839]Alonso, F.; Lorenzo, E.; Yus, M. *J. Org. Chem.*, ***1996***, *61*, 6058.

[840]Aurell, M.J.; Danhui, Y.; Einhorn, J.; Einhorn, C.; Luche, J.L. *Synlett* ***1995***, 459. Also see, Aurell, M.J.; Einhorn, C.; Einhorn, J.; Luche, J.L. *J. Org. Chem.* ***1995***, *60*, 8.

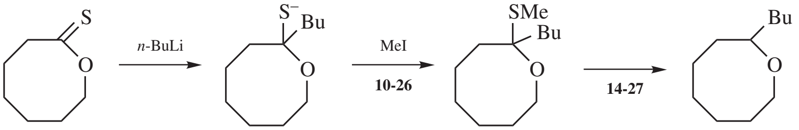
[841]Gooßen, L.J.; Ghosh, K. *Chem. Commun.* ***2001***, 2084.

[842]For reviews of the reaction between organometallic compounds and CO_2, see Volpin, M.E.; Kolomnikov, I.S. *Organomet. React.* ***1975***, *5*, 313; Sneeden, R.P.A., in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 137–173; Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 913–948. For a more general review, see Lapidus, A.L.; Ping, Y.Y. *Russ. Chem. Rev.* ***1981***, *50*, 63.

available, this is a good method for the preparation of carboxylic acids labeled in the carboxyl group. Other organometallic compounds have also been used (RLi,[843] RNa, RCaX, RBa,[844] etc.), but much less often. The formation of the salt of a carboxylic acid after the addition of CO_2 to a reaction mixture is regarded as a positive test for the presence of a carbanion or of a reactive organometallic intermediate in that reaction mixture (see also, **16-42**).

When chiral additives, such as (−)-sparteine, have added to the initial reaction with the organolithium reagent, quenching with CO_2 produces carboxylic acids with good asymmetric induction.[845]

In a closely related reaction, Grignard reagents add to CS_2 to give salts of dithiocarboxylic acids.[846] These salts can be trapped with amines to form thioamides.[847] Two other reactions are worthy of note. (*1*) Lithium dialkylcopper reagents react with dithiocarboxylic esters to give tertiary thiols[848] (*2*) Thiono lactones can be converted to cyclic ethers,[849] for example:



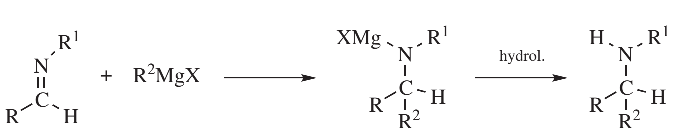
This is a valuable procedure because medium and large ring ethers are not easily made, while the corresponding thiono lactones can be prepared from the readily available lactones (see, e.g., **16-63**) by reaction **16-11**.

A terminal alkyne can be converted to the anion under electrolytic conditions, in the presence of CO_2, to give propargylic acids, R—C≡C—COOH.[850]

OS **I**, 361, 524; **II**, 425; **III**, 413, 553, 555; **V**, 890, 1043; **VI**, 845; **IX**, 317.

16-31 The Addition of Organometallic Compounds to C=N Compounds

***N*-Hydro-*C*-alkyl-addition**



[843]The kinetics of this reaction have been studied, see Nudelman, N.S.; Doctorovich, F. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 1233.

[844]Yanagisawa, A.; Yasue, K.; Yamamoto, H. *Synlett* ***1992***, 593.

[845]Park, Y.S.; Beak, P. *J. Org. Chem.* ***1997***, *62*, 1574.

[846]For a review of the addition of Grignard reagents to C=S bonds, see Paquer, D. *Bull. Soc. Chim. Fr.* ***1975***, 1439. For a review of the synthesis of dithiocarboxylic acids and esters, see Ramadas, S.R.; Srinivasan, P.S.; Ramachandran, J.; Sastry, V.V.S.K. *Synthesis* ***1983***, 605.

[847]Katritzky, A.R.; Moutou, J.-L.; Yang, Z. *Synlett* ***1995***, 99.

[848]Bertz, S.H.; Dabbagh, G.; Williams, L.M. *J. Org. Chem.* ***1985***, *50*, 4414.

[849]Nicolaou, K.C.; McGarry, D.G.; Somers, P.K.; Veale, C.A.; Furst, G.T. *J. Am. Chem. Soc.* ***1987***, *109*, 2504.

[850]Köster, F.; Dinjus, E.; Duñach, E. *Eur. J. Org. Chem.* ***2001***, 2507.

Aldimines can be converted to secondary amines by treatment with Grignard reagents.[851] Ketimines generally give reduction instead of addition. However, organolithium compounds give the normal addition product with both aldimines and ketimines.[852] For the addition of an organometallic compound to an imine to give a primary amine, R′ in RCH=NR′ would have to be H, and such compounds are seldom stable. However, the conversion has been done, for R = aryl, by the use of the masked reagents $(ArCH{=}N)_2SO_2$ [prepared from an aldehyde RCHO and sulfamide $(NH_2)_2SO_2$]. Addition of R^2MgX or R^2Li to these compounds gives $ArCHR^2NH_2$ after hydrolysis.[853] An intramolecular version of the addition or organolithium reagents is known, and treatment of the *N*-(3-chloropropyl)aldimine of benzaldehyde with lithium and DTBB, followed by hydrolysis with water, gave 2-phenylpyrrolidine.[854] Grignard regents add to imines in the presence of various transition metal catalysts, including $Sc(OTf)_3$[855] or Cp_2ZrCl_2.[856] When chiral additives are used in conjunction with the organolithium reagent, chiral amines are produced[857] with good asymmetric induction.[858] Chiral auxiliaries have been used in addition reactions to imines,[859] and to oxime derivatives.[860] Chiral catalysts lead to enantioselective addition of alkynes to imines to give a homopropargylic amine.[861]

Zinc metal reacts with allylic bromides to form an allylic zinc complex, which reacts with imines to give the homoallylic amine.[862] This reaction is catalyzed by TMSCl.[863] Allylzinc bromide adds to imines.[864] Dialkylzinc reagents add to imines to give the amine, and in the presence of a chiral ligand the reaction proceeds with

[851]For reviews of the addition of organometallic reagents to C=N bonds, see Harada, K., in Patai, S. *The Chemistry of the Carbon–Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 266–272; Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 1204–1227. For recent examples, see Wang, D.-K.; Dai, L.-X.; Hou, X.-L.; Zhang, Y. *Tetrahedron Lett.* ***1996***, *37*, 4187; Bambridge, K.; Begley, M.J.; Simpkins, N.S. *Tetrahedron Lett.* ***1994***, *35*, 3391.

[852]Huet, J. *Bull. Soc. Chim. Fr.* ***1964***, 952, 960, 967, 973.

[853]Davis, F.A.; Giangiordano, M.A.; Starner, W.E. *Tetrahedron Lett.* ***1986***, *27*, 3957.

[854]Yus, M.; Soler, T.; Foubelo, F. *J. Org. Chem.* ***2001***, *66*, 6207.

[855]Saito, S.; Hatanaka, K.; Yamamoto, H. *Synlett* ***2001***, 1859.

[856]Gandon, V.; Bertus, P.; Szymoniak, J. *Eur. J. Org. Chem.* ***2001***, 3677.

[857]For a review see Enders, D.; Reinhold, U. *Tetrahedron Asymmetry*, ***1997***, *8*, 1895.

[858]Andersson, P.G.; Johansson, F.; Tanner, D. *Tetrahedron* ***1998***, *54*, 11549; Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* ***1991***, *32*, 3095; Denmark, S.E.; Stiff, C.M. *J. Org. Chem.* ***2000***, *65*, 5875; Chrzanowska, M.; Sokołowska, J. *Tetrahedron Asymmetry* ***2001***, *12*, 1435.

[859]Hashimoto, Y.; Kobayashi, N.; Kai, A.; Saigo, K. *Synlett* ***1995***, 961.

[860]Dieter, R.K.; Datar, R. *Can. J. Chem.* ***1993***, *71*, 814.

[861]Benaglia, M.; Negri, D.; Dell'Anna, G. *Tetrahedron Lett.* ***2004***, *45*, 8705.

[862]Lee, C.-L.K.; Ling, H.-Y.; Loh, T.-P. *J. Org. Chem.* ***2004***, *69*, 7787.

[863]Legros, J.; Meyer, F.; Coliboeuf, M.; Crousse, B.; Bonnet-Delpon, D.; Bégué, J.-P. *J. Org. Chem.* ***2003***, *68*, 6444.

[864]van der Sluis, M.; Dalmolen, J.; de Lange, B.; Kaptein, B.; Kellogg, R.M.; Broxterman, Q.B. *Org. Lett.* ***2001***, *3*, 3943.

good enantioselectivity.[865] Dialkylzinc reagents add to *N*-tosyl imines using a copper catalyst, and with a chiral ligand leads to good enantioselectivity.[866] α-Bromo esters are converted to an organometallic reagent with Zn/Cu, and addition to *N*-arylimines gives *N*-aryl β-amino esters.[867] The reaction of imines, such as ArN=CHCO$_2$Et, where R = a chiral benzylic substituent, and ZnBr$_2$, followed by R′ZnBr leads to a chiral α-amino ester.[868] Terminal alkynes add to imines using ZnCl$_2$ and TMSCl, and with a chiral ligand attached to nitrogen the reaction proceeds with some enantioselectivity.[869]

Other organometallic compounds,[870] including allylic stannanes,[871] allylic samarium, [872] allylic germanium,[873] and allylic indium compounds[874] add to aldimines in the same manner. Aryltrialkylstannanes also add the aryl group to *N*-tosyl imines using a rhodium catalyst and sonication.[875] Catalytic enantioselective addition reactions are well known,[876] including reactions in an ionic liquid.[877] Allylic

[865]For an example using a Zr catalyst with a chiral ligand, see Porter J.R.; Traverse, J.F.; Hoveyda, A.H.; Snapper, M.L. *J. Am. Chem. Soc.* ***2001***, *123*, 984. With a Pd catalyst, see Inoue, A.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* ***2003***, *125*, 1484. With a Zr catalyst, see Porter, J.R.; Traverse, J.F.; Hoveyda, A.H.; Snapper, M.L. *J. Am. Chem. Soc.* ***2001***, *123*, 10409. See also, Zhang, X.-M.; Zhang, H.-L.; Lin, W.-Q.; Gong, L.-Z.; Mi, A.-Q.; Cui, X.; Jiang, Y.-Z.; Yu, K.B. *J. Org. Chem.* ***2003***, *68*, 4322; Jensen, D.R.; Schultz, M.J.; Mueller, J.A.; Sigman, M.S. *Angew. Chem. Int. Ed.* ***2003***, *42*, 3810.

[866]Fujihara, H.; Nagai, K.; Yomioka, K. *J. Am. Chem. Soc.* ***2000***, *122*, 12055. See Wang, C.-J.; Shi, M. *J. Org. Chem.* ***2003***, *68*, 6229.

[867]Adrian Jr., J.C.; Barkin, J.L.; Hassib, L. *Tetrahedron Lett.* ***1999***, *40*, 2457.

[868]Chiev, K.P.; Roland, S.; Mangeney, P. *Tetrahedron Asymmetry* ***2001***, *13*, 2205.

[869]Jiang, B.; Si, Y.-G. *Tetrahedron Lett.* ***2003***, *44*, 6767.

[870]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 847–863.

[871]Keck, G.E.; Enholm, E.J. *J. Org. Chem.* ***1985***, *50*, 146; Nakamura, H.; Nakamura, K.; Yamamoto, Y. *J. Am. Chem. Soc.* ***1998***, *120*, 4242; Kobayashi, S.; Iwamoto, S.; Nagayama, S. *Synlett* ***1997***, 1099; Wang, D.-K.; Dai, L.-X.; Hou, X.-L. *Tetrahedron Lett.* ***1995***, *36*, 8649. Catalytic amounts of metal compounds can be used with the allyl stannane, including: **Pd**: Nakamura, H.; Iwama, H.; Yamamoto, Y. *Chem. Commun.* ***1996***, 1459 and Fernandes, R.A.; Yamamoto, Y. *J. Org. Chem.* ***2004***, *69*, 3562; **Zr**: Gastner, T.; Ishitani, H.; Akiyama, R.; Kobayashi, S. *Angew. Chem. Int. Ed.* ***2001***, *40*, 1896; **Ta**: Shibata, I.; Nose, K.; Sakamoto, K.; Yasuda, M.; Baba, A. *J. Org. Chem.* ***2004***, *69*, 2185; **La**: Aspinall, H.C.; Bissett, J.S.; Greeves, N.; Levin, D. *Tetrahedron Lett.* ***2002***, *43*, 323; **Al**: Niwa, Y.; Shimizu, M. *J. Am. Chem. Soc.* ***2003***, *125*, 3720; **Nb**: Andrade, C.K.Z.; Oliveira, G.R. *Tetrahedron Lett.* ***2002***, *43*, 1935; Akiyama, T.; Onuma, Y. *J. Chem. Soc., Perkin Trans. 1* ***2002***, 1157. With **LiClO$_4$**: Yadav, J.S.; Reddy, B.V.S.; Reddy, P.S.R.; Rao, M.S. *Tetrahedron Lett.* ***2002***, *43*, 6245.

[872]Wang, J.; Zhang, Y.; Bao, W. *Synth. Commun.* ***1996***, *26*, 2473. For an example using an allylic bromide with SmI$_2$, see Kim, B.; Han, R.; Park, R.; Bai, K.; Jun, Y.; Baik, W. *Synth. Commun.* ***2001***, *31*, 2297.

[873]Akiyama, T.; Iwai, J.; Onuma, Y.; Kagoshima, H. *Chem. Commun.* ***1999***, 2191.

[874]Chan, T.H.; Lu, W. *Tetrahedron Lett.* ***1998***, *39*, 8605; Jin, S.-J.; Araki, S.; Butsugan, Y. *Bull Chem. Soc. Jpn.* ***1993***, *66*, 1528; Beuchet, P.; Le Marrec, N.; Mosset, P. *Tetrahedron Lett.* ***1992***, *33*, 5959; Vilaivan, T.; Winotapan, C.; Shinada, T.; Ohfune, Y. *Tetrahedron Lett.* ***2001***, *42*, 9073.

[875]Ding, R.; Zhao, C.H.; Chen, Y.J.; Lu, L.; Wang, D.; Li, C.J. *Tetrahedron Lett.* ***2004***, *45*, 2995.

[876]For a review, see Kobayashi, Sh.; Ishitani, H. *Chem. Rev.* ***1999***, *99*, 1069.

[877]In bmim BF$_4$, 1-butyl-3-methylimidazolium tetrafluoroborate: Chowdari, N.S.; Ramachary, D.B.; Barbas III, C.F. *Synlett* ***2003***, 1906.

halides react with imines in the presence of indium metal[878] or $InCl_3$[879] to give the homoallylic amine, and with *N*-sulfonyl imines to give the homoallylic sulfonamide.[880] In this latter reaction, antiselectivity was observed when the reaction was done in water, and syn selectivity when done in aqueous THF.[881] Propargylic halides add to imines in the presence of indium metal, in aq. THF.[882] Imines react with allylic halides and gallium metal, with ultrasound.[883] Imines also react with allylic halides and Yb, in the presence of Me_3SiCl.[884] Aryl iodides add to *N*-aryl imines in the presence of a rhodium catalyst.[885] Titanium enolates add to imines to give β-amino esters.[886] Terminal alkynes react with aryl aldehydes and aryl amines to give propargylic amine without a catalyst,[887] and an iridium[888] or a copper catalyst[889] also leads to a propargylic amine.[890] Terminal alkynes add to imines to give a propargylic amine with high enantioselectivity using a chiral copper complex.[891] Triethylaluminum adds an ethyl group to an imine in the presence of a europium catalyst. Reaction with $PhSnMe_3$ and *N*-tosylimines with a rhodium catalyst, for example, leads to addition of a phenyl group to the carbon of the C=N bond.[892] Other *N*-sulfonyl imines react similarly to give the corresponding sulfonamide, and in the presence of a chiral ligand the reaction proceeds to good enantioselectivity.[893] *N*-Tosyl imines also react with dialkylzinc reagents, giving the sulfonamide with modest enantioselectivity.[894] *N*-Sulfinyl imines, $R_2CH{=}NS({=}O)R'$,[895] react with Grignard reagents (R^2MgX) to give the corresponding *N*-sulfinylamine, $R_2CH(R^2)NHS({=}O)R'$.[896] Enolate anions, generated by reaction of dimethylaminopyridine and a conjugated ketone, add to *N*-tosylimines.[897] *N*-Carbamoyl imines add acetonitrile (via carbon) using DBU and a ruthenium catalyst.[898]

[878]Choucair, B.; Léon, H.; Miré, M.-A.; Lebreton, C.; Mosset, P. *Org. Lett.* ***2000***, *2*, 1851. See Hirashita, T.; Hayashi, Y.; Mitsui, K.; Araki, S. *J. Org. Chem.* ***2003***, *68*, 1309.
[879]Under electrolysis conditions, see Hilt, G.; Smolko, K.I.; Waloch, C. *Tetrahedron Lett.* ***2002***, *43*, 1437.
[880]Lu, W.; Chan, T.H. *J. Org. Chem.* ***2000***, *65*, 8589.
[881]Lu, W.; Chan, T.H. *J. Org. Chem.* ***2001***, *66*, 3467.
[882]Prajapati, D.; Laskar, D.D.; Gogoi, B.J.; Devi, G. *Tetrahedron Lett.* ***2003***, *44*, 6755.
[883]Andrews, P.C.; Peatt, A.C.; Raston, C.L. *Tetrahedron Lett.* ***2004***, *45*, 243.
[884]Su, W.; Li, J.; Zhang, Y. *Synth. Commun.* ***2001***, *31*, 273.
[885]Ishiyama, T.; Hartwig, J. *J. Am. Chem. Soc.* ***2000***, *122*, 12043.
[886]Adrian, Jr., J.C.; Barkin, J.L.; Fox, R.J.; Chick, J.E.; Hunter, A.D.; Nicklow, R.A. *J. Org. Chem.* ***2000***, *65*, 6264.
[887]Li, C.-J.; Wei, C. *Chem. Commun.* ***2002***, 268.
[888]Fischer, C.; Carreira, E.M. *Org. Lett.* ***2001***, *3*, 4319; Fischer, C.; Carreira, E.M. *Synthesis* ***2004***, 1497.
[889]Koradin, C.; Gommermann, N.; Polborn, K.; Knochel, P. *Chem. Eur. J.* ***2003***, *9*, 2797.
[890]Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* ***2002***, *124*, 5638.
[891]Tsvelikhovsky, D.; Gelman, D.; Molander, G.A.; Blum, J. *Org. Lett.* ***2004***, *6*, 1995.
[892]Oi, S.; Moro, M.; Fukuhara, H.; Kawanishi, T.; Inoue, Y. *Tetrahedron Lett.* ***1999***, *40*, 9259.
[893]Hayashi, T.; Ishigedani, M. *J. Am. Chem. Soc.* ***2000***, *122*, 976.
[894]Soeta, T.; Nagai, K.; Fujihara, H.; Kuriyama, M.; Tomioka, K. *J. Org. Chem.* ***2003***, *68*, 9723.
[895]For a review of these reagents, see Ellman, J.A.; Owens, T.D.; Tang, T.P. *Acc. Chem. Res.* ***2002***, *35*, 984.
[896]Tang, T.P.; Volkman, S.K.; Ellman, J.A. *J. Org. Chem.* ***2001***, *66*, 8772.
[897]Shi, M.; Xu, Y.-M. *Chem. Commun.* ***2001***, 1876.
[898]Kumagai, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* ***2004***, *126*, 13632.

Activated aromatic compounds add to *N*-carbamoyl imines in the presence of copper catalysts, and with good enantioselectivity when a chiral catalyst is used.[899] A combination of $AuCl_3$/AgOTf facilitates the addition of arenes to *N*-tosyl imines.[900] Furan derivatives add via C-2 with good enantioselectivity using a chiral phosphoric acid catalyst.[901] Alkenes add to *N*-tosyl imines with a Yb catalyst[902] an allenes add to *N*-carbamoyl imines in the presence of vanadium catalyst.[903] *N*-Carbamoyl imines, formed *in situ*, react with allylic silanes in the presence of an iodine catalyst.[904] The intramolecular addition of an alkene to an imine, facilitated by Cp_2ZrBu_2, gave a cycloalkyl amine.[905]

Arylboronates (p. 815) add to *N*-sulfonyl imines in the presence of a rhodium catalyst to give the corresponding sulfonamide.[906] Vinyl boronates also add to nitrones in the presence of Me_2Zn, transferring the vinyl group to the C=N unit.[907] Aryl boronic acids (p. 815) add the aryl group to *N*-tosyl imines using a rhodium catalyst.[908] Allylic boronates also add to aldehydes, and subsequent treatment with ammonia give the homoallylic amine.[909]

Allylic silanes, such as allyltrimethylsilane, add to *N*-substituted imines in the presence of a palladium catalyst to give the homoallylic amine.[910] Similar results are obtained when the allylic silane and imine are treated with a catalytic amount of tetrabutylammonium fluoride.[911] *N*-Tosyl imines also react with allylic silanes, and the reaction of $EtO_2C{-}CH{=}NTs$ and allyltrimethylsilane with a chiral copper catalyst gave $EtO_2C{-}CH(NHTs)CH_2CH{=}CH_2$, albeit in poor yield with modest enantioselectivity.[912] Another addition reaction converts aryl aldehydes to the imine using $Me_2N{-}SiMe_3$ and $LiClO_4$, and subsequent reaction with $Me_2PhSiCl$ gave the corresponding amine, $ArCH(SiMe_2Ph)NMe_2$.[913] Allylic trichlorosilanes add to hydrazones to give homoallylic hydrazine derivatives with excellent anti-selectivity[914]

[899]Saaby, S.; Fang, X.; Gathergood, N.; Jørgensen, K.A. *Angew. Chem. Int. Ed.* ***2000***, *39*, 4114. See also, Saaby, S.; Bayón, P.; Aburel, P.S.; Jørgensen, K.A. *J. Org. Chem.* ***2002***, *67*, 4352.

[900]Luo, Y.; Li, C.-J. *Chem. Commun.* ***2004***, 1930.

[901]Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* ***2004***, *126*, 11804. See also, Spanedda, M.V.; Ourévitch, M.; Crouse, B.; Bégué, J.-P.; Bonnet-Delpon, D. *Tetrahedron Lett.* ***2004***, *45*, 5023.

[902]Yamanaka, M.; Nishida, A.; Nakagawa, M. *J. Org. Chem.* ***2003***, *68*, 3112.

[903]Trost, B.M.; Jonasson, C. *Angew. Chem. Int. Ed.* ***2003***, *42*, 2063.

[904]Phukan, P. *J. Org. Chem.* ***2004***, *69*, 4005.

[905]Makabe, M.; Sato, Y.; Mori, M. *J. Org. Chem.* ***2004***, *69*, 6238.

[906]Ueda, M.; Saito, A.; Miyaura, N. *Synlett* ***2000***, 1637.

[907]Pandya, A.; S.U.; Pinet, S.; Chavant, P.Y.; Vallée, Y. *Eur. J. Org. Chem.* ***2003***, 3621.

[908]Kuriyama, M.; Soeta, T.; Hao, X.; Chen, Q.; Tomioka, K. *J. Am. Chem. Soc.* ***2004***, *126*, 8128.

[909]Sugiura, M.; Hirano, K.; Kobayashi, S. *J. Am. Chem. Soc.* ***2004***, *126*, 7182.

[910]Nakamura, K.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* ***1999***, *64*, 2614.

[911]Wang, D.-K.; Zhou, Y.-G.; Tang, Y.; Hou, X.-L.; Dai, L.-X. *J. Org. Chem.* ***1999***, *64*, 4233. Tetraallylsilane and TBAF, with a chiral palladium catalyst, gives chiral homoallylic amines, see Fernandes, R.A.; Yamamoto, Y. *J. Org. Chem.* ***2004***, *69*, 735.

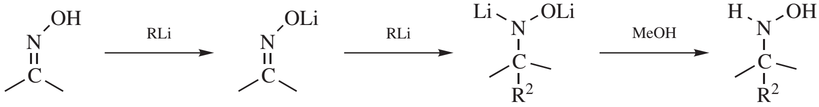
[912]Fang, X.; Johannsen, M.; Yao, S.; Gathergood, N.; Hazell, R.G.; Jørgensen, K.A. *J. Org. Chem.* ***1999***, *64*, 4844.

[913]Naimi-Jamal, M.R.; Mojtahedi, M.M.; Ipaktschi, J.; Saidi, M.R. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 3709.

[914]Hirabayashi, R.; Ogawa, C.; Sugiura, M.; Kobayashi, S. *J. Am. Chem. Soc.* ***2001***, *123*, 9493.

and with good enantioselectivity using a chiral ligand.[915] Chiral allyl silane derivatives have been developed, and add to hydrazones with good enantioselectivity.[916]

Aldehydes add via the α-carbon using proline, to give β-amino aldehydes with good selectivity to give chiral β-amino aldehydes.[917] Silyl enol ethers add to hydrazones in the presence of ZnF_2 and a chiral ligand to give chiral β-hydrazino ketones.[918] Nitro compounds add to *N*-carbamoyl imines with a chiral diamine catalyst with some enantioselectivity.[919] Nitro compounds add via carbon using a copper catalyst, and with good enantioselectivity when a chiral ligand is used.[920] Similar addition to imine derivatives was accomplished using ketene silyl acetals and Amberlyst-15.[921] Alternatively, an imine is reacted first with $Zn(OTf)_2$ and then with a ketene silyl acetal.[922] The conjugate bases of nitro compounds (formed by treatment of the nitro compound with BuLi) react with Grignard reagents in the presence of $ClCH{=}NMe_2^+\ Cl^-$ to give oximes: $RCH{=}N(O)OLi + R'MgX \rightarrow RR'C{=}NOH$.[923]



37

Many other C=N systems (phenylhydrazones, oxime ethers, etc.) give normal addition when treated with Grignard reagents; others give reductions; others give miscellaneous reactions. Organocerium reagents add to hydrazones.[924] Oximes can be converted to hydroxylamines (**37**) by treatment with 2 equivalents of an alkyllithium reagent, followed by methanol.[925] Oxime ethers add an allyl group upon reaction with allyl bromide and indium metal in water.[926] Nitrones, $R_2C{=}N^+(R')–O^-$, react with allylic bromides and Sm to give homoallylic oximes,[927] and with terminal alkynes and a zinc catalyst to give propargylic oximes.[928]

[915]Kobayashi, S.; Ogawa, C.; Konishi, H.; Sugiura, M. *J. Am. Chem. Soc.* ***2003***, *125*, 6610.

[916]Berger, R.; Duff, K.; Leighton, J.L. *J. Am. Chem. Soc.* ***2004***, *126*, 5686.

[917]Córdova, A.; Barbas III, C.F. *Tetrahedron Lett.* ***2003***, *44*, 1923; Notz, W.; Tanaka, F.; Watanabe, S.; Chowdari, N.S.; Turner, J.M.; Thayumanavan, R.; Barbas III, C.F. *J. Org. Chem.* ***2003***, *68*, 9624; Chowdari, N.S.; Suri, J.T.; Barbas III, C.F. *Org. Lett.* ***2004***, *6*, 2507.

[918]Hamada, T.; Manabe, K.; Kobayashi, S. *J. Am. Chem. Soc.* ***2004***, *126*, 7768. For a similar reaction using a bismuth catalyst, see Ollevier, T.; Nadeau, E. *J. Org. Chem.* ***2004***, *69*, 9292.

[919]Nugent, B.M.; Yoder, R.A.; Johnston, J.N. *J. Am. Chem. Soc.* ***2004***, *126*, 3418.

[920]Nishiwaki, N.; Knudson, K.R.; Gothelf, K.V.; Jørgensen, K.A. *Angew. Chem. Int. Ed.* ***2001***, *40*, 2992.

[921]Shimizu, M.; Itohara, S.; Hase, E. *Chem. Commun.* ***2001***, 2318.

[922]Ishimaru, K.; Kojima, T. *J. Org. Chem.* ***2003***, *68*, 4959.

[923]Fujisawa, T.; Kurita, Y.; Sato, T. *Chem. Lett.* ***1983***, 1537.

[924]Denmark, S.E.; Edwards, J.P.; Nicaise, O. *J. Org. Chem.* ***1993***, *58*, 569.

[925]Richey Jr., H.G.; McLane, R.C.; Phillips, C.J. *Tetrahedron Lett.* ***1976***, 233.

[926]Bernardi, L.; Cerè, V.; Femoni, C.; Pollicino, S.; Ricci, A. *J. Org. Chem.* ***2003***, *68*, 3348.

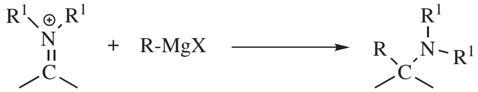
[927]Laskar, D.D.; Prajapati, D.; Sandu, J.S. *Tetrahedron Lett.* ***2001***, *42*, 7883.

[928]Frantz, D.E.; Fässler, R.; Carreira, E.M. *J. Am. Chem. Soc.* ***1999***, *121*, 11245. See Pinet, S.; Pandya, S.U.; Chavant, P.Y.; Ayling, A.; Vallee, Y. *Org. Lett.* ***2002***, *4*, 1463.

Grignard reagents also add to nitrones.[929] Nitrones react with $CH_2{=}CHCH_2InBr$ in aq. DMF to give the homoallylic oxime[930] and silyl ketene acetals add in the presence of a chiral titanium catalyst to good enantioselectivity.[931] Hydrazone derivatives react with iodoalkenes in the presence of $InCl_3$ and $Mn_2(CO)_{10}$ under photochemical conditions to give the hydrazine derivative.[932] Indium metal promotes the addition of alkyl iodides to hydrazones.[933] A hydrazone can be formed *in situ* by reacting an aldehyde with a hydrazine derivative, and in the presence of tetrallyltin and a scandium catalysts, homoallylic hydrazine derivatives are formed.[934] Ketene dithioacetals add to hydrazones using a chiral zirconium catalyst to give a pyrazolidine.[935]

Radical addition to imines is known. Carbon-centered radicals add to imines.[936] The reaction of an alkyl halide with BEt_3 in aqueous methanol, for example, gives the imine addition product, an alkylated amine.[937] Secondary alkyl iodides add to *O*-alkyl oximes in the presence of BEt_3 and AIBN, and this methodology was used to convert $MeO_2C{-}CH{=}NOBn$ to $MeO_2C{-}CH(R)NOBn$.[938] Benzylic halides adds to imines under photochemical conditions, and in the presence of 1-benzyl-1,4-dihydronicotinamide[939] or with BEt_3 in aqueous methanol.[940] Tertiary alkyl iodides add to oxime ethers using $BF_3{\bullet}OEt_2$ in the presence of BEt_3/O_2.[941]

Iminium salts[942] give tertiary amines directly, with just R adding:



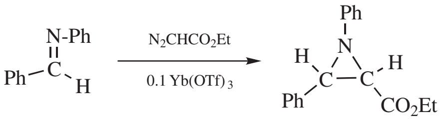
Chloroiminium salts $ClCH{=}NR'_2\ Cl^-$ (generated *in situ* from an amide $HCONR'_2$ and phosgene $COCl_2$) react with 2 equivalents of a Grignard reagent RMgX, one adding to the C=N and the other replacing the Cl, to give tertiary amines $R_2CHNR'_2$.[943]

OS **IV**, 605; **VI**, 64. Also see OS **III**, 329.

[929]See Merino, P.; Tejero, T. *Tetrahedron* ***2001***, *57*, 8125.
[930]Kumar, H.M.S.; Anjaneyulu, S.; Reddy, E.J.; Yadav, J.S. *Tetrahedron Lett.* ***2000***, *41*, 9311.
[931]Murahashi, S.-I.; Imada, Y.; Kawakami, T.; Harada, K.; Yonemushi, Y.; Tomita, N. *J. Am. Chem. Soc.* ***2002***, *124*, 2888.
[932]Friedstad, G.K.; Qin, J. *J. Am. Chem. Soc.* ***2001***, *123*, 9922.
[933]Miyabe, H.; Ueda, M.; Nishimura, A.; Naito, T. *Tetrahedron* ***2004***, *60*, 4227.
[934]Kobayashi, S.; Hamada, T.; Manabe, K. *Synlett* ***2001***, 1140.
[935]Yamshita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* ***2004***, *126*, 11279.
[936]For a review, see Friestad, G.K. *Tetrahedron* ***2001***, *57*, 5461.
[937]Miyabe, H.; Ueda, M.; Naito, T. *J. Org. Chem.* ***2000***, *65*, 5043.
[938]Miyabe, H.; Ueda, M.; Yoshioka, N.; Yamakawa, K.; Naito, T. *Tetrahedron* ***2000***, *56*, 2413.
[939]Jin, M.; Zhang, D.; Yang, L.; Liu, Y.; Liu, Z. *Tetrahedron Lett.* ***2000***, *41*, 7357.
[940]McNabb, S.B.; Ueda, M.; Naito, T. *Org. Lett.* ***2004***, *6*, 1911.
[941]Halland, N.; Jørgensen, K.A. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 1290.
[942]For a review of nucleophilic addition to iminium salts, see Paukstelis, J.V.; Cook, A.G., in Cook, A.G. *Enamines*, 2nd ed., Marcel Dekker, NY, ***1988***, pp. 275–356.
[943]Wieland, G.; Simchen, G. *Liebigs Ann. Chem.* ***1985***, 2178.

16-32 Addition of Carbenes and Diazoalkanes to C=N Compounds

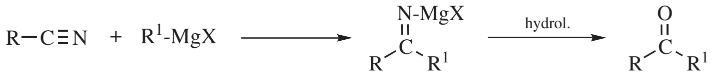
In the presence of metal catalysts such as $Yb(OTf)_3$, diazoalkanes add to imines to generate aziridines. An example is:[944]



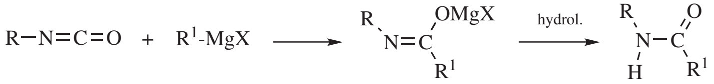
The reaction is somewhat selective for the cis-diastereomer. The use of chiral additives in this reaction leads to aziridines enantioselectively.[945] Imines can be formed by the reaction of an aldehyde and an amine, and subsequent treatment with Me_3SiI and butyllithium gives an aziridine.[946] *N*-Tosyl imines react with diazoalkenes to form *N*-tosyl aziridines, with good cis-selectivity[947] and modest enantioselectivity in the presence of a chiral copper catalyst,[948] but excellent enantioselectivity with a chiral rhodium catalyst.[949]. It is noted that *N*-tosyl aziridines are formed by the reaction of an alkene with PhI=NTs and a copper catalyst.[950] The reaction of alkenes with diazo compounds is discussed in **15-53**.

16-33 The Addition of Grignard Reagents to Nitriles and Isocyanates

Alkyl,oxo-de-nitrilo-tersubstitution (Overall transformation)



***N*-Hydro-*C*-alkyl-addition**



Ketones can be prepared by addition of Grignard reagents to nitriles, followed by hydrolysis of the initially formed imine anion. Many ketones have been made in this manner, though when both R groups are alkyl, yields are not high.[951] Yields

[944]Nagayama, S.; Kobayashi, S. *Chem Lett.* ***1998***, 685. Also see, Rasmussen, K.G.; Jørgensen, K.A. *J. Chem. Soc., Chem. Commun.* ***1995***, 1401.

[945]Hansen, K.B.; Finney, N.S.; Jacobsen, E.N. *Angew. Chem. Int. Ed.* ***1995***, *34*, 676.

[946]Reetz, M.T.; Lee, W.K. *Org. Lett.* ***2001***, *3*, 3119.

[947]Aggarwal, V.K.; Ferrara, M. *Org. Lett.* ***2000***, *2*, 4107; Hori, R.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* ***2000***, *41*, 9455; Krumper, J.R.; Gerisch, M.; Suh, J.M.; Bergman, R.G.; Tilley, T.D. *J. Org. Chem.* ***2003***, *68*, 9705; Williams, A.L.; Johnston, J.N. *J. Am. Chem. Soc.* ***2004***, *126*, 1612; Sun, W.; Xia, C.-G.; Wang, H.-W. *Tetrahedron Lett.* ***2003***, *44*, 2409.

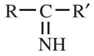
[948]Juhl, K.; Hazell, R.G.; Jørgensen, K.A. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 2293.

[949]Aggarwal, V.K.; Alonso, E.; Fang, G.; Ferrara, M.; Hynd, G.; Porcelloni, M. *Angew. Chem. Int. Ed.* ***2001***, *40*, 1433.

[950]Handy, S.T.; Czopp, M. *Org. Lett.* ***2001***, *3*, 1423.

[951]For a review, see Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 767–845.

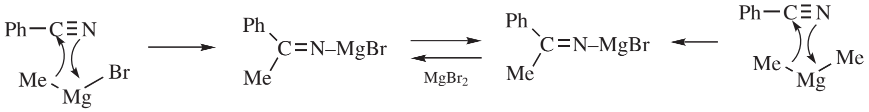
can be improved by the use of Cu(I) salts[952] or by using benzene containing one equivalent of ether as the solvent, rather than ether alone.[953] The ketimine salt does not in general react with Grignard reagents: Hence tertiary alcohols or tertiary alkyl amines are not often side products.[954] By careful hydrolysis of the salt it is sometimes possible to isolate ketimines,[955]



especially when R and R′ = aryl. The addition of Grignard reagents to the C≡N group is normally slower than to the C=O group, and cyano group containing aldehydes add the Grignard reagent without disturbing the CN group.[956] Other metal compounds have been used, including Sm with allylic halides[957] and organocerium compounds such as $MeCeCl_2$.[958] Allylic halides react with an excess of zinc metal in the presence of 40% $AlCl_3$, and in the presence of a nitrile homoallylic ketones are produced after hydrolysis.[959] Benzonitrile reacts as with iodopropane and a mixture of SmI_2 and NiI_2 catalysts to give 1-phenyl-1-butanone.[960]

Addition of Grignard reagents[961] or organolithium reagents[962] to ω-halo nitriles leads to 2-substituted cyclic imines.

The following mechanism has been proposed for the reaction of the methyl Grignard reagent with benzonitrile:[963]



Arenes add to nitriles in the presence of a palladium catalyst in DMSO/trifluoroacetic acid to give a diaryl ketone.[964]

The addition of Grignard reagents to isocyanates gives, after hydrolysis, *N*-substituted amides.[965] This is a very good reaction and can be used to prepare

[952]Weiberth, F.J.; Hall, S.S. *J. Org. Chem.* ***1987***, *52*, 3901.
[953]Canonne, P.; Foscolos, G.B.; Lemay, G. *Tetrahedron Lett.* ***1980***, 155.
[954]For examples where tertiary amines have been made the main products, see Alvernhe, G.; Laurent, A. *Tetrahedron Lett.* ***1973***, 1057; Gauthier, R.; Axiotis, G.P.; Chastrette, M. *J. Organomet. Chem.* ***1977***, *140*, 245.
[955]Pickard, P.L.; Toblert, T.L. *J. Org. Chem.* ***1961***, *26*,4886.
[956]Cason, J.; Kraus, K.W.; McLeod Jr., W.D. *J. Org. Chem.* ***1959***, *24*, 392.
[957]Yu, M.; Zhang, Y.; Guo, H. *Synth. Commun.* ***1997***, *27*, 1495.
[958]Ciganek, E. *J. Org. Chem.* ***1992***, *57*, 4521.
[959]Lee, A.S.-Y.; Lin, L.-S. *Tetrahedron Lett.* ***2000***, *41*, 8803.
[960]Kang, H.-Y.; Song, S.-E. *Tetrahedron Lett.* ***2000***, *41*, 937.
[961]Fry, D.F.; Fowler, C.B.; Dieter, R.K. *Synlett* ***1994***, 836.
[962]Gallulo, V.; Dimas, L.; Zezza, C.A.; Smith, M.B. *Org. Prep. Proceed. Int.* ***1989***, *21*, 297.
[963]Ashby, E.C.; Chao, L.; Neumann, H.M. *J. Am. Chem. Soc.* ***1973***, *95*, 4896, 5186.
[964]Zhou, C.; Larock, R.C. *J. Am. Chem. Soc.* ***2004***, *126*, 2302.
[965]For a review of this and related reactions, see Screttas, C.G.; Steele, B.R. *Org. Prep. Proced. Int.* ***1990***, *22*, 271.

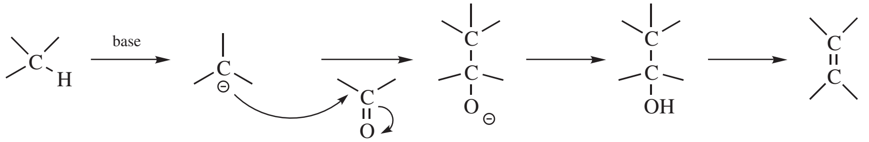
derivatives of alkyl and aryl halides. The reaction has also been performed with alkyllithium compounds.[966] Isothiocyanates give *N*-substituted thioamides. Other organometallic compounds add to isocyanates. Vinyltin reagents lead to conjugated amides.[967]

It is noted that terminal alkynes add to the carbon of an isonitrile in the presence of a uranium complex, giving a propargylic imine.[968]

OS **III**, 26, 562; **V**, 520.

G. Carbon Attack by Active Hydrogen Compounds

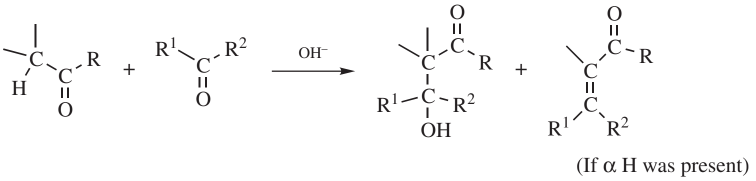
Reactions **16-34–16-50** are base-catalyzed condensations (although some of them are also catalyzed to acids).[969] In **16-34–16-44**, a base removes a C—H proton to give a carbanion, which then adds to a C=O. The oxygen acquires a proton, and the resulting alcohol may or may not be dehydrated, depending on whether an α hydrogen is present and on whether the new double bond would be in conjugation with double bonds already present:



The reactions differ in the nature of the active hydrogen component and the carbonyl component. Table 16.2 illustrates the differences. Reaction **16-50** is an analogous reaction involving addition to C≡N.

16-34 The Aldol Reaction[970]

***O*-Hydro-*C*-(α-acylalkyl)-addition; α-Acylalkylidine-de-oxo-bisubstitution**



[966]LeBel, N.A.; Cherluck, R.M.; Curtis, E.A. *Synthesis* ***1973***, 678; Cooke, Jr., M.P.; Pollock, C.M. *J. Org. Chem.* ***1993***, *58*, 7474. For another method, see Einhorn, J.; Luche, J.L. *Tetrahedron Lett.* ***1986***, *27*, 501.

[967]Niestroj, M.; Neumann, W.P.; Thies, O. *Chem. Ber.* ***1994***, *127*, 1131.

[968]Barnea, E.; Andrea, T.; Kapon, M.; Berthet, J.-C.; Ephritikhine, M.; Eisen, M.S. *J. Am. Chem. Soc.* ***2004***, *126*, 10860.

[969]For reviews, see House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 629–682; Reeves, R.L., in Patai, S. *The Chemistry of the Carbonyl Group*, pt. 1, Wiley, NY, ***1966***, pp. 567–619. See also, Stowell, J.C. *Carbanions in Organic Synthesis*, Wiley, NY, ***1979***.

[970]See Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY, ***2001***, pp. 740–745.

TABLE 16.2. Base-Catalyzed Condensations Showing the Active-Hydrogen Components and the Carbonyl Compounds

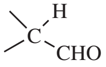
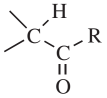
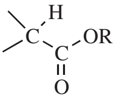
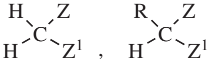
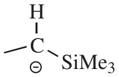
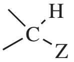
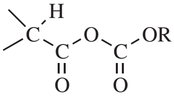
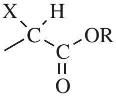
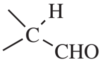
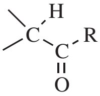
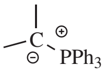
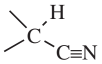
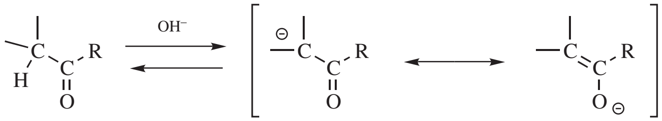
Reaction	Active-Hydrogen Component	Carbonyl Component	Subsequent Reaction
16-34	Aldehyde  Ketone 	Aldehyde, ketone	Dehydration may follow
Aldol reaction			
16-36	Ester 	Aldehyde, ketone (usually without α-hydrogens)	Dehydration may follow
16-38	 and similar molecules	Aldehyde, ketone (usually without α-hydrogens)	Dehydration (usually follows)
Knoevenagel reaction			
16-41		Aldehyde, ketone may follow	Dehydration
Peterson reaction			
16-42	 Z = COR, COOR, NO_2	CO_2, CS_2	
16-39	Anhydride 	Aromatic aldehyde usually follows	Dehydration
Perkin reaction			
16-40	α-Halo Ester 	Aldehyde, Ketone (S_N reaction) follows	Epoxidation
Darzen's reaction			
16-43	Aldehyde  Ketone 	Formaldehyde reaction follows	Crossed-Cannizzaro

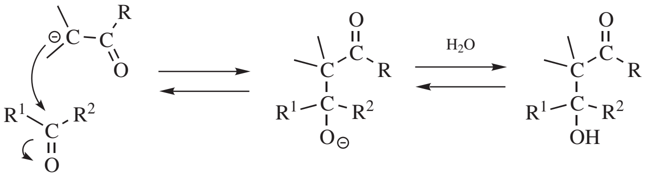
TABLE 16.2. (*Continued*)

Reaction	Active-Hydrogen Component	Carbonyl Component	Subsequent Reaction
Tollens' reaction			
16-44	Phosphorous ylid 	Aldehyde, ketone	"Dehydration" always follows
Wittig reaction			
16-50	Nitrile 	Nitrile	
Thorpe reaction			

In the *aldol reaction*,[971] the α carbon of one aldehyde or ketone molecule adds to the carbonyl carbon of another.[972] Although acid-catalyzed aldol reactions are known,[973] the most common form of the reaction uses a base. There is evidence that an SET mechanism can intervene when the substrate is an aromatic ketone.[974] Although hydroxide was commonly used in early versions of this reaction, stronger bases, such as alkoxides (RO^-) or amides (R_2N^-), are also common. Amine bases have been used.[975] Hydroxide ion is not a strong enough base to convert substantially all of an aldehyde or ketone molecule to the corresponding enolate ion, that is., the equilibrium lies well to the left, for both aldehydes and



ketones. Nevertheless, enough enolate ion is present for the reaction to proceed:



[971]This reaction is also called the *aldol condensation*, though, strictly speaking, this term applies to the formation only of the α,β-unsaturated product, and not the aldol.

[972]For reviews, see Thebtaranonth, C.; Thebtaranonth, Y., in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 1, Wiley, NY, ***1989***, pp. 199–280, 199–212; Hajos, Z.G., in Augustine, R.L. *Carbon–Carbon Bond Formation*, Vol. 1; Marcel Dekker, NY, ***1979***; pp. 1–84; Nielsen, A.T.; Houlihan, W.J. *Org. React.* ***1968***, *16*, 1.

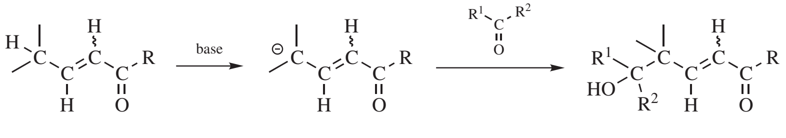
[973]For example, see Mahrwald, R.; Gündogan, B. *J. Am. Chem. Soc.* ***1998***, *120*, 413.

[974]Ashby, E.C.; Argyropoulos, J.N. *J. Org. Chem.* ***1986***, *51*, 472.

[975]Trost, B.M.; Silcoff, E.R.; Ito, H. *Org. Lett.* ***2001***, *3*, 2497.

This equilibrium lies further to the right with alkoxide and especially with amide bases, depending on the solvent. Protic solvents, such as water or alcohol, are acidic enough to react with the enolate anion and shift the equilibrium to the left. In an aprotic solvent, such as ether or THF, with a strong amide base, such as lithium diisopropylamide (LDA, p. 389), the equilibrium lies more to the right.[976] A variety of amide bases can be used to deprotonate the ketone or aldehyde, and in the case of an unsymmetrical ketone removal of the more acidic proton leads to the kinetic enolate anion.[977] Note that a polymer-bound amide base has been used[978] and solid-phase chiral lithium amides are known.[979] A polymer-supported phosphoramide has been used as a catalyst for the aldol condensation.[980] The product is a β-hydroxy aldehyde (called an *aldol*) or ketone, which in some cases is dehydrated during the course of the reaction. In aprotic solvents with a mild workup procedure, however, the aldol is readily isolated unless the substrate is an aromatic aldehyde or ketone. The aldol reaction has been done in ionic liquids.[981] Even if the dehydration is not spontaneous, it can usually be done easily, since the new double bond is in conjugation with the C=O bond; so that this is a method of preparing α,β-unsaturated aldehydes and ketones, as well as β-hydroxy aldehydes and ketones. One-pot procedures have been reported to give the conjugated product.[982] The entire reaction is an equilibrium (including the dehydration step), and α,β-unsaturated and β-hydroxy aldehydes and ketones can be cleaved by treatment with $^-$OH (the *retrograde aldol reaction*). The *retro*-aldol condensation has been exploited for crossed-aldol reactions.[983] A vinylogous aldol reaction is known[984] as is a 1"double" aldol.[985] Enzyme-mediated aldol reactions have been reported using two aldehydes, including formaldehyde.[986]

Under the principle of vinylogy, the active hydrogen can be one in the γ position of an α,β-unsaturated carbonyl compound:



[976]For a discussion of solvent and temperature effects, see Cainelli, G.; Galletti, P.; Giacomini, D.; Orioli, P. *Tetrahedron Lett.* ***2001***, *42*, 7383.

[977]See Xie, L.; Vanlandeghem, K.; Isenberger, K.M.; Bernier, C. *J. Org. Chem.* ***2003***, *68*, 641; Zhao, P.; Lucht, B.L.; Kenkre, S.L.; Collum, D.B. *J. Org. Chem.* ***2004***, *69*, 242; Zhao, P.; Condo, A.; Keresztes, I.; Collum, D.B. *J. Am. Chem. Soc.* ***2004***, *126*, 3113.

[978]Seki, A.; Ishiwata, F.; Takizawa, Y.; Asami, M. *Tetrahedron* ***2004***, *60*, 5001.

[979]Johansson, A.; Abrahamsson, P.; Davidsson, Ö. *Tetrahedron Asymmetry* ***2003***, *14*, 1261.

[980]Flowers II, R.A.; Xu, X.; Timmons, C.; Li, G. *Eur. J. Org. Chem.* ***2004***, 2988.

[981]In bmim BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate: Zheng, X.; Zhang, Y. *Synth. Commun.* ***2003***, 161.

[982]Kourouli, T.; Kefalas, P.; Ragoussis, N.; Ragoussis, V. *J. Org. Chem.* ***2002***, *67*, 4615.

[983]For an example, see Simpura, I.; Nevalainen, V. *Angew. Chem. Int. Ed.* ***2000***, *39*, 3422.

[984]For reviews, see Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G.; *Chem. Rev.* ***2000***, *100*, 1929; Casiraghi, G.; Zanardi, E.; Rassu, G. *Pure Appl. Chem.* ***2000***, *72*, 1645.

[985]For a discussion of the mechanism of this reaction see Abiko, A.; Inoue, T.; Masamune, S. *J. Am. Chem. Soc.* ***2002***, *124*, 10759.

[986]Demir, A.S.; Ayhan, P.; Igdir, A.C.; Duygu, A.N. *Tetrahedron* ***2004***, *60*, 6509.

The scope of the aldol reaction may be discussed under five headings:

1. *Reaction between Two Molecules of the Same Aldehyde*. Hydroxide or alkoxide bases are used in protic solvents,[987] and the reaction is quite feasible. Many aldehydes have been converted to aldols and/or their dehydration products in this manner. The most effective catalysts are basic ion-exchange resins. Of course, the aldehyde must possess an α hydrogen.
2. *Reaction between Two Molecules of the Same Ketone*. With hydroxide or alkoxide bases in protic solvents the equilibrium lies well to the left,[988] and the reaction is feasible only if the equilibrium can be shifted. This can often be done by allowing the reaction to proceed in a Soxhlet extractor (e.g., see OS **I**, 199). Two molecules of the same ketone can also be condensed without a Soxhlet extractor,[989] by treatment with basic Al_2O_3.[990] Unsymmetrical ketones condense on the side that has more hydrogens. An exception is butanone, which reacts at the CH_2 group with acid catalysts, though with basic catalysts, it too reacts at the CH_3 group.

   Alternatively, the use of an amide base, such as LDA or lithium hexamethyldisilazide (p. 389), in aprotic solvents, such as ether or THF, at low temperatures, generates an enolate anion under conditions where the equilibrium lies more to the right. A second equivalent of the ketone can then be added. Clearly, this technique is effective in reactions of aldehydes.
3. *Reaction between Two Different Aldehydes*. In the most general case, this will produce a mixture of four products (eight, if the alkenes are counted). However, if one aldehyde does not have an α hydrogen, only two aldols are possible, and in many cases the crossed product is the main one. The crossed-aldol reaction is often called the *Claisen–Schmidt reaction*.[991] The crossed aldol is readily accomplished using amide bases in aprotic solvent. The first aldehyde is treated with LDA in THF at −78°C, for example, to form the enolate anion. Subsequent treatment with a second aldehyde leads to the mixed aldol product. The crossed aldol of two aldehydes has been done using potassium *tert*-butoxide and $Ti(OBu)_4$.[992]
4. *Reaction between Two Different Ketones*. This is seldom attempted with hydroxide or alkoxide bases in protic solvents since similar considerations apply to those discussed for aldehydes. This reaction is commonly done with amide bases in aprotic solvents, but with somewhat more difficulty than with aldehydes.

[987]For discussions of equilibrium constants in aldol reactions, see Guthrie, J.P.; Wang, X. *Can. J. Chem.* ***1991***, *69*, 339; Guthrie, J.P. *J. Am. Chem. Soc.* ***1991***, *113*, 7249, and references cited therein.

[988]The equilibrium concentration of the product from acetone in pure acetone was determined to be 0.01%: Maple, S.R.; Allerhand, A. *J. Am. Chem. Soc.* ***1987***, *109*, 6609.

[989]For another method, see Barot, B.C.; Sullins, D.W.; Eisenbraun, E.J. *Synth. Commun.* ***1984***, *14*, 397.

[990]Muzart, J. *Synthesis* ***1982***, 60; *Synth. Commun.* ***1985***, *15*, 285.

[991]For an aqueous version, see Buonora, P.T.; Rosauer, K.G.; Dai, L. *Tetrahedron Lett.* ***1995***, *36*, 4009.

[992]Han, Z.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* ***2000***, *41*, 4415.

5. *Reaction between an Aldehyde and a Ketone*. This is usually feasible with hydroxide or alkoxides bases in protic solvents, particularly when the aldehyde has no α hydrogen, since there is no competition from ketone condensing with itself.[993] This is also called the *Claisen–Schmidt reaction*. Even when the aldehyde has an α hydrogen, it is generally the α carbon of the ketone that adds to the carbonyl of the aldehyde, not the other way around. Mixtures are usually produced, however. If the ketone or the aldehyde is treated with an amide base in aprotic solvents, a second aldehyde or ketone can be added to give the aldolate with high regioselectivity. The reaction can be also made regioselective by preparing an enol derivative of the ketone separately[994] and then adding this to the aldehyde (or ketone). Other types of preformed derivatives that react with aldehydes and ketones are enamines (with a Lewis acid catalyst),[995] and enol borinates $R'CH{=}CR^2{-}OBR_2$[996] (which can be synthesized by **15-27**) or directly from an aldehyde or ketone[997]). Preformed metallic enolates are also used. For example, lithium enolates[998] (prepared by **12-23**) react with the substrate in the presence of $ZnCl_2$;[999] in this case the aldol product is stabilized by chelation of its two oxygen atoms with the zinc ion.[1000] Other metallic enolates can be used for aldol reactions, either preformed or generated *in situ* with a catalytic amount of a metal compound. Metals used for this purpose include Mg,[1001] Ti,[1002] Zr,[1003] Pd,[1004]

[993]For a study of the rate and equilibrium constants in the reaction between acetone and benzaldehyde, see Guthrie, J.P.; Cossar, J.; Taylor, K.F. *Can. J. Chem.* ***1984***, *62*, 1958. For a microwave induced reaction using aqueous NaOH, see Kad, G.L.; Kaur, K.P.; Singh, V.; Singh, J. *Synth. Commun.* ***1999***, *29*, 2583.

[994]For some other aldol reactions with preformed enol derivatives, see Mukaiyama, T. *Isr. J. Chem.* ***1984***, *24*, 162; Caine, D., in Augustine, R.L., *Carbon–Carbon Bond Formation*, Vol. 1, Marcel Dekker, NY, ***1979***, pp. 264–276.

[995]Takazawa, O.; Kogami, K.; Hayashi, K. *Bull. Chem. Soc. Jpn.* ***1985***, *58*, 2427.

[996]Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* ***1980***, *53*, 174; Hooz, J.; Oudenes, J.; Roberts, J.L.; Benderly, A. *J. Org. Chem.* ***1987***, *52*, 1347; Nozaki, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* ***1988***, *29*, 1041. For a review, see Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, pp. 324–333. For an *ab initio* study see Murga, J.; Falomir, E.; Carda, M.; Marco, J.A. *Tetrahedron* ***2001***, *57*, 6239.

[997]For conversion of ketones to either (*Z*) or (*E*) enol borinates, see, for example, Evans, D.A.; Nelson, J.V.; Vogel, E.; Taber, T.R. *J. Am. Chem. Soc.* ***1981***, *103*, 3099; Brown, H.C.; Dhar, R.K.; Bakshi, R.K.; Pandiarajan, P.K.; Singaram, B. *J. Am. Chem. Soc.* ***1989***, *111*, 3441; Brown, H.C.; Ganesan, K. *Tetrahedron Lett.* ***1992***, *33*, 3421.

[998]For a complete structure–energy analysis of one such reaction, see Arnett, E.M.; Fisher, F.J.; Nichols, M.A.; Ribeiro, A.A. *J. Am. Chem. Soc.* ***1990***, *112*, 801.

[999]House, H.O.; Crumrine, D.S.; Teranishi, A.Y.; Olmstead, H.D. *J. Am. Chem. Soc.* ***1973***, *95*, 3310.

[1000]It has been contended that such stabilization is not required: Mulzer, J.; Brüntrup, G.; Finke, J.; Zippel, M. *J. Am. Chem. Soc.* ***1979***, *101*, 7723.

[1001]Wei, H.-X.; Jasoni, R.L.; Shao, H.; Hu, J.; Paré, P.W. *Tetrahedron* ***2004***, *60*, 11829.

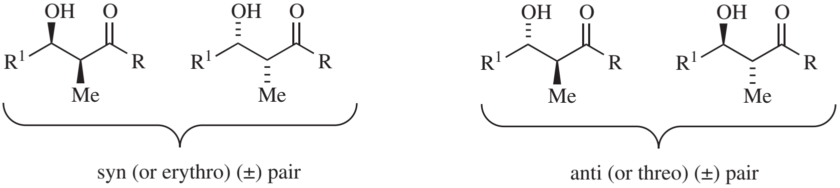
[1002]Stille, J.R.; Grubbs, R.H. *J. Am. Chem. Soc.* ***1983***, *105*, 1664; Mahrwald, R.; Costisella, B.; Gündogan, B. *Tetrahedron Lett.* ***1997***, *38*, 4543. For the use of $Ti(O\textit{i}Pr)_4$ to modify syn/anti ratios of aldol products, see Mahrwald, R.; Costisella, B.; Gündogan, B. *Synthesis* ***1998***, 262.

[1003]Evans, D.A.; McGee, L.R. *Tetrahedron Lett.* ***1980***, *21*, 3975; *J. Am. Chem. Soc.* ***1981***, *103*, 2876.

[1004]Nokami, J.; Mandai, T.; Watanabe, H.; Ohyama, H.; Tsuji, J. *J. Am. Chem. Soc.* ***1989***, *111*, 4126.

In,[1005] Sn,[1006] La,[1007] and Sm,[1008] all of which give products with moderate to excellent diastereoselectivity[1009] and regioselectivity. α-Alkoxy ketones react with lithium enolates particularly rapidly.[1010] A bis(aldol) condensation has been reported with epoxy ketones and aldehydes using SmI_2.[1011] Vinyl silanes react with aldehydes in the presence of a copper catalyst to vie the aldol product.[1012]

The reactions with preformed enol derivatives provide a way to control the stereoselectivity of the aldol reaction.[1013] As with the Michael reaction (**15-24**), the aldol reaction creates two new stereogenic centers, and, in the most general case, there are four stereoisomers of the aldol product (two racemic diastereomers), which can be represented as



Among the preformed enol derivatives used for diastereoselective aldol condensations have been enolates of Li,[1014] Mg, Ti,[1015] Zr,[343] and Sn,[1016] silyl enol

[1005]Loh, T.-P.; Wei, L.-L.; Feng, L.-C. *Synlett* ***1999***, 1059. For an example using ultrasound and $InCl_3$, see Loh, T.-P.; Feng, L.-C.; Wei, L.-L. *Tetrahedron* ***2001***, *57*, 4231.

[1006]Yanagisawa, A.; Kimura, K.; Nakatsuka, Y.; Yamamoto, H. *Synlett* ***1998***, 958.

[1007]Kobayashi, S.; Hachiya, I.; Takahori, T. *Synthesis* ***1993***, 371.

[1008]Yokoyama, Y.; Mochida, K. *Synlett* ***1996***, 445; Sasai, H.; Arai, S.; Shibasaki, M. *J. Org.Chem.* ***1994***, *59*, 2661. Also see, Bao, W.; Zhang, Y.; Wang, J. *Synth. Commun.* ***1996***, *26*, 3025.

[1009]For a review, see Mahrwald, R. *Chem. Rev.* ***1999***, *99*, 1095.

[1010]Das, G.; Thornton, E.R. *J. Am. Chem. Soc.* ***1990***, *112*, 5360.

[1011]Mukaiyama, T.; Arai, H.; Shiina, I. *Chem. Lett.* ***2000***, 580.

[1012]Yang, B.-Y.; Chen, X.-M.; Deng, G.-J.; Zhang, Y.-L.; Fan, Q.-H. *Tetrahedron Lett.* ***2003***, *44*, 3535.

[1013]For reviews, see Heathcock, C.H. *Aldrichimica Acta* ***1990***, *23*, 99; *Science* ***1981***, *214*, 395; Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, ***1986***, pp. 193–220; Heathcock, C.H., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 3, Academic Press, NY, ***1984***, pp. 111–212; Heathcock, C.H., in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, pt. B, Elsevier, NY, ***1984***, pp. 177–237; Evans, D.A.; Nelson, J.V.; Taber, T.R. *Top. Stereochem.* ***1982***, *13*, 1; Evans, D.A. *Aldrichimica Acta* ***1982***, *15*, 23; Braun, M.; Sacha, H.; Galle, D.; Baskaran, S. *Pure Appl. Chem.* ***1996***, *68*, 561. For a discussion of how configuration and conformation influence the stereochemistry of aldols, see Kitamura, M.; Nakano, K.; Miki, T.; Okada, M.; Noyori, R. *J. Am. Chem. Soc.* ***2001***, *123*, 8939.

[1014]Fellmann, P.; Dubois, J.E. *Tetrahedron* ***1978***, *34*, 1349; Heathcock, C.H.; Pirrung, M.C.; Montgomery, S.H.; Lampe, J. *Tetrahedron* ***1981***, *37*, 4087; Masamune, S.; Ellingboe, J.W.; Choy, W. *J. Am. Chem. Soc.* ***1982***, *104*, 5526; Ertas, M.; Seebach, D. *Helv. Chim. Acta* ***1985***, *68*, 961.

[1015]Nerz-Stormes, M.; Thornton, E.R. *Tetrahedron Lett.* ***1986***, 897; Evans, D.A.; Rieger, D.L.; Bilodeau, M.T.; Urpí, F. *J. Am. Chem. Soc.* ***1991***, *113*, 1047; Cosp. A.; Larrosa, I.; Vilasís, I.; Romea, P.; Urpí, F.; Vilarrasa, J. *Synlett* ***2003***, 1109.

[1016]Mukaiyama, T.; Iwasawa, N.; Stevens, R.W.; Haga, T. *Tetrahedron* ***1984***, *40*, 1381; Labadie, S.S.; Stille, J.K. *Tetrahedron* ***1984***, *40*, 2329; Yura, T.; Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* ***1986***, 187. See also, Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* ***1983***, *24*, 3347.

ethers,[1017] enol borinates,[1018] and enol borates $R'CH{=}CR^2{-}OB(OR)_2$.[1019] The nucleophilicity of silyl enol ethers has been examined.[1020] Base-induced formation of the enolate anion generally leads to a mixture of (*E*)- and (*Z*)-isomers, and dialkyl amide bases are used in most cases. The (E/Z) stereoselectivity depends on the structure of the lithium dialkylamide base, with the highest (E/Z) ratios obtained with LiTMP-butyllithium mixed aggregates in THF.[1021] The use of LiHMDS resulted in a reversal of the (E/Z) selectivity. In general, metallic (*Z*) enolates give the syn (or erythro) pair, and this reaction is highly useful for the diastereoselective synthesis of these products.[1022] The (*E*) isomers generally react nonstereoselectively. However, anti (or threo) stereoselectivity has been achieved in a number of cases, with titanium enolates,[1023] with magnesium enolates,[1024] with certain enol borinates,[1025] and with lithium enolates at −78°C.[1026] Enolization accounts for syn–anti isomerization of aldols.[1027] In another variation, a β-keto Weinreb amide (see **16-82**) reacted with $TiCl_4$ and Hünig's base (iPr$_2$NEt) and then an aldehyde to give the β-hydroxy ketone.[1028]

[1017]Matsuda, I.; Izumi, Y. *Tetrahedron Lett.* ***1981***, *22*, 1805; Yamamoto, Y.; Maruyama, K.; Matsumoto, K. *J. Am. Chem. Soc.* ***1983***, *105*, 6963; Sakurai, H.; Sasaki, K.; Hosomi, A. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 3195; Hagiwara, H.; Kimura, K.; Uda, H. *J. Chem. Soc., Chem. Commun.* ***1986***, 860.

[1018]Evans, D.A.; Nelson, J.V.; Vogel, E.; Taber, T.R. *J. Am. Chem. Soc.* ***1981***, *103*, 3099; Evans, D.A.; Bartroli, J.; Shih, T.L. *J. Am. Chem. Soc.* ***1981***, *103*, 2127; Masamune, S.; Choy, W.; Kerdesky, F.A.J.; Imperiali, B. *J. Am. Chem. Soc.* ***1981***, *103*, 1566; Paterson, I.; Goodman, J.M.; Lister, M.A.; Schumann, R.C.; McClure, C.K.; Norcross, R.D. *Tetrahedron* ***1990***, *46*, 4663; Walker, M.A.; Heathcock, C.H. *J. Org. Chem.* ***1991***, *56*, 5747. For reviews, see Paterson, I. *Chem. Ind. (London)* ***1988***, 390; Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, p. 324.

[1019]Hoffmann, R.W.; Ditrich, K.; Fröch, S. *Liebigs Ann. Chem.* ***1987***, 977.

[1020]Patz, M.; Mayr, H. *Tetrahedron Lett.* ***1993***, *34*, 3393.

[1021]Pratt, L. M.; Newman, A.; Cyr, J. S.; Johnson, H.; Miles, B.; Lattier, A.; Austin, E.; Henderson, S.; Hershey, B.; Lin, M.; Balamraju, Y.; Sammonds, L.; Cheramie, J.; Karnes, J.; Hymel, E.; Woodford, B.; Carter, C. *J. Org. Chem.* ***2003***, *68*, 6387.

[1022]For discussion of transition-state geometries in this reaction, see Hoffmann, R.W.; Ditrich, K.; Froech, S.; Cremer, D. *Tetrahedron* ***1985***, *41*, 5517; Anh, N.T.; Thanh, B.T. *Nouv. J. Chim.*, ***1986***, *10*, 681; Li, Y.; Paddon-Row, M.N.; Houk, K.N. *J. Org. Chem.* ***1990***, *55*, 481; Denmark, S.E.; Henke, B.R. *J. Am. Chem. Soc.* ***1991***, *113*, 2177.

[1023]See Murphy, P.J.; Procter, G.; Russell, A.T. *Tetrahedron Lett.* ***1987***, *28*, 2037; Nerz-Stormes, M.; Thornton, E.R. *J. Org. Chem.* ***1991***, *56*, 2489.

[1024]Swiss, K.A.; Choi, W.; Liotta, D.; Abdel-Magid, A.F.; Maryanoff, C.A. *J. Org. Chem.* ***1991***, *56*, 5978.

[1025]Masamune, S.; Sato, T.; Kim, B.M.; Wollmann, T.A. *J. Am. Chem. Soc.* ***1986***, *108*, 8279; Danda, H.; Hansen, M.M.; Heathcock, C.H. *J. Org. Chem.* ***1990***, *55*, 173. See also, Corey, E.J.; Kim, S.S. *Tetrahedron Lett.* ***1990***, *31*, 3715.

[1026]Hirama, M.; Noda, T.; Takeishi, S.; Itô, S. *Bull. Chem. Soc. Jpn.* ***1988***, *61*, 2645; Majewski, M.; Gleave, D.M. *Tetrahedron Lett.* ***1989***, *30*, 5681.

[1027]Ward, D.E.; Sales, M.; Sasmal, P.K. *Org. Lett.* ***2001***, *3*, 3671; Ward, D.E.; Sales, M.; Sasmal, P.K. *J. Org. Chem.* ***2004***, *69*, 4808.

[1028]Calter, M.A.; Guo, X.; Liao, W. *Org. Lett.* ***2001***, *3*, 1499.

These reactions can also be made enantioselective[1029] (in which case only one of the four isomers predominates)[1030] by using[1031] chiral enol derivatives,[1032] chiral aldehydes or ketones,[1033] or both.[1034] Chiral bases[1035] can be used, such as proline,[1036] proline derivatives,[1037] or chiral additives, used in conjunction with the base.[1038] A chiral binaphthol dianion has been used to catalyze the reaction.[1039] Chiral auxiliaries[1040] have been developed that can be used in conjunction with the aldol condensation, as well as chiral catalysts[1041] and chiral ligands[1042]

[1029]For a review, see Allemann, C.; Gordillo, R.; Clemente, F.R.; Cheong, P.H.-Y.; Houk, K.N. *Acc. Chem. Res.* ***2004***, *37*, 558; Saito, S.; Yamamoto, H. *Acc. Chem. res.* ***2004***, *37*, 570. For a discussion of chelation versus nonchelation control, see Yan, T.-H.; Tan, C.-W.; Lee, H.-C.; Lo, H.-C.; Huang, T.-Y. *J. Am. Chem. Soc.* ***1993***, *115*, 2613. For the effects of lithium salts on enantioselective deprotonation, see Majewski, M.; Lazny, R.; Nowak, P. *Tetrahedron Lett.* ***1995***, *36*, 5465. Also see, Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY, ***2001***, pp. 779–790.

[1030]For anti-selective aldol reactions, see Oppolzer, W.; Lienard, P. *Tetrahedron Lett.* ***1993***, *34*, 4321. For a "non-Evans" *syn*-aldol, see Yan, T.-H.; Lee, H.-C.; Tan, C.-W. *Tetrahedron Lett.* ***1993***, *34*, 3559.

[1031]For reviews, see Klein, J., in Patai, S. *Supplement A: The Chemistry of Double-Bonded Functional Groups*, Vol. 2, pt. 1, Wiley, NY, ***1989***, pp. 567–677; Braun, M. *Angew. Chem. Int. Ed.* ***1987***, *26*, 24.

[1032]For examples, see Eichenauer, H.; Friedrich, E.; Lutz, W.; Enders, D. *Angew. Chem. Int. Ed.* ***1978***, *17*, 206; Meyers, A.I.; Yamamoto, Y. *Tetrahedron* ***1984***, *40*, 2309; Ando, A.; Shioiri, T. *J. Chem. Soc., Chem. Commun.* ***1987***, 1620; Muraoka, M.; Kawasaki, H.; Koga, K. *Tetrahedron Lett.* ***1988***, *29*, 337; Paterson, I.; Goodman, J.M. *Tetrahedron Lett.* ***1989***, *30*, 997; Siegel, C.; Thornton, E.R. *J. Am. Chem. Soc.* ***1989***, *111*, 5722; Gennari, C.; Molinari, F.; Cozzi, P.; Oliva, A. *Tetrahedron Lett.* ***1989***, *30*, 5163; Faunce, J.A.; Grisso, B.A.; Mackenzie, P.B. *J. Am. Chem. Soc.* ***1991***, *113*, 3418.

[1033]For example, see Ojima, I.; Yoshida, K.; Inaba, S. *Chem. Lett.* ***1977***, 429; Heathcock, C.H.; Flippin, L.A. *J. Am. Chem. Soc.* ***1983***, *105*, 1667; Reetz, M.T.; Kesseler, K.; Jung, A. *Tetrahedron* ***1984***, *40*, 4327.

[1034]For example, see Heathcock, C.H.; White, C.T.; Morrison, J.J.; VanDerveer, D. *J. Org. Chem.* ***1981***, *46*, 1296; Short, R.P.; Masamune, S. *Tetrahedron Lett.* ***1987***, *28*, 2841.

[1035]For a review, see Notz, W.; Tanaka, F.; Barbas III, C.F. *Acc. Chem. Res.* ***2004***, *37*, 580.

[1036]Notz, W.; List, B. *J. Am. Chem. Soc.* ***2000***, *122*, 7386; List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* ***2001***, *3*, 573; Sakthivel, K.; Notz, W.; Bui, T.; Barbas III, C.F. *J. Am. Chem. Soc.* ***2001***, *123*, 5260; Northrup, A.B.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2002***, *124*, 6798. See Peng, Y.-Y.; Ding, Q.-P.; Li, Z.; Wang, P.G.; Cheng, J.-P. *Tetrahedron Lett.* ***2003***, *44*, 3871; Darbre, T.; Machuqueiro, M. *Chem. Commun.* ***2003***, 1090; Nyberg, A.I.; Usano, A.; Pihko, P.M. *Synlett* ***2004***, 1891. For an example with formaldehyde, see Casas, J.; Sundén, H.; Córdova, A. *Tetrahedron Lett.* ***2004***, *45*, 6117. For a proline-catalyzed high pressure reaction, see Sekiguchi, Y.; Sasaoka, A.; Shimomoto, A.; Fujioka, S.; Kotsuki, H. *Synlett* ***2003***, 1655.

[1037]Tang, Z.; Jiang, F.; Yu, L.-T.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *J. Am. Chem. Soc.* ***2003***, *125*, 5262; Zhong, G.; Fan, J.; Barbas III, C.F. *Tetrahedron Lett.* ***2004***, *45*, 5681.

[1038]See Mahrwald, R. *Org. Lett.* ***2000***, *2*, 4011.

[1039]Nakajima, M.; Orito, Y.; Ishizuka, T.; Hashimoto, S. *Org. Lett.* ***2004***, *6*, 3763.

[1040]Hein, J.E.; Hultin, P.G. *Synlett* ***2003***, 635.

[1041]Suzuki, T.; Yamagiwa, N.; Matsuo, Y.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M.; Noyori, R. *Tetrahedron Lett.* ***2001***, *42*, 4669. For a review, see Alcaidi, B.; Almendros, P. *Eur. J. Org. Chem.* ***2002***, 1595.

[1042]Trost, B.M.; Ito, H. *J. Am. Chem. Soc.* ***2000***, *122*, 12003.

in catalytic reactions. Aldehydes are condensed with ketones with potassium hexamethyldisilazide (KHMDS) and 8% of a chiral lithium catalyst, giving the aldol product with moderate enantioselectivity.[1043] Structural variations in the aldehyde or ketone are compatible with many enantioselective condensation reactions. An α-hydroxy ketone was condensed with an aldehyde using a chiral zinc catalyst to give the aldol (an α,β-dihydroxy ketone) with good syn selectivity and good enantioselectivity.[1044] A catalytic amount of a nicotine metabolite allows an enantioselective reaction in aqueous media.[1045] Chiral vinylogous aldol reactions have been reported.[1046]

Silyl enol ethers react with aldehydes in the presence of chiral boranes[1047] or other additives[1048] to give aldols with good asymmetric induction (see the Mukaiyama aldol reaction in **16-35**). Chiral boron enolates have been used.[1049] Since both new stereogenic centers are formed enantioselectively, this kind of process is called *double asymmetric synthesis*.[1050] Where both the enolate derivative and substrate were achiral, carrying out the reaction in the presence of an optically active boron compound[1051] or a diamine coordinated with a tin compound[1052] gives the aldol product with excellent enantioselectivity for one stereoisomer. Formation of the magnesium enolate anion of a chiral amide, adds to aldehydes to give the alcohol enantioselectively.[1053]

Diamine protonic acids have been used for catalytic asymmetric aldol reaction.[1054] Boron triflate derivatives, R_2BOTf, have been used for the condensation of ketals and ketone to give β-alkoxy ketones.[1055]

[1043]Yoshikawa, N.; Yamada, Y.M.A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* ***1999***, *121*, 4168.

[1044]Kumagai, N.; Matsunaga, S.; Yoshikawa, N.; Ohshima, T.; Shibasaki, M. *Org. Lett.* ***2001***, *3*, 1539; Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshma, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* ***2001***, *123*, 2466; Trost, B.M.; Ito, H.; Silcoff, E.R. *J. Am. Chem. Soc.* ***2001***, *123*, 3367.

[1045]Dickerson, T.J.; Janda, K.D. *J. Am. Chem. Soc.* ***2002***, *124*, 3220.

[1046]Takikawa, H.; Ishihara, K.; Saito, S.; Yamamoto, H. *Synlett* ***2004***, 732; Denmark, S.E.; Heemstra, Jr., J.R. *Synlett* ***2004***, 2411.

[1047]Ishihara, K.; Maruyama, T.; Mouri, M.; Gao, Q.; Furuta, K.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* ***1993***, *66*, 3483.

[1048]Corey, E.J.; Cywin, C.L.; Roper, T.D. *Tetrahedron Lett.* ***1992***, *33*, 6907.

[1049]See Yoshida, K.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* ***2003***, *68*, 1901.

[1050]For a review, see Masamune, S.; Choy, W.; Petersen, J.S.; Sita, L.R. *Angew. Chem. Int. Ed.* ***1985***, *24*, 1.

[1051]Corey, E.J.; Kim, S.S. *J. Am. Chem. Soc.* ***1990***, *112*, 4976; Furuta, K.; Maruyama, T.; Yamamoto, H. *J. Am. Chem. Soc.* ***1991***, *113*, 1041; Kiyooka, S.; Kaneko, Y.; Komura, M.; Matsuo, H.; Nakano, M. *J. Org. Chem.* ***1991***, *56*, 2276. For a review, see Bernardi, A.; Gennari, C.; Goodman, J.M.; Paterson, I. *Tetrahedron Asymmetry* ***1995***, *6*, 2613.

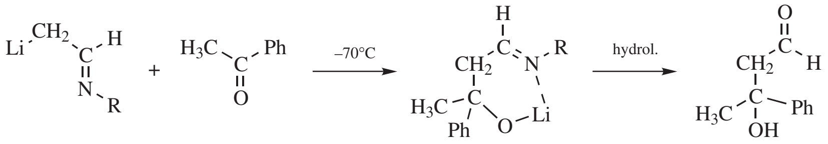
[1052]Mukaiyama, T.; Uchiro, H.; Kobayashi, S. *Chem. Lett.* ***1990***, 1147.

[1053]Evans, D.A.; Tedrow, J.S.; Shaw, J.T.; Downey, C.W. *J. Am. Chem. Soc.* ***2002***, *124*, 392.

[1054]Saito, S.; Nakadai, M.; Yamamoto, H. *Synlett* ***2001***, 1245; Trost, B.M.; Fettes, A.; Shireman, B.T. *J. Am. Chem. Soc.* ***2004***, *126*, 2660.

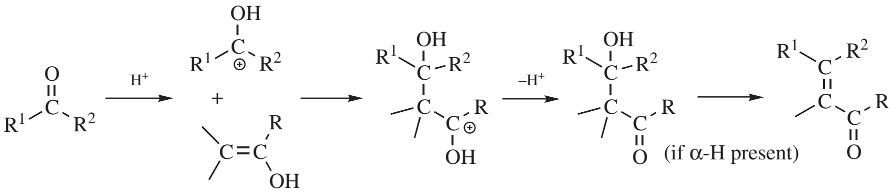
[1055]Li, L.-S.; Das, S.; Sinha, S.C. *Org. Lett.* ***2004***, *6*, 127.

It is possible to make the α carbon of the aldehyde add to the carbonyl carbon of the ketone, by using an imine instead of an aldehyde, and LiN(*i*Pr)$_2$ as the base:[1056]



This is known as a *directed aldol reaction*. Similar reactions have been performed with α-lithiated dimethylhydrazones of aldehydes or ketones[1057] and with α-lithiated aldoximes.[1058]

The aldol reaction can also be performed with acid catalysts, as mentioned above, in which case dehydration usually follows. Here, there is initial protonation of the carbonyl group, which attacks the α carbon of the *enol* form of the other molecule:[1059]



With respect to the enol, this mechanism is similar to that of halogenation (**12-4**). A side reaction that is sometimes troublesome is further condensation, since the product of an aldol reaction is still an aldehyde or ketone. The aldol condensation of aldehydes has also been done using a mixture of pyrrolidine and benzoic acid.[1060]

The intramolecular aldol condensation is well known, and aldol reactions are often used to close five- and six-membered rings. Because of the favorable entropy (p. 303), such ring closures generally take place with ease[1061] when using hydroxide or alkoxide bases in protic solvents. In aprotic solvents with amide bases,

[1056]Wittig, G.; Frommeld, H.D.; Suchanek, P. *Angew. Chem. Int. Ed.* ***1963***, *2*, 683. For reviews, see Mukaiyama, T. *Org. React.* ***1982***, *28*, 203; Wittig, G. *Top. Curr. Chem.* ***1976***, *67*, 1; *Rec. Chem. Prog.* ***1967***, *28*, 45; Wittig, G.; Reiff, H. *Angew. Chem. Int. Ed.* ***1968***, *7*, 7; Reiff, H. *Newer Methods Prep. Org. Chem.* ***1971***, *6*, 48.

[1057]Corey, E.J.; Enders, D. *Tetrahedron Lett.* ***1976***, 11. See also, Beam, C.F.; Thomas, C.W.; Sandifer, R.M.; Foote, R.S.; Hauser, C.R. *Chem. Ind. (London)* ***1976***, 487; Sugasawa, T.; Toyoda, T.; Sasakura, K. *Synth. Commun.* ***1979***, *9*, 515; Depezay, J.; Le Merrer, Y. *Bull. Soc. Chim. Fr.* ***1981***, II-306.

[1058]Hassner, A.; Näumann, F. *Chem. Ber.* ***1988***, *121*, 1823.

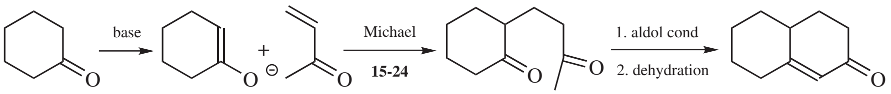
[1059]There is evidence (in the self-condensation of acetaldehyde) that a water molecule acts as a base (even in concentrated H_2SO_4) in assisting the addition of the enol to the protonated aldehyde: Baigrie, L.M.; Cox, R.A.; Slebocka-Tilk, H.; Tencer, M.; Tidwell, T.T. *J. Am. Chem. Soc.* ***1985***, *107*, 3640.

[1060]Ishikawa, T.; Uedo, E.; Okada, S.; Saito, S. *Synlett* ***1999***, 450.

[1061]For rate and equilibrium constants, see Guthrie, J.P.; Guo, J. *J. Am. Chem. Soc.* ***1996***, *118*, 11472. For neighboring-group effects, see Eberle, M.K. *J. Org. Chem.* ***1996***, *61*, 3844.

formation of the enolate anion occurs by deprotonation of the more acidic site, followed by cyclization to the second carbonyl. The acid-catalyzed intramolecular aldol condensation is known, and the mechanism has been studied.[1062] Stereoselective proline-catalyzed intramolecular aldol reactions give the cyclize product with good enantioselectivity.[1063]

An important extension of the intramolecular aldol condensation is the *Robinson annulation* reaction,[1064] which has often been used in the synthesis of steroids and terpenes. In original versions of this reaction, a cyclic ketone is converted to another cyclic ketone under equilibrium conditions using hydroxide or alkoxide bases in a protic solvent, forming one additional six-membered ring containing a double bond. The reaction can be done in a stepwise manner using amide bases in aprotic solvents. In the reaction with hydroxide or alkoxide bases in alcohol or water solvents, the substrate is treated with methyl vinyl ketone (or a simple derivative of methyl vinyl ketone) and a base.[1065] The enolate ion of the substrate adds to the methyl vinyl ketone in a Michael reaction (**15-24**) to give a diketone that undergoes or is made to undergo an internal aldol



reaction and subsequent dehydration to give the product.[1066] The Robinson annulation can be combined with alkylation.[1067] Enantioselective Robinson annulation techniques have been developed, including a proline-catalyzed reaction.[1068] The Robinson annulation has been done in ionic liquids[1069] and a solvent-free version of the reaction is known.[1070]

Because methyl vinyl ketone has a tendency to polymerize, precursors are often used instead, that is., compounds that will give methyl vinyl ketone when treated with a base. One common example, $MeCOCH_2CH_2NEt_2Me^+ I^-$ (see **17-9**), is easily prepared by quaternization of $MeCOCH_2CH_2NEt_2$, which itself is prepared

[1062]Bouillon, J.-P.; Portella, C.; Bouquant, J.; Humbel, S. *J. Org. Chem.* ***2000***, *65*, 5823.

[1063]Bahmanyar, S.; Houk, K.N. *J. Am. Chem. Soc.* ***2001***, *123*, 12911; Pidathala, C.; Hoang, L.; Vignola, N.; List, B. *Angew. Chem. Int. Ed.* ***2003***, *42*, 2785.

[1064]For reviews of this and related reactions, see Gawley, R.E. *Synthesis* ***1976***, 777; Jung, M.E. *Tetrahedron* ***1976***, *32*, 1; Mundy, B.P. *J. Chem. Educ.* ***1973***, *50*, 110. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1356–1358.

[1065]Acid catalysis has also been used: see Heathcock, C.H.; Ellis, J.E.; McMurry, J.E.; Coppolino, A. *Tetrahedron Lett.* ***1971***, 4995.

[1066]For improved procedures, see Sato, T.; Wakahara, Y.; Otera, J.; Nozaki, H. *Tetrahedron Lett.* ***1990***, *31*, 1581, and references cited therein.

[1067]Tai, C.-L.; Ly, T.W.; Wu, J.-D.; Shia, K.-S.; Liu, H.-J. *Synlett* ***2001***, 214.

[1068]Bui, T.; Barbas III, C.F. *Tetrahedron Lett.* ***2000***, *41*, 6951; Rajagopal, D.; Narayanan, R.; Swaminathan, S. *Tetrahedron Lett.* ***2001***, *42*, 4887.

[1069]Morrison, D.W.; Forbes, D.C.; Davis Jr., J.H. *Tetrahedron Lett.* ***2001***, *42*, 6053.

[1070]Miyamoto, H.; Kanetaka, S.; Tanaka, K.; Yoshizawa, K.; Toyota, S.; Toda, F. *Chem. Lett.* ***2000***, 888.

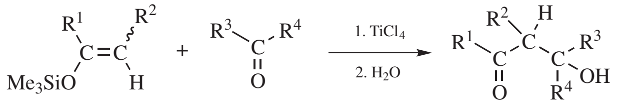
by a Mannich reaction (**16-19**) involving acetone, formaldehyde, and diethylamine. α-Silylated vinyl ketones $RCOC(SiMe_3){=}CH_2$ have also been used successfully in annulation reactions.[1071] The $SiMe_3$ group is easily removed. 1,5-Diketones prepared in other ways are also frequently cyclized by internal aldol reactions. When the ring closure of a 1,5-diketone is catalyzed by the amino acid (*S*)-proline, the product is optically active with high enantiomeric excess.[1072] *Stryker's reagent* [1073]$[(Ph_3P)CuH]_6$ has been used for an intramolecular addition where ketone enolate anion to a conjugated ketone, giving cyclic alcohol with a pendant ketone unit.[1074]

OS **I**, 77, 78, 81, 199, 283, 341; **II**, 167, 214; **III**, 317, 353, 367, 747, 806, 829; **V**, 486, 869; **VI**, 496, 666, 692, 781, 901; **VII**, 185, 190, 332, 363, 368, 473; **VIII**, 87, 208, 241, 323, 339, 620; **IX**, 432, 610; **X**, 339.

16-35 Mukaiyama Aldol and Related Reactions[1075]

***O*-Hydro-*C*-(α-acylalkyl)-addition**

An important variation of the aldol condensation involves treatment of an aldehyde or ketone with a silyl ketene acetal $R_2C{=}C(OSiMe_3)OR'$[1076] in the presence of $TiCl_4$[1077], to give **38**. The silyl ketene acetal can be considered a preformed enolate that gives aldol product



38

with $TiCl_4$ in aqueous solution, or with no catalyst at all.[1078] A combination of $TiCl_4$ and a *N*-tosyl imine has also been used to facilitate the Mukaiyama aldol

[1071]Stork, G.; Singh, J. *J. Am. Chem. Soc.* ***1974***, *96*, 6181; Boeckman, Jr., R.K. *J. Am. Chem. Soc.* ***1974***, *96*, 6179.

[1072]Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed.* ***1971***, *10*, 496; Hajos, Z.G.; Parrish, D.R. *J. Org. Chem.* ***1974***, *39*, 1615. For a review of the mechanism, see Agami, C. *Bull. Soc. Chim. Fr.* ***1988***, 499.

[1073]Mahoney, W.S.; Brestensky, D.M.; Stryker, J.M. *J. Am. Chem. Soc.* ***1988***, *110*, 291; Brestensky, D.M.; Stryker, J.M. *Tetrahedron Lett.* ***1989***, *30*, 5677.

[1074]Chiu, P.; Szeto, C.-P.; Geng, Z.; Cheng, K.-F. *Org. Lett.* ***2001***, *3*, 1901.

[1075]See Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY, ***2001***, pp.755–759.

[1076]For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1745–1752. For methods of preparing silyl ketene acetals, see Revis, A.; Hilty, T.K. *Tetrahedron Lett.* ***1987***, *28*, 4809, and references cited therein.

[1077]Mukaiyama, T. *Pure Appl. Chem.* ***1983***, *55*, 1749; Kohler, B.A.B. *Synth. Commun.* ***1985***, *15*, 39; Mukaiyama, T.; Narasaka, K. *Org. Synth.*, *65*, 6. For a discussion of the mechanism, see Gennari, C.; Colombo, L.; Bertolini, G.; Schimperna, G. *J. Org. Chem.* ***1987***, *52*, 2754. For a review of this and other applications of $TiCl_4$ in organic synthesis, see Mukaiyama, T. *Angew. Chem. Int. Ed.* ***1977***, *16*, 817. See also, Reetz, M.T. *Organotitanium Reagents in Organic Synthesis*, Spinger, NY, ***1986***.

[1078]Lubineau, A.; Meyer, E. *Tetrahedron* ***1988***, *44*, 6065; Miura, K.; Sato, H.; Tamaki, K.; Ito, H.; Hosomi, A. *Tetrahedron Lett.* ***1998***, *39*, 2585. For an uncatalyzed reaction under high pressure, see Bellassoued, M.; Reboul, E.; Dumas, F. *Tetrahedron Lett.* ***1997***, *38*, 5631.

reaction.[1079] The mechanism of this reaction has been explored.[1080] Other catalysts have been used for this reaction as well, including $InCl_3$,[1081] SmI_2,[1082] $Sc(OTf)_3$,[1083] HgI_2,[1084] $Yb(OTf)_3$,[1085] $Cu(OTf)_2$,[1086] $[Cp_2Zr(Ot\text{-}Bu)THF]^+[BPh_4]^-$,[1087] $LiClO_4$,[1088] $VOCl_3$,[1089] an iron catalyst,[1090] and $Bi(OTf)_3$.[1091] The reaction can be done in water using a scandium catalyst[1092] or a Montmorillonite K10 clay.[1093] Silyl enol ethers react with aqueous formaldehyde in the presence of TBAF to give the aldol product.[1094] A catalytic amount of Me_3SiCl facilitates the titanium mediated reaction.[1095] Sulfonamides, such as $HNTf_2$, have been used as a catalyst[1096] as has pyridine *N*-oxide.[1097] A combination of Ph_2BOH and benzoic acid in water catalyzes the reaction.[1098] Lithium perchlorate in acetonitrile (5 *M*) can be used for the reaction of an aldehyde and a silyl enol ether.[1099] When the catalyst is dibutyltin bis (triflate) $Bu_2Sn(OTf)_2$, aldehydes react, but not their acetals, while acetals of ketones react, but not the ketones themselves.[1100] Reaction at the carbonyl of saturated carbonyl compounds is significantly faster than 1,2-addition to unsaturated carbonyl compounds.[1101] Propargylic acetals react with silyl enol ethers and a scandium catalyst to give β-alkoxy ketones.[1102] Imines react with silyl enol ethers n the presence of $BF_3{\bullet}OEt_2$ to give β-amino ketones.[1103] α-Silyl silyl enol ethers

[1079] Miura, K.; Nakagawa, T.; Hosomi, A. *J. Am. Chem. Soc.* ***2002***, *124*, 536.

[1080] Hollis, T.K.; Bosnich, B. *J. Am. Chem. Soc.* ***1995***, *117*, 4570. For the transition-state geometry, see Denmark, S.E.; Lee, W. *J. Org. Chem.* ***1994***, *59*, 707.

[1081] Loh, T.-P.; Pei, J.; Cao, G.-Q. *Chem. Commun.* ***1996***, 1819; Kobayashi, S.; Busujima, T.; Nagayama, S. *Tetrahedron Lett.* ***1998***, *39*, 1579. Both $InCl_3$ and $CeCl_3$ have been used in aqueous media, see Muñoz-Muñiz, O.; Quintanar-Audelo, M.; Juaristi, E. *J. Org. Chem.* ***2003***, *68*, 1622.

[1082] Van de Weghe, P.; Collin, J. *Tetrahedron Lett.* ***1993***, *34*, 3881.

[1083] Kobayashi, S.; Wakabayashi, T.; Nagayama, S.; Oyamada, H. *Tetrahedron Lett.* ***1997***, *38*, 4559; Komoto, I.; Kobayashi, S. *Chem. Commun.* ***2001***, 1842; Komoto, I.; Kobayashi, S. *J. Org. Chem.* ***2004***, *69*, 680.

[1084] Dicker, I.B. *J. Org. Chem.* ***1993***, *58*, 2324.

[1085] This catalyst is tolerated in water. See Kobayashi, S.; Hachiya, I. *J. Org. Chem.* ***1994***, *59*, 3590.

[1086] Kobayashi, S.; Nagayama, S.; Busujima, T. *Chem. Lett.* ***1997***, 959.

[1087] Hong, Y.; Norris, D.J.; Collins, S. *J. Org. Chem.* ***1997***, *58*, 3591.

[1088] Reetz, M.T.; Fox, D.N.A. *Tetrahedron Lett.* ***1993***, *34*, 1119.

[1089] Kurihara, M.; Hayshi, T.; Miyata, N. *Chem. Lett.* ***2001***, 1324.

[1090] Bach, T.; Fox, D.N.A.; Reetz, M.T. *J. Chem. Soc., Chem. Commun.* ***1992***, 1634.

[1091] LeRoux, C.; Ciliberti, L.; Laurent-Robert, H.; Laporterie, A.; Dubac, J. *Synlett* ***1998***, 1249.

[1092] Manabe, K.; Kobayashi, S. *Tetrahedron Lett.* ***1999***, *40*, 3773. For a discussion of the effect of surfactants on this reaction, see Tian, H.-Y.; Chen, Y.-J.; Wang, D.; Bu, Y.-P.; Li, C.-J. *Tetrahedron Lett.* ***2001***, *42*, 1803.

[1093] Loh, T.-P.; Li, X.-R. *Tetrahedron* ***1999***, *55*, 10789.

[1094] Ozasa, N.; Wadamoto, M.; Ishihara, K.; Yamamoto, H. *Synlett* ***2003***, 2219.

[1095] Yoshida, Y.; Matsumoto, N.; Hamasaki, R.; Tanabe, Y. *Tetrahedron Lett* ***1999***, *40*, 4227.

[1096] Ishihara, K.; Hiraiwa, Y.; Yamamoto, H. *Synlett* ***2001***, 1851.

[1097] Denmark, S.E.; Fan, Y. *J. Am. Chem. Soc.* ***2002***, *124*, 4233.

[1098] Mori, Y.; Kobayashi, J.; Manabe, K.; Kobayashi, S. *Tetrahedron* ***2002***, *58*, 8263.

[1099] Sudha, R.; Sankararaman, S. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 383.

[1100] Sato, T.; Otera, J.; Nozaki, H. *J. Am. Chem. Soc.* ***1990***, *112*, 901.

[1101] Shirakawa, S.; Maruoka, K. *Tetrahedron Lett.* ***2002***, *43*, 1469.

[1102] Yoshimatsu, M.; Kuribayashi, M.; Koike, T. *Synlett* ***2001***, 1799.

[1103] Akiyama, T.; Takaya, J.; Kagoshima, H. *Chem. Lett.* ***1999***, 947.

RCH=CH(OTMS)$SiMe_3$ react with acetals in the presence of $SnCl_4$ to give β-alkoxy silyl ketones.[1104]

An interesting variation in this reaction combined an intermolecular Mukaiyama aldol followed by an intramolecular reaction (a "domino" Mukaiyama aldol) that gave cyclic conjugated ketone products.[1105] Borane derivatives such as C=C—OB$(NMe_2)_2$ react with aldehydes to give β-amino ketones.[1106]

Silyl enol ethers[1107] derived from esters (silyl ketene acetals) react with aldehydes in the presence of various catalysts to give β-hydroxy esters. Water accelerates the reaction of an aldehyde and a ketene silyl acetal with no other additives.[1108] The reaction is catalyzed by triphenylphosphine[1109] and also by $SiCl_4$ with a chiral bis(phosphoramide) catalyst.[1110] The reaction was done without a catalyst in an ionic liquid.[1111] A vinylogous reaction is known that gives δ-hydroxy-α,β-unsaturated esters.[1112] Under different conditions, silyl ketene acetals of conjugated esters react with aldehydes to give conjugated lactones.[1113] Imines react with silyl ketene acetals in the presence of SmI_3 to give β-amino esters.[1114] Another variation converted a *N*-(1-trimethylsilyloxyvinyl) imine to a conjugated amide by initial reaction with 2 equivalents of *n*-butyllithium and a zirconium complex followed by reaction with an aldehyde.[1115] Silyl ketene acetals also undergo conjugate addition in reactions with conjugated ketones.[1116] Silyl ketene acetals of thio esters also react with aldehydes to give β-hydroxy thioesters.[1117]

Asymmetric Mukaiyama aldol reactions and reactions of silyl ketene acetals have been reported, [1118] usually using chiral additives[1119] although chiral auxiliaries

[1104]Honda, M.; Oguchi, W.; Segi, M.; Nakajima, T. *Tetrahedron* ***2002***, *58*, 6815.

[1105]Langer, P.; Köhler, V. *Org. Lett.* ***2000***, *2*, 1597.

[1106]Suginome, M.; Uehlin, L.; Yamamoto, A.; Murakami, M. *Org. Lett.* ***2004***, *6*, 1167.

[1107]For a discussion of enantioselective deprotonation to form chiral silyl enol ethers, see Carswell, E.L.; Hayes, D.; Henderson, K.W.; Kerr, W.J.; Russell, C.J. *Synlett* ***2003***, 1017.

[1108]Loh, T.-P.; Feng, L.-C.; Wei, L.-L. *Tetrahedron* ***2000***, *56*, 7309.

[1109]Matsukawa, S.; Okano, N.; Imamoto, T. *Tetrahedron Lett.* ***2000***, *41*, 103.

[1110]Denmark, S.E.; Heemstra, Jr., J.R. *Org. Lett.* ***2003***, *5*, 2303; Denmark, S.E.; Wynn, T.; Beutner, G.L. *J. Am. Chem. Soc.* ***2002***, *124*, 13405.

[1111]In omim Cl, 1-octyl-3-methylimidazolium chloride or in bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Chen, S.-L.; Ji, S.-J.; Loh, T.-P. *Tetrahedron Lett.* ***2004***, *45*, 375.

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[1113]Bluet, G.; Bazán-Tejeda, B.; Campagne, J.-M. *Org. Lett.* ***2001***, *3*, 3807.

[1114]Hayakawa, R.; Shimizu, M. *Chem. Lett.* ***1999***, 591.

[1115]Gandon, V.; Bertus, P.; Szymoniak, J. *Tetrahedron* ***2000***, *56*, 4467.

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[1117]Hamada, T.; Manabe, K.; Ishikawa, S.; Nagayama, S.; Shiro, M.; Kobayashi, S. *J. Am. Chem. Soc.* ***2003***, *125*, 2989.

[1118]Bach, T. *Angew. Chem. Int. Ed.* ***1994***, *33*, 417. For a discussion of stereocontrol, see Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P.G.; Consolandi, E. *J. Org. Chem.* ***1992***, *57*, 456.

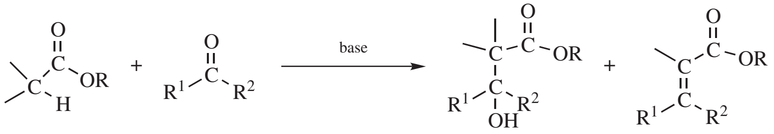
[1119]For examples, see Kobayashi, S.; Kawasuji, T.; Mori, N. *Chem. Lett.* ***1994***, 217; Kobayashi, S.; Uchiro, H.; Shiina, I.; Mukaiyama, T. *Tetrahedron* ***1993***, *49*, 1761; Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* ***1994***, *116*, 4077; Kaneko, Y.; Matsuo, T.; Kiyooka, S. *Tetrahedron Lett.* ***1994***, *35*, 4107; Kiyooka, S.; Kido, Y.; Kaneko, Y. *Tetrahedron Lett.* ***1994***, *35*, 5243.

have also been used.[1120] Chiral catalysts, usually transition-metal complexes using chiral ligands, are quite effective,[1121] but chiral bis(oxazolones)[1122] and chiral quaternary ammonium salts[1123] have also been used. A zirconium BINOL complex gave good enantioselectivity in reactions of silyl ketene acetals, and also good anti selectivity in the product.[1124] This reaction can also be run with the aldehyde or ketone in the form of its acetal $R^3R^4C(OR')_2$, in which case the product is the ether $R^1COCHR_2CR^3R^4OR'$ instead of **38**.[1125] Trichlorosilyl enol ethers react with aldehydes directly in the presence of a chiral phosphoramide to give the aldol with good syn selectivity and good enantioselectivity.[1126] Vinylogous silyl ketene acetals with a chiral oxazolidinone auxiliary attached to the α-vinylic carbon react with aldehydes and $TiCl_4$ to give a δ-hydroxy-α,β-unsaturated amide (an acyl oxazolidinone).[1127]

Enol acetates and enol ethers also give this product when treated with acetals and $TiCl_4$ or a similar catalyst.[1128] A variation of this condensation uses an enol acetate with an aldehyde in the presence of Et_2AlOEt to give the aldol product.[1129]

16-36 Aldol-Type Reactions between Carboxylic Acid Derivatives and Aldehydes or Ketones

O-Hydro-C-(α-alkoxycarbonylalkyl)-addition; α-Alkoxycarbonylalkylidene-de-oxo-bisubstitution



[1120]For an example, see Vasconcellos, M.L.; Desmaële, D.; Costa, P.R.R.; d'Angelo, J. *Tetrahedron Lett.* ***1992***, *33*, 4921.

[1121]Titanium complexes: Imashiro, R.; Kuroda, T. *J. Org. Chem.* ***2003***, *68*, 974. Copper complexes: Kobayashi, S.; Nagayama, S.; Busujima, T. *Tetrahedron* ***1999***, *55*, 8739. Lead complexes: Nagayama, S.; Kobayashi, S. *J. Am. Chem. Soc* ***2000***, *122*, 11531. Cerium complexes: Kobayashi, S.; Hamada, T.; Nagayama, S.; Manabe, K. *Org. Lett.* ***2001***, *3*, 165. Silver complexes: Yanagisawa, A.; Nakatsuka, Y.; Asakawa, K.; Kageyama, H.; Yamamoto, H. *Synlett* ***2001***, 69; Yanigisawa, A.; Nakatsuka, Y.; Asakawa, K.; Wadamoto, M.; Kageyama, H.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* ***2001***, *74*, 1477; Wadamoto, M.; Ozasa, N.; Yanigisawa, A.; Yamamoto, H. *J. Org. Chem.* ***2003***, *68*, 5593. Zirconium complexes: Kobayashi, S.; Ishitani, H.; Yamashita, Y.; Ueno, M.; Shimizu, H. *Tetrahedron* ***2001***, *57*, 861. Scandium complexes: Ishikawa, S.; Hamada, T.; Manabe, K.; Kobayashi, S. *J. Am. Chem. Soc.* ***2004***, *126*, 12236.

[1122]Kobayashi, S.; Nagayama, S.; Busujima, T. *Chem. Lett.* ***1999***, 71.

[1123]Zhang, F.-Y.; Corey, E.J. *Org. Lett.* ***2001***, *3*, 639.

[1124]Ishitani, H.; Yamashita, Y.; Shimizu, H.; Kobayashi, S. *J. Am. Chem. Soc.* ***2000***, *122*, 5403.

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[1127]Shirokawa, S.-i.; Kamiyama, M.; Nakamura, T.; Okada, M.; Nakazaki, A.; Hosokawa, S.; Kobayashi, S. *J. Am. Chem. Soc.* ***2004***, *126*, 13604.

[1128]Kitazawa, E.; Imamura, T.; Saigo, K.; Mukaiyama, T. *Chem. Lett.* ***1975***, 569.

[1129]Mukaiyama, T.; Shibata, J.; Shimamura, T.; Shiina, I. *Chem. Lett.* ***1999***, 951.

In the presence of a strong base, the α carbon of a carboxylic ester or other acid derivative can condense with the carbonyl carbon of an aldehyde or ketone to give a β-hydroxy ester,[1130] amide, and so on., which may or may not be dehydrated to the α,β-unsaturated derivative. This reaction is sometimes called the *Claisen reaction*,[1131] an unfortunate usage since that name is more firmly connected to **16-85**. Early reactions used hydroxide or an alkoxide base in water or alcohol solvents, where self-condensation was the major process. Under such conditions, the aldehyde or ketone was usually chosen for its lack of an α-proton. Much better control of the reaction was achieved when amide bases in aprotic solvents, such as ether or THF, were used. The reaction of *tert*-butyl acetate and LDA[1132] in hexane or more commonly THF at −78°C gives the enolate anion of *tert*-butyl acetate,[1133] (**12-23**, e.g., although self-condensation is occasionally a problem even here. Subsequent reaction a ketone provides a simple rapid alternative to the Reformatsky reaction (**16-28**) as a means of preparing β-hydroxy *tert*-butyl esters. It is also possible for the α carbon of an aldehyde or ketone to add to the carbonyl carbon of a carboxylic ester, but this is a different reaction (**16-86**) involving nucleophilic substitution and not addition to a C=O bond. It can, however, be a side reaction if the aldehyde or ketone has an α hydrogen.

Transition-metal mediated condensation of esters and aldehydes is known. The reaction of a thioester and an aryl aldehyde with $TiCl_4$—NBu_3, for example, gave a β-hydroxy thioester with good syn selectivity.[1134] Selenoamides [$RCH_2C(=Se)NR'_2$] react with LDA and then an aldehyde to give β-hydroxy selenoamides.[1135]

Besides ordinary esters (containing an α hydrogen), the reaction can also be carried out with lactones and, as in **16-34**, with the γ position of α,β-unsaturated esters (vinylogy). The enolate anion of an amide can be condensed with an aldehyde.[1136]

There are a number of variations of the condensation reaction of acid derivatives. The reaction between a cyclic ketone having a pendant alkynyl ester unit and tetrabutylammonium fluoride leads to cyclization to a bicyclic alcohol with an exocyclic allene moiety.[1137] A chain-extension reaction culminates in acyl addition of an ester enolate. The reaction of a β-keto ester, such as methyl 3-oxobutanote and $EtZnCH_2I$, leads to chain extension via a carbenoid-like insertion reaction (p. 803), which reacts with an aldehyde in a second step to give a methyl 3-oxopentanoate derivative with a —CH(OH)R group at C-2 relative to the ester carbonyl.[1138]

[1130]If the reagent is optically active because of the presence of a chiral sulfoxide group, the reaction can be enantioselective. For a review of such cases, see Solladié, G. *Chimia* ***1984***, *38*, 233.

[1131]Because it was discovered by Claisen, L. *Ber.* ***1890***, *23*, 977.

[1132]Huerta, F.F.; Bäckvall, J.-E. *Org. Lett.* ***2001***, *3*, 1209.

[1133]Rathke, M.W.; Sullivan, D.F. *J. Am. Chem. Soc.* ***1973***, *95*, 3050.

[1134]Tanabe, Y.; Matsumoto, N.; Funakoshi, S.; Manta, N. *Synlett* ***2001***, 1959.

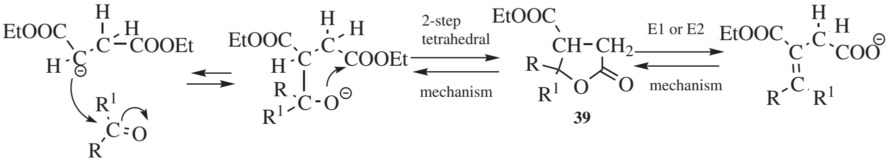
[1135]Murai, T.; Suzuki, A.; Kato, S. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 2711.

[1136]For a case using $CeCl_3$ to promote the reaction, see Shang, X.; Liu, H-.J. *Synth. Commun.* ***1994***, *24*, 2485.

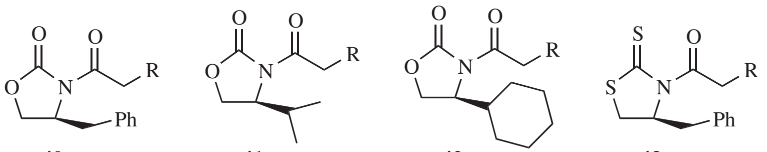
[1137]Wendling, F.; Miesch, M. *Org. Lett.* ***2001***, *3*, 2689.

[1138]Lai, S.; Zercher, C.K.; Jasinski, J.P.; Reid, S.N.; Staples, R.J. *Org. Lett.* ***2001***, *3*, 4169.

For most esters, a much stronger base is needed than for aldol reactions; $(i\text{Pr})_2$-NLi (LDA, p. 389), Ph_3CNa and $LiNH_2$ are among those employed. However, one type of ester reacts more easily, and such strong bases are not needed: diethyl succinate and its derivatives condense with aldehydes and ketones in the presence of bases such as NaOEt, NaH, or $KOCMe_3$. This reaction is called the *Stobbe condensation*.[1139] One of the ester groups (sometimes both) is hydrolyzed in the course of the reaction. The following mechanism accounts for (*1*) the fact the succinic esters react so much better than others; (*2*) one ester group is always cleaved; and (*3*) the alcohol is not the product but the alkene. In addition, intermediate lactones **39** have been isolated from the mixture.[1140] The Stobbe condensation has been extended to di-*tert*-butyl esters of glutaric acid.[1141] The boron-mediated reaction is known.[1142]



Chiral additives, such as diazaborolidines can be added to an ester, and subsequent treatment with a base and then an aldehyde leads to a chiral β-hydroxy ester.[1143] A variety of chiral amide or oxazolidinone derivatives have been used to form amide linkages to carboxylic acid derivatives. These chiral auxiliaries lead to chirality transfer from the enolate anion of such derivatives, in both alkylation reactions and acyl substitution reactions with aldehydes and ketones. The so-called Evans auxiliaries (**40-42**) are commonly used and give good enantioselectivity.[1144] A variation is the magnesium halide-catalyzed anti-aldol reaction of chiral *N*-acylthiazolidinethiones (see **43**).[1145] The use of chiral *N*-acyloxazolidinthiones with $TiCl_4$ and sparteine also gave good selectivity in the acyl addition.[1146] Chiral diazaboron derivatives have also been used to facilitate the condensation of a α-phenylthio ester with an aldehyde.[1147]



40 **41** **42** **43**

[1139]For a review, see Johnson, W.S.; Daub, G.H. *Org. React.* ***1951***, *6*, 1.
[1140]Robinson, R.; Seijo, E. *J. Chem. Soc.* ***1941***, 582.
[1141]Puterbaugh, W.H. *J. Org. Chem.* ***1962***, *27*, 4010. See also, El-Newaihy, M.F.; Salem, M.R.; Enayat, E.I.; El-Bassiouny, F.A. *J. Prakt. Chem.* ***1982***, *324*, 379.
[1142]For a review, see Abiko, A. *Acc. Chem. Res.* ***2004***, *37*, 387.
[1143]Corey, E.J.; Choi, S. *Tetrahedron Lett.* ***2000***, *41*, 2769.
[1144]Evans, D.A.; Takacs, J.M. *Tetrahedron Lett.* ***1980***, *21*, 4233; Sonnet, P.E.; Heath, R.R. *J. Org. Chem.* ***1980***, *45*, 3137; Evans, D.A.; Chapman, K.T.; Bisaha, J. *Tetrahedron Lett.* ***1984***, *25*, 4071.
[1145]Evans, D.A.; Downey, C.W.; Shaw, J.T.; Tedrow, J.S. *Org. Lett.* ***2002***, *4*, 1127.
[1146]Crimmins, M.T.; McDougall, P.J. *Org. Lett.* ***2003***, *5*, 591.
[1147]Corey, E.J.; Choi, S. *Tetrahedron Lett.* ***2000***, *41*, 2769.

The condensation of an ester enolate and a ketone[1148] can be used as part of a Robinson annulation-like sequence (see **16-34**).

OS **I**, 252; **III**, 132; **V**, 80, 564; **70**, 256; **X**, 437; **81**, 157. Also see OS **IV**, 278, 478; **V**, 251.

16-37 The Henry Reaction[1149]

$$CH_3NO_2 + HCHO \xrightarrow{^-OH} HOCH_2CH_2NO_2$$

When aliphatic nitro compounds are used instead of aldehydes or ketones, no reduction occurs, and the reaction has been referred to as a Tollens' reaction (see **16-43**). However, the classical condensation of an aliphatic nitro compound with an aldehyde or ketone is usually called the *Henry reaction*[1150] or the *Kamlet reaction*, and is essentially a nitro aldol reaction. A variety of conditions have been reported, including the use of a silica catalyst,[1151] Mg—Al hydrotalcite,[1152] a tetraalkylammonium hydroxide,[1153] proazaphosphatranes,[1154] or an ionic liquid.[1155] A solvent free Henry reaction was reported in which a nitroalkane and an aldehyde were reacted on KOH powder.[1156] Potassium phosphate has been used with nitromethane and aryl aldehydes.[1157] The Henry reaction has been done using $ZnEt_2$ and 20% ethanolamine.[1158] A gel-entrapped base has been used to catalyze this reaction.[1159]

[1148]Posner, G.H.; Lu, S.; Asirvatham, E.; Silversmith, E.F.; Shulman, E.M. *J. Am. Chem. Soc.* ***1986***, *108*, 511. For an extension of this work to the coupling of four components, see Posner, G.H.; Webb, K.S.; Asirvatham, E.; Jew, S.; Degl'Innocenti, A. *J. Am. Chem. Soc.* ***1988***, *110*, 4754.

[1149]For a review of this reaction with respect to nitroalkanes (the *Henry reaction*, **16-37**), see Baer, H.H.; Urbas, L., in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, Wiley, NY, ***1970***, pp. 76–117. See also, Rosini, G.; Ballini, R.; Sorrenti, P. *Synthesis* ***1983***, 1014; Matsumoto, K. *Angew. Chem. Int. Ed.* ***1984***, *23*, 617; Eyer, M.; Seebach, D. *J. Am. Chem. Soc.* ***1985***, *107*, 3601. For reviews of the nitroalkenes that are the products of this reaction, see Barrett, A.G.M.; Graboski, G.G. *Chem. Rev.* ***1986***, *86*, 751; Kabalka, G.W.; Varma, R.S. *Org. Prep. Proced. Int.* ***1987***, *19*, 283.

[1150]Henry, L. *Compt. Rend.* ***1895***, *120*, 1265; Kamlet, J. *U.S. Patent* 2,151,171 ***1939*** [*Chem. Abstr., 33*: 5003' ***1939***]; Hass, H.B.; Riley, E.F. *Chem. Rev.* ***1943***, *32*, 373 (see p. 406); Lichtenthaler, F.W. *Angew. Chem. Int. Ed.* ***1964***, *3*, 211. For a review, see Luzzio, F.A. *Tetrahedron* ***2001***, *57*, 915.

[1151]Demicheli, G.; Maggi, R.; Mazzacani, A.; Righi, P.; Sartori, G.; Bigi, F. *Tetrahedron Lett.* ***2001***, *42*, 2401.

[1152]Bulbule, V.J.; Deshpande, V.H.; Velu, S.; Sudalai, A.; Sivasankar, S.; Sathe, V.T. *Tetrahedron* ***1999***, *55*, 9325.

[1153]Bulbule, V.J.; Jnaneshwara, G.K.; Deshmukh, R.R.; Borate, H.B.; Deshpande, V.H. *Synth. Commun.* ***2001***, *31*, 3623.

[1154]Kisanga, P.B.; Verkade, J.G. *J. Org. Chem.* ***1999***, *64*, 4298.

[1155]In TMG Lac, tetramethylguanidinium lactate: Jiang, T.; Gao, H.; Han, B.; Zhao, G.; Chang, Y.; Wu, W.; Gao, L.; Yang, G. *Tetrahedron Lett.* ***2004***, *45*, 2699.

[1156]Ballini, R.; Bosica, G.; Parrini, M. *Chem. Lett.* ***1999***, 1105.

[1157]Desai, U.V.; Pore, D.M.; Mane, R.B.; Solabannavar, S.B.; Wadgaonkar, P.P. *Synth. Commun.* ***2004***, *34*, 19.

[1158]Klein, G.; Pandiaraju, S.; Reiser, O. *Tetrahedron Lett.* ***2002***, *43*, 7503.

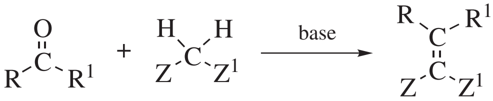
[1159]Bandgar, B.P.; Uppalla, L.S. *Synth. Commun.* ***2000***, *30*, 2071.

Catalytic enantioselective Henry reactions are known,[1160] such as the use of a chiral copper catalyst[1161] or a zinc catalyst.[1162] The Henry reaction of nitromethane an a chiral aldehyde under high pressure gives the β-nitro alcohol with excellent enantioselectivity.[1163]

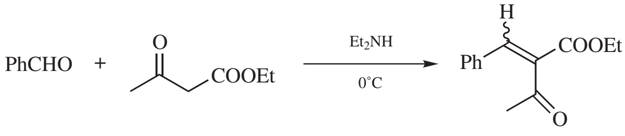
A variation of this reaction converts nitro compounds to nitronates $RCH{=}N^+(OTMS){-}O^-$, which react with aldehydes in the presence of a copper catalyst to give the β-nitro alcohol.[1164]

16-38 The Knoevenagel Reaction

Bis(ethoxycarbonyl)methylene-de-oxo-bisubstitution, and so on



The condensation of aldehydes or ketones, usually not containing an α hydrogen, with compounds of the form Z—CH_2—Z′ or Z—CHR—Z′ is called the *Knoevenagel reaction*.[1165] Both Z and Z′ may be CHO, COR, COOH, COOR, CN, NO_2, SOR, SO_2R, SO_2OR, or similar groups. Such compounds have a significantly higher enol content[1166] and the α-proton is much more acidic (Table 8.1 on p. 360). When Z = COOH, decarboxylation of the product often takes place *in situ*.[1167] If a strong enough base is used, the reaction can be performed on compounds possessing only a single Z (e.g., CH_3Z or RCH_2Z). Other active hydrogen compounds can also be employed, among them $CHCl_3$, 2-methylpyridines, terminal acetylenes, cyclopentadienes, and so on.; in fact any compound that contains a C—H bond the hydrogen of which can be removed by a base. As shown in the example, the reaction of β-keto esters and aldehydes to give **44** is promoted by diethylamine at 0°C. Nitroalkanes[1149] as well as β-keto sulfoxides[1168] undergo the reaction.



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[1160]Christensen, C.; Juhl, K.; Jørgensen, K.A. *Chem. Commun.* ***2001***, 2222; Christensen, C.; Juhl, K.; Hazell, R.G.; Jørgensen, K.A. *J. Org. Chem.* ***2002***, *67*, 4875.

[1161]Evans, D.A.; Seidel, D.; Rueping, M.; Lam, H.W.; Shaw, J.T.; Downey, C.W. *J. Am. Chem. Soc.* ***2003***, *125*, 12692.

[1162]Trost, B.M.; Yeh, V.S.C. *Angew. Chem. Int. Ed.* ***2002***, *41*, 861.

[1163]Misumi, Y.; Matsumoto, K. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1031.

[1164]Risgaard, T.; Gothelf, K.V.; Jørgensen, K.A. *Org. Biomol. Chem.* ***2003***, *1*, 153.

[1165]For reviews, see Jones, G. *Org. React.* ***1967***, *15*, 204; Wilk, B.K. *Tetrahedron* ***1997***, *53*, 7097.

[1166]Rochlin, E.; Rappoport, Z. *J. Org. Chem.* ***2003***, *68*, 1715.

[1167]For a discussion of the mechanism when the reaction is accompanied by decarboxylation, see Tanaka, M.; Oota, O.; Hiramatsu, H.; Fujiwara, K. *Bull. Chem. Soc. Jpn.* ***1988***, *61*, 2473.

[1168]Kuwajima, I.; Iwasawa, H. *Tetrahedron Lett.* ***1974***, 107. See also, Huckin, S.N.; Weiler, L. *Can. J. Chem.* ***1974***, *52*, 2157.

As with **16-34**, these reactions have sometimes been performed with acid catalysts.[1169] Ionic liquid solvents have been used,[1170] and heating on quaternary ammonium salts without solvent leads to a Knoevenagel reaction.[1171] Other solvent-free reactions are known.[1172] Ultrasound has been used to promote the reaction,[1173] and it has also been done using microwave irradiation[1174] or on silica,[1175] with microwave irradiation. Another solid-state variation is done on moist LiBr,[1176] heating with sodium carbonate and molecular sieves 4 Å promotes the reaction,[1177] as do zeolites.[1178] High-pressure conditions have been used.[1179] Transition-metal compounds such as palladium complexes,[1180] SmI_2[1181] or $BiCl_3$[1182] have been used to promote the Knoevenagel reaction.

In the reaction with terminal acetylenes,[1183] sodium acetylides are the most common reagents (when they are used, the reaction is often called the *Nef reaction*), but lithium,[1184] magnesium, and other metallic acetylides have also been used. A particularly convenient reagent is lithium acetylide–ethylenediamine complex,[1185] a stable, free-flowing powder that is commercially available. Alternatively, the substrate may be treated with the alkyne itself in the presence of

[1169]For example, see Rappoport, Z.; Patai, S. *J. Chem. Soc.* ***1962***, 731.

[1170]In bmim Cl, 1-butyl-3-methylimidazolium chloride, with $AlCl_3$: Harjani, J.R.; Nara, S.J.; Salunkhe, M.M. *Tetrahedron Lett.* ***2002***, *43*, 1127. See Morrison, D.W.; Forbes, D.C.; Davis Jr., J.H. *Tetrahedron Lett.* ***2001***, *42*, 6053. In bmim BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate: Su, C.; Chen, Z.-C.; Zheng, Q.G. *Synthesis* ***2003***, 555.

[1171]Bose, D.S.; Narsaiah, A.V. *J. Chem. Res. (S)* ***2001***, 36.

[1172]McCluskey, A.; Robinson, P.J.; Hill, T.; Scott, J.L.; Edwards, J.K. *Tetrahedron Lett.* ***2002***, *43*, 3117; Ren, Z.; Cao, W.; Tong, W. *Synth. Commun.* ***2002***, *32*, 3475; Mogilaiah, K.; Prashanthi, M.; Reddy, G.R.; Reddy, Ch.S.; Reddy, N.V. *Synth. Commun.* ***2003***, *33*, 2309; Zuo, W.-X.; Hua, R.; Qiu, X. *Synth. Commun.* ***2004***, *34*, 3219.

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[1174]de la Cruz, P.; Díez-Barra, E.; Loupy, A.; Langa, F. *Tetrahedron Lett.* ***1996***, *37*, 1113; Mitra, A.K.; De, A.; Karchaudhuri, N. *Synth. Commun.* ***1999***, *29*, 2731; Balalaie, S.; Nemati, N. *Synth. Commun.* ***2000***, *30*, 869; Loupy, A.; Song, S.-J.; Sohn, S.-M.; Lee, Y.-M.; Kwon, T.W.; *J. Chem. Soc., Perkin Trans. 1* ***2001***, 1220; Yadav, J.S.; Reddy, B.V.S.; Basak, A.K.; Visali, B.; Narsaiah, A.V.; Nagaiah, K. *Eur. J. Org. Chem.* ***2004***, 546.

[1175]Kumar, H.M.S.; Reddy, B.V.S.; Reddy, P.T.; Srinivas, D.; Yadav, J.S. *Org. Prep. Proceed. Int.* ***2000***, *32*, 81; Peng, Y.; Song, G.; Qian, X. *J. Chem. Res. (S)* ***2001***, 188.

[1176]Prajapati, D.; Lekhok, K.C.; Sandhu, J.S.; Ghosh, A.C. *J. Chem. Soc. Perkin Trans. 1* ***1996***, 959.

[1177]Siebenhaar, B.; Casagrande, B.; Studer, M.; Blaser, H.-U. *Can. J. Chem.* ***2001***, *79*, 566.

[1178]Reddy, T.I.; Varma, R.S. *Tetrahedron Lett.* ***1997***, *38*, 1721.

[1179]Jenner, G. *Tetrahedron Lett.* ***2001***, *42*, 243.

[1180]You, J.; Verkade, J.G. *J. Org. Chem.* ***2003***, *68*, 8003.

[1181]Chandrasekhar, S.; Yu, J.; Falck, J.R.; Mioskowski, C. *Tetrahedron Lett.* ***1994***, *35*, 5441.

[1182]This catalyst was used in the reaction without solvent. See Prajapati, D.; Sandhu, J.S. *Chem. Lett.* ***1992***, 1945.

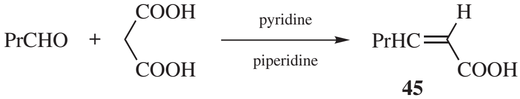
[1183]For reviews, see Ziegenbein, W., in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 207–241; Ried, W. *Newer Methods Prep. Org. Chem.* ***1968***, *4*, 95.

[1184]See Midland, M.M. *J. Org. Chem.* ***1975***, *40*, 2250, for the use of amine-free monolithium acetylide.

[1185]Beumel Jr., O.F.; Harris, R.F. *J. Org. Chem.* ***1963***, *28*, 2775.

a base, so that the acetylide is generated *in situ*. This procedure is called the *Favorskii reaction*, not to be confused with the Favorskii rearrangement (**18-7**).[1186]

With most of these reagents the alcohol is not isolated (only the alkene) *if* the alcohol has a hydrogen in the proper position.[1187] However, in some cases the alcohol is the major product. A β-keto allylic ester was shown to react with an aldehyde to give a β-hydroxy ketone, with loss of the allyl ester moiety, upon treatment with $YbCl_3$ and a palladium catalyst.[1188] With suitable reactants, the Knoevenagel reaction, like the aldol (**16-2**), has been carried out diastereoselectively[1189] and enantioselectively.[1190] When the reactant is of the form ZCH_2Z', aldehydes react much better than ketones and few successful reactions with ketones have been reported. However, it is possible to get good yields of alkene from the condensation of diethyl malonate, $CH_2(COOEt)_2$, with ketones, as well as with aldehydes, if the reaction is run with $TiCl_4$ and pyridine in THF.[1191] In reactions with ZCH_2Z', the catalyst is most often a secondary amine (piperidine is the most common, but see formation of **44**), though many other catalysts have been used. When the catalyst is pyridine (to which piperidine may or may not be added) the reaction is known as the *Doebner modification* of the Knoevenagel reaction and the product is usually the conjugated acid **45**. Alkoxides are also common catalysts. Microwave-induced Doebner condensation reactions are known.[1192]



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A number of special applications of the Knoevenagel reaction follow:

1. The dilithio derivative of *N*-methanesulfinyl-*p*-toluidine[1193] (**46**) adds to aldehydes and ketones to give, after hydrolysis, the hydroxysulfinamides

[1186]For a discussion of the mechanism of the Favorskii addition reaction, see Kondrat'eva, L.A.; Potapova, I.M.; Grigina, I.N.; Glazunova, E.M.; Nikitin, V.I. *J. Org. Chem. USSR* ***1976***, *12*, 948.

[1187]For lists of reagents (with references) that condense with aldehydes and ketones to give alkene products, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 317–325, 341–350. For those that give the alcohol product, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1178–1179, 1540–1541, 1717–1724, 1727, 1732–1736, 1778–1780, 1801–1805.

[1188]Lou, S.; Westbrook J.A.; Schaus, S.E. *J. Am. Chem. Soc.* ***2004***, *126*, 11440.

[1189]See, for example, Trost, B.M.; Florez, J.; Jebaratnam, D.J. *J. Am. Chem. Soc.* ***1987***, *109*, 613; Mahler, U.; Devant, R.M.; Braun, M. *Chem. Ber.* ***1988***, *121*, 2035; Ronan, B.; Marchalin, S.; Samuel, O.; Kagan, H.B. *Tetrahedron Lett.* ***1988***, *29*, 6101; Barrett, A.G.M.; Robyr, C.; Spilling, C.D. *J. Org. Chem.* ***1989***, *54*, 1233; Pyne, S.G.; Boche, G. *J. Org. Chem.* ***1989***, *54*, 2663.

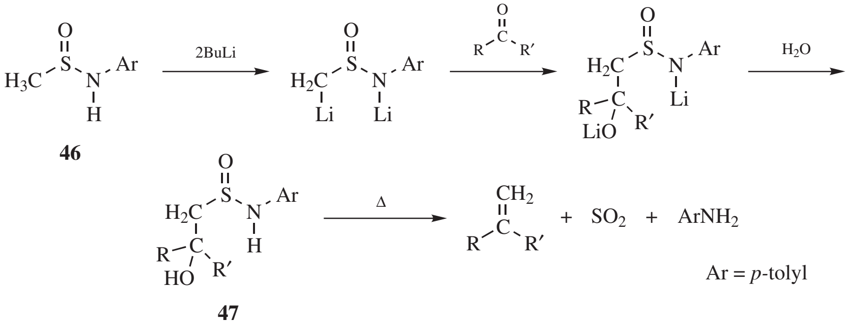
[1190]See, for example, Enders, D.; Lotter, H.; Maigrot, N.; Mazaleyrat, J.; Welvart, Z. *Nouv. J. Chim.*, ***1984***, *8*, 747; Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* ***1986***, *108*, 6405; Togni, A.; Pastor, S.D. *J. Org. Chem.* ***1990***, *55*, 1649; Sakuraba, H.; Ushiki, S. *Tetrahedron Lett.* ***1990***, *31*, 5349; Niwa, S.; Soai, K. *J. Chem. Soc. Perkin Trans. 1* ***1990***, 937.

[1191]Lehnert, W. *Tetrahedron* ***1973***, *29*, 635; *Synthesis* ***1974***, 667, and references cited therein.

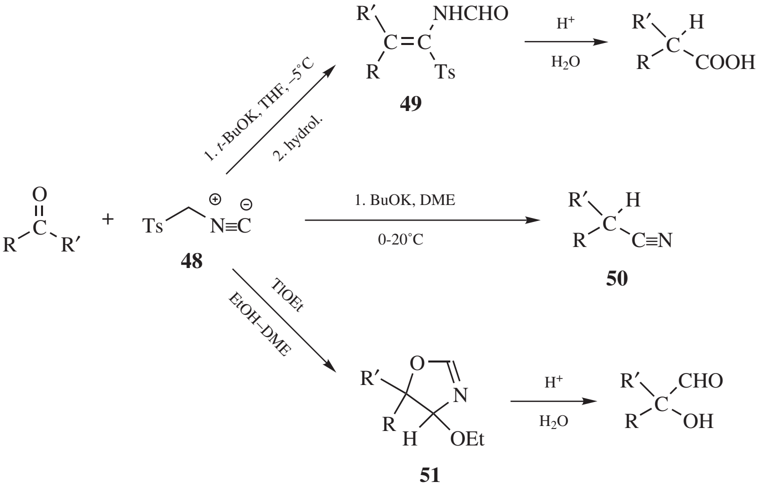
[1192]Mitra, A.K.; De, A.; Karchaudhuri, N. *Synth. Commun.* ***1999***, *29*, 573; Pellón, R.F.; Mamposo, T.; González, E.; Calderón, O. *Synth. Commun.* ***2000***, *30*, 3769.

[1193]For a method of preparing **46**, see Bowlus, S.B.; Katzenellenbogen, J.A. *Synth. Commun.* ***1974***, *4*, 137.

47, which, upon heating, undergo stereospecifically syn eliminations to give alkenes.[1194] The reaction is thus a method for achieving the conversion $RR'CO \rightarrow RR'C{=}CH_2$ and represents an alternative to the Wittig reaction.[1195] Note that sulfones with an amide group at the α-position, $ArSO_2CH(R)N(R)C{=}O$, react with ketones via acyl addition in the presence of SmI_2.[1196]



2. The reaction of ketones with tosylmethylisocyanide (**48**) gives different products,[1197] depending on the reaction conditions.



[1194]Corey, E.J.; Durst, T. *J. Am. Chem. Soc.* ***1968***, *90*, 5548, 5553.

[1195]For similar reactions, see Jung, F.; Sharma, N.K.; Durst, T. *J. Am. Chem. Soc.* ***1973***, *95*, 3420; Kuwajima, I.; Uchida, M. *Tetrahedron Lett.* ***1972***, 649; Johnson, C.R.; Shanklin, J.R.; Kirchhoff, R.A. *J. Am. Chem. Soc.* ***1973***, *95*, 6462; Lau, P.W.K.; Chan, T.H. *Tetrahedron Lett.* ***1978***, 2383; Yamamoto, K.; Tomo, Y.; Suzuki, S. *Tetrahedron Lett.* ***1980***, *21*, 2861; Martin, S.F.; Phillips, G.W.; Puckette, T.A.; Colapret, J.A. *J. Am. Chem. Soc.* ***1980***, *102*, 5866; Arenz, T.; Vostell, M.; Frauenrath, H. *Synlett* ***1991***, 23.

[1196]Yoda, H.; Ujihara, Y.; Takabe, K. *Tetrahedron Lett.* ***2001***, *42*, 9225.

[1197]For reviews of α-metalated isocyanides, see Schöllkopf, U. *Pure Appl. Chem.* ***1979***, *51*, 1347; *Angew. Chem. Int. Ed.* ***1977***, *16*, 339; Hoppe, D. *Angew. Chem. Int. Ed.* ***1974***, *13*, 789.

When the reaction is run with potassium *tert*-butoxide in THF at −5°C, one obtains (after hydrolysis) the normal Knoevenagel product **49**, except that the isocyano group has been hydrated (**16-97**).[1198] With the same base but with 1,2-dimethoxyethane (DME) as solvent the product is the nitrile **50**.[1199] When the ketone is treated with **48** and thallium(I) ethoxide in a 4:1 mixture of absolute ethanol and DME at room temperature, the product is a 4-ethoxy-2-oxazoline **51**.[1200] Since **50** can be hydrolyzed[1201] to a carboxylic acid[1198] and **51** to an α-hydroxy aldehyde,[1200] this versatile reaction provides a means for achieving the conversion of RCOR′ to RCHR′COOH, RCHR′CN, or RCR′(OH)CHO. The conversions to RCHR′COOH and to RCHR′CN[1202] have also been carried out with certain aldehydes (R′ = H).

3. Aldehydes and ketones RCOR′ react with α-methoxyvinyllithium, $CH_2{=}C(Li)OMe$, to give hydroxy enol ethers, $RR'C(OH)C(OMe){=}CH_2$, which are easily hydrolyzed to acyloins, RR′C(OH)COMe.[1203] In this reaction, the $CH_2{=}C(Li)OMe$ is a synthon for the unavailable $H_3C{-}\overset{\ominus}{C}{=}O$,[1204] and is termed an *acyl anion equivalent*. The reagent also reacts with esters RCOOR′ to give $RC(OH)(COMe{=}CH_2)_2$. A synthon for the Ph—C=O ion is $PhC(CN)OSiMe_3$, which adds to aldehydes and ketones RCOR′ to give, after hydrolysis, the α-hydroxy ketones, RR′C(OH) *C(OH)COPh.*[1205]

4. Lithiated allylic carbamates (**52**) (prepared as shown) react with aldehydes or ketones (R^6COR^7), in a reaction accompanied by an allylic rearrangement, to give (after hydrolysis) γ-hydroxy aldehydes or ketones.[1206] The reaction is called *the homoaldol reaction*, since the product is a homolog of the product of **16-34**. The reaction has been performed enantioselectively.[1207]

[1198]Schöllkopf, U.; Schröder, U.; Blume, E. *Liebigs Ann. Chem.* ***1972***, *766*, 130; Schöllkopf, U.; Schröder, U. *Angew. Chem. Int. Ed.* ***1972***, *11*, 311.

[1199]Oldenziel, O.H.; van Leusen, D.; van Leusen, A.M. *J. Org. Chem.* ***1977***, *42*, 3114.

[1200]Oldenziel, O.H.; van Leusen, A.M. *Tetrahedron Lett.* ***1974***, 163, 167. For conversions to α,β-unsaturated ketones and diketones, see, respectively, Moskal, J.; van Leusen, A.M. *Tetrahedron Lett.* ***1984***, *25*, 2585; van Leusen, A.M.; Oosterwijk, R.; van Echten, E.; van Leusen, D. *Recl. Trav. Chim. Pays-Bas* ***1985***, *104*, 50.

[1201]Compound **49** can also be converted to a nitrile; see **17-30**.

[1202]van Leusen, A.M.; Oomkes, P.G. *Synth. Commun.* ***1980***, *10*, 399.

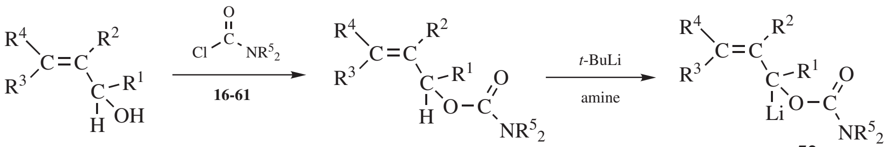
[1203]Baldwin, J.E.; Höfle, G.A.; Lever Jr., O.W. *J. Am. Chem. Soc.* ***1974***, *96*, 7125. For a similar reaction, see Tanaka, K.; Nakai, T.; Ishikawa, N. *Tetrahedron Lett.* ***1978***, 4809.

[1204]For a synthon for the $^{\ominus}$COCOOEt ion, see Reetz, M.T.; Heimbach, H.; Schwellnus, K. *Tetrahedron Lett.* ***1984***, *25*, 511.

[1205]Hünig, S.; Wehner, G. *Synthesis* ***1975***, 391.

[1206]For a review, see Hoppe, D. *Angew. Chem. Int. Ed.* ***1984***, *23*, 932.

[1207]Krämer, T.; Hoppe, D. *Tetrahedron Lett.* ***1987***, *28*, 5149.



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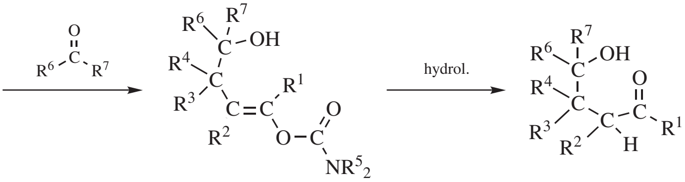
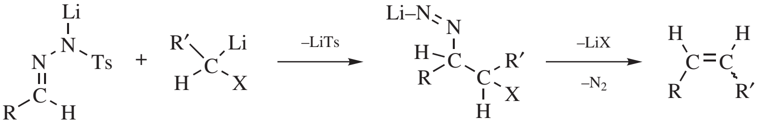


5. The lithium salt of an active hydrogen compound adds to the lithium salt of the tosylhydrazone of an aldehyde to give product **53**. If X = CN, SPh, or SO_2R, **53** spontaneously loses N_2 and LiX to give the alkene **54**. The entire process is done in one reaction vessel: The active hydrogen compound is mixed with the tosylhydrazone and the mixture is treated with (iPr)$_2$NLi to form both salts at once.[1208] This process is another alternative to the Wittig reaction for forming double bonds.



53 **54**

OS **I**, 181, 290, 413; **II**, 202; **III**, 39, 165, 317, 320, 377, 385, 399, 416, 425, 456, 479, 513, 586, 591, 597, 715, 783; **IV**, 93, 210, 221, 234, 293, 327, 387, 392, 408, 441, 463, 471, 549, 573, 730, 731, 777; **V**, 130, 381, 572, 585, 627, 833, 1088, 1128; **VI**, 41, 95, 442, 598, 683; **VII**, 50, 108, 142, 276, 381, 386, 456; **VIII**, 258, 265, 309, 353, 391, 420; **X**, 271. Also see, OS **III**, 395; **V**, 450.

16-39 The Perkin Reaction

α-Carboxyalkylidene-de-oxo-bisubstitution

The condensation of aromatic aldehydes with anhydrides is called the *Perkin reaction*.[1209] When the anhydride has two α hydrogens (as shown), dehydration

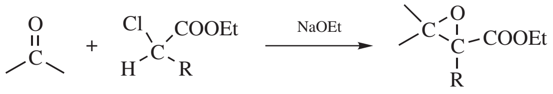
[1208] Vedejs, E.; Dolphin, J.M.; Stolle, W.T. *J. Am. Chem. Soc.* ***1979***, *101*, 249.
[1209] For a review, see Johnson, J.R. *Org. React.* ***1942***, *1*, 210.

always occurs; the β-hydroxy acid salt is never isolated. In some cases, anhydrides of the form $(R_2CHCO)_2O$ have been used, and then the hydroxy compound is the product since dehydration cannot take place. The base in the Perkin reaction is nearly always the salt of the acid corresponding to the anhydride. Although the Na and K salts have been most frequently used, higher yields and shorter reaction times have been reported for the Cs salt.[1210] Besides aromatic aldehydes, their vinylogs ArCH=CHCHO also give the reaction. Otherwise, the reaction is not suitable for aliphatic aldehydes.[1211]

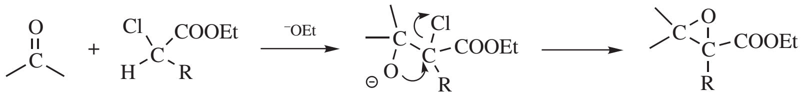
OS **I**, 398; **II**, 61, 229; **III**, 426.

16-40 Darzens Glycidic Ester Condensation

(2 + 1)*OC*,*CC-cyclo*-α-Alkoxycarbonylmethylene-addition



Aldehydes and ketones condense with α-halo esters in the presence of bases to give α,β-epoxy esters, called *glycidic esters*. This is called *the Darzens condensation*.[1212] The reaction consists of an initial Knoevenagel-type reaction (**16-38**), followed by an internal S_N2 reaction (**10-9**):[1213]



Although the intermediate halo alkoxide is generally not isolated,[1214] it has been done, not only with α-fluoro esters (since fluorine is such a poor leaving group in nucleophilic substitutions), but also with α-chloro esters.[1215] This is only one of several types of evidence that rule out a carbene intermediate.[1216] Sodium ethoxide is often used as the base, though other bases, including sodium amide, are sometimes used. Aromatic aldehydes and ketones give good yields, but aliphatic aldehydes react poorly. However, the reaction can be made to give good yields

[1210]Koepp, E.; Vögtle, F. *Synthesis* ***1987***, 177.

[1211]Crawford, M.; Little, W.T. *J. Chem. Soc.* ***1959***, 722.

[1212]For a review, see Berti, G. *Top. Stereochem.* ***1973***, *7*, 93, pp. 210–218. Also see Bakó, P.; Szöllõsy, Á; Bombicz, P.; Töke, L. *Synlett* ***1997***, 291.

[1213]For discussions of the mechanism of the reaction, and especially of the stereochemistry, see Roux-Schmitt, M.; Seyden-Penne, J.; Wolfe, S. *Tetrahedron* ***1972***, *28*, 4965; Bansal, R.K.; Sethi, K. *Bull. Chem. Soc. Jpn.* ***1980***, *53*, 1197.

[1214]The transition state for this reaction has been examined. See Yliniemelä, A.; Brunow, G.; Flügge, J.; Teleman, O. *J. Org. Chem.* ***1996***, *61*, 6723.

[1215]Ballester, M.; Pérez-Blanco, D. *J. Org. Chem.* ***1958***, *23*, 652; Martynov, V.F.; Titov, M.I. *J. Gen. Chem. USSR* ***1963***, *33*, 1350; ***1964***, *34*, 2139; Elkik, E.; Francesch, C. *Bull. Soc. Chim. Fr.* ***1973***, 1277, 1281.

[1216]Another, based on the stereochemistry of the products, is described by Zimmerman, H.E.; Ahramjian, L. *J. Am. Chem. Soc.* ***1960***, *82*, 5459.

($\sim$80%) with simple aliphatic aldehydes, as well as with aromatic aldehydes and ketones by treatment of the α-halo ester with the base lithium bis(trimethylsilyl) amide, $LiN(SiMe_3)_2$, in THF at −78°C (to form the conjugate base of the ester) and addition of the aldehyde or ketone to this solution.[1217] If a preformed dianion of an α-halo carboxylic acid $Cl-\overset{\ominus}{C}R-COO^{\ominus}$ is used instead, α,β-epoxy acids are produced directly.[1218] The Darzens reaction has also been carried out on α-halo ketones, α-halo nitriles,[1219] α-halo sulfoxides[1220] and sulfones,[1221] α-halo *N,N*-disubstituted amides,[1222] α-halo ketimines,[1223] and even on allylic[1224] and benzylic halides. Phase-transfer catalysis has been used.[1225] Note that the reaction of a β-bromo-α-oxo ester and a Grignard reagent leads to the glycidic ester.[1226] Acid-catalyzed Darzens reactions have also been reported.[1227] (see also, **16-46**).

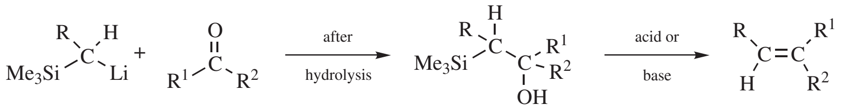
The Darzens reaction has been performed enantioselectively, by coupling optically active α-bromo-β-hydroxy esters with aldehydes.[1228] Chiral phase-transfer agents have been used to give epoxy ketones with modest enantioselectivity.[1229] Chiral additives have proven to be effective.[1230]

Glycidic esters can easily be converted to aldehydes (**12-40**). The reaction has been extended to the formation of analogous aziridines by treatment of an imine with an α-halo ester or an α-halo *N,N*-disubstituted amide and *t*-BuOK in the solvent 1,2-dimethoxyethane.[1231] However, yields were not high.

OS **III**, 727; **IV**, 459, 649.

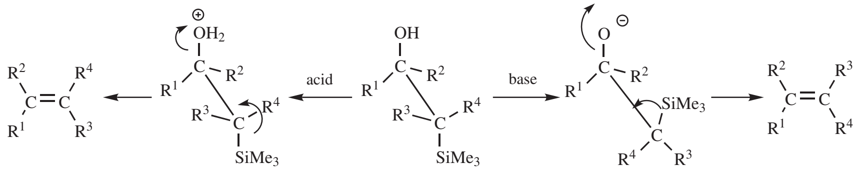
16-41 The Peterson Alkenylation Reaction

Alkylidene-de-oxo-bisubstitution



[1217]Borch, R.F. *Tetrahedron Lett.* ***1972***, 3761.
[1218]Johnson, C.R.; Bade, T.R. *J. Org. Chem.* ***1982***, *47*, 1205.
[1219]See White, D.R.; Wu, D.K. *J. Chem. Soc., Chem. Commun.* ***1974***, 988.
[1220]Satoh, T.; Sugimoto, A.; Itoh, M.; Yamakawa, K. *Tetrahedron Lett.* ***1989***, *30*, 1083.
[1221]Arai, S.; Ishida, T.; Shioiri, T. *Tetrahedron Lett.* ***1998***, *39*, 8299.
[1222]Tung, C.C.; Speziale, A.J.; Frazier, H.W. *J. Org. Chem.* ***1963***, *28*, 1514.
[1223]Mauzé, B. *J. Organomet. Chem.* ***1979***, *170*, 265.
[1224]Sulmon, P.; De Kimpe, N.; Schamp, N.; Declercq, J.; Tinant, B. *J. Org. Chem.* ***1988***, *53*, 4457.
[1225]See Jończyk, A.; Kwast, A.; Makosza, M. *J. Chem. Soc., Chem. Commun.* ***1977***, 902; Gladiali, S.; Soccolini, F. *Synth. Commun.* ***1982***, *12*, 355; Arai, S.; Suzuki, Y.; Tokumaru, K.; Shioiri, T. *Tetrahedron Lett.* ***2002***, *43*, 833. See Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Academic Press, NY, ***1978***, pp. 197–198.
[1226]Jung, M.E.; Mengel, W.; Newton, T.W. *Synth. Commun.* ***1999***, *29*, 3659.
[1227]Sipos, G.; Schöbel, G.; Sirokmán, F. *J. Chem. Soc. Perkin Trans. 2* ***1975***, 805.
[1228]Corey, E.J.; Choi, S. *Tetrahedron Lett.* ***1991***, *32*, 2857. For a review, see Ohkata, K.; Kimura, J.; Shinohara, Y.; Takagi, R.; Hiraga, Y. *Chem. Commun.* ***1996***, 2411.
[1229]Arai, S.; Shirai, Y.; Ishida, T.; Shioiri, T. *Tetrahedron* ***1999***, *55*, 6375.
[1230]Aggarwal, V.K.; Hynd, G.; Picoul, W.; Vasse, J.-L. *J. Am. Chem. Soc.* ***2002***, *124*, 9964.
[1231]Deyrup, J.A. *J. Org. Chem.* ***1969***, *34*, 2724.

In the *Peterson alkenylation reaction*[1232, 1233] the lithio (or sometimes magnesio) derivative of a trialkylsilane adds to an aldehyde or ketone to give a β-hydroxysilane, which spontaneously eliminates water, or can be made to do so by treatment with acid or base, to produce an alkene. This reaction is still another alternative to the Wittig reaction (**16-44**), and is sometimes called the *silyl-Wittig reaction.*[1234] The R group can also be a COOR group, in which case the product is an α,β-unsaturated ester,[1235] or an SO_2Ph group, in which case the product is a vinylic sulfone.[1236] The stereochemistry of the product can often be controlled by whether an acid or a base is used to achieve elimination. The role of Si—O interactions has also been examined.[1237] Use of a base generally gives syn elimination (E^i mechanism, see p. 1507), while an acid usually results in anti elimination (E2 mechanism, see p. 1478).[1238] Samarium(II) iodide in HMPA has also been used for elimination of the hydroxy sulfone.[1239] α-Alkoxy benzotriazoyl sulfones ($ROCH_2SO_2Bt$, where Bt = benzothiazole, reacts with lithium hexamethyldisilazide and an aldehyde to give a vinyl ether.[1240]



[1232]Peterson, D.J. *J. Org. Chem.* ***1968***, *33*, 780. For reviews, see Ager, D.J. *Org. React.* ***1990***, *38*, 1; *Synthesis* ***1984***, 384; Colvin, E.W. *Silicon Reagents in Organic Synthesis*, Academic Press, NY, ***1988***, pp. 63–75; Weber, W.P. *Silicon Reagents for Organic Synthesis*, Springer, NY, ***1983***, pp. 58–78; Magnus, P. *Aldrichimica Acta* ***1980***, *13*, 43; Chan, T. *Acc. Chem. Res.* ***1977***, *10*, 442. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 337–341.

[1233]For reviews of these compounds, see Poirier, J. *Org. Prep. Proced. Int.* ***1988***, *20*, 319; Brownbridge, P. *Synthesis* ***1983***, 1–28, 85; Rasmussen, J.K. *Synthesis* ***1977***, 91. For monographs on silicon reagents in organic synthesis see Colvin, E.W. *Silicon Reagents in Organic Synthesis*, Academic Press, NY, ***1988***. For reviews, see Colvin, E.W., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, pp. 539–621; Ager, D.J. *Chem. Soc. Rev.* ***1982***, *11*, 493; Colvin, E.W. *Chem. Soc. Rev.* ***1978***, *7*, 15, pp. 43–50.

[1234]For discussions of the mechanism, see Bassindale, A.R.; Ellis, R.J.; Lau, J.C.; Taylor, P.G. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 593; Hudrlik, P.F.; Agwaramgbo, E.L.O.; Hudrlik, A.M. *J. Org. Chem.* ***1989***, *54*, 5613.

[1235]Hartzell, S.L.; Sullivan, D.F.; Rathke, M.W. *Tetrahedron Lett.* ***1974***, 1403; Shimoji, K.; Taguchi, H.; Oshima, K.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* ***1974***, *96*, 1620; Chan, T.H.; Moreland, M. *Tetrahedron Lett.* ***1978***, 515; Strekowski, L.; Visnick, M.; Battiste, M.A. *Tetrahedron Lett.* ***1984***, *25*, 5603.

[1236]Craig, D.; Ley, S.V.; Simpkins, N.S.; Whitham, G.H.; Prior, M.J. *J. Chem. Soc. Perkin Trans. 1* ***1985***, 1949.

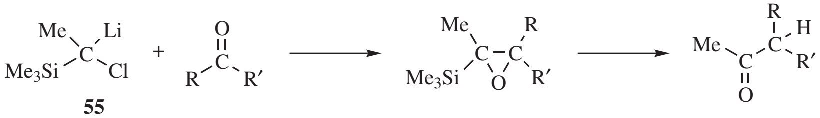
[1237]Bassindale, A.R.; Ellis, R.J.; Taylor, P.G. *J. Chem. Res. (S)* ***1996***, 34.

[1238]See Colvin, E.W. *Silicon Reagents in Organic Synthesis*, Academic Press, NY, ***1988***, pp. 65–69.

[1239]Markò, I.E.; Murphy, F.; Kumps, L.; Ates, A.; Touillaux, R.; Craig, D.; Carballares, S.; Dolan, S. *Tetrahedron* ***2001***, *57*, 2609.

[1240]Surprenant, S.; Chan, W.Y.; Berthelette, C. *Org. Lett.* ***2003***, *5*, 4851.

When aldehydes or ketones are treated with reagents of the form **55**, the product is an epoxy silane (**16-46**), which can be hydrolyzed to a methyl ketone.[1241] For aldehydes, this is a method for converting RCHO to a methyl ketone RCH_2COMe.



55

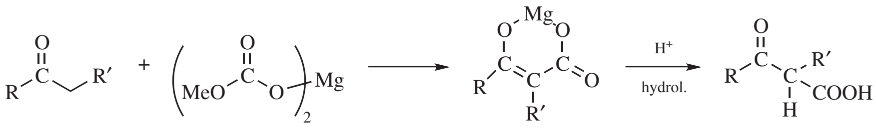
The reagents $Me_3SiCHRM$ (M = Li or Mg) are often prepared from $Me_3SiCHRCl$[1242] (by **12-38** or **12-39**), but they have also been made by **12-22** and by other procedures.[1243]

A new version of the reaction has been developed, reacting $Me_3SiCH_2CO_2Et$ with an aldehyde and a catalytic amount of CsF in DMSO.[1244] A seleno-amide derivative has been used in a similar manner.[1245]

There are no references in *Organic Syntheses*, but see OS **VIII**, 602, for a related reaction.

16-42 The Addition of Active Hydrogen Compounds to CO_2 and CS_2

α-Acylalkyl-de-methoxy-substitution (Overall reaction)



56 **57**

Ketones of the form $RCOCH_3$ and $RCOCH_2R'$ can be carboxylated indirectly by treatment with magnesium methyl carbonate **56**.[1246] Because formation of the chelate **57** provides the driving force of the reaction, carboxylation cannot be achieved at a disubstituted α position. The reaction has also been performed on CH_3NO_2 and compounds of the form RCH_2NO_2[1247] and on certain lactones.[1248] Direct carboxylation has been reported in a number of instances. Ketones have

[1241]Cooke, F.; Roy, G.; Magnus, P. *Organometallics* ***1982***, *1*, 893.

[1242]For a review of these reagents, see Anderson, R. *Synthesis* ***1985***, 717.

[1243]See, for example, Ager, D.J. *J. Chem. Soc. Perkin Trans. 1* ***1986***, 183; Barrett, A.G.M.; Flygare, J.A. *J. Org. Chem.* ***1991***, *56*, 638.

[1244]Bellassoued, M.; Ozanne, N. *J. Org. Chem.* ***1995***, *60*, 6582.

[1245]Murai, T.; Fujishima, A.; Iwamoto, C.; Kato, S. *J. Org. Chem.* ***2003***, *68*, 7979.

[1246]Stiles, M. *J. Am. Chem. Soc.* ***1959***, *81*, 2598; *Ann. N.Y. Acad. Sci.* ***1960***, *88*, 332; Crombie, L.; Hemesley, P.; Pattenden, G. *Tetrahedron Lett.* ***1968***, 3021.

[1247]Finkbeiner, H.L.; Stiles, M. *J. Am. Chem. Soc.* ***1963***, *85*, 616; Finkbeiner, H.L.; Wagner, G.W. *J. Org. Chem.* ***1963***, *28*, 215.

[1248]Martin, J.; Watts, P.C.; Johnson, F. *Chem. Commun.* ***1970***, 27.

been carboxylated in the α position to give β-keto acids.[1249] The base here was lithium 4-methyl-2,16-di-*tert*-butylphenoxide.

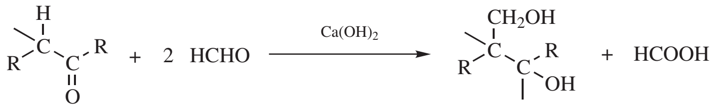
Ketones $RCOCH_2R'$ (as well as other active hydrogen compounds) undergo base-catalyzed addition to CS_2[1250] to give a dianion intermediate $RCOC^{-}R'CSS^{2-}$, which can be dialkylated with a halide R^2X to produce α-dithiomethylene ketones, $RCOCR'{=}C(SR^2)_2$.[1251] Compounds of the form ZCH_2Z' also react with bases and CS_2 to give analogous dianions.[1252]

Although reactions with N=O derivatives do not formally fall into this category of reactions, it is somewhat related. Nitroso compounds react with activated nitriles in the presence of LiBr and microwave irradiation to give a cyano imine, ArN=C(CN)Ar.[1253] This transformation has been called the *Ehrlich–Sachs reaction.*[1254]

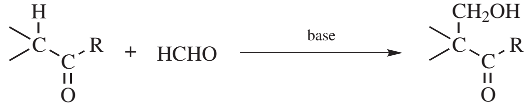
OS **VII**, 476. See also, OS **VIII**, 578.

16-43 Tollens' Reaction

***O*-Hydro-*C*(β-hydroxyalkyl)-addition**



In the *Tollens' reaction* an aldehyde or ketone containing an α hydrogen is treated with formaldehyde in the presence of $Ca(OH)_2$ or a similar base. The first step is a mixed aldol reaction (**16-34**).



The reaction can be stopped at this point, but more often a second equivalent of formaldehyde is permitted to reduce the newly formed aldol to a 1,3-diol, in a crossed Cannizzaro reaction (**19-81**). If the aldehyde or ketone has several α hydrogens, they can all be replaced. An important use of the reaction is to prepare pentaerythritol from acetaldehyde:

$$CH_3CHO \quad + \quad 4\,HCHO \longrightarrow C(CH_2OH)_4 \quad + \quad HCOOH$$

[1249]Tirpak, R.E.; Olsen, R.S.; Rathke, M.W. *J. Org. Chem.* ***1985***, *50*, 4877. For an enantioselective version, see Hogeveen, H.; Menge, W.M.P.B. *Tetrahedron Lett.* ***1986***, *27*, 2767.

[1250]For reviews of the reactions of CS_2 with carbon nucleophiles, see Dunn, A.D.; Rudorf, W. *Carbon Disulphide in Organic Chemistry*, Ellis Horwood, Chichester, ***1989***, pp. 120–225; Yokoyama, M.; Imamoto, T. *Synthesis* ***1984***, 797, pp. 797–804.

[1251]See, for example, Corey, E.J.; Chen, R.H.K. *Tetrahedron Lett.* ***1973***, 3817.

[1252]Jensen, L.; Dalgaard, L.; Lawesson, S. *Tetrahedron* ***1974***, *30*, 2413; Konen, D.A.; Pfeffer, P.E.; Silbert, L.S. *Tetrahedron* ***1976***, *32*, 2507, and references cited therein.

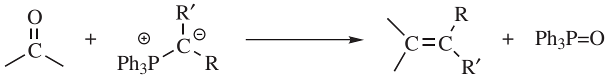
[1253]Laskar, D.D.; Prajapati, D.; Sandhu, J.S. *Synth. Commun.* ***2001***, *31*, 1427.

[1254]Ehrlich, P.; Sachs, F. *Chem. Ber.* ***1899***, *32*, 2341

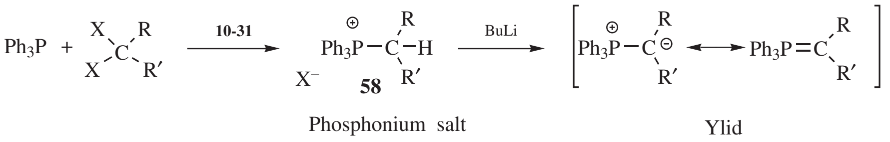
OS **I**, 425; **IV**, 907; **V**, 833.

16-44 The Wittig Reaction

Alkylidene-de-oxo-bisubstitution



In the *Wittig reaction* an aldehyde or ketone is treated with a *phosphorus ylid* (also spelled ylide and called a *phosphorane*) to give an alkene.[1255] The conversion of a carbonyl compound to an alkene with a phosphorus ylid is called the *Wittig reaction*. Phosphorus ylids are usually prepared by treatment of a phosphonium salt with a base,[1256] and phosphonium salts are usually prepared from a triaryl phosphine and an alkyl halide (**10-31**):



The reaction of triphenylphosphine and an alkyl halides is facilitated by the use of microwave irradiation.[1257] Indeed, the Wittig reaction itself is assisted by microwave irradiation.[1258] Phosphonium salts are also prepared by addition of phosphines to Michael alkenes (like **15-8**) and in other ways. The phosphonium salts are most often converted to the ylids by treatment with a strong base such as

[1255]For a general treatise, see Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, ***1979***. For a monograph on the Wittig reaction, see Johnson, A.W. *Ylid Chemistry*, Academic Press, NY, ***1966***. For reviews, see Maryanoff, B.E.; Reitz, A.B. *Chem. Rev.* ***1989***, *89*, 863; Bestmann, H.J.; Vostrowsky, O. *Top. Curr. Chem.* ***1983***, *109*, 85; Pommer, H.; Thieme, P.C. *Top. Curr. Chem.* ***1983***, *109*, 165; Pommer, H. *Angew. Chem. Int. Ed.* ***1977***, *16*, 423; Maercker, A. *Org. React.* ***1965***, *14*, 270; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 682–709; Lowe, P.A. *Chem. Ind. (London)* ***1970***, 1070; Bergelson, L.D.; Shemyakin, M.M., in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 295–340; *Newer Methods Prep. Org. Chem.* ***1968***, *5*, 154. For related reviews, see Tyuleneva, V.V.; Rokhlin, E.M.; Knunyants, I.L. *Russ. Chem. Rev.* ***1981***, *50*, 280; Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Academic Press, NY, ***1978***, pp. 288–297; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, ***1977***; pp. 234–241; Zbiral, E. *Synthesis* ***1974***, 775; Bestmann, H.J. *Bull. Soc. Chim. Fr.* ***1971***, 1619; *Angew. Chem. Int. Ed.* ***1965***, *4*, 583, 645–660, 830–838; *Newer Methods Prep. Org. Chem.* ***1968***, *5*, 1; Horner, L. *Fortschr. Chem. Forsch.*, ***1966***, *7*, 1. For a historical background, see Wittig, G. *Pure Appl. Chem.* ***1964***, *9*, 245. For a list of reagents and references for the Wittig and related reactions, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 327–337.

[1256]When phosphonium *fluorides* are used, no base is necessary, as these react directly with the substrate to give the alkene: Schiemenz, G.P.; Becker, J.; Stöckigt, J. *Chem. Ber.* ***1970***, *103*, 2077.

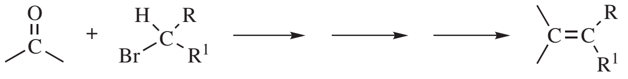
[1257]Kiddle, J.J. *Tetrahedron Lett.* ***2000***, *41*, 1339.

[1258]Frattini, S.; Quai, M.; Cereda, E. *Tetrahedron Lett.* ***2001***, *42*, 6827.; Wu, J.; Wu, H.; Wei, S.; Dai, W.-M. *Tetrahedron Lett.* ***2004***, *45*, 4401.

butyllithium, sodium amide,[1259] sodium hydride, or a sodium alkoxide, though weaker bases can be used if the salt is acidic enough. Unusual bases such as 1,5,7-triazabicyclo [4.4.0]dec-5-ene have been used to promote the Wittig reaction.[1260] In some cases, and excess of fluoride ion is sufficient.[1261] For $(Ph_3P^+)_2CH_2$, sodium carbonate is a strong enough base.[1262] When the base used does not contain lithium, the ylid is said to be prepared under "salt-free" conditions[1263] because the lithium halide (where the halide counterion comes from the phosphonium salt) is absent.

When the phosphorus ylid reacts with the aldehyde or ketone to form an alkene, a phosphine oxide is also formed. When triphenylphosphine is used to give $Ph_3P{=}CRR'$, for example, the by-product is triphenylphosphine oxide, Ph_3PO, which is sometimes difficult to separate from the other reaction products. Ylids are usually prepared from triphenylphosphine, but other triarylphosphines,[1264] trialkylphosphines,[1265] and triphenylarsine[1266] have also been used. Tellurium ylids have been prepared *in situ* from α-halo esters and $BrTeBu_2OTeBu_2Br$ and react with aldehydes to give conjugated esters.[1267] Polymer-bound aryldiphenylphosphino compounds[1268] have been used in reactions with alkyl halides to complete a Wittig reaction. Phosphines that have an α-hydrogen should be avoided, so that reaction with the chosen alkyl halide will lead to a phosphonium salt (**58**) with the α-proton at the desired position. This limitation is essential if a specific ylid is to be formed from the alkyl halide precursor. The Wittig reaction has been carried out with polymer-supported ylids.[1269] It has also been done on silica gel.[1270]

If we view the Wittig reaction from an alkyl halide starting material (alkyl halide phosphonium salt → phosphorus ylid → alkene), the halogen-bearing carbon of an alkyl halide must contain at least one hydrogen as in **59** (for deprotonation at the phosphonium salt stage).



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[1259]For a convenient method of doing this that results in high yields, see Schlosser, M.; Schaub, B. *Chimia* ***1982***, *36*, 396.

[1260]Simoni, D.; Rossi, M.; Rondanin, R.; Mazzali, A.; Baruchello, R.; Malagutti, C.; Roberti, M.; Invidiata, F.P. *Org. Lett.* ***2000***, *2*, 3765.

[1261]Kobayashi, T.; Eda, T.; Tamura, O.; Ishibashi, H. *J. Org. Chem.* ***2002***, *67*, 3156.

[1262]Ramirez, F.; Pilot, J.F.; Desai, N.B.; Smith, C.P.; Hansen, B.; McKelvie, N. *J. Am. Chem. Soc.* ***1967***, *89*, 6273.

[1263]Bestmann, H.J. *Angew. Chem. Int. Ed.* ***1965***, *4*, 586.

[1264]Schiemenz, G.P.; Thobe, J. *Chem. Ber.* ***1966***, *99*, 2663.

[1265]For example, see Johnson, A.W.; LaCount, R.B. *Tetrahedron* ***1960***, *9*, 130; Bestmann, H.J.; Kratzer, O. *Chem. Ber.* ***1962***, *95*, 1894.

[1266]An arsenic ylid has been used in a catalytic version of the Wittig reaction; that is, the R_3AsO product is constantly regenerated to produce more arsenic ylid: Shi, L.; Wang, W.; Wang, Y.; Huang, Y. *J. Org. Chem.* ***1989***, *54*, 2027; Huang, Z.-Z.; Huang, X.; Huang, Y.-Z. *Tetrahedron Lett.* ***1995***, *36*, 425.

[1267]Huang, Z.-Z.; Tang, Y. *J. Org. Chem.* ***2002***, *67*, 5320.

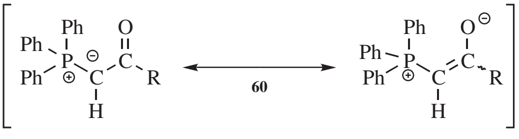
[1268]Betancort, J.M.; Barbas III, C.F. *Org. Lett.* ***2001***, *3*, 3737.

[1269]Bernard, M.; Ford, W.T.; Nelson, E.C. *J. Org. Chem.* ***1983***, *48*, 3164.

[1270]Patil, V.J.; Mävers, U. *Tetrahedron Lett.* ***1996***, *37*, 1281.

The reaction is very general.[1271] The aldehyde or ketone may be aliphatic, alicyclic, or aromatic (including diaryl ketones). Wittig reactions in which the ylid and/or the carbonyl substrate contain double or triple bonds; it may contain various functional groups, such as OH, OR, NR_2, aromatic nitro or halo, acetal, amide,[1272] or even ester groups.[1273] Note, however, that a Wittig reaction has been reported in which the carbonyl group of an ester was converted to a vinyl ether.[1274] An important advantage of the Wittig reaction is that the *position* of the new double bond is always certain, in contrast to the result in most of the base-catalyzed condensations (**16-34–16-43**). Ylids have been shown to react with lactones, however, to form ω-alkenyl alcohols.[1275] β-Lactams have also been converted to alkenyl-azetidine derivatives using phosphorus ylids.[1276] Double or triple bonds *conjugated* with the carbonyl also do not interfere, the attack being at the C=O carbon. The carbonyl partner can be generated *in situ*, in the presence of an ylid; the reaction of an alcohol with a mixture of an oxidizing agent and an ylid generates an alkene. Oxidizing agents used in this manner include $BaMnO_4$,[1277] MnO_2,[1278] and $PhI(OAc)_2$.[1279] Polyhalomethanes, such as CBr_3F, react with triphenylphosphine in the presence of diethylzinc and an aldehyde or ketone to give the *gem*-dihaloalkene, RCH(R′)=CF(Br).[1280]

The phosphorus ylid may also contain double or triple bonds and certain functional groups. Simple ylids (R, R′ = hydrogen or alkyl) are highly reactive, reacting with oxygen, water, hydrohalic acids, and alcohols, as well as carbonyl compounds and carboxylic esters, so the reaction must be run under conditions where these materials are absent. When an electron-withdrawing group, for example, COR, CN, COOR, CHO, is present in the α position, the ylids are much more stable, because the charge on the carbon is delocalized by resonance as in **60**.



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[1271]For a discussion of a cooperative ortho effect, see Dunne, E.C.; Coyne, É.J.; Crowley, P.B.; Gilheany, D.G. *Tetrahedron Lett.* ***2002***, *43*, 2449.

[1272]Smith, M.B.; Kwon, T.W. *Synth. Commun.* ***1992***, *22*, 2865. For the reaction of an acyl imidazole ylid, see Matsunaga, S.; Kinoshita, T.; Okada, S.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* ***2004***, *126*, 7559.

[1273]For an example, see Harcken, C.; Martin, S.F. *Org. Lett.* ***2001***, *3*, 3591; Yu, X.; Huang, X. *Synlett* ***2002***, 1895. Although phosphorus ylids also react with esters, that reaction is too slow to interfere: Greenwald, R.; Chaykovsky, M.; Corey, E.J. *J. Org. Chem.* ***1963***, *28*, 1128.

[1274]Tsunoda, T.; Takagi, H.; Takaba, D.; Kaku, H.; Itô, S. *Tetrahedron Lett.* ***2000***, *41*, 235.

[1275]Brunel, Y.; Rousseau, G. *Tetrahedron Lett.* ***1996***, *37*, 3853.

[1276]Baldwin, J.E.; Edwards, A.J.; Farthing, C.N.; Russell, A.T. *Synlett* ***1993***, 49.

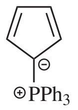
[1277]Shuto, S.; Niizuma, S.; Matsuda, A. *J. Org. Chem.* ***1998***, *63*, 4489.

[1278]Reid, M.; Rowe, D.J.; Taylor, R.J.K. *Chem. Commun.* ***2003***, 2284; Blackburn, L.; Pei, C.; Taylor, R.J.K. *Synlett* ***2002***, 215; Raw, S.A.; Reid, M.; Roman, E.; Taylor, R.J.K. *Synlett* ***2004***, 819.

[1279]Zhang, P.-F.; Chen, Z.-C. *Synth. Commun.* ***2001***, *31*, 1619.

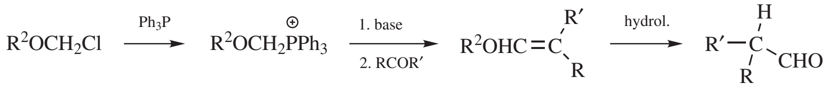
[1280]Lei, X.; Dutheuil, G.; Pannecoucke, X.; Quirion, J.-C. *Org. Lett.* ***2004***, *6*, 2101.

Such ylids react readily with aldehydes, but slowly or not at all with ketones.[1281] In extreme cases (e.g., **61**), the



61

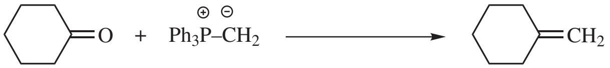
ylid does not react with ketones *or* aldehydes. Besides these groups, the ylid may contain one or two α halogens[1282] or an α OR or OAr group. In the latter case, the product is an enol ether, which can be hydrolyzed



(**10-6**) to an aldehyde,[1283] so that this reaction is a means of achieving the conversion RCOR′ → RR′CHCHO.[1284] However, the ylid may not contain an α nitro group. If the phosphonium salt contains a potential leaving group, such as Br or OMe, in the β position, treatment with a base gives elimination, instead of the ylid:

$$Ph_3\overset{\oplus}{P}CH_2CH_2Br \xrightarrow{\text{base}} Ph_3\overset{\oplus}{P}CH{=}CH_2$$

However, a β COO^- group may be present, and the product is a β,γ-unsaturated acid:[1285] This is the only convenient way to make these compounds, since elimination by any other route gives the thermodynamically more stable α,β-unsaturated isomers. This is an illustration of the utility of the Wittig method for the specific location of a double bond. Another illustration is the conversion of cyclohexanones to alkenes containing exocyclic double bonds, for example,[1286]



[1281]For successful reactions of stabilized ylids with ketones, under high pressure, see Isaacs, N.S.; El-Din, G.N. *Tetrahedron Lett.* ***1987***, *28*, 2191. See also, Dauben, W.G.; Takasugi, J.J. *Tetrahedron Lett.* ***1987***, *28*, 4377.

[1282]Seyferth, D.; Heeren, J.K.; Singh, G.; Grim, S.O.; Hughes, W.B. *J. Organomet. Chem.* ***1966***, *5*, 267; Schlosser, M.; Zimmermann, M. *Synthesis* ***1969***, 75; Burton, D.J.; Greenlimb, P.E. *J. Fluorine Chem.* ***1974***, *3*, 447; Smithers, R.H. *J. Org. Chem.* ***1978***, *43*, 2833; Miyano, S.; Izumi, Y.; Fujii, K.; Ohno, Y.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* ***1979***, *52*, 1197; Stork, G.; Zhao, K. *Tetrahedron Lett.* ***1989***, *30*, 2173.

[1283]For references to the use of the Wittig reaction to give enol ethers or enol thioethers, which are then hydrolyzed, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1441–1444, 1457–1458.

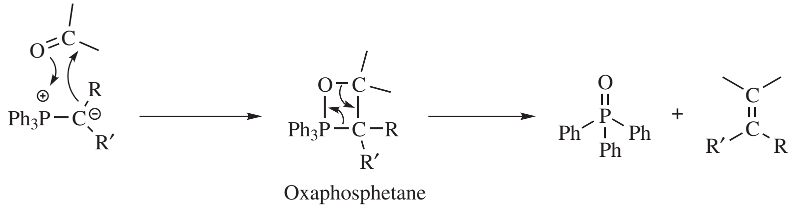
[1284]For other methods of achieving this conversion via Wittig-type reactions, see Ceruti, M.; Degani, I.; Fochi, R. *Synthesis* ***1987***, 79; Moskal, J.; van Leusen, A.M. *Recl. Trav. Chim. Pays-Bas* ***1987***, *106*, 137; Doad, G.J.S. *J. Chem. Res. (S)* ***1987***, 370.

[1285]Corey, E.J.; McCormick, J.R.D.; Swensen, W.E. *J. Am. Chem. Soc.* ***1964***, *86*, 1884.

[1286]Wittig, G.; Schöllkopf, U. *Chem. Ber.* ***1954***, *87*, 1318.

Still another example is the easy formation of anti-Bredt bicycloalkenones[1287] (see p. 229). As indicated above, α,α′-dihalophosphoranes can be used to prepare 1,1-dihaloalkenes. Another way to prepare such compounds[1288] is to treat the carbonyl compound with a mixture of CX_4 (X = Cl, Br, or I) and triphenylphosphine, either with or without the addition of zinc dust (which allows less Ph_3P to be used).[1289] Aryl aldehydes react with these dihalophosphoranes to give aryl alkynes after treatment of the initially formed vinyl halide with potassium *tert*-butoxide.[1290] Formamides have been converted to ynamines by reaction with a mixture of PPh_3/CCl_4 followed by *n*-butyllithium.[1291] The carbonyl compound can be generated *in situ*, in the presence of the phosphorane. A cyclopropylcarbonyl alcohol was converted to a β-cyclopropyl-α,β-unsaturated ester by reaction with MnO_2 in the presence of $Ph_3P{=}CHCO_2Me$.[1292]

The mechanism[1293] of the key step of the Wittig reaction is as follows:[1294]



The energetics of ylid formation and their reaction is solution has been studied.[1295] For many years it was assumed that a diionic compound, called a *betaine*, is an intermediate on the pathway from the starting compounds

[1287]Bestmann, H.J.; Schade, G. *Tetrahedron Lett.* ***1982***, *23*, 3543.

[1288]For a list of references to the preparation of haloalkenes by Wittig reactions, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 725–727.

[1289]See, for example, Rabinowitz, R.; Marcus, R. *J. Am. Chem. Soc.* ***1962***, *84*, 1312; Ramirez, F.; Desai, N.B.; McKelvie, N. *J. Am. Chem. Soc.* ***1962***, *84*, 1745; Corey, E.J.; Fuchs, P.L. *Tetrahedron Lett.* ***1972***, 3769; Posner, G.H.; Loomis, G.L.; Sawaya, H.S. *Tetrahedron Lett.* ***1975***, 1373; Suda, M.; Fukushima, A. *Tetrahedron Lett.* ***1981***, *22*, 759; Gaviña, F.; Luis, S.V.; Ferrer, P.; Costero, A.M.; Marco, J.A. *J. Chem. Soc., Chem. Commun.* ***1985***, 296; Li, P.; Alper, H. *J. Org. Chem.* ***1986***, *51*, 4354.

[1290]Michel, P.; Gennet, D.; Rassat, A. *Tetrahedron Lett.* ***1999***, *40*, 8575. See Michael, P.; Rassat, A. *Tetrahedron Lett.* ***1999***, *40*, 8579.

[1291]Brückner, D. *Synlett* ***2000***, 1402.

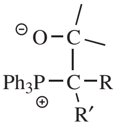
[1292]Blackburn, L.; Wei, X.; Taylor, R.J.K. *Chem. Commun.* ***1999***, 1337.

[1293]For a review of the mechanism, see Cockerill, A.F.; Harrison, R.G., in Patai, S. *The Chemistry of Functional Groups: Supplement A*, pt. 1, Wiley, NY, ***1977***, pp. 232–240. For a thorough discussion, see Vedejs, E.; Marth, C.F. *J. Am. Chem. Soc.* ***1988***, *110*, 3948.

[1294]It has been contended that another mechanism, involving single electron transfer, may be taking place in some cases: Olah, G.A.; Krishnamurthy, V.V. *J. Am. Chem. Soc.* ***1982***, *104*, 3987; Yamataka, H.; Nagareda, K.; Hanafusa, T.; Nagase, S. *Tetrahedron Lett.* ***1989***, *30*, 7187. A diradical mechanism has also been proposed for certain cases: Ward, Jr., W.J.; McEwen, W.E. *J. Org. Chem.* ***1990***, *55*, 493.

[1295]Arnett, E.M.; Wernett, P.C. *J. Org. Chem.* ***1993***, *58*, 301.

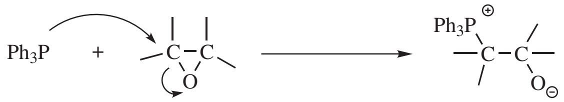
to the oxaphosphetane, and in fact it may be so, but there is little evidence for it.[1296]



Betaine

"Betaine" precipitates have been isolated in certain Wittig reactions,[1297] but these are betaine–lithium halide adducts, and might just as well have been formed from the oxaphosphetane as from a true betaine.[1298] However, there is one report of an observed betaine lithium salt during the course of a Wittig reaction.[1299] An X-ray structure was determined for a gauche betaine from a thio-Wittig reaction.[1300] In contrast, there is much evidence for the presence of the oxaphosphetane intermediates, at least with unstable ylids. For example, ^{31}P NMR spectra taken of the reaction mixtures at low temperatures[1301] are compatible with an oxaphosphetane structure that persists for some time but not with a tetra-coordinated phosphorus species. Since a betaine, an ylid, and a phosphine oxide all have tetracoordinated phosphorus, these species could not be causing the spectra, leading to the conclusion that an oxaphosphetane intermediate is present in the solution. In certain cases oxaphosphetanes have been isolated.[1302] It has even been possible to detect cis and trans isomers of the intermediate oxaphosphetanes by NMR spectroscopy.[1303] According to this mechanism, an optically active phosphonium salt $RR'R^2P^+CHR^2$ should retain its configuration all the way through the reaction, and it should be preserved in the phosphine oxide $RR'R^2PO$. This has been shown to be the case.[1304]

The proposed betaine intermediates can be formed, in a completely different manner, by nucleophilic substitution by a phosphine on an epoxide (**10-35**):



[1296]See Vedejs, E.; Marth, C.F. *J. Am. Chem. Soc.* ***1990***, *112*, 3905.

[1297]Wittig, G.; Weigmann, H.; Schlosser, M. *Chem. Ber.* ***1961***, *94*, 676; Schlosser, M.; Christmann, K.F. *Liebigs Ann. Chem.* ***1967***, *708*, 1.

[1298]Maryanoff, B.E.; Reitz, A.B. *Chem. Rev.* ***1989***, *89*, 863, see p. 865.

[1299]Neumann, R.A.; Berger, S. *Eur. J. Org. Chem.* ***1998***, 1085.

[1300]Puke, C.; Erker, G.; Wibbeling, B.; Fröhlich, R. *Eur. J. Org. Chem.* ***1999***, 1831.

[1301]Vedejs, E.; Meier, G.P.; Snoble, K.A.J. *J. Am. Chem. Soc.* ***1981***, *103*, 2823. See also, Nesmayanov, N.A.; Binshtok, E.V.; Reutov, O.A. *Doklad. Chem.* ***1973***, *210*, 499.

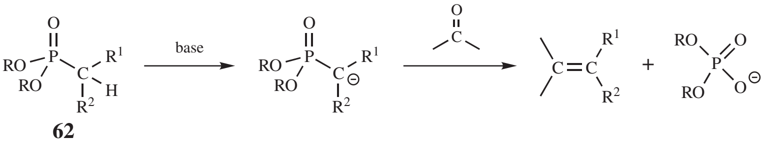
[1302]Birum, G.H.; Matthews, C.N. *Chem. Commun.* ***1967***, 137; Mazhar-Ul-Haque; Caughlan, C.N.; Ramirez, F.; Pilot, J.F.; Smith, C.P. *J. Am. Chem. Soc.* ***1971***, *93*, 5229.

[1303]Maryanoff, B.E.; Reitz, A.B.; Mutter, M.S.; Inners, R.R.; Almond Jr., H.R.; Whittle, R.R.; Olofson, R.A. *J. Am. Chem. Soc.* ***1986***, *108*, 7664. See also, Pískala, A.; Rehan, A.H.; Schlosser, M. *Coll. Czech. Chem. Commun.* ***1983***, *48*, 3539.

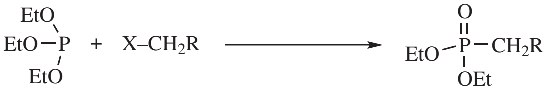
[1304]McEwen, W.E.; Kumli, K.F.; Bladé-Font, A.; Zanger, M.; VanderWerf, C.A. *J. Am. Chem. Soc.* ***1964***, *86*, 2378.

Betaines formed in this way can then be converted to the alkene, and this is one reason why betaine intermediates were long accepted in the Wittig reaction.

The Wittig reaction has also been carried out with phosphorus ylids other than phosphoranes, the most important being prepared from phosphonates, such as **62**.[1305]



This method, sometimes called the *Horner–Emmons*, *Wadsworth–Emmons*, or *Wittig–Horner reaction*,[1306] has several advantages over the use of phosphoranes, including selectivity.[1307] These ylids are more reactive than the corresponding phosphoranes, and when R^1 or R^2 is an electron-withdrawing group, these compounds often react with ketones that are inert to phosphoranes. High pressure has been used to facilitate this reaction.[1308] In addition, the phosphorus product is a phosphate ester and hence soluble in water, unlike Ph_3PO, which makes it easy to separate it from the alkene product. Phosphonates are also cheaper than phosphonium salts and can easily be prepared by the *Arbuzov reaction*:[1309]



Phosphonates have also been prepared from alcohols and $(ArO)_2P(=O)Cl$, NEt_3 and a $TiCl_4$ catalyst.[1310] The reaction of $(RO)_2P(=O)H$ and aryl iodides with a CuI catalyst leads to aryl phosphonates.[1311] Polymer-bound phosphonate esters have been used for olefination.[1312] Dienes are produced when allylic phosphonate esters react with aldehydes.[1313]

[1305]Horner, L.; Hoffmann, H.; Wippel, H.G.; Klahre, G. *Chem. Ber.* ***1959***, *92*, 2499; Wadsworth, Jr., W.S.; Emmons, W.D. *J. Am. Chem. Soc.* ***1961***, *83*, 1733.

[1306]For reviews, see Wadsworth, Jr., W.S. *Org. React.* ***1977***, *25*, 73; Stec, W.J. *Acc. Chem. Res.* ***1983***, *16*, 411; Walker, B.J., in Cadogan, J.I.G. *Organophosphorous Reagents in Organic Synthesis*, Academic Press, NY, ***1979***, pp. 156–205; Dombrovskii, A.V.; Dombrovskii, V.A. *Russ. Chem. Rev.* ***1966***, *35*, 733; Boutagy, J.; Thomas, R. *Chem. Rev.* ***1974***, *74*, 87. For a convenient method of carrying out this reaction, see Seguineau, P.; Villieras, J. *Tetrahedron Lett.* ***1988***, *29*, 477, and other papers in this series.

[1307]Motoyoshiya, J.; Kasaura, T.; Kokin, K.; Yokoya, S.-i.; Takaguchi, Y.; Narita, S.; Aoyama, H. *Tetrahedron* ***2001***, *57*, 1715.

[1308]Has-Becker, S.; Bodmann, K.; Kreuder, R.; Santoni, G.; Rein, T.; Reiser, O. *Synlett* ***2001***, 1395.

[1309]Also known as the *Michaelis-Arbuzov rearrangement*. For reviews, see Petrov, A.A.; Dogadina, A.V.; Ionin, B.I.; Garibina, V.A.; Leonov, A.A. *Russ. Chem. Rev.* ***1983***, *52*, 1030; Bhattacharya, A.K.; Thyagarajan, G. *Chem. Rev.* ***1981***, *81*, 415. For related reviews, see Shokol, V.A.; Kozhushko, B.N. *Russ. Chem. Rev.* ***1985***, *53*, 98; Brill, T.B.; Landon, S.J. *Chem. Rev.* ***1984***, *84*, 577. See also, Kaboudin, B.; Balakrishna, M.S. *Synth. Commun.* ***2001***, *31*, 2773.

[1310]Jones, S.; Selitsianos, D. *Org. Lett.* ***2002***, *4*, 3671.

[1311]Gelman, D.; Jiang, L.; Buchwald, S.L. *Org. Lett.* ***2003***, *5*, 2315.

[1312]Barrett, A.G.M.; Cramp, S.M.; Roberts, R.S.; Zecri, F.J. *Org. Lett.* ***1999***, *1*, 579.

[1313]Wang, Y.; West, F.G. *Synthesis* ***2002***, 99.

Stereoselective alkenylation reactions have been achieved using chiral additives[1314] or auxiliaries.[1315] Ylids formed from phosphine oxides,

$$\underset{\displaystyle \overset{\|}{O}}{Ar_2P}-CHRR'$$

phosphonic acid bisamides, $(R^2_2N)_2POCHRR'$,[1316] and alkyl phosphonothionates, $(MeO)_2PSCHRR'$,[1317] share some of these advantages. Reagents, such as $Ph_2POCH_2NR'_2$, react with aldehydes or ketones (R_2COR^3) to give good yields of enamines ($R^2R^3C{=}CHNR$).[1318] (*Z*)-Selective reagents are also known,[1319] including the use of a di(2,2,2-trifluoroethoxy)phosphonate with KHMDS and 18-crown-6.[1320] An interesting intramolecular version of the Horner–Emmons reaction leads to alkynes.[1321] The reaction of a functionalized aldehyde (R—CHO) with $(MeO)_2POCHN_2$, leads to the alkyne ($R{-}C{\equiv}CH$).[1322]

Some Wittig reactions give the (*Z*)-alkene; some the (*E*), and others give mixtures, and the question of which factors determine the stereoselectivity has been much studied.[1323] It is generally found that ylids containing stabilizing groups or formed from trialkylphosphines give (*E*)-alkenes. However, ylids formed from triarylphosphines and not containing stabilizing groups often give (*Z*) or a mixture of (*Z*) and (*E*)-alkenes.[1324] One explanation for this[1193] is that the reaction of the ylid with the carbonyl compound is a [2 + 2]-cycloaddition, which in order to be concerted must adopt the $[_{\pi}2_s + _{\pi}2_a]$ pathway. As we have seen earlier (p. 1225), this pathway leads to the formation of the more sterically crowded product, in this case the *Z* alkene. If this explanation is correct, it is not easy to explain the predominant formation of (*E*)

[1314]Mizuno, M.; Fujii, K.; Tomioka, K. *Angew. Chem. Int. Ed.* ***1998***, *37*, 515. Also see, Arai, S.; Hamaguchi, S.; Shioiri, T. *Tetrahedron Lett.* ***1998***, *39*, 2997. For a review of asymmetric Wittig-type reactions see Rein, T.; Pedersen, T.M. *Synthesis* ***2002***, 579.

[1315]Abiko, A.; Masamune, S. *Tetrahedron Lett.* ***1996***, *37*, 1077.

[1316]Corey, E.J.; Kwiatkowski, G.T. *J. Am. Chem. Soc.* ***1968***, *90*, 6816; Corey, E.J.; Cane, D.E. *J. Org. Chem.* ***1969***, *34*, 3053. For a chiral derivative, see Hanessian, S.; Beaudoin, S. *Tetrahedron Lett.* ***1992***, *33*, 7655, 7659.

[1317]Corey, E.J.; Kwiatkowski, G.T. *J. Am. Chem. Soc.* ***1966***, *88*, 5654.

[1318]Broekhof, N.L.J.M.; van der Gen, A. *Recl. Trav. Chim. Pays-Bas* ***1984***, *103*, 305; Broekhof, N.L.J.M.; van Elburg, P.; Hoff, D.J.; van der Gen, A. *Recl. Trav. Chim. Pays-Bas* ***1984***, *103*, 317.

[1319]Ando, K. *Tetrahedron Lett.* ***1995***, *36*, 4105.

[1320]Yu, W.; Su, M.; Jin, Z. *Tetrahedron Lett.* ***1999***, *40*, 6725.

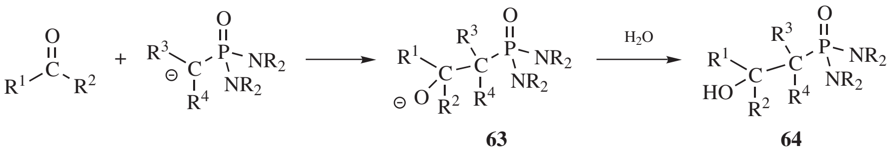
[1321]Nangia, A.; Prasuna, G.; Rao, P.B. *Tetrahedron Lett.* ***1994***, *35*, 3755; Couture, A.; Deniau, E.; Gimbert, Y.; Grandclaudon, P. *J. Chem. Soc. Perkin Trans. 1* ***1993***, 2463.

[1322]Hauske, J.R.; Dorff, P.; Julin, S.; Martinelli, G.; Bussolari, J. *Tetrahedron Lett.* ***1992***, *33*, 3715.

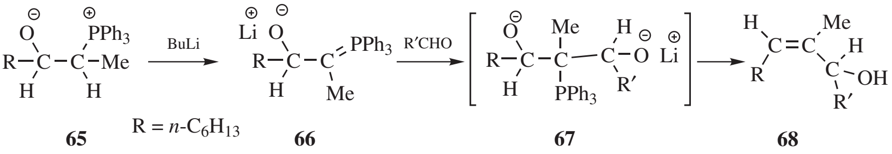
[1323]For reviews of the stereochemistry of the Wittig reactions, see Maryanoff, B.E.; Reitz, A.B. Chem. Rev. ***1989***, *89*, 863; Gosney, I.; Rowley, A.G., in Cadogan, J.I.G. *Organophosphorous Reagents in Organic Synthesis*, Academic Press, NY, ***1979***, pp. 17–153; Reucroft, J.; Sammes, P.G. *Q. Rev. Chem. Soc.* ***1971***, *25*, 135, see pp. 137–148, 169; Schlosser, M. *Top. Stereochem.* ***1970***, *5*, 1. Also see Takeuchi, K.; Paschal, J.W.; Loncharich, R.J. *J. Org. Chem.* ***1995***, *60*, 156.

[1324]For cases where such an ylid gave (*E*)-alkenes, see Maryanoff, B.E.; Reitz, A.B.; Duhl-Emswiler, B.A. *J. Am. Chem. Soc.* ***1985***, *107*, 217; Le Bigot, Y.; El Gharbi, R.; Delmas, M.; Gaset, A. *Tetrahedron* ***1986***, *42*, 3813. For guidance in how to obtain the maximum yields of the *Z* product, see Schlosser, M.; Schaub, B.; de Oliveira-Neto, J.; Jeganathan, S. *Chimia* ***1986***, *40*, 244.

products from stable ylids, but (*E*) compounds are of course generally thermodynamically more stable than the (*Z*) isomers, and the stereochemistry seems to depend on many factors.



The (*E/Z*) ratio of the product can often be changed by a change in solvent or by the addition of salts.[1325] Another way of controlling the stereochemistry of the product is by use of the aforementioned phosphonic acid bisamides. In this case, the betaine (**63**) does form and when treated with water gives the β-hydroxyphosphonic acid bisamides **64**, which can be crystallized and then cleaved to $R^1R^2C{=}CR^3R^4$ by refluxing in benzene or toluene in the presence of silica gel.[1316] **64** are generally formed as mixtures of diastereomers, and these mixtures can be separated by recrystallization. Cleavage of the two diastereomers gives the two isomeric alkenes. Optically active phosphonic acid bisamides have been used to give optically active alkenes.[1326] Another method of controlling the stereochemistry of the alkene [to obtain either the (*Z*) or (*E*) isomer] starting with a phosphine oxide (Ph_2POCH_2R), has been reported.[1327]



In reactions where the betaine–lithium halide intermediate is present, it is possible to extend the chain further if a hydrogen is present α to the phosphorus. For example, reaction of ethylidnetriphenylphosphorane with heptanal at −78°C gave **65**, which with butyllithium gave the ylid **66**. Treatment of this with an aldehyde R′CHO gave the intermediate **67**, which after workup gave **68**.[1328] This reaction gives the unsaturated alcohols **68** stereoselectively. **66** also reacts with other electrophiles. For example, treatment of **66** with *n*-chlorosuccinimide or $PhICl_2$ gives the vinylic chloride RCH=CMeCl stereoselectively: NCS giving the cis and $PhICl_2$

[1325]See, for example, Reitz, A.B.; Nortey, S.O.; Jordan, Jr., A.D.; Mutter, M.S.; Maryanoff, B.E. *J. Org. Chem.* ***1986***, *51*, 3302.

[1326]Hanessian, S.; Delorme, D.; Beaudoin, S.; Leblanc, Y. *J. Am. Chem. Soc.* ***1984***, *106*, 5754; Rein, T.; Reiser, O. *Acta Chem. Scand. B*, ***1996***, *50*, 369. For a review of asymmetric ylid reactions, see Li, A.-H.; Dai, L.-X.; Aggarwal, V.K. *Chem. Rev.* ***1997***, *97*, 2341.

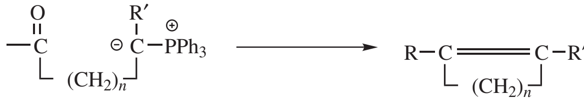
[1327]Ayrey, P.M.; Warren, S. *Tetrahedron Lett.* ***1989***, *30*, 4581.

[1328]Corey, E.J.; Yamamoto, H. *J. Am. Chem. Soc.* ***1970***, *92*, 226; Schlosser, M.; Coffinet, D. *Synthesis* ***1972***, 575; Corey, E.J.; Ulrich, P.; Venkateswarlu, A. *Tetrahedron Lett.* ***1977***, 3231; Schlosser, M.; Tuong, H.B.; Respondek, J.; Schaub, B. *Chimia* ***1983***, *37*, 10.

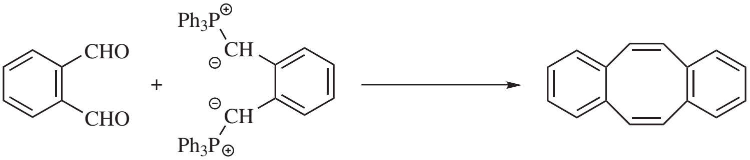
the trans isomer.[1329] The use of Br_2 and $FClO_3$ (see **12-4** for the explosive nature of this reagent) gives the corresponding bromides and fluorides, respectively.[1330] Reactions of **66** with electrophiles have been called *scoopy* reactions (α *s*ubstitution plus *c*arbonyl alkeneylation via β-*o*xido *p*hosphorus *ylid*s).[1331]

The reaction of a phosphonate ester, DBU, NaI, and HMPA with an aldehyde leads to a conjugated ester with excellent (*Z*)-selectivity.[1332] A (*Z*)-selective reaction was reported using a trifluoroethyl phosphonate in a reaction with an aldehyde and potassium *tert*-butoxide.[1333]

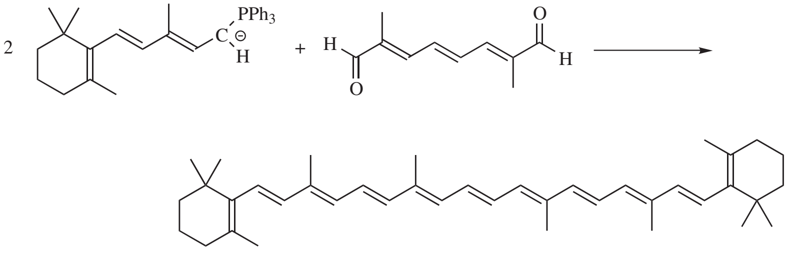
The Wittig reaction has been carried out intramolecularly, to prepare rings containing from 5 to 16 carbons,[1334] both by single ring closure



and double ring closure.[1335]



The Wittig reaction has proved very useful in the synthesis of natural products, some of which are quite difficult to prepare in other ways.[1336] One example out of many is the synthesis of β-carotene:[1337]



β-Carotene

[1329]Schlosser, M.; Christmann, K. *Synthesis* ***1969***, 38; Corey, E.J.; Shulman, J.I.; Yamamoto, H. *Tetrahedron Lett.* ***1970***, 447.

[1330]Schlosser, M.; Christmann, K.-F. *Synthesis* ***1969***, 38.

[1331]Schlosser, M. *Top. Stereochem.* ***1970***, *5*, 1, p. 22.

[1332]Ando, K.; Oishi, T.; Hirama, M.; Ohno, H.; Ibuka, T. *J. Org. Chem.* ***2000***, *65*, 4745.

[1333]Touchard, F.P. *Tetrahedron Lett.* ***2004***, *45*, 5519.

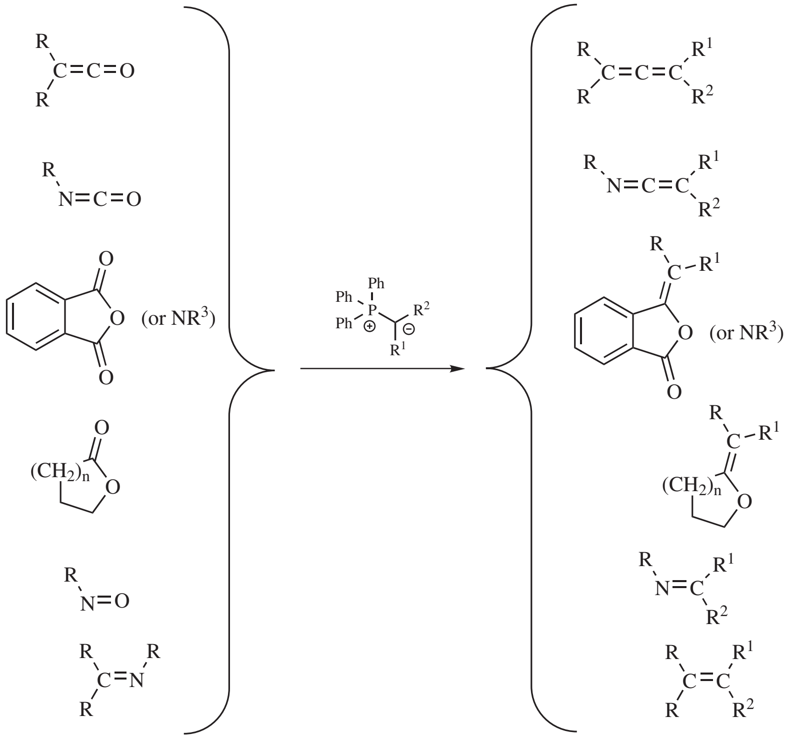
[1334]For a review, see Becker, K.B. *Tetrahedron* ***1980***, *36*, 1717.

[1335]For a review of these double-ring closures, see Vollhardt, K.P.C. *Synthesis* ***1975***, 765.

[1336]For a review of applications of the Wittig reaction to the synthesis of natural products, see Bestmann, H.J.; Vostrowsky, O. *Top. Curr. Chem.* ***1983***, *109*, 85.

[1337]Wittig, G.; Pommer, H. German patent ***1956***, 954,247, [*Chem. Abstr.* ***1959***, *53*, 2279].

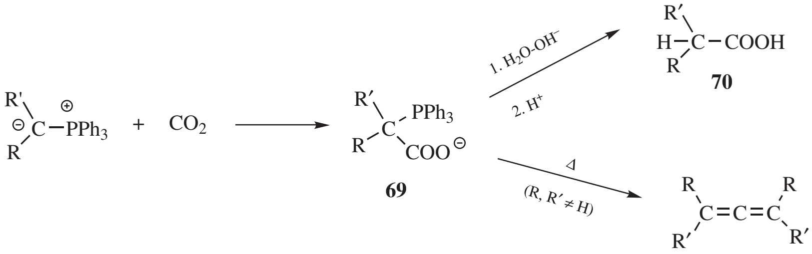
Phosphorus ylids also react in a similar manner with the C=O bonds of ketenes,[1338] isocyanates,[1339] certain anhydrides[1340] lactones,[1341] and imides,[1342] the N=O of nitroso groups, and the C=N of imines,[1343] for example,



Phosphorus ylids react with carbon dioxide to give the isolable salts **69**,[1344] which can be hydrolyzed to the carboxylic acids **70** (thus achieving the conversion

[1338]For example, see Aksnes, G.; Frøyen, P. *Acta Chem. Scand.* ***1968***, *22*, 2347.
[1339]For example, see Frøyen, P. *Acta Chem. Scand. Ser. B* ***1974***, *28*, 586.
[1340]See, for example, Abell, A.D.; Massy-Westropp, R.A. *Aust. J. Chem.* ***1982***, *35*, 2077; Kayser, M.M.; Breau, L. *Can. J. Chem.* ***1989***, *67*, 1401. For a study of the mechanism, see Abell, A.D.; Clark, B.M.; Robinson, W.T. *Aust. J. Chem.* ***1988***, *41*, 1243.
[1341]With microwave irradiation, see Sabitha, G.; Reddy, M.M.; Srinivas, D.; Yadov, J.S. *Tetrahedron Lett.* ***1999***, *40*, 165.
[1342]For a review of the reactions with anhydrides and imides (and carboxylic esters, thiol esters, and amides), see Murphy, P.J.; Brennan, J. *Chem. Soc. Rev.* ***1988***, *17*, 1. For a review with respect to imides, see Flitsch, W.; Schindler, S.R. *Synthesis* ***1975***, 685.
[1343]Bestmann, H.J.; Seng, F. *Tetrahedron* ***1965***, *21*, 1373.
[1344]Bestmann, H.J.; Denzel, T.; Salbaum, H. *Tetrahedron Lett.* ***1974***, 1275.

RR′CHX → RR′CHCOOH) or (if neither R nor R′ is hydrogen) dimerized to allenes.

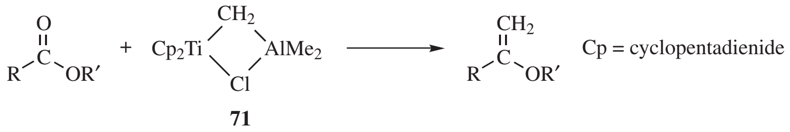


Although phosphorus ylids are most commonly used to alkenylation reactions, nitrogen ylids can occasionally be used. As an example, the reaction of *N*-benzyl-*N*-phenylpiperidinium bromide with base generated a N-ylid, which reacted with benzaldehyde to form styrene.[1345] The structure has been determined for an intermediate in an aza-Wittig reaction.[1346]

OS **V**, 361, 390, 499, 509, 547, 751, 949, 985; **VI**, 358; **VII**, 164, 232; **VIII**, 265, 451; **75**, 139, **OS IX**, 39, 230.

16-45 Tebbe, Petasis and Alternative Alkenylations

Methylene-de-oxo-bisubstitution



A useful alternative to phosphorus ylids are the titanium reagents, such as, **71**, prepared from dicyclopentadienyltitanium dichloride and trimethylaluminum.[1347] Treatment of a carbonyl compound with the titanium cyclopentadienide complex **71** (*Tebbe's reagent*) in toluene–THF containing a small amount of pyridine[1348] leads to the alkene. Dimethyltitanocene (Me_2TiCp_2), called the *Petasis reagent*, is a convenient and highly useful alternative to **71**.[1349] The mechanism of Petasis olefination has been examined.[1350] Tebbe's reagent and the Petasis reagent give good results with ketones.[1351] An important feature of these new reagents is that

[1345]Lawrence, N.J.; Beynek, H. *Synlett* ***1998***, 497.

[1346]Kano, N.; Hua, X.J.; Kawa, S.; Kawashima, T. *Tetrahedron Lett.* ***2000***, *41*, 5237.

[1347]For a method of generating this reagent *in situ*, see Cannizzo, L.F.; Grubbs, R.H. *J. Org. Chem.* ***1985***, *50*, 2386.

[1348]Tebbe, F.N.; Parshall, G.W.; Reddy, G.S. *J. Am. Chem. Soc.* ***1978***, *100*, 3611; Pine, S.H.; Pettit, R.J.; Geib, G.D.; Cruz, S.G.; Gallego, C.H.; Tijerina, T.; Pine, R.D. *J. Org. Chem.* ***1985***, *50*, 1212. See also, Clawson, L.; Buchwald, S.L.; Grubbs, R.H. *Tetrahedron Lett.* ***1984***, *25*, 5733; Clift, S.M.; Schwartz, J. *J. Am. Chem. Soc.* ***1984***, *106*, 8300.

[1349]Petasis N.A.; Bzowej, E.I. *J. Am. Chem. Soc.* ***1990***, *112*, 6392.

[1350]Meurer, E.C.; Santos, L.S.; Pilli, R.A.; Eberlin, M.N. *Org. Lett.* ***2003***, *5*, 1391.

[1351]Pine, S.H.; Shen, G.S.; Hoang, H. *Synthesis* ***1991***, 165.

carboxylic esters and lactones[1352] can be converted in good yields to the corresponding enol ethers. The enol ether can be hydrolyzed to a ketone (**10-6**), so this is also an indirect method for making the conversion RCOOR′ → $RCOCH_3$ (see also, **16-82**). Conjugated esters are converted to alkoxy-dienes with this reagent.[1353] Lactams, including β-lactams, are converted with alkylidene cycloamines (alkylidene azetidines from β-lactams, which are easily hydrolyzed to β-amino ketones).[1354]

Besides stability and ease of preparation, another advantage of the Petasis reagent is that structural analogs can be prepared, including $Cp_2Ti(C_3H_5)_2$[1355] (C_3H_5 = cyclopropyl), $CpTi(CH_2SiMe_3)_3$,[1356] and $Cp_2TiMe(CH{=}CH_2)$.[1357] In another variation, 2 equivalents of $Cp_2Ti[P(OEt)_3]_2$ reacted with a ketone in the presence of 1,1-diphenylthiocyclobutane to give the alkenylcyclobutane derivative.[1358] An alternative titanium reagent was prepared using $TiCl_4$, magnesium metal and dichloromethane, reacting with both ketones[1359] and esters[1360] to give alkenes or vinyl ethers, respectively. Alkenes are generated form ketones and alkyl iodides in the presence of a catalytic amount of $Cp_2Ti[POEt)_3]_2$.[1361]

α,α-Dibromosulfones ($ArSO_2SHBr_2$) react with ketones in the presence of Sm/SmI_2 and a $CrCl_3$ catalyst gives to corresponding vinyl sulfone.[1362] Imides are converted to alkylidene lactams when treated with an alkyl halide, 2.5 equivalents of SmI_2 and a NiI_2 catalyst.[1363]

Carboxylic esters undergo the conversion C=O → C=CHR (R = primary or secondary alkyl) when treated with $RCHBr_2$, Zn,[1364] and $TiCl_4$ in the presence of *N,N,N′,N′*-tetramethylethylenediamine.[1365] Metal carbene complexes[1366] $R_2C = ML_n$ (L = ligand), where M is a transition metal, such as Zr, W, or Ta, have also been

[1352]See Martínez, I.; Andrews, A.E.; Emch, J.D.; Ndakala, A.J.; Wang, J.; Howell, A.R.; Rheingold, A.L.; Figuero, J.S. *Org. Lett.* ***2003***, *5*, 399; Dollinger, L.M.; Ndakala, A.J.; Hashemzadeh, M.; Wang, G.; Wang, Y.; Martínez, K.; Arcari, J.T.; Galluzzo, D.J.; Howell, A.R.; Rheingold, A.L. Figuero. J.S.; *J. Org. Chem.* ***1999***, *64*, 7074.

[1353]Petasis N.A.; Lu, S.-P. *Tetrahedron Lett.* ***1995***, *36*, 2393.

[1354]Tehrani, K.A.; De Kimpe, N. *Tetrahedron Lett.* ***2000***, *41*, 1975. See Martínez, I.; Howell, A.R. *Tetrahedron Lett.* ***2000***, *41*, 5607.

[1355]Petasis N.A.; Browej, E.I. *Tetrahedron Lett.* ***1993***, *34*, 943.

[1356]Petasis N.A.; Akritopoulou, I. *Synlett* ***1992***, 665.

[1357]Petasis N.A.; Hu, Y.-H. *J. Org. Chem.* ***1997***, *62*, 782. Also see, Petasis N.A.; Straszewski, J.P.; Fu, D.-K. *Tetrahedron Lett.* ***1995***, *36*, 3619; Rahim, Md.A.; Taguchi, H.; Watanabe, M.; Fujiwara, T.; Takeda, T. *Tetrahedron Lett.* ***1998***, *39*, 2153; Petasis N.A.; Browej, E.I. *J. Org. Chem.* ***1992***, *57*, 1327.

[1358]Fujiwara, T.; Iwasaki, N.; Takeda, T. *Chem. Lett.* ***1998***, 741. For an example using a *gem*-dichloride, see Takeda, T.; Sasaki, R.; Fujiwara, T. *J. Org. Chem.* ***1998***, *63*, 7286.

[1359]Yan, T.H.; Tsai, C.-C.; Chien, C.-T.; Cho, C.-C. Huang, P.-C. *Org. Lett.* ***2004***, *6*, 4961.

[1360]Yan, T.-H.; Chien, C.-T.; Tsai, C.-C.; Lin, K.-W.; Wu, Y.-H. *Org. Lett.* ***2004***, *6*, 4965.

[1361]Takeda, T.; Shimane, K.; Ito, K.; Saeki, N.; Tsubouchi, A. *Chem. Communn.* ***2002***, 1974.

[1362]Liu, Y.; Wu, H.; Zhang, Y. *Synth. Commun.* ***2001***, *31*, 47.

[1363]Farcas, S.; Namy, J.-L. *Tetrahedron Lett.* ***2001***, *42*, 879.

[1364]Ishino, Y.; Mihara, M.; Nishihama, S.; Nishiguchi, I. *Bull. Chem. Soc. Jpn.* ***1998***, *71*, 2669.

[1365]Okazoe, T.; Takai, K.; Oshima, K.; Utimoto, K. *J. Org. Chem.* ***1987***, *52*, 4410. For the reaction with $CH_2(ZnI)_2$ with $TiCl_2$, see Matsubra, S.; Ukai, K.; Mizuno, T.; Utimoto, K. *Chem. Lett.* ***1999***, 825. This procedure is also successful for silyl esters, to give silyl enol ethers: Takai, K.; Kataoka, Y.; Okazoe, T.; Utimoto, K. *Tetrahedron Lett.* ***1988***, *29*, 1065.

[1366]For a review of the synthesis of such complexes, see Aguero, A.; Osborn, J.A. *New J. Chem.* ***1988***, *12*, 111.

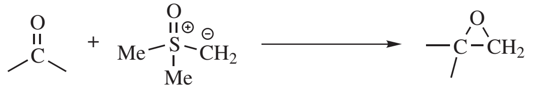
used to convert the C=O of carboxylic esters and lactones to CR_2.[1367] It is likely that the complex $Cp_2Ti=CH_2$ is an intermediate in the reaction with Tebbe's reagent.

There are a few other methods for converting ketones or aldehydes to alkenes. When a ketone is treated with $CH_3CHBr_2/Sm/SmI_2$, with a catalytic amount of $CrCl_3$, for example, the alkene is formed.[1368] α-Halo esters also react with $CrCl_2$ in the presence of a ketone to give vinyl halides.[1369] In another reaction, an aldehydes reacted with EtCHBr(OAc) in the presence of $Zn/CrCl_3$ to give the alkene.[1370] α-Diazo esters react with ketones in the presence of an iron catalyst to give the corresponding alkene.[1371] α-Diazo silylalkanes react similarly in the presence of a rhodium catalyst.[1372] Benzylic alcohols also react with α-diazo silylalknes in the presence of a rhodium catalyst, to give alkenes after pretreatment with oxygen and a palladium catalyst.[1373] The react of aryl aldehydes and $MeC(CO_2Et)_3$ with a catalytic amount of phenol leads to the corresponding conjugated ethyl ester ($ArCH=CHCO_2Et$).[1374]

OS **VIII**, 512, **IX**, 404; **X**, 355.

16-46 The Formation of Epoxides from Aldehydes and Ketones

(1 + 2)*OC*,*CC-cyclo*-Methylene-addition



72

Aldehydes and ketones can be converted to epoxides[1375] in good yields with the sulfur ylids dimethyloxosulfonium methylid (**72**) and dimethylsulfonium

[1367]See, for example, Schrock, R.R. *J. Am. Chem. Soc.* ***1976***, *98*, 5399; Aguero, A.; Kress, J.; Osborn, J.A. *J. Chem. Soc., Chem. Commun.* ***1986***, 531; Hartner, Jr., F.W.; Schwartz, J.; Clift, S.M. *J. Am. Chem. Soc.* ***1990***, *105*, 640.

[1368]Matsubara, S.; Horiuchi, M.; Takai, K.; Utimoto, K. *Chem. Lett.* ***1995***, 259.

[1369]Barma, D.K.; Kundu, A.; Zhang, H.; Mioskowski, C.; Falck, J.R. *J. Am. Chem. Soc.* ***2003***, *125*, 3218.

[1370]Knecht, M.; Boland, W. *Synlett* ***1993***, 837.

[1371]Chen, Y.; Huang, L.; Zhang, X.P. *Org. Lett.* ***2003***, *5*, 2493; Mirafzal, G.A.; Cheng, G.; Woo, L.K. *J. Am. Chem. Soc.* ***2002***, *124*, 176; Aggarwal, V.K.; Fulton, J.R.; Sheldon, C.G.; de Vincente, J. *J. Am. Chem. Soc.* ***2003***, *125*, 6034.

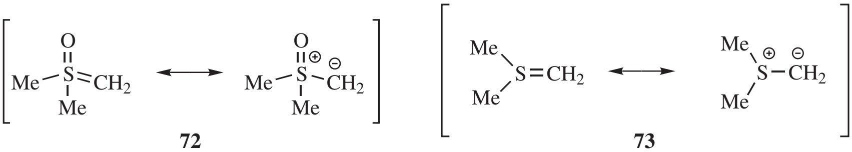
[1372]Lebel, H.; Guay, D.; Paquet, V.; Huard, K. *Org. Lett.* ***2004***, *6*, 3047. For a synthesis of dienes from conjugated aldehydes, see Lebel, H.; Paquet, V. *J. Am. Chem. Soc.* ***2004***, *126*, 320.

[1373]Lebel, H.; Paquet, V. *J. Am. Chem. Soc.* ***2004***, *126*, 11152.

[1374]Kumar, H.M.S.; Rao, M.S.; Joyasawal, S.; Yadav, J.S. *Tetrahedron Lett.* ***2003***, *44*, 4287.

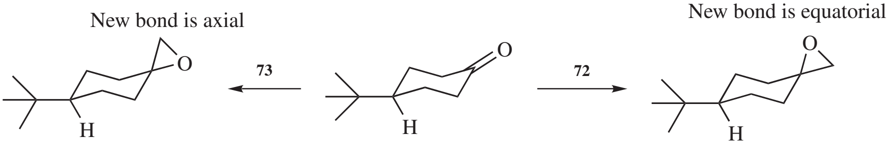
[1375]For reviews, see Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***, pp. 101–105; Berti, G. *Top. Stereochem.* ***1973***, *7*, 93, 218–232. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 944–951.

methylid (**73**).[1376] For most purposes, **72** is the



72 **73**

reagent of choice, because **73** is much less stable and ordinarily must be used as soon as it is formed, while **72** can be stored several days at room temperature. When diastereomeric epoxides can be formed, **73** usually attacks from the more hindered and **72** from the less-hindered side. Thus, 4-*tert*-butylcyclohexanone, treated with **72** gave exclusively **75** while **73** gave mostly **74**.[1377] Another difference in behavior between the



74 **75**

two reagents is that with α,β-unsaturated ketones, **72** gives only cyclopropanes (reaction **15-64**), while **73** gives oxirane formation. Other sulfur ylids have been used in an analogous manner, to transfer CHR or CR_2.[1378] High yields have been achieved by the use of sulfonium ylids anchored to insoluble polymers under phase-transfer conditions.[1379] A solvent-free version of this reaction has been developed using powdered K *tert*-butoxide and $Me_3S^+I^-$.[1380] Note that treatment of epoxides with 2 equivalents of $Me_2S{=}CH_2$ leads to allylic alcohols.[1381] Other sulfur ylids convert aldehydes to epoxides, including the one generated *in situ* from $RR'S^+CH_2COO^-$.[1382] Chiral sulfur ylids[1383] have been prepared, giving

[1376]For reviews, see House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 709–733; Durst, T. *Adv. Org. Chem.* ***1969***, *6*, 285, see pp. 321–330. For a monograph on sulfur ylids, see Trost, B.M.; Melvin, Jr., L.S. *Sulfur Ylids*; Academic Press, NY, ***1975***.

[1377]Corey, E.J.; Chaykovsky, M. *J. Am. Chem. Soc.* ***1965***, *87*, 1353.

[1378]Adams, J.; Hoffman, Jr., L.; Trost, B.M. *J. Org. Chem.* ***1970***, *35*, 1600; Yoshimine, M.; Hatch, M.J. *J. Am. Chem. Soc.* ***1967***, *89*, 5831; Braun, H.; Huber, G.; Kresze, G. *Tetrahedron Lett.* ***1973***, 4033; Corey, E.J.; Jautelat, M.; Oppolzer, W. *Tetrahedron Lett.* ***1967***, 2325.

[1379]Farrall, M.J.; Durst, T.; Fréchet, J.M.J. *Tetrahedron Lett.* ***1979***, 203.

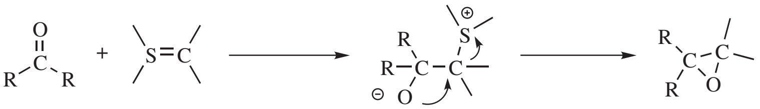
[1380]Toda, F.; Kanemoto, K. *Heterocycles* ***1997***, *46*, 185.

[1381]Harnett, J.J.; Alcaraz, L.; Mioskowski, C.; Martel, J.P.; Le Gall, T.; Shin, D.-S.; Falck, J.R. *Tetrahedron Lett.* ***1994***, *35*, 2009; Alcaraz, L.; Harnett, J.J.; Mioskowski, C.; Martel, J.P.; Le Gall, T.; Shin, D.-S.; Falck, J.R. *Tetrahedron Lett.* ***1994***, *35*, 5449. Also see, Alcaraz, L.; Harnett, J.J.; Mioskowski, C.; Martel, J.P. Le Gall, T.; Shin, D.-S.; Falck, J.R. *Tetrahedron Lett.* ***1994***, *35*, 5453 for generation of alkenes from $Me_2S{=}CH_2$ and alkyl halides or mesylates.

[1382]Forbes, D.C.; Standen, M.C.; Lewis, D.L. *Org. Lett.* ***2003***, *5*, 2283.

[1383]See Aggarwal, V.K.; Angelaud, R.; Bihan, D.; Blackburn, P.; Fieldhouse, R.; Fonguerna, S.J.; Ford, G.D.; Hynd, G.; Jones, E.; Jones, R.V.H.; Jubault, P.; Palmer, M.J.; Ratcliffe, P.D.; Adams, H. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 2604.

the epoxide with good asymmetric induction.[1384] Chiral selenium ylids have been used in a similar manner.[1385]

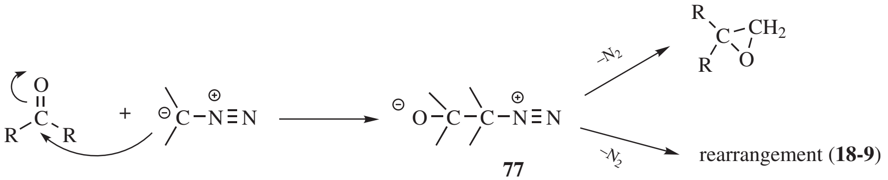


76

The generally accepted mechanism for the reaction between sulfur ylids and aldehydes or ketone is formation of **76**, with displacement of the Me_2S leaving group by the alkoxide.[1386] This mechanism is similar to that of the reaction of sulfur ylids with C=C double bonds (**15-64**).[1387] The stereochemical difference in the behavior of **72** and **73** has been attributed to formation of the betaine **76** being reversible for **72**, but not for the less stable **73**, so that the more-hindered product is the result of kinetic control and the less-hindered of thermodynamic control.[1388]

Phosphorus ylids do not give this reaction, but give **16-44** instead.

Aldehydes and ketones can also be converted to epoxides by treatment with a diazoalkane,[1389] most commonly diazomethane, but an important side reaction is the formation of an aldehyde or ketone with one more carbon than the starting compound (reaction **18-9**). The reaction can be carried out with many aldehydes, ketones, and quinones, usually with a rhodium catalyst.[1390] A mechanism that accounts for both products is



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Compound **77** or nitrogen-containing derivatives of it have sometimes been isolated.

An alternative route to epoxides from ketones uses α-chloro sulfones and potassium *tert*-butoxide to give α,β-epoxy sulfones.[1391] A similar reaction was reported

[1384]Baird, C.P.; Taylor, P.C. *J. Chem. Soc. Perkin Trans. 1* ***1998***, 3399; Domingo, V.M.; Castañer, J. *J. Chem. Soc., Chem. Commun.* ***1995***, 893; Hayakawa, R.; Shimizu, M. *Synlett* ***1999***, 1328; Zanardi, J.; Leriverend, C.; Aubert, D.; Julienne, K.; Metzner, P. *J. Org. Chem.* ***2001***, *66*, 5620; Saito, T.; Akiba, D.; Sakairi, M.; Kanazawa, S. *Tetrahedron Lett.* ***2001***, *42*, 57; Winn, C.L.; Bellenie, B.R.; Goodman, J.M. *Tetrahedron Lett.* ***2002***, *43*, 5427.

[1385]See Takada, H.; Metzner, P.; Philouze, C. *Chem. Commun.* ***2001***, 2350.

[1386]See Aggarwal, V.K.; Harvery, J.N.; Richardson, J. *J. Am. Chem. Soc.* ***2002***, *124*, 5747.

[1387]See, for example, Townsend, J.M.; Sharpless, K.B. *Tetrahedron Lett.* ***1972***, 3313; Johnson, C.R.; Schroeck, C.W.; Shanklin, J.R. *J. Am. Chem. Soc.* ***1973***, *95*, 7424.

[1388]Johnson, C.R.; Schroeck, C.W.; Shanklin, J.R. *J. Am. Chem. Soc.* ***1973***, *95*, 7424.

[1389]For a review, see Gutsche, C.D. *Org. React.* ***1954***, *8*, 364.

[1390]See Davies, H.M.L.; De Meese, J. *Tetrahedron Lett.* ***2001***, *42*, 6803.

[1391]Mąkosza, M.; Urbańska, N.; Chesnokov, A.A. *Tetrahedron Lett.* ***2003***, *44*, 1473.

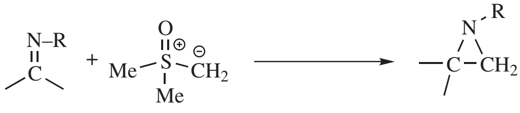
using KOH and 10% of a chiral phase-transfer agent, giving moderate enantioselectivity in the epoxy sulfone product.[1392]

Dihalocarbenes and carbenoids, which readily add to C=C bonds (**15-64**), do not generally add to the C=O bonds of ordinary aldehydes and ketones.[1393] See also, **16-91**.

OS **V**, 358, 755.

16-47 The Formation of Aziridines from Imines

(1 + 2)*NC*,*CC*-*cyclo*-Methylene-addition



72

Just as sulfur ylids react with the carbonyl of an aldehyde or ketone to give an epoxide, tellurium ylids react with imines to give an aziridine. The reaction of an allylic tellurium salt, $RCH{=}CHCH_2Te^+Bu_2\ Br^-$, with lithium hexamethyldisilazide in HMPA/toluene leads to the tellurium ylid via deprotonation. In the presence of an imine, the ylid add to the imine and subsequent displacement of Bu_2Te generates an aziridine with a pendant vinyl group.[1394]

16-48 The Formation of Episulfides and Episulfones[1395]

Epoxides can be converted directly to episulfides by treatment with NH_4SCN and ceric ammonium nitrate.[1396] Diazoalkanes, treated with sulfur, give episulfides.[1397] It is likely that $R_2C{=}S$ is an intermediate, which is attacked by another molecule of diazoalkane, in a process similar to that shown in **16-46**. Thioketones *do* react with diazoalkanes to give episulfides.[1398] Thioketones have also been converted to episulfides with sulfur ylids.[1377] Carbenes, such as the dichlorocarbene from $CHCl_3$ and base, react with thioketones to give an

[1392]Arai, S.; Shioiri, T. *Tetrahedron* ***2002***, *58*, 1407.

[1393]For exceptions, see Greuter, H.; Winkler, T.; Bellus, D. *Helv. Chim. Acta* ***1979***, *62*, 1275; Sadhu, K.M.; Matteson, D.S. *Tetrahedron Lett.* ***1986***, *27*, 795; Araki, S.; Butsugan, Y. *J. Chem. Soc., Chem. Commun.* ***1989***, 1286.

[1394]Liao, W.-W.; Deng, X.-M.; Tang, Y. *Chem. Commun.* ***2004***, 1516.

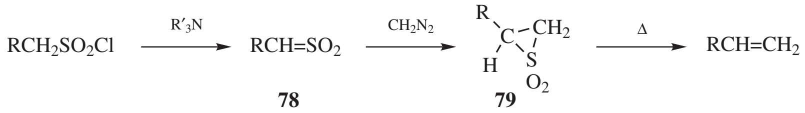
[1395]For a review, see Muller, L.L.; Hamer, J. *1,2-Cycloaddition Reactions*, Wiley, NY, ***1967***, pp. 57–86.

[1396]Iranpoor, N.; Kazemi, F. *Synthesis* ***1996***, 821.

[1397]Schönberg, A.; Frese, E. *Chem. Ber.* ***1962***, *95*, 2810.

[1398]For example, see Beiner, J.M.; Lecadet, D.; Paquer, D.; Thuillier, A. *Bull. Soc. Chim. Fr.* ***1973***, 1983.

α,α-dichloro episufide.[1399]

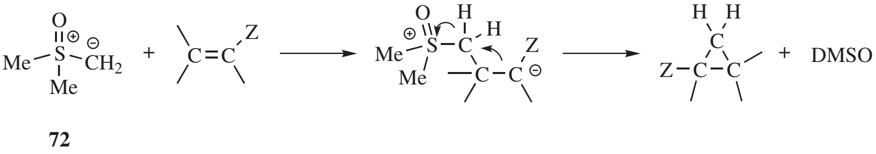


Alkanesulfonyl chlorides, when treated with diazomethane in the presence of a base (usually a tertiary amine), give episulfones (**79**).[1400] The base removes HCl from the sulfonyl halide to produce the highly reactive sulfene (**78**) (**17-14**), which then adds CH_2. The episulfone can then be heated to give off SO_2 (**17-20**), making the entire process a method for achieving the conversion $RCH_2SO_2Cl \rightarrow RCH{=}CH_2$.[1401]

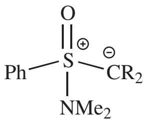
OS **V**, 231, 877.

16-49 Cyclopropanation of Conjugated Carbonyl Compounds

Double-bond compounds that undergo the Michael reaction (**15-24**) can be converted to cyclopropane derivatives with sulfur ylids.[1402] Among the most common of these is dimethyloxosulfonium methylid



72,[1403] which is widely used to transfer CH_2 to activated double bonds, but other sulfur ylids



[1399]Mlosteń, G.; Romański, J.; Swiątek, A.; Hemgartner, H. *Helv. Chim. Acta* ***1999***, *82*, 946.

[1400]Opitz, G.; Fischer, K. *Angew. Chem. Int. Ed.* ***1965***, *4*, 70.

[1401]For a review of this process, see Fischer, N.S. *Synthesis* ***1970***, 393.

[1402]For a monograph on sulfur ylids, see Trost, B.M.; Melvin Jr., L.S. *Sulfur Ylids*, Academic Press, NY, ***1975***. For reviews, see Fava, A., in Bernardi, F.; Csizmadia, I.G.; Mangini, A. *Organic Sulfur Chemistry*, Elsevier, NY, ***1985***, pp. 299–354; Belkin, Yu.V.; Polezhaeva, N.A. *Russ. Chem. Rev.* ***1981***, *50*, 481; Block, E., in Stirling, C.J.M. *The Chemistry of the Sulphonium Group*, pt. 2, Wiley, NY, ***1981***, pp. 680–702; Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***, pp. 91–127. See also, Mamai, A.; Madalengoitia, J.S. *Tetrahedron Lett.* ***2000***, *41*, 9009.

[1403]Truce, W.E.; Badiger, V.V. *J. Org. Chem.* ***1964***, *29*, 3277; Corey, E.J.; Chaykovsky, M. *J. Am. Chem. Soc.* ***1965***, *87*, 1353; Agami, C.; Prevost, C. *Bull. Soc. Chim. Fr.* ***1967***, 2299. For a review of this reagent, see Gololobov, Yu.G.; Nesmeyanov, A.N.; Lysenko, V.P.; Boldeskul, I.E. *Tetrahedron* ***1987***, *43*, 2609.

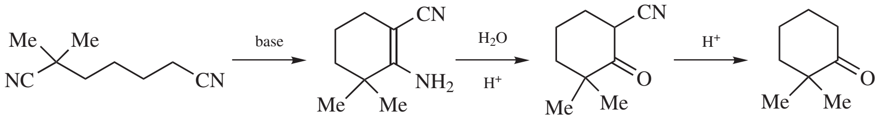
have also been used. A combination of DMSO and KOH in an ionic liquid converts conjugated ketones to α,β-cyclopropyl ketones.[1404] Both CHR and CR_2 can be added in a similar manner with certain nitrogen-containing compounds. For example, ylids,[1405] such as **80**, add various groups to activated double bonds.[1406] Sulfur ylids react with allylic alcohols in the presence of MnO_2 and molecular sieve 4 Å to give the cyclopropyl aldehyde.[1407] Similar reactions have been performed with phosphorus ylids,[1408] with pyridinium ylids,[1409] and with the compounds $(PhS)_3CLi$ and $Me_3Si(PhS)_2CLi$.[1410] The reactions with ylids such as these involve of course nucleophilic acyl addition.

Other reagents can be used to convert an aldehyde or ketone to a cyclopropane derivative. Conjugated ketones react with $Cp_2Zr(CH_2{-}CH_2)$ and PMe_3 to give a vinyl cyclopropane derivative after treatment with aqueous sulfuric acid.[1411]

16-50 The Thorpe Reaction

N-Hydro-*C*-(α-cyanoalkyl)-addition

In the *Thorpe reaction*, the α carbon of one nitrile molecule is added to the CN carbon of another, so this reaction is analogous to the aldol reaction (**16-34**). The C=NH bond is, of course, hydrolyzable (**16-2**), so β-keto nitriles can be prepared in this manner. The Thorpe reaction can be done intramolecularly, in which case it is



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[1404]In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Chandrasekhar, S.; Jagadeshwar, N.V.; Reddy, K.V. *Tetrahedron Lett.* ***2003***, *44*, 3629.

[1405]For a review of sulfoximides ($R_2S(O)NR_2$) and ylids derived from them, see Kennewell, P.D.; Taylor, J.B. *Chem. Soc. Rev.* ***1980***, *9*, 477.

[1406]For reviews, see Johnson, C.R. *Aldrichimica Acta* ***1985***, *18*, 1; *Acc. Chem. Res.* ***1973***, *6*, 341; Kennewell, P.D.; Taylor, J.B. *Chem. Soc. Rev.* ***1975***, *4*, 189; Trost, B.M. *Acc. Chem. Res.* ***1974***, *7*, 85.

[1407]Oswald, M.F.; Raw, S.A.; Taylor, R.J.K. *Org. Lett.* ***2004***, *6*, 3997.

[1408]Bestmann, H.J.; Seng, F. *Angew. Chem. Int. Ed.* ***1962***, *1*, 116; Grieco, P.A.; Finkelhor, R.S. *Tetrahedron Lett.* ***1972***, 3781.

[1409]Shestopalov, A.M.; Sharanin, Yu.A.; Litvinov, V.P.; Nefedov, O.M. *J. Org. Chem. USSR* ***1989***, *25*, 1000.

[1410]Cohen, T.; Myers, M. *J. Org. Chem.* ***1988***, *53*, 457.

[1411]Bertus, P.; Gandon, V.; Szymoniak, J. *Chem. Commun.* ***2000***, 171.

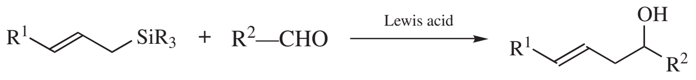
called the *Thorpe-Ziegler reaction*.[1412] This is a useful method for closing large rings. Yields are high for five- to eight-membered rings, fall off to about zero for rings of nine to thirteen members, but are high again for fourteen-membered and larger rings, if high-dilution techniques are employed. The product in the Thorpe–Ziegler reaction is not the imine, but the tautomeric enamine, for example, **81**; if desired this can be hydrolyzed to an α-cyano ketone (**16-2**), which can in turn be hydrolyzed and decarboxylated (**16-4**, **12-40**). Other active-hydrogen compounds can also be added to nitriles.[1413]

OS **VI**, 932.

H. Other Carbon or Silicon Nucleophiles

16-51 Addition of Silanes

***O*-Hydro-*C*-alkyl-addition**



Allylic silanes react with aldehydes, in the presence of Lewis acids, to give a homoallylic alcohol.[1414] In the case of benzylic silanes, this addition reaction has been induced with $Mg(ClO_4)_2$ under photochemical conditions.[1415] Cyclopropylcarbinyl silanes add to acetals in the presence of TMSOTf to give a homoallylic alcohol.[1416] Allyltrichlorosilane adds an allyl group to an aldehyde in the presence of a cyclic urea and AgOTf.[1417] The addition of chiral additives leads to the alcohol with good asymmetric induction.[1418] In a related reaction, allylic silanes react with acyl halides to produce the corresponding carbonyl derivative. The reaction of phenyl chloroformate, allyltrimethylsilane and $AlCl_3$, for example, gave phenyl but-3-enoate.[1419]

Allylic silanes also add to imines, in the presence of $TiCl_4$, to give amines.[1420]

[1412]For a monograph, see Taylor, E.C.; McKillop, A. *The Chemistry of Cyclic Enaminonitriles and ortho-Amino Nitriles*, Wiley, NY, ***1970***. For a review, see Schaefer, J.P.; Bloomfield, J.J. *Org. React.* ***1967***, *15*, 1.

[1413]See, for example, Josey, A.D. *J. Org. Chem.* ***1964***, *29*, 707; Barluenga, J.; Fustero, S.; Rubio, V.; Gotor, V. *Synthesis* ***1977***, 780; Hiyama, T.; Kobayashi, K. *Tetrahedron Lett.* ***1982***, *23*, 1597; Gewald, K.; Bellmann, P.; Jänsch, H. *Liebigs Ann. Chem.* ***1984***, 1702; Page, P.C.B.; van Niel, M.B.; Westwood, D. *J. Chem. Soc. Perkin Trans. 1* ***1988***, 269.

[1414]Panek, J.S.; Liu, P. *Tetrahedron Lett.* ***1997***, *38*, 5127.

[1415]Fukuzumi, S.; Okamoto, T.; Otera, J. *J. Am. Chem. Soc.* ***1994***, *116*, 5503.

[1416]Braddock, D.C.; Badine, D.M.; Gottschalk, T. *Synlett* ***2001***, 1909.

[1417]Chataigner, I.; Piarulli, U.; Gennari, C. *Tetrahedron Lett.* ***1999***, *40*, 3633.

[1418]Ishihara, K.; Mouri, M.; Gao, Q.; Maruyama, T.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* ***1993***, *115*, 11490.

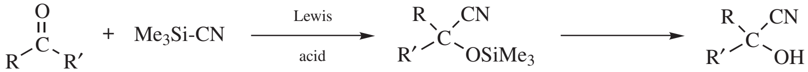
[1419]Mayr, H.; Gabriel, A.O.; Schumacher, R. *Liebigs Ann. Chem.* ***1995***, 1583.

[1420]Kercher, T.; Livinghouse, T. *J. Am. Chem. Soc.* ***1996***, *118*, 4200.

16-52 The Formation of Cyanohydrins

O-Hydro-*C*-cyano-addition

The addition of HCN to aldehydes or ketones produces cyanohydrins.[1421] This is an equilibrium reaction, and for aldehydes and aliphatic ketones the equilibrium lies to the right; therefore the reaction is quite feasible, except with sterically hindered ketones such as diisopropyl ketone. However, ketones ArCOR give poor yields, and the reaction cannot be carried out with ArCOAr since the equilibrium lies too far to the left. With aromatic aldehydes the benzoin condensation (**16-55**) competes. With α,β-unsaturated aldehydes and ketones, 1,4-addition competes (**15-38**). The reaction has been carried out enantioselectively: optically active cyanohydrins were prepared with the aid of optically active catalysts.[1422] Hydrogen cyanide adds to aldehydes in the presence of a lyase to give the cyanohydrin with good enantioselectivity.[1423] Cyanohydrins have been formed using a lyase in an ionic liquid.[1424]



82

Ketones of low reactivity, such as ArCOR, can be converted to cyanohydrins by treatment with diethylaluminum cyanide (Et_2AlCN) (see OS **VI**, 307) or, indirectly, with cyanotrimethylsilane (Me_3SiCN)[1425] in the presence of a Lewis acid or base,[1426]

[1421]For reviews, see Friedrich, K., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 2, Wiley, NY, ***1983***, pp. 1345–1390; Friedrich, K.; Wallenfels, K., in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 72–77.

[1422]See Minamikawa, H.; Hayakawa, S.; Yamada, T.; Iwasawa, N.; Narasaka, K. *Bull. Chem. Soc. Jpn.* ***1988***, *61*, 4379; Jackson, W.R.; Jayatilake, G.S.; Matthews, B.R.; Wilshire, C. *Aust. J. Chem.* ***1988***, *41*, 203; Garner, C.M.; Fernández, J.M.; Gladysz, J.A. *Tetrahedron Lett.* ***1989***, *30*, 3931; Mori, A.; Ikeda, Y.; Kinoshita, K.; Inoue, S. *Chem. Lett.* ***1989***, 2119; Kobayashi, S.; Tsuchiya, Y.; Mukaiyama, T. *Chem. Lett.* ***1991***, 541; Gröger, H.; Capan, E.; Barthuber, A.; Vorlop, K.-D. *Org. Lett.* ***2001***, *3*, 1969, and references cited therein. For a review, see Brune, J.-M.; Holmes, I.P. *Angew. Chem. Int. Ed.* ***2004***, *43*, 2752.

[1423]Gerrits, P.J.; Marcus, J.; Birikaki, L.; van der Gen, A. *Tetrahedron Asymmetry* ***2001***, *12*, 971.

[1424]In bmim BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate: Gaisberger, R.P.; Fechter, M.H.; Griengl, H. *Tetrahedron Asymmetry* ***2004***, *15*, 2959.

[1425]For reviews of Me_3SiCN and related compounds, see Rasmussen, J.K.; Heilmann, S.M.; Krepski, L. *Adv. Silicon Chem.* ***1991***, *1*, 65; Groutas, W.C.; Felker, D. *Synthesis* ***1980***, 861. For procedures using Me_3SiCl and ^-CN instead of Me_3SiCN, see Yoneda, R.; Santo, K.; Harusawa, S.; Kurihara, T. *Synthesis* ***1986***, 1054; Sukata, K. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 3820.

[1426]Kobayashi, S.; Tsuchiya, Y.; Mukaiyama, T. *Chem. Lett.* ***1991***, 537; Belokon', Y.; Flego, M.; Ikonnikov, N.; Moscalenko, M.; North, M.; Orizu, C.; Tararov, V.; Tasinazzo, M. *J. Chem. Soc. Perkin Trans. 1* ***1997***, 1293; Wada, M.; Takahashi, T.; Domae, T.; Fukuma, T.; Miyoshi, N.; Smith, K. *Tetrahedron Asymmetry*, ***1997***, *8*, 3939; Kanai, M.; Hamashima, Y.; Shibasaki, M. *Tetrahedron Lett.* ***2000***, *41*, 2405. The reaction works in some cases without a Lewis acid, see Manju, K.; Trehan, S. *J. Chem. Soc. Perkin Trans. 1* ***1995***, 2383.

followed by hydrolysis of the resulting *O*-trimethylsilyl cyanohydrin **82**. Solvent-free conditions have been reported using TMSCN, an aldehydes and potassium carbonate.[1427] Amine *N*-oxides catalyze the reaction[1428] as does tetra-butylammonium cyanide.[1429] Lithium perchlorate in ether facilitates this reaction.[1430] With $MgBr_2$ as a catalyst, the reaction proceeds to good syn selectivity. [1431] Other useful catalysts include platinum complexes,[1432] Ti(O*i*Pr)$_4$,[1433] and $InBr_3$.[1434] When $TiCl_4$ is used, the reaction between Me_3SiCN and aromatic aldehydes or ketones gives α-chloro nitriles (ClCRR′—CN).[1435] The use of chiral additives in this latter reaction leads to cyanohydrins with good asymmetric induction.[1436] Sulfoximine–titanium reagents have been used in enantioselective trimethylsilyl cyanations of aldehydes.[1437] Chiral transition-metal catalysts have been used to give *O*-trialkylsilyl cyanohydrins with good enantioselectivity, including titanium complexes[1438] as well as complexes of other metals.[1439] A vanadium catalysts has been used in an ionic liquid.[1440] Note that the reaction of an aldehyde and TMSCN in the presence of aniline and a $BiCl_3$ catalyst leads to an α-cyano amine.[1441] α-Cyano amines are also formed by the reaction of an aldehyde with $(Et_2N)_2BCN$.[1442]

[1427]He, B.; Li, Y.; Feng, X.; Zhang, G. *Synlett* ***2004***, 1776.

[1428]Shen, Y.; Feng, X.; Li, Y.; Zhang, G.; Jiang, Y. *Tetrahedron* ***2003***, *59*, 5667. See Bakendale, I.R.; Ley, S.V.; Sneddon, H.F. *Synlett* ***2002***, 775; Shen, Y.; Feng, X.; Li, Y.; Zhang, G.; Jiang, Y. *Eur. J. Org. Chem.* ***2004***, 129.

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[1432]Fossey, J.S.; Richards, C.J. *Tetrahedron Lett.* ***2003***, *44*, 8773.

[1433]Huang, W.; Song, Y.; Bai, C.; Cao, G.; Zheng, Z. *Tetrahedron Lett.* ***2004***, *45*, 4763; He, B.; Chen, F.-X.; Li, Y.; Feng, X.; Zhang, G. *Tetrahedron Lett.* ***2004***, *45*, 5465.

[1434]Bandini, M.; Cozzi, P.G.; Melchiorre, P.; Umani-Ronchi, A. *Tetrahedron Lett* ***2001***, *42*, 3041.

[1435]Kiyooka, S.; Fujiyama, R.; Kawaguchi, K. *Chem. Lett.* ***1984***, 1979.

[1436]Tararov, V.I.; Hibbs, D.E.; Hursthouse, M.B.; Ikonnikov, N.S.; Malik, K.M.A.; North, M.; Orizu, C.; Belokon, Y.N. *Chem. Commun.* ***1998***, 387; Bolm, C.; Müller, P. *Tetrahedron Lett.* ***1995***, *36*, 1625; Ryu, D.H.; Corey, E.J. *J. Am. Chem. Soc.* ***2004***, *126*, 8106.

[1437]Bolm, C.; Müller, P.; Harms, K. *Acta Chem. Scand. B*, ***1996***, *50*, 305.

[1438]Hamashima, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem.Soc.* ***2000***, *122*, 7412; Belokon, Y.N.; Green, B.; Ikonnikov, N.S.; North, M.; Parsons, T.; Tararov, V.I. *Tetrahedron* ***2001***, *57*, 771 and references cited therein; Liang, S.; Bu, X.R. *J. Org. Chem.* ***2002***, *67*, 2702; Li, Y.; He, B.; Qin, B.; Feng, X.; Zhang, G. *J. Org. Chem.* ***2004***, *69*, 7910; Chen, F.-X.; Qin, B.; Feng, X.; Zhang, G.; Jiang, Y. *Tetrahedron* ***2004***, *60*, 10449; Uang, B.-J.; Fu, I.-P.; Hwang, C.-D.; Chang, C.-W.; Yang, C.-T.; Hwang, D.-R. *Tetrahedron* ***2004***, *60*, 10479; Gama, A.; Flores-López, L.-Z.; Aguirre, G.; Parra-Hake, M.; Somanathan, R.; Walsh, P.J. *Tetrahedron Asymmetry* ***2002***, *13*, 149.

[1439]Transition metals used include **Yb**: Aspinall, H.C.; Greeves, N.; Smith, P.M. *Tetrahedron Lett.* ***1999***, *40*, 1763. **Al**: Hamashima, Y.; Sawada, D.; Nogami, H.; Kanai, M.; Shibasaki, M. *Tetrahedron* ***2001***, *57*, 805; Deng, H.; Isler, M.P.; Snapper, M.L.; Hoveyda, A.H. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1009. **Sc**: Karimi, B.; Ma'Mani, L. *Org. Lett.* ***2004***, *6*, 4813.

[1440]In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Baleizão, C.; Gigante, B.; Garcia, H.; Corma, A. *Tetrahedron Lett.* ***2003***, *44*, 6813.

[1441]De, S.K.; Gibbs, R.A. *Tetrahedron Lett.* ***2004***, *45*, 7407.

[1442]Suginome, M.; Yamamoto, A.; Ito, Y. *Chem. Commun.* ***2002***, 1392.

Ketones can be converted to cyanohydrin *O*-carbonates, $R_2C(CN)OCO_2R'$, by reaction with EtO_2C—CN. In the presence of a Cinchona alkaloid, the product is formed with good enantioselectivity.[1443] Potassium cyanide and acetic anhydride reacts with an aldehyde in the presence of a chiral titanium catalyst to give an α-acetoxy nitrile.[1444]

Rather than direct reaction with an aldehyde or ketone, the bisulfite addition product is often treated with cyanide. The addition is nucleophilic and the actual nucleophile is $^{-}$CN, so the reaction rate is increased by the addition of base.[1445] This was demonstrated by Lapworth in 1903, and consequently this was one of the first organic mechanisms to be known.[1446] This method is especially useful for aromatic aldehydes, since it avoids competition from the benzoin condensation. If desired, it is possible to hydrolyze the cyanohydrin *in situ* to the corresponding α-hydroxy acid. This reaction is important in the *Kiliani–Fischer* method of extending the carbon chain of a sugar.

A particularly useful variation of this reaction uses cyanide rather than HCN. α-Amino nitriles[1447] can be prepared in one step by the treatment of an aldehyde or ketone with NaCN and NH_4Cl. This is called the *Strecker synthesis*;[1448] and it is a special case of the Mannich reaction (**16-19**). Since the CN is easily hydrolyzed to the acid, this is a convenient method for the preparation of α-amino acids. The reaction has also been carried out with $NH_3 + HCN$ and with NH_4CN. Salts of primary and secondary amines can be used instead of NH_4^+ to obtain *N*-substituted and *N,N*-disubstituted α-amino nitriles. Unlike **16-52**, the Strecker synthesis is useful for aromatic as well as aliphatic ketones. As in **16-52**, the Me_3SiCN method has been used; **76** is converted to the product with ammonia or an amine.[1449] The effect of pressure on the Strecker synthesis has been studied.[1450]

OS **I**, 336; **II**, 7, 29, 387; **III**, 436; **IV**, 58, 506; **VI**, 307; **VII**, 20, 381, 517, 521. For the reverse reaction, see OS **III**, 101. For the Strecker synthesis, see OS **I**, 21, 355; **III**, 66, 84, 88, 275; **IV**, 274; **V**, 437; **VI**, 334.

[1443]Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* ***2001***, *123*, 6195.

[1444]Belokon, Y.N.; Gutnov, A.V.; Moskalenko, M.A.; Yashkina, L.V.; Lesovoy, D.E.; Ikonnikov, N.S.; Larichev, V.S.; North, M. *Chem. Commun.* ***2002***, 244; Kawasaki, Y.; Fujii, A.; Nakano, Y.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* ***1999***, *64*, 4214.

[1445]For a review, see Ogata, Y.; Kawasaki, A., in Zabicky, J. *The Chemistry of the Carbonyl Group*, Vol. 2, Wiley, NY, ***1970***, pp. 21–32. See also, Okano, V.; do Amaral, L.; Cordes, E.H. *J. Am. Chem. Soc.* ***1976***, *98*, 4201; Ching, W.; Kallen, R.G. *J. Am. Chem. Soc.* ***1978***, *100*, 6119.

[1446]Lapworth, A. *J. Chem. Soc.* ***1903***, *83*, 998.

[1447]For a review of α-amino nitriles, see Shafran, Yu.M.; Bakulev, V.A.; Mokrushin, V.S. *Russ. Chem. Rev.* ***1989***, *58*, 148.

[1448]For a review of asymmetric Strecker syntheses, see Williams, R.M. *Synthesis of Optically Active α-Amino Acids*, Pergamon, Elmsford, NY, ***1989***, pp. 208–229; Yet, L. *Angew. Chem. Int. Ed.* ***2001***, *40*, 875; Gröger, H. *Chem. Rev.* ***2003***, *103*, 2795.

[1449]See Mai, K.; Patil, G. *Tetrahedron Lett.* ***1984***, *25*, 4583; *Synth. Commun.* ***1985***, *15*, 157.

[1450]Jenner, G.; Salem, R.B.; Kim, J.C.; Matsumoto, K. *Tetrahedron Lett.* ***2003***, *44*, 447.

16-53 The Addition of HCN to C=N and C≡N Bonds

N-Hydro-*C*-cyano-addition

W=H, R, Ar, OH, NHAr, etc.

HCN adds to imines, Schiff bases, hydrazones, oximes, and similar compounds. Cyanide can be added to iminium ions to give α-cyano amines (**83**).

83

As in **16-50**, the addition to imines has been carried out enantioselectively.[1451] Chiral ammonium salts have been used with HCN.[1452] TMSCN reacts with *N*-tosyl imines in the presence of BF_3•OEt_2 to give the α-cyano *N*-tosyl amine.[1453] In the presence of a chiral zirconium[1454] or aluminum[1455] catalyst, Bu_3SnCN react with imines to give α-cyanoamines enantioselectively. The reaction of an imine and TMSCN gives the cyano amine with good enantioselectivity using a chiral scandium catalyst.[1456] Titanium catalysts have been used in the presence of a chiral Schiff base.[1457] Treatment of an imine with a chiral 1,4,6- triazabicyclo[3.3.0]oct-4-ene and then HCN give the α-cyano amine with good enantioselectivity.[1458]

The addition of KCN to triisopropylbenzenesulfonyl hydrazones **84** provides an indirect method for achieving the conversion RR′CO → RR′CHCN.[1459] The reaction is successful for hydrazones of aliphatic aldehydes and ketones.

$$\underset{\mathbf{84}}{RR'C{=}NNHSO_2Ar} + KCN \xrightarrow{MeOH} RR'CHCN \qquad Ar = 2,4,6\text{-}(i\text{-}Pr)_3C_6H_2$$

[1451]Saito, K.; Harada, K. *Tetrahedron Lett.* ***1989***, *30*, 4535.

[1452]Huang, J.; Corey, E.J. *Org. Lett.* ***2004***, *6*, 5027.

[1453]Prasad, B.A.B.; Bisai, A.; Singh, V.K. *Tetrahedron Lett.* ***2004***, *45*, 9565.

[1454]Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc.* ***2000***, *122*, 762.

[1455]Nakamura, S.; Sato, N.; Sugimoto, M.; Toru, T. *Tetrahedron Asymmetry* ***2004***, *15*, 1513.

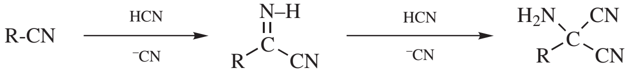
[1456]Chavarot, M.; Byrne, J.J.; Chavant, P.Y.; Vallée, Y. *Tetrahedron Asymmetry* ***2001***, *12*, 1147.

[1457]Krueger, C.A.; Kuntz, K.W.; Dzierba, C.D.; Wirschun, W.G.; Gleason, J.D.; Snapper, M.L.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***1999***, *121*, 4284.

[1458]Corey, E.J.; Grogan, M.J. *Org. Lett.* ***1999***, *1*, 157.

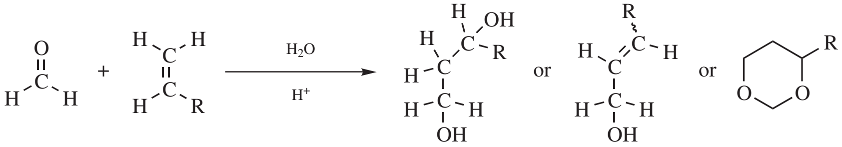
[1459]Jiricny, J.; Orere, D.M.; Reese, C.B. *J. Chem. Soc. Perkin Trans. 1* ***1980***, 1487. For other methods of achieving this conversion, see Ziegler, F.E.; Wender, P.A. *J. Org. Chem.* ***1977***, *42*, 2001; Cacchi, S.; Caglioti, L.; Paolucci, G. *Synthesis* ***1975***, 120; Yoneda, R.; Harusawa, S.; Kurihara, T. *Tetrahedron Lett.* ***1989***, *30*, 3681; Okimoto, M.; Chiba, T. *J. Org. Chem.* ***1990***, *55*, 1070.

HCN can also be added to the C≡N bond to give iminonitriles or α-aminomalononitriles.[1460]

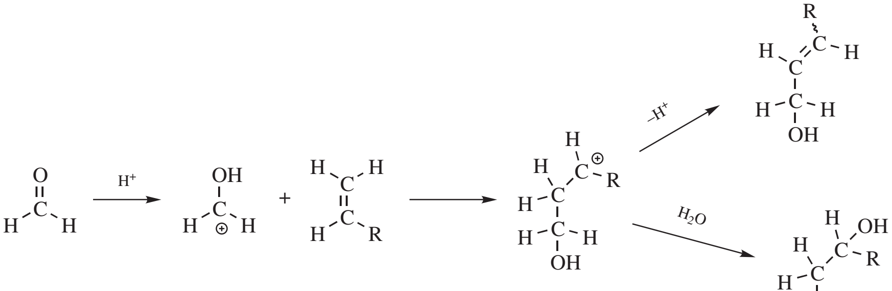


OS **V**, 344. See also, OS **V**, 269.

16-54 The Prins Reaction



The addition of an alkene to formaldehyde in the presence of an acid[1461] catalyst is called the *Prins reaction*.[1462] Three main products are possible; which one predominates depends on the alkene and the conditions. When the product is the 1,3-diol or the dioxane,[1463] the reaction involves addition to the C=C as well as to the C=O. The mechanism is one of electrophilic attack on both double bonds. The acid first protonates the C=O, and the resulting carbocation is attacked by the C=C to give **85**.



The cation product **85** can undergo loss of H^+ to give the alkene or add water to give the diol.[1464] It has been proposed that **85** is stabilized by neighboring-group

[1460]For an example, see Ferris, J.P.; Sanchez, R.A. *Org. Synth. V*, 344.

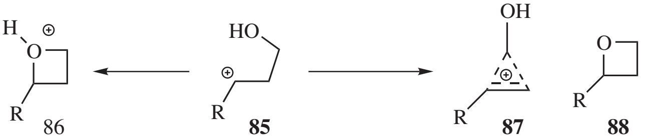
[1461]The Prins reaction has also been carried out with basic catalysts: Griengl, H.; Sieber, W. *Monatsh. Chem.* ***1973***, *104*, 1008, 1027.

[1462]For reviews, see Adams, D.R.; Bhatnagar, S.P. *Synthesis* ***1977***, 661; Isagulyants, V.I.; Khaimova, T.G.; Melikyan, V.R.; Pokrovskaya, S.V. *Russ. Chem. Rev.* ***1968***, *37*, 17. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, p. 248.

[1463]The reaction to produce dioxanes has also been carried out with equimolar mixtures of formaldehyde and another aldehyde RCHO. The R appears in the dioxane on the carbon between the two oxygens: Safarov, M.G.; Nigmatullin, N.G.; Ibatullin, U.G.; Rafikov, S.R. *Doklad. Chem.* ***1977***, *236*, 507.

[1464]Hellin, M.; Davidson, M.; Coussemant, F. *Bull. Soc. Chim. Fr.* ***1966***, 1890, 3217.

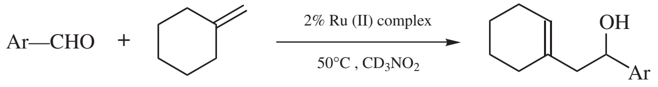
attraction, with either the oxygen[1465] or a carbon[1466] stabilizing the charge (**86** and



86 **85** **87** **88**

87, respectively). This stabilization is postulated to explain the fact that with 2-butenes[1467] and with cyclohexenes the addition is anti. A backside attack of H_2O on the three- or four-membered ring would account for it. Other products are obtained too, which can be explained on the basis of **86** or **87**.[1465,1466] Additional evidence for the intermediacy of **86** is the finding that oxetanes (**88**) subjected to the reaction conditions (which would protonate **88** to give **86**) give essentially the same product ratios as the corresponding alkenes.[1468] An argument against the intermediacy of **86** and **87** is that not all alkenes show the anti-stereoselectivity mentioned above. Indeed, the stereochemical results are often quite complex, with syn, anti, and nonstereoselective addition reported, depending on the nature of the reactants and the reaction conditions.[1469] Since addition to the C=C bond is electrophilic, the reactivity of the alkene increases with alkyl substitution and Markovnikov's rule is followed. The dioxane product may arise from a reaction between the 1,3-diol and formaldehyde[1470] (**16-5**) or between **86** and formaldehyde.

Lewis acids, such as $SnCl_4$, also catalyze the reaction, in which case the species that adds to the alkenes is $H_2C^+—O^-—SnCl_4$.[1471] Montmorillonite K10 clay containing zinc (IV) has been used to promote the reaction.[1472] The reaction can also be catalyzed by peroxides, in which case the mechanism is probably a free-radical one. Other transition metal complexes can be used to form homoallylic alcohols. A typical example is the reaction of methylenecyclohexane with an aryl aldehyde to give **89**.[1473]



89

[1465]Blomquist, A.T.; Wolinsky, J. *J. Am. Chem. Soc.* ***1957***, *79*, 6025; Schowen, K.B.; Smissman, E.E.; Schowen, R.L. *J. Org. Chem.* ***1968***, *33*, 1873.

[1466]Dolby, L.J.; Lieske, C.N.; Rosencrantz, D.R.; Schwarz, M.J. *J. Am. Chem. Soc.* ***1963***, *85*, 47; Dolby, L.J.; Schwarz, M.J. *J. Org. Chem.* ***1963***, *28*, 1456; Safarov, M.G.; Isagulyants, V.I.; Nigmatullin, N.G. *J. Org. Chem. USSR* ***1974***, *10*, 1378.

[1467]Fremaux, B.; Davidson, M.; Hellin, M.; Coussemant, F. *Bull. Soc. Chim. Fr.* ***1967***, 4250.

[1468]Meresz, O.; Leung, K.P.; Denes, A.S. *Tetrahedron Lett.* ***1972***, 2797.

[1469]For example, see LeBel, N.A.; Liesemer, R.N.; Mehmedbasich, E. *J. Org. Chem.* ***1963***, *28*, 615; Portoghese, P.S.; Smissman, E.E. *J. Org. Chem.* ***1962***, *27*, 719; Wilkins, C.L.; Marianelli, R.S. *Tetrahedron* ***1970***, *26*, 4131; Karpaty, M.; Hellin, M.; Davidson, M.; Coussemant, F. *Bull. Soc. Chim. Fr.* ***1971***, 1736; Coryn, M.; Anteunis, M. *Bull. Soc. Chim. Belg.* ***1974***, *83*, 83.

[1470]Hellin, M.; Davidson, M; Coussemant, F *Bull. Soc. Chim. Fr.* ***1966***, 1890, 3217; Isagulyants, V.I.; Isagulyants, G.V.; Khairudinov, I.R.; Rakhmankulov, D.L. *Bull. Acad. Sci. USSR. Div. Chem. Sci.*, ***1973***, *22*, 1810; Sharf, V.Z.; Kheifets, V.I.; Freidlin, V.I. *Bull. Acad. Sci. USSR Div. Chem. Sci.*, ***1974***, *23*, 1681.

[1471]Yang, D.H.; Yang, N.C.; Ross, C.B. *J. Am. Chem. Soc.* ***1959***, *81*, 133.

[1472]Tateiwa, J.-i.; Kimura, A.; Takasuka, M.; Uemura, S. *J. Chem. Soc. Perkin Trans. 1* ***1997***, 2169.

[1473]Ellis, W.W.; Odenkirk, W.; Bosnich, B. *Chem. Commun.* ***1998***, 1311.

Samarium iodide promotes this addition reaction.[1474] In a related reaction, simple alkene units add to esters in the presence of sodium and liquid ammonia to give an alcohol.[1475] Structural variations in the alkene lead to different products. Homoallylic alcohols react with aldehydes in the presence of Montmorillonite KSF clay to give 4-hydroxytetrahydropyrans.[1476] A variation of this reaction converts an aryl aldehyde and a homoallylic alcohol to a 4-chlorotetrahydropyran in the presence of $InCl_3$.[1477] Homoallylic alcohols, protected as –O(CHMeOAc) react with BF_3•OEt_2 and acetic acid to give 4-acetoxytetrahydropyrans or with $SnBr_4$ to give 4-bromotetrahydropyrans.[1478] Homoallylic alcohols with a vinyl silane moiety react with $InCl_3$ and an aldehyde to give a dihydropyran.[1479]

A closely related reaction has been performed with activated aldehydes or ketones; without a catalyst such as chloral and acetoacetic ester, but with heat.[1480] The product in these cases is a β-hydroxy alkene, and the mechanism is pericyclic:[1481]

This reaction is reversible and suitable β-hydroxy alkenes can be cleaved by heat (**17-32**). There is evidence that the cleavage reaction occurs by a cyclic mechanism (p. 1551), and, by the principle of microscopic reversibility, the addition mechanism should be cyclic too.[1482] Note that this reaction is an oxygen analog of the ene synthesis (**15-23**). This reaction can also be done with unactivated aldehydes[1483] and ketones[1484] if Lewis-acid catalysts such as dimethylaluminum chloride (Me_2AlCl) or ethylaluminum dichloride ($EtAlCl_2$) are used.[1485] Lewis acid catalysts

[1474]Sarkar, T.K.; Nandy, S.K. *Tetrahedron Lett.* ***1996***, *37*, 5195.

[1475]Cossy, J.; Gille, B.; Bellosta, V. *J. Org. Chem.* ***1998***, *63*, 3141.

[1476]Yadav, J.S.; Reddy, B.V.S.; Kumar, G.M.; Murthy, Ch.V.S.R. *Tetrahedron Lett.* ***2001***, *42*, 89.

[1477]Yang, J.; Viswanathan, G.S.; Li, C.-J. *Tetrahedron Lett.* ***1999***, *40*, 1627.

[1478]Jaber, J.J.; Mitsui, K.; Rychnovsky, S.D. *J. Org. Chem.* ***2001***, *66*, 4679.

[1479]Dobbs, A.P.; Martinović, S. *Tetrahedron Lett.* ***2002***, *43*, 7055.

[1480]Arnold, R.T.; Veeravagu, P. *J. Am. Chem. Soc.* ***1960***, *82*, 5411; Klimova, E.I.; Abramov, A.I.; Antonova, N.D.; Arbuzov, Yu.A. *J. Org. Chem. USSR* ***1969***, *5*, 1308; Klimova, E.I.; Antonova, N.D.; Arbuzov, Yu.A. *J. Org. Chem. USSR* ***1969***, *5*, 1312, 1315.

[1481]See, for example, Achmatowicz, Jr., O.; Szymoniak, J. *J. Org. Chem.* ***1980***, *45*, 1228; Ben Salem, R.; Jenner, G. *Tetrahedron Lett.* ***1986***, *27*, 1575. There is evidence that the mechanism is somewhat more complicated than shown here: Kwart, H.; Brechbiel, M. *J. Org. Chem.* ***1982***, *47*, 3353.

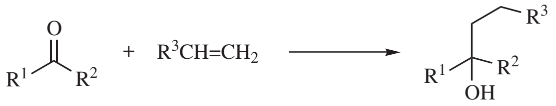
[1482]For other evidence, see Achmatowicz Jr., O.; Szymoniak, J. *J. Org. Chem.* ***1980***, *45*, 1228; Ben Salem, R.; Jenner, G. *Tetrahedron Lett.* ***1986***, *27*, 1575; Papadopoulos, M.; Jenner, G. *Tetrahedron Lett.* ***1981***, *22*, 2773.

[1483]Snider, B.B. *Acc. Chem. Res.* ***1980***, *13*, 426; Cartaya-Marin, C.P.; Jackson, A.C.; Snider, B.B. *J. Org. Chem.* ***1984***, *49*, 2443.

[1484]Jackson, A.C.; Goldman, B.E.; Snider, B.B. *J. Org. Chem.* ***1984***, *49*, 3988.

[1485]For discussions of the mechanism with Lewis acid catalysts, see Stephenson, L.M.; Orfanopoulos, M. *J. Org. Chem.* ***1981***, *46*, 2200; Kwart, H.; Brechbiel, M. *J. Org. Chem.* ***1982***, *47*, 5409; Song, Z.; Beak, P. *J. Org. Chem.* ***1990***, *112*, 8126.

also increase rates with activated aldehydes.[1486] The use of optically active catalysts has given optically active products with high ee.[1487]



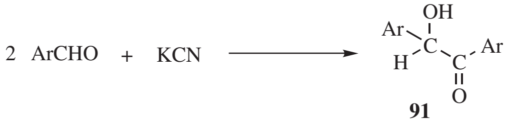
90

In a related reaction, alkenes can be added to aldehydes and ketones to give reduced alcohols **90**. This has been accomplished by several methods,[1488] including treatment with SmI_2[1489] or Zn and Me_3SiCl,[1490] and by electrochemical[1491] and photochemical[1492] methods. Most of these methods have been used for intramolecular addition and most or all involve free-radical intermediates.

OS **IV**, 786. See also, OS **VII**, 102.

16-55 The Benzoin Condensation

Benzoin aldehyde condensation



91

When certain aldehydes are treated with cyanide ion, *benzoins* (**91**) are produced in a reaction called the *benzoin condensation*. The condensation can be regarded as involving the addition of one molecule of aldehyde to the C=O group of another. The reaction only occurs with aromatic aldehydes, but not all of them,[1493] and for glyoxals RCOCHO. The two molecules of aldehyde obviously perform different functions. The one that no longer has a C—H bond in the product is called the *donor*, because it has "donated" its hydrogen to the oxygen of the other molecule, the *acceptor*. Some aldehydes can perform only one of these functions, and hence cannot be self-condensed, though they can often be condensed with a different aldehyde. For example, *p*-dimethylaminobenzaldehyde is not an acceptor but only a donor. Thus it cannot condense with itself, but it can condense with benzaldehyde, which can perform both functions, but is a better acceptor than it is a donor.

[1486]Benner, J.P.; Gill, G.B.; Parrott, S.J.; Wallace, B. *J. Chem. Soc. Perkin Trans. 1* ***1984***, 291, 315, 331.

[1487]Maruoka, K.; Hoshino, Y.; Shirasaka, T.; Yamamoto, H. *Tetrahedron Lett.* ***1988***, *29*, 3967; Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* ***1990***, *112*, 3949.

[1488]For references, see Ujikawa, O.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* ***1989***, *30*, 2837; Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1178–1179.

[1489]Ujikawa, O.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* ***1989***, *30*, 2837.

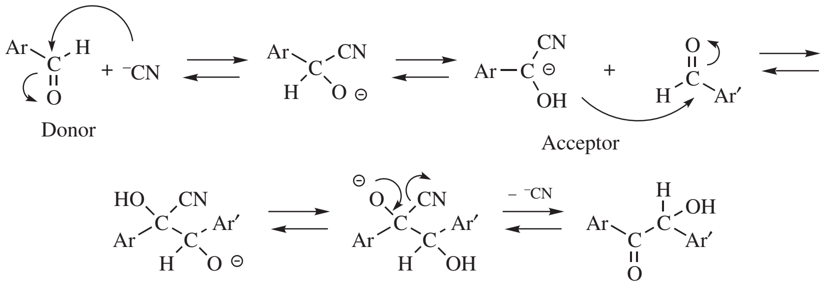
[1490]Corey, E.J.; Pyne, S.G. *Tetrahedron Lett.* ***1983***, *24*, 2821.

[1491]See Shono, T.; Kashimura, S.; Mori, Y.; Hayashi, T.; Soejima, T.; Yamaguchi, Y. *J. Org. Chem.* ***1989***, *54*, 6001.

[1492]See Belotti, D.; Cossy, J.; Pete, J.P.; Portella, C. *J. Org. Chem.* ***1986***, *51*, 4196.

[1493]For a review, see Ide, W.S.; Buck, J.S. *Org. React.* ***1948***, *4*, 269.

The following is the accepted mechanism[1494] for this reversible reaction, which was originally proposed by Lapworth in 1903:[1495]



The key step, the loss of the aldehydic proton, can take place because the acidity of this C—H bond is increased by the electron-withdrawing power of the CN group. Thus, cyanide is a highly specific catalyst for this reaction, because, almost uniquely, it can perform three functions: (*1*) It acts as a nucleophile; (*2*) its electron-withdrawing ability permits loss of the aldehydic proton; and (*3*) having done this, it then acts as a leaving group. Certain thiazolium salts can also catalyze the reaction.[1496] In this case, aliphatic aldehydes can also be used[1497] (the products are called *acyloins*), and mixtures of aliphatic and aromatic aldehydes give mixed α-hydroxy ketones.[1498] The reaction has also been carried out without cyanide, by using the benzoylated cyanohydrin as one of the components in a phase-transfer catalyzed process. By this means, products can be obtained from aldehydes that normally fail to self-condense.[1499] The condensation has also been done with excellent enantioselectivity using benzoylformate decarboxylase.[1500] Using aryl silyl ketones, ArC(=O)$SiMe_2Ph$, and aldehydes with a lanthanum catalyst, a ‘mixed’ benzoin condensation has been accomplished.[1501]

OS **I**, 94; **VII**, 95.

[1494]For a discussion, See Kuebrich, J.P.; Schowen, R.L.; Wang, M.; Lupes, M.E. *J. Am. Chem. Soc.* ***1971***, *93*, 1214.

[1495]Lapworth, A. *J. Chem. Soc.* ***1903***, *83*, 995; ***1904***, *85*, 1206.

[1496]See Ugai, T.; Tanaka, S.; Dokawa, S. *J. Pharm. Soc. Jpn.* ***1943***, *63*, 296 [*Chem. Abstr.* *45*, 5148]; Breslow, R. *J. Am. Chem. Soc.* ***1958***, *80*, 3719; Breslow, R.; Kool, E. *Tetrahedron Lett.* ***1988***, *29*, 1635; Castells, J.; López-Calahorra, F.; Domingo, L. *J. Org. Chem.* ***1988***, *53*, 4433; Diederich, F.; Lutter, H. *J. Am. Chem. Soc.* ***1989***, *111*, 8438. For another catalyst, see Lappert, M.F.; Maskell, R.K. *J. Chem. Soc., Chem. Commun.* ***1982***, 580.

[1497]Stetter, H.; Rämsch, R.Y.; Kuhlmann, H. *Synthesis* ***1976***, 733; Stetter, H.; Kuhlmann, H. *Org. Synth.* ***VII***, 95; Matsumoto, T.; Ohishi, M.; Inoue, S. *J. Org. Chem.* ***1985***, *50*, 603.

[1498]Stetter, H.; Dämbkes, G. *Synthesis* ***1977***, 403.

[1499]Rozwadowska, M.D. *Tetrahedron* ***1985***, *41*, 3135.

[1500]Demir, A.S.; Dünnwald, T.; Iding, H.; Pohl, M.; Müller, M. *Tetrahedron Asymmetry* ***1999***, *10*, 4769.

[1501]Bausch, C.C.; Johnson, J.S. *J. Org. Chem.* ***2004***, *69*, 4283.

16-56 Addition of Radicals to C=O, C=S, C=N Compounds

Radical cyclization is not limited to reaction with a C=C unit (see **15-29** and **15-30**), and reactions with both C=N and C=O moieties are known. Reaction of MeON=CH$(CH_2)_3$CHO with Bu_3SnH and AIBN, for example, led to *trans*-2-(methoxyamino)cyclopentanol in good yield.[1502] Conjugated ketones add to aldehyde via the β-carbon under radical conditions (2 equivalents of Bu_3SnH and 0.1 equivalent of CuCl) to give a β-hydroxy ketone.[1503] Addition of radical to the C=N unit of R—C=N—SPh[1504] or R—C=N—OBz[1505] led to cyclic imines. Radical addition to simple imines leads to aminocycloalkenes.[1506] Radical also add to the carbonyl unit of phenylthio esters to give cyclic ketones.[1507]

N,N-Dimethylaniline reacts with aldehydes under photochemical conditions to give acyl addition via the carbon atom of one of the methyl groups.[1508] The reaction of $PhNMe_2$ and benzaldehyde, for example, gave PhN(Me)CH_2CH(OH)Ph upon photolysis.

ACYL SUBSTITUTION REACTIONS

A. O, N, and S Nucleophiles

16-57 Hydrolysis of Acyl Halides

Hydroxy-de-halogenation

$$\text{RCOCl} + \text{H}_2\text{O} \longrightarrow \text{RCOOH}$$

Acyl halides are so reactive that hydrolysis is easily carried out.[1509] In fact, most simple acyl halides must be stored under anhydrous conditions lest they react with water in the air. Consequently, water is usually a strong enough nucleophile for the reaction, though in difficult cases hydroxide ion may be required. The reaction is seldom synthetically useful, because acyl halides are normally prepared from acids. The reactivity order is $F < Cl < Br < I$.[1510] If a carboxylic acid is used as the nucleophile, an exchange may take place (see **16-79**). The mechanism[1510] of hydrolysis can be either S_N1 or tetrahedral, the former occurring in highly polar solvents

[1502]Tormo, J.; Hays, D.S.; Fu, G.C. *J. Org. Chem.* ***1998***, *63*, 201.

[1503]Ooi, T.; Doda, K.; Sakai, D.; Maruoka, K. *Tetrahedron Lett.* ***1999***, *40*, 2133.

[1504]Boivin, J.; Fouquet, E.; Zard, S.Z. *Tetrahedron* ***1994***, *50*, 1745.

[1505]Boivin, J.; Schiano, A.-M.; Zard, S.Z. *Tetrahedron Lett.* ***1994***, *35*, 249.

[1506]Bowman, W.R.; Stephenson, P.T.; Terrett, N.K.; Young, A.R. *Tetrahedron Lett.* ***1994***, *35*, 6369.

[1507]Kim, S.; Jon, S.Y. *Chem. Commun.* ***1996***, 1335.

[1508]Kim, S.S.; Mah, Y.J.; Kim, A.R. *Tetrahedron Lett.* ***2001***, *42*, 8315.

[1509]See Bentley, T.W.; Shim, C.S. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 1659 for a discussion on the solvolysis of acyl chlorides.

[1510]For a review, see Talbot, R.J.E., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 10; Elsevier, NY, ***1972***, pp. 226–257. For a review of the mechanisms of reactions of acyl halides with water, alcohols, and amines, see Kivinen, A., in Patai, S. *The Chemistry of Acyl Halides*, Wiley, NY, ***1972***, pp. 177–230.

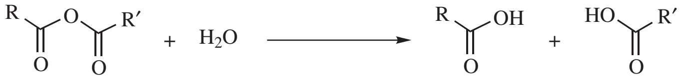
and in the absence of strong nucleophiles.[1511] There is also evidence for the S_N2 mechanism in some cases.[1512]

Hydrolysis of acyl halides is not usually catalyzed by acids, except for acyl fluorides, where hydrogen bonding can assist in the removal of F.[1513] There are several methods available for the hydrolysis of acyl fluorides.[1514]

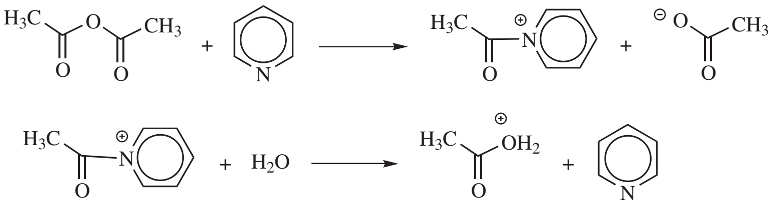
OS **II**, 74.

16-58 Hydrolysis of Anhydrides

Hydroxy-de-acyloxy-substitution



Anhydrides are somewhat more difficult to hydrolyze than acyl halides, but here too water is usually a strong enough nucleophile. The mechanism is usually tetrahedral.[1515] Only under acid catalysis does the S_N1 mechanism occur and seldom even then.[1516] Anhydride hydrolysis can also be catalyzed by bases. Of course, hydroxide ion attacks more readily than water, but other bases can also catalyze the reaction. This phenomenon, called *nucleophilic catalysis* (p. 1258), is actually the result of two successive tetrahedral mechanisms. For example, pyridine catalyzes the hydrolysis of acetic anhydride in this manner.[1517]



Many other nucleophiles similarly catalyze the reaction.

OS **I**, 408; **II**, 140, 368, 382; **IV**, 766; **V**, 8, 813.

[1511] Bender, M.L.; Chen, M.C. *J. Am. Chem. Soc.* ***1963***, *85*, 30. See also, Song, B.D.; Jencks, W.P. *J. Am. Chem. Soc.* ***1989***, *111*, 8470; Bentley, T.W.; Koo, I.S.; Norman, S.J. *J. Org. Chem.* ***1991***, *56*, 1604.

[1512] Bentley, T.W.; Carter, G.E.; Harris, H.C.*J. Chem. Soc. Perkin Trans. 2* ***1985***, 983; Guthrie, J.P.; Pike, D.C. *Can. J. Chem.* ***1987***, *65*, 1951. See also, Lee, I.; Sung, D.D.; Uhm, T.S.; Ryu, Z.H. *J. Chem. Soc. Perkin Trans. 2* ***1989***, 1697.

[1513] Bevan, C.W.L.; Hudson, R.F. *J. Chem. Soc.* ***1953***, 2187; Satchell, D.P.N. *J. Chem. Soc.* ***1963***, 555.

[1514] Motie, R.E.; Satchell, D.P.N.; Wassef, W.N. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 859; ***1993***, 1087.

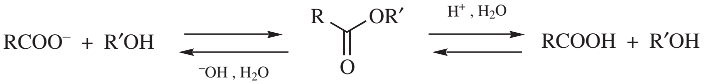
[1515] The kinetics of the acid hydrolysis has been determined. See Satchell, D.P.N.; Wassef, W.N.; Bhatti, Z.A. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 2373.

[1516] Satchell, D.P.N. *Q. Rev. Chem. Soc.* ***1963***, *17*, 160, 172–173. For a review of the mechanism, see Talbot, R.J.E., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 10, Elsevier, NY, ***1972***, pp. 280–287.

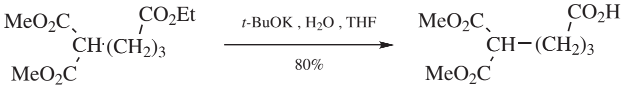
[1517] Butler, A.R.; Gold, V. *J. Chem. Soc.* ***1961***, 4362; Fersht, A.R.; Jencks, W.P. *J. Am. Chem. Soc.* ***1970***, *92*, 5432, 5442; Deady, L.W.; Finlayson, W.L. *Aust. J. Chem.* ***1983***, *36*, 1951.

16-59 Hydrolysis of Carboxylic Esters

Hydroxy-de-alkoxylation



Ester hydrolysis is usually catalyzed by acids or bases. Since OR is a much poorer leaving group than halide or OCOR, water alone does not hydrolyze most esters. When bases catalyze the reaction, the attacking species is the more powerful nucleophile $^{-}$OH. This reaction is called *saponification* and gives the salt of the acid. Acids catalyze the reaction by making the carbonyl carbon more positive and therefore more susceptible to attack by the nucleophile. Both reactions are equilibrium reactions, so they are practicable only when there is a way of shifting the equilibrium to the right. Since formation of the salt does just this, ester hydrolysis is almost always done for preparative purposes in basic solution, unless the compound is base sensitive. Even in the case of **92**, however, selective base hydrolysis of the ethyl ester gave an 80%



92 **93**

yield of the acid-dimethyl ester (**93**).[1518] Ester hydrolysis can also be catalyzed[1519] by metal ions, by cyclodextrins,[1520] by enzymes,[1521] and by nucleophiles.[14] Other reagents used to cleave carboxylic esters include Dowex-50,[1522] Me_3SiI,[1523] and $InCl_3$ on moist silica gel using microwave irradiation.[1524] Cleavage of phenolic esters is usually faster than carboxylic esters derived from aliphatic acids. The reagent Sm/I_2 at $-78°C$ has been used,[1525] ammonium acetate in aqueous methanol,[1526]

[1518]Wilk, B.K. *Synth. Commun.* ***1996***, *26*, 3859.

[1519]For a list of catalysts and reagents that have been used to convert carboxylic esters to acids, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1959-1968.

[1520]See Bender, M.L.; Komiyama, M. *Cyclodextrin Chemistry*, Springer, NY, ***1978***, pp. 34–41. The mechanism is shown in Saenger, W. *Angew. Chem. Int. Ed.* ***1980***, *19*, 344.

[1521]For reviews of ester hydrolysis catalyzed by pig liver esterase, see Zhu, L.; Tedford, M.C. *Tetrahedron* ***1990***, *46*, 6587; Ohno, M.; Otsuka, M. *Org. React.* ***1989***, *37*, 1. For reviews of enzymes as catalysts in synthetic organic chemistry, see Wong, C. *Chemtracts: Org. Chem.* ***1990***, *3*, 91; *Science* ***1989***, *244*, 1145; Whitesides, G.M.; Wong, C. *Angew. Chem. Int. Ed.* ***1985***, *24*, 617. Addition of crown ethers can enhance the rate of hydrolysis, see Itoh, T.; Hiyama, Y.; Betchaku, A.; Tsukube, H. *Tetrahedron Lett.* ***1993***, *34*, 2617.

[1522]Basu, M.K.; Sarkar, D.C.; Ranu, B.C. *Synth. Commun.* ***1989***, *19*, 627.

[1523]See Olah, G.A.; Narang, S.C. *Tetrahedron* ***1982***, *38*, 2225; Olah, G.A.; Husain, A.; Singh, B.P.; Mehrotra, A.K. *J. Org. Chem.* ***1983***, *48*, 3667.

[1524]Ranu, B.C.; Dutta, P.; Sarkar, A. *Synth. Commun.* ***2000***, *30, 4167.*

[1525]Yanada, R.; Negoro, N.; Bessho, K.; Yanada, K. *Synlett* ***1995***, 1261.

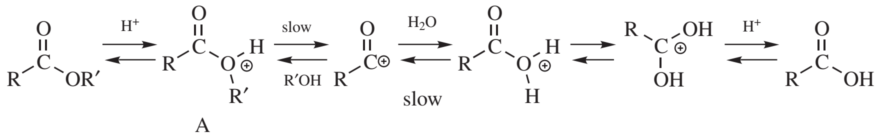
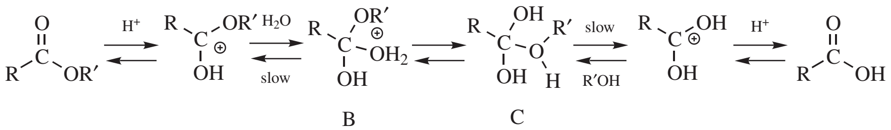
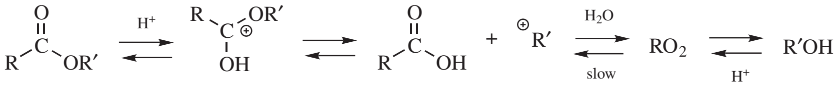
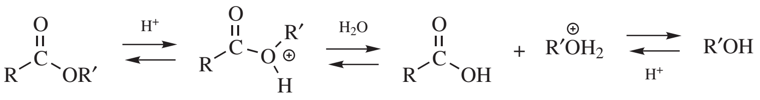
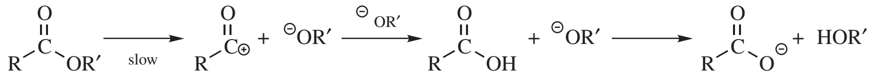
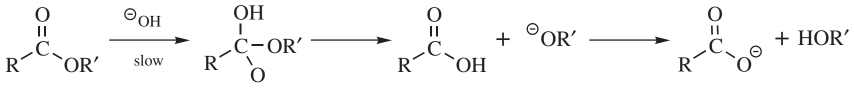
[1526]Ramesh, C.; Mahender, G.; Ravindranath, N.; Das, B. *Tetrahedron* ***2003***, *59*, 1049.

Amberlyst 15 in methanol,[1527] and phenolic esters have been selectively hydrolyzed in the presence of alkyl esters on alumina with microwave irradiation.[1528] Thiophenol with K_2CO_3 in NMP quantitatively converted methyl benzoate to benzoic acid.[1529] Allylic esters were cleaved with 2% Me_3SiOTf in dichloromethane,[1530] with $CeCl_3$•7 H_2O—NaI,[1531] and with $NaHSO_4$•silica gel.[1532] Lactones also undergo the reaction[1533] (though if the lactone is five- or six-membered, the hydroxy acid often spontaneously reforms the lactone) and thiol esters (RCOSR′) give thiols R′SH. Typical reagents for this latter transformation include NaSMe in methanol,[1534] borohydride exchange resin-Pd$(OAc)_2$ for reductive cleavage of thiol esters to thiols,[1535] and $TiCl_4$/Zn for the conversion of phenylthioacetates to thiophenols.[1536] Sterically hindered esters are hydrolyzed with difficulty (p. 479), but reaction of 2 equivalents of *t*-BuOK with 1 equivalent of water is effective.[1537] Hindered esters can also be cleaved by sequential treatment with zinc bromide and then water,[1538] with silica gel in refluxing toluene,[1539] and on alumina when irradiated with microwaves.[1540] For esters insoluble in water the rate of two-phase ester saponification can be greatly increased by the application of ultrasound,[1541] and phase-transfer techniques have been applied.[1542] Enzymatic hydrolysis of diesters with esterase has been shown to give the hydroxy ester,[1543] and selective hydrolysis of dimethyl succinate to monomethyl succinic acid was accomplished with aq. NaOH in THF.[1544] Hydrolysis of vinyl esters leads to ketones, and the reaction of C-substituted vinyl acetates with an esterase derived from *Marchantia polymorpha* gave substituted ketones with high enantioselectivity.[1545] Scandium triflate was shown to hydrolyze α-acetoxy ketones to α-hydroxy ketones.[1546]

[1527]Das, B.; Banerjee, J.; Ramu, R.; Pal, R.; Ravindranath, N.; Ramesh, C. *Tetrahedron Lett.* ***2003***, *44*, 5465.
[1528]Varma, R.S.; Varma, M.; Chatterjee, A.K. *J. Chem. Soc. Perkin Trans. 1* ***1993***, 999; Blay, G.; Cardona, L.; Garcia, B.; Pedro, J.R. *Synthesis* ***1989***, 438.
[1529]Sharma, L.; Nayak, M.K.; Chakraborti, A.K. *Tetrahedron* ***1999***, *55*, 9595.
[1530]Nishizawa, M.; Yamamoto, H.; Seo, K.; Imagawa, H.; Sugihara, T. *Org. Lett.* ***2002***, *4*, 1947.
[1531]Yadav, J.S.; Reddy, B.V.S.; Rao, C.V.; Chand, P.K.; Prasad, A.R. *Synlett* ***2002***, 137.
[1532]Ramesh, C.; Mahender, G.; Ravindranath, N.; Das, B. *Tetrahedron Lett.* ***2003***, *44*, 1465.
[1533]For a review of the mechanisms of lactone hydrolysis, see Kaiser, E.T.; Kézdy, F.J. *Prog. Bioorg. Chem.* ***1976***, *4*, 239, pp. 254–265.
[1534]Wallace, O.B.; Springer, D.M. *Tetrahedron Lett.* ***1998***, *39*, 2693.
[1535]Choi, J.; Yoon, N.M. *Synth. Commun.* ***1995***, *25*, 2655.
[1536]Jin, C.K.; Jeong, H.J.; Kim, M.K.; Kim, J.Y.; Yoon, Y.-J.; Lee, S.-G. *Synlett* ***2001***, 1956.
[1537]Gassman, P.G.; Schenk, W.N. *J. Org. Chem.* ***1977***, *42*, 918.
[1538]Wu, Y.-g.; Limburg, D.C.; Wilkinson, D.E.; Vaal, M.J.; Hamilton, G.S. *Tetrahedron Lett.* ***2000***, *41*, 2847.
[1539]Jackson, R.W. *Tetrahedron Lett.* ***2001***, *42*, 5163.
[1540]Ley, S.V.; Mynett, D.M. *Synlett* ***1993***, 793.
[1541]Moon, S.; Duchin, L.; Cooney, J.V. *Tetrahedron Lett.* ***1979***, 3917.
[1542]Loupy, A.; Pedoussaut, M.; Sansoulet, J. *J. Org. Chem.* ***1986***, *51*, 740.
[1543]Houille, O.; Schmittberger, T.; Uguen, D. *Tetrahedron Lett.* ***1996***, *37*, 625; Nair, R.V.; Shukla, M.R.; Patil, P.N.; Salunkhe, M.M. *Synth. Commun.* ***1999***, *29*, 1671.
[1544]Niwayama, S. *J. Org. Chem.* ***2000***, *65*, 5834.
[1545]Hirata, T.; Shimoda, K.; Kawano, T. *Tetrahedron Asymmetry* ***2000***, *11*, 1063.
[1546]Kajiro, H.; Mitamura, S.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* ***1999***, *72*, 1553.

Ingold[1547] has classified the acid- and base-catalyzed hydrolyses of esters (and the formation of esters, since these are reversible reactions and thus have the same mechanisms) into eight possible mechanisms (Table 16.3), depending on the

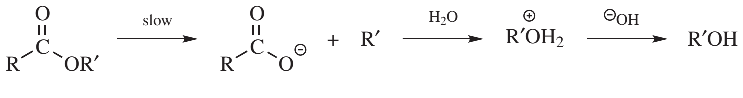
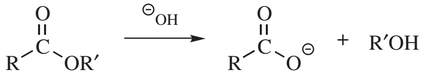
TABLE 16.3. Classification of the Eight Mechanisms for Ester Hydrolysis and Formation[1547]

Name		
Ingold	IUPAC[1548]	Type
$A_{AC}1$	$A_h + D_N + A_N + D_h$	S_N1
		
$A_{AC}2$	$A_h + A_N + A_hD_h + D_h$	Tetrahedral
		
$A_{AL}1$	$A_h + D_N + A_N + D_h$	S_N1
		
$A_{AL}2$	$A_h + A_ND_N + D_h$	S_N2
		
$B_{AC}1$	$D_N + A_N + A_{xh}D_h$	S_N1
		
$B_{AC}2$	$A_N + D_N + A_{xh}D_h$	Tetrahedral
		

[1547]Ingold, C.K. *Structure and Mechanism in Organic Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, ***1969***, pp. 1129–1131.

[1548]As given here, the IUPAC designations for $B_{AC}1$ and $B_{AL}1$ are the same, but Rule A.2 adds further symbols so that they can be distinguished: Su-AL for $B_{AL}1$ and Su-AC for $B_{AC}1$. See the IUPAC rules: Guthrie, R.D. *Pure Appl. Chem.* ***1989***, *61*, 23, see p. 49.

TABLE 16.3. (*Continued*)

Name		
Ingold	IUPAC	Type
$B_{AL}1$	$D_N + A_N + A_{xh}D_h$	S_N1
		
$B_{AL}2$	A_ND_N	S_N2
		

following criteria: (*1*) acid- or base-catalyzed, (*2*) unimolecular or bimolecular, and (*3*) acyl cleavage or alkyl cleavage.[1549] All eight of these are S_N1, S_N2, or tetrahedral mechanisms. The acid-catalyzed mechanisms are shown with reversible arrows. They are not only reversible, but symmetrical; that is, the mechanisms for ester formation are exactly the same as for hydrolysis, except that H replaces R. Internal proton transfers, such as shown for **B** and **C**, may not actually be direct but may take place through the solvent. There is much physical evidence to show that esters are initially protonated on the carbonyl and not on the alkyl oxygen (Chapter 8, Ref. 17). We have nevertheless shown the $A_{AC}1$ mechanism as proceeding through the ether-protonated intermediate **A**, since it is difficult to envision OR′ as a leaving group here. It is of course possible for a reaction to proceed through an intermediate even if only a tiny concentration is present. The designations $A_{AC}1$, and so on., are those of Ingold. The $A_{AC}2$ and $A_{AC}1$ mechanisms are also called A2 and A1, respectively. Note that the $A_{AC}1$ mechanism is actually the same as the S_N1cA mechanism for this type of substrate and that $A_{AL}2$ is analogous to S_N2cA. Some authors use A1 and A2 to refer to all types of nucleophilic substitution in which the leaving group first acquires a proton. The base-catalyzed reactions are not shown with reversible arrows, since they are reversible only in theory and not in practice. Hydrolyses taking place under neutral conditions are classified as B mechanisms.

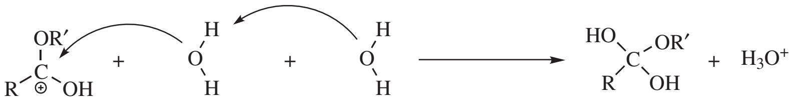
Of the eight mechanisms, seven have actually been observed in hydrolysis of carboxylic esters. The one that has not been observed is the $B_{AC}1$ mechanism.[1550] The most common mechanisms are the $B_{AC}2$ for basic catalysis and the $A_{AC}2$[1551]

[1549]For reviews of the mechanisms of ester hydrolysis and formation, see Kirby, A.J., in Bamford, C.H.; Tipper, C.F.H., *Comprehensive Chemical Kinetics*, Vol. 10, ***1972***, pp. 57–207; Euranto, E.K., in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 505–588.

[1550]This is an S_N1 mechanism with OR′ as leaving group, which does not happen.

[1551]For a discussion of this mechanism with specific attention to the proton transfers involved, see Zimmermann, H.; Rudolph, J. *Angew. Chem. Int. Ed.* ***1965***, *4*, 40.

for acid catalysis, that is, the two tetrahedral mechanisms. Both involve acyl-oxygen cleavage. The evidence is (*1*) hydrolysis with $H_2{}^{18}O$ results in the ^{18}O appearing in the acid and not in the alcohol;[1552] (*2*) esters with chiral R′ groups give alcohols with *retention* of configuration;[1553] (*3*) allylic R′ gives no allylic rearrangement;[1554] (*4*) neopentyl R′ gives no rearrangement;[1555] all these facts indicate that the O—R′ bond is not broken. It has been concluded that two molecules of water are required in the $A_{AC}2$ mechanism.



If this is so, the protonated derivatives **B** and **C** would not appear at all. This conclusion stems from a value of *w* (see p. 371) of ~5, indicating that water acts as a proton donor here, as well as a nucleophile.[1556] Termolecular processes are rare, but in this case the two water molecules are already connected by a hydrogen bond. (A similar mechanism, called $B_{AC}3$, also involving two molecules of water, has been found for esters that hydrolyze without a catalyst.[1557] Such esters are mostly those containing halogen atoms in the R group.)

The other mechanism involving acyl cleavage is the $A_{AC}1$ mechanism. This is rare, being found only where R is very bulky, so that bimolecular attack is sterically hindered, and only in ionizing solvents. The mechanism has been demonstrated for esters of 2,4,6-trimethylbenzoic acid (mesitoic acid). This acid depresses the freezing point of sulfuric acid four times as much as would be predicted from its molecular weight, which is evidence for the equilibrium

$$\text{ArCOOH} + 2\,H_2SO_4 \rightleftharpoons \text{ArCO}^{\oplus} + H_3O^+ + 2\,HSO_4^-$$

In a comparable solution of benzoic acid the freezing point is depressed only twice the predicted amount, indicating only a normal acid-base reaction. Further, a sulfuric acid solution of methyl mesitoate when poured into water gave mesitoic acid, while a similar solution of methyl benzoate similarly treated did not.[1558] The $A_{AC}1$ mechanism is also found when acetates of phenols or of primary alcohols are

[1552]For one of several examples, see Polanyi, M.; Szabo, A.L. *Trans. Faraday Soc.* ***1934***, *30*, 508.
[1553]Holmberg, B. *Ber.* ***1912***, *45*, 2997.
[1554]Ingold, C.K.; Ingold, E.H. *J. Chem. Soc.* ***1932***, 758.
[1555]Norton, H.M.; Quayle, O.R. *J. Am. Chem. Soc.* ***1940***, *62*, 1170.
[1556]Martin, R.B. *J. Am. Chem. Soc.* ***1962***, *84*, 4130. See also, Lane, C.A.; Cheung, M.F.; Dorsey, G.F. *J. Am. Chem. Soc.* ***1968***, *90*, 6492; Yates, K. *Acc. Chem. Res.* ***1971***, *6*, 136; Huskey, W.P.; Warren, C.T.; Hogg, J.L. *J. Org. Chem.* ***1981***, *46*, 59.
[1557]Euranto, E.K.; Kanerva, L.T.; Cleve, N.J. *J. Chem. Soc. Perkin Trans. 2* ***1984***, 2085; Neuvonen, H. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 1141; Euranto, E.K.; Kanerva, L.T. *Acta Chem. Scand. Ser. B* ***1988***, *42* 717.
[1558]Treffers, H.P.; Hammett, L.P. *J. Am. Chem. Soc.* ***1937***, *59*, 1708. For other evidence for this mechanism, see Bender, M.L.; Chen, M.C. *J. Am. Chem. Soc.* ***1963***, *85*, 37.

hydrolyzed in concentrated (>90%) H_2SO_4 (the mechanism under the more usual dilute acid conditions is the normal $A_{AC}2$).[1559]

The mechanisms involving alkyl-oxygen cleavage are ordinary S_N1 and S_N2 mechanisms in which OCOR (an acyloxy group) or its conjugate acid is the leaving group. Two of the three mechanisms, the $B_{AL}1$ and $A_{AL}1$ mechanisms, occur most readily when R′ comes off as a stable carbocation, that is, when R′ is tertiary alkyl, allylic, benzylic, and so on. For acid catalysis, most esters with this type of alkyl group (especially tertiary alkyl) cleave by this mechanism, but even for these substrates, the $B_{AL}1$ mechanism occurs only in neutral or weakly basic solution, where the rate of attack by hydroxide is so slowed that the normally slow (by comparison) unimolecular cleavage takes over. These two mechanisms have been established by kinetic studies, ^{18}O labeling, and isomerization of R′.[1560] Secondary and benzylic acetates hydrolyze by the $A_{AC}2$ mechanism in dilute H_2SO_4, but in concentrated acid the mechanism changes to $A_{AL}1$.[1559] Despite its designation, the $B_{AL}1$ mechanism is actually uncatalyzed (as is the unknown $B_{AC}1$ mechanism).

The two remaining mechanisms, $B_{AL}2$ and $A_{AL}2$, are very rare, the $B_{AL}2$ because it requires hydroxide ion to attack an alkyl carbon when an acyl carbon is also available,[1561] and the $A_{AL}2$ because it requires water to be a nucleophile in an S_N2 process. Both have been observed, however. The $B_{AL}2$ has been seen in the hydrolysis of β-lactones under neutral conditions[1562] (because cleavage of the C—O bond in the transition state opens the four-membered ring and relieves strain), the alkaline hydrolysis of methyl 2,4,6-tri-*tert*-butyl benzoate,[1563] and in the unusual reaction[1564]

$$ArCOOMe + RO^- \longrightarrow ArCOO^- + ROMe$$

When it does occur, the $B_{AL}2$ mechanism is easy to detect, since it is the only one of the base-catalyzed mechanisms that requires inversion at R′. However, in the last example given, the mechanism is evident from the nature of the product, since the ether could have been formed in no other way. The $A_{AL}2$ mechanism has been reported in the acid cleavage of γ-lactones.[1565]

To sum up the acid-catalysis mechanisms, $A_{AC}2$ and $A_{AL}1$ are the common mechanisms, the latter for R′ that give stable carbocations, the former for practically

[1559]Yates, K. *Acc. Chem. Res.* ***1971***, *6*, 136; Al-Shalchi, W.; Selwood, T.; Tillett J.G. *J. Chem. Res. (S)* ***1985***, 10.

[1560]For discussions, see Kirby, A.J., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 86–101; Ingold, C.K. *Structure and Mechanism in Organic Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, ***1969***, pp. 1137–1142, 1157–1163.

[1561]Douglas, J.E.; Campbell, G.; Wigfield, D.C. *Can. J. Chem.* ***1993***, *71*, 1841.

[1562]Cowdrey, W.A.; Hughes, E.D.; Ingold, C.K.; Masterman, S.; Scott, A.D. *J. Chem. Soc.* ***1937***, 1264; Long, F.A.; Purchase, M. *J. Am. Chem. Soc.* ***1950***, *73*, 3267.

[1563]Barclay, L.R.C.; Hall, N.D.; Cooke, G.A. *Can. J. Chem.* ***1962***, *40*, 1981.

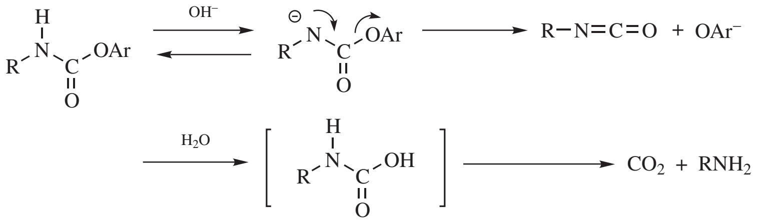
[1564]Sneen, R.A.; Rosenberg, A.M. *J. Org. Chem.* ***1961***, *26*, 2099. See also, Müller, P.; Siegfried, B. *Helv. Chim. Acta* ***1974***, *57*, 987.

[1565]Moore, J.A.; Schwab, J.W. *Tetrahedron Lett.* ***1991***, *32*, 2331.

all the rest. The $A_{AC}1$ mechanism is rare, being found mostly with strong acids and sterically hindered R. The $A_{AL}2$ mechanism is even rarer. For basic catalysis, $B_{AC}2$ is almost universal; $B_{AL}1$ occurs only with R′ that give stable carbocations and then only in weakly basic or neutral solutions; $B_{AL}2$ is very rare; and $B_{AC}1$ has never been observed.

The above results pertain to reactions in solution. In the gas-phase[1566] reactions can take a different course, as illustrated by the reaction of carboxylic esters with MeO^-, which in the gas phase was shown to take place only by the $B_{AL}2$ mechanism,[1567] even with aryl esters,[1568] where this means that an S_N2 mechanism takes place at an aryl substrate. However, when the gas-phase reaction of aryl esters was carried out with MeO^- ions, each of which was solvated with a single molecule of MeOH or H_2O, the $B_{AC}2$ mechanism was observed.[1567]

In the special case of alkaline hydrolysis of *N*-substituted aryl carbamates, there is another mechanism[1569] involving elimination–addition:[1570]



This mechanism does not apply to unsubstituted or *N,N*-disubstituted aryl carbamates, which hydrolyze by the normal mechanisms. Carboxylic esters substituted in the a position by an electron-withdrawing group (e.g., CN or COOEt) can also hydrolyze by a similar mechanism involving a ketene intermediate.[1571]

[1566]Takashima, K.; José, S.M.; do Amaral, A.T.; Riveros, J.M. *J. Chem. Soc., Chem. Commun.* ***1983***, 1255.

[1567]Comisarow, M. *Can. J. Chem.* ***1977***, *55*, 171.

[1568]Fukuda, E.K.; McIver Jr., R.T. *J. Am. Chem. Soc.* ***1979***, *101*, 2498.

[1569]For a review of elimination–addition mechanisms at a carbonyl carbon, see Williams, A.; Douglas, K.T. *Chem. Rev.* ***1975***, *75*, 627649.

[1570]Bender, M.L.; Homer, R.B. *J. Org. Chem.* ***1965***, *30*, 3975; Williams, A. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 808; ***1973***, 1244; Hegarty, A.F.; Frost, L.N. *J. Chem. Soc. Perkin Trans. 2* ***1973***, 1719; Menger, F.M.; Glass, L.E. *J. Org. Chem.* ***1974***, *39*, 2469; Sartoré, G.; Bergon, M.; Calmon, J.P. *J. Chem. Soc. Perkin Trans. 2* ***1977***, 650; Moravcová, J.; Večeřa, M. *Collect. Czech. Chem. Commun.* ***1977***, *42*, 3048; Broxton, T.J.; Chung, R.P. *J. Org. Chem.* ***1986***, *51*, 3112.

[1571]Casanova, J.; Werner, N.D.; Kiefer, H.R. *J. Am. Chem. Soc.* ***1967***, *89*, 2411; Holmquist, B.; Bruice, T.C. *J. Am. Chem. Soc.* ***1969***, *91*, 2993, 3003; Campbell, D.S.; Lawrie, C.W. *Chem. Commun.* ***1971***, 355; Kirby, A.J.; Lloyd, G.J. *J. Chem. Soc. Perkin Trans. 2* ***1976***, 1762; Broxton, T.J.; Duddy, N.W. *J. Org. Chem.* ***1981***, *46*, 1186; Inoue, T.C.; Bruice, T.C. *J. Am. Chem. Soc.* ***1982***, *104*, 1644; *J. Org. Chem.* ***1983***, *48*, 3559; ***1986***, *51*, 959; Alborz, M.; Douglas, K.T. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 331; Thea, S.; Cevasco, G.; Guanti, G.; Kashefi-Naini, N.; Williams, A. *J. Org. Chem.* ***1985***, *50*, 1867; Isaacs, N.S.; Najem, T.S. *Can. J. Chem.* ***1986***, *64*, 1140; *J. Chem. Soc. Perkin Trans. 2* ***1988***, 557.

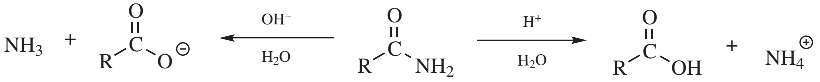
These elimination–addition mechanisms usually are referred to as E1cB mechanisms, because that is the name given to the elimination portion of the mechanism (p. 1488).

The acid-catalyzed hydrolysis of enol esters RCOOCR′=CR can take place either by the normal $A_{AC}2$ mechanism or by a mechanism involving initial protonation on the double-bond carbon, similar to the mechanism for the hydrolysis of enol ethers given in **10-6**,[1572] depending on reaction conditions.[1573] In either case, the products are the carboxylic acid RCOOH and the aldehyde or ketone R–CHCOR′.

OS **I**, 351, 360, 366, 379, 391, 418, 523; **II**, 1, 5, 53, 93, 194, 214, 258, 299, 416, 422, 474, 531, 549; **III**, 3, 33, 101, 209, 213, 234, 267, 272, 281, 300, 495, 510, 526, 531, 615, 637, 652, 705, 737, 774, 785, 809 (but see OS **V**, 1050), 833, 835; **IV**, 15, 55, 169, 317, 417, 444, 532, 549, 555, 582, 590, 608, 616, 628, 630, 633, 635, 804; **V**, 8, 445, 509, 687, 762, 887, 985, 1031; **VI**, 75, 121, 560, 690, 824, 913, 1024; **VII**, 4, 190, 210, 297, 319, 323, 356, 411; **VIII**, 43, 141, 219, 247, 258, 263, 298, 486, 516, 527. Ester hydrolyses with concomitant decarboxylation are listed at reaction **12-40**.

16-60 Hydrolysis of Amides

Hydroxy-de-amination



Unsubstituted amides ($RCONH_2$) can be hydrolyzed with either acidic or basic catalysis, the products being, respectively, the free acid and the ammonium ion or the salt of the acid and ammonia. *N*-Substituted (RCONHR′) and *N,N*-disubstituted ($RCONR''_2$) amides can be hydrolyzed analogously, with the primary or secondary amine, respectively (or their salts), being obtained instead of ammonia. Lactams, imides, cyclic imides, hydrazides, and so on., also undergo the reaction. Water alone is not sufficient to hydrolyze most amides,[1574] since NH_2 is even a poorer leaving group than OR.[1575] Prolonged heating is often required, even with acidic or basic catalysts.[1576] Treatment of primary

[1572]Alkynyl esters also hydrolyze by this mechanism; see Allen, A.D.; Kitamura, T.; Roberts, K.A.; Stang, P.J.; Tidwell, T.T. *J. Am. Chem. Soc.* ***1988***, *110*, 622.

[1573]See, for example, Noyce, D.S.; Pollack, R.M. *J. Am. Chem. Soc.* ***1969***, *91*, 119, 7158; Monthéard, J.; Camps, M.; Chatzopoulos, M.; Benzaïd, A. *Bull. Soc. Chim. Fr.* ***1984***, II-109. For a discussion, see Euranto, E.K. *Pure Appl. Chem.* ***1977***, *49*, 1009.

[1574]See Zahn, D. *Eur. J. Org. Chem.* ***2004***, 4020.

[1575]The very low rate of amide hydrolysis by water alone has been measured: Kahne, D.; Still, W.C. *J. Am. Chem. Soc.* ***1988***, *110*, 7529.

[1576]For a list of catalysts and reagents that have been used to hydrolyze amides, with references, see Larock, R.C. *Comprehensive Organic Transformatinos*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1976–1977. Also see, Bagno, A.; Lovato, G.; Scorrano, G. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 1091.

amides with phthalic anhydride at 250°C and 4 atm gives the carboxylic acid and phthalimide.[1577] The conversion of acylhydrazine derivatives to the corresponding carboxylic acid with PhI(OH)(OTs) and water is a variation of amide hydrolysis.[1578] Hydrolysis of carbamates ($RNHCO_2R$) to the corresponding amine can be categorized in this section. Although the product is an amine and the carboxyl unit fragments, this reaction is simply a variation of amide hydrolysis. Strong acids, such as trifluoroacetic acid (in dichloromethane), are usually employed.[1579] Treatment of *N*-Boc derivatives ($RNHCO_2t$-Bu) with $AlCl_3$[1580] or with aqueous sodium *tert*-butoxide[1581] gave the amine. The by-products of this reaction are typically carbon dioxide and isobutylene.

In difficult cases, nitrous acid, NOCl, N_2O_4,[1582] or a similar compound can be used (unsubstituted amides only[1583]).These reactions involve a diazonium ion (see **13-19**) and are much faster than ordinary hydrolysis; for benzamide the nitrous acid reaction took place 2.5×10^7 times faster than ordinary hydrolysis.[1584] Another procedure for difficult cases involves treatment with aqueous sodium peroxide.[1585] In still another method, the amide is treated with water and *t*-BuOK at room temperature.[1586] The strong base removes the proton from **107**, thus preventing the reaction marked k_{-1}. A kinetic study has been done on the alkaline hydrolyses of *N*-trifluoroacetyl aniline derivatives.[1587] Amide hydrolysis can also be catalyzed by nucleophiles (see p. 1259).

The same framework of eight possible mechanisms that was discussed for ester hydrolysis can also be applied to amide hydrolysis.[1588] Both the acid- and base-catalyzed hydrolyses are essentially irreversible, since salts are formed in both

[1577]Chemat, F. *Tetrahedron Lett.* ***2000***, *41*, 3855.

[1578]Wuts, P.G.M.; Goble, M.P. *Org. Lett.* ***2000***, *2*, 2139.

[1579]Schwyzer, R.; Costopanagiotis, A.; Sieber, P. *Helv. Chim. Acta* ***1963***, *46*, 870.

[1580]Bose, D.S.; Lakshminarayana, V. *Synthesis* ***1999***, 66.

[1581]Tom, N.J.; Simon, W.M.; Frost, H.N.; Ewing, M. *Tetrahedron Lett.* ***2004***, *45*, 905.

[1582]Kim, Y.H.; Kim, K.; Park, Y.J. *Tetrahedron Lett.* ***1990***, *31*, 3893.

[1583]*N*-Substituted amides can be converted to *N*-nitrosoamides, which are more easily hydrolyzable than the orginal amide. For example, see Rull, M.; Serratosa, F.; Vilarrasa, J. *Tetrahedron Lett.* ***1977***, 4549. For another method of hydrolyzing *N*-substituted amides, see Flynn, D.L.; Zelle, R.E.; Grieco, P.A. *J. Org. Chem.* ***1983***, *48*, 2424.

[1584]Ladenheim, H.; Bender, M.L. *J. Am. Chem. Soc.* ***1960***, *82*, 1895.

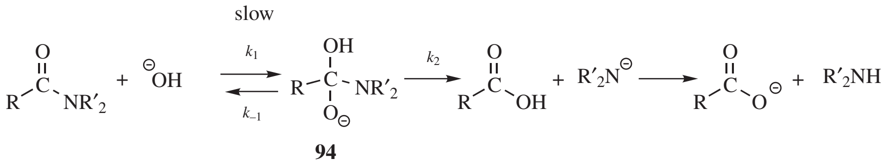
[1585]Vaughan, H.L.; Robbins, M.D. *J. Org. Chem.* ***1975***, *40*, 1187.

[1586]Gassman, P.G.; Hodgson, P.K.G.; Balchunis, R.J. *J. Am. Chem. Soc.* ***1976***, *98*, 1275.

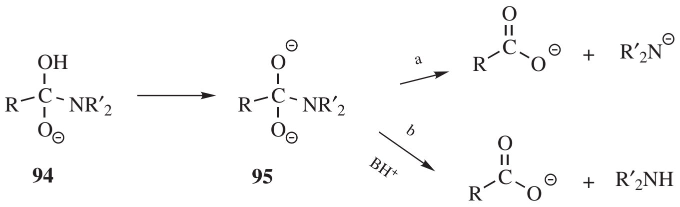
[1587]Hibbert, F.; Malana, M.A. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 755.

[1588]For reviews, see O'Connor, C. *Q. Rev. Chem. Soc.* ***1970***, *24*, 553; Talbot, R.J.E., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 257–280; Challis, B.C.; Challis, J.C., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 731–857.

cases. For basic catalysis,[1589] the mechanism is $B_{AC}2$.



There is much evidence for this mechanism, similar to that discussed for ester hydrolysis. A molecular-orbital study on the mechanism of amide hydrolysis is available.[1590] In certain cases, kinetic studies have shown that the reaction is second order in OH^-, indicating that **94** can lose a proton to give **95**.[1591] Depending on the nature



of R′, **95** can cleave directly to give the two negative ions (path *a*) or become *N*-protonated prior to or during the act of cleavage (path *b*), in which case the products are obtained directly and a final proton transfer is not necessary.[1592] Studies of the effect, on the rate of hydrolysis and on the ratio k_{-1}/k_2, of substituents on the aromatic rings in a series of amides $CH_3CONHAr$ led to the conclusion that path *a* is taken when Ar contains electron-withdrawing substituents and path *b* when electron-donating groups are present.[1593] The presence of electron-withdrawing groups helps stabilize the negative charge on the nitrogen, so that $NR_2'^-$ can be a leaving group (path *a*). Otherwise, the C—N bond does not cleave until the nitrogen is protonated (either prior to or in the act of cleavage), so that the leaving group, *even in the base-catalyzed reaction*, is not $NR_2'^-$ but the conjugate NHR_2'(path *b*). Though we have shown formation of **94** as the rate-determining step in the $B_{AC}2$ mechanism, this is true only at high base concentrations. At lower concentrations of base, the cleavage of **107** or **95** becomes rate determining.[1594]

[1589]For a comprehensive list of references, see DeWolfe, R.H.; Newcomb, R.C. *J. Org. Chem.* ***1971***, *36*, 3870.

[1590]Hori, K.; Kamimura, A.; Ando, K.; Mizumura, M.; Ihara, Y. *Tetrahedron* ***1997***, *53*, 4317.

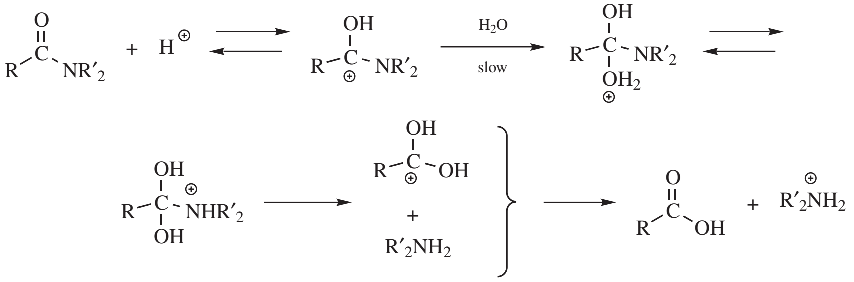
[1591]Biechler, S.S.; Taft, R.W. *J. Am. Chem. Soc.* ***1957***, *79*, 4927. For evidence that a similar intermediate can arise in base-catalyzed ester hydrolysis see Khan, M.N.; Olagbemiro, T.O. *J. Org. Chem.* ***1982***, *47*, 3695.

[1592]Eriksson, S.O. *Acta Chem. Scand.* ***1968***, *22*, 892; *Acta Pharm. Suec.*, ***1969***, *6*, 139.

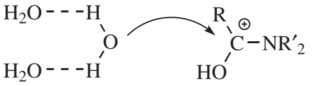
[1593]Schowen, R.L.; Hopper, C.R.; Bazikian, C.M. *J. Am. Chem. Soc.* ***1972***, *94*, 3095. Gani, V.; Viout, P. *Tetrahedron Lett.* ***1972***, 5241; Menger, F.M.; Donohue, J.A. *J. Am. Chem. Soc.* ***1973***, *95*, 432; Pollack, R.M.; Dumsha, T.C. *J. Am. Chem. Soc.* ***1973***, *95*, 4463; Kijima, A.; Sekiguchi, S. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 1203.

[1594]Schowen, R.L.; Jayaraman, H.; Kershner, L. *J. Am. Chem. Soc.* ***1966***, *88*, 3373. See also, Gani, V.; Viout, P. *Tetrahedron* ***1976***, *32*, 1669, 2883; Bowden, K.; Bromley, K. *J. Chem. Soc. Perkin Trans. 2* ***1990***, 2103.

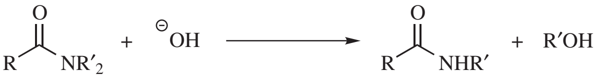
For acid catalysis, matters are less clear. The reaction is generally second order, and it is known that amides are primarily protonated on the oxygen (Chapter 8, Ref. 24). Because of these facts it has been generally agreed that most acid-catalyzed amide hydrolysis takes place by the $A_{AC}2$ mechanism.



Further evidence for this mechanism is that a small but detectable amount of ^{18}O exchange (see p. 1256) has been found in the acid-catalyzed hydrolysis of benzamide.[1595] (^{18}O exchange has also been detected for the base-catalyzed process,[1596] in accord with the $B_{AC}2$ mechanism). Kinetic data have shown that three molecules of water are involved in the rate-determining step,[1597] suggesting that, as in the $A_{AC}2$ mechanism for ester hydrolysis (**16-59**), additional water molecules take part in a process, such as



The four mechanisms involving alkyl—N cleavage (the AL mechanisms) do not apply to this reaction. They are not possible for unsubstituted amides, since the only N—C bond is the acyl bond. They are possible for *N*-substituted and *N,N*-disubstituted amides, but in these cases they give entirely different products and are not amide hydrolyses at all.



[1595]McClelland, R.A. *J. Am. Chem. Soc.* ***1975***, *97*, 5281; Bennet, A.J.; Ślebocka-Tilk, H.; Brown, R.S.; Guthrie, J.P.; Jodhan, A. *J. Am. Chem. Soc.* ***1990***, *112*, 8497.

[1596]Bender, M.L.; Thomas, R.J. *J. Am. Chem. Soc.* ***1961***, *83*, 4183, Bunton, C.A.; Nayak, B.; O'Connor, C. *J. Org. Chem.* ***1968***, *33*, 572; lebocka-Tilk, H.; Bennet, A.J.; Hogg, H.J.; Brown, R.S. *J. Am. Chem. Soc.* ***1991***, *113*, 1288; McClelland, R.A. *J. Am. Chem. Soc.* ***1975***, *97*, 5281; Bennet, A.J.; Ślebocka-Tilk, H.; Brown, R.S.; Guthrie, J.P.; Jodhan, A. *J. Am. Chem. Soc.* ***1990***, *112*, 8497.

[1597]Moodie, R.B.; Wale, P.D.; Whaite, K. *J. Chem. Soc.* ***1963***, 4273; Yates, K.; Stevens, J.B. *Can. J. Chem.* ***1965***, *43*, 529; Yates, K.; Riordan, J.C. *Can. J. Chem.* ***1965***, *43*, 2328.

This reaction, while rare, has been observed for various *N-tert*-butylamides in 98% sulfuric acid, where the mechanism was the $A_{AL}1$ mechanism,[1598] and for certain amides containing an azo group, where a $B_{AL}1$ mechanism was postulated.[1599] Of the two first-order acyl cleavage mechanisms, only the $A_{AC}1$ has been observed, in concentrated sulfuric acid solutions.[1600] Of course, the diazotization of unsubstituted amides might be expected to follow this mechanism, and there is evidence that this is true.[1584]

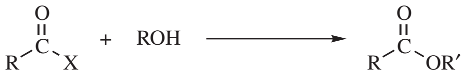
OS **I**, 14, 111, 194, 201, 286; **II**, 19, 25, 28, 49, 76, 208, 330, 374, 384, 457, 462, 491, 503, 519, 612; **III**, 66, 88, 154, 256, 410, 456, 586, 591, 661, 735, 768, 813; **IV**, 39, 42, 55, 58, 420, 441, 496, 664; **V**, 27, 96, 341, 471, 612, 627; **VI**, 56, 252, 507, 951, 967; **VII**, 4, 287; **VIII**, 26, 204, 241, 339, 451.

The oxidation of aldehydes to carboxylic acids can proceed by a nucleophilic mechanism, but more often it does not. The reaction is considered in Chapter 19 (**19-23**). Basic cleavage of β-keto esters and the haloform reaction could be considered at this point, but they are also electrophilic substitutions and are treated in Chapter 12 (**12-43** and **12-44**).

B. Attack by OR at an Acyl Carbon

16-61 Alcoholysis of Acyl Halides

Alkoxy-de-halogenation



The reaction between acyl halides and alcohols or phenols is the best general method for the preparation of carboxylic esters. It is believed to proceed by a S_N2 mechanism.[1601] As with **16-57**, the mechanism can be S_N1 or tetrahedral.[1510] Pyridine catalyzes the reaction by the nucleophilic catalysis route (see **16-58**). Lewis acids such as lithium perchlorate can be used.[1602] The reaction is of wide scope, and many functional groups do not interfere. A base is frequently added to combine with the HX formed. When aqueous alkali is used, this is called the *Schotten–Baumann procedure*, but pyridine is also frequently used. Both R and R′ may be primary, secondary, or tertiary alkyl or aryl. Enol esters can also be prepared by this method, though *C*-acylation competes in these cases. In difficult cases, especially with hindered acids or tertiary R′, the alkoxide can be used instead of the alcohol.[1603] Activated alumina has also been used as a catalyst, for

[1598]Lacey, R.N. *J. Chem. Soc.* ***1960***, 1633; Druet, L.M.; Yates, K. *Can. J. Chem.* ***1984***, *62*, 2401.

[1599]Stodola, F.H. *J. Org. Chem.* ***1972***, *37*, 178.

[1600]Duffy, J.A.; Leisten, J.A. *J. Chem. Soc.* ***1960***, 545, 853; Barnett, J.W.; O'Connor, C.J. *J. Chem. Soc., Chem. Commun.* ***1972***, 525; *J. Chem. Soc. Perkin Trans. 2* ***1972***, 2378.

[1601]Bentley, T.W.; Llewellyn, G.; McAlister, J.A. *J. Org. Chem.* ***1996***, *61*, 7927; Kevill, D.N.; Knauss, D.C. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 307; Fleming, I.; Winter, S.B.D. *Tetrahedron Lett.* ***1993***, *34*, 7287.

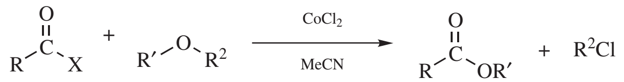
[1602]Bandgar, B.P.; Kamble, V.T.; Sadavarte, V.S.; Uppalla, L.S. *Synlett* ***2002***, 735.

[1603]For an example, see Kaiser, E.M.; Woodruff, R.A. *J. Org. Chem.* ***1970***, *35*, 1198.

tertiary R′.[1604] Thallium salts of phenols give very high yields of phenolic esters,[1605] and BiOCl is very effective for the preparation of phenolic acetates.[1606] Phase-transfer catalysis has been used for hindered phenols.[1607] Zinc has been used to couple alcohols and acyl chlorides,[1608] and catalytic $Cu(acac)_2$ and benzoyl chloride was used to prepare the mono-benzoate of ethylene glycol.[1609] Selective acylation is possible in some cases.[1610]

Acyl halides react with thiols, in the presence of zinc, to give the corresponding thio-ester.[1611] The reaction of acid chlorides or anhydrides (see **16-62**) with diphenyldiselenide, in the presence of $Sm/CoCl_2$[1612] or $Sm/CrCl_3$[1613] gave the corresponding seleno ester (PhSeCOMe).

Acyl halides can also be converted to carboxylic acids by using ethers instead of alcohols, in MeCN in the presence of certain catalysts such as cobalt(II) chloride.[1614] A variation of this reaction has been reported that uses acetic anhydride.[1615]

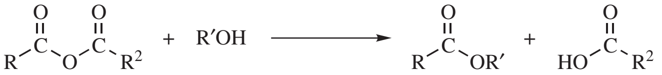


This is a method for the cleavage of ethers (see also, **10-49**).

OS **I**, 12; **III**, 142, 144, 167, 187, 623, 714; **IV**, 84, 263, 478, 479, 608, 616, 788; **V**, 1, 166, 168, 171; **VI**, 199, 259, 312, 824; **VII**, 190; **VIII**, 257, 516.

16-62 Alcoholysis of Anhydrides

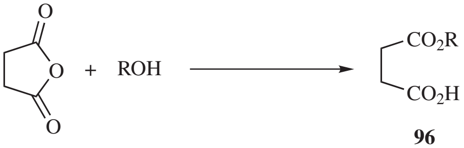
Alkoxy-de-acyloxy-substitution



The scope of this reaction is similar to that of **16-61**. Anhydrides are somewhat less reactive than acyl halides, and they are often used to prepare carboxylic esters. Benzyl acetates have been prepared via microwave irradiation of benzylic alcohols

[1604]Nagasawa, K.; Yoshitake, S.; Amiya, T.; Ito, K. *Synth. Commun.* ***1990***, *20*, 2033.
[1605]Taylor, E.C.; McLay, G.W.; McKillop, A. *J. Am. Chem. Soc.* ***1968***, *90*, 2422.
[1606]Ghosh, R.; Maiti, S.; Chakraborty, A. *Tetrahedron Lett.* ***2004***, *45*, 6775.
[1607]Illi, V.O. *Tetrahedron Lett.* ***1979***, 2431. For another method, see Nekhoroshev, M.V.; Ivakhnenko, E.P.; Okhlobystin, O.Yu. *J. Org. Chem. USSR* ***1977***, *13*, 608.
[1608]Yadav, J.S.; Reddy, G.S.; Svinivas, D.; Himabindu, K. *Synth. Commun.* ***1998***, *28*, 2337.
[1609]Sirkecioglu, O.; Karliga, B.; Talinli, N. *Tetrahedron Lett.* ***2003***, *44*, 8483.
[1610]Srivastava, V.; Tandon, A.; Ray, S. *Synth. Commun.* ***1992***, *22*, 2703.
[1611]Meshram, H.M.; Reddy, G.S.; Bindu, K.H.; Yadav, J.S. *Synlett* ***1998***, 877.
[1612]Chen, R.; Zhang, Y. *Synth. Commun.* ***2000***, *30* , 1331.
[1613]Liu, Y.; Zhang, Y. *Synth. Commun.* ***1999***, *29* , 4043.
[1614]See Ahmad, S.; Iqbal, J. *Chem. Lett.* ***1987***, 953, and references cited therein.
[1615]Lakouraj, M.; Movassaghi, B.; Fasihi, J. *J. Chem. Res. (S)* ***2001***, 378.

and acetic anhydride.[1616] Acids,[1617] Lewis acids,[1618] and bases, such as pyridine are often used as catalysts.[1619] Acetic anhydride and $NiCl_2$ with microwave irradiation converts benzylic alcohols to the corresponding acetate.[1620] The monoacetate of 1,2-diols have been prepared using $CeCl_3$ as a catalyst.[1621] Pyridine is a nucleophilic-type catalyst (see **16-58**). 4-(*N,N*-Dimethylamino)pyridine is a better catalyst and can be used in cases where pyridine fails.[1622] *N*-Bromosuccinimide has been shown to catalyzed esterification of alcohols with acetic anhydride.[1623] Formic anhydride is not a stable compound but esters of formic acid can be prepared by treating alcohols[1624] or phenols[1625] with acetic-formic anhydride. Cyclic anhydrides give mono-esterified dicarboxylic acids, such as **96**.[1626] The asymmetric alcoholysis of cyclic anhydrides has been reviewed.[1627]



96

Alcohols can also be acylated by mixed organic–inorganic anhydrides, such as acetic-phosphoric anhydride, $MeCOOPO(OH)_2$[1628] (see **16-68**). Thioesters of the type ArS(C=O)Me have been prepared from diphenyl disulfide and PBu_3, followed by treatment with acetic anhydride.[1629]

[1616]Bandgar, B.P.; Kasture, S.P.; Kamble, V.T. *Synth. Commun.* ***2001***, *31*, 2255.

[1617]Nafion-H has been used: Kumareswaran, R.; Pachamuthu, K.; Vankar, Y.D. *Synlett* ***2000***, 1652.

[1618]Some of the catalysts used are **Cu(OTf)$_2$**: Saravanan, P.; Singh, V.K. *Tetrahedron Lett.* ***1999***, *40*, 2611. **In(OTf)$_3$**: Barrero, A.F.; Alvarez-Manzaneda, E.J.; Chahboun, R.; Meneses, R. *Synlett* ***1999***, 1663. $InCl_3$: Chakraborti, A.K.; Gulhane, R. *Tetrahedron Lett.* ***2003***, *44*, 6749. **TiCl$_4$**: Chandrasekhar, S.; Ramachandar, T.; Reddy, M.V.; Takhi, M. *J. Org. Chem.* ***2000***, *65*, 4729. **LiClO$_4$:** Nakae, Y.; Kusaki, I.; Sato, T. *Synlett* ***2001***, 1584; **Ce(OTf)$_3$**: Dalpozzo, R.; DeNino, A.; Maiuolo, L.; Procopio, A.; Nardi, M.; Bartoli, G.; Romeo, R. *Tetrahedron Lett.* ***2003***, *44*, 5621. **Yb(OTf)$_3$**: Dumeunier, R.; Markó, I.E. *Tetrahedron Lett.* ***2004***, *45*, 825. **RuCl$_3$**: De, S.K. *Tetrahedron Lett.* ***2004***, *45*, 2919. **Mg(ClO$_4$)$_2$**: Bartoli, G.; Bosco, M.; Dalpozzo, R.; Marcantoni, E.; Massaccesi, M.; Sambri, L. *Eur. J. Org. Chem.* ***2003***, 4611.

[1619]For a list of catalysts, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1955–1957.

[1620]Constantinou-Kokotou, V.; Peristeraki, A. *Synth. Commun.* ***2004***, *34*, 4227.

[1621]Clarke, P.A.; Kayaleh, N.E.; Smith, M.A.; Baker, J.R.; Bird, S.J.; Chan, C. *J. Org. Chem.* ***2002***, *67*, 5226; Clarke, P.A. *Tetrahedron Lett.* ***2002***, *43*, 4761.

[1622]For reviews, see Scriven, E.F.V. *Chem. Soc. Rev.* ***1983***, *12*, 129; Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem. Int. Ed.* ***1978***, *17*, 569.

[1623]Karimi, B.; Seradj, H. *Synlett* ***2001***, 519.

[1624]For example, see Stevens, W.; van Es, A. *Recl. Trav. Chim. Pays-Bas* ***1964***, *83*, 1287; van Es, A.; Stevens, W. *Recl. Trav. Chim. Pays-Bas* ***1965***, *84*, 704.

[1625]For example, see Stevens, W.; van Es, A. *Recl. Trav. Chim. Pays-Bas* ***1964***, *83*, 1294; Sōfuku, S.; Muramatsu, I.; Hagitani, A. *Bull. Chem. Soc. Jpn.* ***1967***, *40*, 2942.

[1626]For conversion of an anhydride to a mono-ester with high enantioselectivity, see Chen, Y.; Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* ***2000***, *122*, 9542.

[1627]Chen, Y.; McDaid, P.; Deng, L. *Chem. Rev.* ***2003***, *103*, 2965.

[1628]Fatiadi, A.J. *Carbohydr. Res.* ***1968***, *6*, 237.

[1629]Ayers, J.T.; Anderson, S.R. *Synth. Commun* ***1999***, *29*, 351. This transformation has also been accomplished with Zn/$AlCl_3$: see Movassagh, B. Lakouraj, M.M.; Fadaei, Z. *J. Chem. Res. (S)* ***2001***, 22.

OS **I**, 285, 418; **II**, 69, 124; **III**, 11, 127, 141, 169, 237, 281, 428, 432, 690, 833; **IV**, 15, 242, 304; **V**, 8, 459, 591, 887; **VI**, 121, 245, 560, 692; 486; **VIII**, 141, 258.

16-63 Esterification of Carboxylic Acids

Alkoxy-de-hydroxylation

$$\text{RCOOH} \quad + \quad \text{R'OH} \quad \overset{\text{H+}}{\rightleftharpoons} \quad \text{RCOOR'} \quad + \quad \text{H}_2\text{O}$$

The esterification of carboxylic acids with alcohols[1630] is the reverse of **16-60** and can be accomplished only if a means is available to drive the equilibrium to the right.[1631] There are many ways of doing this, among which are (*1*) addition of an excess of one of the reactants, usually the alcohol; (*2*) removal of the ester or the water by distillation; (*3*) removal of water by azeotropic distillation; and (*4*) removal of water by use of a dehydrating agent, silica gel,[1632] or a molecular sieve. When R′ is methyl, the most common way of driving the equilibrium is by adding excess MeOH; when R′ is ethyl, it is preferable to remove water by azeotropic distillation.[1633] The most common catalysts are H_2SO_4 and TsOH, although some reactive acids (e.g., formic,[1634] trifluoroacetic[1635]) do not require a catalyst. Ammonium salts have been used to initiate esterification,[1636] and boric acid has been used to esterify α-hydroxy acids.[1637] The R′ group may be primary or secondary alkyl groups other than methyl or ethyl, but tertiary alcohols usually give carbocations and elimination. Phenols can sometimes be used to prepare phenolic esters, but yields are generally very low. Selective esterification of an aliphatic carboxylic acid in the presence of an aromatic acid was accomplished with $NaHSO_4{\bullet}SiO_2$ and methanol.[1638]

Diphenylammonium triflate was useful for direct esterification of carboxylic acids with longer chain aliphatic alcohols.[1639] Photoirradiation of carboxylic acid with CBr_4[1640] or CCl_4[1641] in methanol was shown to give the methyl ester, with high selectivity for nonconjugated acids in the case of CBr_4. *O*-Alkylisoureas react

[1630]For a review of some methods, see Haslam, E. *Tetrahedron* ***1980***, *36*, 2409.

[1631]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1932–1941.

[1632]Nascimento, M.de G.; Zanotto, S.P.; Scremin, M.; Rezende, M.C. *Synth. Commun.* ***1996***, *26*, 2715.

[1633]Newman, M.S. *An Advanced Organic Laboratory Course*; Macmillan, NY, ***1972***, pp. 8–10.

[1634]Formates can be prepared if diisopropyl ether is used to remove water by azeotropic distillation: Werner, W. *J. Chem. Res. (S)* ***1980***, 196. For an alternative synthesis of formate esters using trifluoroethyl formate, see Hill, D.R.; Hsiao, C.-N.; Kurukulasuriya, R.; Wittenberger, S.J. *Org. Lett.* ***2002***, *4*, 111.

[1635]Johnston, B.H.; Knipe, A.C.; Watts, W.E. *Tetrahedron Lett.* ***1979***, 4225.

[1636]Wakasugi, K.; Nakamura, A.; Tanabe, Y. *Tetrahedron Lett.* ***2001***, *42*, 7427; Gacem, B.; Jenner, G. *Tetrahedron Lett.* ***2003***, *44*, 1391.

[1637]Houston, T.A.; Wilkinson, B.L.; Blanchfield, J.T. *Org. Lett.* ***2004***, *6*, 679.

[1638]Das, B.; Venkataiah, B.; Madhsudhan, P. *Synlett* ***2000***, 59.

[1639]Wakasugi, K.; Misaki, T.; Yamada, K.; Tanabe, Y. *Tetrahedron Lett.* ***2000***, *41*, 5249.

[1640]Lee, A.S.-Y.; Yang, H.-C.; Su, F.-Y. *Tetrahedron Lett.* ***2001*** *42*, 301.

[1641]Hwu, J.R.; Hsu, C.-Y.; Jain, M.L. *Tetrahedron Lett.* ***2004*** *45*, 5151.

with conjugated carboxylic acids to give the corresponding ester with microwave irradiation,[1642] and a polymer-bound *O*-alkylurea has been used as well.[1643]

Mixing the carboxylic acid and alcohol with *p*-toluenesulfonic acid (neat), gave the ester in 3 min with microwave irradiation.[1644] Esterification has also been accomplished using ionic liquids as the reaction medium,[1645] and a solid-state esterification was reported on P_2O_5/SiO_2.[1646] Diols are converted to the mono-acetate by heating with acetic acid on a zeolite.[1647]

97

Both γ- and δ-hydroxy acids such as **97** are easily converted to a lactone by treatment with acids, or often simply on standing, but larger and smaller lactone rings cannot be made in this manner, because polyester formation occurs more readily.[1648] Often the conversion of a group, such as keto or halogen, γ or δ to a carboxyl group, to a hydroxyl group gives the lactone directly, since the hydroxy acid cyclizes too rapidly for isolation. β-Substituted β-hydroxy acids can be converted to β-lactones by treatment with benzenesulfonyl chloride in pyridine at 0–5°C.[1649] ε-Lactones (seven-membered rings) have been made by cyclization of ε-hydroxy acids at high dilution.[1650] Macrocyclic lactones[1651] can be prepared indirectly in very good yields by conversion of the hydroxy acids to 2-pyridinethiol esters and adding these to refluxing xylene.[1652] Palladium-catalyzed aromatic carboxylation

[1642]Crosignani, S.; White, P.D.; Linclau, B. *Org. Lett.* ***2002***, *4*, 2961.

[1643]Crosignani, S.; White, P.D.; Steinauer, R.; Linclau, B. *Org. Lett.* ***2003***, *5*, 853; Crosignani, S.; White, P.D.; Linclau, B. *J. Org. Chem.* ***2004***, *69*, 5897.

[1644]Loupy, A.; Petit, A.; Ramdan, M.; Yvanaeff, C.; Majdoub, M.; Labiad, B.; Villemin, D. *Can. J. Chem.* ***1993***, *71*, 90. See also, Zhang, Z.; Zhou, L.; Zhang, M.; Wu, H.; Chen, Z. *Synth. Commun.* ***2001***, *31*, 2435; Fan, X.; Yuan, K.; Hao, C. Li, N.; Tan, G.; Yu, X. *Org. Prep. Proceed. Int.* ***2000***, *32*, 287.

[1645]Isobe, T.; Ishikawa, T. *J. Org. Chem.* ***1999***, *64*, 6984.

[1646]Eshghi, H.; Rafei, M.; Karimi, M.H. *Synth. Commun.* ***2001***, *31*, 771.

[1647]Srinivas, K.V.N.S.; Mahender, I.; Das, B. *Synlett* ***2003***, 2419.

[1648]For a review of the synthesis of lactones and lactams, see Wolfe, J.F.; Ogliaruso, M.A., in Patai, S. *The Chemistry of Acid Derivatives*, pt. 2, Wiley, NY, ***1979***, pp. 1062–1330. For a list of methods for converting hydroxy acids to lactones, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1989***, pp. 1861–1867.

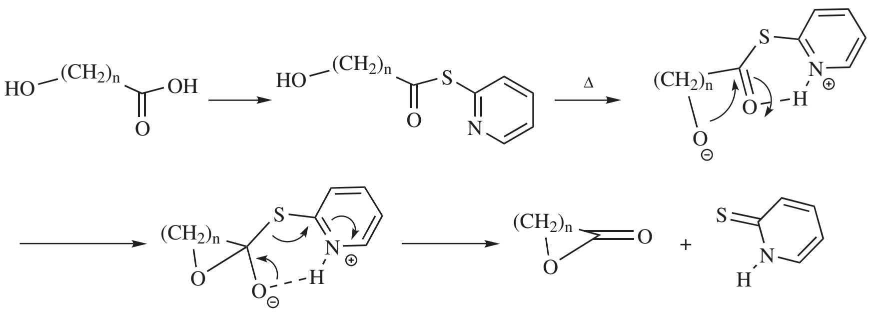
[1649]Adam, W.; Baeza, J.; Liu, J. *J. Am. Chem. Soc.* ***1972***, *94*, 2000. For other methods of converting β-hydroxy acids to β-lactones, see Merger, F. *Chem. Ber.* ***1968***, *101*, 2413; Blume, R.C. *Tetrahedron Lett.* ***1969***, 1047.

[1650]Lardelli, G.; Lamberti,V.; Weller, W.T.; de Jonge, A.P. *Recl. Trav. Chim. Pays-Bas* ***1967***, *86*, 481.

[1651]For reviews on the synthesis of macrocyclic lactones, see Nicolaou, K.C. *Tetrahedron* ***1977***, *33*, 683; Back, T.G. *Tetrahedron* ***1977***, *33*, 3041; Masamune, S.; Bates, G.S.; Corcoran, J.W. *Angew. Chem. Int. Ed.* ***1977***, *16*, 585.

[1652]Corey, E.J.; Brunelle, D.J.; *Tetrahedron Lett.* ***1976***, 3409; Wollenberg, R.H.; Nimitz, J.S.; Gokcek, D.Y. *Tetrahedron Lett.* ***1980***, *21*, 2791; Thalmann, A.; Oertle, K.; Gerlach, H. *Org. Synth.* ***VII***, 470. See also, Schmidt, U.; Heermann, D. *Angew. Chem. Int. Ed.* ***1979***, *18*, 308. For a ruthenium-catalyzed macrocyclization see Trost, B.M.; Chisholm, J.D. *Org. Lett.* ***2002***, *4*, 3743.

reactions generated carboxylic acids *in situ*, and when an alcohol unit is present elsewhere in the molecule cyclization gives the corresponding lactone.[1653]



A closely related method, which often gives higher yields of a macrocyclic lactone, involves treatment of the hydroxy acids with 1-methyl- or 1-phenyl-2-halopyridinium salts, especially 1-methyl-2-chloropyridinium iodide (*Mukaiyama's reagent*).[1654] Another method uses organotin oxides[1655] and both $TiCl_4/AgClO_4$[1656] and $TiCl_2(OSO_2CF_3)_2$[1657] have been used.

Esterification is catalyzed by acids (not bases) in ways that were discussed on p. 1402.[1549] The mechanisms are usually $A_{AC}2$, but $A_{AC}1$ and $A_{AL}1$ have also been observed.[1658] Certain acids, such as 2,6-di-ortho-substituted benzoic acids, cannot be esterified by the $A_{AC}2$ mechanism because of steric hindrance (p. 481). In such cases, esterification can be accomplished by dissolving the acid in 100% H_2SO_4 (forming the ion RCO^+) and pouring the solution into the alcohol ($A_{AC}1$ mechanism). The reluctance of hindered acids to undergo the normal $A_{AC}2$ mechanism can sometimes be put to advantage when, in a molecule containing two COOH groups,

[1653]Kayaki, Y.; Noguchi, Y.; Iwasa, S.; Ikariya, T.; Noyori, R. *Chem. Commun.* ***1999***, 1235.

[1654]For a review of reactions with this and related methods, see Mukaiyama, T. *Angew. Chem. Int. Ed.* ***1979***, *18*, 707. For a polymer-supported Mukaiyama reagent, see Convers, E.; Tye, H.; Whittaker, M. *Tetrahedron Lett.* ***2004***, *45*, 3401.

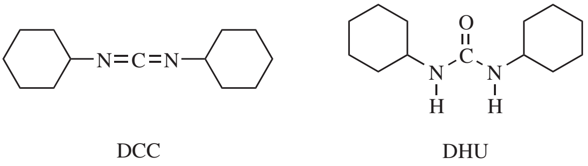
[1655]Steliou, K.; Szczygielska-Nowosielska, A.; Favre, A.; Poupart, M.A.; Hanessian, S. *J. Am. Chem. Soc.* ***1980***, *102*, 7578; Steliou, K.; Poupart, M.A. *J. Am. Chem. Soc.* ***1983***, *105*, 7130. For some other methods, see Masamune, S.; Kamata, S.; Schilling, W. *J. Am. Chem. Soc.* ***1975***, *97*, 3515; Scott, L.T.; Naples, J.O. *Synthesis* ***1976***, 738; Kurihara, T.; Nakajima, Y.; Mitsunobu, O. *Tetrahedron Lett.* ***1976***, 2455; Corey, E.J.; Brunelle, D.J.; Nicolaou, K.C. *J. Am. Chem. Soc.* ***1977***, *99*, 7359; Vorbrüggen, H.; Krolikiewicz, K. *Angew. Chem. Int. Ed.* ***1977***, *16*, 876; Nimitz, J.S.; Wollenberg, R.H. *Tetrahedron Lett.* ***1978***, 3523; Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* ***1979***, *52*, 1989; Venkataraman, K.; Wagle, D.R. *Tetrahedron Lett.* ***1980***, *21*, 1893; Schmidt, U.; Dietsche, M. *Angew. Chem. Int. Ed.* ***1981***, *20*, 771; Taniguchi, N.; Kinoshita, H.; Inomata, K.; Kotake, H. *Chem. Lett.* ***1984***, 1347; Cossy, J.; Pete, J. *Bull. Soc. Chim. Fr.* ***1988***, 989.

[1656]Shiina, I.; Miyoshi, S.; Miyashita, M.; Mukaiyama, T. *Chem. Lett.* ***1994***, 515; Mukaiyama, T.; Izumi, J.; Miyashita, M.; Shiina, I. *Chem. Lett.* ***1993***, 907.

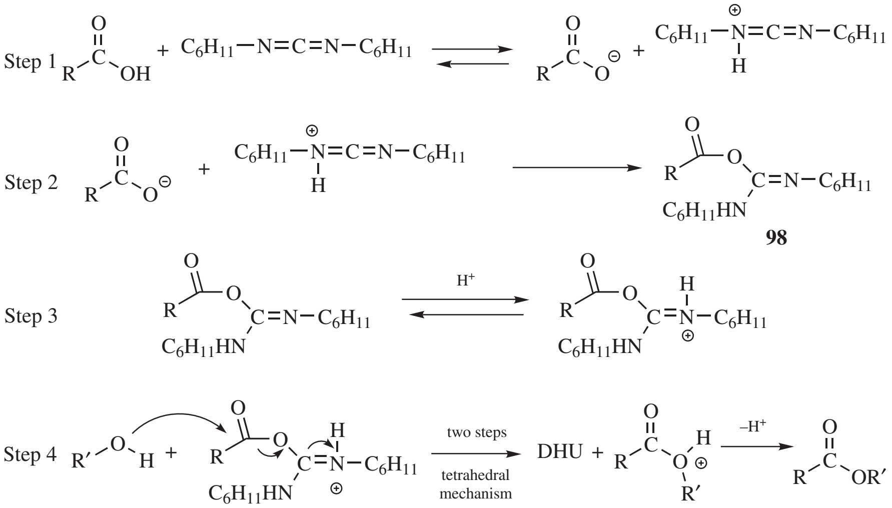
[1657]Hojo, M.; Nagayoshi, M.; Fujii, A.; Yanagi, T.; Ishibashi, N.; Miura, K.; Hosomi, A. *Chem. Lett.* ***1994***, 719.

[1658]For a review of aspects of the mechanism, see Salomaa, P.; Kankaanperä, A.; Pihlaja, K., in Patai, S. *The Chemistry of the Hydroxyl Group, pt. 1*, Wiley, NY, ***1971***, pp. 466–481.

only the less hindered one is esterified. The $A_{AC}1$ pathway cannot be applied to unhindered carboxylic acids.



Another way to esterify a carboxylic acid is to treat it with an alcohol in the presence of a dehydrating agent.[1631] One of these is dicyclohexylcarbodiimide (DCC), which is converted in the process to dicyclohexylurea (DHU). The mechanism[1659] has much in common with the nucleophilic catalysis mechanism; the acid is converted to a compound with a better leaving group. However, the conversion is not by a tetrahedral mechanism (as it is in nucleophilic catalysis), since the C—O bond remains intact during this step:



Evidence for this mechanism was the preparation of *O*-acylureas similar to **98** and the finding that when catalyzed by acids they react with alcohols to give esters.[1660] Hindered tertiary alcohols can be coupled via DCC to give the hindered ester.[1661] A polymer-bound carbodiimide has been used to prepare macrocyclic lactones.[1662] In at least one case, the reaction of $HOOCCH_2CN$ with DCC and *tert*-butanol gave the *tert*-butyl ester via a ketene intermediate.[1663]

[1659]Smith, M.; Moffatt, J.G.; Khorana, H.G. *J. Am. Chem. Soc.* ***1958***, *80*, 6204; Balcom, B.J.; Petersen, N.O. *J. Org. Chem.* ***1989***, *54*, 1922.

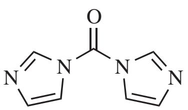
[1660]Doleschall, G.; Lempert, K. *Tetrahedron Lett.* ***1963***, 1195.

[1661]Shimizu, T.; Hiramoto, K.; Nakata, T. *Synthesis* ***2001***, 1027.

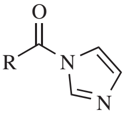
[1662]Keck, G.E.; Sanchez, C.; Wager, C.A. *Tetrahedron Lett.* ***2000***, *41*, 8673.

[1663]Nahmany, M.; Melman, A. *Org. Lett.* ***2001***, *3*, 3733.

There are limitations to the use of DCC; yields are variable and *N*-acylureas are side products. Many other dehydrating agents[1664] have been used, including DCC and an aminopyridine,[1665] Amberlyst-15,[1666] chlorosilanes,[1667] $MeSO_2Cl$-Et_3N,[1668] and *N*,*N*′-carbonyldiimidazole(**99**).[1669] In the latter case, imidazolides (**100**) are intermediates that readily react with alcohols.



99



100

It is known that the Lewis acid BF_3 promotes the esterification by converting the acid to RCO^+—BF_3 ^-OH, so the reaction proceeds by an $A_{AC}1$ type of mechanism. The use of BF_3-etherate is simple and gives high yields.[1670] Other Lewis acids can be used.[1671] Esterification has been done using a LaY zeolite.[1672]

Carboxylic esters can also be prepared by treating carboxylic acids with *tert*-butyl ethers and acid catalysts.[1673]

$$\text{RCOOH} \quad + \quad t\text{-Bu-OR}' \longrightarrow \text{RCOOR}' \quad + \quad \text{H}_2\text{C=CMe}_2 \quad + \text{H}_2\text{O}$$

Carboxylic acids can be converted to *tert*-butyl esters by treatment with *tert*-butyl 2,2,2-trichloroacetimidate (see **10-10**) and BF_3•OEt_2.[1173] Carboxylic esters can be formed from the carboxylate anion and a suitable alkylating agent (**10-26**).

Thioesters of the type RSC(=S)R′ (a dithiocarboxylic ester) and RSC(C=O)R′ (a thiocarboxylic ester) can be generated by reaction of carboxylic acids with thiols.

[1664]For a list of many of these with references, see Arrieta, A.; García, T.; Lago, J.M.; Palomo, C. *Synth. Commun.* ***1983***, *13*, 471.

[1665]Hassner, A.; Alexanian, V. *Tetrahedron Lett.* ***1978***, 4475; Neises, B.; Steglich, W. *Angew. Chem. Int. Ed.* ***1978***, *17*, 522; Boden, E.P.; Keck, G.E. *J. Org. Chem.* ***1985***, *50*, 2394.

[1666]Petrini, M.; Ballini, R.; Marcantoni, E.; Rosini, G. *Synth. Commun.* ***1988***, *18*, 847.

[1667]Nakao, R.; Oka, K.; Fukumoto, T. *Bull. Chem. Soc. Jpn.* ***1981***, *54*, 1267; Brook, M.A.; Chan, T.H. *Synthesis* ***1983***, 201.

[1668]Chandrasekaran, S.; Turner, J.V. *Synth. Commun.* ***1982***, *12*, 727.

[1669]For a review, see Staab, H.A.; Rohr, W. *Newer Methods Prep. Org. Chem.* ***1968***, *5*, 61. See also, Morton, R.C.; Mangroo, D.; Gerber, G.E. *Can. J. Chem.* ***1988***, *66*, 1701.

[1670]For examples, see Marshall, J.L.; Erickson, K.C.; Folsom, T.K. *Tetrahedron Lett.* ***1970***, 4011; Kadaba, P.K. *Synthesis* ***1972***, 628; *Synth. Commun.* ***1974***, *4*, 167.

[1671]Lewis acids used for esterification include **$FeCl_3$**: Sharma, G.V.M.; Mahalingam, A.K.; Nagarajan, M.; Ilangovan, P.; Radhakrishna, P. *Synlett* ***1999***, 1200. **$Hf(Cl_4(thf)_2$:** Ishihara, K.; Nakayama, M.; Ohara, S.;Yamamoto, H. *Synlett* ***2001***, 1117 and Ishihara, K.; Nakayama, M.; Ohara, S.; Yamamoto, H. *Tetrahedron* ***2002***, *58*, 8179; **$Bi(OTf)_3$•*x* H_2O**: Carrigan,. D.; Freiberg, D.A.; Smith, R.C.; Zerth, H.M.; Mohan, R.S. *Synthesis* ***2001***, 2091; **$BiCl_3$**: Mohammadpoor-Baltork, I.; Khosropour, A.R.; Aliyan, H. *J. Chem. Res* ***2001***, 280; **$Fe_2(SO_4)_3$•*x* H_2O**: Zhang, G.-S. *Synth. Commun.* ***1999***, *29*, 607. **Ceric ammonium nitrate**: Pan, W.-B.; Chang, F.-R.; Wei, L.-M.; Wu, M.J.; Wu, Y.-C. *Tetrahedron Lett.* ***2003***, *44*, 331.

[1672]Narender, N.; Srinivasu, P.; Kulkarni, S.J.; Raghavan, K.V. *Synth. Commun.* ***2000***, *30* , 1887.

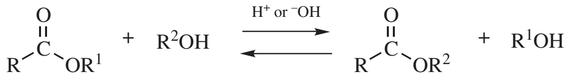
[1673]Derevitskaya, V.A.; Klimov, E.M.; Kochetkov, N.K. *Tetrahedron Lett.* ***1970***, 4269. See also, Mohacsi, E. *Synth. Commun.* ***1982***, *12*, 453.

In one example, phosphorous pentasulfide was used in conjunction with a thiol to make dithiocarboxylic esters[1674] or thiocarboxylic esters.[1675] Thiocarboxylic esters were prepared from thiols and triflic acid.[1676]

OS **I**, 42, 138, 237, 241, 246, 254, 261, 451; **II**, 260, 264, 276, 292, 365, 414, 526; **III**, 46, 203, 237, 381, 413, 526, 531, 610; **IV**, 169, 178, 302, 329, 390, 398, 427, 506, 532, 635, 677; **V**, 80, 762, 946; **VI**, 471, 797; **VII**, 93, 99, 210, 319, 356, 386, 470; **VIII**, 141, 251, 597; **IX**, 24, 58; **75**, 116; **75**, 129. Also see, OS **III**, 536, 742.

16-64 Transesterification

Alkoxy-de-alkoxylation



Transesterification[1677] is catalyzed[1678] by acids[1679] or bases,[1680] or performed under neutral conditions.[1681] It is an equilibrium reaction and must be shifted in the desired direction. In many cases low-boiling esters can be converted to higher boiling ones by the distillation of the lower boiling alcohol as fast as it is formed. Reagents used to catalyze[1682] transesterification include Montmorillonite K10[1683] and various Lewis acids.[1684] A polymer-bound siloxane has been used to induce transesterification.[1685] This reaction has been used as a method for the acylation of a primary OH in the presence of a secondary OH.[1686] Regioselectivity has

[1674]Sudalai, A.; Kanagasabapathy, S.; Benicewicz, B.C. *Org. Lett.* ***2000***, *2*, 3213.

[1675]Curphey, T.J. *Tetrahedron Lett.* ***2002***, *43*, 371.

[1676]Iimura, S.; Manabe, K.; Kobayashi, S. *Chem. Commun.* ***2002***, 94.

[1677]Otera, J. *Chem. Rev.* ***1993***, *93*, 1449.

[1678]For a list of catalysts, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1969–1973.

[1679]Catalysts other than mineral acids can be used, for example, Amberlyst-15 resin. See Chavan, S.P.; Subbarao, Y.T.; Dantale, S.W.; Sivappa, R. *Synth. Commun.* ***2001***, *31*, 289.

[1680]Stanton, M.G.; Gagné, M.R. *J. Org. Chem.* ***1997***, *62*, 8240; Vasin, V.A.; Razin, V.V. *Synlett* ***2001***, 658.

[1681]For some methods of transesterification under neutral conditions, see Otera, J.; Yano, T.; Kawabata, A.; Nozaki, H. *Tetrahedron Lett.* ***1986***, *27*, 2383; Imwinkelried, R.; Schiess, M.; Seebach, D. *Org. Synth.*, *65*, 230; Bandgar, B.P.; Uppalla, L.S.; Sadavarte, V.S. *Synlett* ***2001***, 1715.

[1682]For a review see Grasa, G.A.; Singh, R.; Nolan, S.P. *Synthesis* ***2004***, 971.

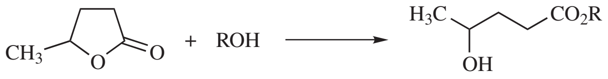
[1683]Ponde, D.E.; Deshpande, V.H.; Bulbule, V.J.; Sudalai, A.; Gajare, A.S. *J. Org. Chem.* ***1998***, *63*, 1058.

[1684]Lewis acids used for this reaction include **$Ti(OEt)_4$**: Krasik, P. *Tetrahedron Lett.* ***1998***, *39*, 4223. **$TlCl_4$**: Mahrwald, R.; Quint, S. *Tetrahedron* ***2000***, *56*, 7463. **$Cu(NO_3)_2$:** Iranpoor, N.; Firouzabadi, H.; Zolfigol, M.A. *Synth. Commun.* ***1998***, *28*, 1923. **$Sn(OTf)_2$**: Mukaiyama, T.; Shiina, I.; Miyashita, M. *Chem. Lett.* ***1992***, 625. **$Yb(OTf)_3$:** Sharma, G.V.M.; Ilangovan, A. *Synlett* ***1999***, 1963. **$LiClO_4$:** Bandgar, B.P.; Sadavarte, V.S.; Uppalla, L.S. *Synlett* ***2001***, 1338. **$FeSO_4$**: Bandgar, B.P.; Sadavarte, V.S.; Uppalla, L.S. *Synth. Commun.* ***2001***, *31*, 2063. **Ceric ammonium nitrate**: Štefane, B.; Kočevar, M.; Polanc, S. *Synth. Commun.* ***2002***, *32*, 1703.

[1685]Hagiwara, H.; Koseki, A.; Isobe, K.; Shimizu, K.-i.; Hoshi, T.; Suzuki, T. *Synlett* ***2004***, 2188.

[1686]Yamada, S. *Tetrahedron Lett.* ***1992***, *33*, 2171. See also, Costa, A.; Riego, J.M. *Can. J. Chem.* ***1987***, *65*, 2327.

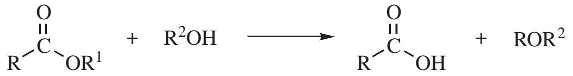
also been accomplished by using enzymes (lipases) as catalysts.[1687] Lactones, such as **101**, are easily opened by treatment with alcohols[1688] to give open-chain hydroxy esters.



101

Transesterification has been carried out with phase-transfer catalysts, without an added solvent.[1689] Nonionic superbases (see p. 365) of the type $P(RNCH_2CH_2)_3N$ catalyze the transesterification of carboxylic acid esters at 25°C.[1690] Silyl esters ($R'CO_2SiR_3$) have been converted to alkyl esters ($R'CO_2R$) via reaction with alkyl halides and tetrabutylammonium fluoride.[1691] Thioesters are converted to phenolic esters by treatment with triphosgene–pyridine and then phenol.[1692]

Transesterification occurs by mechanisms[1693] that are identical with those of ester hydrolysis, except that ROH replaces HOH (by the acyl-oxygen fission mechanisms). When alkyl fission takes place, the products are the *acid* and the *ether*:



Therefore, transesterification reactions frequently fail when R′ is tertiary, since this type of substrate most often reacts by alkyl–oxygen cleavage. In such cases, the reaction is of the Williamson type with OCOR as the leaving group (see **10-10**).

102

With enol esters such as **102**, reaction with an alcohol gives an ester and the enol of a ketone, which readily tautomerizes to the ketone as shown. Hence, enol esters are good acylating agents for alcohols.[1694] This transformation has been

[1687]Wong, C.H.; Whitesides, G. M. in Baldwin, J.E. *Enzymes in Synthetic Organic Chemistry, Tetrahedron Organic Chemistry Series* Vol. 12, Pergamon Press, NY, ***1994***; Faber, K. *Biotransformations in Organic Chemistry. A Textbook*, 2nd ed; Springer-Verlag, NY, ***1995***; Córdova, A.; Janda, K.D. *J. Org. Chem.* ***2001***, *66*, 1906; Ciuffreda, P.; Casati, S.; Santaniello, E. *Tetrahedron Lett.* ***2003***, *44*, 3663.

[1688]Anand, R.C.; Sevlapalam, N. *Synth. Commun.* ***1994***, *24*, 2743.

[1689]Barry, J.; Bram, G.; Petit, A. *Tetrahedron Lett.* ***1988***, *29*, 4567. See also, Nishiguchi, T.; Taya, H. *J. Chem. Soc. Perkin Trans. 1* ***1990***, 172.

[1690]Ilankumaran, P.; Verkade, J.G. *J. Org. Chem.* ***1999***, *64*, 3086.

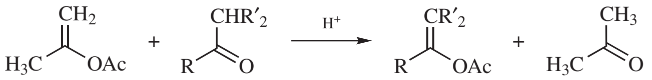
[1691]Ooi, T.; Sugimoto, H.; Maruoka, K. *Heterocycles* ***2001***, *54*, 593.

[1692]Joshi, U.M.; Patkar, L.N.; Rajappa, S. *Synth. Commun.* ***2004***, *34*, 33.

[1693]For a review, see Koskikallio, E.A., in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 103–136.

[1694]Rothman, E.S.; Hecht, S.S.; Pfeffer, P.E.; Silbert, L.S. *J. Org. Chem.* ***1972***, *37*, 3551; Ilankumaran, P.; Verkade, J.G. *J. Org. Chem.* ***1999***, *64*, 9063.

accomplished in ionic liquid media,[1695] and there is a $PdCl_2/CuCl_2$ mediated version.[1696] Isopropenyl acetate can also be used to convert other ketones to the corresponding enol acetates in an exchange reaction:[1697]



Enol esters can also be prepared in the opposite type of exchange reaction, catalyzed by mercuric acetate[1698] or Pd(II) chloride,[1699] for example,

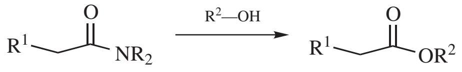
$$\text{RCOOH} + \text{R}'\text{COOCH=CH}_2 \xrightleftharpoons[\text{H}_2\text{SO}_4]{\text{Hg(OAc)}_2} \text{RCOOCH=CH}_2 + \text{R}'\text{COOH}$$

A closely related reaction is equilibration of a dicarboxylic acid and its diester to produce monoesters: The reaction of a carboxylic acid with ethyl acetate, in the presence of $NaHSO_4$•SiO_2, was shown to give the corresponding ethyl ester.[1700] Iodine catalyzes the transesterification of β-keto esters.[1701]

OS **II**, 5, 122, 360; **III**, 123, 146, 165, 231, 281, 581, 605; **IV**, 10, 549, 630, 977; **V**, 155, 545, 863; **VI**, 278; **VII**, 4, 164, 411; **VIII**, 155, 201, 235, 263, 350, 444, 528. See also, OS **VII**, 87; **VIII**, 71.

16-65 Alcoholysis of Amides

Alkoxy-de-amidation



Alcoholysis of amides is possible,[1702] although it is usually difficult. It has been most common with the imidazolide type of amides (e.g., **100**). For other amides, an activating agent is usually necessary before the alcohol will replace the NR_2 unit. Dimethylformamide, however, reacted with primary alcohols in the presence of 2,4,6-trichloro-1,3,5-pyrazine (cyanuric acid) to give the corresponding formate ester.[1703] Treatment of an amide with triflic anhydride ($CF_3SO_2OSO_2CF_3$) in the

[1695]Grasa, G.A.; Kissling, R.M.; Nolan, S.P. *Org. Lett.* ***2002***, *4*, 3583.

[1696]Bosco, J.W.J.; Saikia, A.K. *Chem. Commun.* ***2004***, 1116.

[1697]For examples, see Deghenghi, R.; Engel, C.R. *J. Am. Chem. Soc.* ***1960***, *82*, 3201; House, H.O.; Trost, B.M. *J. Org. Chem.* ***1965***, *30*, 2502.

[1698]For example, see Hopff, H.; Osman, M.A. *Tetrahedron* ***1968***, *24*, 2205, 3887; Mondal, M.A.S.; van der Meer, R.; German, A.L.; Heikens, D. *Tetrahedron* ***1974***, *30*, 4205.

[1699]Henry, P.M. *J. Am. Chem. Soc.* ***1971***, *93*, 3853; *Acc. Chem. Res.* ***1973***, *6*, 16.

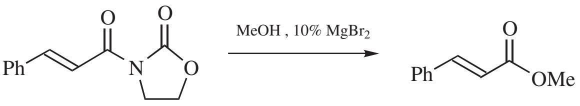
[1700]Das, B.; Venkataiah, B. *Synthesis* ***2000***, 1671.

[1701]Chavan, S.P.; Kale, R.R.; Shivasankar, K.; Chandake, S.I.; Benjamin, S.B. *Synthesis* ***2003***, 2695.

[1702]For example, see Czarnik, A.W. *Tetrahedron Lett.* ***1984***, *25*, 4875. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 197–1978.

[1703]DeLuca, L.; Giacomelli, G.; Porcheddu, A. *J. Org. Chem.* ***2002***, *67*, 5152.

presence of pyridine and then with an excess of alcohol leads to the ester,[1704] as does treatment with $Me_2NCH(OMe)_2$ followed by the alcohol.[1705] Trimethyloxonium tetrafluoroborate converted primary amides to methyl esters.[1706] The reaction of acetanilide derivatives with sodium nitrite in the presence of acetic anhydride–acetic acid leads to phenolic acetates.[1707] Acyl hydrazides ($RCONHNH_2$) were converted to esters by reaction with alcohols and various reagents,[1708] and methoxyamides (RCONHOMe) were converted to esters with $TiCl_4$/ROH.[1709] The reaction of an oxazolidinone amide **103** with methanol and 10% $MgBr_2$ gave the corresponding methyl ester.[1710]



103

C. Attack by OCOR at an Acyl Carbon

16-66 Acylation of Carboxylic Acids With Acyl Halides

Acyloxy-de-halogenation

$$RCOCl \quad + \quad R'COO^- \longrightarrow RCOOCOR'$$

Unsymmetrical, as well as symmetrical, anhydrides are often prepared by the treatment of an acyl halide with a carboxylic acid salt. Cobalt(II) chloride ($CoCl_2$) has been used as a catalyst.[1711] If a metallic salt is used, Na^+, K^+, or Ag^+ are the most common cations, but more often pyridine or another tertiary amine is added to the free acid and the resulting salt is subsequently treated with the acyl halide. Mixed formic anhydrides are prepared from sodium formate and an aryl halide, by use of a solid-phase copolymer of pyridine-1-oxide.[1712] Symmetrical anhydrides can be prepared by reaction of the acyl halide with aq. NaOH or

[1704]Charette, A.B.; Chua, P. *Synlett* ***1998***, 163.
[1705]Anelli, P.L.; Brocchetta, M.; Palano, D.; Visigalli, M. *Tetrahedron Lett.* ***1997***, *38*, 2367.
[1706]Kiessling, A.J.; McClure, C.K. *Synth. Commun.* ***1997***, *27*, 923.
[1707]Glatzhofer, D.T.; Roy, R.R.; Cossey, K.N. *Org. Lett.* ***2002***, *4*, 2349.
[1708]Prakash, O.; Sharma, V.; Sadana, A. *J. Chem. Res. (S)* ***1996***, 100; Štefane, B.; Koevar, M.; Polanc, S. *Tetrahedron Lett.* ***1999***, *40*, 4429; Yamaguchi, J.-i.; Aoyagi, T.; Fujikura, R.; Suyama, T. *Chem. Lett.* ***2001***, 466.
[1709]Fisher, L.E.; Caroon, J.M.; Stabler, S.R.; Lundberg, S.; Zaidi, S.; Sorensen, C.M.; Sparacino, M.L.; Muchowski, J.M. *Can. J. Chem.* ***1994***, *72*, 142.
[1710]Orita, A.; Nagano, Y.; Hirano, J.; Otera, J. *Synlett* ***2001***, 637.
[1711]Srivastava, R.R.; Kabalka, G.W. *Tetrahedron Lett.* ***1992***, *33*, 593.
[1712]Fife, W.K.; Zhang, Z. *J. Org. Chem.* ***1986***, *51*, 3744. See also, Fife, W.K.; Zhang, Z., *Tetrahedron Lett.* ***1986***, *27*, 4933, 4937. For a review of acetic formic anhydride see Strazzolini, P.; Giumanini, A.G.; Cauci, S. *Tetrahedron* ***1990***, *46* 1081.

$NaHCO_3$ under phase-transfer conditions,[1713] or with sodium bicarbonate with ultrasound.[1714]

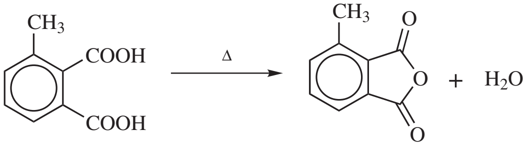
OS **III**, 28, 422, 488; **IV**, 285; **VI**, 8, 910; **VIII**, 132. See also, OS **VI**, 418.

16-67 Acylation of Carboxylic Acids With Carboxylic Acids

Acyloxy-de-hydroxylation

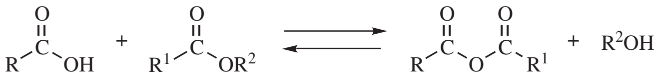
$$2\ RCOOH \xrightleftharpoons{P_2O_5} (RCO)_2O + H_2O$$

Anhydrides can be formed from two molecules of an ordinary carboxylic acid only if a dehydrating agent is present so that the equilibrium can be driven to the right. Common dehydrating agents[1715] are acetic anhydride, trifluoroacetic anhydride, dicyclohexylcarbodiimide,[1716] and P_2O_5. Triphenylphosphine/CCl_3CN with triethylamine has also been used with benzoic acid derivatives.[1717] The method is very poor for the formation of mixed anhydrides, which in any case generally undergo disproportionation to the two simple anhydrides when they are heated. However, simple heating of dicarboxylic acids does give cyclic anhydrides, provided that the ring formed contains five, six, or seven members, for example,



Malonic acid and its derivatives, which would give four-membered cyclic anhydrides, do not give this reaction when heated but undergo decarboxylation (**12-40**) instead.

Carboxylic acids exchange with amides and esters; these methods are sometimes used to prepare anhydrides if the equilibrium can be shifted, for example,



[1713]Plusquellec, D.; Roulleau, F.; Lefeuvre, M.; Brown, E. *Tetrahedron* ***1988***, *44*, 2471; Wang, J.; Hu, Y.; Cui, W. *J. Chem. Res. (S)* ***1990***, 84.

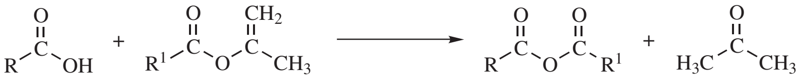
[1714]Hu, Y.; Wang, J.-X.; Li, S. *Synth. Commun.* ***1997***, *27*, 243.

[1715]For lists of other dehydrating agents with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1930–1932; Ogliaruso, M.A.; Wolfe, J.F., in Patai, S. *The Chemistry of Acid Derivatives*, pt.1, Wiley, NY, ***1979***, pp. 437–438.

[1716]For example, see Schüssler, H.; Zahn, H. *Chem. Ber.* ***1962***, *95*, 1076; Rammler, D.H.; Khorana, H.G. *J. Am. Chem. Soc.* ***1963***, *85*, 1997. See also, Hata, T.; Tajima, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* ***1968***, *41*, 2746.

[1717]Kim, J.; Jang, D.O. *Synth. Commun.* ***2001***, *31*, 395.

Enolic esters are especially good for this purpose, because the equilibrium is shifted by formation of the ketone.



The combination of KF with 2-acetoxypropene under microwave conditions was effective.[1718] Carboxylic acids also exchange with anhydrides; indeed, this is how acetic anhydride acts as a dehydrating agent in this reaction.

Anhydrides can be formed from certain carboxylic acid salts; for example, by treatment of trimethylammonium carboxylates with phosgene:[1719]

$$2\,RCO\overset{\ominus}{O}\;\;\overset{\oplus}{N}HEt_3 \xrightarrow{COCl_2} RCOOCOR \;+\; 2\,\overset{\oplus}{N}HEt_3\;\;Cl^{\ominus} \;+\; CO_2$$

or of thallium(I) carboxylates with thionyl chloride,[1605] or of sodium carboxylates with CCl_4 and a catalyst such as CuCl or $FeCl_2$.[1720]

OS **I**, 91, 410; **II**, 194, 368, 560; **III**, 164, 449; **IV**, 242, 630, 790; **V**, 8, 822; **IX**, 151. Also see, OS **VI**, 757; **VII**, 506.

16-68 Preparation of Mixed Organic–Inorganic Anhydrides

Nitrooxy-de-acyloxy-substitution

$$(RCO)_2O \;+\; HONO_2 \longrightarrow RCOONO_2$$

Mixed organic–inorganic anhydrides are seldom isolated, though they are often intermediates when acylation is carried out with acid derivatives catalyzed by inorganic acids. Sulfuric, perchloric, phosphoric, and other acids form similar anhydrides, most of which are unstable or not easily obtained because the equilibrium lies in the wrong direction. These intermediates are formed from amides, carboxylic acids, and esters, as well as anhydrides. Organic anhydrides of phosphoric acid are more stable than most others and, for example, $RCOOPO(OH)_2$ can be prepared in the form of its salts.[1721] Mixed anhydrides of carboxylic and sulfonic acids ($RCOOSO_2R'$) are obtained in high yields by treatment of sulfonic acids with acyl halides or (less preferred) anhydrides.[1722]

OS **I**, 495; **VI**, 207; **VII**, 81.

[1718]Villemin, D.; Labiad, B.; Loupy, A. *Synth. Commun.* ***1993***, *23*, 419.

[1719]Rinderknecht, H.; Ma, V. *Helv. Chim. Acta* ***1964***, *47*, 152. See also, Nangia, A.; Chandrasekaran, S. *J. Chem. Res. (S)* ***1984***, 100.

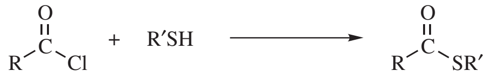
[1720]Weiss, J.; Havelka, F.; Nefedov, B.K. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1978***, *27*, 193.

[1721]Avison, A.W.D. *J. Chem. Soc.* ***1955***, 732.

[1722]Karger, M.H.; Mazur, Y. *J. Org. Chem.* ***1971***, *36*, 528.

16-69 Attack by SH or SR at an Acyl Carbon[1723]

Mercapto-de-halogenation



Alkylthio-de-halogenation

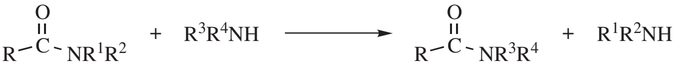
Thiol acids and thiol esters[1724] can be prepared in this manner, which is analogous to **16-57** and **16-64**. Anhydrides[1725] and aryl esters (RCOOAr)[1726] are also used as substrates, but the reagents in these cases are usually HS^- and RS^-. Thiol esters can also be prepared by treatment of carboxylic acids with P_4S_{10}—Ph_3SbO,[1727] or with a thiol RSH and either polyphosphate ester or phenyl dichlorophosphate $PhOPOCl_2$.[1728] Esters RCOOR′ can be converted to thiol esters $RCOSR^2$ by treatment with trimethylsilyl sulfides Me_3SiSR^2 and $AlCl_3$.[1729]

Alcohols, when treated with a thiol acid and zinc iodide, give thiol esters (R′COSR)[1730]

OS **III**, 116, 599; **IV**, 924, 928; **VII**, 81; **VIII**, 71.

16-70 Transamidation

Alkylamino-de-amidation



It is sometimes necessary to replace one amide group with another, particularly when the group attached to nitrogen functions as a protecting group[1731] *N*-Benzyl amides can be converted to the corresponding *N*-allyl amide with allylamine and titanium catalysts.[1732] Reaction of *N*-Boc 2-phenylethylamine (Boc = *tert*-butoxy carbonyl) with $Ti(OiPr)_4$ and benzyl alcohol, for example, gives the *N*-Cbz derivative (Cbz = carbobenzoylcarbonyl).[1733] *N*-Carbamoyl amines were converted to

[1723]For a review, see Satchell, D.P.N. *Q. Rev. Chem. Soc.* ***1963***, *17*, 160, pp. 182–184.

[1724]For a review of these compounds, see Scheithauer, S.; Mayer, R. *Top. Sulfur Chem.* ***1979***, *4*, 1.

[1725]Ahmad, S.; Iqbal, J. *Tetrahedron Lett.* ***1986***, *27*, 3791.

[1726]Hirabayashi, Y.; Mizuta, M.; Mazume, T. *Bull. Chem. Soc. Jpn.* ***1965***, *38*, 320.

[1727]Nomura, R.; Miyazaki, S.; Nakano, T.; Matsuda, H. *Chem. Ber.* ***1990***, *123*, 2081.

[1728]Imamoto, T.; Kodera, M.; Yokoyama, M. *Synthesis* ***1982***, 134; Liu, H.; Sabesan, S.I. *Can. J. Chem.* ***1980***, *58*, 2645. For other methods of converting carboxylic acids to thiol esters, see the references given in these papers. See also, Dellaria, Jr., F.F.; Nordeen, C.; Swett, L.R. *Synth. Commun.* ***1986***, *16*, 1043.

[1729]Mukaiyama, T.; Takeda, T.; Atsumi, K. *Chem. Lett.* ***1974***, 187. See also, Hatch, R.P.; Weinreb, S.M. *J. Org. Chem.* ***1977***, *42*, 3960; Cohen, T.; Gapinski, R.E. *Tetrahedron Lett.* ***1978***, 4319.

[1730]Gauthier, J.Y.; Bourdon, F.; Young, R.N. *Tetrahedron Lett.* ***1986***, *27*, 15.

[1731]See, for example, Swain, C.G.; Ketley, A.D.; Bader, R.F.W. *J. Am. Chem. Soc.* ***1959***, *81*, 2353; Knipe, A.C. *J. Chem. Soc. Perkin Trans. 2* ***1973***, 589.

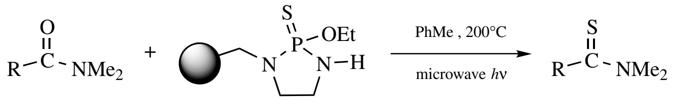
[1732]Eldred, S.E.; Stone, D.A.; Gellman, S.H.; Stahl, S.S. *J. Am. Chem. Soc.* ***2003***, *125*, 3422.

[1733]Shapiro, G.; Marzi, M. *J. Org. Chem.* ***1997***, *62*, 7096.

N-acetyl amines with acetic anhydride, Bu_3SnH, and $Pd(PPh_3)_4$.[1734] Triethylaluminum converts methyl carbamates ($ArNHCO_2Me$) to the corresponding propanamide.[1735]

A related process reacts acetamide with amines and aluminum chloride to give the *N*-acetyl amine.[1736] Another related process converted imides to *O*-benzyloxy amides by the samarium-catalyzed reaction with *O*-benzylhydroxylamine.[1737]

Thioamides can be prepared from amide by reaction with an appropriate sulfur reagent. The reaction of *N,N*-dimethylacetamide under microwave irradiation, with the polymer-bound reagent **104** gave **105**.[1738] Reaction of the thioamide with $Bi(NO_3)_3$•5 H_2O converts regenerates the amide.[1739] Oxone® and a thioamide, on the solid-phase, regenerates the amide.[1740] Selenoamides (RC(=Se)NR$'_2$ have also been prepared from amides.[1741]



104 **105**

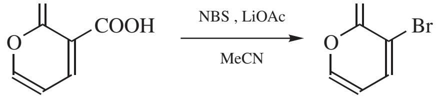
D. Attack by Halogen

16-71 The Conversion of Carboxylic Acids to Halides

Halo-de-oxido,oxo-tersubstitution

$$\text{RCOOH} \longrightarrow \text{R–X}$$

In certain cases, carboxyl groups can be replaced by halide. Acrylic acid derivatives ArCH=CHCOOH, for example, react with 3 equivalents of Oxone in the presence of NaBr to give a vinyl bromide ArCH=CHBr.[1742] In other cases, conjugated acids, such as, **106**, have been converted to the bromide by reaction with *N*-bromosuccinimide (NBS, p. 962) and LiOAc.[1743]



106

[1734]Roos, E.C.; Bernabé, P.; Hiemstra, H.; Speckamp, W.N.; Kaptein, B.; Boesten, W.H.J. *J. Org. Chem.* ***1995***, *60*, 1733.
[1735]El Kaim, L.; Grimaud, L.; Lee, A.; Perroux, Y.; Tiria, C. *Org. Lett.* ***2004***, *6*, 381.
[1736]Bon, E.; Bigg, D.C.H.; Bertrand, G. *J. Org. Chem.* ***1994***, *59*, 4035.
[1737]Sibi, M.P.; Hasegawa, H.; Ghorpade, S.R. *Org. Lett.* ***2002***, *4*, 3343.
[1738]Ley, S.V.; Leach, A.G.; Storer, R.I. *J. Chem. Soc. Perkin Trans. 1* ***2001***, 358.
[1739]Mohammadpoor-Baltork, I.; Khodaei, M.M.; Nikoofar, K. *Tetrahedron Lett.* ***2003***, *44*, 591.
[1740]Mohammadpoor-Baltork, I.; Sadeghi, M.M.; Esmayilpour, K. *Synth. Commun.* ***2003***, *33*, 953.
[1741]Saravanan, V.; Mukherjee, C.; Das, S.; Chandrasekaran, S. *Tetrahedron Lett.* ***2004***, *45*, 681.
[1742]You, H.-W.; Lee, K.-J. *Synlett* ***2001***, 105.
[1743]Cho, C.-G.; Park, J.-S.; Jung, I.-H.; Lee, H. *Tetrahedron Lett.* ***2001***, *42*, 1065.

E. Attack by Nitrogen at an Acyl Carbon[1744]

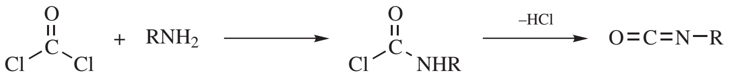
16-72 Acylation of Amines by Acyl Halides

Amino-de-halogenation

$$\text{RCOX} + \text{NH}_3 \longrightarrow \text{RCONH}_2 + \text{HX}$$

The treatment of acyl halides with ammonia or amines is a very general reaction for the preparation of amides.[1745] The reaction is highly exothermic and must be carefully controlled, usually by cooling or dilution. Ammonia gives unsubstituted amides, primary amines give *N*-substituted amides,[1746] and secondary amines give *N,N*-disubstituted amides. Arylamines can be similarly acylated. Hydroxamic acids have been prepared by this route.[1747] In some cases, aqueous alkali is added to combine with the liberated HCl. This is called the *Schotten–Baumann procedure*, as in **16-61**. Activated zinc can be used to increase the rate of amide formation when hindered amines and/or acid chlorides are used.[1748] An indium-mediated amidation reaction[1749] and a BiOCl-mediated reaction[1750] have been reported. A variation of this basic reaction uses DMF with acyl halides to give *N,N*-dimethylamides.[1751] A solvent-free reaction was reported using DABCO and methanol.[1752]

Hydrazine and hydroxylamine also react with acyl halides to give, respectively, hydrazides ($RCONHNH_2$)[1753] and hydroxamic acids (RCONHOH).[1754] When phosgene is the acyl halide, both aliphatic and aromatic primary amines give chloroformamides (ClCONHR) that lose HCl to give isocyanates (RNCO).[1755] This is one of the most common methods for



[1744]For a review, see Challis, M.S.; Butler, A.R., in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, pp. 279–290.

[1745]For a review, see Beckwith, A.L.J., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 73–185. See Jedrzejczak, M.; Motie, R.E.; Satchell, D.P.N. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 599 for a discussion of the kinetics of this reaction.

[1746]See Bhattacharyya, S.; Gooding, O.W.; Labadie, J. *Tetrahedron Lett.* ***2003***, *44*, 6099.

[1747]Reddy, A.S.; Kumar, M.S.; Reddy, G.R. *Tetrahedron Lett.* ***2000***, *41*, 6285.

[1748]Meshram, H.M.; Reddy, G.S.; Reddy, M.M.; Yadav, J.S. *Tetrahedron Lett.* ***1998***, *39*, 4103.

[1749]Cho, D.H.; Jang, D.O. *Tetrahedron Lett.* ***2004***, *45*, 2285.

[1750]Ghosh, R.; Maiti, S.; Chakraborty, A. *Tetrahedron Lett.* ***2004***, *45*, 6775.

[1751]Lee, W.S.; Park, K.H.; Yoon, Y-J. *Synth. Commun.* ***2000***, *30*, 4241.

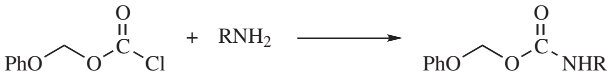
[1752]Hajipour, A.R.; Mazloumi, Gh. *Synth. Commun.* ***2002***, *32*, 23.

[1753]For a review of hydrazides, see Paulsen, H.; Stoye, D., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 515–600.

[1754]For an improved method, see Ando, W.; Tsumaki, H. *Synth. Commun.* ***1983***, *13*, 1053.

[1755]For reviews of the preparation and reactions of isocyanates and isothiocyanates, see, respectively, the articles by Richter, R.; Ulrich, H. pp. 619–818, and Drobnica, L.; Kristián, P.; Augustín, J. pp. 1003–1221, in Patai S. *The Chemistry of Cyanates and Their Thio Derivatives*, pt. 2, Wiley, NY, ***1977***.

the preparation of isocyanates.[1756] Thiophosgene,[1757] similarly treated, gives isothiocyanates. A safer substitute for phosgene in this reaction is trichloromethyl chloroformate CCl_3OCOCl.[1758] When chloroformates ROCOCl are treated with primary amines, carbamates ROCONHR′ are obtained.[1759] An example of this reaction is the use of benzyl chloroformate to protect the amino group of amino acids and peptides.



107

The $PhCH_2OCO$ group in **107** is called the carbobenzoxy group,[1760] and is often abbreviated Cbz or Z. Another important group similarly used is the *tert*-butoxycarbonyl group Me_3COCO, abbreviated as Boc. In this case, the chloride ($Me_3COCOCl$) is unstable, so the anhydride, $(Me_3COCO)_2O$, is used instead, in an example of **16-73**. Amino groups in general are often protected by conversion to amides.[1761] The treatment of acyl halides with lithium nitride gives *N,N*-diacyl amides (triacylamines), **108**.[1762] The reactions proceed by the tetrahedral mechanism.[1763]

$$3\,RCOCl \;+\; Li_3N \longrightarrow (RCO)_3N$$

108

A novel variation of this reaction uses nitrogen gas as the nitrogen source in the amide. The reaction of benzoyl chloride with $TiCl_4/Li/Me_3SiCl/CsF$ and N_2, gave a 77% yield of benzamide.[1764]

An interesting variation of this transformation reacts carbamoyl chlorides with organocuprates to give the corresponding amide.[1765]

[1756]For examples, see Ozaki, S. *Chem. Rev.* ***1972***, *72*, 457, see pp. 457–460. For a review of the industrial preparation of isocyanates by this reaction, see Twitchett, H.J. *Chem. Soc. Rev.* ***1974***, *3*, 209.

[1757]For a review of thiophosgene, see Sharma, S. *Sulfur Rep.* ***1986***, *5*, 1.

[1758]Kurita, K.; Iwakura, Y. *Org. Synth.* ***VI***, 715.

[1759]For example see Ariza, X.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* ***1999***, *40*, 7515. See also, Mormeneo, D.; Llebaria, A.; Delgado, A. *Tetrahedron Lett.* ***2004***, *45*, 6831. For a variation involving azide and a palladium catalyst, see Okumoto, H.; Nishihara, S.; Yamamoto, S.; Hino, H.; Nozawa, A.; Suzuki, A. *Synlett* ***2000***, 991.

[1760]For an alternative reagent to prepare *N*- Cbz derivatives, see Yasuhara, T.; Nagaoka, Y.; Tomioka, K. *J. Chem. Soc. Perkin Trans. 1* ***1999***, 2233.

[1761]Greene, T.W. *Protective Groups in Organic Synthesis*, Wiley, NY, ***1980***, pp. 222–248, 324–326; Wuts, P.G.M.; Greene, T.W. *Protective Groups in Organic Synthesis*, 2nd ed., Wiley, NY, ***1991***, pp. 327–330; Wuts, P.G.M.; Greene, T.W. *Protective Groups in Organic Synthesis*, 3rd ed., Wiley, NY, ***1999***, pp. 518–525; 737–739.

[1762]Baldwin, F.P.; Blanchard, E.J.; Koening, P.E. *J. Org. Chem.* ***1965***, *30*, 671.

[1763]Kivinen, A., in Patai, S. *The Chemistry of Acyl Halides*, Wiley, NY, ***1972***; Bender, M.L.; Jones, J.M. *J. Org. Chem.* ***1962***, *27*, 3771. See also, Song, B.D.; Jencks, W.P. *J. Am. Chem. Soc.* ***1989***, *111*, 8479.

[1764]Kawaguchi, M.; Hamaoka, S.; Mori, M. *Tetrahedron Lett.* ***1993***, *34*, 6907.

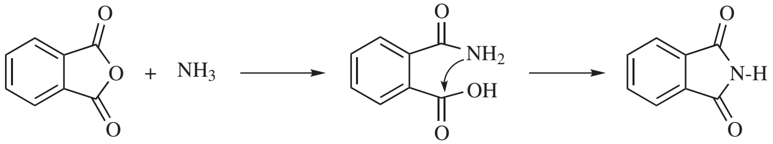
[1765]Lemoucheux, L.; Seitz, T.; Rouden, J.; Lasne, M.-C. *Org. Lett.* ***2004***, *6*, 3703.

OS **I**, 99, 165; **II**, 76, 208, 278, 328, 453; **III**, 167, 375, 415, 488, 490, 613; **IV**, 339, 411, 521, 620, 780; **V**, 201, 336; **VI**, 382, 715; **VII**, 56, 287, 307; **VIII**,16, 339; **IX**, 559; **81**, 254. See also, OS **VII**, 302.

16-73 Acylation of Amines by Anhydrides

Amino-de-acyloxy-substitution

This reaction, similar in scope and mechanism[1766] to **16-72**, can be carried out with ammonia or primary or secondary amines.[1767] Note that there is a report where a tertiary amine (an *N*-alkylpyrrolidine) reacted with acetic anhydride at 120°C, in the presence of a BF_3•etherate catalyst, to give *N*-acetylpyrrolidine (an acylative dealkylation).[1768] Amino acids can be *N*-acylated using acetic anhydride and ultrasound.[1769] However, ammonia and primary amines can also give imides, in which two acyl groups are attached to the nitrogen. The conversion of cyclic anhydrides to cyclic imides is generally facile,[1770] although elevated temperatures are occasionally required to generate the imide.[1771] Microwave irradiation of formamide and a cyclic anhydride generates the cyclic imide.[1772] Cyclic imides have also been formed in ionic liquids.[1773] Cyclic imides were also formed by microwave irradiation of a polymer-bound phthalate after initial reaction with an amine.[1774]



The second step for imide formation, which is much slower than the first, is the attack of the amide nitrogen on the carboxylic carbon. Unsubstituted and *N*-substituted amides have been used instead of ammonia. Since the other product

[1766]For a discussion of the mechanism, see Kluger, R.; Hunt, J.C. *J. Am. Chem. Soc.* ***1989***, *111*, 3325.

[1767]For a review, see Beckwith, A.L.J., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 86–96. See also, Naik, S.; Bhattacharjya, G.; Talukdar, B.; Patel, B.K. *Eur. J. Org. Chem.* ***2004***, 1254.

[1768]Dave, P. R.; Kumar, K. A.; Duddu, R.; Axenrod, T.; Dai, R.; Das, K. K.; Guan, X.-P.; Sun, J.; Trivedi, N. J.; Gilardi, R. D. *J. Org. Chem.* ***2000***, *65*, 1207.

[1769]Anuradha, M.V.; Ravindranath, B. *Tetrahedron* ***1997***, *53*, 1123.

[1770]For reviews of imides, see Wheeler, O.H.; Rosado, O., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 335–381; Hargreaves, M.K.; Pritchard, J.G.; Dave, H.R. *Chem. Rev.* ***1970***, *70*, 439 (cyclic imides).

[1771]Tsubouchi, H.; Tsuji, K.; Ishikawa, H. *Synlett* ***1994***, 63.

[1772]Peng, Y.; Song, G.; Qian, X. *Synth. Commun.* ***2001***, *31*, 1927; Kacprzak, K. *Synth. Commun.* ***2003***, *33*, 1499.

[1773]In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Le, Z.-G.; Chen, Z.-C.; Hu, Y.; Zheng, Q.-G. *Synthesis* ***2004***, 995.

[1774]Martin, B.; Sekljic, H.; Chassaing, C. *Org. Lett.* ***2003***, *5*, 1851.

of this reaction is RCOOH, this is a way of "hydrolyzing" such amides in the absence of water.[1775]

Even though formic anhydride is not a stable compound (see p. 723), amines can be formylated with the mixed anhydride of acetic and formic acids (HCOO-COMe)[1776] or with a mixture of formic acid and acetic anhydride. Acetamides are not formed with these reagents. Secondary amines can be acylated in the presence of a primary amine by conversion to their salts and addition of 18-crown-6.[1777] The crown ether complexes the primary ammonium salt, preventing its acylation, while the secondary ammonium salts, which do not fit easily into the cavity, are free to be acylated. Dimethyl carbonate can be used to prepare methyl carbamates in a related procedure.[1778] *N*-Acetylsulfonamides were prepared from acetic anhydride and a primary sulfonamide, catalyzed by Montmorillonite K10–FeO[1779] or sulfuric acid.[1780]

The reaction of anhydrides with aryl azides, in the presence of Me_3SiCl and NaI, gives *N*-aryl imides.[1781]

OS **I**, 457; **II**, 11; **III**, 151, 456, 661, 813; **IV**, 5, 42, 106, 657; **V**, 27, 373, 650, 944, 973; **VI**, 1; **VII**, 4, 70; **VIII**, 132; **76**, 123.

16-74 Acylation of Amines by Carboxylic Acids

Amino-de-hydroxylation

$$RCOOH + NH_3 \longrightarrow RCOO^-NH_4^+ \xrightarrow{\text{pyrolysis}} RCONH_2$$

When carboxylic acids are treated with ammonia or amines, salts are obtained. The salts of ammonia or primary or secondary amines can be pyrolyzed to give amides,[1782] but the method is less convenient than **16-72**, **16-73**, and **16-75** and is seldom of preparative value.[1783] Heating in the presence of a base such as hexamethyldisilazide makes the amide-forming process more efficient.[1784] Boronic acids catalyze the direct conversion of carboxylic acid and amine to amides.[1785]

[1775]Eaton, J.T.; Rounds, W.D.; Urbanowicz, J.H.; Gribble, G.W. *Tetrahedron Lett.* ***1988***, *29*, 6553.

[1776]For the formylation of amines with the mixed anhydride of formic and trimethylacetic acid, see Vlietstra, E.J.; Zwikker, J.W.; Nolte, R.J.M.; Drenth, W. *Recl. Trav. Chim. Pays-Bas* ***1982***, *101*, 460.

[1777]Barrett, A.G.M.; Lana, J.C.A. *J. Chem. Soc., Chem. Commun.* ***1978***, 471.

[1778]Vauthey, I.; Valot, F.; Gozzi, C.; Fache, F.; Lemaire, M. *Tetrahedron Lett.* ***2000***, *41*, 6347.

[1779]Singh, D.U.; Singh, P.R.; Samant, S.D. *Tetahedron Lett.* ***2004***, *45*, 4805.

[1780]Martin, M.T.; Roschangar, F.; Eaddy, J.F. *Tetrahedron Lett.* ***2003***, *44*, 5461.

[1781]Kamal, A.; Laxman, E.; Laxman, N.; Rao, N.V. *Tetrahedron Lett.* ***1998***, *39*, 8733.

[1782]For example, see Mitchell, J.A.; Reid, E.E. *J. Am. Chem. Soc.* ***1931***, *53*, 1879. Also see, Jursic, B.S.; Zdravkovski, Z. *Synth. Commun.* ***1993***, *23*, 2761.

[1783]For a review of amide formation from carboxylic acids, see Beckwith, A.L.J., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 105–109.

[1784]Chou, W.-C.; Chou, M.-C.; Lu, Y.-Y.; Chen, S.-F. *Tetrahedron Lett.* ***1999***, *40*, 3419. For alternative approaches using specialized reagents, see Jang, D.O.; Park, D.J.; Kim, J. *Tetrahedron Lett.* ***1999***, *40*, 5323; Bailén, M.A.; Chinchilla, R.; Dodsworth, D.J.; Nájera, C. *Tetrahedron Lett.* ***2000***, *41*, 9809 and ***2001***, *42*, 5013; White, J.M.; Tunoori, A.R.; Turunen, B.J.; Georg, G.I *J. Org. Chem.* ***2004***, *69*, 2573.

[1785]Ishihara, K.; Kondo, S.; Yamamoto, H. *Synlett* ***2001***, 1371.

Polymer-bound reagents have also been used.[1786] The synthetically important Weinreb amides [RCON(Me)OMe, see **16-82**] can be prepared from the carboxylic acid and MeO(Me)NH•HCl in the presence of tributylphosphine and 2-pyridine-*N*-oxide disulfide.[1787] Di(2-pyridyl)carbonate has been used in a related reaction that generates amides directly.[1788] The reaction of a carboxylic acid and imidazole under microwave irradiation gives the amide.[1789] Microwave irradiation of a secondary amine, formic acid, 2-chloro-4,6-dimethoxy[1,3,5]triazine, and a catalytic amount of DMAP (4-dimethylaminopyridine) leads to the formamide.[1790] Ammonium bicarbonate and formamide converts acids to amides with microwave irradiation.[1791] Lactams are readily produced from γ- or δ-amino acids,[1792] for example,

This lactamization process can be promoted by enzymes, such as pancreatic porcine lipase.[1793] Reduction of ω-azido carboxylic acids leads to macrocyclic lactams.[1794]

Although treatment of carboxylic acids with amines does not directly give amides, the reaction can be made to proceed in good yield at room temperature or slightly above by the use of coupling agents,[1795] the most important of which is dicyclohexylcarbodiimide. This reagent is very convenient and is used[1796] a great deal in peptide synthesis.[1797] A polymer-supported carbodiimide has been used.[1798] The mechanism is probably the same as in **16-63** up to the formation

[1786]Buchstaller, H.P.; Ebert, H.M.; Anlauf, U. *Synth. Commun.* ***2001***, *31*, 1001; Crosignani, S.; Gonzalez, J.; Swinnen, D. *Org. Lett.* ***2004***, *6*, 4579; Chichilla, R.; Dodsworth, D.J.; Nájera, C.; Soriano, J.M. *Tetrahedron Lett.* ***2003***, *44*, 463.

[1787]Banwell, M.; Smith, J. *Synth. Commun.* ***2001***, *31*, 2011. For another procedure, see Kim, M.; Lee, H.; Han, K.-J.; Kay,K.-Y. *Synth. Commun.* ***2003***, *33*, 4013.

[1788]Shiina, I.; Suenaga, Y.; Nakano, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* ***2000***, *73*, 2811.

[1789]Khalafi-Nezhad, A.; Mokhtari, B.; Rad, M.N.S. *Tetrahedron Lett.* ***2003***, *44*, 7325; Perreux, L.; Loupy, A.; Volatron, F. *Tetrahedron* ***2002***, *58*, 2155.

[1790]De Lucca, L.; Giacomelli, G.; Porcheddu, A.; Salaris, M. *Synlett* ***2004***, 2570.

[1791]Peng, Y.; Song, G. *Org. Prep. Proceed. Int.* ***2002***, *34*, 95.

[1792]See, for example, Bladé-Font, A. *Tetrahedron Lett.* ***1980***, *21*, 2443. See Wei, Z.-Y.; Knaus, E.E. *Tetrahedron Lett.* ***1993***, *34*, 4439 for a variation of this reaction.

[1793]Gutman, A.L.; Meyer, E.; Yue, X.; Abell, C. *Tetrahedron Lett.* ***1992***, *33*, 3943.

[1794]Bosch, I.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* ***1993***, *34*, 4671. See Bai, D.; Shi, Y. *Tetrahedron Lett.* ***1992***, *33*, 943 for the preparation of lactam units in para-cyclophanes.

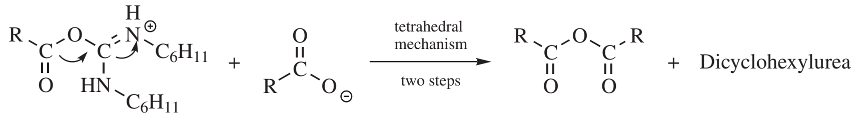
[1795]For a review of peptide synthesis with dicyclohexylcarbodiimide and other coupling agents, see Klausner, Y.S.; Bodansky, M. *Synthesis* ***1972***, 453.

[1796]It was first used this way by Sheehan, J.C.; Hess, G.P. *J. Am. Chem. Soc.* ***1955***, *77*, 1067.

[1797]For a treatise on peptide synthesis, see Gross, E.; Meienhofer, J. *The Peptides*, 3 vols., Academic Press, NY, ***1979–1981***. For a monograph, see Bodanszky, M.; Bodanszky, A. *The Practice of Peptide Synthesis*, Springer, NY, ***1984***.

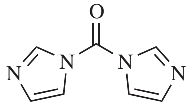
[1798]Feuerstein, M.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* ***2001***, *42*, 6667.

of **109**. This intermediate is then attacked by another molecule of $RCOO^-$ to give the anhydride $(RCO)_2O$, which is the actual species that reacts with the amine:



109

The anhydride has been isolated from the reaction mixture and then used to acylate an amine.[1799] Other promoting agents[1800] are $ArB(OH)_2$ reagents,[1801] $Sn[N(TMS)_2]_2$,[1802] *N,N′*-carbonyldiimidazole (**110**, p. 1418),[1803] which behaves as in reaction **16-63**, $POCl_3$,[1804] $TiCl_4$,[1805] molecular sieves,[1806] Lawesson's reagent (p. 1278),[1807] and $(MeO)_2POCl$.[1808] Certain dicarboxylic acids form amides simply on treatment with primary aromatic amines. In these cases, the cyclic anhydride is an intermediate and is the species actually attacked by the amine.[1809] Carboxylic acids can also be converted to amides by heating with amides of carboxylic acids (exchange),[1810] sulfonic acids, or phosphoric acids, for example,[1811]



110

$$RCOOH + Ph_2PONH_2 \longrightarrow RCONH_2 + Ph_2POOH$$

[1799] Schüssler, H.; Zahn, H. *Chem. Ber.* ***1962***, *95*, 1076; Rebek, J.; Feitler, D. *J. Am. Chem. Soc.* ***1974***, *96*, 1606. There is evidence that some of the **98** is converted to products by another mechanism. See Rebek, J.; Feitler, D. *J. Am. Chem. Soc.* ***1973***, *95*, 4052.

[1800] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1941–1949.

[1801] Ishihara, K.; Ohara, S.; Yamamoto, H. *J. Org. Chem.* ***1996***, *61*, 4196.

[1802] Burnell-Curty, C.; Roskamp, E.J. *Tetrahedron Lett.* ***1993***, *34*, 5193.

[1803] See Vaidyanathan, R.; Kalthod, V.G.; Ngo, D.; Manley, J.M.; Lapekas, S.P. *J. Org. Chem.* ***2004***, *69*, 2565. A modified but related reagent has also been used. See Grzyb, J.A.; Batey, R.A. *Tetrahedron Lett.* ***2003***, *44*, 7485.

[1804] Klosa, J. *J. Prakt. Chem.* ***1963***, *[4] 19*, 45.

[1805] Wilson, J.D.; Weingarten, H. *Can. J. Chem.* ***1970***, *48*, 983.

[1806] Cossy, J.; Pale-Grosdemange, C. *Tetrahedron Lett.* ***1989***, *30*, 2771.

[1807] Thorsen, M.; Andersen, T.P.; Pedersen, U.; Yde, B.; Lawesson, S. *Tetrahedron* ***1985***, *41*, 5633.

[1808] Jászay, Z.M.; Petneházy, I.; Töke, L. *Synth. Commun.* ***1998***, *28*, 2761.

[1809] Higuchi, T.; Miki, T.; Shah, A.C.; Herd, A.K. *J. Am. Chem. Soc.* ***1963***, *85*, 3655.

[1810] For example, see Schindbauer, H. *Monatsh. Chem.* ***1968***, *99*, 1799.

[1811] Zhmurova, I.N.; Voitsekhovskaya, I.Yu.; Kirsanov, A.V. *J. Gen. Chem. USSR* ***1959***, *29*, 2052. See also, Kopecky, J.; Smejkal, J. *Chem. Ind. (London)* ***1966***, 1529; Liu, H.; Chan, W.H.; Lee, S.P. *Synth. Commun.* ***1979***, *9*, 31.

or by treatment with trisalkylaminoboranes, $B(NHR')_3$, with trisdialkylaminoboranes, $B(NR'_2)_3$,[1812]

$$RCOOH \quad + \quad B(NR_2')_3 \longrightarrow RCONR_2'$$

or with bis(diorganoamino)magnesium reagents $(R_2N)_2Mg$.[1813] The reaction of thiocarboxylic acids and azides, in the presence of triphenylphosphine, gives the corresponding amide.[1814]

An important technique, discovered by R.B. Merrifield in 1963[1815] and since used for the synthesis of many peptides,[1816] is called *solid phase synthesis* or *polymer-supported synthesis*.[1817] The reactions used are the same as in ordinary synthesis, but one of the reactants is anchored onto a solid polymer. For example, if it is desired to couple two amino acids (to form a dipeptide), the polymer selected might be polystyrene with CH_2Cl side chains. One of the amino acids, protected by a *tert*-butoxycarbonyl group (Boc), would then be coupled to the side chains. It is not necessary that all the side chains be converted, but a random selection will be. The Boc group is then removed by hydrolysis with trifluoroacetic acid in CH_2Cl_2 and the second amino acid is coupled to the first, using DCC or some other coupling agent. The second Boc group is removed, resulting in a dipeptide that is still anchored to the polymer. If this dipeptide is the desired product, it can be cleaved from the polymer by various methods,[1818] one of which is treatment with HF. If a longer peptide is wanted, additional amino acids can be added by repeating the requisite steps.

[1812]Pelter, A.; Levitt, T.E.; Nelson, P. *Tetrahedron* ***1970***, *26*, 1539; Pelter, A.; Levitt, T.E. *Tetrahedron* ***1970***, *26*, 1545, 1899.

[1813]Sanchez, R.; Vest, G.; Despres, L. *Synth. Commun.* ***1989***, *19*, 2909.

[1814]Park, S.-D.; Oh, J.-H.; Lim, D. *Tetrahedron Lett.* ***2002***, *43*, 6309.

[1815]Merrifield, R.B. *J. Am. Chem. Soc.* ***1963***, *85*, 2149.

[1816]For a monograph on solid-state peptide synthesis, see Birr, C. *Aspects of the Merrifield Peptide Synthesis*, Springer, NY, ***1978***. For reviews, see Bayer, E. *Angew. Chem. Int. Ed.* ***1991***, *30*, 113; Kaiser, E.T. *Acc. Chem. Res.* ***1989***, *22*, 47; Jacquier, R. *Bull. Soc. Chim. Fr.* ***1989***, 220; Barany, G.; Kneib-Cordonier, N.; Mullen, D.G. *Int. J. Pept. Protein Res.* ***1987***, *30*, 705; Andreev, S.M.; Samoilova, N.A.; Davidovich, Yu.A.; Rogozhin, S.V. *Russ. Chem. Rev.* ***1987***, *56*, 366; Gross, E.; Meienhofer, J. *The Peptides*, Vol. 2, Academic Press, NY, ***1980***, the articles by Barany, G.; Merrifield, R.B. pp. 1–184, Fridkin, M. pp. 333–363; Erickson, B.W.; Merrifield, R.B. in Neurath, H.; Hill, R.L.; Boeder, C.-L. *The Proteins*, 3rd ed., Vol. 2, Academic Press, NY, ***1976***, pp. 255–527. For R. B. Merrifield's Nobel Prize lecture, see Merrifield, R.B. *Angew. Chem. Int. Ed.* ***1985***, *24*, 799; *Chem. Scr.* ***1985***, *25*, 121.

[1817]For monographs on solid-phase synthesis in general, see Laszlo, P. *Preparative Organic Chemistry Using Supported Reagents*, Academic Press, NY, ***1987***; Mathur, N.K.; Narang, C.K.; Williams, R.E. *Polymers as Aids in Organic Chemistry*, Academic Press, NY ***1980***; Hodge, P.; Sherrington, D.C. *Polymer-Supported Reactions in Organic Synthesis*, Wiley, NY, ***1980***. For reviews, see Pillai, V.N.R.; Mutter, M. *Top. Curr. Chem.* ***1982***, *106*, 119; Akelah, A.; Sherrington, D.C. *Chem. Rev.* ***1981***, *81*, 557; Akelah, A. *Synthesis* ***1981***, 413; Rebek, J. *Tetrahedron* ***1979***, *35*, 723; McKillop, A.; Young, D.W. *Synthesis* ***1979***, 401, 481; Crowley, J.I.; Rapoport, H. *Acc. Chem. Res.* ***1976***, *9*, 135; Patchornik, A.; Kraus, M.A. *Pure Appl. Chem.* ***1975***, *43*, 503.

[1818]For some of these methods, see Whitney, D.B.; Tam, J.P.; Merrifield, R.B. *Tetrahedron* ***1984***, *40*, 4237.

The basic advantage of the polymer-support techniques is that the polymer (including all chains attached to it) is easily separated from all other reagents, because it is insoluble in the solvents used. Excess reagents, other reaction products (e.g., dicyclohexylurea), side products, and the solvents themselves are quickly washed away. Purification of the polymeric species is rapid and complete. The process can even be automated,[1819] to the extent that six or more amino acids can be added to a peptide chain in one day. Commercial automated peptide synthesizers are now available.[1820]

Although the solid-phase technique was first developed for the synthesis of peptide chains and has seen considerable use for this purpose, it has also been used to synthesize chains of polysaccharides and polynucleotides; in the latter case, solid-phase synthesis has almost completely replaced synthesis in solution.[1821] The technique has been applied less often to reactions in which only two molecules are brought together (nonrepetitive syntheses), but many examples have been reported.[1822] Combinatorial chemistry had its beginning with the Merrifield synthesis, particularly when applied to peptide synthesis, and continues as an important part of modern organic chemistry.[1823]

OS **I**, 3, 82, 111, 172, 327; **II**, 65, 562; **III**, 95, 328, 475, 590, 646, 656, 768; **IV**, 6, 62, 513; **V**, 670, 1070; **VIII**, 241; **81**, 262. Also see OS **III**, 360; **VI**, 263; **VIII**, 68.

16-75 Acylation of Amines by Carboxylic Esters

Amino-de-alkoxylation

$$RCOOR' + NH_3 \longrightarrow RCONH_2 + R'OH$$

The conversion of carboxylic esters to amides is a useful reaction, and unsubstituted, *N*-substituted, and *N,N*-disubstituted amides can be prepared this way from the appropriate amine.[1824] Both R and R′ can be alkyl or aryl, but an especially

[1819]This was first reported by Merrifield, R.B.; Stewart, J.M.; Jernberg, N. *Anal. Chem.* ***1966***, *38*, 1905.

[1820]For a discussion of automated organic synthesis, see Frisbee, A.R.; Nantz, M.H.; Kramer, G.W.; Fuchs, P.L. *J. Am. Chem. Soc.* ***1984***, *106*, 7143. For an improved method, see Schnorrenberg, G.; Gerhardt, H. *Tetrahedron* ***1989***, *45*, 7759.

[1821]For a review, see Bannwarth, W. *Chimia* ***1987***, *41*, 302.

[1822]For reviews, see Fréchet, J.M.J. *Tetrahedron* ***1981***, *37*, 663; Fréchet, J.M.J. in Hodge, P.; Sherrington, D.C. *Polymer-Supported Reactions in Organic Synthesis*, Wiley, NY, ***1980***, pp. 293–342, Leznoff, C.C. *Acc. Chem. Res.* ***1978***, *11*, 327; *Chem. Soc. Rev.* ***1974***, *3*, 64.

[1823]Czarnik, A.W.; DeWitt, S.H. *A Practical Guide to Combinatorial Chemistry*, American Chemical Society, Washington, DC, ***1997***; Chaiken, I.N.; Janda, K.D. *Molecular Diversity and Combinatorial Chemistry: Libraries and Drug Discovery*, American Chemical Society, Washington, DC ***1996***; Balkenhol, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem. Int. Ed.* ***1996***, *35*, 2289; Thompson, L.A.; Ellman, J.A. *Chem. Rev.* ***1996***, 96, 555; Pavia, M.R.; Sawyer, T.K.; Moos, W.H. *Bioorg. Med. Chem. Lett. Symposia–in–print no. 4* ***1993***, *3*, 387; Crowley, J.I.; Rapoport, H. *Acc. Chem. Res.* ***1976***, *9*, 135; Leznoff, C.C. *Acc. Chem. Res.* ***1978***, *11*, 327.

[1824]For a review, see Beckwith, A.L.J., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 96–105. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1973–1976.

good leaving group is *p*-nitrophenyl. Ethyl trifluoroacetate was found to react selectively with primary amines to form the corresponding trifluoroacetyl amide.[1825] Many simple esters (R = Me, Et, etc.) are not very reactive, and strongly basic catalysis has been used in such cases,[1826] but catalysis by cyanide ion[1827] $MgBr_2$,[1828] InI_3,[1829] and acceleration by high pressure[1830] have been reported. Methyl esters have been converted to the corresponding amide under microwave irradiation,[1831] and also ethyl esters.[1832] Lithium amides have been used to convert esters to amides as well.[1833] β-Keto esters undergo the reaction especially easily.[1834] In another procedure, esters are treated with dimethylaluminum amides (Me_2AlNRR') to give good yields of amides under mild conditions.[1835] The reagents are easily prepared from Me_3Al and NH_3 or a primary or secondary amine or their salts. This is particularly effective when a reactive substituent, such as a primary halide, is present elsewhere in the molecule.[1836] Tin reagents, such as $Sn[N(TMS)_2]_2$, in the presence of an amine can also be use to convert an ester to an amide.[1837] This reagent can also be used to convert β-amino esters to β-lactams.[1838] Aniline was treated with *n*-butyllithium to form the lithium amide, which reacted with an ester to give the amide.[1839] The ester-to-amide conversion has also been accomplished electrochemically, by passing electric current in the cathodic compartment.[1840] An enzyme-mediated amidation is known using amino cyclase I.[1841] The reaction of dimethyl carbonate and an amine is an effective way to prepare methyl carbamates.[1842]

[1825]Xu, D.; Prasad, K.; Repic, O.; Blacklock, T.J. *Tetrahedron Lett.* ***1995***, *36*, 7357.

[1826]For references, see Matsumoto, K.; Hashimoto, S.; Uchida, T.; Okamoto, T.; Otani, S. *Chem. Ber.* ***1989***, *122*, 1357.

[1827]Högberg, T.; Ström, P.; Ebner, M.; Rämsby, S. *J. Org. Chem.* ***1987***, *52*, 2033.

[1828]Guo, Z.; Dowdy, E.D.; Li, W.-S.; Polniaszek, R.; Delaney, E. *Tetrahedron Lett.* ***2001***, *42*, 1843.

[1829]Ranu, B.C.; Dutta, P. *Synth. Commun.* ***2003***, *33*, 297.

[1830]Matsumoto, K.; Hashimoto, S.; Uchida, T.; Okamoto, T.; Otani, S. *Chem. Ber.* ***1989***, *122*, 1357.

[1831]Varma, R.S.; Naicker, K.P. *Tetrahedron Lett.* ***1999***, *40*, 6177.

[1832]Suri, O.P.; Satti, N.K.; Suri, K.A. *Synth. Commun.* ***2000***, *30*, 3709; Zradni, F.-Z.; Hamelin, J.; Derdour, A. *Synth. Commun.* ***2002***, *32*, 3525.

[1833]See Wang, J.; Rosingana, M.; Discordia, R.P.; Soundararajan, N.; Polniaszek, R. *Synlett* ***2001***, 1485.

[1834]Labelle, M.; Gravel, D. *J. Chem. Soc., Chem. Commun.* ***1985***, 105.

[1835]Basha, A.; Lipton, M.; Weinreb, S.M. *Org. Synth.* ***VI***, 492; Levin, J.I.; Turos, E.; Weinreb, S.M. *Synth. Commun.* ***1982***, *12*, 989; Barrett, A.G.M.; Dhanak, D. *Tetrahedron Lett.* ***1987***, *28*, 3327. For the extension of this method to the formation of hydrazides, see Benderly, A.; Stavchansky, S. *Tetrahedron Lett.* ***1988***, *29*, 739.

[1836]Shimizu, T.; Osako, K.; Nakata, T. *Tetrahedron Lett.* ***1997***, *38*, 2685.

[1837]Smith, L.A.; Wang, W.-B.; Burnell-Curty, C.; Roskamp, E.J. *Synlett* ***1993***, 850; Wang, W.-B.; Roskamp, E.J. *J. Org. Chem.* ***1992***, *57*, 6101.

[1838]Wang, W.-B.; Roskamp, E.J. *J. Am. Chem. Soc.* ***1993***, *115*, 9417.

[1839]Ooi, T.; Tayama, E.; Yamada, M.; Maruoka, K. *Synlett.* ***1999***, 729.

[1840]Arai, K.; Shaw, C.; Nozawa, K.; Kawai, K.; Nakajima, S. *Tetrahedron Lett.* ***1987***, *28*, 441.

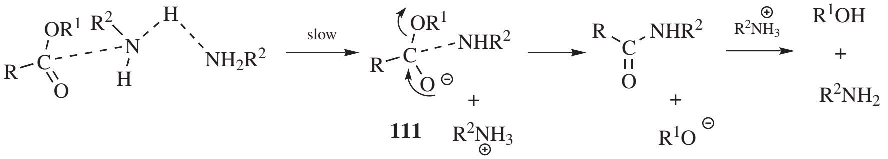
[1841]Youshko, M.I.; van Rantwijk, F.; Sheldon, R.A. *Tetrahedron Asymmetry* ***2001***, *12*, 3267.

[1842]Distaso, M.; Quaranta, E. *Tetrahedron* ***2004***, *60*, 1531; Curini, M.; Epifano, F.; Maltese, F.; Rosati, O. *Tetrahedron Lett.* ***2002***, *43*, 4895.

As in **16-72**, hydrazides and hydroxamic acids can be prepared from carboxylic esters, with hydrazine and hydroxylamine, respectively. Both hydrazine and hydroxylamine react more rapidly than ammonia or primary amines (the alpha effect, p. 495). Imidates RC(=NH)OR′ give amidines $RC(=NH)NH_2$. Lactones, when treated with ammonia or primary amines, give lactams. Lactams are also produced from γ- and δ-amino esters in an internal example of this reaction. Isopropenyl formate is a useful compound for the formylation of primary and secondary amines.[1843]

$$R_2NH + HCOOCMe = CH_2 \longrightarrow R_2NCHO + CH_2 = CMeOH \longrightarrow MeCOMe$$

Although more studies have been devoted to the mechanism of the acylation of amines with carboxylic esters than with other reagents, the mechanistic details are not yet entirely clear.[1844] In its broad outlines, the mechanism appears to be essentially $B_{AC}2$.[1845] Under the normal basic conditions, the reaction is general base-catalyzed,[1846] indicating that a proton is being transferred in the rate-determining step and that two molecules of amine are involved.[1847]



Alternatively, another base, such as H_2O or OH^-, can substitute for the second molecule of amine. With some substrates and under some conditions, especially at low pH, the breakdown of **111** can become rate determining.[1848] The reaction also takes place under acidic conditions and is general acid catalyzed, so that

[1843]van Melick, J.E.W.; Wolters, E.T.M. *Synth. Commun.* ***1972***, *2*, 83.

[1844]For a discussion of the mechanism, see Satchell, D.P.N.; Satchell, R.S., in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 410–431. For a computational study see Ilieva, S.; Galabov, B.; Musaev, D.G.; Morokuma, K.; Schaefer III, H.F. *J. Org. Chem.* ***2003***, *68*, 1496.

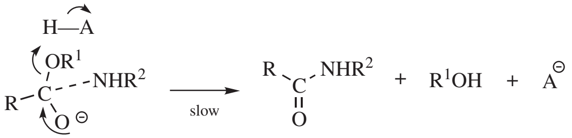
[1845]Bunnett, J.F.; Davis, G.T. *J. Am. Chem. Soc.* ***1960***, *82*, 665; Bruice, T.C.; Donzel, A.; Huffman, R.W.; Butler, A.R. *J. Am. Chem. Soc.* ***1967***, *89*, 2106.

[1846]Bunnett, J.F.; Davis, G.T. *J. Am. Chem. Soc.* ***1960***, *82*, 665, Jencks, W.P.; Carriuolo, J. *J. Am. Chem. Soc.* ***1960***, *82*, 675; Bruice, T.C.; Mayahi, M.F. *J. Am. Chem. Soc.* ***1960***, *82*, 3067.

[1847]Blackburn, G.M.; Jencks, W.P. *J. Am. Chem. Soc.* ***1968***, *90*, 2638; Bruice, T.C.; Felton, S.M. *J. Am. Chem. Soc.* ***1969***, *91*, 2799; Felton, S.M.; Bruice, T.C. *J. Am. Chem. Soc.* ***1969***, *91*, 6721; Nagy, O.B.; Reuliaux,V.; Bertrand, N.; Van Der Mensbrugghe, A.; Leseul, J.; Nagy, J.B. *Bull. Soc. Chim. Belg.* ***1985***, *94*, 1055.

[1848]Hansen, B. *Acta Chem. Scand.* ***1963***, *17*, 1307; Gresser, M.J.; Jencks, W.P. *J. Am. Chem. Soc.* ***1977***, *99*, 6963, 6970. See also, Yang, C.C.; Jencks, W.P. *J. Am. Chem. Soc.* ***1988***, *110*, 2972.

breakdown of **111** is rate determining and proceeds as follows:[1849]



111

HA may be $R^2NH_3^+$ or another acid. Intermediate **111** may or may not be further protonated on the nitrogen. Even under basic conditions, a proton donor may be necessary to assist leaving-group removal. Evidence for this is that the rate is lower with NR_2^- in liquid ammonia than with NHR_2 in water, apparently owing to the lack of acids to protonate the leaving oxygen.[1850]

In the special case of β-lactones, where small-angle strain is an important factor, alkyl–oxygen cleavage is observed ($B_{AL}2$ mechanism, as in the similar case of hydrolysis of β-lactones, **16-59**), and the product is not an amide but a β-amino acid (β-alanine).

β-Alanine

A similar result has been found for certain sterically hindered esters.[1851] This reaction is similar to **10-31**, with OCOR as the leaving group. Other lactones have been opened to ω-hydroxy amides with Dibal:$BnNH_2$.[1852]

OS **I**, 153, 179; **II**, 67, 85; **III**, 10, 96, 108, 404, 440, 516, 536, 751, 765; **IV**, 80, 357, 441, 486, 532, 566, 819; **V**, 168, 301, 645; **VI**, 203, 492, 620, 936; **VII**, 4, 30, 41, 411; **VIII**, 26, 204, 528. Also see, OS **I**, 5; **V**, 582; **VII**, 75.

16-76 Acylation of Amines by Amides

Alkylamino-de-amination

$$RCONH_2 \quad + \quad R'\overset{\oplus}{N}H_3 \longrightarrow RCONHR' \quad + \quad NH_4^+$$

This is an exchange reaction and is usually carried out with the salt of the amine.[1853] The leaving group is usually NH_2 rather than NHR or NR_2 and primary

[1849] Blackburn, G.M.; Jencks, W.P. *J. Am. Chem. Soc.* ***1968***, *90*, 2638.

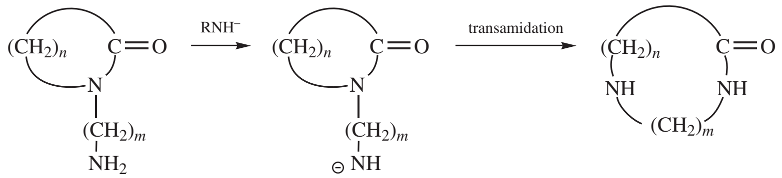
[1850] Bunnett, J.F.; Davis, G.T. *J. Am. Chem. Soc.* ***1960***, *82*, 665.

[1851] Zaugg, H.E.; Helgren, P.F.; Schaefer, A.D. *J. Org. Chem.* ***1963***, *28*, 2617. See also, Weintraub, L.; Terrell, R. *J. Org. Chem.* ***1965***, *30*, 2470; Harada, R.; Kinoshita, Y. *Bull. Chem. Soc. Jpn.* ***1967***, *40*, 2706.

[1852] Huang, P.-Q.; Zheng, X.; Deng, X.-M. *Tetrahedron Lett.* ***2001***, *42*, 9039. See also, Taylor, S.K.; Ide, N.D.; Silver, M.E.; Stephan, M. *Synth. Commun.* ***2001***, *31*, 2391.

[1853] For a list of procedures, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1978–1982.

amines (in the form of their salts) are the most common reagents. Boron trifluoride can be added to complex with the leaving ammonia. Neutral amines also react in some cases to give the new amide.[1854] The reaction is often used to convert urea to substituted ureas: $NH_2CONH_2 + RNH_3^+ \rightarrow NH_2CONHR + NH_4^+$.[1855] An *N*-aryl group of a urea can be converted to a *N,N*-dialkyl group by heating the urea with the amine in an autoclave.[1856] *N*-R-Substituted amides are converted to *N*-R′-substituted amides by treatment with N_2O_4 to give an *N*-nitroso compound, followed by treatment of this with a primary amine $R'NH_2$.[1857] Lactams can be converted to ring-expanded lactams if



a side chain containing an amino group is present on the nitrogen. A strong base is used to convert the NH_2 to NH^-, which then acts as a nucleophile, expanding the ring by means of a transamidation.[1858] The discoverers call it the *Zip reaction*, by analogy with the action of zippers.[1859]

Lactams can be opened to ω-amino amides by reaction with amines at 10 kbar.[1860]

OS **I**, 302 (but see **V**, 589), 450, 453; **II**, 461; **III**, 151, 404; **IV**, 52, 361. See also, OS **VIII**, 573.

16-77 Acylation of Amines by Other Acid Derivatives

Acylamino-de-halogenation or dealkoxlaton

$$RCOCl \quad + \quad H_2NCOR' \longrightarrow RCONHCOR'$$

Acid derivatives that can be converted to amides include thiol acids RCOSH, thiol esters RCOSR,[1861] acyloxyboranes $RCOB(OR')_2$,[1862] silicic esters $(RCOO)_4Si$,

[1854]Murakami, Y.; Kondo, K.; Miki, K.; Akiyama, Y.; Watanabe, T.; Yokoyama, Y. *Tetrahedron Lett.* ***1997***, *38*, 3751.

[1855]For a discussion of the mechanism, see Chimishkyan, A.L.; Snagovskii, Yu.S.; Gulyaev, N.D.; Leonova, T.V.; Kusakin, M.S. *J. Org. Chem. USSR* ***1985***, *21*, 1955.

[1856]Yang, Y.; Lu, S. *Org. Prep. Proceed. Int.* ***1999***, *31*, 559.

[1857]Garcia, J.; Vilarrasa, J. *Tetrahedron Lett.* ***1982***, *23*, 1127.

[1858]Askitoğlu, E.; Guggisberg, A.; Hesse, M. *Helv. Chim. Acta* ***1985***, *68*, 750, and references cited therein. For a carbon analog, see Süsse, M.; Hájiček, J.; Hesse, M. *Helv. Chim. Acta* ***1985***, *68*, 1986.

[1859]For a review of this reaction, and of other ring expansions to form macrocyclic rings, see Stach, H.; Hesse, M. *Tetrahedron* ***1988***, *44*, 1573.

[1860]Kotsuki, H.; Iwasaki, M.; Nishizawa, H. *Tetrahedron Lett.* ***1992***, *33*, 4945.

[1861]For a discussion of the mechanism, see Douglas, K.T. *Acc. Chem. Res.* ***1986***, *19*, 186.

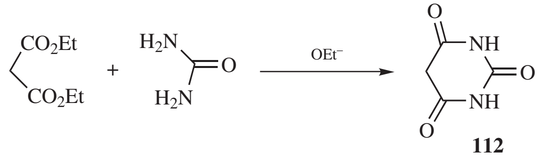
[1862]The best results are obtained when the acyloxyboranes are made from a carboxylic acid and catecholborane (p. 1123): Collum, D.B.; Chen, S.; Ganem, B. *J. Org. Chem.* ***1978***, *43*, 4393.

1,1,1-trihalo ketones $RCOCX_3$,[1863] α-keto nitriles, acyl azides, and non-enolizable ketones (see the Haller–Bauer reaction **12-34**). A polymer-bound acyl derivative was converted to an amide using tributylvinyl tin, trifluoroacetic acid, $AsPh_3$ and a palladium catalyst.[1864] The source of amine in this reaction was the polymer itself, which was an amide resin. *N*-Acylsulfonamides react with primary amines to the amide (AcNHR).[1865] Aniline derivatives are converted to acetamides with *N*-acyl oxymethylpyradazin-3-ones in dichloromethane.[1866] Carbonylation reactions can be used to prepare amides and related compounds. The reaction of a primary amine, an alkyl halide with CO_2, in the presence of Cs_2CO_3/Bu_4NI, gave the corresponding carbamate.[1867]

OS **III**, 394; **IV**, 6, 569; **V**, 160, 166; **VI**, 1004.

Imides can be prepared by the attack of amides or their salts on acyl halides, anhydrides, and carboxylic acids or esters.[1868] The best synthetic method for the preparation of acyclic imides is the reaction between an amide and an anhydride at 100°C catalyzed by H_2SO_4.[1869] When acyl chlorides are treated with amides in a 2:1 molar ratio at low temperatures in the presence of pyridine, the products are *N,N*-diacylamides, $(RCO)_3N$.[1870]

This reaction is often used to prepare urea derivatives, an important example being the preparation of barbituric acid, **112**.[1871]



112

When the substrate is oxalyl chloride (ClCOCOCl) and the reagent an unsubstituted amide, an acyl isocyanate (RCONCO) is formed. The "normal" product (RCONH-COCOCl) does not form, or if it does, it rapidly loses CO and HCl.[1872]

OS **II**, 60, 79, 422; **III**, 763; **IV**, 245, 247, 496, 566, 638, 662, 744; **V**, 204, 944.

[1863]See, for example, Salim, J.R.; Nome, F.; Rezende, M.C. *Synth. Commun.* ***1989***, *19*, 1181; Druzian, J.; Zucco, C.; Rezende, M.C.; Nome, F. *J. Org. Chem.* ***1989***, *54*, 4767.

[1864]Deshpande, M.S. *Tetrahedron Lett.* ***1994***, *35*, 5613.

[1865]Coniglio, S.; Aramini, A.; Cesta, M.C.; Colagioia, S.; Curti, R.; D'Alessandro, F.; D'anniballe, G.; D'Elia, V.; Nano, G.; Orlando, V.; Allegretti, M. *Tetrahedron Lett.* ***2004***, *45*, 5375.

[1866]Kang, Y.-J.; Chung, H.-A.; Kim, J.-J.; Yoon, Y.-J. *Synthesis* ***2002***, 733.

[1867]Salvatore, R.N.; Shin, S.I.; Nagle, A.S.; Jung, K.W. *J. Org. Chem.* ***2001***, *66*, 1035.

[1868]For a review, see Challis, B.C.; Challis, J.A., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 759–773.

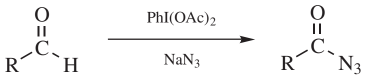
[1869]Baburao, K.; Costello, A.M.; Petterson, R.C.; Sander, G.E. *J. Chem. Soc. C* ***1968***, 2779; Davidson, D.; Skovronek, H. *J. Am. Chem. Soc.* ***1958***, *80*, 376.

[1870]For example, see LaLonde, R.T.; Davis, C.B. *J. Org. Chem.* ***1970***, *35*, 771.

[1871]For a review of barbituric acid, see Bojarski, J.T.; Mokrosz, J.L.; Barto, H.J.; Paluchowska, M.H. *Adv. Heterocycl. Chem.* ***1985***, *38*, 229.

[1872]Speziale, A.J.; Smith, L.R.; Fedder, J.E. *J. Org. Chem.* ***1965***, *30*, 4306.

16-78 Acylation of Azides



The reaction of an aldehyde with sodium azide and Et_4 $I(OAc)_2$ or polymer-bound $PhI(OAc)_2$ leads to an acyl azide.[1873]

F. Attack by Halogen at an Acyl Carbon

16-79 Formation of Acyl Halides from Carboxylic Acids

Halo-de-hydroxylation

$$\text{RCOOH} + \underset{\text{agent}}{\text{Halogenating}} \longrightarrow \text{RCOX}$$

Halogenating agent = $SOCl_2$, $SOBr_2$, PCl_3, $POCl_3$, PBr_3, and so on.

The same inorganic acid halides that convert alcohols to alkyl halides (**10-48**) also convert carboxylic acids to acyl halides.[1874] The reaction is the best and the most common method for the preparation of acyl chlorides. Bromides and iodides[1875] are also made in this manner, but much less often. Acyl bromides can be prepared with BBr_3 on alumina.[1876] Thionyl chloride[1877] is a good reagent, since the by-products are gases and the acyl halide is easily isolated, but PX_3 and PX_5 (X = Cl or Br) are also commonly used.[1878] Hydrogen halides do not give the reaction. A particularly mild procedure, similar to one mentioned in **10-48**, involves reaction of the acid with Ph_3P in CCl_4, whereupon acyl chlorides are produced without obtaining any acidic compound as a by-product.[1879] Acyl fluorides can be prepared by treatment of carboxylic acids with cyanuric fluoride.[1880] Acid salts

[1873]Marinescu, L.G.; Pedersen, C.M.; Bols, M. *Tetrahedron* ***2005***, *61*, 123. Aldehydes are converted to acyl azides by reaction with IN_3, see Marinescu, L.; Thinggaard, J.; Thomsen, I. B.; Bols, M. *J. Org. Chem.* ***2003***, *68*, 9453. See Hünig, S.; Schaller, R. *Angew. Chem. Int. Ed.* ***1982***, *21*, 36.

[1874]For a review, see Ansell, M.F., in Patai, S. *The Chemistry of Acyl Halides*, Wiley, NY, ***1972***, pp. 35–68.

[1875]Carboxylic acids and some of their derivatives react with diiodosilane SiH_2I_2 to give good yields of acyl iodides: Keinan, E.; Sahai, M. *J. Org. Chem.* ***1990***, *55*, 3922.

[1876]Bains, S.; Green, J.; Tan, L.C.; Pagni, R.M.; Kabalka, G.W. *Tetrahedron Lett.* ***1992***, *33*, 7475.

[1877]For a review of thionyl chloride ($SOCl_2$), see Pizey, J.S. *Synthetic Reagents*, Vol. 1, Wiley, NY, ***1974***, pp. 321–357. See Mohanazadeh, F.; Momeni, A.R. *Org. Prep. Proceed. Int.* ***1996***, *28*, 492 for the use of $SOCl_2$ on silica gel.

[1878]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1929–1930.

[1879]Lee, J.B. *J. Am. Chem. Soc.* ***1966***, *88*, 3440. For other methods of preparing acyl chlorides, see Venkataraman, K.; Wagle, D.R. *Tetrahedron Lett.* ***1979***, 3037; Devos, A.; Remion, J.; Frisque-Hesbain, A.; Colens, A.; Ghosez, L. *J. Chem. Soc., Chem. Commun.* ***1979***, 1180.

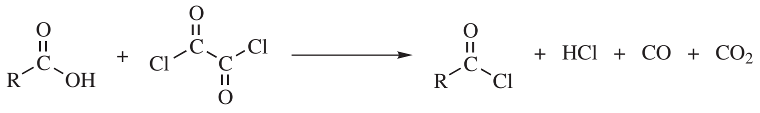
[1880]Olah, G.A.; Nojima, M.; Kerekes, I. *Synthesis* ***1973***, 487. For other methods of preparing acyl fluorides, see Mukaiyama, T.; Tanaka, T. *Chem. Lett.* ***1976***, 303; Ishikawa, N.; Sasaki, S. *Chem. Lett.* ***1976***, 1407.

are also sometimes used as substrates. Acyl halides are also used as reagents in an exchange reaction:

$$\text{RCOOH} + \text{R'COCl} \rightleftharpoons \text{RCOCl} + \text{R'COOH}$$

which probably involves an anhydride intermediate. This is an equilibrium reaction that must be driven to the desired side.

A mild, and often superior reagent is oxalyl chloride (**113**) and oxalyl bromide, since oxalic acid decomposes to CO and CO_2, and the equilibrium is thus driven to the side of the other acyl halide.[1881] These reagents are commonly the reagent of choice, particularly when sensitive functionality is present elsewhere in the molecule.



113

OS **I**, 12, 147, 394; **II**, 74, 156, 169, 569; **III**, 169, 490, 547, 555, 613, 623, 712, 714; **IV**, 34, 88, 154, 263, 339, 348, 554, 608, 616, 620, 715, 739, 900; **V**, 171, 258, 887; **VI**, 95, 190, 549, 715; **VII**, 467; **VIII**, 441, 486, 498.

16-80 Formation of Acyl Halides from Acid Derivatives

Halo-de-acyloxy-substitution

Halo-de-halogenation

$$(\text{RCO})_2\text{O} + \text{HF} \longrightarrow \text{RCOF}$$
$$\text{RCOCl} + \text{HF} \longrightarrow \text{RCOF}$$

These reactions are most important for the preparation of acyl fluorides.[1882] Acyl chlorides and anhydrides can be converted to acyl fluorides by treatment with polyhydrogen fluoride–pyridine solution[1883] or with liquid HF at $-10°C$.[1884] Formyl fluoride, which is a stable compound, was prepared by the latter procedure from the mixed anhydride of formic and acetic acids.[1885] Acyl fluorides can also be obtained by reaction of acyl chlorides with KF in acetic acid[1886] or with diethylaminosulfur trifluoride (DAST).[1887] Carboxylic esters and anhydrides can be

[1881]Adams, R.; Ulich, L.H., *J. Am. Chem. Soc.* ***1920***, *42*, 599; Wood, T.R.; Jackson, F.L.; Baldwin, A.R.; Longenecker, H.E. *J. Am. Chem. Soc.* ***1944***, *66*, 287. For a typical example see Zhang, A.; Nie, J. *J. Agric. Food Chem.* ***2005***, *53*, 2451.

[1882]For lists of reagents converting acid derivatives to acyl halides, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1950–1951, 1955, 1968.

[1883]Olah, G.A.; Welch, J.; Vankar, Y.D.; Nojima, M.; Kerekes, I.; Olah, J.A. *J. Org. Chem.* ***1979***, *44*, 3872. See also, Yin, J.; Zarkowsky, D.S.; Thomas, D.W.; Zhao, M.W.; Huffman, M.A. *Org. Lett.* ***2004***, *6*, 1465.

[1884]Olah, G.A.; Kuhn, S.J. *J. Org. Chem.* ***1961***, *26*, 237.

[1885]Olah, G.A.; Kuhn, S.J. *J. Am. Chem. Soc.* ***1960***, *82*, 2380.

[1886]Emsley, J.; Gold, V.; Hibbert, F.; Szeto, W.T.A. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 923.

[1887]Markovski, L.N.; Pashinnik, V.E. *Synthesis* ***1975***, 801.

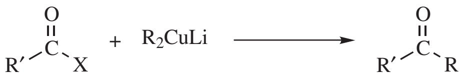
converted to acyl halides other than fluorides by the inorganic acid halides mentioned in **16-79**, as well as with Ph_3PX_2 (X = Cl or Br),[1888] but this is seldom done. Halide exchange can be carried out in a similar manner. When halide exchange is done, it is always acyl bromides and iodides that are made from chlorides, since chlorides are by far the most readily available.[1889]

OS **II**, 528; **III**, 422; **V**, 66, 1103; **IX**, 13. See also, OS **IV**, 307.

G. Attack by Carbon at an Acyl Carbon[1890]

16-81 The Conversion of Acyl Halides to Ketones With Organometallic Compounds[1891]

Alkyl-de-halogenation



Acyl halides react cleanly and under mild conditions with lithium dialkylcopper reagents (see **10-58**)[1892] to give high yields of ketones.[1893] The R′ group may be primary, secondary, or tertiary alkyl or aryl and may contain iodo, keto, ester, nitro, or cyano groups. The R groups that have been used successfully are methyl, primary alkyl, and vinylic. Secondary and tertiary alkyl groups can be introduced by the use of PhS(R)CuLi (p. 602) instead of R_2CuLi,[1894] or by the use of either the mixed homocuprate $(R'SO_2CH_2CuR)^-\ Li^+$,[1895] or a magnesium dialkylcopper reagent "RMeCuMgX."[1896] Secondary alkyl groups can also be introduced with the copper–zinc reagents RCu(CN)ZnI.[1897] The R group may be alkynyl if a

[1888]Burton, D.J.; Koppes, W.M. *J. Chem. Soc., Chem. Commun.* ***1973***, 425; *J. Org. Chem.* ***1975***, *40*, 3026; Anderson Jr., A.G.; Kono, D.H. *Tetrahedron Lett.* ***1973***, 5121.

[1889]For methods of converting acyl chlorides to bromides or iodides, see Schmidt, A.H.; Russ, M.; Grosse, D. *Synthesis* ***1981***, 216; Hoffmann, H.M.R.; Haase, K. *Synthesis* ***1981***, 715.

[1890]For a discussion of many of the reactions in this section, see House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 691–694, 734–765.

[1891]For a review, see Cais, M.; Mandelbaum, A., in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, Vol. 1, pp. 303–330.

[1892]See Posner, G.H. *An Introduction to Synthesis Using Organocopper Reagents*,Wiley, NY, ***1980***, pp. 81–85. Ryu, I.; Ikebe, M.; Sonoda, N.; Yamamoto, S.-y.; Yamamura, G.-h.; Komatsu, M. *Tetrahedron Lett.* ***2002***, *43*, 1257.

[1893]Vig, O.P.; Sharma, S.D.; Kapur, J.C. *J. Indian Chem. Soc.* ***1969***, *46*, 167; Jukes, A.E.; Dua, S.S.; Gilman, H. *J. Organomet. Chem.* ***1970***, *21*, 241; Posner, G.H.; Whitten, C.E.; McFarland, P.E. *J. Am. Chem. Soc.* ***1972***, *94*, 5106; Luong-Thi, N.; Rivière, H. *J. Organomet. Chem.* ***1974***, *77*, C52.

[1894]Posner, G.H.; Whitten, C.E.; Sterling, H.J. *J. Am. Chem. Soc.* ***1973***, *95*, 7788; Posner, G.H.; Whitten, C.E. *Tetrahedron Lett.* ***1973***, 1815; Bennett, G.B.; Nadelson, J.; Alden, L.; Jani, A. *Org. Prep. Proced. Int.* ***1976***, *8*, 13.

[1895]Johnson, C.R.; Dhanoa, D.S. *J. Org. Chem.* ***1987***, *52*, 1885.

[1896]Bergbreiter, D.E.; Killough, J.M. *J. Org. Chem.* ***1976***, *41*, 2750.

[1897]Knochel, P.; Yeh, M.C.P.; Berk, S.C.; Talbert, J. *J. Org. Chem.* ***1988***, *53*, 2390.

cuprous acetylide $R^2C{\equiv}CCu$ is the reagent.[1898] Organocopper reagents generated *in situ* from highly reactive copper, and containing such functional groups as cyano, chloro, and ester, react with acyl halides to give ketones.[1899]

Many other organometallic reagents[1900] give good yields of ketones when treated with acyl halides because, as with R_2CuLi, R_2Cd, these compounds do not generally react with the ketone product. A particularly useful class of organometallic reagent are organocadmium reagents R_2Cd, prepared from Grignard reagents (**12-22**). In this case, R may be aryl or primary alkyl. In general, secondary and tertiary alkylcadmium reagents are not stable enough to be useful in this reaction.[1901] An ester group may be present in either R′COX or R_2Cd. Direct treatment of the acid chloride with an alkyl halide and cadmium metal leads to the ketone in some cases.[1902] Organozinc compounds behave similarly to dialkylcadmium reagents, but are used less often.[1903] Organotin reagents R_4Sn react with acyl halides to give high yields of ketones, if a Pd complex is present.[1904] Organolead reagents R_4Pb behave similarly.[1905] Allylic halides and indium metal react with acyl chlorides to give the ketone.[1906] Various other groups, for example, nitrile, ester, and aldehyde can be present in the acyl halide without interference. Other reagents include organomanganese compounds[1907] (R can be primary, secondary, or tertiary alkyl, vinylic, alkynyl, or aryl), organozinc,[1908] and organothallium compounds (R can be primary alkyl or aryl).[1909] The reaction of an α-halo-ketone and an acyl chloride with SmI_2 leads to a β-diketone.[1910] Initial reaction of an acyl chloride with palladium(0), followed by reaction with potassium acetate and then a trialkylborane gave a ketone.[1911] Arylboronic acids and acid chloride give the ketone in

[1898]Castro, C.E.; Havlin, R.; Honwad, V.K.; Malte, A.; Mojé, S. *J. Am. Chem. Soc.* ***1969***, *91*, 6464. For methods of preparing acetylenic ketones, see Verkruijsse, H.D.; Heus-Kloos, Y.A.; Brandsma, L. *J. Organomet. Chem.* ***1988***, *338*, 289.

[1899]Wehmeyer, R.M.; Rieke, R.D. *Tetrahedron Lett.* ***1988***, *29*, 4513; Stack, D.E.; Dawson, B.T.; Rieke, R.D. *J. Am. Chem. Soc.* ***1992***, *114*, 5110.

[1900]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1389–1400.

[1901]Cason, J.; Fessenden, R. *J. Org. Chem.* ***1960***, *25*, 477.

[1902]Baruah, B.; Boruah. A.; Prajapati, D.; Sandhu, J.S. *Tetrahedron Lett.* ***1996***, *37*, 9087.

[1903]For examples, see Grey, R.A. *J. Org. Chem.* ***1984***, *49*, 2288; Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Org. Synth. 67*, 98.

[1904]Labadie, J.W.; Stille, J.K. *J. Am. Chem. Soc.* ***1983***, *105*, 669, 6129; Labadie, J.W.; Tueting, D.; Stille, J.K. *J. Org. Chem.* ***1983***, *48*, 4634. For a Me_3SiSnR_3 reagent, see Geng, F.; Maleczka, Jr., R.E. *Tetrahedron Lett.* ***1999***, *40*, 3113. For an allylic SnR_3 reagent, see Inoue, K.; Shimizu, Y.; Shibata, I.; Baba, A. *Synlett* ***2001***, 1659.

[1905]Yamada, J.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* ***1987***, 1302.

[1906]Yadav, J.S.; Srinivas, D.; Reddy, G.S.; Bindu, K.H. *Tetrahedron Lett.* ***1997***, *38*, 8745. Also see, Bryan, V.J.; Chan, T.-H. *Tetrahedron Lett.* ***1997***, *38*, 6493 for a similar reaction with an acyl imidazole.

[1907]Kim, S.-H.; Rieke, R.D. *J. Org. Chem.* ***1998***, *63*, 6766; Cahiez, G.; Martin, A.; Delacroix, T. *Tetrahedron Lett.* ***1999***, *40*, 6407.

[1908]Hanson, M.V.; Brown, J.D.; Rieke, R.D.; Niu, Q.J. *Tetrahedron Lett.* ***1994***, *35*, 7205; Filon, H.; Gosmini, C.; Périchon, J. *Tetrahedron* ***2003***, *59*, 8199.

[1909]Markó, I.E.; Southern, J.M. *J. Org. Chem.* ***1990***, *55*, 3368.

[1910]Ying, T.; Bao, W.; Zhang, Y.; Xu, W. *Tetrahedron Lett.* ***1996***, *37*, 3885.

[1911]Kabalka, G.W.; Malladi, R.R.; Tejedor, D.; Kelley, S. *Tetrahedron Lett.* ***2000***, *41*, 999.

the presence of a palladium catalyst.[1912] Similar reaction of acid chlorides, $NaBPh_4$, KF, and a palladium catalyst gave the aryl ketone.[1913] Antimony alkynes such as Ph_2Sb—C≡C—Ph react with acid chloride in the presence of a palladium catalyst to give the conjugated alkynyl ketone.[1914] Such conjugated ketones can also be prepared from an acyl halide, a terminal alkyne and a CuI catalyst[1915] a palladium catalyst,[1916] or with indium metal.[1917] Terminal alkynes react with chloroformates and a palladium catalyst to give the corresponding propargyl ester.[1918] Similar reaction of an alkyne with an acid chloride and a palladium–copper[1919] or CuI catalyst,[1920] both with microwave irradiation, gave the alkynyl ketones.

When the organometallic compound is a Grignard reagent,[1921] ketones are generally not obtained because the initially formed ketone reacts with a second molecule of RMgX to give the salt of a tertiary alcohol (**16-82**). Ketones *have* been prepared in this manner by the use of low temperatures, inverse addition (i.e., addition of the Grignard reagent to the acyl halide rather than the other way), excess acyl halide, and so on., but the yields are usually low, though high yields have been reported in THF at −78°C.[1922] Pretreatment with a trialkylphosphine and then the Grignard reagent can lead to the ketone.[1923] Using CuBr[1924] or a nickel catalyst[1925] with the Grignard reagent can lead to the ketone. Some ketones are unreactive toward Grignard reagents for steric or other reasons; these can be prepared in this way.[1926] Other methods involve running the reaction in the presence of Me_3SiCl[1927] (which reacts with the initial adduct in the tetrahedral mechanism, p. 1254), and the use of a combined Grignard-lithium diethylamide reagent.[1928] Also, certain metallic halides, notably ferric and cuprous halides, are catalysts

[1912]Urawa, Y.; Ogura, K. *Tetrahedron Lett.* ***2003***, *44*, 271.

[1913]Wang, J.-X.; Wei, B.; Hu, Y.; Liu, Z.; Yang, Y. *Synth. Commun.* ***2001***, *31*, 3885.

[1914]Kakusawa, N.; Yamaguchi, K.; Kurita, J.; Tsuchiya, T. *Tetrahedron Lett.* ***2000***, *41*, 4143.

[1915]Chowdhury, C.; Kundu, N.G. *Tetrahedron* ***1999***, *55*, 7011; Wang, J.-X.; Wei, B.; Hu, Y.; Liua, Z.; Kang, L. *J. Chem. Res. (S)* ***2001***, 146.

[1916]Karpov, A.S.; Müller, T.J.J. *Org. Lett.* ***2003***, *5*, 3451.

[1917]Augé, J.; Lubin-Germain, N.; Seghrouchni, L. *Tetrahedron Lett.* ***2003***, *44*, 819.

[1918]Böttcher, A.; Becker, H.; Brunner, M.; Preiss, T.; Henkelmann, J..; De Bakker, C.; Gleiter, R. *J. Chem. Soc., Perkin Trans.1* ***1999***, 3555.

[1919]Wang, J.-x.; Wei, B.; Huang, D.; Hu, Y.; Bai, L. *Synth. Commun.* ***2001***, *31*, 3337.

[1920]Wang, J.-X.; Wei, B.; Hu, Y.; Liu, Z.; Fu, Y. *Synth. Commun.* ***2001***, *31*, 3527.

[1921]For a review, see Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood, NJ, ***1954***, pp. 712–724.

[1922]Sato, M.; Inoue, M.; Oguro, K.; Sato, M. *Tetrahedron Lett.* ***1979***, 4303; Eberle, M.K.; Kahle, G.G. *Tetrahedron Lett.* ***1980***, *21*, 2303; Föhlisch, B.; Flogaus, R. *Synthesis* ***1984***, 734.

[1923]Maeda, H.; Okamoto, J.; Ohmori, H. *Tetrahedron Lett.* ***1996***, *37*, 5381.

[1924]Babudri, F.; Fiandanese, V.; Marchese, G.; Punzi, A. *Tetrahedron* ***1996***, *52*, 13513; *Tetrahedron Lett.* ***1995***, *36*, 7305.

[1925]Malanga, C.; Aronica, L.A.; Lardicci, L. *Tetrahedron Lett.* ***1995***, *36*, 9185. For the preparation of an amide from a *N,N*-dialkylcarbamyl chloride (R_2NCOCl) and a Grignard reagent, with a nickel catalyst, see Lemoucheux, L.; Rouden, J.; Lasne, M.-C. *Tetrahedron Lett.* ***2000***, *41*, 9997.

[1926]For example, see Lion, C.; Dubois, J.E.; Bonzougou, Y. *J. Chem. Res. (S)* ***1978***, 46; Dubois, J.E.; Lion, C.; Arouisse, A. *Bull. Soc. Chim. Belg.* ***1984***, *93*, 1083.

[1927]Cooke, Jr., M.P. *J. Org. Chem.* ***1986***, *51*, 951.

[1928]Fehr, C.; Galindo, J.; Perret, R. *Helv. Chim. Acta* ***1987***, *70*, 1745.

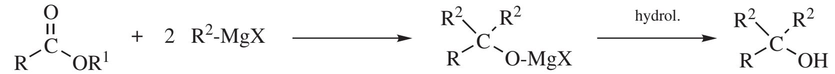
that improve the yields of ketone at the expense of tertiary alcohol.[1929] For these catalysis, both free radical and ionic mechanisms have been proposed.[1930]

Grignard reagents react with ethyl chloroformate to give carboxylic esters $EtOCOCl + RMgX \rightarrow EtOCOR$. Acyl halides can also be converted to ketones by treatment with $Na_2Fe(CO)_4$ followed by R′X (**10-76**).

OS **II**, 198; **III**, 601; **IV**, 708; **VI**, 248, 991; **VII**, 226, 334; **VIII**, 268, 274, 371, 441, 486.

16-82 The Conversion of Anhydrides, Carboxylic Esters, or Amides to Ketones With Organometallic Compounds[1931]

Dialkyl,hydroxy-de-alkoxy,oxo-tersubstitution; Alkyl-de-acyloxy- or de-amido substitution



When carboxylic esters are treated with Grignard reagents, addition to the carbonyl (**16-24**) generates a ketone. Under the reaction conditions, the initially formed ketones usually undergoes acyl substitution of R^2 for OR′ (**16-81**), so that tertiary alcohols are formed in which two R groups are the same. Isolation of the ketone as the major product is possible in some cases, particularly when the reaction is done at low temperature[1932] and when there is steric hindrance to the carbonyl in the first-formed ketone. Esters, RCO_2Me, react with $Zn(BH_4)_2$/EtMgBr to give an alcohol, RCH(OH)Et.[1933] Formates give secondary alcohols and carbonates give tertiary alcohols in which all three R groups are the same: $(EtO)_2C{=}O + RMgX \rightarrow R_3COMgX$. Acyl halides and anhydrides behave similarly, though these substrates are employed less often.[1934] Many side reactions are possible, especially when the acid derivative or the Grignard reagent is branched: enolizations, reductions (not for esters, but for halides), condensations, and cleavages, but the most important is simple substitution (**16-81**), which in some cases can be made to predominate. When 1,4-dimagnesium compounds are used, carboxylic esters are converted to cyclopentanols.[1935] 1,5-Dimagnesium

[1929]For examples, see Cason, J.; Kraus, K.W. *J. Org. Chem.* ***1961***, *26*, 1768, 1772; MacPhee, J.A.; Dubois, J.E. *Tetrahedron Lett.* ***1972***, 467; Cardellicchio, C.; Fiandanese, V.; Marchese, G.; Ronzini, L. *Tetrahedron Lett.* ***1987***, *28*, 2053; Fujisawa, T.; Sato, T. *Org. Synth.* *66*, 116; Babudri, F.; D'Ettole, A.; Fiandanese, V.; Marchese, G.; Naso, F. *J. Organomet. Chem.* ***1991***, *405*, 53.

[1930]For example, see Dubois, J.E.; Boussu, M. *Tetrahedron Lett.* ***1970***, 2523; *Tetrahedron* ***1973***, *29*, 3943; MacPhee, J.A.; Boussu, M.; Dubois, J.E. *J. Chem. Soc. Perkin Trans. 2* ***1974***, 1525.

[1931]For a review, see Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood, NJ, ***1954***, pp. 561–562, 846–908.

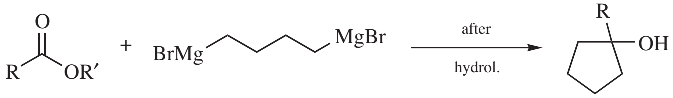
[1932]Deskus, J.; Fan, D.; Smith, M.B. *Synth. Commun.* ***1998***, *28*, 1649.

[1933]Hallouis, S.; Saluzzo, C.; Amouroux, R. *Synth. Commun.* ***2000***, *30*, 313.

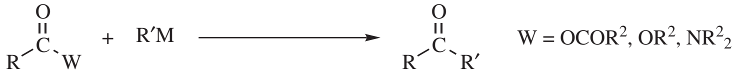
[1934]For a review of these reactions, see Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 549–766, 846–869.

[1935]Canonne, P.; Bernatchez, M. *J. Org. Chem.* ***1986***, *51*, 2147; ***1987***, *52*, 4025.

compounds give cyclohexanols, but in lower yields.[1936]



As is the case with acyl halides (**16-81**), anhydrides and carboxylic esters give tertiary alcohols (**16-82**) when treated with Grignard reagents. Low temperatures,[1937] the solvent HMPA,[1938] and inverse addition have been used to increase the yields of ketone.[1939] Amides give better yields of ketone at room temperature, but still not very high.[1940] Anhydrides can react with arylmagnesium halides at low temperature, and in the presence of (−)-sparteine, to give a keto acid with good enantioselectivity.[1941] Organocadmium reagents are less successful with these substrates than with acyl halides (**16-81**). Esters of formic acid, dialkylformamides, and lithium or sodium formate[1942] give good yields of aldehydes, when treated with Grignard reagents.



Alkyllithium compounds have been used to give ketones from carboxylic esters. The reaction must be carried out in a high-boiling solvent, such as toluene, since reaction at lower temperatures gives tertiary alcohols.[1943] Alkyllithium reagents also give good yields of carbonyl compounds with *N*,*N*-disubstituted amides.[1944] Dialkylformamides give aldehydes and other disubstituted amides give ketones and other acid derivatives have been used.[1945]

[1936]Kresge, A.J.; Weeks, D.P. *J. Am. Chem. Soc.* ***1984***, *106*, 7140. See also, Fife, T.H. *J. Am. Chem. Soc.* ***1967***, *89*, 3228; Craze, G.; Kirby, A.J.; Osborne, R. *J. Chem. Soc. Perkin Trans. 2* ***1978***, 357; Amyes, T.L.; Jencks, W.P. *J. Am. Chem. Soc.* ***1989***, *111*, 7888, 7900.

[1937]See, for example, Newman, M.S.; Smith, A.S. *J. Org. Chem.* ***1948***, *13*, 592; Edwards, Jr., W.R.; Kammann Jr., K.P. *J. Org. Chem.* ***1964***, *29*, 913; Araki, M.; Sakat, S.; Takei, H.; Mukaiyama, T. *Chem. Lett.* ***1974***, 687.

[1938]Huet, F.; Pellet, M.; Conia, J.M. *Tetrahedron Lett.* ***1976***, 3579.

[1939]For a list of preparations of ketones by the reaction of organometallic compounds with carboxylic esters, salts, anhydyrides, or amides, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1386–1389, 1400–1419.

[1940]For an improved procedure with amides, see Olah, G.S.; Prakash, G.K.S.; Arvanaghi, M. *Synthesis* ***1984***, 228. See Martín, R.; Romea, P.; Tey, C.; Urpí, F.; Vilarrasa, J. *Synlett* ***1997***, 1414 for reaction with an amide derived from morpholine and Grignard reagents, which gives the ketone in good yield. See Kashima, C.; Kita, I.; Takahashi, K.; Hosomi, A. *J. Heterocyclic Chem.* ***1995***, *32*, 25 for a related reaction.

[1941]Shintani, R.; Fu, G.C. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1057.

[1942]Bogavac, M.; Arsenijević, L.; Pavlov, S.; Arsenijević, V. *Tetrahedron Lett.* ***1984***, *25*, 1843.

[1943]Petrov, A.D.; Kaplan, E.P.; Tsir, Ya. *J. Gen. Chem. USSR* ***1962***, *32*, 691.

[1944]Evans, E.A. *J. Chem. Soc.* ***1956***, 4691. For the synthesis of a silyl ketone from a silyllithium reagent, see Clark, C.T.; Milgram, B.C.; Scheidt, K.A. *Org. Lett.* ***2004***, *6*, 3977. For a review, see Wakefield, B.J. *Organolithium Methods*, Academic Press, NY, ***1988***, pp. 82–88.

[1945]Mueller-Westerhoff, U.T.; Zhou, M. *Synlett* ***1994***, 975.

Ketones can also be obtained by treatment of the lithium salt of a carboxylic acid with an alkyllithium reagent (**16-28**). For an indirect way to convert carboxylic esters to ketones, see **16-82**. A similar reaction with hindered aryl carboxylic acids has been reported.[1946] Treatment of a β-amido acid with two equivalents of *n*-butyllithium, followed by reaction with an acid chloride leads to a β-keto amide.[1947] Carboxylic acids can be treated with 2-chloro-4,6-dimethoxy[1,3,5]-triazine and the RMgX/CuI to give ketones.[1948]

Disubstituted formamides can give addition of 2 equivalents of Grignard reagent. The products of this reaction (called *Bouveault reaction*) are an aldehyde and a tertiary amine.[1949] The use of an amide other than a formamide

can give a ketone instead of an aldehyde, but yields are generally low. The addition of 2 equivalents of phenyllithium to a carbamate gave good yields of the ketone, however.[1950] When butyllithium reacted with an α-carbamoyl secondary amide [$RCH(NHCO_2R')C(=O)NR^2_2$] at −78°C, the amide reacted preferentially to give the α-carbamoyl ketone.[1951] The reaction of *N*-(3-bromopropyl) lactams with *tert*-butyllithium gave cyclization to the bicyclic amino alcohol, and subsequent reduction with $LiAlH_4$ (**19-64**) gave the bicyclic amine.[1952] Ketones can also be prepared by treatment of thioamides with organolithium compounds (alkyl or aryl).[1953] Cerium reagents, such as $MeCeCl_2$, also add two R groups to an amide.[1954] More commonly, an organolithium reagent is treated with $CeCl_3$ to generate the organocerium reagent *in situ*.[1955] It has proven possible to add two different R groups by sequential addition of two Grignard reagents.[1956] Diketones have also been produced by using the bis(imidazole) derivative of oxalic acid.[1957] Alternatively, if R′ contains an α hydrogen, the product may be an enamine, and enamines have been synthesized in goods yields by this method.[1958] When an amide having a *gem*-dibromocyclopropyl unit elsewhere in the molecule was treated

[1946]Zhang, P.; Terefenko, E.A.; Slavin, J. *Tetrahedron Lett.* ***2001***, *42*, 2097.

[1947]Chen, Y.; Sieburth, S.Mc.N. *Synthesis* ***2002***, 2191.

[1948]DeLuca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* ***2001***, *3*, 1519.

[1949]For a review, see Spialtr, L.; Pappalardo, J.A. *The Acyclic Aliphatic Tertiary Amines*, Macmillan, NY, ***1965***, pp. 59–63.

[1950]Prakash, G.K.S.; York, C.; Liao, Q.; Kotian, K.; Olah, G.A. *Heterocycles* ***1995***, *40*, 79.

[1951]Sengupta, S.; Mondal, S.; Das, D. *Tetrahedron Lett.* ***1999***, *40*, 4107.

[1952]Jones, K.; Storey, J.M.D. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 769.

[1953]Tominaga, Y.; Kohra, S.; Hosomi, A. *Tetrahedron Lett.* ***1987***, *28*, 1529.

[1954]Calderwood, D.J.; Davies, R.V.; Rafferty, P.; Twigger, H.L.; Whelan, H.M. *Tetrahedron Lett.* ***1997***, *38*, 1241.

[1955]Ahn, Y.; Cohen, T. *Tetrahedron Lett.* ***1994***, *35*, 203.

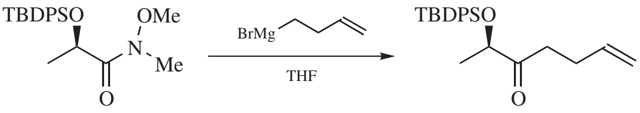
[1956]Comins, D.L.; Dernell, W. *Tetrahedron Lett.* ***1981***, *22*, 1085.

[1957]Mitchell, R.H.; Iyer, V.S. *Tetrahedron Lett.* ***1993***, *34*, 3683. Also see, Sibi, M.P.; Sharma, R.; Paulson, K.L. *Tetrahedron Lett.* ***1992***, *33*, 1941.

[1958]Hansson, C.; Wickberg, B. *J. Org. Chem.* ***1973***, *38*, 3074.

with methyllithium, Li—Br exchange was accompanied by intramolecular acyl addition to the amide carbonyl, giving a bicyclic amino alcohol.[1959]

N-Methoxy-*N*-methyl amides, such as, **114**, are referred to as a **Weinreb amide**.[1960] When a Weinreb amide reacts with a Grignard reagent or an organolithium reagent,[1961] the product is the ketone. The reaction of **56** with 3-butenylmagnesium bromide to give ketone **115** is a typical example.[1962] Aryloxy carbamates with a Weinreb amide unit, ArO_2C—NMe(OMe), react with RMgBr and then R′Li to give an unsymmetrical ketone, RC(=O)R′.[1963] Intramolecular displacement of a Weinreb amide by an organolithium reagent generated *in situ* from an iodide precursor leads to cyclic ketones.[1964] Reaction with vinylmagnesium bromide led to a β-*N*-methoxy-*N*-methylamino ketone, presumably by initial formation of the conjugated ketone followed by Michael addition (**15-24**) of the liberated amine.[1965] An interesting extension of this acyl substitution reaction coupled vinylmagnesium bromide with a Weinreb amide to give a conjugated ketone, which reacted with a secondary amine in a second step (see **15-31**) to give a β-amino ketone.[1966]



114 **115**

By the use of the compound *N*-methoxy-*N*,*N*′,*N*′-trimethylurea, it is possible to add two R groups as RLi, the same or different, to a CO group.[1967]

N,*N*-Disubstituted amides can be converted to alkynyl ketones by treatment with alkynylboranes: $RCONR^2_2 + (R'C{\equiv}C)_3B \rightarrow RCOC{\equiv}CR'$.[1968] Lactams react with triallylborane to give cyclic 2,2-diallyl amines after treatment with methanol, and then aqueous hydroxide.[1969] Triallylborane reacts with the carbonyl group of lactams, and after treatment with methanol and then aqueous NaOH gives the

[1959]Baird, M.S.; Huber, F.A.M.; Tverezovsky, V.V.; Bolesov, I.G. *Tetrahedron* ***2001***, *57*, 1593.

[1960]Nahm, S.; Weinreb, S.M. *Tetrahedron Lett.* ***1981***, *22*, 3815.

[1961]See Tallier, C.; Bellosta, V.; Meyer, C.; Cossy, J. *Org. Lett.* ***2004***, *6*, 2145.

[1962]Xie, W.; Zou, B.; Pei, D.; Ma, D. *Org. Lett.* ***2005***, *7*, 2775. For other exmaples see Andrés, J.M.; Pedrosa, R. Pérez-Encabo, A. *Tetrahedron* ***2000***, *56*, 1217.

[1963]Lee, N.R.; Lee, J.I. *Synth. Commun.* ***1999***, *29*, 1249.

[1964]Ruiz, J.; Sotomayor, N.; Lete, E. *Org. Lett.* ***2003***, *5*, 1115.

[1965]Gomtsyan, A. *Org. Lett.* ***2000***, *2*, 11. For a reaction with methyl esters with an excess of vinylmagnesium halide and a copper catalyst to give a 3-butenyl ketone by a similar acyl substitution–Michael addition route, see Hansford, K.A.; Dettwiler, J.E.; Lubell, W.D. *Org. Lett.* ***2003***, *5*, 4887.

[1966]Gomtsyan, A.; Koenig, R.J.; Lee, C.-H. *J. Org. Chem.* ***2001***, *66*, 3613.

[1967]Hlasta, D.J.; Court, J.J. *Tetrahedron Lett.* ***1989***, *30*, 1773. See also, Nahm, S.; Weinreb, S.M. *Tetrahedron Lett.* ***1981***, *22*, 3815.

[1968]Yamaguchi, M.; Waseda, T.; Hirao, I. *Chem. Lett.* ***1983***, 35.

[1969]Bubnov, Y.N.; Pastukhov, F.V.; Yampolsky, I.V.; Ignatenko, A.V. *Eur. J. Org. Chem.* ***2000***, 1503; Li, Z.; Zhang, Y. *Tetrahedron Lett.* ***2001***, *42*, 8507.

gem-diallyl amine: 2-pyrrolidinone → 2,2-diallylpyrrolidine.[1970] *N*,*N*-Disubstituted carbamates ($X = OR^2$) and carbamoyl chlorides (X = Cl) react with 2 equivalents of an alkyl- or aryllithium or Grignard reagent to give symmetrical ketones, in which both R groups are derived from the organometallic compound: $R'_2NCOX + 2\,RMgX \rightarrow R_2CO$.[1971] *N*,*N*-Disubstituted amides give ketones in high yields when treated with alkyllanthanum triflates $RLa(OTf)_2$.[1972]

Other organometallic reagents give acyl substitution. Sodium naphthalenide reacts with esters to give naphthyl ketones.[1973] Trimethylaluminum, which exhaustively methylates ketones (**16-24**), also exhaustively methylates carboxylic acids to give *tert*-butyl compounds[1974] (see also, **10-63**). Trimethylaluminum reacts with esters to form ketones, in the presence of *N*,*N*′-dimethylethyelnediamine.[1975] Thioesters (RCOSR′) react with arylboronic acids, in the presence of a palladium catalyst, to give the corresponding ketone,[1976] and esters react similarly with arylboronic acids (a palladium catalyst)[1977] or arylboronates (a ruthenium catalyst).[1978] Trialkylboranes have been similarly used to convert thioesters to ketones.[1979] Thioesters give good yields of ketones when treated with lithium dialkylcopper reagents R''_2CuLi (R″ = primary or secondary alkyl or aryl).[1980] Organozinc reagents also convert thioesters to ketones.[1981] Arylboronic acids also react with dialkyl anhydrides, with a rhodium catalyst[1982] or a palladium catalyst,[1983] to give the ketone. Aryl iodides react with acetic anhydride, with a palladium catalyst, to give the aryl methyl ketone.[1984] Diaryl- or dialkylzinc reagents react with anhydrides and a palladium catalyst[1985] or a nickel catalyst[1986] to give the ketone. Note that in the presence of a SmI_2 catalyst and 2 equivalents of allyl bromide, lactones were converted to the diallyl diol.[1987] *N*-(3-Iodopropyl)succinimide derivatives react with SmI_2 and an iron catalyst to give bicyclic pyrrolizidinone derivatives

[1970]Bubnov, Yu.N.; Klimkina, E.V.; Zhun', I.V.; Pastukhov, F.V.; Yampolsky, I.V. *Pure Appl. Chem.* ***2000***, *72*, 1641.

[1971]Michael, U.; Hörnfeldt, A. *Tetrahedron Lett.* ***1970***, 5219; Scilly, N.F. *Synthesis* ***1973***, 160.

[1972]Collins, S.; Hong, Y. *Tetrahedron Lett.* ***1987***, *28*, 4391.

[1973]Periasamy, M.; Reddy, M.R.; Bharathi, P. *Synth. Commun.* ***1999***, *29*, 677.

[1974]Meisters, A.; Mole, T. *Aust. J. Chem.* ***1974***, *27*, 1665.

[1975]Chung, E.-A.; Cho, C.-W.; Ahn, K.H. *J. Org. Chem.* ***1998***, *63*, 7590.

[1976]Liebeskind, L.S.; Srogl, J. *J. Am. Chem. Soc.* ***2000***, *122*, 11260; Wittenberg, R.; Srogi, J.; Egi, M.; Liebeskind, L.S. *Org. Lett.* ***2003***, *5*, 3033.

[1977]Tatanidani, H.; Kakiuchi, F.; Chatani, N. *Org. Lett.* ***2004***, *6*, 3597.

[1978]Tatanidani, H.; Yokota, K.; Kakiuchi, F.; Chatani, N. *J. Org. Chem.* ***2004***, *69*, 5615.

[1979]Yu, Y.; Liebeskind, L.S. *J. Org. Chem.* ***2004***, *69*, 3554.

[1980]Anderson, R.J.; Henrick, C.A.; Rosenblum, L.D. *J. Am. Chem. Soc.* ***1974***, *96*, 3654. See also, Kim, S.; Lee, J.I. *J. Org. Chem.* ***1983***, *48*, 2608.

[1981]Shimizu, T.; Seki, M. *Tetrahedron Lett.* ***2002***, *43*, 1039.

[1982]Frost, C.G.; Wadsworth, K.J. *Chem. Commun.* ***2001***, 2316.

[1983]Gooßen, L.J.; Ghosh, K. *Eur. J. Org. Chem.* ***2002***, 3254.

[1984]Cacchi, S.; Fabrizi, G.; Gavazza, F.; Goggiamani, A. *Org. Lett.* ***2003***, *5*, 289.

[1985]Wang, D.; Zhang, Z. *Org. Lett.* ***2003***, *5*, 4645; Bercot, E.A.; Rovis, T. *J. Am. Chem. Soc.* ***2004***, *126*, 10248.

[1986]Bercot, E.A.; Rovis, T. *J. Am. Chem. Soc.* ***2002***, *124*, 174; O'Brien, E.M.; Bercot, E.A.; Rovis, T. *J. Am. Chem. Soc.* ***2003***, *125*, 10498.

[1987]Lannou, M.-I.; Hélion, F.; Namy, J.-L. *Tetrahedron Lett.* ***2002***, *43*, 8007.

via intramolecular addition of the organometallic intermediate to one carbonyl.[1988] The reaction of alkylzinc halides and thioesters leads to ketones in the presence of 1.5% Pd/C,[1989] in what has been called *Fukuyama coupling*.[1990]

Carboxylic esters can be converted to their homologs (RCOOEt → RCH_2-COOEt) by treatment with Br_2CHLi followed by BuLi at −90°C. The ynolate RC≡COLi is an intermediate.[1991] If the ynolate is treated with 1,3-cyclohexadiene, followed by $NaBH_4$, the product is the alcohol RCH_2CH_2OH.[1992]

Note that acyl benzotriazoles react with β-keto esters to give diketones via acyl substitution.[1993] Acyl cyanides, RC(=O)CN, react with allylic bromides and indium metal to give the corresponding ketone.[1994] Coupling an acid chloride and a silyl amide, $R_3SiC(=O)NR'_2$, leads to an α-keto amide.[1995] Acyl benzotriazoles have been coupled with SmI_2 to give the 1,2-diketone.[1996] α-Cyanoketone (acyl nitriles) were coupled with YbI_2 in a similar manner.[1997]α-Keto phosphonate esters undergo radical acyl substitution to give cyclic ketones under photochemical conditions.[1998]

Silyl esters are converted to the enolate anion upon treatment with *n*-butyllithium, and subsequent addition of an aldehyde followed by saponification leads to the β-hydroxy acid.[1999]

Vinyl organometallic reagents can be added to acyl derivatives. Reaction of an alkyne with Cp_2ZrEt_2 generates the vinyl zirconium reagent, which react with ethyl chloroformate to give an α,β-unsaturated ester.[2000]

OS **I**, 226; **II**, 179, 602; **III**, 237, 831, 839; **IV**, 601; **VI**, 240, 278; **VIII**, 474, 505. OS **II**, 282; **72**, 32; **III**, 353; **IV**, 285; **VI**, 611; **VII**, 323, 451; **81**, 14.

16-83 The Coupling of Acyl Halides

De-halogen-coupling

$$2\,RCOCl \xrightarrow{\text{pyrophoric } \mathbf{Pb}} RCOCOR$$

[1988]Ha, D.-C.; Yun, C.-S.; Lee, Y. *J. Org. Chem.* ***2000***, *65*, 621.

[1989]Shimizu, T.; Seki, M. *Tetrahedron Lett.* ***2001***, *42*, 429.

[1990]See Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. *Tetrahedron Lett.* ***1998***, *39*, 3189; Mori, Y.; Seki, M. *Tetrahedron Lett.* ***2004***, *45*, 7343. For a different but related cross-coupling, see Zhang, Y.; Rovis, T. *J. Am. Chem. Soc.* ***2004***, *126*, 15964.

[1991]Kowalski, C.J.; Haque, M.S.; Fields, K.W. *J. Am. Chem. Soc.* ***1985***, *107*, 1429; Kowalski, C.J.; Haque, M.S. *J. Org. Chem.* ***1985***, *50*, 5140.

[1992]Kowalski, C.J.; Haque, M.S. *J. Am. Chem. Soc.* ***1986***, *108*, 1325.

[1993]Katritzky, A.R.; Wang, Z.; Wang, M.; Wilkerson, C.R.; Hall, C.D.; Akhmedov, N.G. *J. Org. Chem.* ***2004***, *69*, 6617.

[1994]Yoo, B.W.; Choi, K.H.; Lee, S.J.; Nam, G.S.; Chang, K.Y.; Kim, S.H.; Kim, J.H. *Synth. Commun.* ***2002***, *32*, 839.

[1995]Chen, J.; Cunico, R.F. *J. Org. Chem.* ***2004***, *69*, 5509.

[1996]Wang, X.; Zhang, Y. *Tetrahedron Lett.* ***2002***, *43*, 5431.

[1997]Saikia, P.; Laskar, D.D.; Prajapati, D.; Sandhu, J.S. *Tetahedron Lett.* ***2002***, *43*, 7525.

[1998]Kim, S.; Cho, C.H.; Lim, C.J. *J. Am. Chem. Soc.* ***2003***, *125*, 9574.

[1999]Bellassoued, M.; Grugier, J.; Lensen, N.; Catheline, A. *J. Org. Chem.* ***2002***, *67*, 5611.

[2000]Takahashi, T.; Xi, C.; Ura, Y.; Nakajima, K. *J. Am. Chem. Soc.* ***2000***, *122*, 3228.

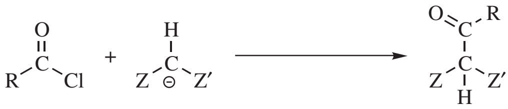
Acyl halides can be coupled with pyrophoric lead to give symmetrical α-diketones in a Wurtz-type reaction.[2001] The reaction has been performed with R = Me and Ph. Samarium iodide SmI_2[2002] gives the same reaction. Benzoyl chloride was coupled to give benzil by subjecting it to ultrasound in the presence of Li wire:

$$2\,PhCOCl + Li \longrightarrow PhCOCOPh.$$ [2003]

Unsymmetrical α-diketones, RCOCR′, have been prepared by treatment of an acyl halide RCOCl with an acyltin reagent ($R'COSnBu_3$), with a palladium complex catalyst.[2004]

16-84 Acylation at a Carbon Bearing an Active Hydrogen

Bis(ethoxycarbonyl)methyl-de-halogenation, and so on



This reaction is similar to **10-67**, but there are fewer examples.[2005] Either Z or Z′ may be any of the groups listed in **10-67**.[2006] Anhydrides react similarly but are used less often. The product contains three Z groups, since RCO is a Z group. One or two of these can be cleaved (**12-40**, **12-43**). In this way, a compound ZCH_2Z' can be converted to ZCH_2Z^2 or an acyl halide (RCOCl) to a methyl ketone ($RCOCH_3$). *O*-Acylation is sometimes a side reaction.[2007] When thallium(I) salts of ZCH_2Z' are used, it is possible to achieve regioselective acylation at either the C or the O position. For example, treatment of the thallium(I) salt of $MeCOCH_2COMe$ with acetyl chloride at −78°C gave >90% *O*-acylation, while acetyl fluoride at room temperature gave >95% *C*-acylation.[2008] The use of an alkyl chloroformate gives triesters.[2009]

The application of this reaction to simple ketones[2010] (in parallel with **10-68**) requires a strong base, such as $NaNH_2$ or Ph_3CNa, and is often complicated by

[2001]Mészáros, L. *Tetrahedron Lett.* ***1967***, 4951.

[2002]Souppe, J.; Namy, J.; Kagan, H.B. *Tetrahedron Lett.* ***1984***, *25*, 2869. See also, Collin, J.; Namy, J.; Dallemer, F.; Kagan, H.B. *J. Org. Chem.* ***1991***, *56*, 3118.

[2003]Han, B.H.; Boudjouk, P. *Tetrahedron Lett.* ***1981***, *22*, 2757.

[2004]Verlhac, J.; Chanson, E.; Jousseaume, B.; Quintard, J. *Tetrahedron Lett.* ***1985***, *26*, 6075. For another procedure, see Olah, G.A.; Wu, A. *J. Org. Chem.* ***1991***, *56*, 902.

[2005]For examples of reactions in this section, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1484–1485, 1522–1527.

[2006]For an improved procedure, see Rathke, M.W.; Cowan, P.J. *J. Org. Chem.* ***1985***, *50*, 2622.

[2007]When phase-transfer catalysts are used, *O*-acylation becomes the main reaction: Jones, R.A.; Nokkeo, S.; Singh, S. *Synth. Commun.* ***1977***, *7*, 195.

[2008]Taylor, E.C.; Hawks III, G.H.; McKillop, A. *J. Am. Chem. Soc.* ***1968***, *90*, 2421.

[2009]See, for example, Skarżewski, J. *Tetrahedron* ***1989***, *45*, 4593. For a review of triesters, see Newkome, G.R.; Baker, G.R. *Org. Prep. Proced. Int.* ***1986***, *19*, 117.

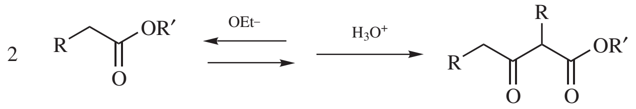
[2010]Hegedus, L.S.; Williams, R.E.; McGuire, M.A.; Hayashi, T. *J. Am. Chem. Soc.* ***1980***, *102*, 4973.

O-acylation, which in many cases becomes the principal pathway because acylation at the oxygen is usually much faster. It is possible to increase the proportion of *C*-acylated product by employing an excess (2–3 equivalents) of enolate anion (and adding the substrate to this, rather than vice versa), by the use of a relatively nonpolar solvent and a metal ion (e.g., Mg^{2+}), which is tightly associated with the enolate oxygen atom, by the use of an acyl halide rather than an anhydride,[2011] and by working at low temperatures.[2012] In cases where the use of an excess of enolate anion results in *C*-acylation, it is because *O*-acylation takes place first, and the *O*-acylated product (an enol ester) is then *C*-acylated. Simple ketones can be acylated by treatment of their silyl enol ethers with an acyl chloride in the presence of $ZnCl_2$ or $SbCl_3$.[2013] Ketones can be acylated by anhydrides to give β-diketones, with BF_3 as catalyst.[2014] Simple esters RCH_2COOEt can be acylated at the a carbon (at −78°C) if a strong base such as lithium *N*-isopropylcyclohexylamide is used to remove the proton.[2015]

OS **II**, 266, 268, 594, 596; **III**, 16, 390, 637; **IV**, 285, 415, 708; **V**, 384, 937; **VI**, 245; **VII**, 213, 359; **VIII**, 71, 326, 467. See also, OS **VI**, 620.

16-85 Acylation of Carboxylic Esters by Carboxylic Esters: The Claisen and Dieckmann Condensations

Alkoxycarbonylalkyl-de-alkoxy-substitution



When carboxylic esters containing an α hydrogen are treated with a strong base, such as sodium ethoxide, a condensation occurs to give a β-keto ester via an ester enolate anion.[2016] This reaction is called the *Claisen condensation*. When it is carried out with a mixture of two different esters, each of which possesses an α hydrogen (this reaction is called a mixed Claisen or a crossed Claisen condensation), a mixture of all four products is generally obtained and the reaction is seldom useful synthetically.[2017] However, if only one of the esters has an

[2011]See House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 762–765; House, H.O.; Auerbach, R.A.; Gall, M.; Peet, N.P. *J. Org. Chem.* ***1973***, *38*, 514.

[2012]Seebach, D.; Weller, T.; Protschuk, G.; Beck, A.K.; Hoekstra, M.S. *Helv. Chim. Acta* ***1981***, *64*, 716.

[2013]Tirpak, R.E.; Rathke, M.W. *J. Org. Chem.* ***1982***, *47*, 5099.

[2014]For a review, see Hauser, C.R.; Swamer, F.W.; Adams, J.T. *Org. React.* ***1954***, *8*, 59, 98–106.

[2015]For example, see Rathke, M.W.; Deitch, J. *Tetrahedron Lett.* ***1971***, 2953; Logue, M.W. *J. Org. Chem.* ***1974***, *39*, 3455; Couffignal, R.; Moreau, J. *J. Organomet. Chem.* ***1977***, *127*, C65; Ohta, S.; Shimabayashi, A.; Hayakawa, S.; Sumino, M.; Okamoto, M. *Synthesis* ***1985***, 45; Hayden, W.; Pucher, R.; Griengl, H. *Monatsh. Chem.* ***1987***, *118*, 415.

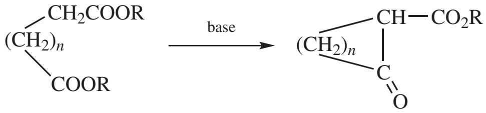
[2016]For a study of ester and amide enolate stabilization, see Rablen, P.R.; Bentrup, KL.H. *J. Am. Chem. Soc.* ***2003***, *125*, 2142.

[2017]For a method of allowing certain crossed-Claisen reactions to proceed with good yields, see Tanabe, Y. *Bull. Chem. Soc. Jpn.* ***1989***, *62*, 1917.

α hydrogen, the mixed reaction is frequently satisfactory. Among esters lacking a hydrogens (hence acting as the substrate ester) that are commonly used in this way are esters of aromatic acids, and ethyl carbonate and ethyl oxalate. When the ester enolate reacts with ethyl carbonate, the product is a malonic ester, and reaction with ethyl formate introduces a formyl group. Claisen condensation of phenyl esters with $ZrCl_4$ and diisopropylethylamine (Hünigs base) give the corresponding keto ester.[2018]

As with ketone enolate anions (see **16-34**), the use of amide bases under kinetic control conditions (strong base with a weak conjugate acid, aprotic solvents, low temperatures), allows the mixed Claisen condensation to proceed. Self-condensation of the lithium enolate with the parent ester is a problem when LDA is used as a base,[2019] but this is minimized with LICA (lithium isopropylcyclohexyl amide).[2020] Note that solvent-free Claisen condensation reactions have been reported.[2021]

When the two ester groups involved in the condensation are in the same molecule, the product is a cyclic β-keto ester and the reaction is called the *Dieckmann condensation*.[2022]



The Dieckmann condensation is most successful for the formation of five-, six-, and seven-membered rings. Yields for rings of 9–12 members are very low or nonexistent; larger rings can be closed with high-dilution techniques. Reactions in which large rings are to be closed are generally assisted by high dilution, since one end of the molecule has a better chance of finding the other end than of finding another molecule. A solvent-free Dieckmann condensation has been reported on solid potassium *tert*-butoxide.[2023] Dieckmann condensation of unsymmetrical substrates can be made regioselective (unidirectional) by the use of solid-phase supports.[2024]

The mechanism of the Claisen and Dieckmann reactions is the ordinary tetrahedral mechanism,[2025] with one molecule of ester being converted to a nucleophile by

[2018]Tanabe, Y.; Hamasaki, R.; Funakoshi, S. *Chem. Commun.* ***2001***, 1674.

[2019]Rathke, M.W.; Sullivan, D.F. *J. Am. Chem. Soc.* ***1973***, *95*, 3050; Lochmann, L.; Lím, D. *J. Organomet. Chem.* ***1973***, *50*, 9; Sullivan, D.F.; Woodbury, R.P.; Rathke, M.W. *J. Org. Chem.* ***1977***, *42*, 2038.

[2020]Rathke, M.W.; Lindert, A. *J. Am. Chem. Soc.* ***1971***, *93*, 2318.

[2021]Yoshizawa, K.; Toyota, S.; Toda, F. *Tetrahedron Lett.* ***2001***, *42*, 7983.

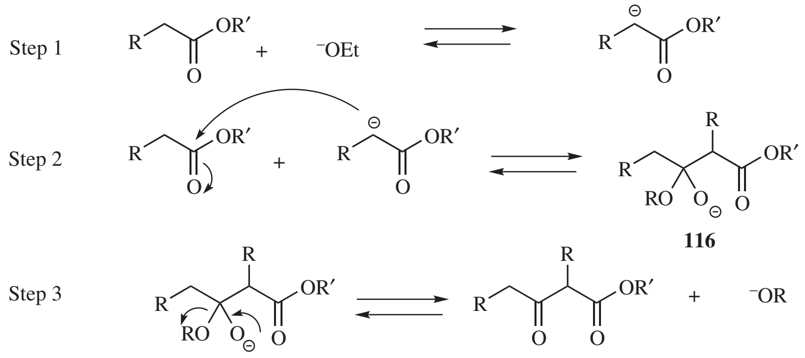
[2022]For a review, see Schaefer, J.P.; Bloomfield, J.J. *Org. React.* ***1967***, *15*, 1.

[2023]Toda, F.; Suzuki, T.; Higa, S. *J. Chem. Soc. Perkin Trans. 1* ***1998***, 3521.

[2024]Crowley, J.I.; Rapoport, H. *J. Org. Chem.* ***1980***, *45*, 3215. For another method, see Yamada, Y.; Ishii, T.; Kimura, M.; Hosaka, K. *Tetrahedron Lett.* ***1981***, *22*, 1353.

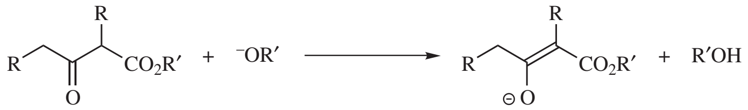
[2025]There is evidence that, at least in some cases, an SET mechanism is involved: Ashby, E.C.; Park, W. *Tetrahedron Lett.* ***1983***, 1667. The transition structures have also been examined by Nishimura, T.; Sunagawa, M.; Okajima, T.; Fukazawa, Y. *Tetrahedron Lett.* ***1997***, *38*, 7063.

the base and the other serving as the substrate.



This reaction illustrates the striking difference in behavior between carboxylic esters on the one hand and aldehydes and ketones on the other. When a carbanion, such as an enolate anion, is added to the carbonyl group of an aldehyde or ketone (**16-38**), the H or R is not lost, since these groups are much poorer leaving groups than OR. Instead the intermediate similar to **116** adds a proton at the oxygen to give a hydroxy compound.

In contrast to **10-67** ordinary esters react quite well, that is, two Z groups are not needed. A lower degree of acidity is satisfactory because it is not necessary to convert the attacking ester entirely to its ion. Step 1 is an equilibrium that lies well to the left. Nevertheless, the small amount of enolate anion formed is sufficient to attack the readily approachable ester substrate. All the steps are equilibria. The reaction proceeds because the product is converted to its conjugate base by the base present (i.e., a β-keto ester is a stronger acid than an alcohol):



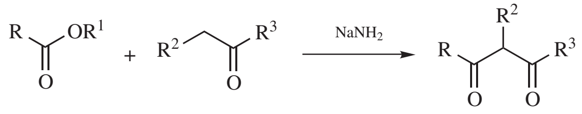
The use of a stronger base, such as $NaNH_2$, NaH, or KH,[2026] often increases the yield. For some esters stronger bases *must* be used, since sodium ethoxide is ineffective. Among these are esters of the type $R_2CHCOOEt$, the products of which ($R_2CHCOCR_2COOEt$) lack an acidic hydrogen, so that they cannot be converted to enolate anions by sodium ethoxide.[2027] The Dieckmann condensation has also been done using $TiCl_3/NBu_3$ with a TMSOTf catalyst.[2028] A Dieckmann-like condensation was reported where an α,ω-dicarboxylic acid was hated to 450°C on graphite, with microwave irradiation, to give the cyclic ketone.[2029]

[2026]Brown, C.A. *Synthesis* ***1975***, 326.
[2027]For a discussion, see Garst, J.F. *J. Chem. Educ.* ***1979***, *56*, 721.
[2028]Yoshida, Y.; Hayashi, R.; Sumihara, H.; Tanabe, Y. *Tetrahedron Lett.* ***1997***, *38*, 8727.
[2029]Marquié, J.; Laporterie, A.; Dubac, J.; Roques, N. *Synlett* ***2001***, 493.

OS **I**, 235; **II**, 116, 194, 272, 288; **III**, 231, 300, 379, 510; **IV**, 141; **V**, 288, 687, 989; **VIII**, 112.

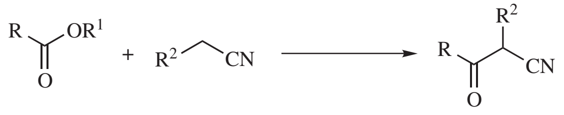
16-86 Acylation of Ketones and Nitriles by Carboxylic Esters

α-Acylalkyl-de-alkoxy-substitution



Carboxylic esters can be treated with ketones to give β-diketones. The reaction is so similar that it is sometimes also called the Claisen reaction, though this usage may be confusing. A strong base, such as sodium amide or sodium hydride, is required. Yields can be increased by the catalytic addition of crown ethers.[2030] Esters of formic acid (R = H) give β-keto aldehydes and ethyl carbonate gives β-keto esters. β-Keto esters can also be obtained by treating the lithium enolates of ketones with methyl cyanoformate MeOCOCN[2031] (in this case CN is the leaving group) and by treating ketones with KH and diethyl dicarbonate, $(EtOCO)_2O$.[2032]

In the case of unsymmetrical ketones, the attack usually comes from the less highly substituted side, so that CH_3 is more reactive than RCH_2, and the R_2CH group rarely attacks. This reaction has been used to effect cyclization, especially to prepare five- and six-membered rings. Nitriles are frequently used instead of ketones, the products being β-keto nitriles.



Other nucleophilic carbon reagents, such as acetylide ions, and ions derived from α-methylpyridines have also been used. A particularly useful nucleophile is the methylsulfinyl carbanion, $CH_3SOCH_2–$,[2033] the conjugate base of DMSO, since the β-keto sulfoxide produced can easily be reduced to a methyl ketone (p. 624). The methylsulfonyl carbanion ($CH_3SO_2CH_2^-$), the conjugate base of dimethyl sulfone, behaves similarly,[2034] and the product can be similarly reduced. Certain carboxylic esters, acyl halides, and DMF will acylate 1,3-dithianes[2035] (see **10-71**) to give, after oxidative hydrolysis with NBS or NCS, α-keto aldehydes or

[2030]Popik, V.V.; Nikolaev, V.A. *J. Org. Chem. USSR* ***1989***, *25*, 1636.

[2031]Mander, L.N.; Sethi, P. *Tetrahedron Lett.* ***1983***, *24*, 5425.

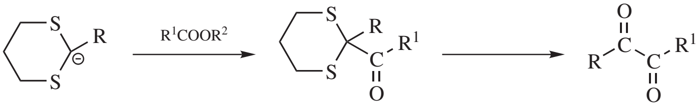
[2032]Hellou, J.; Kingston, J.F.; Fallis, A.G. *Synthesis* ***1984***, 1014.

[2033]See Durst, T. *Adv. Org. Chem.* ***1969***, *6*, 285, pp. 296–301.

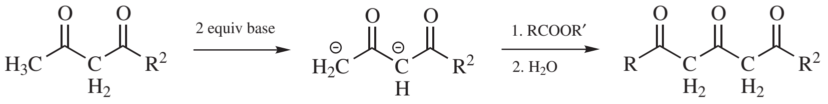
[2034]Schank, K.; Hasenfratz, H.; Weber, A. *Chem. Ber.* ***1973***, *106*, 1107, House, H.O.; Larson, J.K. *J. Org. Chem.* ***1968***, *33*, 61.

[2035]Corey, E.J.; Seebach, D. *J. Org. Chem.* ***1975***, *40*, 231

α-diketones,[254] for example,



As in **10-67**, a ketone attacks with its second most acidic position if 2 equivalents of base are used. Thus, β-diketones have been converted to 1,3,5-triketones.[2036]

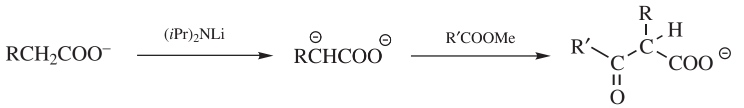


Side reactions are condensation of the ketone with itself (**16-34**), of the ester with itself, and of the ketone with the ester, but with the ester supplying the a position (**16-36**). The mechanism is the same as in **16-85**.[2037]

OS **I**, 238; **II**, 126, 200, 287, 487, 531; **III**, 17, 251, 291, 387, 829; **IV**, 174, 210, 461, 536; **V**, 187, 198, 439, 567, 718, 747; **VI**, 774; **VII**, 351.

16-87 Acylation of Carboxylic Acid Salts

α-Carboxyalkyl-de-alkoxy-substitution



We have previously seen (**10-70**) that dianions of carboxylic acids can be alkylated in the α position. These ions can also be acylated on treatment with a carboxylic ester[2038] to give salts of β-keto acids. As in **10-70**, the carboxylic acid can be of the form RCH_2COOH or $RR^2CHCOOH$. Since β-keto acids are so easily converted to ketones (**12-40**), this is also a method for the preparation of ketones $R'COCH_2R$ and $R'COCHRR^2$, where R′ can be primary, secondary, or tertiary alkyl, or aryl. If the ester is ethyl formate, an α-formyl carboxylate salt (R′ = H) is formed, which on acidification spontaneously decarboxylates into an aldehyde.[2039] This method accomplishes the conversion $RCH_2COOH \rightarrow RCH_2CHO$, and is an alternative to the reduction methods discussed in **19-39**. When the carboxylic acid is of the form RR″CHCOOH, better yields are obtained by acylating with acyl halides rather than esters.[2040]

[2036]Miles, M.L.; Harris, T.M.; Hauser, C.R. *J. Org. Chem.* ***1965***, *30*, 1007.
[2037]Hill, D.G.; Burkus, T.; Hauser, C.R. *J. Am. Chem. Soc.* ***1959***, *81*, 602.
[2038]Kuo, Y.; Yahner, J.A.; Ainsworth, C. *J. Am. Chem. Soc.* ***1971***, *93*, 6321; Angelo, B. *C.R. Seances Acad. Sci. Ser. C* ***1973***, *276*, 293.
[2039]Pfeffer, P.E.; Silbert, L.S. *Tetrahedron Lett.* ***1970***, 699; Koch, G.K.; Kop, J.M.M. *Tetrahedron Lett.* ***1974***, 603.
[2040]Krapcho, A.P.; Kashdan, D.S.; Jahngen, Jr., E.G.E.; Lovey, A.J. *J. Org. Chem.* ***1977***, *42*, 1189; Lion, C.; Dubois, J.E. *J. Chem. Res. (S)* ***1980***, 44.

16-88 Preparation of Acyl Cyanides

Cyano-de-halogenation

$$\text{RCOX} + \text{CuCN} \longrightarrow \text{RCOCN}$$

Acyl cyanides[2041] can be prepared by treatment of acyl halides with copper cyanide. The mechanism could be free-radical or nucleophilic substitution. The reaction has also been accomplished with thallium(I) cyanide,[2042] with Me_3SiCN and an $SnCl_4$ catalyst,[2043] and with Bu_3SnCN,[2044] but these reagents are successful only when R = aryl or tertiary alkyl. KCN has also been used, along with ultrasound,[2045] as has NaCN with phase-transfer catalysts.[2046]

OS **III**, 119.

16-89 Preparation of Diazo Ketones

Diazomethyl-de-halogenation

$$\text{RCOX} + \text{CH}_2\text{N}_2 \longrightarrow \text{RCOCHN}_2$$

The reaction between acyl halides and diazomethane is of wide scope and is the best way to prepare diazo ketones.[2047] Diazomethane must be present in excess or the HX produced will react with the diazo ketone (**10-52**). This reaction is the first step of the *Arndt–Eistert synthesis* (**18-8**). Diazo ketones can also be prepared directly from a carboxylic acid and diazomethane or diazoethane in the presence of DCC.[2048]

OS **III**, 119; **VI**, 386, 613; **VIII**, 196.

16-90 Ketonic Decarboxylation[2049]

Alkyl-de-hydroxylation

$$2\ \text{RCOOH} \xrightarrow[\text{ThO}_2]{400\text{–}500°\text{C}} \text{RCOR} + \text{CO}_2$$

[2041]For a review of acyl cyanides, see Hünig, S.; Schaller, R. *Angew. Chem. Int. Ed.* ***1982***, *21*, 36.

[2042]Taylor, E.C.; Andrade, J.G.; John, K.C.; McKillop, A. *J. Org. Chem.* ***1978***, *43*, 2280.

[2043]Olah, G.A.; Arvanaghi, M.; Prakash, G.K.S. *Synthesis* ***1983***, 636.

[2044]Tanaka, M. *Tetrahedron Lett.* ***1980***, *21*, 2959. See also Tanaka, M.; Koyanagi, M. *Synthesis* ***1981***, 973.

[2045]Ando, T.; Kawate, T.; Yamawaki, J.; Hanafusa, T. *Synthesis* ***1983***, 637.

[2046]Koenig, K.E.; Weber, W.P. *Tetrahedron Lett.* ***1974***, 2275. See also, Sukata, K. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 1085.

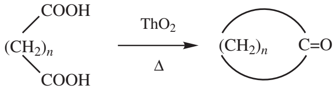
[2047]For reviews, see Fridman, A.L.; Ismagilova, G.S.; Zalesov, V.S.; Novikov, S.S. *Russ. Chem. Rev.* ***1972***, *41*, 371; Ried, W.; Mengler, H. *Fortshr. Chem. Forsch.*, ***1965***, *5*, 1.

[2048]Hodson, D.; Holt, G.; Wall, D.K. *J. Chem. Soc. C* ***1970***, 971.

[2049]For a review, see Kwart, H.; King, K., in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 362–370.

Carboxylic acids can be converted to symmetrical ketones by pyrolysis in the presence of thorium oxide. In a mixed reaction, formic acid and another acid heated over thorium oxide give aldehydes. Mixed alkyl aryl ketones have been prepared by heating mixtures of ferrous salts.[2050] When the R group is large, the methyl ester rather than the acid can be decarbmethoxylated over thorium oxide to give the symmetrical ketone.

The reaction has been performed on dicarboxylic acids, whereupon cyclic ketones are obtained:



This process, called *Ruzicka cyclization*, is good for the preparation of rings of six and seven members and, with lower yields, of C_8 and C_{10}–C_{30} cyclic ketones.[2051]

Not much work has been done on the mechanism of this reaction. However, a free-radical mechanism has been suggested on the basis of a thorough study of all the side products.[2052]

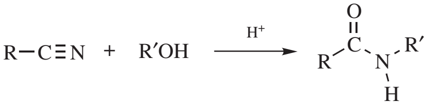
OS **I**, 192; **II**, 389; **IV**, 854; **V**, 589. Also see, OS **IV**, 55, 560.

REACTIONS IN WHICH CARBON ADDS TO THE HETEROATOM

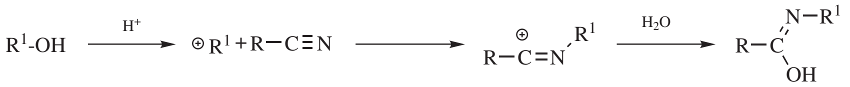
A. Oxygen Adding to the Carbon

16-91 The Ritter Reaction

***N*-Hydro,*N*-alkyl-*C*-oxo-biaddition**



Alcohols can be added to nitriles in an entirely different manner from that of reaction **16-9**. In this reaction, the alcohol is converted by a strong acid to a carbocation, which is attacked by the nucleophilic nitrogen atom to give **117**. Subsequent addition of water to the electrophilic carbon atom leads to the enol form of the amide (see **118**), which tautomerizes (p. 98) to the *N*-alkyl amide.



117 **118**

[2050]Granito, C.; Schultz, H.P. *J. Org. Chem.* ***1963***, *28*, 879.

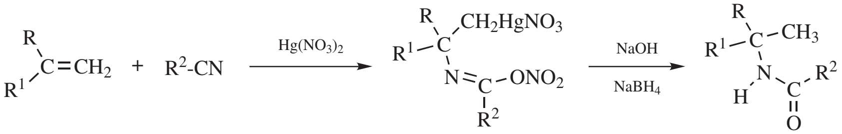
[2051]See, for example, Ruzicka, L.; Stoll, M.; Schinz, H. *Helv. Chim. Acta* ***1926***, *9*, 249; ***1928***, *11*, 1174; Ruzicka, L.; Brugger, W.; Seidel, C.F.; Schinz, H. *Helv. Chim. Acta* ***1928***, *11*, 496.

[2052]Hites, R.A.; Biemann, K. *J. Am. Chem. Soc.* ***1972***, *94*, 5772. See also, Bouchoule, C.; Blanchard, M.; Thomassin, R. *Bull. Soc. Chim. Fr.* ***1973***, 1773.

Only alcohols that give rise to fairly stable carbocations react (secondary, tertiary, benzylic, etc.); non-benzylic primary alcohols do not give the reaction. The carbocation need not be generated from an alcohol, but may come from protonation of an alkene or from other sources. In any case, the reaction is called the *Ritter reaction*.[2053] Lewis acids, such as $Mg(HSO_4)_2$, have been used to promote the reaction.[2054] Highly sterically hindered nitriles have been converted to *N*-methyl amides by heating with methanol and sulfuric acid.[2055] HCN also gives the reaction, the product being a formamide. Trimethylsilyl cyanide has also been used.[2056]

Since the amides (especially the formamides) are easily cleaved under hydrolysis conditions to amines, the Ritter reaction provides a method for achieving the conversions $R'OH \rightarrow R'NH_2$ (see **10-32**) and alkene $\rightarrow R'NH_2$ (see **15-8**) in those cases where R′ can form a relatively stable carbocation. The reaction is especially useful for the preparation of tertiary alkyl amines because there are few alternate ways of preparing these compounds. The reaction can be extended to primary alcohols by treatment with triflic anhydride[2057] or $Ph_2CCl^+ \ SbCl_6^-$ or a similar salt[2058] in the presence of the nitrile.

Alkenes of the form RCH=CHR′ and RR′C=CH_2 add to nitriles in the presence of mercuric nitrate to give, after treatment with $NaBH_4$, the same amides that would be obtained by the Ritter reaction.[2059] This method has the advantage of avoiding strong acids.



Benzylic compounds, such as ethylbenzene, react with alkyl nitriles, ceric ammonium nitrate, and a catalytic amount of *N*-hydroxysuccinimide to give the Ritter product, the amide.[2060]

The Ritter reaction can be applied to cyanamides RNHCN to give ureas RNHCONHR′.[2061]

OS **V**, 73, 471.

[2053]Ritter, J.J.; Minieri, P.P. *J. Am. Chem. Soc.* ***1948***, *70*, 4045. For reviews, see Krimen, L.I.; Cota, D.J. *Org. React.* ***1969***, *17*, 213; Beckwith, A.L.J., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 125–130; Johnson, F.; Madroñero, R. *Adv. Heterocycl. Chem.* ***1966***, *6*, 95; Tongco, E.C.; Prakash, G.K.S.; Olah, G.A. *Synlett* ***1997***, 1193.

[2054]Salehi, P.; Khodaei, M.M.; Zolfigol, M.A.; Keyvan, A. *Synth. Commun.* ***2001***, *31*, 1947.

[2055]Lebedev, M.Y.; Erman, M.B. *Tetrahedron Lett.* ***2002***, *43*, 1397.

[2056]Chen, H.G.; Goel, O.P.; Kesten, S.; Knobelsdorf, J. *Tetrahedron Lett.* ***1996***, *37*, 8129.

[2057]Martinez, A.G.; Alvarez, R.M.; Vilar, E.T.; Fraile, A.G.; Hanack, M.; Subramanian, L.R. *Tetrahedron Lett.* ***1989***, *30*, 581.

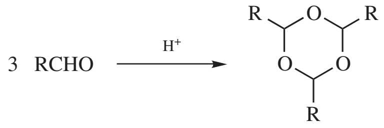
[2058]Barton, D.H.R.; Magnus, P.D.; Garbarino, J.A.; Young, R.N. *J. Chem. Soc. Perkin Trans. 1* ***1974***, 2101. See also, Top, S.; Jaouen, G. *J. Org. Chem.* ***1981***, *46*, 78.

[2059]Sokolov, V.I.; Reutov, O.A. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1968***, 225; Brown, H.C.; Kurek, J.T. *J. Am. Chem. Soc.* ***1969***, *91*, 5647; Chow, D.; Robson, J.H.; Wright, G.F. *Can. J. Chem.* ***1965***, *43*, 312; Fry, A.J.; Simon, J.A. *J. Org. Chem.* ***1982***, *47*, 5032.

[2060]Sakaguchi, S.; Hirabayashi, T.; Ishii, Y. *Chem. Commun.* ***2002***, 516.

[2061]Anatol, J.; Berecoechea, J. *Bull. Soc. Chim. Fr.* ***1975***, 395; *Synthesis* ***1975***, 111.

16-92 The Addition of Aldehydes to Aldehydes



When catalyzed by acids, low-molecular-weight aldehydes add to each other to give cyclic acetals, the most common product being the trimer.[2062] The cyclic trimer of formaldehyde is called *trioxane*,[2063] and that of acetaldehyde is known as *paraldehyde*. Under certain conditions, it is possible to get tetramers[2064] or dimers. Aldehydes can also polymerize to linear polymers, but here a small amount of water is required to form hemiacetal groups at the ends of the chains. The linear polymer formed from formaldehyde is called *paraformaldehyde*. Since trimers and polymers of aldehydes are acetals, they are stable to bases, but can be hydrolyzed by acids. Because formaldehyde and acetaldehyde have low boiling points, it is often convenient to use them in the form of their trimers or polymers.

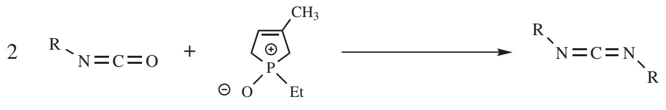
Aryl aldehydes condense with aliphatic aldehydes in the presence of benzoylformate decarboxylase and thiamin diphosphate to give an α-hydroxy ketone with god enantioselectivity.[2065]

A slightly related reaction involves nitriles, which can be trimerized with various acids, bases, or other catalysts to give triazines (see OS **III**, 71).[2066] Here HCl is most often used. Most nitriles with an α hydrogen do not give the reaction.

B. Nitrogen Adding to the Carbon

16-93 The Addition of Isocyanates to Isocyanates (Formation of Carbodiimides)

Alkylimino-de-oxo-bisubstitution



119

The treatment of isocyanates with 3-methyl-1-ethyl-3-phospholene-1-oxide (**119**) is a useful method for the synthesis of carbodiimides[2067] in good

[2062]For a review, see Bevington, J.C. *Q. Rev. Chem. Soc.* ***1952***, *6*, 141.

[2063]For a synthesis of trioxanes using bentonitic earth catalysts, see Camarena, R.; Cano, A.C.; Delgado, F.; Zúñiga, N.; Alvarez, C. *Tetrahedron Lett.* ***1993***, *34*, 6857.

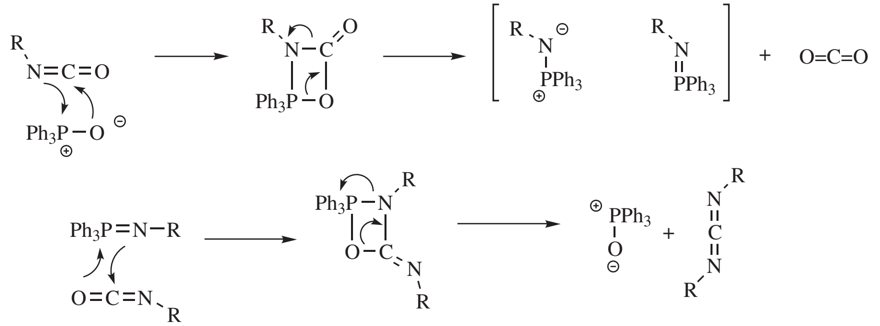
[2064]Barón, M.; de Manderola, O.B.; Westerkamp, J.F. *Can. J. Chem.* ***1963***, *41*, 1893.

[2065]Dünnwald, T.; Demir, A.S.; Siegert, P.; Pohl, M.; Müller, M. *Eur. J. Org. Chem.* ***2000***, 2161.

[2066]For a review, see Martin, D.; Bauer, M.; Pankratov, V.A. *Russ. Chem. Rev.* ***1978***, *47*, 975. For a review with respect to cyanamides RNH—CN, see Pankratov, V.A.; Chesnokova, A.E. *Russ. Chem. Rev.* ***1989***, *58*, 879. For reviews of the chemistry of carb.

[2067]For reviews of the chemistry of carbodiimides, see Williams, A.; Ibrahim, I.T. *Chem. Rev.* ***1981***, *81*, 589; Mikołajczyk, M.; Kiełbasiński, P. *Tetrahedron* ***1981***, *37*, 233; Kurzer, F.; Douraghi-Zadeh, K. *Chem. Rev.* ***1967***, *67*, 107.

yields.[2068] The mechanism does not simply involve the addition of one molecule of isocyanate to another, since the kinetics are first order in isocyanate and first order in catalyst. The following mechanism has been proposed (the catalyst is here represented as R_3P^+—O^-:[2069]



According to this mechanism, one molecule of isocyanate undergoes addition to C=O, and the other addition to C=N. Evidence is that ^{18}O labeling experiments have shown that each molecule of CO_2 produced contains one oxygen atom derived from the isocyanate and one from **119**,[2070] precisely what is predicted by this mechanism. Certain other catalysts are also effective.[2071] High-load, soluble oligomeric carbodiimides have been prepared.[2072]

OS **V**, 501.

16-94 The Conversion of Carboxylic Acid Salts to Nitriles

Nitrilo-de-oxido,oxo-tersubstitution

$$RCOO^- + BrCN \xrightarrow{250\text{–}300°C} RCN + CO_2$$

Salts of aliphatic or aromatic carboxylic acids can be converted to the corresponding nitriles by heating with BrCN or ClCN. Despite appearances, this is not a substitution reaction. When $R^{14}COO^-$ was used, the label appeared in the nitrile, not in the CO_2,[2073] and optical activity in R was retained.[2074] The acyl isocyanate RCON=C=O could be isolated from the reaction mixture; hence the

[2068]Campbell, T.W.; Monagle, J.J.; Foldi, V.S. *J. Am. Chem. Soc.* ***1962***, *84*, 3673.

[2069]Monagle, J.J.; Campbell, T.W.; McShane Jr., H.F. *J. Am. Chem. Soc.* ***1962***, *84*, 4288.

[2070]Monagle, J.J.; Mengenhauser, J.V. *J. Org. Chem.* ***1966***, *31*, 2321.

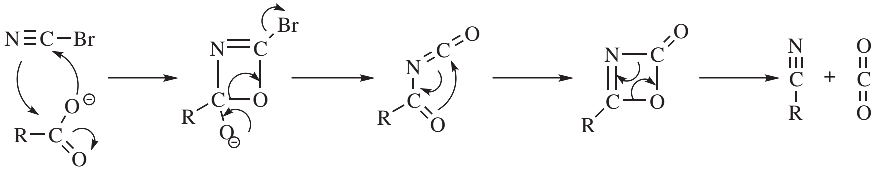
[2071]Monagle, J.J. *J. Org. Chem.* ***1962***, *27*, 3851; Appleman, J.O.; DeCarlo, V.J. *J. Org. Chem.* ***1967***, *32*, 1505; Ulrich, H.; Tucker, B.; Sayigh, A.A.R. *J. Org. Chem.* ***1967***, *32*, 1360; *Tetrahedron Lett.* ***1967***, 1731; Ostrogovich, G.; Kerek, F.; Buzás, A.; Doca, N. *Tetrahedron* ***1969***, *25*, 1875.

[2072]Zhang, M.; Vedantham, P.; Flynn, D.L.; Hanson, P.R. *J. Org. Chem.* ***2004***, *69*, 8340.

[2073]Douglas, D.E.; Burditt, A.M. *Can. J. Chem.* ***1958***, *36*, 1256.

[2074]Barltrop, J.A.; Day, A.C.; Bigley, D.B. *J. Chem. Soc.* ***1961***, 3185.

following mechanism was proposed:[2073]

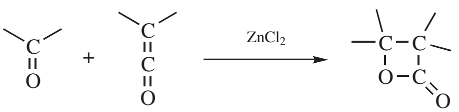


C. Carbon Adding to the Carbon.

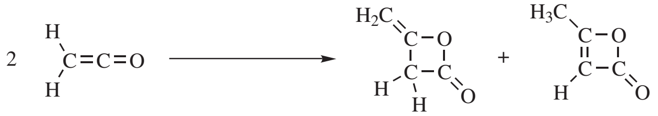
The reactions in this group are cycloadditions.

16-95 The Formation of β-Lactones and Oxetanes

(2+2)*OC*,*CC*-*cyclo*-[oxoethylene]-1/2/addition



Aldehydes, ketones, and quinones react with ketenes to give β-lactones,[2075] diphenylketene being used most often.[2076] The reaction is catalyzed by Lewis acids, and without them most ketenes do not give adducts because the adducts decompose at the high temperatures necessary when no catalyst is used. When ketene was added to chloral (Cl_3CCHO) in the presence of the chiral catalyst (+)-quinidine, one enantiomer of the β-lactone was produced with excellent enantioselectivity.[2077] The use of a chiral aluminum catalyst also led to β-lactones with good syn selectivity and good enantioselectivity.[2078] Other di- and trihalo aldehydes and ketones also give the reaction enantioselectively, with somewhat lower enantioselectivity.[2079] Ketene adds to another molecule of itself:



This dimerization is so rapid that ketene does not form β-lactones with aldehydes or ketones, except at low temperatures. Other ketenes dimerize more slowly. In

[2075]See Nelson, S.G.; Wan, Z.; Peclen, Y.J.; Spencer, K.L. *Tetrahedron Lett.* ***1999***, *40*, 6535; Cortez, G.S.; Tennyson, R.L.; Romo, D. *J. Am. Chem. Soc.* ***2001***, *123*, 7945.

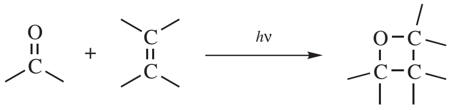
[2076]For reviews, see Muller, L.L.; Hamer, J. *1,2-Cycloaddition Reactions*, Wiley, NY, ***1967***, pp. 139–168; Ulrich, H. *Cycloaddition Reactions of Heterocumulenes*; Academic Press, NY, ***1967***, pp. 39–45, 64–74.

[2077]Wynberg, H.; Staring, E.G.J. *J. Am. Chem. Soc.* ***1982***, *104*, 166; *J. Chem. Soc., Chem. Commun.* ***1984***, 1181.

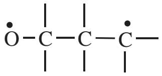
[2078]Nelson, S.G.; Zhu, C.; Shen, X. *J. Am. Chem. Soc.* ***2004***, *126*, 14.

[2079]Wynberg, H.; Staring, E.G.J. *J. Org. Chem.* ***1985***, *50*, 1977.

these cases, the major dimerization product is not the β-lactone, but a cyclobutanedione (see **15-63**). However, the proportion of ketene that dimerizes to β-lactone can be increased by the addition of catalysts, such as triethylamine or triethyl phosphite.[2080] Ketene acetals $R_2C{=}C(OR')_2$ add to aldehydes and ketones in the presence of $ZnCl_2$ to give the corresponding oxetanes.[2081]



Ordinary aldehydes and ketones can add to alkenes, under the influence of *UV* light, to give oxetanes. Quinones also react to give spirocyclic oxetanes.[2082] This reaction, called the *Paterno–Büchi reaction*,[2083] is similar to the photochemical dimerization of alkenes discussed at **15-63**. In general, the mechanism consists of the addition of an excited state of the carbonyl compound to the ground state of the alkene. Both singlet (S_1)[2084] and n,π^* triplet[2085] states have been shown to add to alkenes to give oxetanes. A diradical intermediate[2086]



has been detected by spectroscopic methods.[2087] Yields in the Paterno–Büchi reaction are variable, ranging from very low to fairly high (90%). The reaction can be

[2080]Farnum, D.G.; Johnson, J.R.; Hess, R.E.; Marshall, T.B.; Webster, B. *J. Am. Chem. Soc.* ***1965***, *87*, 5191; Elam, E.U. *J. Org. Chem.* ***1967***, *32*, 215.

[2081]Aben, R.W.; Hofstraat, R.; Scheeren, J.W. *Recl. Trav. Chim. Pays-Bas* ***1981***, *100*, 355. For a discussion of oxetane cycloreversion, see Miranda, M.A.; Izquierdo, M.A.; Galindo, F. *Org. Lett.* ***2001***, *3*, 1965.

[2082]Ciufolini, M.A.; Rivera-Fortin, M.A.; Byrne, N.E. *Tetrahedron Lett.* ***1993***, *34*, 3505.

[2083]For reviews, see Ninomiya, I.; Naito, T. *Photochemical Synthesis*, Academic Press, NY, ***1989***, pp. 138–152; Carless, H.A.J., in Coyle, J.D. *Photochemistry in Organic Synthesis*, Royal Society of Chemistry, London, ***1986***, pp. 95–117; Carless, H.A.J., in Horspool, W.M. *Synthetic Organic Photochemistry*, Plenum, NY, ***1984***, pp. 425–487; Jones II, M. *Org. Photochem.* ***1981***, *5*, 1; Arnold, D.R. *Adv. PhotoChem.* ***1968***, *6*, 301–423; Chapman, O.L.; Lenz, G. *Org. Photochem.* ***1967***, *1*, 283, pp. 283–294; Muller, L.L.; Hamer, J. *1,2-Cycloaddition Reactions*, Wiley, NY, ***1967***, pp. 111–139. Also see, Bosch, E.; Hubig, S.M.; Kochi, J.K. *J. Am. Chem. Soc.* ***1998***, *120*, 386; Bach, T.; Jödicke, K.; Kather, K.; Frölich, R. *J. Am. Chem. Soc.* ***1997***, *119*, 2437; Hu, S.; Neckers, D.C. *J. Org. Chem.* ***1997***, *62*, 564.

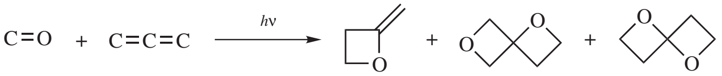
[2084]See, for example, Turro, N.J. *Pure Appl. Chem.* ***1971***, *27*, 679; Yang, N.C.; Kimura, M.; Eisenhardt, W. *J. Am. Chem. Soc.* ***1973***, *95*, 5058; Singer, L.A.; Davis, G.A.; Muralidharan, V.P. *J. Am. Chem. Soc.* ***1969***, *91*, 897; Barltrop, J.A.; Carless, H.A.J. *J. Am. Chem. Soc.* ***1972***, *94*, 1951, 8761.

[2085]Arnold, D.R.; Hinman, R.L.; Glick, A.H. *Tetrahedron Lett.* ***1964***, 1425; Yang, N.C.; Nussim, M.; Jorgenson, M.J.; Murov, S. *Tetrahedron Lett.* ***1964***, 3657.

[2086]For other evidence for these diradical intermediates, see references cited in Griesbeck, A.G.; Stadmüller, S. *J. Am. Chem. Soc.* ***1990***, *112*, 1281. See also, Kutateladze, A.G. *J. Am. Chem. Soc.* ***2001***, *123*, 9279.

[2087]Freilich, S.C.; Peters, K.S. *J. Am. Chem. Soc.* ***1981***, *103*, 6255; ***1985***, *107*, 3819. For a review, see Griesbeck, A.G.; Mauder, H.; Stadmüller, S. *Accts. Chem. Res.* ***1994***, *27*, 70.

highly diastereoselective,[2088] and allylic alcohols were shown to react with aldehydes to give an oxetane with syn selectivity.[2089] There are several side reactions. When the reaction proceeds through a triplet state, it can in general be successful only when the alkene possesses a triplet energy comparable to, or higher than, the carbonyl compound; otherwise energy transfer from the excited carbonyl group to the ground-state alkene can take place (triplet-triplet photosensitization, see p. 340).[2090] In most cases, quinones react normally with alkenes, giving oxetane products, but other α,β-unsaturated ketones usually give preferential cyclobutane formation (**15-63**). Aldehydes and ketones also add photochemically to allenes to give the corresponding alkylideneoxetanes and dioxaspiro compounds:[2091] Aldehydes add to silyl enol ethers.[2092] An intramolecular reaction of ketones was reported to give a bicyclic oxetane via photolysis on the solid state.[2093]



OS **III**, 508; **V**, 456. For the reverse reaction, see OS **V**, 679.

16-96 The Formation of β-Lactams

(2+2)*NC*,*CC-cyclo*-[oxoethylene]-1/2/addition

Ketenes add to imines to give β-lactams.[2094] The reaction is generally carried out with ketenes of the form $R_2C{=}C{=}O$. It has not been successfully applied to

[2088]Bach, T.; Jödicke, K.; Wibbeling, B. *Tetrahedron* ***1996***, *52*, 10861; Fleming, S.A.; Gao, J.J. *Tetrahedron Lett.* ***1997***, *38*, 5407; Vasudevan, S.; Brock, C.P.; Watt, D.S.; Morita, H. *J. Org. Chem.* ***1994***, *59*, 4677; Adam, W.; Stegmann, V.R.; Weinkötz, S. *J. Am. Chem. Soc.* ***2001***, *123*, 2452; Adam, W.; Stegmann, V.R. *J. Am. Chem. Soc.* ***2002***, *124*, 3600. For a discussion of the origins of regioselectivity, see Ciufolini, M.A.; Rivera-Fortin, M.A.; Zuzukin, V.; Whitmire, K.H. *J. Am. Chem. Soc.* ***1994***, *116*, 1272.

[2089]Greisbeck, A.G.; Bondock, S. *J. Am. Chem. Soc.* ***2001***, *123*, 6191. See also, Adam, W.; Stegmann, V.R. *Synthesis* ***2001***, 1203.

[2090]For a spin-directed reaction, see Griesbeck, A.G.; Fiege, M.; Bondock, S.; Gudipati, M.S. *Org. Lett.* ***2000***, *2*, 3623.

[2091]Howell, A.R.; Fan, R.; Truong, A. *Tetrahedron Lett.* ***1996***, *37*, 8651. For a review of the formation of heterocycles by cycloadditions of allenes, see Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis*, Wiley, NY, ***1984***, pp. 317–326.

[2092]Abe, M.; Tachibana, K.; Fujimoto, K.; Nojima, M. *Synthesis* ***2001***, 1243.

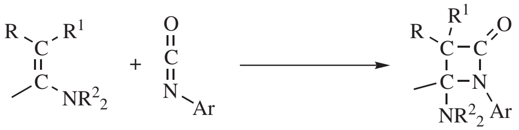
[2093]Kang, T.; Scheffer, J.R. *Org. Lett.* ***2001***, *3*, 3361.

[2094]For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1919–1921. For reviews of the formation of β-lactams, see Brown, M.J. *Heterocycles* ***1989***, *29*, 2225; Isaacs, N.S. *Chem. Soc. Rev.* ***1976***, *5*, 181; Mukerjee, A.K.; Srivastava, R.C. *Synthesis* ***1973***, 327; Muller, L.L.; Hamer, J. *1,2-Cycloaddition Reactions*, Wiley, NY, ***1967***, pp. 173–206; Ulrich, H. *Cycloaddition Reactions of Heterocumulenes*, Academic Press, NY, ***1967***, pp. 75–83, 135–152; Anselme, J., in Patai, S. *The Chemistry of the Carbon–Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 305–309. For a review of cycloaddition reactions of imines, see Sandhu, J.S.; Sain, B. *Heterocycles* ***1987***, *26*, 777.

RCH=C=O, except when these are generated *in situ* by decomposition of a diazo ketone (the Wolff rearrangement, **18-8**) in the presence of the imine. It has been done with ketene, but the more usual course with this reagent is an addition to the enamine tautomer of the substrate. Thioketenes[2095] ($R_2C=C=S$) give β-thiolactams.[2096] Imines also form β-lactams when treated with (*1*) zinc (or another metal[2097]) and an α-bromo ester (Reformatsky conditions, **16-28**),[2098] or (*2*) the chromium carbene complexes $(CO)_5Cr=C(Me)OMe$.[2099] The latter method has been used to prepare optically active β-lactams.[2100] Ketenes have also been added to certain hydrazones (e.g., $PhCH=NNMe_2$) to give *N*-amino β-lactams.[2101] A polymer-bound pyridinium salt facilitates β-lactam formation from carboxylic acids and imines.[2102]

N-Tosyl imines react with ketenes, Proton Sponge (p. 365) and a chiral amine to give the *N*-tosyl β-lactam with good enantioselectivity.[2103] A chiral ferrocenyl catalyst also gives good enantioselectivity,[2104] and chiral ammonium salts have been used as catalysts.[2105] A catalytic amount of benzoyl quinine gives β-lactams with good enantioselectivity.[2106] An intramolecular version of this ketene-imine reaction is known.[2107]

Like the similar cycloaddition of ketenes to alkenes (**15-63**), most of these reactions probably take place by the diionic mechanism *c* (p. 1224).[2108] β-Lactams have also been prepared in the opposite manner: by the addition of enamines to isocyanates:[2109]



[2095]For a review of thioketenes, see Schaumann, E. *Tetrahedron* ***1988***, *44*, 1827.
[2096]Schaumann, E. *Chem. Ber.* ***1976***, *109*, 906.
[2097]With In: Banik, B.K.; Ghatak, A.; Becker, F.F. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 2179.
[2098]For a review, see Hart, D.J.; Ha, D. *Chem. Rev.* ***1989***, *89*, 1447.
[2099]Hegedus, L.S.; McGuire, M.A.; Schultze, L.M.; Yijun, C.; Anderson, O.P. *J. Am. Chem. Soc.* ***1984***, *106*, 2680; Hegedus, L.S.; McGuire, M.A.; Schultze, L.M. *Org. Synth. 65*, 140.
[2100]Hegedus, L.S.; Imwinkelried, R.; Alarid-Sargent, M.; Dvorak, D.; Satoh, Y. *J. Am. Chem. Soc.* ***1990***, *112*, 1109.
[2101]Sharma, S.D.; Pandhi, S.B. *J. Org. Chem.* ***1990***, *55*, 2196.
[2102]Donati, D.; Morelli, C.; Porcheddu, A.; Taddei, M. *J. Org. Chem.* ***2004***, *69*, 9316.
[2103]Taggi, A.E.; Hafez, A.M.; Wack, H.; Young, B.; Drury III, W.J.; Lectka, T. *J. Am. Chem. Soc.* ***2000***, *122*, 7831.
[2104]Hodous, B.L.; Fu, G.C. *J. Am. Chem. Soc.* ***2002***, *124*, 1578.
[2105]Taggi, A.E.; Hafez, A.M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. *J. Am. Chem. Soc.* ***2002***, *124*, 6626.
[2106]Shah, M.H.; France, S.; Lectka, T. *Synlett* ***2003***, 1937.
[2107]Clark, A.J.; Battle, G.M.; Bridge, A. *Tetrahedron Lett.* ***2001***, *42*, 4409.
[2108]See Moore, H.W.; Hernandez Jr., L.; Chambers, R. *J. Am. Chem. Soc.* ***1978***, *100*, 2245; Pacansky, J.; Chang, J.S.; Brown, D.W.; Schwarz, W. *J. Org. Chem.* ***1982***, *47*, 2233; Brady, W.T.; Shieh, C.H. *J. Org. Chem.* ***1983***, *48*, 2499.
[2109]For example, see Perelman, M.; Mizsak, S.A. *J. Am. Chem. Soc.* ***1962***, *84*, 4988; Opitz, G.; Koch, J. *Angew. Chem. Int. Ed.* ***1963***, *2*, 152.

The reactive compound chlorosulfonyl isocyanate ($ClSO_2NCO$)[2110] forms β-lactams even with unactivated alkenes,[2111] as well as with imines,[2112] allenes,[2113] conjugated dienes,[2114] and cyclopropenes.[2115] With microwave irradiation, alkyl isocyanates also react.[2116]

α-Diazo ketones react with imines and microwave irradiation to give β-lactams.[2117] Allylic phosphonate esters react with imines, in the presence of a palladium catalyst, to give β-lactams.[2118] Alkynyl reagents, such as $BuC{\equiv}CO{-}Li^{+}$, react with imines to form β-lactams.[2119] Imines and benzylic halides react to give β-lactams in the presence of CO and a palladium catalyst.[2120] Conjugated amides react with NBS and 20% sodium acetate to give an α-bromo β-lactam.[2121] A different approach to β-lactams heated aziridines with CO and a cobalt catalyst.[2122] Aziridines also react with CO and a dendrimer catalyst to go a β-lactam.[2123]

OS **V**, 673; **VIII**, 3, 216.

ADDITION TO ISOCYANIDES[2124]

Addition to $R{-}^{+}N{\equiv}C^{-}$ is not a matter of a species with an electron pair adding to one atom and a species without a pair adding to the other, as is addition to the other types of double and triple bonds in this chapter and Chapter 15. In these additions, the electrophile and the nucleophile *both add to the carbon*. No species

[2110]For reviews of this compound, see Kamal, A.; Sattur, P.B. *Heterocycles* ***1987***, *26*, 1051; Szabo, W.A. *Aldrichimica Acta* ***1977***, *10*, 23; Rasmussen, J.K.; Hassner, A. *Chem. Rev.* ***1976***, *76*, 389; Graf, R. *Angew. Chem. Int. Ed.* ***1968***, *7*, 172.

[2111]Graf, R. *Liebigs Ann. Chem.* ***1963***, *661*, 111; Bestian, H. *Pure Appl. Chem.* ***1971***, *27*, 611. See also, Barrett, A.G.M.; Betts, M.J.; Fenwick, A. *J. Org. Chem.* ***1985***, *50*, 169.

[2112]McAllister, M.A.; Tidwell, T.T. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 2239; Sordo, J.A.; González, J.; Sordo, T.L. *J. Am. Chem. Soc.* ***1992***, *114*, 6249.

[2113]Moriconi, E.J.; Kelly, J.F. *J. Org. Chem.* ***1968***, *33*, 3036. See also, Martin, J.C.; Carter, P.L.; Chitwood, J.L. *J. Org. Chem.* ***1971***, *36*, 2225.

[2114]Moriconi, E.J.; Meyer, W.C. *J. Org. Chem.* ***1971***, *36*, 2841; Malpass, J.R.; Tweddle, N.J. *J. Chem. Soc. Perkin Trans. 1* ***1977***, 874.

[2115]Moriconi, E.J.; Kelly, J.F.; Salomone, R.A. *J. Org. Chem.* ***1968***, *33*, 3448.

[2116]Taguchi, Y.; Tsuchiya, T.; Oishi, A.; Shibuya, I. *Bull. Chem. Soc. Jpn.* ***1996***, *69*, 1667.

[2117]Linder, M.R.; Podlech, J. *Org. Lett.* ***2001***, *3*, 1849.

[2118]Torii, S.; Okumoto, H.; Sadakane, M.; Hai, A.K.M.A.; Tanaka, H. *Tetrahedron Lett.* ***1993***, *34*, 6553.

[2119]Shindo, M.; Oya, S.; Sato, Y.; Shishido, K. *Heterocycles* ***1998***, *49*, 113.

[2120]Cho, C.S.; Jiang, L.H.; Shim, S.C. *Synth. Commun.* ***1999***, *29*, 2695.

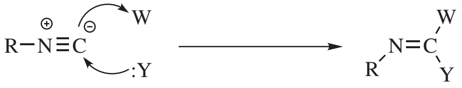
[2121]Naskar, D.; Roy, S. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 2435.

[2122]Davoli, P.; Forni, A.; Moretti, I.; Prati, F.; Torre, G. *Tetrahedron* ***2001***, *57*, 1801; Davoli, P.; Prati, F. *Heterocycles* ***2000***, *53*, 2379.

[2123]Lu, S.-M.; Alper, H. *J. Org. Chem.* ***2004***, *69*, 3558.

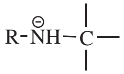
[2124]For a monograph, see Ugi, I. *Isonitrile Chemistry*, Academic Press, NY, ***1971***. For reviews, see Walborsky, H.M.; Periasamy, M.P., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 2, Wiley, NY, ***1983***, pp. 835–887; Hoffmann, P.; Marquarding, D.; Kliimann, H.; Ugi, I., in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 853–883.

add to the



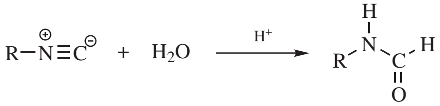
120

nitrogen, which, however, loses its positive charge by obtaining as an unshared pair one of the triple-bond pairs of electrons to give **120**. In most of the reactions considered below, **120** undergoes a further reaction, so the product is of the form.

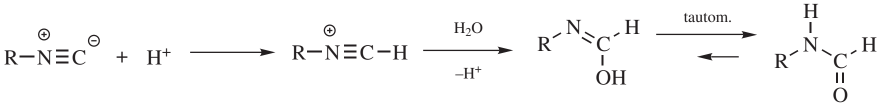


16-97 The Addition of Water to Isocyanides

1/*N*,2/*C*-Dihydro-2/*C*-oxo-biaddition



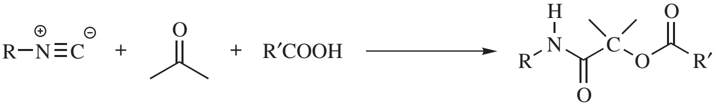
Formamides can be prepared by the acid-catalyzed addition of water to isocyanides. The mechanism is probably[2125]



The reaction has also been carried out under alkaline conditions, with hydroxide in aqueous dioxane.[2126] The mechanism here involves nucleophilic attack by hydroxide at the carbon atom. An intramolecular addition of an alkyne (in an ortho alkynyl phenyl isonitrile) to the carbon of an isonitrile occurred with heating in methanol to give quinoline derivatives.[2127]

16-98 The Passerini and Ugi Reactions[2128]

1/*N*-Hydro-2/*C*-(α-acyloxyalkyl),2/*C*-oxo-biaddition



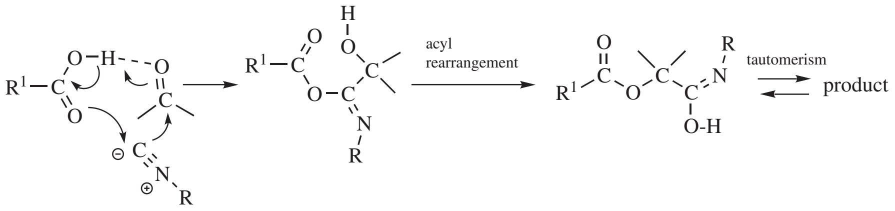
[2125]Drenth, W. *Recl. Trav. Chim. Pays-Bas* ***1962***, *81*, 319; Lim, Y.Y.; Stein, A.R. *Can. J. Chem.* ***1971***, *49*, 2455.

[2126]Cunningham, I.D.; Buist, G.J.; Arkle, S.R. *J. Chem. Soc. Perkin Trans. 2* ***1991***, 589.

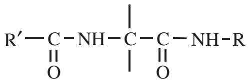
[2127]Suginome, M.; Fukuda, T.; Ito, Y. *Org. Lett.* ***1999***, *1*, 1977.

[2128]For reviews, see Ugi, I. *Angew. Chem. Int. Ed.* ***1982***, *21*, 810; Marquarding, D.; Gokel, G.W.; Hoffmann, P.; Ugi, I. in Ugi, I. *Isonitrile Chemistry*, Academic Press, NY, ***1971***, pp. 133–143, Gokel, G.W.; Lüdke, G.; Ugi, I. in Ugi, I. Ref. 936, pp. 145–199, 252–254.

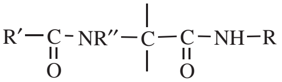
When an isocyanide is treated with a carboxylic acid and an aldehyde or ketone, an α-acyloxy amide is prepared. This is called the *Passerini reaction*. A $SiCl_4$-mediated reaction in the presence of a chiral bis-phosphoramide gives an α-hydroxy amide with good enantioselectivity.[2129] The following mechanism has been postulated for the basic reaction:[2130]



If ammonia or an amine is also added to the mixture (in which case the reaction is known as the *Ugi reaction*, or the *Ugi four-component condensation*, abbreviated 4 CC), the product is the corresponding bis(amide)



(from NH_3) or



(from a primary amine R^2NH_2).

Repetitive Ugi reactions are known.[2131] This product probably arises from a reaction between the carboxylic acid, the isocyanide, and the *imine* formed from the aldehyde or ketone and ammonia or the primary amine. The use of an *N*-protected amino acid[2132] or peptide as the carboxylic acid component and/or the use of an isocyanide containing a C-protected carboxyl group allows the reaction to be used for peptide synthesis.[2133]

[2129]Denmark, S.E.; Fan, Y. *J. Am. Chem. Soc.* ***2003***, *125*, 7825.

[2130]For the effect of high pressure of sterically hindered reactions, see Jenner, G. *Tetrahedron Lett.* ***2000***, *43*, 1235.

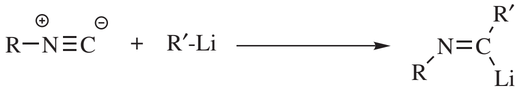
[2131]Constabel, F.; Ugi, I. *Tetrahedron* ***2001***, *57*, 5785.

[2132]See, for example, Godet, T.; Bovin, Y.; Vincent, G.; Merle, D.; Thozet, A.; Ciufolini, M.A. *Org. Lett.* ***2004***, *6*, 3281.

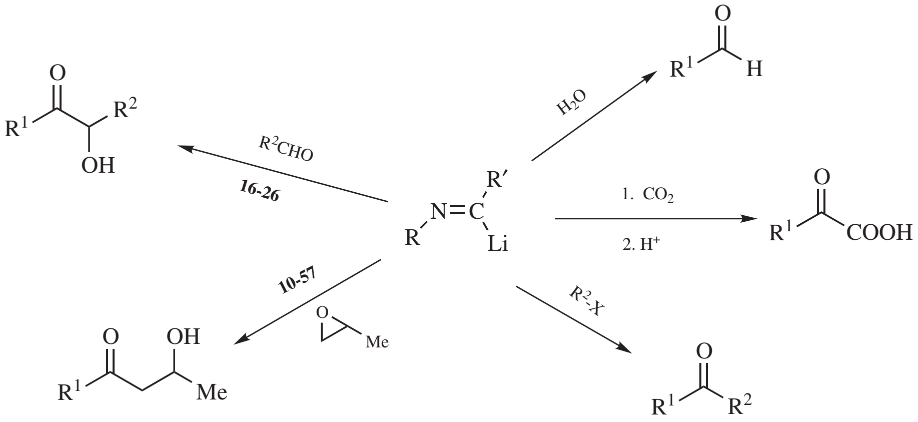
[2133]For reviews, see Ugi, I., in Gross, E.; Meienhofer, J. *The Peptides*, Vol. 2, Academic Press, NY, ***1980***, pp. 365–381, *Intra-Sci. Chem. Rep.* ***1971***, *5*, 229; *Rec. Chem. Prog.* ***1969***, *30*, 289; Gokel, G.W.; Hoffmann, P.; Kleimann, H.; Klusacek, H.; Lüdke, G.; Marquarding, D.; Ugi, I., in Ugi, I. *Isonitrile Chemistry*, Academic Press, NY, ***1971***, pp. 201–215. See also, Kunz, H.; Pfrengle, W. *J. Am. Chem. Soc.* ***1988***, *110*, 651.

16-99 The Formation of Metalated Aldimines

1/1/Lithio-alkyl-addition



Isocyanides that do not contain an α hydrogen react with alkyllithium compounds,[2134] as well as with Grignard reagents, to give lithium (or magnesium) aldimines.[2135] These metalated aldimines are versatile nucleophiles and react with various substrates as follows:



The reaction therefore constitutes a method for converting an organometallic compound R′M to an aldehyde R′CHO (see also, **12-33**), an α-keto acid,[2136] a ketone R′COR (see also, **12-33**), an α-hydroxy ketone, or a β-hydroxy ketone. In each case, the C=N bond is hydrolyzed to a C=O bond (**16-2**).

[2134]For a review of other metallation reactions of isocyanides, see Ito, Y.; Murakami, M. *Synlett* ***1990***, 245.

[2135]Niznik, G.E.; Morrison III, W.H.; Walborsky, H.M. *J. Org. Chem.* ***1974***, *39*, 600; Marks, M.J.; Walborsky, H.M. *J. Org. Chem.* ***1981***, *46*, 5405; ***1982***, *47*, 52. See also, Walborsky, H.M.; Ronman, P. *J. Org. Chem.* ***1978***, *43*, 731. For the formation of zinc aldimines, see Murakami, H.; Ito, H.; Ito, Y. *J. Org. Chem.* ***1988***, *53*, 4158.

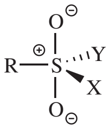
[2136]For a review of the synthesis and properties of α-keto acids, see Cooper, A.J.L.; Ginos, J.Z.; Meister, A. *Chem. Rev.* ***1983***, *83*, 321.

In a related reaction, isocyanides can be converted to aromatic aldimines by treatment with an iron complex followed by irradiation in benzene solution: $RNC + C_6H_6 \rightarrow PhCH{=}NR$.[2137]

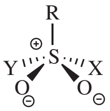
OS **VI**, 751.

NUCLEOPHILIC SUBSTITUTION AT A SULFONYL SULFUR ATOM[2138]

Nucleophilic substitution at RSO_2X is similar to attack at RCOX. Many of the reactions are essentially the same, though sulfonyl halides are less reactive than halides of carboxylic acids.[2139] The mechanisms[2140] are not identical, because a "tetrahedral" intermediate in this case (**121**) would have five groups on the central atom. This is possible since sulfur can accommodate up to 12 electrons in its valence shell, but it seems more likely that these mechanisms more closely resemble the S_N2 mechanism, with a trigonal-bipyramidal transition state (**122**). There are two major experimental results leading to this conclusion.



121



122

1. The stereospecificity of this reaction is more difficult to determine than that of nucleophilic substitution at a saturated carbon, where chiral compounds are relatively easy to prepare, but it may be recalled (p. 142) that optical activity is possible in a compound of the form RSO_2X if one oxygen is ^{16}O and the other ^{18}O. When a sulfonate ester possessing this type of chirality was converted to a sulfone with a Grignard reagent (**16-105**), inversion of configuration was found.[2141] This is not incompatible with an intermediate such as **121** but it is also in good accord with an S_N2-like mechanism with backside attack.

[2137] Jones, W.D.; Foster, G.P.; Putinas, J.M. *J. Am. Chem. Soc.* ***1987***, *109*, 5047.

[2138] For a review of mechanisms of nucleophilic substitutions at di-, tri-, and tetracoordinated sulfur atoms, see Ciuffarin, E.; Fava, A. *Prog. Phys. Org. Chem.* ***1968***, *6*, 81.

[2139] For a comparative reactivity study, see Hirata, R.; Kiyan, N.Z.; Miller, J. *Bull. Soc. Chim. Fr.* ***1988***, 694.

[2140] For a review of mechanisms of nucleophilic substitution at a sulfonyl sulfur, see Gordon, I.M.; Maskill, H.; Ruasse, M. *Chem. Soc. Rev.* ***1989***, *18*, 123.

[2141] Sabol, M.A.; Andersen, K.K. *J. Am. Chem. Soc.* ***1969***, *91*, 3603. See also, Jones, M.R.; Cram, D.J. *J. Am. Chem. Soc.* ***1974***, *96*, 2183.

2. More direct evidence against **121** (though still not conclusive) was found in an experiment involving acidic and basic hydrolysis of aryl arenesulfonates, where it has been shown by the use of ^{18}O that an intermediate like **121** is not reversibly formed, since ester recovered when the reaction was stopped before completion contained no ^{18}O when the hydrolysis was carried out in the presence of labeled water.[2142]

Other evidence favoring the S_N2-like mechanism comes from kinetics and substituent effects.[2143] However, evidence for the mechanism involving **121** is that the rates did not change much with changes in the leaving group[2144] and the ρ values were large, indicating that a negative charge builds up in the transition state.[2145]

In certain cases in which the substrate carries an α hydrogen, there is strong evidence[2146] that at least some of the reaction takes place by an elimination-addition mechanism (E1cB, similar to the one shown on p. 1406), going through a *sulfene* intermediate,[2147] for example, the reaction between methanesulfonyl chloride and aniline.

$$CH_3{-}SO_2Cl \xrightarrow{\text{base}} \underset{\text{A sulfene}}{CH_2{=}SO_2} \xrightarrow{PhNH_2} CH_3{-}SO_2{-}NHPh$$

[2142]Christman, D.R.; Oae, S. *Chem. Ind. (London)* ***1959***, 1251; Oae, S.; Fukumoto, T.; Kiritani, R. *Bull. Chem. Soc. Jpn.* ***1963***, *36*, 346; Kaiser, E.T.; Zaborsky, O.R. *J. Am. Chem. Soc.* ***1968***, *90*, 4626.

[2143]See, for example, Robertson, R.E.; Rossall, B. *Can. J. Chem.* ***1971***, *49*, 1441; Rogne, O. *J. Chem. Soc. B* ***1971***, 1855; *J. Chem. Soc. Perkin Trans. 2* ***1972***, 489; Gnedin, B.G.; Ivanov, S.N.; Spryskov, A.A. *J. Org. Chem. USSR* ***1976***, *12*, 1894; Banjoko, O.; Okwuiwe, R. *J. Org. Chem.* ***1980***, *45*, 4966; Ballistreri, F.P.; Cantone, A.; Maccarone, E.; Tomaselli, G.A.; Tripolone, M. *J. Chem. Soc. Perkin Trans. 2* ***1981***, 438; Suttle, N.A.; Williams, A. *J. Chem. Soc. Perkin Trans. 2* ***1983***, 1563; D'Rozario, P.; Smyth, R.L.; Williams, A. *J. Am. Chem. Soc.* ***1984***, *106*, 5027; Lee, I.; Kang, H.K.; Lee, H.W. *J. Am. Chem. Soc.* ***1987***, *109*, 7472; Arcoria, A.; Ballistreri, F.P.; Spina, E.; Tomaselli, G.A.; Maccarone, E. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 1793; Gnedin, B.G.; Ivanov, S.N.; Shchukina, M.V. *J. Org. Chem. USSR* ***1988***, *24*, 731.

[2144]Ciuffarin, E.; Senatore, L.; Isola, M. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 468.

[2145]Ciuffarin, E.; Senatore, L. *Tetrahedron Lett.* ***1974***, 1635.

[2146]For a review, see Opitz, G. *Angew. Chem. Int. Ed.* ***1967***, *6*, 107. See also, King, J.F.; Lee, T.W.S. *J. Am. Chem. Soc.* ***1969***, *91*, 6524; Skrypnik, Yu.G.; Bezrodnyi, V.P. *Doklad. Chem.* ***1982***, *266*, 341; Farng, L.O.; Kice, J.L. *J. Am. Chem. Soc.* ***1981***, *103*, 1137; Thea, S.; Guanti, G.; Hopkins, A.; Williams, A. *J. Am. Chem. Soc.* ***1982***, *104*, 1128, *J. Org. Chem.* ***1985***, *50*, 5592; Bezrodnyi, V.P.; Skrypnik, Yu.G. *J. Org. Chem. USSR* ***1984***, *20*, 1660, 2349; King, J.F.; Skonieczny, S. *Tetrahedron Lett.* ***1987***, *28*, 5001; Pregel, M.J.; Buncel, E. *J. Chem. Soc. Perkin Trans. 2* ***1991***, 307.

[2147]For reviews of sulfenes, see King, J.F. *Acc. Chem. Res.* ***1975***, *8*, 10; Nagai, T.; Tokura, N. *Int. J. Sulfur Chem. Part B* ***1972***, 207; Truce, W.E.; Liu, L.K. *Mech. React. Sulfur Compd.* ***1969***, *4*, 145; Opitz, G. *Angew. Chem. Int. Ed.* ***1967***, *6*, 107; Wallace, T.J. *Q. Rev. Chem. Soc.* ***1966***, *20*, 67.

In the special case of nucleophilic substitution at a sulfonic ester RSO_2OR', where R′ is alkyl, R′—O cleavage is much more likely than S—O cleavage because the OSO_2R group is such a good leaving group (p. 497).[2148] Many of these reactions have been considered previously (e.g., **10-4**, **10-10**), because they are nucleophilic substitutions at an alkyl carbon atom and not at a sulfur atom. However, when R′ is aryl, then the S—O bond is much more likely to cleave because of the very low tendency aryl substrates have for nucleophilic substitution.[2149]

The order of nucleophilicity toward a sulfonyl sulfur has been reported as $OH^- > RNH_2 > N_3^- > F^- > AcO^- > Cl^- > H_2O > I^-$.[2150] This order is similar to that at a carbonyl carbon (p. $$$). Both of these substrates can be regarded as relatively hard acids, compared to a saturated carbon which is considerably softer and which has a different order of nucleophilicity (p. 494).

16-100 Attack by OH: Hydrolysis of Sulfonic Acid Derivatives

***S*-Hydroxy-de-chlorination**, etc.

$$RSO_2X \xrightarrow[H_2O + H^+]{H_2O \quad \text{or}} RSO_2OH \qquad (X = Cl, OR', NR'_2)$$

Sulfonyl chlorides as well as esters and amides of sulfonic acids can be hydrolyzed to the corresponding acids. Sulfonyl chlorides can by hydrolyzed with water or with an alcohol in the absence of acid or base. Basic catalysis is also used, though of course the salt is the product obtained. Esters are readily hydrolyzed, many with water or dilute alkali. This is the same reaction as **10-4**, and usually involves R′—O cleavage, except when R′ is aryl. However, in some cases retention of configuration has been shown at alkyl R′, indicating S—O cleavage in these cases.[2151] Sulfonamides are generally *not* hydrolyzed by alkaline treatment, not even with hot concentrated alkali. Acids, however, do hydrolyze sulfonamides, but less readily than they do sulfonyl halides or sulfonic esters. Of course, ammonia or the amine appears as the salt. However, sulfonamides can be hydrolyzed with base if the solvent is HMPA.[2152]

Magnesium in methanol has been used to convert sulfonate esters to the parent alcohol.[2153] Likewise, $CeCl_3 \cdot 7\,H_2O$—NaI in acetonitrile converted aryl tosylates to the parent phenol derivative.[2154]

[2148]A number of sulfonates in which R contains a branching, for example, $Ph_2C(CF_3)SO_2OR'$, can be used to ensure that there will be no S—O cleavage: Netscher, T.; Prinzbach, H. *Synthesis* ***1987***, 683.
[2149]See Tagaki, W.; Kurusu, T.; Oae, S. *Bull. Chem. Soc. Jpn.* ***1969***, *42*, 2894.
[2150]Kice, J.L.; Kasperek, G.J.; Patterson, D. *J. Am. Chem. Soc.* ***1969***, *91*, 5516; Rogne, O. *J. Chem. Soc. B* ***1970***, 1056; Kice, J.L.; Legan, E. *J. Am. Chem. Soc.* ***1973***, *95*, 3912.
[2151]Chang, F.C. *Tetrahedron Lett.* ***1964***, 305.
[2152]Cuvigny, T.; Larchevêque, M. *J. Organomet. Chem.* ***1974***, *64*, 315.
[2153]Sridhar, M.; Kumar, B.A.; Narender, R. *Tetrahedron Lett.* ***1998***, *39*, 2847.
[2154]Reddy, G.S.; Mohan, G.H.; Iyengar, D.S. *Synth. Commun.* ***2000***, *30*, 3829.

OS **I**, 14; **II**, 471; **III**, 262; **IV**, 34; **V**, 406; **VI**, 652, 727. Also see, OS **V**, 673; **VI**, 1016.

16-101 Attack by OR. Formation of Sulfonic Esters

***S*-Alkoxy-de-chlorination**, and so on

$$RSO_2Cl \quad + \quad R'OH \xrightarrow{\text{base}} RSO_2OR'$$

$$RSO_2NR_2'' \quad + \quad R'OH \xrightarrow{\text{base}} RSO_2OR' \quad + \quad NHR_2''$$

Sulfonic esters are most frequently prepared by treatment of the corresponding sulfonyl halides with alcohols in the presence of a base. This procedure is the most common method for the conversion of alcohols to tosylates, brosylates, and similar sulfonic esters. Both R and R′ may be alkyl or aryl. The base is often pyridine, which functions as a nucleophilic catalyst,[2155] as in the similar alcoholysis of carboxylic acyl halides (**16-61**). Propylenediamines have also been used to facilitate tosylation of an alcohol.[2156] Silver oxide has been used, in conjunction with KI.[2157] Primary alcohols react the most rapidly, and it is often possible to sulfonate selectively a primary OH group in a molecule that also contains secondary or tertiary OH groups. The reaction with sulfonamides has been much less frequently used and is limited to *N*,*N*-disubstituted sulfonamides; that is, R— may not be hydrogen. However, within these limits it is a useful reaction. The nucleophile in this case is actually RO^-. However, R′ may be hydrogen (as well as alkyl) if the nucleophile is a phenol, so that the product is RSO_2OAr. Acidic catalysts are used in this case.[2158] Sulfonic acids have been converted directly to sulfonates by treatment with triethyl or trimethyl orthoformate, $HC(OR)_3$, without catalyst or solvent;[2159] and with a trialkyl phosphite, $P(OR)_3$.[2160]

Mono-tosylation of a 1,2-diol was achieved using tosyl chloride and triethylamine, with a tin oxide catalyst.[2161]

OS **I**, 145; **III**, 366; **IV**, 753; **VI**, 56, 482, 587, 652; **VII**, 117; **66**, 1; **68**, 188. Also see, OS **IV**, 529; **VI**, 324, 757; **VII**, 495; **VIII**, 568.

[2155]Rogne, O. *J. Chem. Soc. B* ***1971***, 1334. See also, Litvinenko, M.; Shatskaya, V.A.; Savelova, V.A. *Doklad. Chem.* ***1982***, *265*, 199.

[2156]Yoshida, Y; Shimonishi, K.; Sakakura, Y.; Okada, S.; Aso, N.; Tanabe, Y. *Synthesis* ***1999***, 1633.

[2157]Bouzide, A.; LeBerre, N.; Sauvé, G. *Tetrahedron Lett.* ***2001***, *42*, 8781.

[2158]Klamann, D.; Fabienke, E. *Chem. Ber.* ***1960***, *93*, 252.

[2159]Padmapriya, A.A.; Just, G.; Lewis, N.G. *Synth. Commun.* ***1985***, *15*, 1057.

[2160]Karaman, R.; Leader, H.; Goldblum, A.; Breuer, E. *Chem. Ind. (London)* ***1987***, 857.

[2161]Martinelli, M.J.; Vaidyanathan, R.; Khau, V.V. *Tetrahedron Lett.* ***2000***, *41*, 3773; Bucher, B.; Curran, D.P. *Tetrahedron Lett.* ***2000***, *41*, 9617.

16-102 Attack by Nitrogen: Formation of Sulfonamides

S-Amino-de-chlorination

$$RSO_2Cl \quad + \quad NH_3 \longrightarrow RSO_2NH_2$$

The treatment of sulfonyl chlorides with ammonia or amines is the usual way of preparing sulfonamides. Primary amines give *N*-alkyl sulfonamides, and secondary amines give *N*,*N*-dialkyl sulfonamides. The reaction is the basis of the *Hinsberg test* for distinguishing between primary, secondary, and tertiary amines. *N*-Alkyl sulfonamides, having an acidic hydrogen, are soluble in alkali, while *N*,*N*-dialkyl sulfonamides are not. Since tertiary amines are usually recovered unchanged, primary, secondary, and tertiary amines can be told apart. However, the test is limited for at least two reasons.[2162] (*1*) Many *N*-alkyl sulfonamides in which the alkyl group has six or more carbons are insoluble in alkali, despite their acidic hydrogen,[2163] so that a primary amine may appear to be a secondary amine. (*2*) If the reaction conditions are not carefully controlled, tertiary amines may not be recovered unchanged.[2160]

A primary or a secondary amine can be protected by reaction with phenacylsulfonyl chloride, ($PhCOCH_2SO_2Cl$), to give a sulfonamide, $RNHSO_2CH_2COPh$ or $R_2NSO_2CH_2COPh$.[2164] The protecting group can be removed when desired with zinc and acetic acid. Sulfonyl chlorides react with azide ion to give sulfonyl azides (RSO_2N_3).[2165] Chlorothioformates, ROC(=S)Cl, react with triethylamine to give the *N*,*N*-diethylthioamide.[2166]

A quite different synthesis of sulfonamides treated allyltributyltin with PhI=NTs, in the presence of copper (II) triflate.[2167] another alternative method treats silyl enol ethers with sulfur dioxide, and subsequent and reaction with a secondary amine gave the β-sulfonamido ester.[2168]

OS **IV**, 34, 943; **V**, 39, 179, 1055; **VI**, 78, 652; **VII**, 501; **VIII**, 104. See also, OS **VI**, 788.

16-103 Attack by Halogen: Formation of Sulfonyl Halides

S-Halo-de-hydroxylation

$$RSO_2OH \quad + \quad PCl_5 \longrightarrow RSO_2Cl$$

[2162]For directions for performing and interpreting the Hinsberg test, see Gambill, C.R.; Roberts, T.D.; Shechter, H. *J. Chem. Educ.* ***1972***, *49*, 287.

[2163]Fanta, P.E.; Wang, C.S. *J. Chem. Educ.* ***1964***, *41*, 280.

[2164]Hendrickson, J.B.; Bergeron R. *Tetrahedron Lett.* ***1970***, 345.

[2165]For an example, see Regitz, M.; Hocker, J.; Liedhegener, A. *Org. Synth.* *V*, 179.

[2166]Milan, D.S.; Prager, R.H. *Aust. J. Chem.* ***1999***, *52*, 841.

[2167]Kim, D.Y.; Kim. H.S.; Choi, Y.J.; Mang, J.Y.; Lee, K. *Synth. Commun.* ***2001***, *31*, 2463.

[2168]Bouchez, L.C.; Dubbaka, S.R.; Urks, M.; Vogel, P. *J. Org. Chem.* ***2004***, *69*, 6413.

This reaction, parallel with **16-79**, is the standard method for the preparation of sulfonyl halides. Also used are PCl_3 and $SOCl_2$, and sulfonic acid salts can also serve as substrates. Cyanuric acid (2,4,6-trichloro[1,3,5]triazene) also serves as a chlorinating agent.[2169] Sulfonyl bromides and iodides have been prepared from sulfonyl hydrazides ($ArSO_2NHNH_2$, themselves prepared by **16-102**) by treatment with bromine or iodine.[2170] Sulfonyl fluorides are generally prepared from the chlorides, by halogen exchange.[2171]

OS **I**, 84; **IV**, 571, 693, 846, 937; **V**, 196. See also, OS **VII**, 495.

16-104 Attack by Hydrogen: Reduction of Sulfonyl Chlorides

***S*-Hydro-de-chlorination** or ***S*-Dechlorination**

$$2\ RSO_2Cl \quad + \quad Zn \longrightarrow (RSO_2)_2Zn \xrightarrow{H+} 2\ RSO_2H$$

Sulfinic acids can be prepared by reduction of sulfonyl chlorides. Though mostly done on aromatic sulfonyl chlorides, the reaction has also been applied to alkyl compounds. Besides zinc, sodium sulfite, hydrazine, sodium sulfide, and other reducing agents have been used. For reduction of sulfonyl chlorides to thiols, see **19-78**.

OS **I**, 7, 492; **IV**, 674.

16-105 Attack by Carbon: Preparation of Sulfones

***S*-Aryl-de-chlorination**

$$ArSO_2Cl \quad + \quad Ar'MgX \longrightarrow ArSO_2Ar'$$

Grignard reagents convert aromatic sulfonyl chlorides or aromatic sulfonates to sulfones. Organolithium reagents react with sulfonyl fluorides at −78°C to give the corresponding sulfone.[2172] Aromatic sulfonates have also been converted to sulfones with organolithium compounds,[2173] with aryltin compounds,[2174] and with alkyl halides and Zn metal.[2175] Vinylic and allylic sulfones have been prepared by treatment of sulfonyl chlorides with a vinylic or allylic stannane and a palladium complex catalyst.[2176] Alkynyl sulfones can be prepared by treatment of sulfonyl chlorides with trimethylsilylalkynes, with an $AlCl_3$ catalyst.[2177] Note that

[2169]Blotny, G. *Tetrahedron Lett.* ***2003***, *44*, 1499.

[2170]Poshkus, A.C.; Herweh, J.E.; Magnotta, F.A. *J. Org. Chem.* ***1963***, *28*, 2766; Litvinenko, L.M.; Dadali, V.A.; Savelova, V.A.; Krichevtsova, T.I. *J. Gen. Chem. USSR* ***1964***, *34*, 3780.

[2171]See Bianchi, T.A.; Cate, L.A. *J. Org. Chem.* ***1977***, *42*, 2031, and references cited therein.

[2172]Frye, L.L.; Sullivan, E.L.; Cusack, K.P.; Funaro, J.M. *J. Org. Chem*, ***1992***, *57*, 697.

[2173]Baarschers, W.H. *Can. J. Chem.* ***1976***, *54*, 3056.

[2174]Neumann, W.P.; Wicenec, C. *Chem. Ber.* ***1993***, *126*, 763.

[2175]Sun, X.; Wang, L.; Zhang, Y. *Synth. Commun.* ***1998***, *28*, 1785.

[2176]Labadie, S.S. *J. Org. Chem.* ***1989***, *54*, 2496.

[2177]See Waykole, L.; Paquette, L.A. *Org. Synth.* *67*, 149.

trifluoromethylsulfones were converted to methyl sulfones by reaction with methylmagneisum bromide.[2178]

Arylboronic acids (p. 815) react with sulfonyl chlorides in the presence of $PdCl_2$ to give the corresponding sulfone.[2179] arylboronic acids also react with sulfinate anions (RSO_2Na) in the presence of $Cu(OAc)_2$ to give the sulfone.[2180]

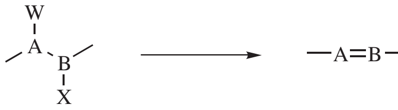
OS **VIII**, 281.

[2178]Steensma, R.W.; Galabi, S.; Tagat, J.R.; McCombie, S.W. *Tetrahedron Lett.* ***2001***, *42*, 2281.
[2179]Bandgar, B.P.; Bettigeri, S.V.; Phopase, J. *Org. Lett.* ***2004***, *6*, 2105.
[2180]Beaulieu, C.; Guay, D.; Wang, Z.; Evans, D.A. *Tetrahedron Lett.* ***2004***, *45*, 3233.

CHAPTER 17

Eliminations

When two groups are lost from adjacent atoms so that a new double[1]



(or triple) bond is formed the reaction is called β-*elimination*; one atom is the α, the other the β atom. In an α elimination, both groups are lost from the same atom to give a carbene (or a nitrene):

In a γ elimination, a three-membered ring is formed:

Some of these processes were discussed in Chapter 10. Another type of elimination involves the expulsion of a fragment from within a chain or ring (X–Y–Z → X–Z + Y). Such reactions are called *extrusion reactions*. This chapter discusses β-elimination and (beginning on p. 1553) extrusion reactions; however, β-elimination in which both X and W are hydrogens are oxidation reactions and are treated in Chapter 19.

[1]See Williams, J.M.J. *Preparation of Alkenes, A Practical Approach*, Oxford University Press, Oxford, ***1996***.

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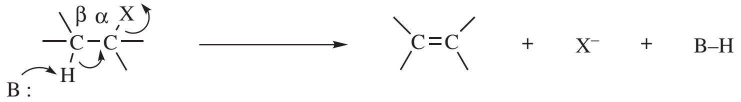
MECHANISMS AND ORIENTATION

β-Elimination reactions may be divided into two types; one type taking place largely in solution, the other (pyrolytic eliminations) mostly in the gas phase. In the reactions in solution, one group leaves with its electrons and the other without, the latter most often being hydrogen. In these cases, we refer to the former as the leaving group or nucleofuge. For pyrolytic eliminations, there are two principal mechanisms, one pericyclic and the other a free-radical pathway. A few photochemical eliminations are also known (the most important is Norrish type II cleavage of ketones, p. 344), but these are not generally of synthetic importance[2] and will not be discussed further. In most β-eliminations the new bonds are C=C or C≡C; our discussion of mechanisms is largely confined to these cases.[3] Mechanisms in solution (E2, E1)[4] and E1cB are discussed first.

The E2 Mechanism

In the E2 mechanism (elimination, bimolecular), the two groups depart simultaneously, with the proton being pulled off by a base:



The mechanism thus takes place in one step and kinetically is second order: first order in substrate and first order in base. An *ab initio* study has produced a model for the E2 transition state geometry.[5] The IUPAC designation is $A_{xH}D_HD_N$, or more generally (to include cases where the electrofuge is not hydrogen), $A_nD_ED_N$. It is analogous to the S_N2 mechanism (p. 426) and often competes with it. With respect

[2]For synthetically useful examples of Norrish type II cleavage, see Neckers, D.C.; Kellogg, R.M.; Prins, W.L.; Schoustra, B. *J. Org. Chem.* ***1971***, *36*, 1838.

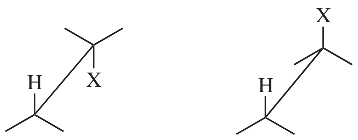
[3]For a monograph on elimination mechanisms, see Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***. For reviews, see Gandler, J.R., in Patai, S. *Supplement A: The Chemistry of Double-Bonded Functional Groups*, Vol. 2, pt. 1, Wiley, NY, ***1989***, pp. 733–797; Aleskerov, M.A.; Yufit, S.S.; Kucherov, V.F. *Russ. Chem. Rev.* ***1978***, *47*, 134; Cockerill, A.F.; Harrison, R.G., in Patai, S. *The Chemistry of Functional Groups, Supplement A* pt. 1, Wiley, NY, ***1977***, pp. 153–221; Willi, A.V. *Chimia*, ***1977***, *31*, 93; More O'Ferrall, R.A., in Patai, S. *The Chemistry of the Carbon-Halogen Bond*, pt. 2, Wiley, NY, ***1973***, pp. 609–675; Cockerill, A.F., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 163–372; Saunders, Jr., W.H. *Acc. Chem. Res.* ***1976***, *9*, 19; Stirling, C.J.M. *Essays Chem.* ***1973***, *5*, 123; Bordwell, F.G. *Acc. Chem. Res.* ***1972***, *5*, 374; Fry, A. *Chem. Soc. Rev.* ***1972***, *1*, 163; LeBel, N.A. *Adv. Alicyclic Chem.* ***1971***, *3*, 195; Bunnett, J.F. *Surv. Prog. Chem.* ***1969***, *5*, 53; in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, ***1964***, the articles by Saunders, Jr., W.H. pp. 149–201 (eliminations in solution); and by Maccoll, A. pp. 203–240 (pyrolytic eliminations); Köbrich, G. *Angew. Chem. Int. Ed.* ***1965***, *4*, 49, pp. 59–63 (for the formation of triple bonds).

[4]Thibblin, A. *Chem. Soc. Rev.* ***1993***, *22*, 427.

[5]Schrøder, S.; Jensen, F. *J. Org. Chem.* ***1997***, *62*, 253.

to the substrate, the difference between the two pathways is whether the species with the unshared pair attacks the carbon (and thus acts as a nucleophile) or the hydrogen (and thus acts as a base). As in the case of the S_N2 mechanism, the leaving group may be positive or neutral and the base may be negatively charged or neutral.

Among the evidence for the existence of the E2 mechanism are (*1*) the reaction displays the proper second-order kinetics; (*2*) when the hydrogen is replaced by deuterium in second-order eliminations, there is an isotope effect of from 3 to 8, consistent with breaking of this bond in the rate-determining step.[6] However, neither of these results alone could prove an E2 mechanism, since both are compatible with other mechanisms also (e.g., see E1cB p. 1488). The most compelling evidence for the E2 mechanism is found in stereochemical studies.[7] As will be illustrated in the examples below, the E2 mechanism is stereospecific: The five atoms involved (including the base) in the transition state must be in one plane. There are two ways for this to happen. The H and X may be



A **B**

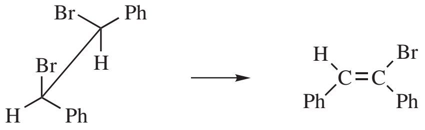
trans to one another (**A**) with a dihedral angle of 180°, or they may be cis (**B**) with a dihedral angle of 0°.[8] Conformation **A** is called *anti-periplanar*, and this type of elimination, in which H and X depart in opposite directions, is called *anti-elimination*. Conformation **B** is *syn-periplanar*, and this type of elimination, with H and X leaving in the same direction, is called *syn-elimination*. Many examples of both kinds have been discovered. In the absence of special effects (discussed below) anti-elimination is usually greatly favored over syn-elimination, probably because **A** is a staggered conformation (p. 199) and the molecule requires less energy to reach this transition state than it does to reach the eclipsed transition state **B**. A few of the many known examples of predominant or exclusive anti-elimination follow.

[6]See, for example, Saunders, Jr., W.H.; Edison, D.H. *J. Am. Chem. Soc.* ***1960***, *82*, 138; Shiner, Jr., V.J.; Smith, M.L. *J. Am. Chem. Soc.* ***1958***, *80*, 4095; ***1961***, *83*, 593. For a review of isotope effects in elimination reactions, see Fry, A. *Chem. Soc. Rev.* ***1972***, *1*, 163.

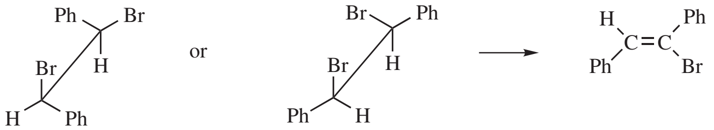
[7]For reviews, see Bartsch, R.A.; Závada, J. *Chem. Rev.* ***1980***, *80*, 453; Coke, J.L. *Sel. Org. Transform.* ***1972***, *2*, 269; Sicher, J. *Angew. Chem. Int. Ed.* ***1972***, *11*, 200; *Pure Appl. Chem.* ***1971***, *25*, 655; Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***, pp. 105–163; Cockerill, A.F., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 217–235; More O'Ferrall, R.A., in Patai, S. *The Chemistry of the Carbon–Halogen Bond*, pt. 2, Wiley, NY, ***1973***, pp. 630–640.

[8]DePuy, C.H.; Morris, G.F.; Smith, J.S.; Smat, R.J. *J. Am. Chem. Soc.* ***1965***, *87*, 2421.

1. Elimination of HBr from *meso*-1,2-dibromo-1,2-diphenylethane gave *cis*-2-bromostilbene, while the (+) or (−) isomer gave the trans alkene. This stereospecific result, which

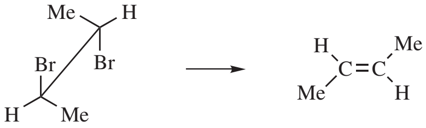


meso cis

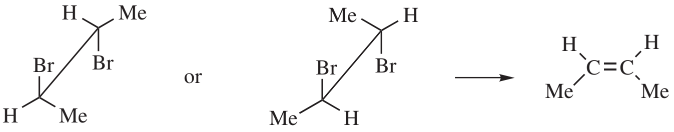


dl pair trans

was obtained in 1904,[9] demonstrates that in this case elimination is anti. Many similar examples have been discovered since. Obviously, this type of experiment need not be restricted to compounds that have a meso form. Anti-elimination requires that an erythro *dl* pair (or either isomer) give the cis alkene, and the threo *dl* pair (or either isomer) give the trans isomer, and this has been found many times. Anti-elimination has also been demonstrated in cases where the electrofuge is not hydrogen. In the reaction of 2,3-dibromobutane with iodide ion, the two bromines are removed (**17-22**). In this case, the meso compound gave the trans alkene and the *dl* pair the cis:[10]



meso trans

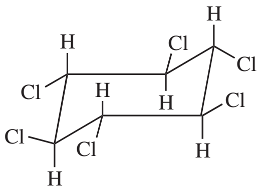


dl pair cis

2. In open-chain compounds, the molecule can usually adopt that conformation in which H and X are anti-periplanar. However, in cyclic systems this is not always the case. There are nine stereoisomers of 1,2,3,4,5,6-hexachlorocyclohexane: seven meso forms and a *dl* pair (see p. 165). Four of the meso compounds and the *dl* pair (all that were then known) were subjected to

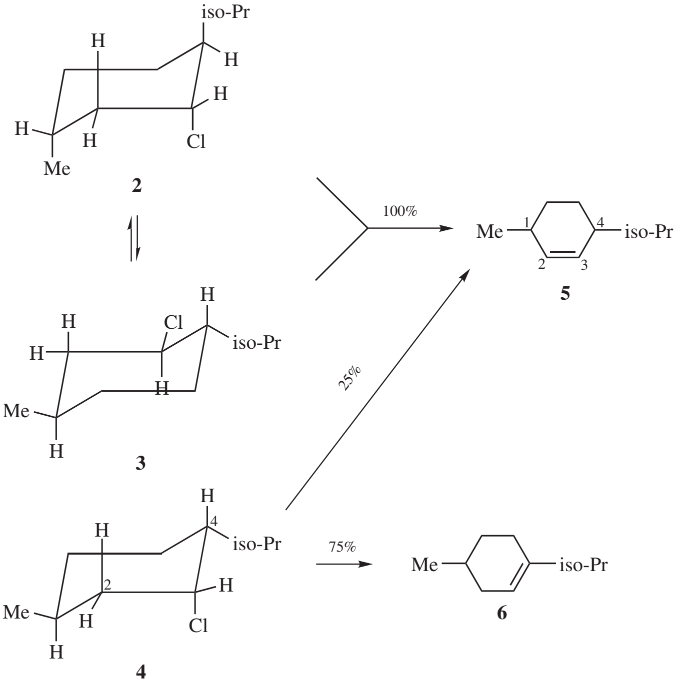
[9]Pfeiffer, P. *Z. Phys. Chem.* ***1904***, *48*, 40.
[10]Winstein, S.; Pressman, D.; Young, W.G. *J. Am. Chem. Soc.* ***1939***, *61*, 1645.

elimination of HCl. Only one of these (**1**) has no Cl trans to an H. Of the other isomers, the fastest elimination rate was about three times as fast as the slowest, but the rate for **1** was 7000 times slower than that of the slowest of the other isomers.[11] This result demonstrates that with these compounds anti elimination is greatly favored over syn elimination, although the latter must be taking place on **1**, very slowly, to be sure.



1

3. The preceding result shows that elimination of HCl in a six-membered ring proceeds best when the H and X are trans to each other. However, there is an additional restriction. Adjacent trans groups on a six-membered ring can be diaxial or diequatorial (p. 204) and the molecule is generally free to adopt either conformation, although one may have a higher energy than the other. Anti-periplanarity of the leaving groups requires that they be diaxial, even if this is the conformation of higher energy. The results with menthyl and neomenthyl chlorides are easily



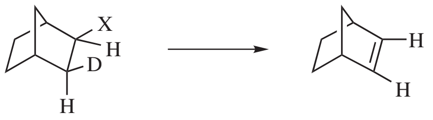
[11]Cristol, S.J.; Hause, N.L.; Meek, J.S. *J. Am. Chem. Soc.* ***1951***, *73*, 674.

interpretable on this basis. Menthyl chloride has two chair conformations, **2** and **3**. Compound **3**, in which the three substituents are all equatorial, is the more stable. The more stable chair conformation of neomenthyl chloride is **4**, in which the chlorine is axial; there are axial hydrogens on both C-2 and C-4. The results are: neomenthyl chloride gives rapid E2 elimination and the alkene produced is predominantly **6** (**6**/**5** ratio is 3:1) in accord with Zaitsev's rule (p. 767). Since an axial hydrogen is available on both sides, this factor does not control the direction of elimination and Zaitsev's rule is free to operate. However, for menthyl chloride, elimination is much slower and the product is entirely the anti-Zaitsev, **5**. It is slow because the unfavorable conformation **2** has to be achieved before elimination can take place, and the product is **5** because only on this side is there an axial hydrogen.[12]

4. That anti-elimination also occurs in the formation of triple bonds is shown by elimination from *cis*- and *trans*-HOOC–CH=C(Cl)COOH. In this case, the product in both cases is HOOCC≡CCOOH, but the trans isomer reacts ~50 times faster than the cis compound.[13]

Some examples of syn-elimination have been found in molecules where H and X could not achieve an anti-periplanar conformation.

1. The deuterated norbornyl bromide (**7**, X = Br) gave 94% of the product containing no deuterium.[14] Similar results were obtained with other leaving groups and with bicyclo[2.2.2] compounds.[15] In these cases the exo X group cannot achieve a dihedral angle of 180° with the endo β hydrogen because of the rigid structure of the molecule. The dihedral angle here is ~120°. These leaving groups prefer syn-elimination with a dihedral angle of ~0° to anti-elimination with an angle of ~120°.



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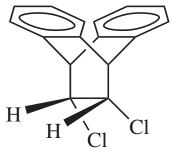


8

[12]Hughes, E.D.; Ingold, C.K.; Rose, J.B. *J. Chem. Soc.* ***1953***, 3839.

[13]Michael, A. *J. Prakt. Chem.* ***1895***, *52*, 308. See also, Marchese, G.; Naso, F.; Modena, G. *J. Chem. Soc. B* ***1968***, 958.

[14]Kwart, H.; Takeshita, T.; Nyce, J.L. *J. Am. Chem. Soc.* ***1964***, *86*, 2606.

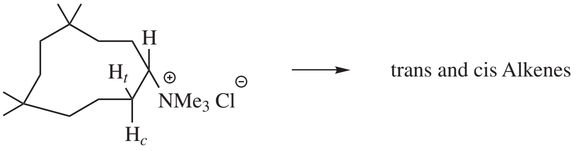
[15]For example, see Bird, C.W.; Cookson, R.C.; Hudec, J.; Williams, R.O. *J. Chem. Soc.* ***1963***, 410; Stille, J.K.; Sonnenberg, F.M.; Kinstle, T.H. *J. Am. Chem. Soc.* ***1966***, *88*, 4922; Coke, J.L.; Cooke, Jr., M.P. *J. Am. Chem. Soc.* ***1967***, *89*, 6701; DePuy, C.H.; Naylor, C.G.; Beckman, J.A. *J. Org. Chem.* ***1970***, *35*, 2750; Brown, H.C.; Liu, K. *J. Am. Chem. Soc.* ***1970***, *92*, 200; Sicher, J.; Pánkova, M.; Závada, J.; Kniežo, L.; Orahovats, A. *Collect. Czech. Chem. Commun.* ***1971***, *36*, 3128; Bartsch, R.A.; Lee, J.G. *J. Org. Chem.* ***1991***, *56*, 212, 2579.

2. Molecule **8** is a particularly graphic example of the need for a planar transition state. In **8**, each Cl has an adjacent hydrogen trans to it, and if planarity of leaving groups were not required, anti-elimination could easily take place. However, the crowding of the rest of the molecule forces the dihedral angle to be ~120°, and elimination of HCl from **8** is much slower than from corresponding nonbridged compounds.[16] (Note that syn elimination from **8** is even less likely than anti-elimination.) Syn-elimination can take place from the trans isomer of **8** (dihedral angle ~0°); this isomer reacted about eight times faster than **8**.[16]

The examples so far given illustrate two points. (*1*) Anti-elimination *requires* a dihedral angle of 180°. When this angle cannot be achieved, anti-elimination is greatly slowed or prevented entirely. (*2*) For the simple systems so far discussed syn-elimination is not found to any significant extent unless anti elimination is greatly diminished by failure to achieve the 180° angle.

As noted in Chapter 4 (p. 223), six-membered rings are the only ones among rings of 4–13 members in which strain-free anti-periplanar conformations can be achieved. It is not surprising, therefore, that syn elimination is least common in six-membered rings. Cooke and Coke subjected cycloalkyltrimethylammonium hydroxides to elimination (**17-7**) and found the following percentages of syn-elimination with ring size: four-membered, 90%; five-membered, 46%; six-membered, 4% seven-membered, 31 to 37%.[17] Note that the NMe_3^+ group has a greater tendency to syn-elimination than do other common leaving groups, such as OTs, Cl, and Br.

Other examples of syn-elimination have been found in medium-ring compounds, where both cis and trans alkenes are possible (p. 184). As an illustration, we can look at experiments performed by, Svoboda, and Sicher.[18] These workers subjected 1,1,4,4-tetramethyl-7-cyclodecyltrimethylammonium chloride (**9**) to



9

elimination and obtained mostly *trans*-, but also some *cis*-tetramethylcyclodecenes as products. (Note that *trans*-cyclodecenes, although stable, are less stable than the cis isomers). In order to determine the stereochemistry of the reaction, they repeated the elimination, this time using deuterated substrates. They found that

[16]Cristol, S.J.; Hause, N.L. *J. Am. Chem. Soc.* ***1952***, *74*, 2193.

[17]Cooke, Jr., M.P.; Coke, J.L. *J. Am. Chem. Soc.* ***1968***, *90*, 5556. See also, Coke, J.L.; Smith, G.D.; Britton, Jr., G.H. *J. Am. Chem. Soc.* ***1975***, *97*, 4323.

[18]Závada, J.; Svoboda, M.; Sicher, J. *Tetrahedron Lett.* ***1966***, 1627; *Collect. Czech. Chem. Commun.* ***1968***, *33*, 4027.

when **9** was deuterated in the trans position ($H_t = D$), there was a substantial isotope effect in the formation of *both* cis and trans alkenes, but when **9** was deuterated in the cis position ($H_c = D$), there was *no* isotope effect in the formation of either alkene. Since an isotope effect is expected for an E2 mechanism,[19] these results indicated that *only* the trans hydrogen (H_t) was lost, whether the product was the cis or the trans isomer.[20] This in turn means that *the cis isomer must have been formed by anti-elimination and the trans isomer by syn-elimination.* (Anti-elimination could take place from approximately the conformation shown, but for syn elimination the molecule must twist into a conformation in which the C–H_t and C–NMe_3^+ bonds are syn-periplanar.) This remarkable result, called the *syn–anti dichotomy*, has also been demonstrated by other types of evidence.[21] The fact that syn-elimination in this case predominates over anti (as indicated by the formation of trans isomer in greater amounts than cis) has been explained by conformational factors.[22] The syn–anti dichotomy has also been found in other medium-ring systems (8–12 membered),[23] although the effect is greatest for 10-membered rings. With leaving groups,[24] the extent of this behavior decreases in the order $^+NMe_3 > OTs > Br > Cl$, which parallels steric requirements. When the leaving group is uncharged, syn-elimination is favored by strong bases and by weakly ionizing solvents.[25]

Syn-elimination and the syn—anti dichotomy have also been found in open-chain systems, although to a lesser extent than in medium-ring compounds. For example, in the conversion of 3-hexyl-4-*d*-trimethylammonium ion to 3-hexene with potassium *sec*-butoxide, ~67% of the reaction followed the syn–anti dichotomy.[26] In general syn-elimination in open-chain systems is only important in cases where certain types of steric effect are present. One such type is compounds in which substituents are found on both the β′ and the γ carbons (the unprimed letter refers to the branch in which the elimination takes place). The factors that cause these results are not

[19]Other possible mechanisms, such as E1cB (p. 1488) or α′,β elimination (p. 1524), were ruled out in all these cases by other evidence.

[20]This conclusion has been challenged by Coke, J.L. *Sel. Org. Transform* ***1972***, *2*, 269.

[21]Sicher, J.; Závada, J. *Collect. Czech. Chem. Commun.* ***1967***, *32*, 2122; Závada, J.; Sicher, J. *Collect. Czech. Chem. Commun.* ***1967***, *32*, 3701. For a review, see Bartsch, R.A.; Závada, J. *Chem. Rev.* ***1980***, *80*, 453.

[22]For discussions, see Bartsch, R.A.; Závada, J. *Chem. Rev.* ***1980***, *80*, 453; Coke, J.L. *Sel. Org. Transform.* ***1972***, *2*, 269; Sicher, J. *Angew. Chem. Int. Ed.* ***1972***, *11*, 200; *Pure Appl. Chem.* ***1971***, *25*, 655.

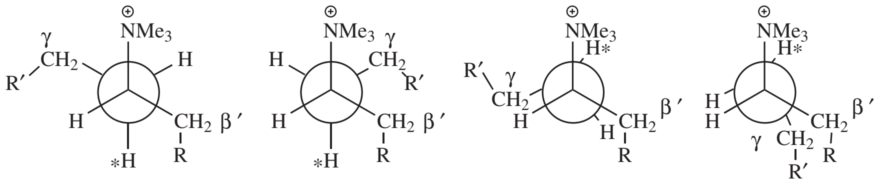
[23]For example, see Coke, J.L.; Mourning, M.C. *J. Am. Chem. Soc.* ***1968***, *90*, 5561, where the experiment was performed on cyclooctyltrimethylammonium hydroxide, and *trans*-cyclooctene was formed by a 100% syn mechanism, and *cis*-cyclooctene by a 51% syn and 49% anti mechanism.

[24]For examples with other leaving groups, see Sicher, J.; Jan, G.; Schlosser, M. *Angew. Chem. Int. Ed.* ***1971***, *10*, 926; Závada, J.; Pánková, M. *Collect. Czech. Chem. Commun.* ***1980***, *45*, 2171, and references.cited therein.

[25]See, for example, Sicher, J.; Závada, J. *Collect. Czech. Chem. Commun.* ***1968***, *33*, 1278.

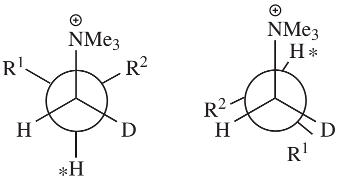
[26]Bailey, D.S.; Saunders Jr., W.H. *J. Am. Chem. Soc.* ***1970***, *92*, 6904. For other examples of syn-elimination and the syn-anti dichotomy in open-chain systems, see Pánková, M.; Vítek, A.; Vasíšková, S.; Řeřicha, R.; Závada, J. *Collect. Czech. Chem. Commun.* ***1972***, *37*, 3456; Schlosser, M.; An, T.D. *Helv. Chim. Acta* ***1979***, *62*, 1194; Sugita, T.; Nakagawa, J.; Nishimoto, K.; Kasai, Y.; Ichikawa, K. *Bull. Chem. Soc. Jpn.* ***1979***, *52*, 871; Pánková, M.; Kocián, O.; Krupička, J.; Závada, J. *Collect. Czech. Chem. Commun.* ***1983***, *48*, 2944.

completely understood, but the following conformational effects have been proposed as a partial explanation.[27] The two anti- and two syn-periplanar conformations are, for a quaternary ammonium salt:



C anti ⟶ trans   D anti ⟶ cis   E syn ⟶ trans   F syn ⟶ cis

In order for an E2 mechanism to take place, a base must approach the proton marked *. In **C**, this proton is shielded on both sides by R and R′. In **D**, the shielding is on only one side. Therefore, when anti-elimination does take place in such systems, it should give more cis product than trans. Also, when the normal anti elimination pathway is hindered sufficiently to allow the syn pathway to compete, the anti → trans route should be diminished more than the anti → cis route. When syn-elimination begins to appear, it seems clear that **E**, which is less eclipsed than **F**, should be the favored pathway and syn-elimination should generally give the trans isomer. In general, deviations from the syn–anti dichotomy are greater on the trans side than on the cis. Thus, trans alkenes are formed partly or mainly by syn-elimination, but cis alkenes are formed entirely by anti-elimination. Predominant syn-elimination has also been found in compounds of the form $R^1R^2CHCHDNMe_3^+$, where R^1 and R^2 are both bulky.[28] In this case, the conformation leading to syn-elimination (**H**) is also less strained than **G**, which gives anti-elimination. The **G** compound has three bulky groups (including NMe_3^+) in the *gauche* position to each other.



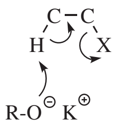
G   H

It was mentioned above that weakly ionizing solvents promote syn-elimination when the leaving group is uncharged. This is probably caused by ion pairing, which

[27]Bailey, D.S.; Saunders, Jr., W.H. *J. Am. Chem. Soc.* ***1970***, *92*, 6904; Chiao, W.; Saunders, Jr., W.H. *J. Am. Chem. Soc.* ***1977***, *99*, 6699.

[28]Dohner, B.R.; Saunders Jr., W.H. *J. Am. Chem. Soc.* ***1986***, *108*, 245.

is greatest in nonpolar solvents.[29] Ion pairing can



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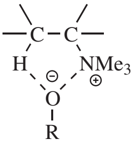
cause syn-elimination with an uncharged leaving group by means of the transition state shown in **10**. This effect was graphically illustrated by elimination from 1,1,4,4-tetramethyl-7-cyclodecyl bromide.[30] The ratio of syn-to-anti-elimination when this compound was treated with *t*-BuOK in the nonpolar benzene was 55.0. But when the crown ether dicyclohexano-18-crown-6 was added (this compound selectively removes K^+ from the *t*-BuO^- K^+ ion pair and thus leaves *t*-BuO^- as a free ion), the syn/anti ratio decreased to 0.12. Large decreases in the syn/anti ratio on addition of the crown ether were also found with the corresponding tosylate and with other nonpolar solvents.[31] However, with positively charged leaving groups the effect is reversed. Here, ion pairing *increases* the amount of anti-elimination.[32] In this case, a relatively free base (e.g., PhO^-) can be attracted to the leaving group, putting it in a favorable position for attack on the syn β hydrogen, while ion pairing would reduce this attraction.



We can conclude that anti-elimination is generally favored in the E2 mechanism, but that steric (inability to form the anti-periplanar transition state), conformational, ion pairing, and other factors cause syn-elimination to intervene (and even predominate) in some cases.

[29]For reviews of ion pairing in this reaction, see Bartsch, R.A.; Závada, J. *Chem. Rev.* ***1980***, *80*, 453; Bartsch, R.A. *Acc. Chem. Res.* ***1975***, *8*, 239.

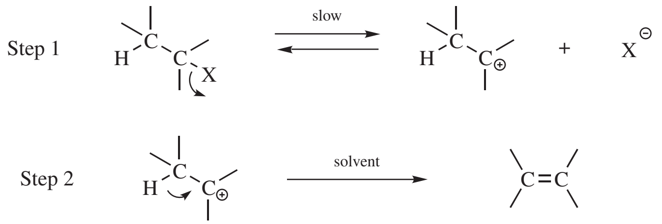
[30]Svoboda, M.; Hapala, J.; Závada, J. *Tetrahedron Lett.* ***1972***, 265.

[31]For other examples of the effect of ion pairing, see Bayne, W.F.; Snyder, E.I. *Tetrahedron Lett.* ***1971***, 571; Bartsch, R.A.; Wiegers, K.E. *Tetrahedron Lett.* ***1972***, 3819; Fiandanese, V.; Marchese, G.; Naso, F.; Sciacovelli, *O. J. Chem. Soc. Perkin Trans. 2* ***1973***, 1336; Borchardt, J.K.; Swanson, J.C.; Saunders, Jr., W.H. *J. Am. Chem. Soc.* ***1974***, *96*, 3918; Mano, H.; Sera, A.; Maruyama, K. *Bull. Chem. Soc. Jpn.* ***1974***, *47*, 1758; Závada, J.; Pánková, M.; Svoboda, M. *Collect. Czech. Chem. Commun.* ***1976***, *41*, 3778; Baciocchi, E.; Ruzziconi, R.; Sebastiani, G.V. *J. Org. Chem.* ***1979***, *44*, 3718; Croft, A.P.; Bartsch, R.A. *Tetrahedron Lett.* ***1983***, *24*, 2737; Kwart, H.; Gaffney, A.H.; Wilk, K.A. *J. Chem. Soc. Perkin Trans. 2* ***1984***, 565.

[32]Borchardt, J.K.; Saunders Jr., W.H. *J. Am. Chem. Soc.* ***1974***, *96*, 3912.

The E1 Mechanism

The E1 mechanism is a two-step process in which the rate-determining step is ionization of the substrate to give a carbocation that rapidly loses a β proton to a base, usually the solvent:

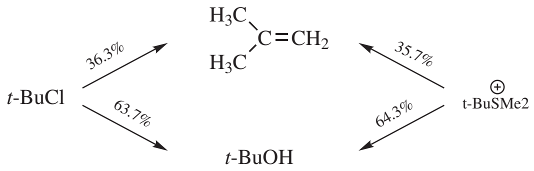


The IUPAC designation is $D_N + D_E$ (or $D_N + D_H$). This mechanism normally operates without an *added* base. Just as the E2 mechanism is analogous to and competes with the S_N2, so is the E1 mechanism related to the S_N1. In fact, the first step of the E1 is exactly the same as that of the S_N1 mechanism. The second step differs in that the solvent pulls a proton from the β carbon of the carbocation rather than attacking it at the positively charged carbon, as in the S_N1 process. In a pure E1 reaction (without ion pairs, etc.), the product should be completely nonstereospecific, since the carbocation is free to adopt its most stable conformation before giving up the proton.

Some of the evidence for the E1 mechanism is as follows:

1. The reaction exhibits first-order kinetics (in substrate) as expected. Of course, the solvent is not expected to appear in the rate equation, even if it were involved in the rate-determining step (p. 316), but this point can be easily checked by adding a small amount of the conjugate base of the solvent. It is generally found that such an addition does not increase the rate of the reaction. If this more powerful base does not enter into the rate-determining step, it is unlikely that the solvent does. An example of an E1 mechanism with a rate-determining second step (proton transfer) has been reported.[33]
2. If the reaction is performed on two molecules that differ only in the leaving group (e.g., *t*-BuCl and *t*-$BuSMe_2^+$), the rates should obviously be different, since they depend on the ionizing ability of the molecule. However, once the carbocation is formed, if the solvent and the temperature are the same, it should suffer the same fate in both cases, since the nature of the leaving group does not affect the second step. This means that *the ratio of elimination to substitution should be the same*. The compounds mentioned in the example were solvolyzed at 65.3°C in 80% aqueous ethanol with the following results:[34]

[33]Baciocchi, E.; Clementi, S.; Sebastiani, G.V.; Ruzziconi, R. *J. Org. Chem.* ***1979***, *44*, 32.
[34]Cooper, K.A.; Hughes, E.D.; Ingold, C.K.; MacNulty, B.J. *J. Chem. Soc.* ***1948***, 2038.



Although the rates were greatly different (as expected with such different leaving groups), the product ratios were the same, within 1%. If this had taken place by a second-order mechanism, the nucleophile would not be expected to have the same ratio of preference for attack at the β hydrogen compared to attack at a *neutral* chloride as for attack at the β hydrogen compared to attack at a *positive* SMe_2 group.

3. Many reactions carried out under first-order conditions on systems where E2 elimination is anti proceed quite readily to give alkenes where a cis hydrogen must be removed, often in preference to the removal of a trans hydrogen. For example, menthyl chloride (**2**, p. 1482), which by the E2 mechanism gave only **5**, under E1 conditions gave 68% **6** and 32% **5**, since the steric nature of the hydrogen is no longer a factor here, and the more stable alkene (Zaitsev's rule, p. 1482) is predominantly formed.

4. If carbocations are intermediates, we should expect rearrangements with suitable substrates. These have often been found in elimination reactions performed under E1 conditions.

E1 reactions can involve ion pairs, just as is true for S_N1 reactions (p. 437).[35] This effect is naturally greatest for nondissociating solvents: It is least in water, greater in ethanol, and greater still in acetic acid. It has been proposed that the ion-pair mechanism (p. 439) extends to elimination reactions too, and that the S_N1, S_N2, E1, and E2 mechanisms possess in common an ion-pair intermediate, at least occasionally.[36]

The E1cB Mechanism[37]

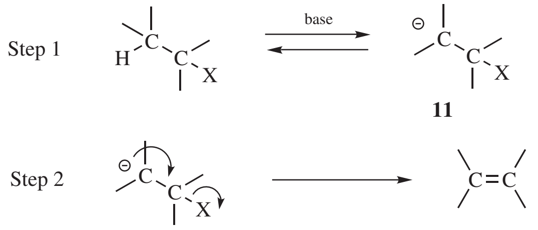
In the E1 mechanism, X leaves first and then H. In the E2 mechanism, the two groups leave at the same time. There is a third possibility: The H leaves first,

[35]Cocivera, M.; Winstein, S. *J. Am. Chem. Soc.* ***1963***, *85*, 1702; Smith, S.G.; Goon, D.J.W. *J. Org. Chem.* ***1969***, *34*, 3127; Bunnett, J.F.; Eck, D.L. *J. Org. Chem.* ***1971***, *36*, 897; Sridharan, S.; Vitullo, V.P. *J. Am. Chem. Soc.* ***1977***, *99*, 8093; Seib. R.C.; Shiner Jr., V.J.; Sendijarević, V.; Humski, K. *J. Am. Chem. Soc.* ***1978***, *100*, 8133; Jansen, M.P.; Koshy, K.M.; Mangru, N.N.; Tidwell, T.T. *J. Am. Chem. Soc.* ***1981***, *103*, 3863; Coxon, J.M.; Simpson, G.W.; Steel, P.J.; Whiteling, S.C. *Tetrahedron* ***1984***, *40*, 3503; Thibblin, A. *J. Am. Chem. Soc.* ***1987***, *109*, 2071; *J. Phys. Org. Chem.* ***1989***, *2*, 15.

[36]Sneen, R.A. *Acc. Chem. Res.* ***1973***, *6*, 46; Thibblin, A.; Sidhu, H. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 1423. See, however, McLennan, D.J. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 1577.

[37]For reviews, see Cockerill, A.F.; Harrison, R.G., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 158–178; Hunter, D.H. *Intra-Sci. Chem. Rep.* ***1973***, *7(3)*, 19; McLennan, D.J. *Q. Rev. Chem. Soc.* ***1967***, *21*, 490. For a general discussion, see Koch, H.F. *Acc. Chem. Res.* ***1984***, *17*, 137.

and then the X. This is a two-step process, called the E1cB *mechanism*,[38] or the *carbanion mechanism*, since the intermediate is a carbanion:



The name E1cB comes from the fact that it is the conjugate base of the substrate that is giving up the leaving group (see the S_N1cB mechanism, p. 521). The IUPAC designation is $A_nD_E + D_N$ or $A_{xh}D_H + D_N$ (see p. 420). We can distinguish three limiting cases: (*1*) The carbanion returns to starting material faster than it forms product: step 1 is reversible; step 2 is slow. (*2*) Step 1 is the slow step, and formation of product is faster than return of the carbanion to starting material. In this case, step 1 is essentially irreversible. (*3*) Step 1 is rapid, and the carbanion goes slowly to product. This case occurs only with the most stable carbanions. Here, too, step 1 is essentially irreversible. These cases have been given the designations: (*1*) $(E1cB)_R$, (*2*) $(E1cB)_I$ (or $E1cB_{irr}$), and (*3*) $(E1)_{anion}$. Their characteristics are listed in Table 17.1.[39] Investigations of the reaction order are generally not very useful (except for case 3, which is first order), because cases 1 and 2 are second order and thus difficult or impossible to distinguish from the E2 mechanism by this procedure.[40] We would expect the greatest likelihood of finding the E1cB mechanism in substrates that have (a) a poor nucleofuge and (b) an acidic hydrogen, and most investigations have concerned such substrates. The following is some of the evidence in support of the E1cB mechanism:

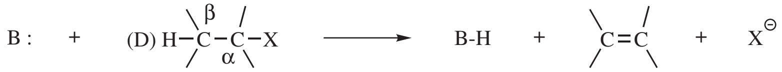
1. The first step of the $(E1cB)_R$ mechanism involves a reversible exchange of protons between the substrate and the base. In that case, if deuterium is present in the base, recovered starting material should contain deuterium. This was found to be the case in the treatment of $Cl_2C{=}CHCl$ with NaOD to give $ClC{\equiv}CCl$. When the reaction was stopped before completion, there *was*

[38]For a discussion, see Ryberg, P.; Matsson, O. *J. Org. Chem.* ***2002***, *67*, 811.

[39]This table, which appears in Cockerill, A.F.; Harrison, R.G. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, p. 161, was adapted from a longer one, in Bordwell, F.G. *Acc. Chem. Res.* ***1972***, *5*, 374, see p. 375.

[40]$(E1cB)_I$ cannot be distinguished from E2 by this means, because it has the identical rate law: Rate $= k$[substrate][B^-]. The rate law for $(E1cB)_R$ is different: Rate $= k$[substrate][B^-]/[BH], but this is often not useful because the only difference is that the rate is also dependent (inversely) on the concentration of the conjugate acid of the base, and this is usually the solvent, so that changes in its concentration cannot be measured.

TABLE 17.1. Kinetic Predictions for Base-Induced β-Eliminations[39]



Mechanism	Kinetic[a] Order	β-Hydrogen Exchange Faster Than Elimination	General or Specific Base Catalysis	k_H/k_D	Electron Withdrawal at Cβ[d]	Electron release at Cα[d]	Leaving-Group Isotope Effect or Element Effect
$(E1)_{anion}$	1	Yes	General[c]	1.0	Rate decrease	Rate increase	Substantial
$(E1cB)_R$	2	Yes	Specific	1.0	Small rate increase	Small rate increase	Substantial
$(E1cB)_{ip}$	2	No	General[e]	1.0 → 1.2	Small rate increase	Small rate increase	Substantial
$(E1cB)_I$	2	No	General	2 → 8	Rate increase	Little effect	Small to negligible
E2[b]	2	No	General	2 → 8	Rate increase	Small rate increase	Small

[a]All mechanism exhibit first-order kinetics in substrate.
[b]Only transition states with considerable carbanion character considered in this table.
[c]Specific base catalysis predicted if extent of substrate ionization reduced from almost complete.
[d]Effect on rate assuming no change in mechanism is caused; steric factors upon substitution at Cα and rise to Cβ have not been considered. The rate reductions are geared to substituent effects such as those giving rise to Hammett reaction constants on β- and α-aryl substitution.
[e]Depends on whether an ion pair assists in removal of leaving group.

deuterium in the recovered alkene.[41] A similar result was found for pentahaloethanes.[42] These substrates are relatively acidic. In both cases the electron-withdrawing halogens increase the acidity of the hydrogen, and in the case of trichloroethylene there is the additional factor that a hydrogen on an sp^2 carbon is more acidic than one on an sp^3 carbon (p. 388). Thus, the E1cB mechanism is more likely to be found in eliminations yielding triple bonds than in those giving double bonds. Another likely place for the E1cB mechanism should be in reaction of a substrate like $PhCH_2CH_2Br$, since the carbanion is stabilized by resonance with the phenyl group. Nevertheless, no deuterium exchange was found here.[43] If this type of evidence is a guide, then it may be inferred that the $(E1cB)_R$ mechanism is quite rare, at least for eliminations with common leaving groups such as Br, Cl, or OTs, which yield C=C double bonds.

[41]Houser, J.J.; Bernstein, R.B.; Miekka, R.G.; Angus, J.C. *J. Am. Chem. Soc.* ***1955***, *77*, 6201.
[42]Hine, J.; Wiesboeck, R.; Ghirardelli, R.G. *J. Am. Chem. Soc.* ***1961***, *83*, 1219; Hine, J.; Wiesboeck, R.; Ramsay, O.B. *J. Am. Chem. Soc.* ***1961***, *83*, 1222.
[43]Skell, P.S.; Hauser, C.R. *J. Am. Chem. Soc.* ***1945***, *67*, 1661.

2. When the reaction

$$p\text{-}NO_2C_6H_4\text{—}CH_2\text{—}\overset{\oplus}{CH_2}\text{—}NR_4 + B^{\ominus} \longrightarrow p\text{-}NO_2C_6H_4\text{—}CH_2{=}CH_2 + BH + NR_3$$

was carried out in water containing acetohydroxamate buffers, a plot of the rate against the buffer concentration was curved and the rate leveled off at high buffer concentrations, indicating a change in rate-determining step.[44] This rules out an E2 mechanism, which has only one step.[45] When D_2O was used instead of H_2O as solvent, there was an initial inverse solvent isotope effect of 7.7 (the highest inverse solvent isotope effect yet reported).

That is, the reaction took place faster in D_2O than in H_2O. This is compatible only with an E1cB mechanism in which the proton-transfer step is not entirely rate determining. The isotope effect arises from a partitioning of the carbanion intermediate **11**. This intermediate either can go to product or it can revert to starting compound, which requires taking a proton from the solvent. In D_2O, the latter process is slower (because the O–D bond of D_2O cleaves less easily than the O–H bond of H_2O), reducing the rate at which **11** returns to starting compound. With the return reaction competing less effectively, the rate of conversion of **11** to product is increased.

3. We have predicted that the E1cB mechanism would most likely be found with substrates containing acidic hydrogens and poor leaving groups. Compounds of the type ZCH_2CH_2OPh, where Z is an electron-withdrawing group (e.g., NO_2, SMe_2^+, $ArSO_2$, CN, COOR), belong to this category, because OPh is a very poor leaving group (p. 438). There is much evidence to show that the mechanism here is indeed E1cB.[46] Isotope effects, measured for $MeSOCD_2CH_2OPh$ and $Me_2S^+CD_2CH_2OPh$ with NaOD in D_2O, are ~0.7. This is compatible with an $(E1cB)_R$ mechanism, but not with an E2 mechanism for which an isotope effect of perhaps 5 might be expected (of course, an E1 mechanism is precluded by the extremely poor nucleofugal ability of OPh). The fact that k_H/k_D is less than the expected value of 1 is attributable to solvent and secondary isotope effects. Among other evidence for an E1cB mechanism in these systems is that changes in the identity of Z had a dramatic effect on the relative rates: a span of 10^{11} between NO_2 and COO^-. Note that elimination from substrates of the type $RCOCH_2CH_2Y$ is the reverse of Michael-type addition to C=C bonds. We have seen (p. $$$) that such addition involves initial attack by a nucleophile Y and subsequent attack by a proton. Thus the initial loss of a proton from substrates of this type (i.e., an E1cB mechanism) is in accord with the principle of microscopic

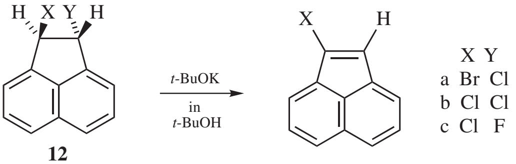
[44]Keeffe, J.R.; Jencks, W.P. *J. Am. Chem. Soc.* ***1983***, *105*, 265.

[45]For a borderline E1cB–E2 mechanism, see Jia, Z.S.; Rudziń sci, J.; Panethy, P.; Thibblin, A. *J. Org. Chem.* ***2002***, *67*, 177.

[46]Cann, P.F.; Stirling, C.J.M. *J. Chem. Soc. Perkin Trans. 2* ***1974***, 820. For other examples; see Fedor, L.R. *J. Am. Chem. Soc.* ***1969***, *91*, 908; More O'Ferrall, R.A.; Slae, S. *J. Chem. Soc. B* ***1970***, 260; Kurzawa, J.; Leffek, K.T. *Can. J. Chem.* ***1977***, *55*, 1696.

reversibility.[47] It may also be recalled that benzyne formation (p. 859) can occur by such a process. It has been suggested that all base-initiated eliminations wherein the proton is activated by a strong electron-withdrawing group are E1cB reactions,[48] but there is evidence that this is not the case that when there is a good nucleofuge, the mechanism is E2 even when strong electron-withdrawing groups are present.[49] On the other hand, Cl^- has been found to be a leaving group in an E1cB reaction.[50]

Of the three cases of the E1cB mechanism, the one most difficult to distinguish from E2 is $(\text{E1cB})_{\text{I}}$. One way to make this distinction is to study the effect of a change in leaving group. This was done in the case of the three acenaphthylenes **12**, where it was found that (*1*) the three rates were fairly similar, the largest being only about



12

four times that of the smallest, and (*2*) in compound *c* (X = Cl, Y = F), the only product contained Cl and no F, that is, only the poorer nucleofuge F departed while Cl remained.[51] Result (*1*) rules out all the E1cB mechanisms except $(\text{E1cB})_{\text{I}}$, because the others should all have considerable leaving group effects (Table 17.1). An ordinary E2 mechanism should also have a large leaving group effect, but an E2 mechanism with substantial carbanionic character (see the next section) might not. However, no E2 mechanism can explain result (*2*), which can be explained by the fact that an a Cl is more effective than an a F in stabilizing the planar carbanion that remains when the proton is lost. Thus (as in the somewhat similar case of aromatic nucleophilic substitution, see p. 868), when X^- leaves in the second step, the one that leaves is not determined by which is the better nucleofuge, but by which has had its β hydrogen removed.[52] Additional evidence for the existence of the

[47]Patai, S.; Weinstein, S.; Rappoport, Z. *J. Chem. Soc.* ***1962***, 1741. See also, Hilbert, J.M.; Fedor, L.R. *J. Org. Chem.* ***1978***, *43*, 452.

[48]Bordwell, F.G.; Vestling, M.M.; Yee, K.C. *J. Am. Chem. Soc.* ***1970***, *92*, 5950; Bordwell, F.G. *Acc. Chem. Res.* ***1972***, *5*, 374.

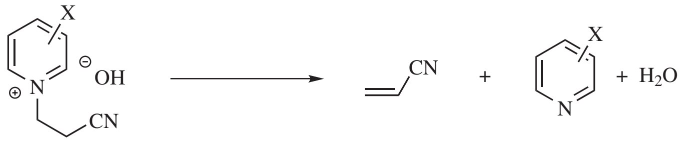
[49]Marshall, D.R.; Thomas, P.J.; Stirling, C.J.M. *J. Chem. Soc. Perkin Trans. 2* ***1977***, 1898, 1914; Banait, N.S.; Jencks, W.P. *J. Am. Chem. Soc.* ***1990***, *112*, 6950.

[50]Ölwegård, M.; McEwen, I.; Thibblin, A.; Ahlberg, P. *J. Am. Chem. Soc.* ***1985***, *107*, 7494.

[51]Baciocchi, E.; Ruzziconi, R.; Sebastiani, G.V. *J. Org. Chem.* ***1982***, *47*, 3237.

[52]For other evidence for the existence of the $(\text{E1cB})_{\text{I}}$ mechanism, see Bordwell, F.G.; Vestling, M.M.; Yee, K.C. *J. Am. Chem. Soc.* ***1970***, *92*, 5950; Fedor, L.R.; Glave, W.R. *J. Am. Chem. Soc.* ***1971***. *93*, 985; Redman, R.P.; Thomas, P.J.; Stirling, C.J.M. *J. Chem. Soc. Perkin Trans. 2* ***1978***. 1135; Thibblin, A. *Chem. Scr.* ***1980***, *15*, 121; Carey, E.; More O'Ferrall, R.A.; Vernon, N.M. *J. Chem. Soc. Perkin Trans. 2* ***1982*** 1581; Baciocchi, E.; Ruzziconi, R. *J. Org. Chem.* ***1984***, *49*, 3395; Jarczewski, A.; Waligorska, M.; Leffek, K.T. *Can. J Chem.* ***1985***, *63*, 1194; Gula, M.J.; Vitale, D.E.; Dostal, J.M.; Trometer, J.D.; Spencer, T.A. *J. Am. Chem. Soc.* ***1988*** *110*, 4400; Garay, R.O.; Cabaleiro, M.C. *J. Chem. Res. (S)*, ***1988***, 388; Gandler, J.R.; Storer, J.W.; Ohlberg, D.A.A. *J. Am. Chem. Soc.* ***1990***, *112*, 7756.

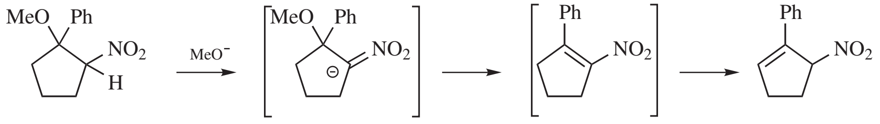
$(E1cB)_I$ mechanism was the observation of a change in the rate-determining step in the elimination reaction of *N*-(2-cyanoethyl)pyridinium



13

ions **13**, treated with base, when X was changed.[53] Once again, the demonstration that two steps are involved precludes the one-step E2 mechanism.

4. An example of an $(E1)_{anion}$ mechanism has been found with the substrate **14**, which when treated with methoxide ion undergoes elimination to **16**, which is unstable under the reaction conditions and rearranges as

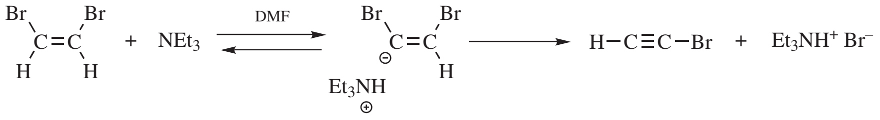


14 15 16

shown.[54] Among the evidence for the proposed mechanism in this case were kinetic and isotope-effect results, as well as the spectral detection of **15**.[55]

5. In many eliminations to form C=O and C≡N bonds the initial step is loss of a positive group (normally a proton) from the oxygen or nitrogen. These may also be regarded as E1cB processes.

There is evidence that some E1cB mechanisms can involve carbanion ion pairs, for example,[56]



This case is designated $(E1cB)_{ip}$; its characteristics are shown in Table 17.1.

[53]Bunting, J.W.; Toth, A.; Heo, C.K.M.; Moors, R.G. *J. Am. Chem. Soc.* ***1990***, *112*, 8878. See also, Bunting, J.W.; Kanter, J.P. *J. Am. Chem. Soc.* ***1991***, *113*, 6950.

[54]Bordwell, F.G.; Yee, K.C.; Knipe, A.C. *J. Am. Chem. Soc.* ***1970***, *92*, 5945.

[55]For other examples of this mechanism, see Berndt, A. *Angew. Chem. Int. Ed.* ***1969***, *8*, 613; Albeck, M.; Hoz, S.; Rappoport, Z. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 1248; ***1975***, 628.

[56]Kwok, W.K.; Lee, W.G.; Miller, S.I. *J. Am. Chem. Soc.* ***1969***, *91*, 468. See also Lord, E.; Naan, M.P.; Hall, C.D. *J. Chem. Soc. B* ***1971***, 220; Rappoport, Z.; Shohamy, E. *J. Chem. Soc. B* ***1971***, 2060; Fiandanese, V.; Marchese, G.; Naso, F. *J. Chem. Soc., Chem. Commun.* ***1972***, 250; Koch, H.F.; Dahlberg, D.B.; Toczko, A.G.; Solsky, R.L. *J. Am. Chem. Soc.* ***1973***, *95*, 2029; Hunter, D.H.; Shearing, D.J. *J. Am. Chem. Soc.* ***1973***, *95*, 8333; Thibblin, A.; Ahlberg, P. *J. Am. Chem. Soc.* ***1979***, *101*, 7311; Petrillo, G.; Novi, M.; Garbarino, G.; Dell'Erba, C.; Mugnoli, A. *J. Chem. Soc. Perkin Trans. 2* ***1985***, 1291.

The E1-E2-E1cB Spectrum

In the three mechanisms so far considered, the similarities are greater than the differences. In each case, there is a leaving group that comes off with its pair of electrons and another group (usually hydrogen) that comes off without them. The only difference is in the order of the steps. It is now generally accepted that there is a spectrum of mechanisms ranging from one extreme, in which the leaving group departs well before the proton (pure E1), to the other extreme, in which the proton comes off first and then, after some time, the leaving group follows (pure E1cB). The *pure* E2 case would be somewhere in the middle, with both groups leaving simultaneously. However, most E2 reactions are not exactly in the middle, but somewhere to one side or the other. For example, the nucleofuge might depart just before the proton. This case may be described as an E2 reaction with a small amount of E1 character. The concept can be expressed by the question: In the transition state, which bond (C–H or C–X) has undergone more cleavage?[57]

One way to determine just where a given reaction stands on the E1-E2-E1cB spectrum is to study isotope effects, which ought to tell something about the behavior of bonds in the transition state.[58] For example, $CH_3CH_2NMe_3^+$ showed a nitrogen isotope effect (k^{14}/k^{15}) of 1.017, while $PhCH_2CH_2NMe_3^+$ gave a corresponding value of 1.009.[59] It would be expected that the phenyl group would move the reaction toward the E1cB side of the line, which means that for this compound the C–N bond is not as greatly broken in the transition state as it is for the unsubstituted one. The isotope effect bears this out, for it shows that in the phenyl compound, the mass of the nitrogen has less effect on the reaction rate than it does in the unsubstituted compound. Similar results have been obtained with SR_2^+ leaving groups by the use of $^{32}S/^{34}S$ isotope effects[60] and with Cl ($^{35}Cl/^{37}Cl$).[61] The position of reactions along the spectrum has also been studied from the other side of the newly forming double bond by the use of H/D and H/T isotope effects,[62] although interpretation of these results is clouded by the fact that β hydrogen isotope effects are expected to change smoothly from small to large to small again as the degree of transfer of the

[57]For discussions, see Cockerill, A.F.; Harrison, R.G., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 178–189; Saunders, Jr., W.H. *Acc. Chem. Res.* ***1976***, *9*, 19; Bunnett, J.F. *Surv. Prog. Chem.* ***1969***, *5*, 53; Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***, pp. 47–104; Bordwell, F.G. *Acc. Chem. Res.* ***1972***, *5*, 374.

[58]For a review, see Fry, A. *Chem. Soc. Rev.* ***1972***, *1*, 163. See also Hasan, T.; Sims, L.B.; Fry, A. *J. Am. Chem. Soc.* ***1983***, *105*, 3967; Pulay, A.; Fry, A. *Tetrahedron Lett.* ***1986***, *27*, 5055.

[59]Ayrey, G.; Bourns, A.N.; Vyas, V.A. *Can. J. Chem.* ***1963***, *41*, 1759. Also see, Simon, H.; Müllhofer, G. *Chem. Ber.* ***1963***, *96*, 3167; ***1964***, *97*, 2202; *Pure Appl. Chem.* ***1964***, *8*, 379, 536; Smith, P.J.; Bourns, A.N. *Can. J. Chem.* ***1970***, *48*, 125.

[60]Wu, S.; Hargreaves, R.T.; Saunders Jr., W.H. *J. Org. Chem.* ***1985***, *50*, 2392, and references cited therein.

[61]Grout, A.; McLennan, D.J.; Spackman, I.H. *J. Chem. Soc. Perkin Trans. 2* ***1977***, 1758.

[62]For example, see Hodnett, E.M.; Sparapany, J.J. *Pure Appl. Chem.* ***1964***, *8*, 385, 537; Finley, K.T.; Saunders, Jr., W.H. *J. Am. Chem. Soc.* ***1967***, *89*, 898; Ghanbarpour, A.; Willi, A.V. *Liebigs Ann. Chem.* ***1975***, 1295; Simon, H.; Müllhofer, G. *Chem. Ber.* ***1964***, *97*, 2202; Thibblin, A. *J. Am. Chem. Soc.* ***1988***, *110*, 4582; Smith, P.J.; Amin, M. *Can. J. Chem.* ***1989***, *67*, 1457.

β hydrogen from the β carbon to the base increases[63] (recall, p. $$$, that isotope effects are greatest when the proton is half-transferred in the transition state), by the possibility of secondary isotope effects (e.g., the presence of a β deuterium or tritium may cause the leaving group to depart more slowly), and by the possibility of tunneling.[64] Other isotope-effect studies have involved labeled a or β carbon, labeled a hydrogen, or labeled base.[58]

Another way to study the position of a given reaction on the spectrum involves the use of β-aryl substitution. Since a positive Hammet ρ value is an indication of a negatively charged transition state, the ρ value for substituted β-aryl groups should increase as a reaction moves from E1- to E1cB-like along the spectrum. This has been shown to be the case in a number of studies;[65] for example, ρ values of $ArCH_2CH_2X$ increase as the leaving-group ability of X decreases. A typical set of ρ values was X = I, 2.07; Br, 2.14; Cl, 2.61; SMe_2^+, 2.75; F, 3.12.[66] As we have seen, decreasing leaving-group ability correlates with increasing E1cB character.

Still another method measures volumes of activation.[67] These are negative for E2 and positive for E1cB mechanisms. Measurement of the activation volume therefore provides a continuous scale for deciding just where a reaction lies on the spectrum.

The E2C Mechanism[68]

Certain alkyl halides and tosylates undergo E2 eliminations faster when treated with such weak bases as Cl^- in polar aprotic solvents or PhS^- than with the usual E2 strong bases, such as RO^- in ROH.[69] In order to explain these results, Parker

[63]There is controversy as to whether such an effect has been established in this reaction: See Cockerill, A.F. *J. Chem. Soc. B* ***1967***, 964; Blackwell, L.F. *J. Chem. Soc. Perkin Trans. 2* ***1976***, 488.

[64]For examples of tunneling in elimination reactions, see Miller, D.J.; Saunders, Jr., W.H. *J. Org. Chem.* ***1981***, *46*, 4247 and previous papers in this series. See also, Shiner, Jr., V.J.; Smith, M.L. *J. Am. Chem. Soc.* ***1961***, *83*, 593; McLennan, D.J. *J. Chem. Soc. Perkin Trans. 2* ***1977***, 1753; Fouad, F.M.; Farrell, P.G. *Tetrahedron Lett.* ***1978***, 4735; Koth, H.F.; McLennan, D.J.; Koch, J.G.; Tumas, W.; Dobson, B.; Koch, J.G. *J. Am. Chem. Soc.* ***1983***, *105*, 1930; Kwart, H.; Wilk, K.A. *J. Org. Chem.* ***1985***, *50*, 817; Amin, M.; Price, R.C.; Saunders, Jr., W.H. *J. Am. Chem. Soc.* ***1990***, *112*, 4467.

[65]Saunders Jr., W.H.; Bushman, D.G.; Cockerill, A.F. *J. Am. Chem. Soc.* ***1968***, *90*, 1775; Yano, Y.; Oae, S. *Tetrahedron* ***1970***, *26*, 27, 67; Blackwell, L.F.; Buckley, P.D.; Jolley, K.W.; MacGibbon, A.K.H. *J. Chem. Soc. Perkin Trans. 2* ***1973***, 169; Smith, P.J.; Tsui, S.K. *J. Am. Chem. Soc.* ***1973***, *95*, 4760; *Can. J. Chem.* ***1974***, *52*, 749.

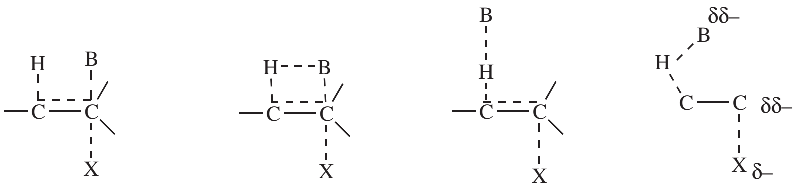
[66]DePuy, C.H.; Froemsdorf, D.H. *J. Am. Chem. Soc.* ***1957***, *79*, 3710; DePuy, C.H.; Bishop, C.A. *J. Am. Chem. Soc.* ***1960***, *82*, 2532, 2535.

[67]Brower, K.R.; Muhsin, M.; Brower, H.E. *J. Am. Chem. Soc.* ***1976***, *98*, 779. For a review, see van Eldik, R.; Asano, T.; le Noble, W.J. *Chem. Rev.* ***1989***, *89*, 549.

[68]For reviews, see McLennan, D.J. *Tetrahedron* ***1975***, *31*, 2999; Ford, W.T. *Acc. Chem. Res.* ***1973***, *6*, 410; Parker, A.J. *CHEMTECH* ***1971***, 297.

[69]For example; see Winstein, S.; Darwish, D.; Holness, N.J. *J. Am. Chem. Soc.* ***1956***, *78*, 2915; de la Mare, P.B.D.; Vernon, C.A. *J. Chem. Soc.* ***1956***, 41; Eliel, E.L.; Ro, R.S. *Tetrahedron* ***1958***, *2*, 353; Bunnett, J.F.; Davis, G.T.; Tanida, H. *J. Am. Chem. Soc.* ***1962***, *84*, 1606; McLennan, D.J. *J. Chem. Soc. B* ***1966***, 705, 709; Hayami, J.; Ono, N.; Kaji, A. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 1628.

and co-workers proposed[70] that there is a spectrum[71] of E2 transition states in which the base can interact in the transition state with the α carbon, as well as with the β hydrogen. At one end of this spectrum is



E2C 　 **17** 　 E2H 　 **18**

a mechanism (called E2C) in which, in the transition state, the base interacts mainly with the carbon. The E2C mechanism is characterized by strong nucleophiles that are weak bases. At the other extreme is the normal E2 mechanism, here called E2H to distinguish it from E2C, characterized by strong bases. Transition state **17** represents a transition state between these extremes. Additional evidence[72] for the E2C mechanism is derived from Brønsted equation considerations (p. 373), from substrate effects, from isotope effects, and from the effects of solvents on rates.

However, the E2C mechanism has been criticized, and it has been contended that all the experimental results can be explained by the normal E2 mechanism.[73] McLennan has suggested that the transition state is that shown as **18**.[74] An ion-pair mechanism has also been proposed.[75] Although the actual mechanisms involved may be a matter of controversy, there is no doubt that a class of elimination reactions exists that is characterized by second-order attack by weak bases.[76] These reactions also have the following general characteristics:[77] (*1*) they are favored by good leaving groups; (*2*) they are favored by polar aprotic solvents;

[70]Parker, A.J.; Ruane, M.; Biale, G.; Winstein, S. *Tetrahedron Lett.* ***1968***, 2113.

[71]This is apart from the E1-E2-E1cB spectrum.

[72]Lloyd, D.J.; Parker, A.J. *Tetrahedron Lett.* ***1968***, 5183; ***1970***, 5029; Alexander, R.; Ko, E.C.F.; Parker, A.J.; Broxton, T.J. *J. Am. Chem. Soc.* ***1968***, *90*, 5049; Ko, E.C.F.; Parker, A.J. *J. Am. Chem. Soc.* ***1968***, *90*, 6447; Parker, A.J.; Ruane, M.; Palmer, D.A.; Winstein, S. *J. Am. Chem. Soc.* ***1972***, *94*, 2228; Biale, G.; Parker, A.J.; Stevens, I.D.R.; Takahashi, J.; Winstein, S. *J. Am. Chem. Soc.* ***1972***, *94*, 2235; Cook, D. *J. Org. Chem.* ***1976***, *41*, 2173, and references cited therein; Muir, D.M.; Parker, A.J. *Aust. J. Chem.* ***1983***, *36*, 1667; Kwart, H.; Wilk, K.A. *J. Org. Chem.* ***1985***, *50*, 3038.

[73]McLennan, D.J.; Wong, R.J. *J. Chem. Soc. Perkin Trans. 2* ***1974***, 1818, and references cited therein; Ford, W.T.; Pietsek, D.J.J. *J. Am. Chem. Soc.* ***1975***, *97*, 2194; Loupy, A. *Bull. Soc. Chim. Fr.* ***1975***, 2662; Miller, D.J.; Saunders Jr., W.H. *J. Am. Chem. Soc.* ***1979***, *101*, 6749; Bordwell, F.G.; Mrozack, S.R. *J. Org. Chem.* ***1982***, *47*, 4813; Bunnett, J.F.; Migdal, C.A. *J. Org. Chem.* ***1989***, *54*, 3037, 3041, and references cited therein.

[74]McLennan, D.J.; Lim, G. *Aust. J. Chem.* ***1983***, *36*, 1821. For an opposing view, see Kwart, H.; Gaffney, A. *J. Org. Chem.* ***1983***, *48*, 4502.

[75]Ford, W.T. *Acc. Chem. Res.* ***1973***, *6*, 410.

[76]For convenience, we will refer to this class of reactions as E2C reactions, though the actual mechanism is in dispute.

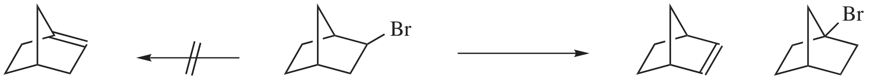
[77]Beltrame, P.; Biale, G.; Lloyd, D.J.; Parker, A.J.; Ruane, M.; Winstein, S. *J. Am. Chem. Soc.* ***1972***, *94*, 2240; Beltrame, P.; Ceccon, A.; Winstein, S. *J. Am. Chem. Soc.* ***1972***, *94*, 2315.

(*3*) the reactivity order is tertiary > secondary > primary, the opposite of the normal E2 order (p. 1503); (*4*) the elimination is always anti- (syn-elimination is not found), but in cyclohexyl systems, a diequatorial anti-elimination is about as favorable as a diaxial anti-elimination (unlike the normal E2 reaction, p. 1481); (*5*) they follow Zaitsev's rule (see below), where this does not conflict with the requirement for anti-elimination.

Regiochemistry of the Double Bond

With some substrates, a β hydrogen is present on only one carbon and (barring rearrangements) there is no doubt as to the identity of the product. For example, $PhCH_2CH_2Br$ can give only $PhCH{=}CH_2$. However, in many other cases two or three alkenyl products are possible. In the simplest such case, a *sec*-butyl compound can give either 1- or 2-butene. There are a number of rules that enable us to predict, in many instances, which product will predominantly form.[78]

1. No matter what the mechanism, a double bond does not go to a bridgehead carbon unless the ring sizes are large enough (Bredt's rule, see p. 229). This means, for example, not only that **19** gives only **20** and not **21** (indeed **21** is not a known compound), but also that **22** does not undergo elimination.



21 **19** **20** **22**

2. No matter what the mechanism, if there is a double bond (C=C or C=O) or an aromatic ring already in the molecule that can be in conjugation with the new double bond, the conjugated product usually predominates, sometimes even when the stereochemistry is unfavorable (for an exception, see p. 1501).
3. In the E1 mechanism the leaving group is gone before the choice is made as to which direction the new double bond takes. Therefore the direction is determined almost entirely by the relative stabilities of the two (or three) possible alkenes. In such cases, *Zaitsev's rule*[79] operates. This rule states that *the double bond goes mainly toward the most highly substituted carbon*. That is, a *sec*-butyl compound gives more 2-butene than 1-butene, and 3-bromo-2,3-dimethylpentane gives more 2,3-dimethyl-2-pentene than either 3,4-dimethyl-2-pentene or 2-ethyl-3-methyl-1-butene. Thus Zaitsev's rule predicts that the alkene predominantly formed will be the one with the largest possible number of alkyl groups on the C=C carbons, and in most cases this is what is found. From heat of combustion data (see p. 29) it is known that

[78]For a review of orientation in cycloalkyl systems, see Hückel, W.; Hanack, M. *Angew. Chem. Int. Ed.* ***1967***, *6*, 534.
[79]Often given the German spelling: Saytzeff.

alkene stability increases with alkyl substitution, although just why this should be is a matter of conjecture. The most common explanation is hyperconjugation. For E1 eliminations, Zaitsev's rule governs the orientation whether the leaving group is neutral or positive, since, as already mentioned, the leaving group is not present when the choice of direction is made. This statement does not hold for E2 eliminations, and it may be mentioned here, for contrast with later results, that E1 elimination of $Me_2CHCHMeSMe_2^+$ gave 91% of the Zaitsev product and 9% of the other.[80] However, there *are* cases in which the leaving group affects the direction of the double bond in E1-eliminations.[81] This may be attributed to ion pairs; that is, the leaving group is not completely gone when the hydrogen departs. Zaitsev's rule breaks down in cases where the non-Zaitsev product is more stable for steric reasons. For example, E1 or E1-like eliminations of 1,2-diphenyl-2-X-propanes $PhMeCXCH_2Ph$ were reported to give ~50% $CH_2{=}CPhCH_2Ph$, despite the fact that the double bond of the Zaitsev product ($PhMeC{=}CHPh$) is conjugated with two benzene rings.[82]

4. For the anti E2 mechanism a trans β proton is necessary; if this is available in only one direction, that is the way the double bond will form. Because of the free rotation in acyclic systems (except where steric hindrance is great), this is a factor only in cyclic systems. Where trans β hydrogens are available on two or three carbons, two types of behavior are found, depending on substrate structure and the nature of the leaving group. Some compounds follow Zaitsev's rule and give predominant formation of the most highly substituted alkene, but others follow *Hofmann's rule: The double bond goes mainly toward the least highly substituted carbon.* although many exceptions are known, the following general statements can be made: In most cases, compounds containing uncharged nucleofuges (those that come off as negative ions) follow Zaitsev's rule, just as they do in E1 elimination, no matter what the structure of the substrate. However, elimination from compounds with charged nucleofuges, for example, NR_3^+, SR_2^+ (those that come off as neutral molecules), follow Hofmann's rule if the substrate is acyclic,[83] but Zaitsev's rule if the leaving group is attached to a six-membered ring.[84]

Much work has been devoted to searching for the reasons for the differences in orientation. Since Zaitsev orientation almost always gives the

[80]de la Mare, P.B.D. *Prog. Stereochem.* ***1954***, *1*, 112.

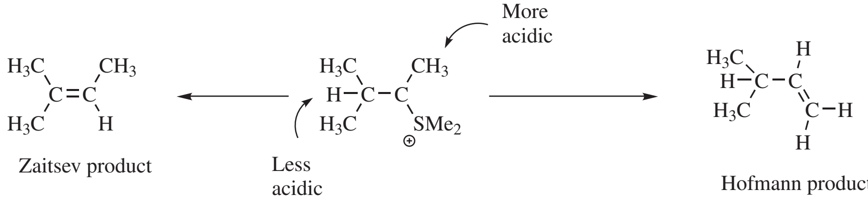
[81]Cram, D.J.; Sahyun, M.R.V. *J. Am. Chem. Soc.* ***1963***, *85*, 1257; Silver, M.S. *J. Am. Chem. Soc.* ***1961***, *83*, 3482.

[82]Ho, I.; Smith, J.G. *Tetrahedron* ***1970***, *26*, 4277.

[83]An example of an acyclic quaternary ammonium salt that follows Zaitsev's rule is found, in Feit, I.N.; Saunders, Jr., W.H. *J. Am. Chem. Soc.* ***1970***, *92*, 5615.

[84]For examples where Zaitsev's rule is followed with charged leaving groups in cyclohexyl systems, see Gent, B.B.; McKenna, J. *J. Chem. Soc.* ***1959***, 137; Hughes, E.D.; Wilby, J. *J. Chem. Soc.* ***1960***, 4094; Brownlee, T.H.; Saunders Jr., W.H. *Proc. Chem. Soc.* ***1961***, 314; Booth, H.; Franklin, N.C.; Gidley, G.C. *J. Chem. Soc. C* ***1968***, 1891. For a discussion of the possible reasons for this, see Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***, pp. 192–193.

thermodynamically more stable isomer, what needs to be explained is why in some cases the less stable Hofmann product predominates. Three explanations have been offered for the change in orientation in acyclic systems with a change from uncharged to charged nucleofuges. The first of these, by Hughes and Ingold,[85] is that Hofmann orientation is caused by the fact that the acidity of the β hydrogen is decreased by the presence of the electron-donating alkyl groups. For example, under E2 conditions $Me_2CHCHMeSMe_2^+$ gives more of the Hofmann product; it is the more acidic hydrogen that is removed by the base.



Of course, the CH_3 hydrogens would still be more acidic than the Me_2CH hydrogen even if a neutral leaving group were present, but the explanation of Hughes and Ingold is that acidity matters with charged and not with neutral leaving groups, because the charged groups exert a strong electron-withdrawing effect, making differences in acidity greater than they are with the less electron-withdrawing neutral groups.[85] The explanation of Bunnett[86] is similar. According to this, the change to a positive leaving group causes the mechanism to shift toward the E1cB end of the spectrum, where there is more C–H bond breaking in the rate-determining step and where, consequently, acidity is more important. In this view, when there is a neutral leaving group, the mechanism is more E1-like, C–X bond breaking is more important, and alkene stability determines the direction of the new double bond. The third explanation, by H.C. Brown, is completely different. In this picture, field effects are unimportant, and the difference in orientation is largely a steric effect caused by the fact that charged groups are usually larger than neutral ones. A CH_3 group is more open to attack than a CH_2R group and a CHR_2 group is still less easily attacked. Of course, these considerations also apply when the leaving group is neutral, but, according to Brown, they are much less important here because the neutral groups are smaller and do not block access to the hydrogens as much. Brown showed that Hofmann elimination increases with the size of the leaving group. Thus the percentage of 1-ene obtained from $CH_3CH_2CH_2CHXCH_3$ was as follows (X listed in order of increasing size): Br, 31%; I, 30%; OTs, 48%; SMe_2^+, 87%; SO_2Me, 89%;

[85]For summaries of this position, see Ingold, C.K. *Proc. Chem. Soc.* ***1962***, 265; Banthorpe, D.V.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1960***, 4054.
[86]Bunnett, J.F. *Surv. Prog. Chem.* ***1969***, *5*, 53.

NMe_3^+, 98%.[87] Hofmann elimination was also shown to increase with increase in bulk of the substrate.[88] With large enough compounds, Hofmann orientation can be obtained even with halides, for example, *tert*-amyl bromide ogave 89% of the Hofmann product. Even those who believe in the acidity explanations concede that these steric factors operate in extreme cases.[89]

There is one series of results incompatible with the steric explanation E2 elimination from the four 2-halopentanes gave the following percentages of 1-pentene: F, 83%; Cl, 37%; Br, 25%; I, 20%.[90] The same order was found for the four-2-halohexanes.[91] Although there is some doubt about the relative steric requirements of Br, Cl, and I, there is no doubt that F is the smallest of the halogens, and if the steric explanation were the only valid one, the fluoroalkanes could not give predominant Hofmann orientation. Another result that argues against the steric explanation is the effect of changing the nature of the base. An experiment in which the effective size of the base was kept constant while its basicity was increased (by using as bases a series of $XC_6H_4O^-$ ions) showed that the percentage of Hofmann elimination increased with increasing base strength, although the size of the base did not change.[92] These results are in accord with the explanation of Bunnett, since an increase in base strength moves an E2 reaction closer to the E1cB end of the spectrum. In further experiments, a large series of bases of different kinds was shown to obey linear free-energy relationships between basicity and percentage of Hofmann elimination,[93] although certain very large bases (e.g., 2,6-di-*tert*-butyl-phenoxide) did not obey the relationships, steric effects becoming important in these cases. How large the base must be before steric effects are observed depends on the pattern of alkyl substitution in the substrate, but not on the nucleofuge.[94] One further result may be noted. In the gas phase, elimination of H and BrH^+ or H and ClH^+ using Me_3N as the base predominantly followed Hofmann's rule,[95] although BrH^+ and ClH^+ are not very large.

[87]Brown, H.C.; Wheeler, O.H. *J. Am. Chem. Soc.* ***1956***, *78*, 2199.

[88]Brown, H.C.; Moritani, I.; Nakagawa, M. *J. Am. Chem. Soc.* ***1956***, *78*, 2190; Brown, H.C.; Moritani, I. *J. Am. Chem. Soc.* ***1956***, *78*, 2203; Bartsch, R.A. *J. Org. Chem.* ***1970***, *35*, 1334. See also, Charton, M. *J. Am. Chem. Soc.* ***1975***, *97*, 6159.

[89]For example, see Banthorpe, D.V.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1960***, 4054.

[90]Saunders, Jr., W.H.; Fahrenholtz, S.R.; Caress, E.A.; Lowe, J.P.; Schreiber, M.R. *J. Am. Chem. Soc.* ***1965***, *87*, 3401. Similar results were obtained by Brown, H.C.; Klimisch, R.L. *J. Am. Chem. Soc.* ***1966***, *88*, 1425.

[91]Bartsch, R.A.; Bunnett, J.F. *J. Am. Chem. Soc.* ***1968***, *90*, 408.

[92]Froemsdorf, D.H.; Robbins, M.D. *J. Am. Chem. Soc.* ***1967***, *89*, 1737. See also, Froemsdorf, D.H.; Dowd, W.; Leimer, K.E. *J. Am. Chem. Soc.* ***1966***, *88*, 2345; Bartsch, R.A.; Kelly, C.F.; Pruss, G.M. *Tetrahedron Lett.* ***1970***, 3795; Feit, I.N.; Breger, I.K.; Capobianco, A.M.; Cooke, T.W.; Gitlin, L.F. *J. Am. Chem. Soc.* ***1975***, *97*, 2477; Feit, I.N.; Suanders, Jr., W.H. *J. Am. Chem. Soc.* ***1970***, *92*, 5615.

[93]Bartsch, R.A.; Roberts, D.K.; Cho, B.R. *J. Org. Chem.* ***1979***, *44*, 4105.

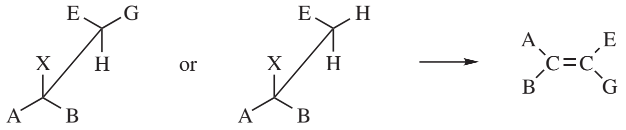
[94]Bartsch, R.A.; Read, R.A.; Larsen, D.T.; Roberts, D.K.; Scott, K.J.; Cho, B.R. *J. Am. Chem. Soc.* ***1979***, *101*, 1176.

[95]Angelini, G.; Lilla, G.; Speranza, M. *J. Am. Chem. Soc.* ***1989***, *111*, 7393.

5. Only a few investigations on the orientation of syn E2 eliminations have been carried out, but these show that Hofmann orientation is greatly favored over Zaitsev.[96]
6. In the E1cB mechanism the question of orientation seldom arises because the mechanism is generally found only where there is an electron-withdrawing group in the β position, and that is where the double bond goes.
7. As already mentioned, E2C reactions show a strong preference for Zaitsev orientation.[97] In some cases, this can be put to preparative use. For example, the compound $PhCH_2CHOTsCHMe_2$ gave ~98% $PhCH{=}CHCHMe_2$ under the usual E2 reaction conditions (*t*-BuOK in *t*-BuOH). In this case, the double bond goes to the side with more hydrogens because on that side it will be able to conjugate with the benzene ring. However, with the weak base $Bu_4N^+ Br^-$ in acetone the Zaitsev product $PhCH_2CH{=}CMe_2$ was formed in 90% yield.[98]

Stereochemistry of the Double Bond

When elimination takes place on a compound of the form CH_3–CABX or CHAB–CGGX, the new alkene does not have cis–trans isomerism, but for compounds of the form CHEG–CABX (E and G *not* H) (**23**) and CH_2E–CABX (**24**), cis and trans isomers are possible. When the anti E2 mechanism is in operation, **23** gives the isomer



23 **24**

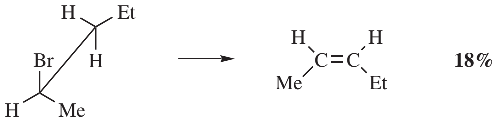
arising from trans orientation of X and H and, as we have seen before (p. 1478), an erythro compound gives the cis alkene and a threo compound the trans. For **24**, two conformations are possible for the transition state; these lead to different isomers and often both are obtained. However, the one that predominates is often determined by an eclipsing effect.[99] For example, Zaitsev elimination from 2-bromopentane can occur as follows:

[96]Sicher, J.; Svoboda, M.; Pánková, M.; Závada, J. *Collect. Czech. Chem. Commun.* ***1971***, *36*, 3633; Bailey, D.S.; Saunders, Jr., W.H. *J. Am. Chem. Soc.* ***1970***, *92*, 6904.

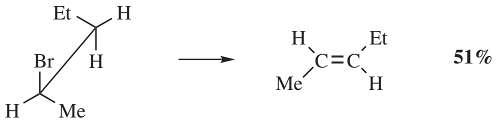
[97]For example; see Ono, N. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 1369; Bailey, D.S.; Saunders, Jr., W.H. *J. Org. Chem.* ***1973***, *38*, 3363; Muir, D.M.; Parker, A.J. *J. Org. Chem.* ***1976***, *41*, 3201.

[98]Lloyd, D.J.; Muir, D.M.; Parker, A.J. *Tetrahedron Lett.* ***1971***, 3015

[99]See Cram, D.J.; Greene, F.D.; DePuy, C.H. *J. Am. Chem. Soc.* ***1956***, *78*, 790; Cram, D.G., in Newman, M.S. *Steric Effects in Organic Chemistry*, Wiley, NY, ***1956***, pp. 338–345.



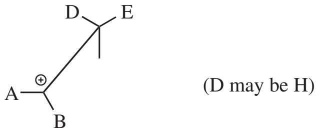
I



J

In conformation **I**, the ethyl group is between Br and Me, while in **J** it is between Br and H. This means that **J** is more stable, and most of the elimination should occur from this conformation. This is indeed what happens, and 51% of the trans isomer is formed (with KOEt) compared to 18% of the cis (the rest is the Hofmann product).[100] These effects become larger with increasing size of A, B, and E.

However, eclipsing effects are not the only factors that affect the cis/trans ratio in anti E2 eliminations. Other factors are the nature of the leaving group, the base, the solvent, and the substrate. Not all these effects are completely understood.[101]



25

For E1 eliminations, if there is a free carbocation (**25**), it is free to rotate, and no matter what the geometry of the original compound, the more stable situation is the one where the larger of the D–E pair is opposite the smaller of the A–B pair and the corresponding alkene should form. If the carbocation is not completely free, then to that extent, E2-type products are formed. Similar considerations apply in E1cB eliminations.[102]

REACTIVITY

In this section, we examine the effects of changes in the substrate, base, leaving group, and medium on (*1*) overall reactivity, (*2*) E1 versus E2 versus E1cB,[103] and (*3*) elimination versus substitution.

[100]Brown, H.C.; Wheeler, O.H. *J. Am. Chem. Soc.* ***1956***, *78* 2199.

[101]For discussions, see Bartsch, R.A.; Bunnett, J.F. *J. Am. Chem. Soc.* ***1969***, *91*, 1376, 1382; Feit, I.N.; Saunders, Jr., W.H. *J. Am. Chem. Soc.* ***1970***, *92*, 1630, 5615; Alunni, S.; Baciocchi, E. *J. Chem. Soc. Perkin Trans. 2* ***1976***, 877; Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***, pp. 165–193.

[102]See, for example, Redman, R.P.; Thomas, P.J.; Stirling, C.J.M. *J. Chem. Soc., Chem. Commun.* ***1978***, 43.

[103]For discussions, see Cockerill, A.F.; Harrison, R.G., in Patai, S. *The Chemistry of Functional Groups*, Supplement A, pt. 1, Wiley, NY, ***1977***, pp. 178–189.

Effect of Substrate Structure

1. *Effect on Reactivity.* We refer to the carbon containing the nucleofuge (X) as the a carbon and to the carbon that loses the positive species as the β carbon. Groups attached to the α or β carbons can exert at least four kinds of influence:

   a. They can stabilize or destabilize the incipient double bond (both α and β groups).

   b. They can stabilize or destabilize an incipient negative charge, affecting the acidity of the proton (β groups only).

   c. They can stabilize or destabilize an incipient positive charge (α groups only).

   d. They can exert steric effects (e.g., eclipsing effects) (both α and β groups).

   Effects a and d can apply in all three mechanisms, although steric effects are greatest for the E2 mechanism. Effect b does not apply in the E1 mechanism, and effect c does not apply in the E1cB mechanism. Groups, such as Ar and C=C, increase the rate by any mechanism, except perhaps when formation of the C=C bond is not the rate-determining step, whether they are α or β (effect a). Electron-withdrawing groups increase the acidity when in the β position, but have little effect in the a position unless they also conjugate with the double bond. Thus Br, Cl, CN, Ts, NO_2, CN, and SR in the β position all increase the rate of E2 eliminations.

2. *Effect on* E1 *versus* E2 *versus* E1cB. The α alkyl and α aryl groups stabilize the carbocation character of the transition state, shifting the spectrum toward the E1 end. β alkyl groups also shift the mechanism toward E1, since they *decrease* the acidity of the hydrogen. However, β aryl groups shift the mechanism the other way (toward E1cB) by stabilizing the carbanion. Indeed, as we have seen (p. $$$), all electron-withdrawing groups in the β position shift the mechanism toward E1cB.[104] α alkyl groups also increase the extent of elimination with weak bases (E2C reactions).

3. *Effect on Elimination versus Substitution.* Under second-order conditions, a branching increases elimination, to the point where tertiary substrates undergo few S_N2 reactions, as we saw in Chapter 10. For example, Table 17.2 shows results on some simple alkyl bromides. Similar results were obtained with SMe_2^+ as the leaving group.[105] Two reasons can be presented for this trend. One is statistical: As a branching increases, there are usually more hydrogens for the base to attack. The other is that a branching presents steric hindrance to attack of the base at the carbon. Under first-order conditions, increased a branching also increases the amount of elimination (E1 vs. S_N1), although not

[104]For a review of eliminations with COOH, COOR, $CONH_2$, and CN groups in the β position, see Butskus, P.F.; Denis, G.I. *Russ. Chem. Rev.* ***1966***, *35*, 839.

[105]Dhar, M.L.; Hughes, E.D.; Ingold, C.K.; Masterman, S. *J. Chem. Soc.* ***1948***, 2055.

TABLE 17.2. The Effect of α and β Branching on the Rate of E2 Elimination and the Amount of Alkene Formed[a]

Substrate	Temperature, °C	Alkene, %	Rate × 10^5 of E2 Reaction	Reference
CH_3CH_2Br	55	0.9	1.6	108
$(CH_3)_2CHBr$	24	80.3	0.237	109
$(CH_3)_3CBr$	25	97	4.17	107
$CH_3CH_2CH_2Br$	55	8.9	5.3	105
$(CH_3)_2CHCH_2Br$	55	59.5	8.5	105

[a]The reactions were between the alkyl bromide and $^-$OEt The rate for isopropyl bromide was actually greater than that for ethyl bromide, if the temperature difference is considered. Neopentyl bromide, the next compound in the β-branching series, cannot be compared because it has no β-hydrogen and cannot give an elimination product without rearrangement.

so much, and usually the substitution product predominates. For example, solvolysis of *tert*-butyl bromide gave only 19% elimination[106] (cf. with Table 17.2). β Branching also increases the amount of E2 elimination with respect to S_N2 substitution (Table 17.2), not because elimination is faster, but because the S_N2 mechanism is so greatly slowed (p. 478). Under first-order conditions too, β branching favors elimination over substitution, probably for steric reasons.[107] However, E2 eliminations from compounds with charged leaving groups are slowed by β branching. This is related to Hofmann's rule (p. 1498). Electron-withdrawing groups in the β position not only increase the rate of E2 eliminations and shift the mechanisms toward the E1cB end of the spectrum, but also increase the extent of elimination as opposed to substitution.

Effect of the Attacking Base

1. *Effect on* E1 *versus* E2 *versus* E1cB. In the E1 mechanism, an external base is generally not required: The solvent acts as the base. Hence, when external bases are added, the mechanism is shifted toward E2. Stronger bases and higher base concentrations cause the mechanism to move toward the E1cB end of the E1-E2-E1cB spectrum.[110] However, weak bases in polar aprotic solvents can also be effective in elimination reactions with certain substrates (the E2C reaction). Normal E2 elimination has been accomplished with the following bases:[111] H_2O, NR_3, ^-OH, ^-OAc, ^-OR, ^-OAr, $^-NH_2$, CO_3^{2-},

[106]Dhar, M.L.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1948***, 2058.

[107]Hughes, M.L.; Ingold, C.K.; Maw, G.A. *J. Chem. Soc.* ***1948***, 2065.

[108]Hughes, E.D.; Ingold, C.K.; Maw, G.A. *J. Chem. Soc.* ***1948***, 2072; Hughes, E.D.; Ingold, C.K.; Woolf, L.I. *J. Chem. Soc.* ***1948***, 2084.

[109]Brown, H.C.; Berneis, H.L. *J. Am. Chem. Soc.* ***1953***, *75*, 10.

[110]For a review, see Baciocchi, E. *Acc. Chem. Res.* ***1979***, *12*, 430. See also, Baciocchi, E.; Ruzziconi, R.; Sebastiani, G.V. *J. Org. Chem.* ***1980***, *45*, 827.

[111]This list is from Banthorpe, D.V. *Elimination Reactions*; Elsevier, NY, ***1963***, p. 4.

$LiAlH_4$, I^-, CN^-, and organic bases. However, the only bases of preparative importance in the normal E2 reaction are OH^-, OR^-, and NH_2^-, usually in the conjugate acid as solvent, and certain amines. Weak bases effective in the E2C reaction are Cl^-, Br^- F^-, ^-OAc, and RS^-. These bases are often used in the form of their R_4N^+ salts.

2. *Effect on Elimination versus Substitution.* Strong bases not only benefit E2 as against E1, but also benefit elimination as against substitution. With a high concentration of strong base in a non-ionizing solvent, bimolecular mechanisms are favored and E2 predominates over S_N2. At low base concentrations, or in the absence of base altogether, in ionizing solvents, unimolecular mechanisms are favored, and the S_N1 mechanism predominates over the E1. In Chapter 10, it was pointed out that some species are strong nucleophiles, but weak bases (p. 490). The use of these obviously favors substitution, except that, as we have seen, elimination can predominate if polar aprotic solvents are used. It has been shown for the base cyanide that in polar aprotic solvents, the less the base is encumbered by its counterion in an ion pair (i.e., the freer the base), the more substitution is favored at the expense of elimination.[112]

Effect of the Leaving Group

1. *Effect on Reactivity.* The leaving groups in elimination reactions are similar to those in nucleophilic substitution. The E2 eliminations have been performed with the following groups: NR_3^+, PR_3^+, SR_2^+, OHR^+, SO_2R, OSO_2R, OCOR, OOH, OOR, NO_2,[113] F, Cl, Br, I, and CN (*not* OH_2^+). The E1 eliminations have been carried out with: NR_3^+, SR_2^+, OH_2^+, OHR^+, OSO_2R, OCOR, Cl, Br, I, and N_2^+.[114] However, the major leaving groups for preparative purposes are OH_2^+ (always by E1) and Cl, Br, I, and NR_3^+ (usually by E2).
2. *Effect on* E1 *versus* E2 *versus* E1cB. Better leaving groups shift the mechanism toward the E1 end of the spectrum, since they make ionization easier. This effect has been studied in various ways. One way already mentioned was a study of ρ values (p. 1495). Poor leaving groups and positively charged leaving groups shift the mechanism toward the E1cB end of the spectrum because the strong electron-withdrawing field effects increase the acidity of the β hydrogen.[115] The E2C reaction is favored by good leaving groups.
3. *Effect on Elimination versus Substitution.* As we have already seen (p. 1487), for first-order reactions the leaving group has nothing to do with the

[112]Loupy, A.; Seyden-Penne, J. *Bull. Soc. Chim. Fr.* ***1971***, 2306.
[113]For a review of eliminations in which NO_2 is a leaving group, see Ono, N., in Feuer, H.; Nielsen, A.T. *Nitro Compounds; Recent Advances in Synthesis and Chemistry*, VCH, NY, ***1990***, pp. 1–135, 86–126.
[114]These lists are from Banthorpe, D.V. *Elimination Reactions*, Elsevier, NY, ***1963***, pp. 4, 7.
[115]For a discussion of leaving-group ability, see Stirling, C.J.M. *Acc. Chem. Res.* ***1979***, *12*, 198. See also, Varma, M.; Stirling, C.J.M. *J. Chem. Soc., Chem. Commun.* ***1981***, 553.

competition between elimination and substitution, since it is gone before the decision is made as to which path to take. However, where ion pairs are involved, this is not true, and results have been found where the nature of the leaving group does affect the product.[116] In second-order reactions, the elimination/substitution ratio is not greatly dependent on a halide leaving group, although there is a slight increase in elimination in the order $I > Br > Cl$. When OTs is the leaving group, there is usually much more substitution. For example, n-$C_{18}H_{37}Br$ treated with t-BuOK gave 85% elimination, while n-$C_{18}H_{37}OTs$ gave, under the same conditions, 99% substitution.[117] On the other hand, positively charged leaving groups increase the amount of elimination.

Effect of the Medium

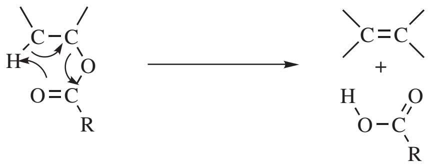
1. *Effect of Solvent on* E1 *versus* E2 *versus* E1cB. With any reaction a more polar environment enhances the rate of mechanisms that involve ionic intermediates. For neutral leaving groups, it is expected that E1 and E1cB mechanisms will be aided by increasing polarity of solvent and by increasing ionic strength. With certain substrates, polar aprotic solvents promote elimination with weak bases (the E2C reaction).
2. *Effect of Solvent on Elimination versus Substitution.* Increasing polarity of solvent favors S_N2 reactions at the expense of E2. In the classical example, alcoholic KOH is used to effect elimination, while the more polar aqueous KOH is used for substitution. Charge-dispersal discussions, similar to those on p. 503,[118] only partially explain this. In most solvents, S_N1 reactions are favored over E1. The E1 reactions compete best in polar solvents that are poor nucleophiles, especially dipolar aprotic solvents.[119] A study made in the gas phase, where there is no solvent, has shown that when 1-bromopropane reacts with MeO^- only elimination takes place (no substitution) even with this primary substrate.[120]
3. *Effect of Temperature.* Elimination is favored over substitution by increasing temperature, whether the mechanism is first or second order.[121] The reason is that the activation energies of eliminations are higher than those of substitutions (because eliminations have greater changes in bonding).

[116]For example, see Skell, P.S.; Hall, W.L. *J. Am. Chem. Soc.* ***1963***, *85* 2851; Cocivera, M.; Winstein, S. *J. Am. Chem. Soc.* ***1963***, *85*, 1702; Feit, I.N.; Wright, D.G. *J. Chem. Soc., Chem. Commun.* ***1975***, 776. See, however, Cavazza, M. *Tetrahedron Lett.* ***1975***, 1031.
[117]Veeravagu, P.; Arnold, R.T.; Eigenmann, E.W. *J. Am. Chem. Soc.* ***1964***, *86*, 3072.
[118]Cooper, K.A.; Dhar, M.L.; Hughes, E.D.; Ingold, C.K.; MacNulty, B.J.; Woolf, L.I. *J. Chem. Soc.* ***1948***, 2043.
[119]Aksnes, G.; Stensland, P. *Acta Chem. Scand.* ***1989***, *43*, 893, and references cited therein.
[120]Jones, M.E.; Ellison, G.B. *J. Am. Chem. Soc.* ***1989***, *111*, 1645. For a different result with other reactants, see Lum, R.C.; Grabowski, J.J. *J. Am. Chem. Soc.* ***1988***, *110*, 8568.
[121]Cooper, K.A.; Hughes, E.D.; Ingold, C.K.; Maw, G.A.; MacNulty, B.J. *J. Chem. Soc.* ***1948***, 2049.

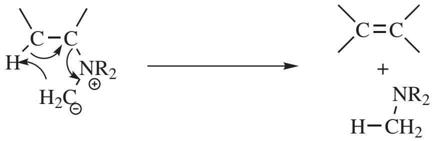
MECHANISMS AND ORIENTATION IN PYROLYTIC ELIMINATIONS

Mechanisms[122]

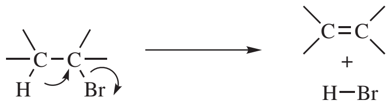
Several types of compound undergo elimination on heating, with no other reagent present. Reactions of this type are often run in the gas phase. The mechanisms are obviously different from those already discussed, since all those require a base (which may be the solvent) in one of the steps, and there is no base or solvent present in pyrolytic elimination. Two mechanisms have been found to operate. One involves a cyclic transition state, which may be four, five, or six membered. Examples of each size are



(17-4)

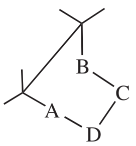


(17-8)



(17-13)

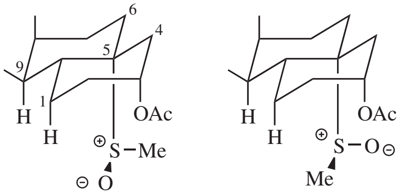
In this mechanism, the two groups leave at about the same time and bond to each other as they are doing so. The designation is E^i in the Ingold terminology and *cyclo*-$D_ED_NA_n$ in the IUPAC system. The elimination must be syn and, for the four- and five-membered transition states, the four or five atoms making up the ring must be coplanar. Coplanarity is not required for the six-membered transition state, since there is room for the outside atoms when the leaving atoms are staggered.



[122]For reviews, see Taylor, R., in Patai, S. *The Chemistry of Functional Groups, Supplement B*, pt. 2, Wiley, NY, ***1979***, pp. 860–914; Smith, G.G.; Kelly, F.W. *Prog. Phys. Org. Chem.* ***1971***, *8*, 75, pp. 76–143, 207–234; in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 5, Elsevier, NY, ***1972***, the articles by Swinbourne, E.S. pp. 149–233 (pp. 158–188), and by Richardson, W.H.; O'Neal, H.E. pp. 381–565 (pp. 381–446); Maccoll, A. *Adv. Phys. Org. Chem.* ***1965***, *3*, 91. For reviews of mechanisms in pyrolytic eliminations of halides, see Egger, K.W.; Cocks, A.T., in Patai's. *The Chemistry of the Carbon-Halogen Bond*, pt. 2, Wiley, NY, ***1973***, pp. 677–745; Maccoll, A. *Chem. Rev.* ***1969***, *69*, 33.

As in the E2 mechanism, it is not necessary that the C–H and C–X bond be equally broken in the transition state. In fact, there is also a spectrum of mechanisms here, ranging from a mechanism in which C–X bond breaking is a good deal more advanced than C–H bond breaking to one in which the extent of bond breaking is virtually identical for the two bonds. Evidence for the existence of the E^i mechanism is

1. The kinetics are first order, so only one molecule of the substrate is involved in the reaction (i.e., if one molecule attacked another, the kinetics would be second order in substrate).[123]
2. Free-radical inhibitors do not slow the reactions, so no free-radical mechanism is involved.[124]
3. The mechanism predicts exclusive syn elimination, and this behavior has been found in many cases.[125] The evidence is inverse to that for the anti E2 mechanism and generally involves the following facts: (*1*) an erythro isomer gives a trans alkene and a threo isomer gives a cis alkene; (*2*) the reaction takes place only when a cis β hydrogen is available; (*3*) if, in a cyclic compound, a cis hydrogen is available on only one side, the elimination goes in that direction. Another piece of evidence involves a pair of steroid molecules. In 3β-acetoxy-(*R*)-5α-methylsulfinylcholestane (**26** shows rings A and B of this compound) and in 3β-acetoxy-(*S*)-5α-methylsulfinylcholestane (**27:** rings A and B), the *only* difference is the configuration of



26 **27**

oxygen and methyl about the sulfur. Yet pyrolysis of **26** gave only elimination to the 4-side (86% 4-ene), while **27** gave predominant elimination to the 6-side (65% 5-ene and 20% 4-ene).[126] Models show that interference from the 1- and 9-hydrogens causes the two groups on the sulfur to lie *in front of it* with respect to the rings, rather than behind it. Since the sulfur is chiral, this

[123]O'Connor, G.L.; Nace, H.R. *J. Am. Chem. Soc.* ***1953***, *75*, 2118.

[124]Barton, D.H.R.; Head, A.J.; Williams, R.J. *J. Chem. Soc.* ***1953***, 1715.

[125]In a few instances anti or nonstereoselective elimination has been found; this behavior is generally ascribed to the intervention of other mechanisms. For example, see Bordwell, F.G.; Landis, P.S. *J. Am. Chem. Soc.* ***1958***, *80*, 2450, 6383; Briggs, W.S.; Djerassi, C. *J. Org. Chem.* ***1968***, *33*, 1625; Smissman, E.E.; Li, J.P.; Creese, M.W. *J. Org. Chem.* ***1970***, *35*, 1352.

[126]Jones, D.N.; Saeed, M.A. *Proc. Chem. Soc.* ***1964***, 81. See also, Goldberg, S.I.; Sahli, M.S. *J. Org. Chem.* ***1967***, *32*, 2059.

means that in **26** the oxygen is near the 4-hydrogen, while in **27** it is near the 6-hydrogen. This experiment is compatible only with syn-elimination.[127]

4. The ^{14}C isotope effects for the Cope elimination (**17-9**) show that both the C–H and C–N bonds have been extensively broken in the transition state.[128]
5. Some of these reactions have been shown to exhibit negative entropies of activation, indicating that the molecules are more restricted in geometry in the transition state than they are in the starting compound.

Where a pyrolytic elimination lies on the mechanistic spectrum seems to depend mostly on the leaving group. When this is halogen, all available evidence suggests that in the transition state the C–X bond is cleaved to a much greater extent than the C–H bond, that is, there is a considerable amount of carbocation character in the transition state. This is in accord with the fact that a completely nonpolar four-membered cyclic transition state violates the Woodward–Hoffmann rules (see the similar case of **15-63**). Evidence for the carbocation-like character of the transition state when halide is the leaving group is that relative rates are in the order $I > Br > Cl$[129] (see p. 496), and that the effects of substituents on reaction rates are in accord with such a transition state.[130] Rate ratios for pyrolysis of some alkyl bromides at 320°C were ethyl bromide, 1; isopropyl bromide, 280; *tert*-butyl bromide, 78,000. Also, α-phenylethyl bromide had about the same rate as *tert*-butyl bromide. On the other hand, β-phenylethyl bromide was only slightly faster than ethyl bromide.[131] This indicates that C–Br cleavage was much more important in the transition state than C–H cleavage, since the incipient carbocation was stabilized by a alkyl and α-aryl substitution, while there was no incipient carbanion to be stabilized by β-aryl substitution. These substituent effects, as well as those for other groups, are very similar to the effects found for the S_N1 mechanism and thus in very good accord with a carbocation-like transition state.

For carboxylic esters, the rate ratios were much smaller,[132] although still in the same order, so that this reaction is closer to a pure E^i mechanism, although the transition state still has some carbocationic character. Other evidence for a greater initial C–O cleavage with carboxylic esters is that a series of 1-arylethyl acetates followed σ^+ rather than σ, showing carbocationic character at the 1 position.[133]

[127] For other evidence for syn-elimination, see Curtin, D.Y.; Kellom, D.B. *J. Am. Chem. Soc.* ***1953***, *75*, 6011; Skell, P.S.; Hall, W.L. *J. Am. Chem. Soc.* ***1964***, *86*, 1557; Bailey, W.J.; Bird, C.N. *J. Org. Chem.* ***1977***, *42*, 3895.

[128] Wright, D.R.; Sims, L.B.; Fry, A. *J. Am. Chem. Soc.* ***1983***, *105*, 3714.

[129] Maccoll, A., in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, ***1964***, pp. 215–216.

[130] For reviews of such studies, see Maccoll, A. *Chem. Rev.* ***1969***, *69*, 33.

[131] For rate studies of pyrolysis of some β-alkyl substituted ethyl bromides, see Chuchani, G.; Rotinov, A.; Dominguez, R.M.; Martin, I. *Int. J. Chem. Kinet.* ***1987***, *19*, 781.

[132] For example, see Scheer, J.C.; Kooyman, E.C.; Sixma, F.L.J. *Recl. Trav. Chim. Pays-Bas* ***1963***, *82*, 1123. See also, Louw, R.; Vermeeren, H.P.W.; Vogelzang, M.W. *J. Chem. Soc. Perkin Trans. 2* ***1983***, 1875.

[133] Taylor, R.; Smith, G.G.; Wetzel, W.H. *J. Am. Chem. Soc.* ***1962***, *84*, 4817; Smith, G.G.; Jones, D.A.K.; Brown, D.F. *J. Org. Chem.* ***1963***, *28*, 403; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* ***1978***, 1255. See also, Ottenbrite, R.M.; Brockington, J.W. *J. Org. Chem.* ***1974***, *39*, 2463; Jordan, E.A.; Thorne, M.P. *J. Chem. Soc. Perkin Trans. 2* ***1984***, 647; August, R.; McEwen, I.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 1683, and other papers in this series; Al-Awadi, N.A. *J. Chem. Soc. Perkin Trans. 2* ***1990***, 2187.

The extent of E1 character in the transition state increases in the following order of ester types: acetate < phenylacetate < benzoate < carbamate < carbonate.[134] Cleavage of xanthates (**17-5**), cleavage of sulfoxides (**17-12**), the Cope reaction (**17-9**), and reaction **17-8** are probably very close to straight E^i mechanisms.[135]

The second type of pyrolysis mechanism is completely different and involves free radicals. Initiation occurs by pyrolytic homolytic cleavage. The remaining steps may vary, and a few are shown

$$\text{Initiation} \quad R_2CHCH_2X \longrightarrow R_2CHCH_2\bullet + X\bullet$$
$$\text{Propagation} \quad R_2CHCH_2X + X\bullet \longrightarrow R_2\dot{C}CH_2X + HX$$
$$R_2\dot{C}CH_2X \longrightarrow CH_2 = CH_2X\bullet$$
$$\text{Termination (disproportionation)} \quad 2R_2\dot{C}CH_2X \longrightarrow R_2C = CH_2 + R_2CXCH_2X$$

Free-radical mechanisms are mostly found in pyrolyses of polyhalides and of primary monohalides,[136] although they also have been postulated in pyrolysis of certain carboxylic esters.[137] β-Elimination of tosyl radicals is known.[138] Much less is known about these mechanisms and we will not consider them further. Free-radical eliminations in solution are also known, but are rare.[139]

Orientation in Pyrolytic Eliminations

As in the E1-E2-E1cB mechanistic spectrum, Bredt's rule applies; and if a double bond is present, a conjugated system will be preferred, if sterically possible. Apart from these considerations, the following statements can be made for E^i eliminations:

1. In the absence of considerations mentioned below, orientation is statistical and is determined by the number of β hydrogens available (therefore *Hofmann's rule* is followed). For example, *sec*-butyl acetate gives 55–62%

[134]Taylor, R. *J. Chem. Soc. Perkin Trans. 2* ***1975***, 1025.

[135]For a review of the mechanisms of **17-12**, **17-9**, and the pyrolysis of sulfilimines, see Oae, S.; Furukawa, N. *Tetrahedron* ***1977***, *33*, 2359.

[136]For example, see Barton, D.H.R.; Howlett, K.E. *J. Chem. Soc.* ***1949***, 155, 165.

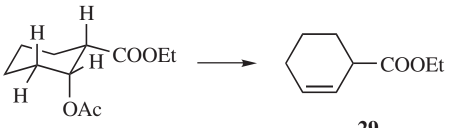
[137]For example, see Rummens, F.H.A. *Recl. Trav. Chim. Pays-Bas* ***1964***, *83*, 901; Louw, R.; Kooyman, E.C. *Recl. Trav. Chim. Pays-Bas* ***1965***, *84*, 1511.

[138]Timokhin, V.I.; Gastaldi, S.; Bertrand, M.P.; Chatgilialoglu, C. *J. Org. Chem.* ***2003***, *68*, 3532.

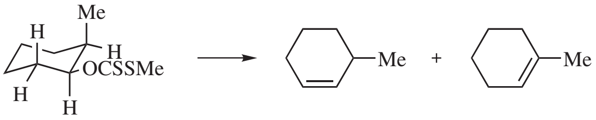
[139]For examples; see Kampmeier, J.A.; Geer, R.P.; Meskin, A.J.; D'Silva, R.M. *J. Am. Chem. Soc.* ***1966***, *88*, 1257; Kochi, J.K.; Singleton, D.M.; Andrews, L.J. *Tetrahedron* ***1968***, *24*, 3503; Boothe, T.E.; Greene Jr., J.L.; Shevlin, P.B. *J. Org. Chem.* ***1980***, *45*, 794; Stark, T.J.; Nelson, N.T.; Jensen, F.R. *J. Org. Chem.* ***1980***, *45*, 420; Kochi, J.K. *Organic Mechanisms and Catalysis*, Academic Press, NY, ***1978***, pp. 346–349; Kamimura, A.; Ono, N. *J. Chem. Soc., Chem. Commun.* ***1988***, 1278.

1-butene and 38–45% 2-butene,[140] which is close to the 3:2 distribution predicted by the number of hydrogens available.[141]

2. A cis β hydrogen is required. Therefore in cyclic systems, if there is a cis hydrogen on only one side, the double bond will go that way. However, when there is a six-membered transition state, this does not necessarily mean that the leaving groups must be cis to each other, since such transition states need not be completely coplanar. If the leaving group is axial, then the hydrogen obviously must be equatorial (and consequently cis to the leaving group), since the transition state cannot be realized when the groups are both axial. But if the leaving group is equatorial, it can form a transition state with a β hydrogen that is either axial (hence, cis) or equatorial (hence, trans). Thus **28**, in which the leaving group is most likely axial, does not form a double bond in the



28 **29** **(17-4)**



30 **(17-5)**

direction of the carbethoxyl group, even although that would be conjugated, because there is no equatorial hydrogen on that side. Instead it gives 100% **29**.[142] On the other hand, **30**, with an equatorial leaving group, gives ~50% of each alkene, even although, for elimination to the 1-ene, the leaving group must go off with a trans hydrogen.[143]

3. In some cases, especially with cyclic compounds, the more stable alkene forms and Zaitsev's rule applies. For example, menthyl acetate gives 35% of the Hofmann product and 65% of the Zaitsev, even although a cis β hydrogen is present on both sides and the statistical distribution is the other way. A similar result was found for the pyrolysis of menthyl chloride.[144]

4. There are also steric effects. In some cases, the direction of elimination is determined by the need to minimize steric interactions in the transition state or to relieve steric interactions in the ground state.

[140]Froemsdorf, D.H.; Collins, C.H.; Hammond, G.S.; DePuy, C.H. *J. Am. Chem. Soc.* ***1959***, *81*, 643; Haag, W.O.; Pines, H. *J. Org. Chem.* ***1959***, *24*, 877.

[141]DePuy, C.H.; King, R.W. *Chem. Rev.* ***1960***, *60*, 431, have tables showing the product distribution for many cases.

[142]Bailey, W.J.; Baylouny, R.A. *J. Am. Chem. Soc.* ***1959***, *81*, 2126.

[143]Botteron D.G.; Shulman, G.P. *J. Org. Chem.* ***1962***, *27*, 2007.

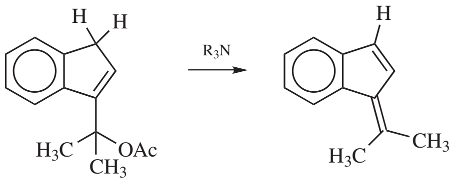
[144]Barton, D.H.R.; Head, A.J.; Williams, R.J. *J. Chem. Soc.* ***1952***, 453; Bamkole, T.; Maccoll, A. *J. Chem. Soc. B* ***1970***, 1159.

1,4 Conjugate Eliminations[145]

1,4-Eliminations of the type

$$\text{H-C-C=C-C-X} \longrightarrow \text{C=C-C=C}$$

are much rarer than conjugate additions (Chapter 15), but some examples are known.[146] One such is[147]



REACTIONS

First, we consider reactions in which a C=C or a C≡C bond is formed. From a synthetic point of view, the most important reactions for the formation of double bonds are **17-1** (usually by an E1 mechanism), **17-7**, **17-13**, and **17-22** (usually by an E2 mechanism), and **17-4**, **17-5**, and **17-9** (usually by an E^i mechanism). The only synthetically important method for the formation of triple bonds is **17-13**.[148] In the second section, we treat reactions in which C≡N bonds and C=N bonds are formed, and then eliminations that give C=O bonds and diazoalkanes. Finally, we discuss extrusion reactions.

REACTIONS IN WHICH C=C AND C≡C BONDS ARE FORMED

A. Reactions in which Hydrogen Is Removed from One Side

In **17-1–17-6**, the other leaving atom is oxygen. In **17-7–17-11**, it is nitrogen. For reactions in which hydrogen is removed from both sides, see **19-1–19-6**.

[145]Taylor, R., in Patai *The Chemistry of Functional Groups, Supplement B*, pt. 2, Wiley, NY, ***1979***, pp. 885–890; Smith, G.G.; Mutter, L.; Todd, G.P. *J. Org. Chem.* ***1977***, *42*, 44; Chuchani, G.; Dominguez, R.M. *Int. J. Chem. Kinet.* ***1981***, *13*, 577; Hernández, A.; Chuchani, G. *Int. J. Chem. Kinet.* ***1983***, *15*, 205.

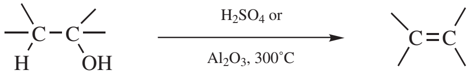
[146]For a review of certain types of 1,4- and 1,6-eliminations, see Wakselman, M. *Nouv. J. Chem.* ***1983***, *7*, 439.

[147]Thibblin, A. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 321; Ölwegård, M.; Ahlberg, P. *Acta Chem. Scand.* ***1990***, *44*, 642. For studies of the stereochemistry of 1,4-eliminations, see Hill, R.K.; Bock, M.G. *J. Am. Chem. Soc.* ***1978***, *100*, 637; Moss, R.J.; Rickborn, B. *J. Org. Chem.* ***1986***, *51*, 1992; Ölwegård, M.; Ahlberg, P. *J. Chem. Soc., Chem. Commun.* ***1989***, 1279.

[148]For reviews of methods for preparing alkynes, see Friedrich, K., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 2, Wiley, NY, ***1983***; pp. 1376–1384; Ben-Efraim, D.A., in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, pt. 2, Wiley, NY, ***1978***, pp. 755–790. For a comparative study of various methods, see Mesnard, D.; Bernadou, F.; Miginiac, L. *J. Chem. Res. (S)* ***1981***, 270, and references cited therein.

17-1 Dehydration of Alcohols

Hydro-hydroxy-elimination



Dehydration of alcohols can be accomplished in several ways. Both H_2SO_4 and H_3PO_4 are common reagents, but in many cases these lead to rearrangement products and to ether formation (**10-12**). If the alcohol can be evaporated, vapor-phase elimination over Al_2O_3 is an excellent method since side reactions are greatly reduced. This method has even been applied to such high-molecular-weight alcohols as 1-dodecanol.[149] Other metallic oxides (e.g., Cr_2O_3, TiO_2, WO_3) have also been used, as have been sulfides, other metallic salts, and zeolites. The presence of an electron-withdrawing group usually facilitates elimination of water, as in the aldol condensation (**16-35**). 2-Nitroalcohols, for example, give conjugated nitro compounds when heated with zeolite Y–Y.[150] Treating a 4-hydroxy lactam with DMAP (*N,N*-dimethylaminopyridine) and Boc anhydride leads to the conjugated lactam.[151] Elimination of serine derivatives to α-alkylidene amino acid derivatives was accomplished with $(EtO)_2POCl$.[152] Another method of avoiding side reactions is the conversion of alcohols to esters, and the pyrolysis of these (**17-4**–**17-6**). The ease of dehydration increases with α branching, and tertiary alcohols are dehydrated so easily with only a trace of acid that it sometimes happens even when the investigator desires otherwise. It may also be recalled that the initial alcohol products of many base-catalyzed condensations dehydrate spontaneously (Chapter 16) because the new double bond can be in conjugation with one already there. Many other dehydrating agents[153] have been used on occasion: P_2O_5, I_2, $ZnCl_2$, Ph_3BiBr_2/I_2,[154] PPh_3–I_2,[155] BF_3–etherate, DMSO, SiO_2–Cl/Me_3SiCl,[156] $KHSO_4$, anhydrous $CuSO_4$, and phthalic anhydride, among others. Secondary and tertiary alcohols can also be dehydrated, without rearrangements, simply on refluxing in HMPA.[157] With nearly all reagents, dehydration follows Zaitsev's rule.

[149]For example, see Spitzin, V.I.; Michailenko, I.E.; Pirogowa, G.N. *J. Prakt. Chem.* ***1964***, *[4] 25*, 160; Bertsch, H.; Greiner, A.; Kretzschmar, G.; Falk, F. *J. Prakt. Chem.* ***1964***, *[4] 25*, 184.

[150]Anbazhagan, M.; Kumaran, G.; Sasidharan, M. *J. Chem. Res. (S)* ***1997***, 336.

[151]Mattern, R.-H. *Tetrahedron Lett.* ***1996***, *37*, 291.

[152]Berti, F.; Ebert, C.; Gardossi, L. *Tetrahedron Lett.* ***1992***, *33*, 8145.

[153]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 291–294.

[154]Dorta, R.L.; Suárez, E.; Betancor, C. *Tetrahedron Lett.* ***1994***, *35*, 5035.

[155]Alvarez-Manzaneda, E.J.; Chahboun, R.; Torres, E.C.; Alvarez, E.; Alvarez-Manzaneda, R.; Haidour, A.; Ramos, J. *Tetrahedron Lett.* ***2004***, *45*, 4453.

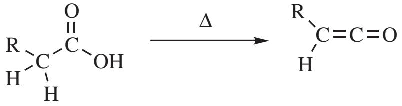
[156]Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H.; Karimi, B. *Synth. Commun.* ***2003***, *33*, 3653.

[157]Monson, R.S. *Tetrahedron Lett.* ***1971***, 567; Monson, R.S.; Priest, D.N. *J. Org. Chem.* ***1971***, *36*, 3826; Lomas, J.S.; Sagatys, D.S.; Dubois, J.E. *Tetrahedron Lett.* ***1972***, 165.

An exception involves the passage of hot alcohol vapors over thorium oxide at 350–450°C, under which conditions Hofmann's rule is followed,[158] and the mechanism is probably different. Cyclobutanol derivatives can be opened in the presence of a palladium catalyst. 2-Phenylbicyclo[3.2.0]octan-2-ol, for example, reacted with a catalytic amount of palladium acetate in the presence of pyridine and oxygen to give phenyl methylenecyclohexane ketone.[159]

Transition metals can induce the dehydration of certain alcohols. β-Hydroxy ketones are converted to conjugated ketones by treatment with $CeCl_3$ and NaI.[160] In the presence of a palladium complex, alkyl cyclopropanols undergo a dehydration reaction to give a conjugated ketone.[161] A δ-hydroxy-α,β-unsaturated aldehyde was converted to a dienyl aldehyde with a hafnium catalyst.[162] β-Hydroxy esters are converted to conjugated esters when treated with 2 equivalents of SmI_2.[163] The reaction of a β-hydroxy nitrile with methylmagneisum chloride[164] or with MgO[165] leads to a conjugated nitrile. In another variation of the dehydration reaction, vicinal bromohydrins are converted to alkenes upon treatment with In, $InCl_3$, and a palladium catalyst.[166] Chlorohydrins react similarly when treated with samarium, and then diiodomethane.[167]

Carboxylic acids can be dehydrated by pyrolysis, the product being a ketene:



Ketene itself is commercially prepared in this manner. Carboxylic acids have also been converted to ketenes by treatment with certain reagents, among them TsCl,[168] dicyclohexylcarbodiimide,[169] and 1-methyl-2-chloropyridinium iodide (*Mukaiyama's reagent*).[170] Analogously, amides can be dehydrated with P_2O_5, pyridine,

[158]Lundeen, A.J.; Van Hoozer, R. *J. Am. Chem. Soc.* ***1963***, *85*, 2180; *J. Org. Chem.* ***1967***, *32*, 3386. See also, Davis, B.H. *J. Org. Chem.* ***1982***, *47*, 900; Iimori, T.; Ohtsuka, Y.; Oishi, T. *Tetrahedron Lett.* ***1991***, *32*, 1209.

[159]Nishimura, T.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc.* ***1999***, *121*, 2645.

[160]Bartoli, G.; Bellucci, M.C.; Petrini, M.; Marcantoni, E.; Sambri, L.; Torregiani, E. *Org. Lett.* ***2000***, *2*, 1791.

[161]Okumoto, H.; Jinnai, T.; Shimizu, H.; Harada, Y.; Mishima, H.; Suzuki, A. *Synlett* ***2000***, 629.

[162]Saito, S.; Nagahara, T.; Yamamoto, H. *Synlett* ***2001***, 1690.

[163]Concellón, J.M.; Pérez-Andrés, J.A.; Rodríguez-Solla, H. *Angew. Chem. Int. Ed.* ***2000***, *39*, 2773.

[164]Fleming, F.F.; Shook, B.C. *Tetrahedron Lett.* ***2000***, *41*, 8847.

[165]Fleming, F.F.; Shook, B.C. *J. Org. Chem.* ***2002***, *67*, 3668.

[166]Cho, S.; Kang, S.; Keum, G.; Kang, S.B.; Han, S.-Y.; Kim, Y. *J. Org. Chem.* ***2003***, *68*, 180.

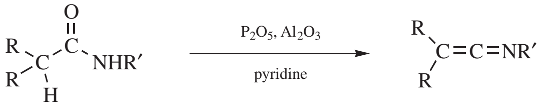
[167]Concellón, J.M.; Rodríguez-Solla, H.; Huerta, M..; Pérez-Andrés, J.A. *Eur. J. Org. Chem.* ***2002***, 1839.

[168]Brady, W.T.; Marchand, A.P.; Giang, Y.F.; Wu, A. *Synthesis* ***1987***, 395; *J. Org. Chem.* ***1987***, *52*, 3457.

[169]Olah, G.A.; Wu, A.; Farooq, O. *Synthesis* ***1989***, 568.

[170]Brady, W.T.; Marchand, A.P.; Giang, Y.F.; Wu, A. *J. Org. Chem.* ***1987***, *52*, 3457; Funk, R.L.; Abelman, M.M.; Jellison, K.M. *Synlett* ***1989***, 36.

and Al_2O_3 to give ketenimines:[171]



There is no way in which dehydration of alcohols can be used to prepare triple bonds: *gem*-diols and vinylic alcohols are not normally stable compounds and *vic*-diols[172] give either conjugated dienes or lose only 1 equivalent of water to give an aldehyde or ketone. Dienes can be prepared, however, by heating alkynyl alcohols with triphenyl phosphine.[173]

When proton acids catalyze alcohol dehydration, the mechanism is E1.[174] The principal process involves conversion of ROH to ROH_2^+ and cleavage of the latter to R^+ and H_2O, although with some acids a secondary process probably involves conversion of the alcohol to an inorganic ester and ionization of *this* (illustrated for H_2SO_4):

$$\text{ROH} \xrightarrow{H_2SO_4} \text{ROSO}_2\text{OH} \longrightarrow \text{R}^+ + \text{HSO}_4^-$$

Note that these mechanisms are the reverse of those involved in the acid-catalyzed hydration of double bonds (**15-3**), in accord with the principle of microscopic reversibility. With anhydrides (e.g., P_2O_5, phthalic anhydride), as well as with some other reagents, such as HMPA,[175] it is likely that an ester is formed, and the leaving group is the conjugate base of the corresponding acid. In these cases, the mechanism can be E1 or E2. The mechanism with Al_2O_3 and other solid catalysts has been studied extensively, but is poorly understood.[176]

Magnesium alkoxides (formed by $ROH + Me_2Mg \rightarrow ROMgMe$) have been decomposed thermally, by heating at 195–340°C to give the alkene, CH_4, and MgO.[177] Syn-elimination is found and an E^i mechanism is likely. Similar decomposition of aluminum and zinc alkoxides has also been accomplished.[178,189]

[171]Stevens, C.L.; Singhal, G.H. *J. Org. Chem.* ***1964***, *29*, 34.

[172]For a review on the dehydration of 1,2- and 1,3-diols, see Bartók, M.; Molnár, A., in Patai, S. *The Chemistry of Functional Groups, Supplement E*, pt. 2, Wiley, NY, ***1980***, pp. 721–760.

[173]Guo, C.; Lu, X. *J. Chem. Soc., Chem. Commun.* ***1993***, 394.

[174]For reviews of dehydration mechanisms, see Vinnik, M.I.; Obraztsov, P.A. *Russ. Chem. Rev.* ***1990***, *59*, 63; Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***, pp. 221–274, 317–331; Knözinger, H., in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 2, Wiley, NY, ***1971***, pp. 641–718.

[175]See, for example, Kawanisi, M.; Arimatsu, S.; Yamaguchi, R.; Kimoto, K. *Chem. Lett.* ***1972***, 881.

[176]For reviews, see Beránek, L.; Kraus, M., in Bamford, C,H; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 20, Elsevier, NY, ***1978***, pp. 274–295; Pines, H. *Intra-Sci. Chem. Rep.* ***1972***, *6*(2), 1, pp. 17–21; Noller, H.; Andréu, P.; Hunger, M. *Angew. Chem. Int. Ed.* ***1971***, *10*, 172; Knözinger, H. *Angew. Chem. Int. Ed.* ***1968***, *7*, 791. See also, Berteau, P.; Ruwet, M.; Delmon, B. *Bull. Soc. Chim. Belg.* ***1985***, *94*, 859.

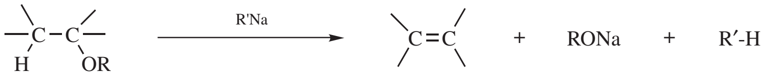
[177]Ashby, E.C.; Willard, G.F.; Goel, A.B. *J. Org. Chem.* ***1979***, *44*, 1221.

[178]Brieger, G.; Watson, S.W.; Barar, D.G.; Shene, A.L. *J. Org. Chem.* ***1979***, *44*, 1340.

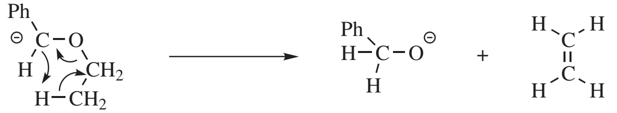
OS **I**, 15, 183, 226, 280, 345, 430, 473, 475; **II**, 12, 368, 408, 606; **III**, 22, 204, 237, 312, 313, 353, 560, 729, 786; **IV**, 130, 444, 771; **V**, 294; **VI**, 307, 901; **VII**, 210, 241, 363, 368, 396; **VIII**, 210, 444. See also, OS **VII**, 63; **VIII**, 306, 474. No attempt has been made to list alkene-forming dehydration reactions accompanying condensations or rearrangements.

17-2 Cleavage of Ethers to Alkenes

Hydro-alkoxy-elimination



Alkenes can be formed by the treatment of ethers with very strong bases, such as alkylsodium or alkyllithium[179] compounds, sodium amide,[180] or LDA,[181] although there are side reactions with many of these reagents. The reaction is aided by electron-withdrawing groups in the β position, and, for example, $EtOCH_2CH(COOEt)_2$ can be converted to $CH_2{=}C(COOEt)_2$ without any base at all, but simply on heating.[182] *tert*-Butyl ethers are cleaved more easily than others. Several mechanisms are possible. In many cases, the mechanism is probably E1cB or on the E1cB side of the mechanistic spectrum,[183] since the base required is so strong, but it has been shown (by the use of $PhCD_2OEt$) that $PhCH_2OEt$ reacts by the five-membered E^i mechanism:[184] Propargylic benzyl ethers are converted to conjugated dienes by heating with a ruthenium catalyst.[185]



Ethers have also been converted to alkenes and alcohols by passing vapors over hot P_2O_5 or Al_2O_3 (this method is similar to **17-1**), but this is not a general reaction. Cyclic ethers, such as THF, react slowly with organolithium reagents with cleavage that produces a C=C unit.[186] Fragmentation of 2,5-dihydrofuran with ethylmagnesium chloride and a chiral zirconium catalyst leads to a chiral, homoallylic alcohol.[187] However, acetals can be converted to enol ethers (**31**) in this manner.

[179]Hodgson, D.M.; Stent, M.A.H.; Wilson, F.X. *Org. Lett.* ***2001***, *3*, 3401.

[180]For a review, see Maercker, A. *Angew. Chem. Int. Ed.* ***1987***, *26*, 972.

[181]Fleming, F.F.; Wang, Q.; Steward, O.W. *J. Org. Chem.* ***2001***, *66*, 2171.

[182]Feely, W.; Boekelheide, V. *Org Synth.* ***IV***, 298.

[183]For an investigation in the gas phase, see DePuy, C.H.; Bierbaum, V.M. *J. Am. Chem. Soc.* ***1981***, *103*, 5034.

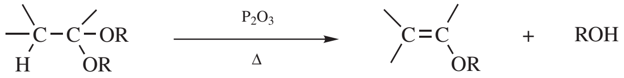
[184]Letsinger, R.L.; Pollart, D.F. *J. Am. Chem. Soc.* ***1956***, *78*, 6079.

[185]Yeh, K.-L.; Liu, B.; Lo, C.-Y.; Huang, H.-L.; Liu, R.-S. *J. Am. Chem. Soc.* ***2002***, *124*, 6510.

[186]For the mechanism of *n*-butyllithium cleavage of 2-methyltetrahydrofuran, see Cohen, T.; Stokes, S. *Tetrahedron Lett.* ***1993***, *34*, 8023.

[187]Morken, J.P.; Didiuk, M.T.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***1993***, *115*, 6997.

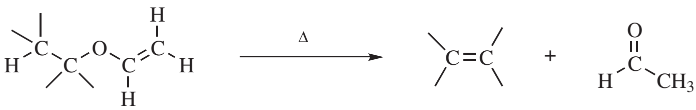
When ketals react with 2 equivalents of triisobutylaluminum, the product is a vinyl ether.[188]



31

This can also be done at room temperature by treatment with trimethylsilyl triflate and a tertiary amine[189] or with Me_3SiI in the presence of hexamethyldisilazane.[190]

Enol ethers can be pyrolyzed to alkenes and aldehydes in a manner similar to that of **17-4**

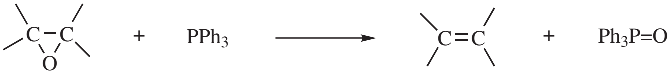


The rate of this reaction for R–O–CH=CH_2 increased in the order Et < *i*Pr < *t*-Bu.[191] The mechanism is similar to that of **17-4**.

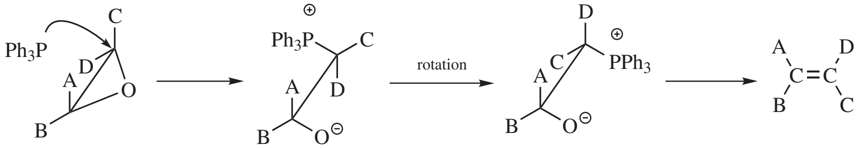
OS **IV**, 298, 404; **V**, 25, 642, 859, 1145; **VI**, 491, 564, 584, 606, 683, 948; **VIII**, 444.

17-3 The Conversion of Epoxides and Episulfides to Alkenes

***epi*-Oxy-elimination**



Epoxides can be converted to alkenes[192] by treatment with triphenylphosphine[193] or triethyl phosphite $P(OEt)_3$.[194] The first step of the mechanism is nucleophilic substitution (**10-35**), followed by a four-center elimination. Since inversion accompanies the substitution, the overall elimination is anti, that is, if two groups A and C are cis in the epoxide, they will be trans in the alkene:



Betaine

[188]Cabrera, G.; Fiaschi, R.; Napolitano, E. *Tetrahedron Lett.* ***2001***, *42*, 5867.

[189]Gassman, P.G.; Burns, S.J. *J. Org. Chem.* ***1988***, *53*, 5574.

[190]Miller, R.D.; McKean, D.R. *Tetrahedron Lett.* ***1982***, *23*, 323. For another method, see Marsi, M.; Gladysz, J.A. *Organometallics* ***1982***, *1*, 1467.

[191]McEwen, I.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 1179. See also Taylor, R. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 737.

[192]For reviews, see Wong, H.N.C.; Fok, C.C.M.; Wong, T. *Heterocycles* ***1987***, *26*, 1345; Sonnet, P.E. *Tetrahedron* ***1980***, *36*, 557, pp. 576.

[193]Wittig, G.; Haag, W. *Chem. Ber.* ***1955***, *88*, 1654.

[194]Scott, C.B. *J. Org. Chem.* ***1957***, *22*, 1118.

Alternatively, the epoxide can be treated with lithium diphenylphosphide, Ph_2PLi, and the product quaternized with methyl iodide.[195] Alkenes have also been obtained from epoxides by reaction with a large number of reagents,[196] among them Li in THF,[197] TsOH and NaI,[198] trimethylsilyl iodide,[199] PI_3,[200] F_3COOH–NaI,[201] SmI_2,[202] $Mo(CO)_6$, $TpReO_3$, where Tp is a pyrazolyl borate,[203] and the tungsten reagents mentioned in **17-18**. Some of these methods give syn elimination. Treatment of cyclooctane oxide with Ph_3P–$OPPh_3$ and NEt_3 gave cyclooctadiene.[204] Sodium amalgam with a cobalt–salen complex converted epoxides to alkenes.[205]

Epoxides can be converted to allylic alcohols[206] by treatment with several reagents, including *sec*-butyllithium,[207] *tert*-butyldimethylsilyl iodide,[208] and *i*Pr_2N-Li–*t*-BuOK (the *LIDAKOR reagent*).[209] Phenyllithium reacts with epoxides in the presence of lithium tetramethylpiperidide (LTMP) to give a trans alkene.[210] Sulfur ylids, such as $Me_2S{=}CH_2$, also convert epoxides to allylic alcohols.[211] Bromomethyl epoxides react with $InCl_3/NaBH_4$ to give an allylic alcohol.[212] α,β-Epoxy ketones are converted to conjugated ketones by treatment with NaI in acetone in the presence of Amberlyst 15,[213] or with 2.5 equivalents of SmI_2.[214] Cyclic epoxides are converted to conjugated dienes by heating with $(NMe_2)_2P({=}O)Cl$ and H_2O.[215]

[195]Vedejs, E.; Fuchs, P.L. *J. Am. Chem. Soc.* ***1971***, *93*, 4070; ***1973***, *95*, 822.

[196]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 272–277.

[197]Gurudutt, K.N.; Ravindranath, B. *Tetrahedron Lett.* ***1980***, *21*, 1173.

[198]Baruah, R.N.; Sharma, R.P.; Baruah, J.N. *Chem. Ind. (London)* ***1983***, 524.

[199]Denis, J.N.; Magnane, R.; Van Eenoo, M.; Krief, A. *Nouv. J. Chim.* ***1979***, *3*, 705. For other silyl reagents, see Reetz, M.T.; Plachky, M. *Synthesis* ***1976***, 199; Dervan, P.B.; Shippey, M.A. *J. Am. Chem. Soc.* ***1976***, *98*, 1265; Caputo, R.; Mangoni, L.; Neri, O.; Palumbo, G. *Tetrahedron Lett.* ***1981***, *22*, 3551.

[200]Denis, J.N.; Magnaane, R.; Van Eenoo, M.; Krief, A. *Nouv. J. Chim.* ***1979***, *3*, 705.

[201]Sarma, D.N.; Sharma, R.P. *Chem. Ind. (London)* ***1984***, 712.

[202]Girard, P.; Namy, J.L.; Kagan, H.B. *J. Am. Chem. Soc.* ***1980***, *102*, 2693; Matsukawa, M.; Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Chem. Lett.* ***1987***, 2101.

[203]Gable, K.P.; Brown, E.C. *Synlett* ***2003***, 2243.

[204]Hendrickson, J.B.; Walker, M.A.; Varvak, A.; Hussoin, Md.S. *Synlett* ***1996***, 661.

[205]Isobe, H.; Branchaud, B.P. *Tetrahedron Lett.* ***1999***, *40*, 8747.

[206]For reviews, see Smith, J.G. *Synthesis* ***1984***, 629, pp. 637–642; Crandall, J.K.; Apparu, M. *Org. React.* ***1983***, *29*, 345. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 231–233. See also, Okovytyy, S.; Gorb, L.; Leszczynski, J. *Tetrahedron* ***2001***, *57*, 1509.

[207]Doris, E.; Dechoux, L.; Mioskowski, C. *Tetrahedron Lett.* ***1994***, *35*, 7943.

[208]Detty, M.R. *J. Org. Chem.* ***1980***, *45*, 924. For another silyl reagent, see Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* ***1979***, *101*, 2738.

[209]Mordini, A.; Ben Rayana, E.; Margot, C.; Schlosser, M. *Tetrahedron* ***1990***, *46*, 2401; Degl'Innocenti, A.; Mordini, A.; Pecchi, S.; Pinzani, D.; Reginato, G.; Ricci, A. *Synlett* ***1992***, 753, 803; Thurner, A.; Faigl, F.; Töke, L.; Mordini, A.; Valacchi, M.; Reginato, G.; Czira, G. *Tetrahedron* ***2001***, *57*, 8173.

[210]Hodgson, D.M.; Fleming, M.J.; Stanway, S.J. *J. Am. Chem. Soc.* ***2004***, *126*, 12250.

[211]Alcaraz, L.; Cridland, A.; Kinchin, E. *Org. Lett.* ***2001***, *3*, 4051.

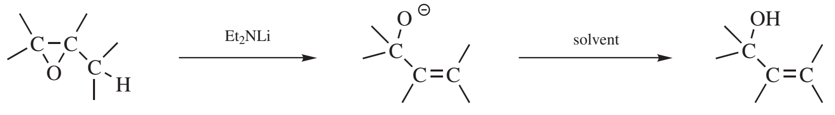
[212]Ranu, B.C.; Banerjee, S.; Das, A. *Tetrahedron Lett.* ***2004***, *45*, 8579.

[213]Righi, G.; Bovicelli, P.; Sperandio, A. *Tetrahedron* ***2000***, *56*, 1733.

[214]Concellón, J.M.; Bardales, E. *J. Org. Chem.* ***2003***, *68*, 9492; Concellón, J.M.; Bardales, E. *Org. Lett.* ***2002***, *4*, 189. In a similar manner, epoxy amides are converted to conjugated amides, see Concellón, J.M.; Bardales, E. *Eur. J. Org. Chem.* ***2004***, 1523.

[215]Demir, A.S. *Tetrahedron* ***2001***, *57*, 227.

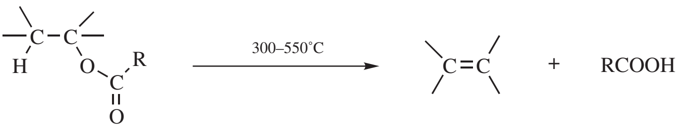
When an optically active reagent is used, optically active allylic alcohols can be produced from achiral epoxides.[216] Sparteine and *sec*-butyllithium generate a chiral base that leads to formation of chiral allylic alcohols.[217] Chiral diamines react with organolithium reagents to produce chiral bases that convert epoxides to allylic alcohols with good enantioselectivity.[218] Chiral diamines with a mixture of LDA and DBU (p. 1132) give similar results.[219]



Episulfides[220] can be converted to alkenes.[221] However, in this case the elimination is syn, so the mechanism cannot be the same as that for conversion of epoxides. The phosphite attacks sulfur rather than carbon. Among other reagents that convert episulfides to alkenes are Bu_3SnH,[222] certain rhodium complexes,[223] $LiAlH_4$[224] (this compound behaves quite differently with epoxides, see **19-35**), and meI.[225] The reaction of H_2S/PPh_3 and $MeReO_3$ converts episulfides to alkenes.[226] Episulfoxides can be converted to alkenes and sulfur monoxide simply by heating.[227]

17-4 Pyrolysis of Carboxylic Acids and Esters of Carboxylic Acids

Hydro-acyloxy-elimination



[216]Su, H.; Walder, L.; Zhang, Z.; Scheffold, R. *Helv. Chim. Acta* ***1988***, *71*, 1073, and references cited therein. Also see, Asami, M.; Suga, T.; Honda, K.; Inoue, S. *Tetrahedron Lett.* ***1997***, *38*, 6425.; Lill, S.O.N.; Pettersen, D.; Amedjkouh, M.; Ahlberg, P. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 3054; Brookes, P.C.; Milne, D.J.; Murphy, P.J.; Spolaore, B. *Tetrahedron* ***2002***, *58*, 4675.

[217]Alexakis, A.; Vrancken, E.; Mangeney, P. *J. Chem. Soc. Perkin Trans. 1* ***2000***, 3354.

[218]de Sousa, S.E.; O'Brien, P.; Steffens, H.C. *Tetrahedron Lett.* ***1999***, *40*, 8423; Equey, O.; Alexakis, A. *Tetrahedron Asymmetry* ***2004***, *15*, 1069.

[219]Bertilsson, S.K.; Södergren, M.J.; Andersson, P.G. *J. Org. Chem.* ***2002***, *67*, 1567; Bertilsson, S.K.; Andersson, P.G. *Tetrahedron* ***2002***, *58*, 4665.

[220]For a review of this reaction, see Sonnet, P.E. *Tetrahedron* ***1980***, *36*, 557, see p. 587. For a review of episulfides, see Goodman, L.; Reist, E.J., in Kharasch; Meyers *The Chemistry of Organic Sulfur Compounds*, Vol. 2; Pergamon: Elmsford, NY, ***1966***, pp. 93–113.

[221]Neureiter, N.P.; Bordwell, F.G. *J. Am. Chem. Soc.* ***1959***, *81*, 578; Davis, R.E. *J. Org. Chem.* ***1957***, *23*, 1767.

[222]Schauder, J.R.; Denis, J.N.; Krief, A. *Tetrahedron Lett.* ***1983***, *24*, 1657.

[223]Calet, S.; Alper, H. *Tetrahedron Lett.* ***1986***, *27*, 3573.

[224]Lightner, D.A.; Djerassi, C. *Chem. Ind. (London)* ***1962***, 1236; Latif, N.; Mishriky, N.; Zeid, I. *J. Prakt. Chem.* ***1970***, *312*, 421.

[225]Culvenor, C.J.; Davies, W.; Heath, N.S. *J. Chem. Soc.* ***1949***, 282; Helmkamp, G.K.; Pettitt, D.J. *J. Org. Chem.* ***1964***, *29*, 3258.

[226]Jacob, J.; Espenson, J.H. *Chem. Commun.* ***1999***, 1003.

[227]Hartzell, G.E.; Paige, J.N. *J. Am. Chem. Soc.* ***1966***, *88*, 2616, *J. Org. Chem.* ***1967***, *32*, 459; Aalbersberg, W.G.L.; Vollhardt, K.P.C. *J. Am. Chem. Soc.* ***1977***, *99*, 2792.

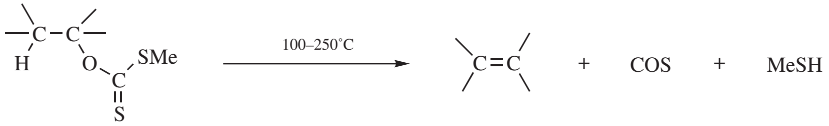
Direct elimination of a carboxylic acid to an alkene has been accomplished by heating in the presence of palladium catalysts.[228] Carboxylic esters in which the alkyl group has a β hydrogen can be pyrolyzed, most often in the gas phase, to give the corresponding acid and an alkene.[229] No solvent is required. Since rearrangement and other side reactions are few, the reaction is synthetically very useful and is often carried out as an indirect method of accomplishing **17-1**. The yields are excellent and the workup is easy. Many alkenes have been prepared in this manner. For higher alkenes (above $\sim C_{10}$) a better method is to pyrolyze the alcohol in the presence of acetic anhydride.[230]

The mechanism is E^i (see p. 1507). Lactones can be pyrolyzed to give unsaturated acids, provided that the six-membered transition state required for E^i reactions is available (it is not available for five- and six-membered lactones, but it is for larger rings[231]). Amides give a similar reaction, but require higher temperatures.

Allylic acetates give dienes when heated with certain palladium[232] or molybdenum[233] compounds.

OS **III**, 30; **IV**, 746; **V**, 235; **IX**, 293.

17-5 The Chugaev Reaction



Methyl xanthates are prepared by treatment of alcohols with NaOH and CS_2 to give RO–C(=S)–SNa, followed by treatment of this with methyl iodide.[234] Pyrolysis of the xanthate to give the alkene, COS, and the thiol is called the *Chugaev reaction*.[235] The reaction is thus, like **17-4**, an indirect method of accomplishing **17-2**. The temperatures required with xanthates are lower than with ordinary esters, which is advantageous because possible isomerization of the resulting alkene is minimized. The mechanism is E^i, similar to that of **17-4**. For a time there was doubt as to which sulfur atom closed the ring, but now there is much evidence, including

[228]Miller, J.A.; Nelson, J.A.; Byrne, M.P. *J. Org. Chem.* ***1993***, *58*, 18; Gooßen, L.J.; Rodríguez, N. *Chem. Commun.* ***2004***, 724.

[229]For a review, see DePuy, C.H.; King, R.W. *Chem. Rev.* ***1960***, *60*, 431, 432. For some procedures, see Jenneskens, L.W.; Hoefs, C.A.M.; Wiersum, U.E. *J. Org. Chem.* ***1989***, *54*, 5811, and references cited therein.

[230]Aubrey, D.W.; Barnatt, A.; Gerrard, W. *Chem. Ind. (London)* ***1965***, 681.

[231]See, for example, Bailey, W.J.; Bird, C.N. *J. Org. Chem.* ***1977***, *42*, 3895.

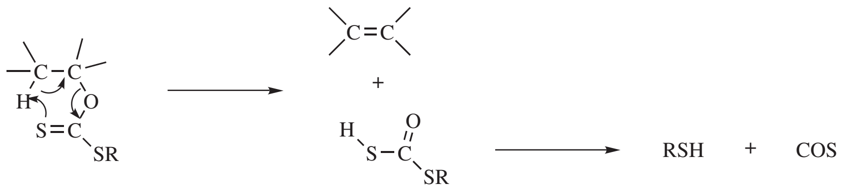
[232]For a review, see Heck, R.F. *Palladium Reagents in Organic Synthesis*; Academic Press, NY, ***1985***, pp. 172–178.

[233]Trost, B.M.; Lautens, M.; Peterson, B. *Tetrahedron Lett.* ***1983***, *24*, 4525.

[234]For a method of preparing xanthates from alcohols in one laboratory step, see Lee, A.W.M.; Chan, W.H.; Wong, H.C.; Wong, M.S. *Synth. Commun.* ***1989***, *19*, 547; Nagle, A.S.; Salvataore, R.N.; Cross, R.M.; Kapxhiu, E.A.; Sahab, S.; Yoon, C.H.; Jung, K.W. *Tetrahedron Lett.* ***2003***, *44*, 5695.

[235]For reviews, see DePuy, C.H.; King, R.W. *Chem. Rev.* ***1960***, *60*, 431, see p. 444; Nace, H.R. *Org. React.* ***1962***, *12*, 57.

the study of ^{34}S and ^{13}C isotope effects, to show that it is the C=S sulfur:[236] In a structural variation of this reaction, heating a propargylic xanthate with 2,4,6-trimethylpyridinium trifluoromethyl sulfonate leads to formation of an alkene.[237]

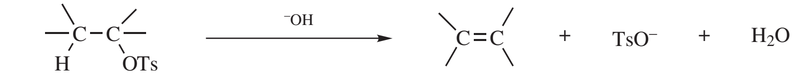


The mechanism is thus exactly analogous to that of **17-5**.

OS **VII**, 139.

17-6 Decomposition of Other Esters

Hydro-tosyloxy-elimination

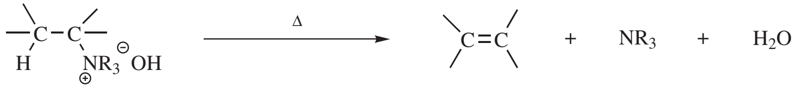


Several types of inorganic ester can be cleaved to alkenes by treatment with bases. Esters of sulfuric, sulfurous, and other acids undergo elimination in solution by E1 or E2 mechanisms, as do tosylates and other esters of sulfonic acids.[238] It has been shown that bis(tetra-*n*-butylammonium) oxalate, $(Bu_4N^+)_2\ (COO^-)_2$, is an excellent reagent for inducing tosylates to undergo elimination rather than substitution.[239] Aryl sulfonates have also been cleaved without a base. Esters of 2-pyridinesulfonic acid and 8-quinolinesulfonic acid gave alkenes in high yields simply on heating, without a solvent.[240] Phosphonate esters have been cleaved to alkenes by treatment with Lawesson's reagent.[241] Esters of $PhSO_2OH$ and TsOH behaved similarly when heated in a dipolar aprotic solvent, such as Me_2SO or HMPA.[242]

OS, **VI**, 837; **VII**, 117.

17-7 Cleavage of Quaternary Ammonium Hydroxides

Hydro-trialkylammonio-elimination



[236]Bader, R.F.W.; Bourns, A.N. *Can. J. Chem.* ***1961***, *39*, 348.

[237]Fauré-Tromeur, M.; Zard, S.Z. *Tetrahedron Lett.* ***1999***, *40*, 1305.

[238]For a list of reagents used for sulfonate cleavages, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 294–295.

[239]Corey, E.J.; Terashima, S. *Tetrahedron Lett.* ***1972***, 111.

[240]Corey, E.J.; Posner, G.G.; Atkinson, R.F.; Wingard, A.K.; Halloran, D.J.; Radzik, D.M.; Nash, J.J. *J. Org. Chem.* ***1989***, *54*, 389.

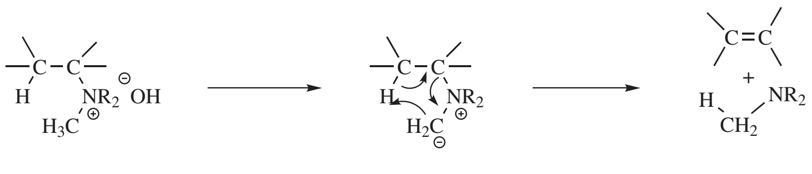
[241]Shimagaki, M.; Fujieda, Y.; Kimura, T.; Nakata, T. *Tetrahedron Lett.* ***1995***, *36*, 719.

[242]Nace, H.R. *J. Am. Chem. Soc.* ***1959***, *81*, 5428.

Cleavage of quaternary ammonium hydroxides is the final step of the process known as *Hofmann exhaustive methylation or Hofmann degradation*.[243] In the first step, a primary, secondary, or tertiary amine is treated with enough methyl iodide to convert it to the quaternary ammonium iodide (**10-31**). In the second step, the iodide is converted to the hydroxide by treatment with silver oxide. In the cleavage step, an aqueous or alcoholic solution of the hydroxide is distilled, often under reduced pressure. The decomposition generally takes place at a temperature between 100 and 200°C. Alternatively, the solution can be concentrated to a syrup by distillation or freeze-drying.[244] When the syrup is heated at low pressures, the cleavage reaction takes place at lower temperatures than are required for the reaction in the ordinary solution, probably because the base (HO^- or RO^-) is less solvated.[245] The reaction has never been an important synthetic tool, but in the nineteenth century and the first part of the twentieth century, it saw much use in the determination of the structure of unknown amines, especially alkaloids. In many of these compounds, the nitrogen is in a ring, or even at a ring junction, and in such cases the alkene still contains nitrogen. Repetitions of the process are required to remove the nitrogen completely, as in the conversion of 2-methylpiperidine to 1,5-hexadiene by two rounds of exhaustive methylation followed by pyrolysis.

A side reaction involving nucleophilic substitution to give an alcohol (R_4N^+ $^-OH \rightarrow ROH + R_3N$) generally accompanies the normal elimination reaction,[246] but seldom causes trouble. However, when none of the four groups on the nitrogen has a β hydrogen, substitution is the only reaction possible. On heating Me_4N^+ ^-OH in water, methanol is obtained, although without a solvent the product is not methanol, but dimethyl ether.[247]

The mechanism is usually E2. Hofmann's rule is generally obeyed by acyclic and Zaitsev's rule by cyclohexyl substrates (p. 1498). In certain cases, where the molecule is highly hindered, a five-membered E^i mechanism, similar to that in **17-8**, has been shown to operate. That is, the hydroxide in these cases does not attract the β hydrogen, but instead removes one of the methyl hydrogens:



[243]For reviews, see Bentley, K.W., in Bentley, K.W.; Kirby, G.W *Elucidation of Organic Structures by Physical and Chemical Methods*, 2nd ed. (Vol. 4 of Weissberger *Techniques of Chemistry*), pt. 2, Wiley, NY, ***1973***, pp. 255–289; White, E.H.; Woodcock, D.J., in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, pp. 409–416; Cope, A.C.; Trumbull, E.R. *Org. React.* ***1960***, *11*, 317.

[244]Archer, D.A. *J. Chem. Soc. C* ***1971***, 1327.

[245]Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***, pp. 4–5.

[246]Baumgarten, R.J. *J. Chem. Educ.* ***1968***, *45*, 122.

[247]Musker, W.K. *J. Chem. Educ.* ***1968***, *45*, 200; Musker, W.K.; Stevens, R.R. *J. Am. Chem. Soc.* ***1968***, *90*, 3515; Tanaka, J.; Dunning, J.E.; Carter, J.C. *J. Org. Chem.* ***1966***, *31*, 3431.

The obvious way to distinguish between this mechanism and the ordinary E2 mechanism is by the use of deuterium labeling. For example, if the reaction is carried out on a quaternary hydroxide deuterated on the β carbon ($R_2CDCH_2NMe_3^+$ ^-OH), the fate of the deuterium indicates the mechanism. If the E2 mechanism is in operation, the trimethylamine produced would contain no deuterium (which would be found only in the water). But if the mechanism is E^i, the amine would contain deuterium. In the case of the highly hindered compound $(Me_3C)_2CDCH_2NMe_3^+$ ^-OH, the deuterium did appear in the amine, demonstrating an Ei mechanism for this case.[248] With simpler compounds, the mechanism is E2, since here the amine was deuterium-free.[249]

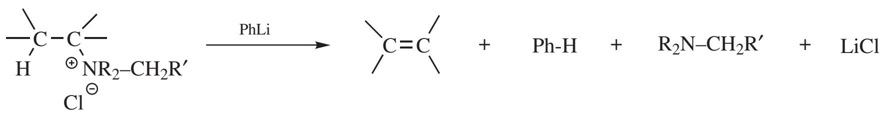
When the nitrogen bears more than one group possessing a β hydrogen, which group cleaves? The Hofmann rule says that *within* a group the hydrogen on the least alkylated carbon cleaves. This tendency is also carried over to the choice of which group cleaves: thus ethyl with three β hydrogens cleaves more readily than any longer *n*-alkyl group, all of which have two β hydrogens. "The β hydrogen is removed most readily if it is located on a methyl group, next from RCH_2, and least readily from R_2CH."[250] In fact, the Hofmann rule as first stated[251] in 1851 applied only to which group cleaved, not to the orientation within a group; the latter could not have been specified in 1851, since the structural theory of organic compounds was not formulated until 1857–1860. Of course, the Hofmann rule (applied to which group cleaves *or* to orientation within a group) is superseded by conjugation possibilities. Thus $PhCH_2CH_2NMe_2Et^+$ ^-OH gives mostly styrene instead of ethylene.

Triple bonds have been prepared by pyrolysis of 1,2-bis(ammonium) salts.[252]

OS **IV**, 980; **V**, 315, 608; **VI**, 552. Also see, OS **V**, 621, 883; **VI**, 75.

17-8 Cleavage of Quaternary Ammonium Salts With Strong Bases

Hydro-trialkylammonio-elimination



[248]Cope, A.C.; Mehta, A.S. *J. Am. Chem. Soc.* ***1963***, *85*, 1949. See also, Baldwin, M.A.; Banthorpe, D.V.; Loudon, A.G.; Waller, F.D. *J. Chem. Soc. B* ***1967***, 509.

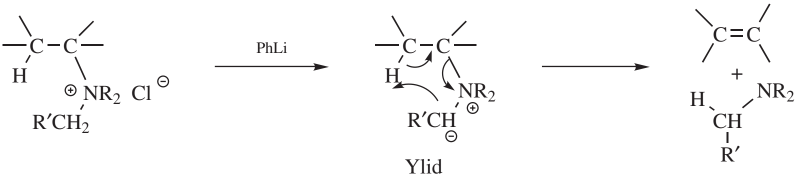
[249]Cope, A.C.; LeBel, N.A.; Moore, P.T.; Moore, W.R. *J. Am. Chem. Soc.* ***1961***, *83*, 3861.

[250]Cope, A.C.; Trumbull, E.R. *Org. React.* ***1960***, *11*, 317, see p. 348.

[251]Hofmann, A.W. *Liebigs Ann. Chem.* ***1851***, *78*, 253.

[252]For a review, see Franke, W.; Ziegenbein, W.; Meister, H. *Angew. Chem.* ***1960***, *72*, 391, see p. 397–398.

When quaternary ammonium halides are treated with strong bases (e.g., PhLi, KNH_2 in liquid NH_3[253]), an elimination can occur that is similar in products, although not in mechanism, to **17-7**. This is an alternative to **17-7** and is done on the quaternary ammonium halide, so that it is not necessary to convert this to the hydroxide. The mechanism is E^i:



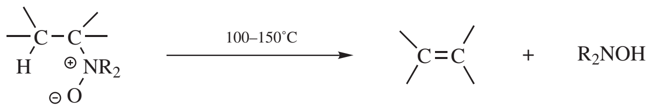
An α′ hydrogen is obviously necessary in order for the ylid to be formed. This type of mechanism is called α′,β elimination, since a β hydrogen is removed by the α′ carbon. The mechanism has been confirmed by labeling experiments similar to those described at **17-7**,[254] and by isolation of the intermediate ylids.[255] An important synthetic difference between this and most instances of **17-7** is that syn-elimination is observed here and anti-elimination in **17-7**, so products of opposite configuration are formed when the alkene exhibits cis–trans isomerism.

An alternative procedure that avoids the use of a very strong base is heating the salt with KOH in polyethylene glycol monomethyl ether.[256]

Benzotriazole has been shown to be a good leaving group for elimination reactions. The reaction of an allylic benzotriazole (3-benzotriazoyl-4-trimethylsilyl-1-butene) with *n*-butyllithium, and then an alkyl halide leads to an alkylated 1,3-diene upon heating.[257]

17-9 Cleavage of Amine Oxides

Hydro-(Dialkyloxidoammonio)-elimination



Cleavage of amine oxides to produce an alkene and a hydroxylamine is called the *Cope reaction* or *Cope elimination* (not to be confused with the Cope *rearrangement*, **18-32**). It is an alternative to **17-7** and **17-8**.[258] The reaction is usually

[253]Bach, R.D.; Bair, K.W.; Andrzejewski, D. *J. Am. Chem. Soc.* ***1972***, *94*, 8608; *J. Chem. Soc., Chem. Commun.* ***1974***, 819.

[254]Weygand, F.; Daniel, H.; Simon, H. *Chem. Ber.* ***1958***, *91*, 1691; Bach, R.D.; Knight, J.W. *Tetrahedron Lett.* ***1979***, 3815.

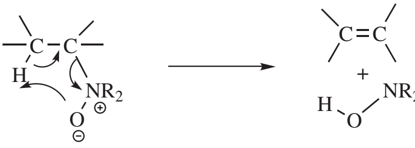
[255]Wittig, G.; Burger, T.F. *Liebigs Ann. Chem.* ***1960***, *632*, 85.

[256]Hünig, S.; Öller, M.; Wehner, G. *Liebigs Ann. Chem.* ***1979***, 1925.

[257]Katritzky, A.R.; Serdyuk, L.; Toader, D.; Wang, X. *J. Org. Chem.* ***1999***, *64*, 1888.

[258]For reviews, see Cope, A.C.; Trumbull, E.R. *Org. React.* ***1960***, *11*, 317, see p. 361; DePuy, C.H.; King, R.W. *Chem. Rev.* ***1960***, *60*, 431, see pp. 448–451.

performed with a mixture of amine and oxidizing agent (see **19-29**) without isolation of the amine oxide. Because of the mild conditions side reactions are few, and the alkenes do not usually rearrange. The reaction is thus very useful for the preparation of many alkenes. A limitation is that it does not open six-membered rings containing nitrogen, although it does open rings of 5 and 7–10 members.[259] Rates of the reaction increase with increasing size of α and β-substituents.[260] The reaction can be carried out at room temperature in dry Me_2SO or THF.[261] The elimination is a stereoselective syn process,[262] and the five-membered E^i mechanism operates:



Almost all evidence indicates that the transition state must be planar. Deviations from planarity as in **17-4** (see p. 1507) are not found here, and indeed this is why six-membered heterocyclic nitrogen compounds do not react. Because of the stereoselectivity of this reaction and the lack of rearrangement of the products, it is useful for the formation of trans-cycloalkenes (eight-membered and higher). A polymer-bound Cope elimination reaction has been reported.[263]

OS **IV**, 612.

17-10 Pyrolysis of Keto-ylids

Hydro-(oxophosphoryl)-elimination

Phosphorus ylids are quite common (see **16-44**) and keto-phosphorus ylids [$RCOCH{=}PPh_3$] are also known. When these compounds are heating (flash vacuum pyrolysis, FVP) to > 500°C, alkynes are formed. Simple alkynes[264] can be formed as well as keto-alkynes[265] and en-ynes.[266] Rearrangement from ylids derived from tertiary amines an α-diazo ketones is also known.[267]

[259]Cope, A.C.; LeBel, N.A. *J. Am. Chem. Soc.* ***1960***, *82*, 4656; Cope, A.C.; Ciganek, E.; Howell, C.F.; Schweizer, E.E. *J. Am. Chem. Soc.* ***1960***, *82*, 4663.

[260]Závada, J.; Pánková, M.; Svoboda, M. *Collect. Czech. Chem. Commun.* ***1973***, *38*, 2102.

[261]Cram, D.J.; Sahyun, M.R.V.; Knox, G.R. *J. Am. Chem. Soc.* ***1962***, *84*, 1734.

[262]See, for example, Bach, R.D.; Andrzejewski, D.; Dusold, L.R. *J. Org. Chem.* ***1973***, *38*, 1742.

[263]Sammelson, R.E.; Kurth, M.J. *Tetrahedron Lett.* ***2001***, *42*, 3419.

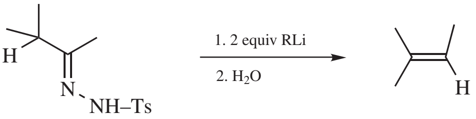
[264]Aitken, R.A.; Atherton, J.I. *J. Chem. Soc. Perkin Trans. 1* ***1994***, 1281.

[265]Aitken, R.A.; Hérion, H.; Janosi, A.; Karodia, N.; Raut, S.V.; Seth, S.; Shannon, I.J.; Smith, F.C. *J. Chem. Soc. Perkin Trans. 1* ***1994***, 2467.

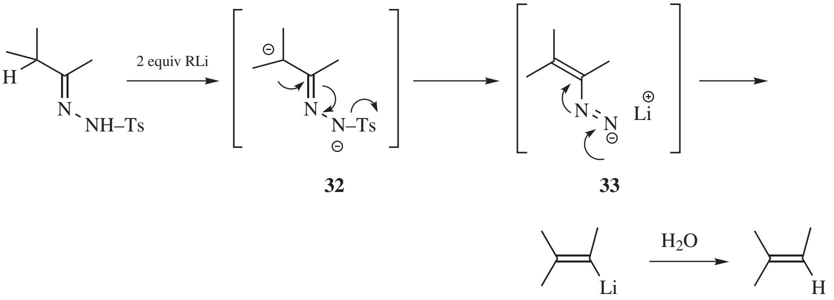
[266]Aitken, R.A.; Boeters, C; Morrison, J.J. *J. Chem. Soc. Perkin Trans. 1* ***1994***, 2473.

[267]DelZotto, A.; Baratta, W.; Miani, F.; Verardo, G.; Rigo, P. *Eur. J. Org. Chem.* ***2000***, 3731.

17-11 Decomposition of Toluene-*p*-sulfonylhydrazones



Treatment of the tosylhydrazone of an aldehyde or a ketone with a strong base leads to the formation of an alkene, the reaction being formally an elimination accompanied by a hydrogen shift.[268] The reaction (called the *Shapiro reaction*) has been applied to tosylhydrazones of many aldehydes and ketones. The most useful method synthetically involves treatment of the substrate with at least 2 equivalents of an organolithium compound[269] (usually MeLi) in ether, hexane, or tetramethylenediamine.[270] This procedure gives good yields of alkenes without side reactions and, where a choice is possible, predominantly gives the less highly substituted alkene. Tosylhydrazones of α,β-unsaturated ketones give conjugated dienes.[271] The mechanism[272] has been formulated as:



32 33

34

Evidence for this mechanism is (*1*) 2 equivalents of RLi are required; (*2*) the hydrogen in the product comes from the water and not from the adjacent carbon, as shown by deuterium labeling;[273] and (*3*) the intermediates **32–34** have been trapped.[274] This reaction, when performed in tetramethylenediamine, can be a synthetically useful method[275] of generating vinylic lithium compounds (**34**), which

[268]For reviews, see Adlington, R.M.; Barrett, A.G.M. *Acc. Chem. Res.* ***1983***, *16*, 55; Shapiro, R.H. *Org. React.* ***1976***, *23*, 405.

[269]Shapiro, R.H.; Heath, M.J. *J. Am. Chem. Soc.* ***1967***, *89*, 5734; Kaufman, G.; Cook, F.; Shechter, H.; Bayless, J.; Friedman, L. *J. Am. Chem. Soc.* ***1967***, *89*, 5736; Shapiro, R.H. *Tetrahedron Lett.* ***1968***, 345; Meinwald, J.; Uno, F. *J. Am. Chem. Soc.* ***1968***, *90*, 800.

[270]Stemke, J.E.; Bond, F.T. *Tetrahedron Lett.* ***1975***, 1815.

[271]See Dauben, W.G.; Rivers, G.T.; Zimmerman, W.T. *J. Am. Chem. Soc.* ***1977***, *99*, 3414.

[272]For a review of the mechanism, see Casanova, J.; Waegell, B. *Bull. Soc. Chim. Fr.* ***1975***, 922.

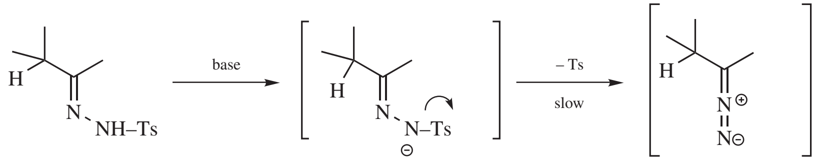
[273]Ref. 269; Shapiro, R.H.; Hornaman, E.C. *J. Org. Chem.* ***1974***, *39*, 2302.

[274]Lipton, M.F.; Shapiro, R.H. *J. Org. Chem.* ***1978***, *43*, 1409.

[275]See Traas, P.C.; Boelens, H.; Takken, H.J. *Tetrahedron Lett.* ***1976***, 2287; Stemke, J.E.; Chamberlin, A.R.; Bond, F.T. *Tetrahedron Lett.* ***1976***, 2947.

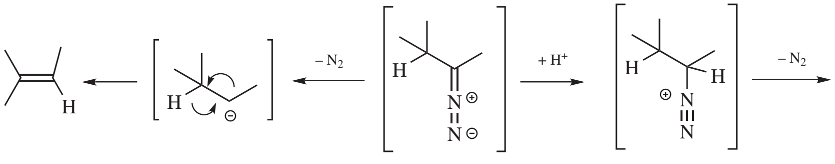
can be trapped by various electrophiles[276] such as D_2O (to give deuterated alkenes), CO_2 (to give α,β-unsaturated carboxylic acids, **16-30**), or DMF (to give α,β-unsaturated aldehydes, **16-82**). Treatment of *N*-aziridino hydrazones with LDA leads to alkenes with high cis selectivity.[277]

The reaction also takes place with other bases (e.g., LiH,[278] Na in ethylene glycol, NaH, $NaNH_2$) or with smaller amounts of RLi, but in these cases side reactions are common and the orientation of the double bond is in the other direction (to give the more highly substituted alkene). The reaction with Na in ethylene glycol is called the *Bamford–Stevens reaction*.[279] For these reactions two mechanisms are possible: a carbenoid and a carbocation mechanism.[280] The side reactions found are those expected of carbenes and carbocations. In general, the carbocation mechanism is chiefly found in protic solvents and the carbenoid mechanism in aprotic solvents. Both routes involve formation of a diazo compound (**35**) which in some cases can be isolated.

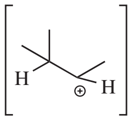


35

In fact, this reaction has been used as a synthetic method for the preparation of diazo compounds.[281] In the absence of protic solvents, **36** loses N_2, and hydrogen migrates, to give the alkene product. The migration of



35 **36**



[276]For a review, see Chamberlin, A.R.; Bloom, S.H. *Org. React.* ***1990***, *39*, 1.

[277]Maruoka, K.; Oishi, M.; Yamamoto, H. *J. Am. Chem. Soc.* ***1996***, *118*, 2289.

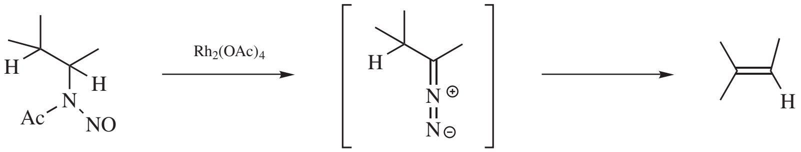
[278]Biellmann, J.F.; Pète, J. *Bull. Soc. Chim. Fr.* ***1967***, 675.

[279]Bamford, W.R.; Stevens, R.R. *J. Chem. Soc.* ***1952***, 4735. For a tandem Bamford-Stevens–Claisen rearrangement, see May, J.A.; Stoltz, B.M. *J. Am. Chem. Soc.* ***2002***, *124*, 12426.

[280]Powell, J.W.; Whiting, M.C. *Tetrahedron* ***1959***, *7*, 305; ***1961***, *12* 168; DePuy, C.H.; Froemsdorf, D.H. *J. Am. Chem. Soc.* ***1960***, *82*, 634; Bayless, J.H.; Friedman, L.; Cook, F.B.; Shechter, H. *J. Am. Chem. Soc.* ***1968***, *90*, 531; Nickon, A.; Werstiuk, N.H. *J. Am. Chem. Soc.* ***1972***, *94*, 7081.

[281]For a review, see Regitz, M.; Maas, G. *Diazo Compounds*; Academic Press, NY, ***1986***, pp. 257–295. For an improved procedure, see Wulfman, D.S.; Yousefian, S.; White, J.M. *Synth. Commun.* ***1988***, *18*, 2349.

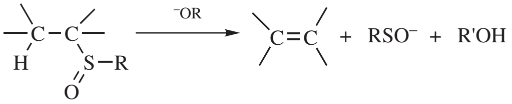
hydrogen may immediately follow, or be simultaneous with, the loss of N_2. In a protic solvent, **35** becomes protonated to give the diazonium ion **36**, which loses N_2 to give the corresponding carbocation, that may then undergo elimination or give other reactions characteristic of carbocations. A diazo compound is an intermediate in the formation of alkenes by treatment of *N*-nitrosoamides with a rhodium(II) catalyst.[282]



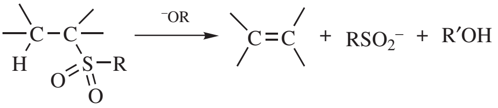
OS **VI**, 172; **VII**, 77; **IX**, 147. For the preparation of a diazo compound, see OS **VII**, 438.

17-12 Cleavage of Sulfoxides, Selenoxides, and Sulfones

Hydro-alkylsulfinyl-elimination



Hydro-alkylsulfinyl-elimination



Sulfonium compounds ($–C–^+SR_2$) undergo elimination similar to that of their ammonium counterparts (**17-7** and **17-8**) in scope and mechanism but this reaction is not of great synthetic importance. These syn-elimination reactions are related to the Cope elimination (**17-9**) and the Hofmann elimination (**17-7**).[283]

Sulfones and sulfoxides[284] with a β hydrogen, on the other hand, undergo elimination on treatment with an alkoxide or, for sulfones,[285] even with hydroxide.[286] Sulfones also eliminate in the presence of an organolithium reagent and a palladium catalyst.[287] Mechanistically, these reactions belong on the E1-E2-E1cB spectrum.[288] Although the leaving groups are uncharged, the orientation follows Hofmann's rule, not Zaitsev's. Sulfoxides (but not sulfones) also undergo elimination

[282]Godfrey, A.G.; Ganem, B. *J. Am. Chem. Soc.* ***1990***, *112*, 3717.

[283]For a discussion and leading references of this class of eliminations, see Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY, ***2001***, pp. 135–141.

[284]See Cubbage, J.W.; Guo, Y.; McCulla, R.D.; Jenks, W.S. *J. Org. Chem.* ***2001***, *66*, 8722.

[285]Certain sulfones undergo elimination with 5% HCl in THF: Yoshida, T.; Saito, S. *Chem. Lett.* ***1982***, 165.

[286]Hofmann, J.E.; Wallace, T.J.; Argabright, P.A.; Schriesheim, A. *Chem. Ind. (London)* ***1963***, 1234.

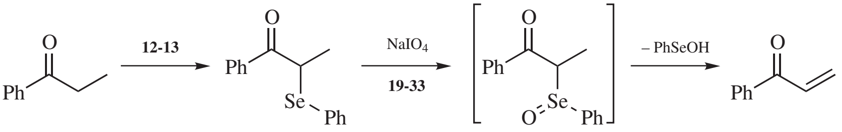
[287]Gai, Y.; Jin, L.; Julia, M.; Verpeaux, J.-N. *J. Chem. Soc., Chem. Commun.* ***1993***, 1625.

[288]Hofmann, J.E.; Wallace, T.L.; Schriesheim, A. *J. Am. Chem. Soc.* ***1964***, *86*, 1561.

on pyrolysis at ~80°C in a manner analogous to **17-9**. The mechanism is also analogous, being the five-membered E^i mechanism with syn elimination.[289]

Selenoxides[290] and sulfinate esters R_2CH–CHR–SO–OMe[291] also undergo elimination by the E^i mechanism, the selenoxide reaction taking place at room temperature. The reaction with selenoxides has been extended to the formation of triple bonds.[292]

Both the selenoxide[293] and sulfoxide[294] reactions have been used in a method for the conversion of ketones, aldehydes, and carboxylic esters to their α,β-unsaturated derivatives (illustrated for the selenoxide).



Because of the mildness of the procedure, this is probably the best means of accomplishing this conversion. Treatment of ketones with LDA and then PhClS=N*t*-Bu leads to the conjugated ketone.[295] Allylic sulfoxides undergo 1,4-elimination to give dienes.[296] Ketones also react with hypervalent iodine cmpound in DMSO to give conjugated ketone.[297] In a simialr manner, keotnes are converted to conjugated keotnes by heating with HIO_5/I_2O_5 in DMSO.[298]

[289]Schmitz, C.; Harvey, J.N.; Viehe, H.G. *Bull. Soc. Chim. Belg.* ***1994***, *103*, 105; Yoshimura, T.; Tsukurimichi, E.; Iizuka, Y.; Mizuno, H.; Isaji, H.; Shimasaki, C. *Bull. Chem. Soc. Jpn.* ***1989***, *62*, 1891.

[290]For reviews, see Back, T.G., in Patai, S. *The Chemistry of Organic Selenium and Telurium Compounds*, Vol. 2, Wiley, NY, ***1987***, pp. 91–213, 95–109; Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*, Pergamon, Elmsford, NY, ***1986***, pp. 132–143; Reich, H.J. *Acc. Chem. Res.* ***1979***, *12*, 22, in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. C, Academic Press, NY, ***1978***, pp. 15–101; Sharpless, K.B.; Gordon, K.M.; Lauer, R.F.; Patrick, D.W.; Singer, S.P.; Young, M.W. *Chem. Scr.* ***1975***, *8A*; 9. See also, Liotta, D. *Organoselenium Chemistry*, Wiley, NY, ***1987***.

[291]Jones, D.N.; Higgins, W. *J. Chem. Soc. C* ***1970***, 81.

[292]Reich, H.J.; Willis, Jr., W.W. *J. Am. Chem. Soc.* ***1980***, *102*, 5967.

[293]Clive, D.L.J. *J. Chem. Soc., Chem. Commun.* ***1973***, 695; Reich, H.J.; Renga, J.M.; Reich, I.L. *J. Am. Chem. Soc.* ***1975***, *97*, 5434, and references cited therein; Sharpless, K.B.; Lauer, R.F.; Teranishi, A.Y. *J. Am. Chem. Soc.* ***1973***, *95*, 6137; Grieco, P.A.; Miyashita, M. *J. Org. Chem.* ***1974***, *39*, 120; Crich, D.; Barba, G.R. *Org. Lett.* ***2000***, *2*, 989. For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 287–290. For a discussion of the effect of ortho substituents, see Sayama, S.; Onami, T. *Tetrahedron Lett.* ***2000***, *41*, 5557.

[294]Trost, B.M.; Salzmann, T.N.; Hiroi, K. *J. Am. Chem. Soc.* ***1976***, *98*, 4887. For a review of this and related methods, see Trost, B.M. *Acc. Chem. Res.* ***1978***, *11*, 453.

[295]Mukaiyama, T.; Matsuo, J.-i.; Kitgawa, H. *Chem. Lett.* ***2000***, 1250.

[296]de Groot, A.; Jansen, B.J.M.; Reuvers, J.T.A.; Tedjo, E.M. *Tetrahedron Lett.* ***1981***, *22*, 4137.

[297]Nicolaou, K.C.; Montagnon, T.; Baran, P.S.; Zhong, Y.-L. *J. Am. Chem. Soc.* ***2002***, *124*, 2245; Nicolaou, K.C.; Gray, D.L.F.; Montagnon, T.; Harrison, S.T. *Angew. Chem. Int. Ed.* ***2002***, *41*, 996.

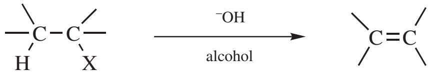
[298]Nicolaou, K.C.; Montagnon, T.; Baran, P.S. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1386.

A radical elimination reaction generates alkenes from sulfoxides. The reaction of a 2-bromophenyl alkylsulfoxide with Bu_3SnH and AIBN (see p. 935 for a discussion of these standard radical conditions) leads to an alkene.[299]

OS **VI**, 23, 737; **VIII**, 543; **IX**, 63.

17-13 Dehydrohalogenation of Alkyl Halides

Hydro-halo-elimination



The elimination of HX from an alkyl halide is a very general reaction and can be accomplished with chlorides, fluorides, bromides, and iodides.[300] Hot alcoholic KOH is the most frequently used base, although stronger bases[301] ($^-$OR, $^-NH_2$, etc.) or weaker ones (e.g., amines) are used where warranted.[302] The bicyclic amidines 1,5-diazabicyclo[3.4.0]nonene-5 (DBN)[303] and 1,8-diazabicyclo[5.4.0]undecene-7 (DBU)[304] are good reagents for difficult cases.[305] Dehydrohalogenation with the non-ionic base $(Me_2N)_3P{=}N\text{-}P(NMe_2)_2{=}NMe$ is even faster.[306] Phase-transfer catalysis has been used with hydroxide as base.[307] As previously mentioned (p. 1495), certain weak bases in dipolar aprotic solvents are effective reagents for dehydrohalogenation. Among those most often used for synthetic purposes are LiCl or LiBr–$LiCO_3$ in DMF.[308] Dehydrohalogenation has also been effected by heating of the alkyl halide in HMPA with no other reagent present.[309] As in

[299]Imboden, C.; Villar, F.; Renaud, P. *Org. Lett.* ***1999***, *1*, 873.

[300]For a review of eliminations involving the carbon–halogen bond, see Baciocchi, E., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement D*, pt. 2, Wiley, NY, ***1983***, pp. 1173–1227.

[301]Triphenylmethylpotassium rapidly dehydrohalogenates secondary alkyl bromides and iodides, in >90% yields, at 0°C: Anton, D.R.; Crabtree, R.H. *Tetrahedron Lett.* ***1983***, *24*, 2449.

[302]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 256–258.

[303]Truscheit, E.; Eiter, K. *Liebigs Ann. Chem.* ***1962***, *658*, 65; Oediger, H.; Kabbe, H.; Möller, F.; Eiter, K. *Chem. Ber.* ***1966***, *99*, 2012; Vogel, E.; Klärner, F. *Angew. Chem. Int. Ed.* ***1968***, *7*, 374.

[304]Oediger, H.; Möller, F. *Angew. Chem. Int. Ed.* ***1967***, *6*, 76; Wolkoff, P. *J. Org. Chem.* ***1982***, *47*, 1944.

[305]For a review of these reagents, see Oediger, H.; Möller, F.; Eiter, K. *Synthesis* ***1972***, 591.

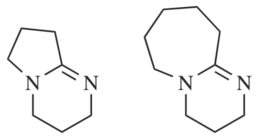
[306]Schwesinger, R.; Schlemper, H. *Angew. Chem. Int. Ed.* ***1987***, *26*, 1167.

[307]Kimura, Y.; Regen, S.L. *J. Org. Chem.* ***1983***, *48*, 195; Halpern, M.; Zahalka, H.A.; Sasson, Y.; Rabinovitz, M. *J. Org. Chem.* ***1985***, *50*, 5088. See also, Barry, J.; Bram, G.; Decodts, G.; Loupy, A.; Pigeon, P.; Sansoulet, J. *J. Org. Chem.* ***1984***, *49*, 1138.

[308]For a discussion, see Fieser, L.F.; Fieser, M. *Reagents for Organic Syntheses*, Vol. 1, Wiley, NY, ***1967***, pp. 606–609. For a review of alkali-metal fluorides in this reaction, see Yakobson, G.G.; Akhmetova, N.E. *Synthesis* ***1983***, 169, see pp. 170–173.

[309]Hanna, R. *Tetrahedron Lett.* ***1968***, 2105; Monson, R.S. *Chem. Commun.* ***1971***, 113; Hutchins, R.O.; Hutchins, M.G.; Milewski, C.A. *J. Org. Chem.* ***1972***, *37*, 4190; Hoye, T.R.; van Deidhuizen, J.J.; Vos, T.J.; Zhao, P. *Synth. Commun.* ***2001***, *31*, 1367.

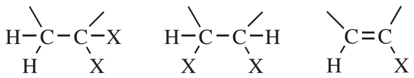
nucleophilic substitution (p. 496), the order of leaving group reactivity is I > Br > Cl > F.[310]



DBN DBU

Tertiary halides undergo elimination most easily. Eliminations of chlorides, bromides, and iodides follow Zaitsev's rule, except for a few cases where steric effects are important (for an example, see p. 1499). Eliminations of fluorides follow Hofmann's rule (p. 1500).

This reaction is by far the most important way of introducing a triple bond into a molecule.[311] Alkyne formation can be accomplished with substrates of the types:[312]



When the base is $NaNH_2$ 1-alkynes predominate (where possible), because this base is strong enough to form the salt of the alkyne, shifting any equilibrium between 1- and 2-alkynes. When the base is ^{-}OH or ^{-}OR, the equilibrium tends to be shifted to the internal alkyne, which is thermodynamically more stable. If another hydrogen is suitably located (e.g., $-CRH-CX_2-CH_2-$), allene formation can compete, although alkynes are usually more stable. 1,1,2-Trihalocyclopropanes are converted to alkynes by ring opening reactions.[313]

Dehydrohalogenation is generally carried out in solution, with a base, and the mechanism is usually E2, although the E1 mechanism has been demonstrated in some cases. However, elimination of HX can be accomplished by pyrolysis of the halide, in which case the mechanism is E^i (p. 1507) or, in some instances, the free-radical mechanism (p. 1510). Pyrolysis is normally performed without a catalyst at ~400°C. The pyrolysis reaction is not generally useful synthetically, because of its reversibility. Less work has been done on pyrolysis with a catalyst[314] (usually a metallic oxide or salt), but the mechanisms here are probably E1 or E2.

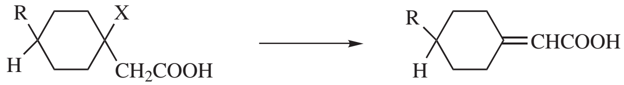
[310]Matsubara, S.; Matsuda, H.; Hamatani, T.; Schlosser, M. *Tetrahedron* ***1988***, *44*, 2855.

[311]For reviews, see Ben-Efraim, D.A. in Patai, S. *The Chemistry of the Carbon-Carbon Triple Bond*, pt. 2, Wiley, NY, ***1978***, p. 755; Köbrich, G.; Buck, P., in Viehe, H. G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 100–134; Franke, W.; Ziegenbein, W.; Meister, H. *Angew. Chem.* ***1960***, *72*, 391, see p. 391; Köbrich, G. *Angew. Chem. Int. Ed.* ***1965***, *4*, 49, see pp. 50–53.

[312]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 569–571.

[313]For a review, see Sydnes, L.K. *Eur. J. Org. Chem.* ***2000***, 3511.

[314]For a review, see Noller, H.; Andréu, P.; Hunger, M. *Angew. Chem. Int. Ed.* ***1971***, *10*, 172.



37

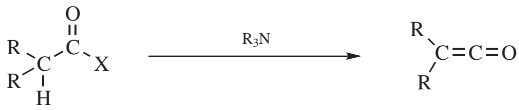
In the special case of the prochiral carboxylic acids **37**, dehydrohalogenation with an optically active lithium amide gave an optically active product with ee as high as 82%.[315]

Other regents lead to dehydrohalogenation. 1,1,1-Trichloro compounds are converted to vinyl chlorides with $CrCl_2$.[316]

OS **I**, 191, 205, 209, 438; **II**, 10, 17, 515; **III**, 125, 209, 270, 350, 506, 623, 731, 785; **IV**, 128, 162, 398, 404, 555, 608, 616, 683, 711, 727, 748, 755, 763, 851, 969; **V**, 285, 467, 514; **VI**, 87, 210, 327, 361, 368, 427, 462, 505, 564, 862, 883, 893, 954, 991, 1037; **VII**, 126, 319, 453, 491; **VIII**, 161, 173, 212, 254; **IX**, 191, 656, 662. Also see, OS **VI**, 968.

17-14 Dehydrohalogenation of Acyl Halides and Sulfonyl Halides

Hydro-halo-elimination



Ketenes can be prepared by treatment of acyl halides with tertiary amines[317] or with NaH and a crown ether.[318] The scope is broad, and most acyl halides possessing an α hydrogen give the reaction, but if at least one R is hydrogen, only the ketene dimer, not the ketene, is isolated. However, if it is desired to use a reactive ketene in a reaction with a given compound, the ketene can be generated *in situ* in the presence of the given compound.[319]

$$RCH_2SO_2Cl \xrightarrow{R_3N} [\,RCH{=}SO_2\,]_{\text{Sulfene}} \longrightarrow RCH{=}CHR \;+\; \text{Other products}$$

Closely related is the reaction of tertiary amines with sulfonyl halides that contain an a hydrogen. In this case, the initial product is the highly reactive sulfene, which cannot be isolated but reacts further to give products, one of which may be the alkene that is the dimer of RCH.[320] Reactions of sulfenes *in situ* are also common (e.g., see **16-48**).

OS **IV**, 560; **V**, 294, 877; **VI**, 549, 1037; **VII**, 232; **VIII**, 82.

[315] Duhamel, L.; Ravard, A.; Plaquevent, J.C.; Plé, G.; Davoust, D. *Bull. Soc. Chim. Fr.* ***1990***, 787.

[316] Baati, R.; Barma, D.K.; Krishna, U.M.; Mioskowski, C.; Falck, J.R. *Tetrahedron Lett.* ***2002***, *43*, 959.

[317] For a monograph on the chemistry of ketenes, see Tidwell, T.T. *Ketenes*, Wiley, NY, ***1995***.

[318] Taggi, A.E.; Wack, H.; Hafez, A.M.; France, S.; Lectka, T. *Org. Lett.* ***2002***, *4*, 627.

[319] For a review of this procedure, see Luknitskii, F.I.; Vovsi, B.A. *Russ. Chem. Rev.* ***1969***, *38*, 487.

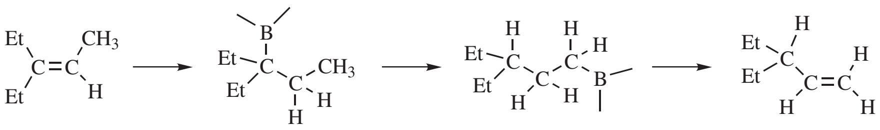
[320] For reviews of sulfenes, see King, J.F. *Acc. Chem. Res.* ***1975***, *8*, 10; Nagai, T.; Tokura, N. *Int. J. Sulfur Chem. Part B* ***1972***, 207; Truce, W.E.; Liu, L.K. *Mech. React. Sulfur Compd.* ***1969***, *4*, 145; Opitz, G. *Angew. Chem. Int. Ed.* ***1967***, *6*, 107; Wallace, T.J. *Q. Rev. Chem. Soc.* ***1966***, *20*, 67.

17-15 Elimination of Boranes

Hydro-boranetriyl-elimination

$$(R_2CH—CH_2)_3B \quad + \quad 3 \text{ 1-Decene} \rightleftharpoons 3\ R_2C{=}CH_2 \quad + \quad [CH_3(CH_2)_8CH_2]_3B$$

Trialkylboranes are formed from an alkene and BH_3 (**15-16**). When the resulting borane is treated with another alkene, an exchange reaction occurs.[321] This is an equilibrium process that can be shifted by using a large excess of alkene, by using an unusually reactive alkene, or by using an alkene with a higher boiling point than the displaced alkene and removing the latter by distillation. The reaction is useful for shifting a double bond in the direction opposite to that resulting from normal isomerization methods (**12-2**). This cannot be accomplished simply by treatment of a borane, such as **39**, with an alkene, because elimination in this reaction follows Zaitsev's rule: It is in the direction of the most stable alkene, and the product would be **38**, not **41**. However, if it is desired to convert **38** to **41**, this can be accomplished by converting **38** to **39**, isomerizing **39** to **40** (**18-11**) and then subjecting **40** to the exchange reaction with a higher boiling alkene (e.g., 1-decene), whereupon **41** is produced. In the usual isomerizations (**12-2**), **41** could be isomerized to **38**, but not the other way around. The reactions **39** → **40** and **40** → **41** proceed essentially without rearrangement. The mechanism is probably the reverse of borane addition (**15-16**).



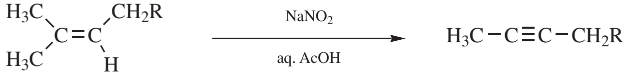
38 **39** **40** **41**

A similar reaction, but irreversible, has been demonstrated for alkynes.[322]

$$(R_2CH—CH_2)_3B \quad + \quad R'C{\equiv}CR' \longrightarrow 3\ R_2C{=}CH_2 \quad + \quad (R'CH{=}CR')_3B$$

17-16 Conversion of Alkenes to Alkynes

Hydro-methyl-elimination



Alkenes of the form shown lose the elements of methane when treated with sodium nitrite in acetic acid and water, to form alkynes in moderate-to-high yields.[323] The R may contain additional unsaturation, as well as OH, OR, OAc,

[321]Brown, H.C.; Bhatt, M.V.; Munekata, T.; Zweifel, G. *J. Am. Chem. Soc.* ***1967***, *89*, 567; Taniguchi, H. *Bull. Chem. Soc. Jpn.* ***1979***, *52*, 2942.

[322]Hubert, A.J. *J. Chem. Soc.* ***1965***, 6669.

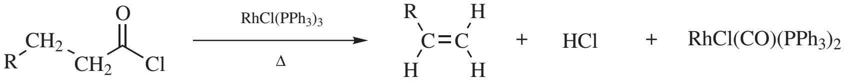
[323]Abidi, S.L. *Tetrahedron Lett.* ***1986***, *27*, 267; *J. Org. Chem.* ***1986***, *51*, 2687.

C=O, and other groups, but the $Me_2C{=}CHCH_2$ portion of the substrate is necessary for the reaction to take place. The mechanism is complex, beginning with a nitration that takes place with allylic rearrangement [$Me_2C{=}CHCH_2R \rightarrow H_2C{=}CMeCH(NO_2)CH_2R$], and involving several additional intermediates.[324] The CH_3 lost from the substrate appears as CO_2, as demonstrated by the trapping of this gas.[324]

1,1-Dibromoalkenes are converted to alkynes when treated with *n*-butyllithium.[325] This transformation is a modification of the *Fritsch–Buttenberg–Wiechell rearrangement*.[326] Vinyl sulfoxides that contain a leaving group, such as chloride on the double bond, react with *tert*-butyllithium to give a lithio alkyne, and hydrolysis leads to the final product, an alkyne.

17-17 Decarbonylation of Acyl Halides

Hydro-chloroformyl-elimination

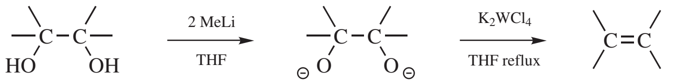


Acyl chlorides containing an a hydrogen are smoothly converted to alkenes, with loss of HCl and CO, on heating with chlorotris(triphenylphosphine)rhodium, with metallic platinum, or with certain other catalysts.[327] The mechanism probably involves conversion of RCH_2CH_2COCl to RCH_2CH_2–$RhCO(Ph_3P)_2Cl_2$ followed by a concerted syn elimination of Rh and H[328] (see also, **14-32** and **19-12**).

B. Reactions in Which Neither Leaving Atom Is Hydrogen

17-18 Deoxygenation of Vicinal Diols

Dihydroxy-elimination



vic-Diols can be deoxygenated by treatment of the dilithium dialkoxide with the tungsten halide (K_2WCl_6), or with certain other tungsten reagents, in refluxing THF.[329] Tetrasubstituted diols react most rapidly. The elimination is largely, but

[324] Corey, E.J.; Seibel, W.L.; Kappos, J.C. *Tetrahedron Lett.* ***1987***, *28*, 4921.

[325] Chernick, E.T.; Eisler, S.; Tykwinski, R.R. *Tetrahedron Lett.* ***2001***, *42*, 8575.

[326] Fritsch, P. *Ann.* ***1894***, *279*, 319; Buttenberg, W.P. *Ann.*, ***1894***, *279*, 324; Wiechell, H. *Ann.* ***1894***, *279*, 337; Stang, P.J.; Fox, D.P.; Collins, C.J.; Watson, Jr., C.R. *J. Org. Chem.* ***1978***, *43*, 364. For a review, see Stang, P.J. *Chem. Rev.* ***1978***, *78*, 383.

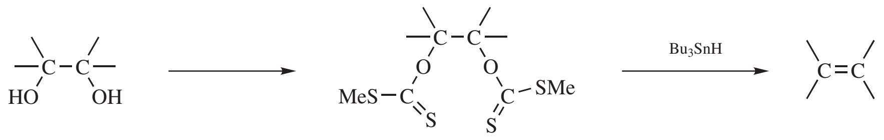
[327] For a review, see Tsuji, J.; Ohno, K. *Synthesis* ***1969***, 157. For extensions to certain other acid derivatives, see Minami, I.; Nisar, M.; Yuhara, M.; Shimizu, I.; Tsuji, J. *Synthesis* ***1987***, 992.

[328] Lau, K.S.Y.; Becker, Y.; Huang, F.; Baenziger, N.; Stille, J.K. *J. Am. Chem. Soc.* ***1977***, *99*, 5664.

[329] Sharpless, K.B.; Flood, T.C. *J. Chem. Soc., Chem. Commun.* ***1972***, 370; Sharpless, K.B.; Umbreit, M.A.; Nieh, T.; Flood, T.C. *J. Am. Chem. Soc.* ***1972***, *94*, 6538.

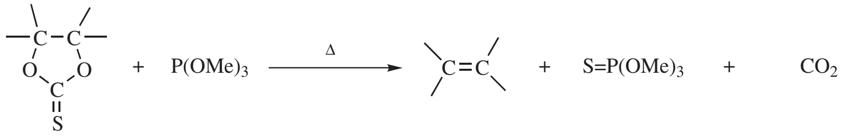
not entirely, syn. Several other methods have been reported,[330] in which the diol is deoxygenated directly, without conversion to the dialkoxide. These include treatment with titanium metal,[331] with TsOH–NaI,[332] and by heating with $CpReO_3$, where Cp is cyclopentadienyl.[333]

vic-Diols can also be deoxygenated indirectly, through sulfonate ester derivatives. For example, *vic*-dimesylates and *vic*-ditosylates have been converted to alkenes by treatment, respectively, with naphthalene-sodium[334] and with NaI in DMF.[335] In another procedure, the diols are converted to bisdithiocarbonates (bis xanthates), which undergo elimination (probably by a free-radical mechanism) when



treated with tri-*n*-butylstannane in toluene or benzene.[336] *vic*-Diols can also be deoxygenated through cyclic derivatives (**17-19**).

17-19 Cleavage of Cyclic Thionocarbonates



42

Cyclic thionocarbonates (**42**) can be cleaved to alkenes (the *Corey–Winter reaction*)[337] by heating with trimethyl phosphite[338] or other trivalent phosphorus compounds[339] or by treatment with bis(1,5-cyclooctadiene)nickel.[340] The

[330]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 297–299.

[331]McMurry, J.E. *Acc. Chem. Res.* ***1983***, *16*, 405, and references cited therein.

[332]Sarma, J.C.; Sharma, R.P. *Chem. Ind. (London)* ***1987***, 96.

[333]Cook, G.K.; Andrews, M.A. *J. Am. Chem. Soc.* ***1996***, *118*, 9448.

[334]Carnahan Jr., J.C.; Closson, W.D. *Tetrahedron Lett.* ***1972***, 3447.

[335]Dafaye, J. *Bull. Soc. Chim. Fr.* ***1968***, 2099.

[336]Barrett, A.G.M.; Barton, D.H.R.; Bielski, R. *J. Chem. Soc. Perkin Trans. 1* ***1979***, 2378.

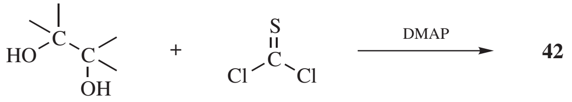
[337]For reviews, see Block, E. *Org. React.* ***1984***, *30*, 457; Sonnet, P.E. *Tetrahedron* ***1980***, *36*, 557, 593–598; Mackie, R.K., in Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, ***1979***, pp. 354–359.

[338]Corey, E.J.; Winter, R.A.E. *J. Am. Chem. Soc.* ***1963***, *85*, 2677.

[339]Corey, E.J. *Pure Appl. Chem.* ***1967***, *14*, 19, see pp. 32–33.

[340]Semmelhack, M.F.; Stauffer, R.D. *Tetrahedron Lett.* ***1973***, 2667. For another method, see Vedejs, E.; Wu, E.S.C. *J. Org. Chem.* ***1974***, *39*, 3641.

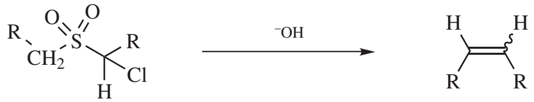
thionocarbonates can be prepared by treatment of 1,2-diols with thiophosgene and 4-dimethylaminopyridine (DMAP):[341]



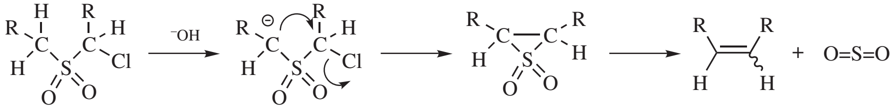
The elimination is of course syn, so the product is sterically controlled. Alkenes that are not sterically favored can be made this way in high yield, (e.g., *cis*-$PhCH_2CH{=}CHCH_2Ph$).[342] Certain other five-membered cyclic derivatives of 1,2-diols can also be converted to alkenes.[343]

17-20 The Ramberg–Bäcklund Reaction

Ramberg–Bäcklund halosulfone transformation



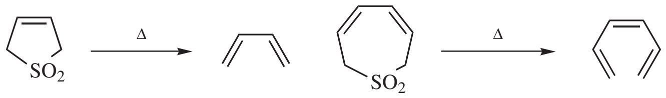
The reaction of an α-halo sulfone with a base to give an alkene is called the *Ramberg–Bäcklund reaction*.[344] The reaction is quite general for α-halo sulfones with an α' hydrogen, despite the unreactive nature of α-halo sulfones in normal S_N2 reactions (p. 486). Halogen reactivity is in the order I > Br ≫ Cl. Phase-transfer catalysis has been used.[345] In general, mixtures of cis and trans isomers are obtained, but usually the less stable cis isomer predominates. The mechanism involves formation of an episulfone, and then elimination of SO_2. There is much



[341]Corey, E.J.; Hopkins, P.B. *Tetrahedron Lett.* ***1982***, *23*, 1979.
[342]Corey, E.J.; Carey, F.A.; Winter, R.A.E. *J. Am. Chem. Soc.* ***1965***, *87*, 934.
[343]See Hines, J.N.; Peagram, M.J.; Whitham, G.H.; Wright, M. *Chem. Commun.* ***1968***, 1593; Josan, J.S.; Eastwood, F.W. *Aust. J. Chem.* ***1968***, *21*, 2013; Hiyama, T.; Nozaki, H. *Bull. Chem. Soc. Jpn.* ***1973***, *46*, 2248; Marshall, J.A.; Lewellyn, M.E. *J. Org. Chem.* ***1977***, *42*, 1311; Breuer, E.; Bannet, D.M. *Tetrahedron* ***1978***, *34*, 997; Hanessian, S.; Bargiotti, A.; LaRue, M. *Tetrahedron Lett.* ***1978***, 737; Hatanaka, K.; Tanimoto, S.; Oida, T.; Okano, M. *Tetrahedron Lett.* ***1981***, *22*, 5195; Ando, M.; Ohhara, H.; Takase, K. *Chem. Lett.* ***1986*** 879; King, J.L.; Posner, B.A.; Mak, K.T.; Yang, N.C. *Tetrahedron Lett.* ***1987***, *28*, 3919; Beels, C.M.D.; Coleman, M.J.; Taylor, R.J.K. *Synlett* ***1990***, 479.
[344]For reviews, see Paquette, L.A. *Org. React.* ***1977***, *25*, 1; *Mech. Mol. Migr.* ***1968***, *1*, 121; *Acc. Chem. Res.* ***1968***, *1*, 209; Meyers, C.Y.; Matthews, W.S.; Ho, L.L.; Kolb, V.M.; Parady, T.E., in Smith, G.V. *Catalysis in Organic Synthesis*, Academic Press, NY, ***1977***, pp. 197–278; Rappe, C., in Patai, S. *The Chemistry of the Carbon-Halogen Bond*, pt. 2, Wiley, NY, ***1973***, pp. 1105–1110; Bordwell, F.G. *Acc. Chem. Res.* ***1970***, *3*, 281, pp. 285–286; in Janssen, M.J. *Organosulfur Chemistry*, Wiley, NY, ***1967***, pp. 271–284.
[345]Hartman, G.D.; Hartman, R.D. *Synthesis* ***1982***, 504.

evidence for this mechanism,[346] including the isolation of the episulfone intermediate,[347] and the preparation of episulfones in other ways and the demonstration that they give alkenes under the reaction conditions faster than the corresponding α-halo sulfones.[348] Episulfones synthesized in other ways (e.g., **16-48**) are reasonably stable compounds, but eliminate SO_2 to give alkenes when heated or treated with base.

If the reaction is run on the unsaturated bromo sulfones $RCH_2CH{=}CHSO_2CH_2Br$ (prepared by reaction of $BrCH_2SO_2Br$ with $RCH_2CH{=}CH_2$ followed by treatment with Et_3N), the dienes $RCH{=}CHCH{=}CH_2$ are produced in moderate-to-good yields.[349] The compound mesyltriflone $CF_3SO_2CH_2SO_2CH_3$ can be used as a synthon for the tetraion $^{2-}C{=}C^{2-}$. Successive alkylation (**10-67**) converts it to $CF_3SO_2CR^1R^2SO_2CHR^3R^4$ (anywhere from one to four alkyl groups can be put in), which, when treated with base, gives $R^1R^2C{=}CR^3R^4$.[350] The nucleofuge here is the $CF_3SO_2^-$ ion.



43 **44**

2,5-Dihydrothiophene-1,1-dioxides (**43**) and 2,17-dihydrothiepin-1,1-dioxides (**44**) undergo analogous 1,4- and 1,6-eliminations, respectively (see also, **17-36**). These are concerted reactions and, as predicted by the orbital-symmetry rules (p. 1207), the former[351] is a suprafacial process and the latter[352] an antarafacial process. The rules also predict that elimination of SO_2 from episulfones cannot take place by a concerted mechanism (except antarafacially, which is unlikely for such a small ring), and the evidence shows that this reaction occurs by a nonconcerted pathway.[353] The eliminations of SO_2 from **43** and **44** are examples of *cheletropic reactions*,[354] which are defined as reactions in which two σ bonds that terminate

[346]See, for example, Paquette, L.A. *J. Am. Chem. Soc.* ***1964***, *86*, 4089; Neureiter, N.P. *J. Am. Chem. Soc.* ***1966***, *88*, 558; Bordwell, F.G.; Wolfinger, M.D. *J. Org. Chem.* ***1974***, *39*, 2521; Bordwell, F.G.; Doomes, E. *J. Org. Chem.* ***1974***, *39*, 2526, 2531.

[347]Sutherland, A.G.; Taylor, R.J.K. *Tetrahedron Lett.* ***1989***, *30*, 3267.

[348]Bordwell, F.G.; Williams Jr., J.M.; Hoyt, Jr., E.B.; Jarvis, B.B. *J. Am. Chem. Soc.* ***1968***, *90*, 429; Bordwell, F.G.; Williams, Jr., J.M. *J. Am. Chem. Soc.* ***1968***, *90*, 435.

[349]Block, E.; Aslam, M.; Eswarakrishnan, V.; Gebreyes, K.; Hutchinson, J.; Iyer, R.; Laffitte, J.; Wall, A. *J. Am. Chem. Soc.* ***1986***, *108*, 4568.

[350]Hendrickson, J.B.; Boudreaux, G.J.; Palumbo, P.S. *J. Am. Chem. Soc.* ***1986***, *108*, 2358.

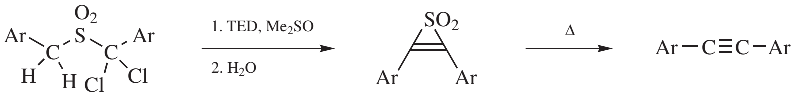
[351]Mock, W.L. *J. Am. Chem. Soc.* ***1966***, *88*, 2857; McGregor, S.D.; Lemal, D.M. *J. Am. Chem. Soc.* ***1966***, *88*, 2858.

[352]Mock, W.L. *J. Am. Chem. Soc.* ***1969***, *91*, 5682.

[353]Bordwell, F.G.; Williams, Jr., J.M.; Hoyt, Jr., E.B.; Jarvis, B.B. *J. Am. Chem. Soc.* ***1968***, *90*, 429; Bordwell, F.G.; Williams Jr., J.M. *J. Am. Chem. Soc.* ***1968***, *90*, 435. See also, Vilsmaier, E.; Tropitzsch, R.; Vostrowsky, O. *Tetrahedron Lett.* ***1974***, 3987.

[354]For a review, see Mock, W.L., in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, ***1977***, pp. 141–179.

at a single atom (in this case the sulfur atom) are made or broken in concert.[355]



45 **46** **47**

α,α-Dichlorobenzyl sulfones (**45**) react with an excess of the base triethylenediamine (TED) in DMSO at room temperature to give 2,3-diarylthiiren-1,1-dioxides (**46**), which can be isolated.[356] Thermal decomposition of **46** gives the alkynes **47**.[357]

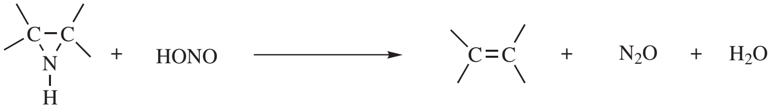
A Ramberg–Bäcklund-type reaction has been carried out on the α-halo *sulfides* ($ArCHClSCH_2Ar$), which react with *t*-BuOK and PPh_3 in refluxing THF to give the alkenes (ArCH=CHAr).[358] Cyclic sulfides lead to ring-contracted cyclic alkenes upon treatment with NCS in CCl_4 followed by oxidation with *m*-chloroperoxybenzoic acid.[359]

The Ramberg–Bäcklund reaction can be regarded as a type of extrusion reaction (see p. 1553).

OS **V**, 877; **VI**, 454, 555; **VIII**, 212.

17-21 The Conversion of Aziridines to Alkenes

epi-Imino-elimination



Aziridines not substituted on the nitrogen atom react with nitrous acid to produce alkenes.[360] An *N*-nitroso compound is an intermediate (**12-50**); other reagents that produce such intermediates also give alkenes. The reaction is stereospecific: cis aziridines give cis alkenes and trans aziridines give trans alkenes.[361] Aziridines carrying *N*-alkyl substituents can be converted to alkenes by treatment with ferrous iodide[362] or with *m*-chloroperoxybenzoic acid.[363] An *N*-oxide intermediate

[355]Woodward, R.B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Academic Press, NY, ***1970***, pp. 152–163.

[356]Philips, J.C.; Swisher, J.V.; Haidukewych, D.; Morales, O. *Chem. Commun.* ***1971***, 22.

[357]Carpino, L.A.; McAdams, L.V.; Rynbrandt, R.H.; Spiewak, J.W. *J. Am. Chem. Soc.* ***1971***, *93*, 476; Philips, J.C.; Morales, O. *J. Chem. Soc., Chem. Commun.* ***1977***, 713.

[358]Mitchell, R.H. *Tetrahedron Lett.* ***1973***, 4395. For a similar reaction without base treatment, see Pommelet, J.; Nyns, C.; Lahousse, F.; Merényi, R.; Viehe, H.G. *Angew. Chem. Int. Ed.* ***1981***, *20*, 585.

[359]MacGee, D.I.; Beck, E.J. *J. Org. Chem.* ***2000***, *65*, 8367.

[360]For reviews, see Sonnet, P.E. *Tetrahedron* ***1980***, *36*, 557, see p. 591; Dermer, O.C.; Ham, G.E. *Ethylenimine and other Aziridines*, Academic Press, NY, ***1969***, pp. 293–295.

[361]Clark, R.D.; Helmkamp, G.K. *J. Org. Chem.* ***1964***, *29*, 1316; Carlson, R.M.; Lee, S.Y. *Tetrahedron Lett.* ***1969***, 4001.

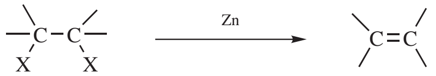
[362]Imamoto, T.; Yukawa, Y. *Chem. Lett.* ***1974***, 165.

[363]Heine, H.W.; Myers, J.D.; Peltzer III, E.T. *Angew. Chem. Int. Ed.* ***1970***, *9*, 374.

(**19-29**) is presumably involved in the latter case. *N*-Tosyl aziridines are converted to *N*-tosyl imines when treated with boron trifluoride.[364] 2-Tosylmethyl *N*-tosylaziridines react with Te^{2-} in the presence of Adogen 464 to give allylic *N*-tosyl amines.[365] 2-Halomethyl *N*-tosyl aziridines also react with indium metal in methanol to give *N*-tosyl allylic amines.[366]

17-22 Elimination of Vicinal Dihalides

Dihalo-elimination



Dehalogenation has been accomplished with many reagents, the most common being zinc, magnesium, and iodide ion.[367] Heating in HMPA is often enough to convert a *vic*-dibromide to an alkene.[368] Among reagents used less frequently have been phenyllithium, phenylhydrazine, $CrCl_2$, Na_2S in DMF,[369] and $LiAlH_4$.[370] Electrochemical reduction has also been used.[371] Treatment with In[372] or Sm[373] metal in CH_3OH, $InCl_3/NaBH_4$,[374] a Grignard reagent and Ni(dppe)Cl_2, (dppe = 1, 2-diphenylphosphinoethane),[375] nickel compounds with Bu_3SnH,[376] or SmI_2[377] leads to the alkene. Although the reaction usually gives good yields, it is not very useful because the best way to prepare *vic*-dihalides is by the addition of halogen to a double bond (**15-39**). One useful feature of this reaction is that there is no doubt about the *position* of the new double bond, so that it can be used to give double bonds exactly where they are wanted. For example, allenes, which are not easily prepared by other methods, can be prepared from X–C–CX_2–C–X or X–C–CX=C– systems.[378] Cumulenes

[364]Sugihara, Y.; Iimura, S.; Nakayama, J. *Chem. Commun.* ***2002***, 134.

[365]Chao, B.; Dittmer, D.C. *Tetrahedron Lett.* ***2001***, *42*, 5789.

[366]Yadav, J.S.; Bandyapadhyay, A.; Reddy, B.V.S. *Synlett* ***2001***, 1608.

[367]For a review of this reaction, see Baciocchi, E., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement D*, pt. 1, Wiley, NY, ***1983***, pp. 161–201. Also see, Bosser, G.; Paris, J. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 2057.

[368]Khurana, J.M.; Bansal, G.; Chauhan, S. *Bull. Chem. Soc. Jpn.* ***2001***, *74*, 1089.

[369]Fukunaga, K.; Yamaguchi, H. *Synthesis* ***1981***, 879. See also, Nakayama, J.; Machida, H.; Hoshino, M. *Tetrahedron Lett.* ***1983***, *24* 3001; Landini, D.; Milesi, L.; Quadri, M.L.; Rolla, F. *J. Org. Chem.* ***1984***, *49*, 152.

[370]For a lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 259–263.

[371]See Shono, T. *Electroorganic Chemistry as a New Tool in Organic Synthesis*, Springer, NY, ***1984***, pp. 145–147; Fry, A.J. *Synthetic Organic Electrochemistry*, 2nd ed., Wiley, NY, ***1989***, pp. 151–154.

[372]Ranu, B.C.; Guchhait, S.K.; Sarkar, A. *Chem. Commun.* ***1998***, 2113.

[373]Yanada, R.; Negoro, N.; Yanada, K.; Fujita, T. *Tetrahedron Lett.* ***1996***, *37*, 9313.

[374]Ranu, B.C.; Das, A.; Hajra, A. *Synthesis* ***2003***, 1012.

[375]Malanga, C.; Aronica, L.A.; Lardicci, L. *Tetrahedron Lett.* ***1995***, *36*, 9189.

[376]Malanga, C.; Mannucci, S.; Lardicci, L. *Tetrahedron* ***1998***, *54*, 1021.

[377]Yanada, R.; Bessho, K.; Yanada, K. *Chem. Lett*, ***1994***, 1279.

[378]For reviews of allene formation, see Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis*, Wiley, NY, ***1984***, pp. 9–56; Landor, P.D., in Landor, S.R. *The Chemistry of the Allenes*, Vol. 1, Academic Press, NY, ***1982***; pp. 19–233; Taylor, D.R. *Chem. Rev.* ***1967***, *67*, 317.

have been obtained from 1,4-elimination:

$$BrCH2{-}C{\equiv}C{-}CH_2Br \quad + \quad Zn \longrightarrow CH_2{=}C{=}C{=}CH_2$$

Cumulenes have also been prepared by treating alkynyl epoxides with boron trifluoride.[379] 1,4-Elimination of BrC–C=C–CBr has been used to prepare conjugated dienes C=C–C=C.[380] Allenes are formed by heating propargylic alcohols with arylboronic acids (p. 815) and a palladium catalyst.[381] Allenes are also formed from propargylic amines using a CuI and a palladium catalyst.[382]

The reaction of a vicinal dibromide with triethylamine and DMF with microwave irradiation leads to vinyl bromide.[383] Alkenes are formed from vicinal bromides by heating with iron in methanol[384] or samarium in the presence of TMSCl and a trace of water.[385] α,β-Dibromo amides are converted to conjugated amides upon photolysis in methanol.[386]

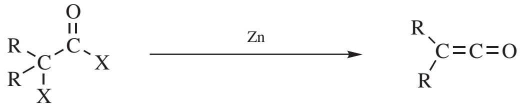
The reaction can be carried out for any combination of halogens, except where one is fluorine. Mechanisms are often complex and depend on the reagent and reaction conditions.[387] For different reagents, mechanisms involving carbocations, carbanions, and free-radical intermediates, as well as concerted mechanisms, have been proposed. When the reagent is zinc, anti stereospecificity has been observed in some cases,[388] but not in others.[389]

Note that geminal dibromo cyclopropanes (1,1-dibromocyclopropanes) are opened to conjugated dienes by heating to 500°C.[390]

OS **III**, 526, 531; **IV**, 195, 268; **V**, 22, 255, 393, 901; **VI**, 310, **VII**, 241. Also see, OS **IV**, 877, 914, 964.

17-23 Dehalogenation of α-Halo Acyl Halides

Dihalo-elimination



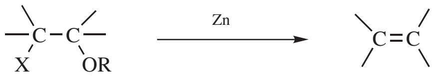
[379]Wang, X.; Ramos, B.; Rodriguez, A. *Tetrahedron Lett.* ***1994***, *35*, 6977.
[380]Engman, L.; Byström, S.E. *J. Org. Chem.* ***1985***, *50*, 3170.
[381]Yoshida, M.; Gotou, T.; Ihara, M. *Tetrahedron Lett.* ***2004***, *45*, 5573.
[382]Nakmura, H.; Kamakura, T.; Ishikura, M.; Biellmann, J.-F. *J. Am. Chem. Soc.* ***2004***, *126*, 5958.
[383]Kuang, C.; Senboku, H.; Tokuda, M. *Tetrahedron Lett.* ***2001***, *42*, 3893.
[384]Thakur, A.J.; Boruah, A.; Baruah, B.; Sandhu, J.S. *Synth. Commun.* ***2000***, *30*, 157.
[385]Xu, X.; Lu, P.; Zhang, Y. *Synth. Commun.* ***2000***, *30*, 1917.
[386]Aruna, S.; Kalyanakumar, R.; Ramakrishnan, V.T. *Synth. Commun.* ***2001***, *31*, 3125.
[387]For discussion, see Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***, pp. 332–368; Baciocchi, W., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Grups, Supplement D*, pt. 2, Wiley, NY, ***1983***, p. 161.
[388]For example, see House, H.O.; Ro, R.S. *J. Am. Chem. Soc.* ***1958***, *80*, 182; Gordon, M.; Hay, J.V. *J. Org. Chem.* ***1968***, *33*, 427.
[389]For example, see Stevens, C.L.; Valicenti, J.A. *J. Am. Chem. Soc.* ***1965***, *87*, 838; Sicher, J.; Havel, M.; Svoboda, M. *Tetrahedron Lett.* ***1968***, 4269.
[390]Werstiuk, N.H.; Roy, C.D. *Tetrahedron Lett.* ***2001***, *42*, 3255.

Ketenes can be prepared by dehalogenation of α-halo acyl halides with zinc or with triphenylphosphine.[391] The reaction generally gives good results when the two R groups are aryl or alkyl, but not when either one is hydrogen.[392]

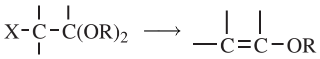
OS **IV**, 348; **VIII**, 377.

17-24 Elimination of a Halogen and a Hetero Group

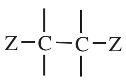
Alkoxy-halo-elimination



The elimination of OR and halogen from β-halo ethers is called the *Boord reaction*. It can be carried out with zinc, magnesium, sodium, or certain other reagents.[393] The yields are high and the reaction is of broad scope. β-Halo acetals readily yield vinylic ethers



and 2 equivalents of SmI_2 in HMPA is effective.[394] Besides β-halo ethers, the reaction can also be carried out on compounds of the formula



where X is halogen and Z is OCOR, OTs,[395] NR_2,[396] or SR.[397] When X = Cl and Z = OAc, heating in THF with an excess of SmI_2 followed by treatment with dilute aq. HCl gives an alkene.[398] When Z = I and the other Z is an oxygen of an oxazolone (a carbamate unit), heating with indium metal in methanol leads to an allylic amine.[399] The Z group may also be OH, but then X is limited to Br and I.[400] Like **17-22**, this method ensures that the new double bond will be in a specific position.

[391]Darling, S.D.; Kidwell, R.L. *J. Org. Chem.* ***1968***, *33*, 3974.

[392]For a procedure that gives 60–65% yields when one R = H, see McCarney, C.C.; Ward, R.S. *J. Chem. Soc. Perkin Trans. 1* ***1975***, 1600. See also, Masters, A.P.; Sorensen, T.S.; Ziegler, T. *J. Org. Chem.* ***1986***, *51*, 3558.

[393]See Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 263–267, for reagents that produce olefins from β-halo ethers and esters, and from halohydrins.

[394]Park, H.S.; Kim, S.H.; Park, M.Y.; Kim, Y.H. *Tetrahedron Lett.* ***2001***, *42*, 3729.

[395]Cristol, S.J.; Rademacher, L.E. *J. Am. Chem. Soc.* ***1959***, *81*, 1600; Reeve, W.; Brown, R.; Steckel, T.F. *J. Am. Chem. Soc.* ***1971***, *93*, 4607.

[396]Gurien, H. *J. Org. Chem.* ***1963***, *28*, 878.

[397]Amstutz, E.D. *J. Org. Chem.* ***1944***, *9*, 310.

[398]Concellón, J.M.; Bernad, P.L.; Bardales, E. *Org. Lett.* ***2001***, *3*, 937.

[399]Yadav, J.S.; Bandyopadhyay, A.; Reddy, B.V.S. *Tetrahedron Lett.* ***2001***, *42*, 6385.

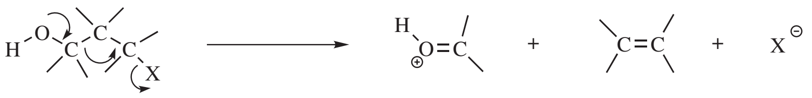
[400]Concellón, J.M.; Pérez-Andrés, J.A.; Rodríguez-Solla, H. *Chem. Eur. J.* ***2001***, *7*, 3062.

The fact that magnesium causes elimination in these cases limits the preparation of Grignard reagents from these compounds. It has been shown that treatment of β-halo ethers and esters with zinc gives nonstereospecific elimination,[401] so the mechanism was not E2. An E1cB mechanism was postulated because of the poor leaving-group ability of OR and OCOR. Bromohydrins can be converted to alkenes (elimination of Br, OH) in high yields by treatment with $LiAlH_4$–$TiCl_3$.[402]

OS **III**, 698, **IV**, 748; **VI**, 675.

FRAGMENTATIONS

When carbon is the positive leaving group (the electrofuge) in an elimination, the reaction is called *fragmentation*.[403] These processes occur on substrates of the form W–C–C–X, where X is a normal nucleofuge (e.g., halogen, OH_2^+, OTs, NR_3^+) and W is a positive-carbon electrofuge. In most of the cases, W is HO–C– or R_2N–C–, so that the positive charge on the carbon atom is stabilized by the unshared pair of the oxygen or nitrogen, for example,

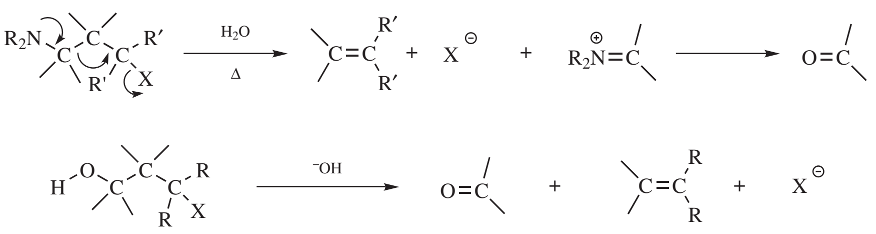


The mechanisms are mostly E1 or E2. We will discuss only a few fragmentations, since many are possible and not much work has been done on most of them. Reactions **17-25–17-28** and **17-30** may be considered fragmentations (see also **19-12** and **19-13**).

17-25 1,3-Fragmentation of γ-Amino, γ-Hydroxy Halides, and 1,3-Diols

Dialkylaminoalkyl-halo-elimination, and so on

Hydroxyalkyl-hydroxy-elimination

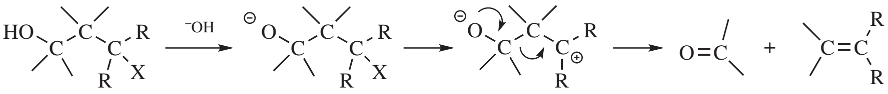


[401]House, H.O.; Ro, R.S. *J. Am. Chem. Soc.* ***1965***, *87*, 838.

[402]McMurry, J.E.; Hoz, T. *J. Org. Chem.* ***1975***, *40*, 3797.

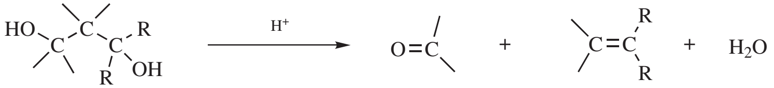
[403]For reviews, see Becker, K.B.; Grob, C.A., in Patai, S. *The Chemistry of Functional Groups, Supplement A*, pt. 2, Wiley, NY, ***1977***, pp. 653–723; Grob, C.A. *Angew. Chem. Int. Ed.* ***1969***, *8*, 535; Grob, C.A.; Schiess, P.W. *Angew. Chem. Int. Ed.* ***1967***, *6*, 1.

γ-Dialkylamino halides undergo fragmentation when heated with water to give an alkene and an iminium salt, which under the reaction conditions is hydrolyzed to an aldehyde or ketone (**16-2**).[404] γ-Hydroxy halides and tosylates are fragmented with base. In this instance, the base does not play its usual role in elimination reactions, but instead serves to remove a proton from the OH group, which enables the carbon leaving group to come off more easily:



The mechanism of these reactions is often E1. However, in at least some cases, an E2 mechanism operates.[405] It has been shown that stereoisomers of cyclic γ-amino halides and tosylates in which the two leaving groups can assume an antiperiplanar conformation react by the E2 mechanism, while those isomers in which the groups cannot assume such a conformation either fragment by the E1 mechanism or do not undergo fragmentation at all, but in either case give rise to side products characteristic of carbocations.[406]

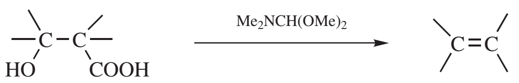
γ-Dialkylamino alcohols do not give fragmentation, since for ionization the OH group must be converted to OH_2^+ and this would convert NR_2 to NR_2H^+, which does not have the unshared pair necessary to form the double bond with the carbon.[407]



1,3-Diols in which at least one OH group is tertiary or is located on a carbon with aryl substituents can be cleaved by acid treatment.[408] The reaction is most useful synthetically when at least one of the OH groups is on a ring.[409]

17-26 Decarboxylation of β-Hydroxy Carboxylic Acids and of β-Lactones

Carboxy-hydroxy-elimination



An OH and a COOH group can be eliminated from β-hydroxy carboxylic acids by refluxing with excess dimethylformamide dimethyl acetal.[410] Mono-, di-, tri-, and tetrasubstituted alkenes have been prepared by this method in good yields.[411]

[404]Grob, C.A.; Ostermayer, F.; Raudenbusch, W. *Helv. Chim. Acta* ***1962***, *45*, 1672.

[405]Fischer, W.; Grob, C.A. *Helv. Chim. Acta* ***1978***, *61*, 2336, and references cited therein.

[406]Geisel, M.; Grob, C.A.; Wohl, R.A. *Helv. Chim. Acta* ***1969***, *52*, 2206, and references cited therein.

[407]Grob, C.A.; Hoegerle, R.M.; Ohta, M. *Helv. Chim. Acta* ***1962***, *45*, 1823.

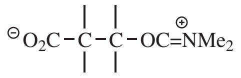
[408]Zimmerman, H.E.; English, Jr., J. *J. Am. Chem. Soc.* ***1954***, *76*, 2285, 2291, 2294.

[409]For a review of such cases, see Caine, D. *Org. Prep. Proced. Int.* ***1988***, *20*, 1.

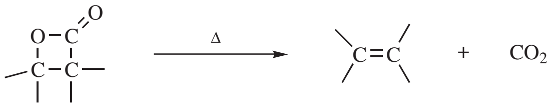
[410]Hara, S.; Taguchi, H.; Yamamoto, H.; Nozaki, H. *Tetrahedron Lett.* ***1975***, 1545.

[411]For a 1,4 example of this reaction, see Rüttimann, A.; Wick, A.; Eschenmoser, A. *Helv. Chim. Acta* ***1975***, *58*, 1450.

There is evidence that the mechanism involves E1 or E2 elimination from the zwitterionic intermediate[412]



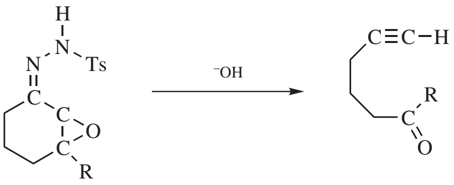
The reaction has also been accomplished[413] under extremely mild conditions (a few seconds at 0°C) with PPh_3 and diethyl azodicarboxylate EtOOC–N=N–COOEt.[414] In a related procedure, β-lactones undergo thermal decarboxylation to give alkenes in high yields. The reaction has been shown to be a stereospecific syn-elimination.[415] There is evidence that this reaction also involves a zwitterionic intermediate.[416]



There are no OS references, but see OS **VII**, 172, for a related reaction.

17-27 Fragmentation of α,β-Epoxy Hydrazones

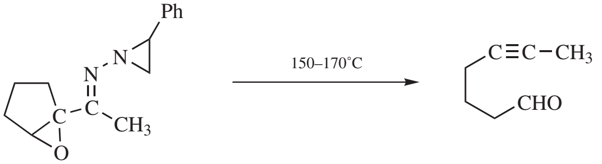
Eschenmoser–Tanabe ring cleavage



Cyclic α,β-unsaturated ketones[417] can be cleaved by treatment with base of their epoxy tosylhydrazone derivatives to give acetylenic ketones.[418] The reaction can be applied to the formation of acetylenic aldehydes (R = H) by using the

[412]Mulzer, J.; Brüntrup, G. *Tetrahedron Lett.* ***1979***, 1909.
[413]For another method, see Tanzawa, T.; Schwartz, J. *Organometallics* ***1990***, *9*, 3026.
[414]Mulzer, J.; Brüntrup, G. *Angew. Chem. Int. Ed.* ***1977***, *16*, 255; Mulzer, J.; Lammer, O. *Angew. Chem. Int. Ed.* ***1983***, *22*, 628.
[415]Noyce, D.S.; Banitt, E.H. *J. Org. Chem.* ***1966***, *31*, 4043; Adam, W.; Baeza, J.; Liu, J. *J. Am. Chem. Soc.* ***1972***, *94*, 2000; Krapcho, A.P.; Jahngen, Jr., E.G.E. *J. Org. Chem.* ***1974***, *39*, 1322, 1650; Mageswaran, S.; Sultanbawa, M.U.S. *J. Chem. Soc. Perkin Trans. 1* ***1976***, 884; Adam, W.; Martinez, G.; Thompson, J.; Yany, F. *J. Org. Chem.* ***1981***, *46*, 3359.
[416]Mulzer, J.; Zippel, M.; Brüntrup, G. *Angew. Chem. Int. Ed.* ***1980***, *19*, 465; Mulzer, J.; Zippel, M. *Tetrahedron Lett.* ***1980***, *21*, 751. See also, Moyano, A.; Pericàs, M.A.; Valentí, E. *J. Org. Chem.* ***1989***, 573.
[417]For other methods of fragmentation of an α,β-epoxy ketone derivatives, see MacAlpine, G.A.; Warkentin, J. *Can. J. Chem.* ***1978***, *56*, 308, and references cited therein.
[418]Eschenmoser, A.; Felix, D.; Ohloff, G. *Helv. Chim. Acta* ***1967***, *50*, 708; Tanabe, M.; Crowe, D.F.; Dehn, R.L.; Detre, G. *Tetrahedron Lett.* ***1967***, 3739; Tanabe, M.; Crowe, D.F.; Dehn, R.L. *Tetrahedron Lett.* ***1967***, 3943.

corresponding, 2,4-dinitro-tosylhydrazone derivatives.[419] Hydrazones (e.g., **48**) prepared from epoxy ketones and ring-substituted *N*-aminoaziridines undergo similar fragmentation when heated.[420]

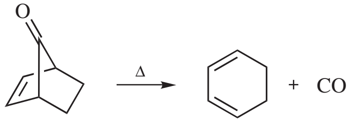


48

OS **VI**, 679.

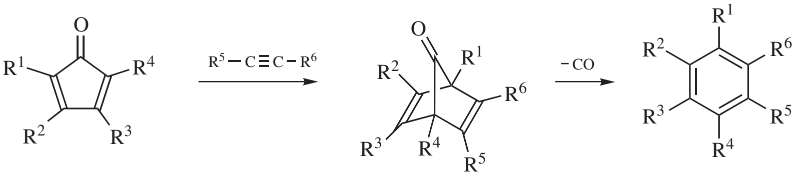
17-28 Elimination of CO and CO_2 from Bridged Bicyclic Compounds

***seco*-Carbonyl-1/4/elimination**



49

On heating, bicyclo[2.2.1]hept-2,3-en-17-ones (**49**) usually lose CO to give cyclohexadienes,[421] in a type of reverse Diels–Alder reaction. Bicyclo[2.2.1]hepta-dienones (**50**) undergo the reaction so readily (because of the



50

stability of the benzene ring produced) that they cannot generally be isolated. The parent **50** has been obtained at 10–15°K in an Ar matrix, where its spectrum could be studied.[422] Both **49** and **50** can be prepared by Diels–Alder reactions between a cyclopentadienone and an alkyne or alkene, so that this reaction is a useful method for the preparation of specifically substituted benzene rings and cyclohexadienes.[423]

[419]Corey, E.J.; Sachdev, H.S. *J. Org. Chem.* ***1975***, *40*, 579.

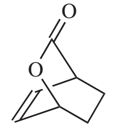
[420]Felix, D.; Müller, R.K.; Horn, U.; Joos, R.; Schreiber, J.; Eschenmoser, A. *Helv. Chim. Acta* ***1972***, *55*, 1276.

[421]For a review, see Stark, B.P.; Duke, A.J. *Extrusion Reactions*, Pergamon, Elmsford, NY, ***1967***, pp. 16–46.

[422]LeBlanc, B.F.; Sheridan, R.S. *J. Am. Chem. Soc.* ***1985***, *107*, 4554; Birney, D.M.; Wiberg, K.B.; Berson, J.A. *J. Am. Chem. Soc.* ***1988***, *110*, 6631.

[423]For a review with many examples; see Ogliaruso, M.A.; Romanelli, M.G.; Becker, E.I. *Chem. Rev.* ***1965***, *65*, 261, 300–348. For references to this and related reactions, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 207–213.

Unsaturated bicyclic lactones of the type **51** can also undergo the reaction, losing CO_2 (see also **17-35**).



51

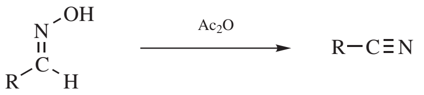
OS **III**, 807; **V**, 604, 1037.

Reversal of the Diels–Alder reaction may be considered a fragmentation (see **15-50**).

REACTIONS IN WHICH C≡N OR C=N BONDS ARE FORMED

17-29 Dehydration of Oximes and Similar Compounds

***C*-Hydro-*N*-hydroxy-elimination; *C*-Acyl-*N*-hydroxy-elimination**



Aldoximes can be dehydrated to nitriles[424] by many dehydrating agents, of which acetic anhydride is the most common. Among reagents that are effective under mild conditions[425] (room temperature) are $Ph_3P–CCl_4$,[426] SeO_2,[427] Me_2t-BuSiCl/imidazole,[428] ferric sulfate,[429] $SOCl_2$/benzotriazole,[430] $TiCl_3$(OTf),[431] CS_2, and Amberlyst A26 ($^-$OH),[432] Montmorillonite KSF clay,[433] (*S,S*)-dimethyl dithiocarbonates,[434] and chloromethylene dimethylammonium chloride $Me_2N=CHCl^+\ Cl^-$.[435] Heating an oxime with a ruthenium catalyst gives the nitrile.[436] Heating with the *Burgess reagent* [$Et_3N^+\ {}^-SO_2N–CO_2Me$] in polyethylene glycol

[424]For reviews, see Friedrich, K., in Patai, S.; Rappoport, Z. *The Chemistry of the Carbon–Carbon Triple Bond*, pt. 2, Wiley, NY, ***1978***, pp. 1345–1390; Friedrich, K.; Wallenfels, K., in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 92–96. For a review of methods of synthesizing nitriles, see Fatiadi, K., in Friedrich, K. in Patai, S.; Rappoport, Z. *The Chemistry of the Carbon–Carbon Triple Bond*, pt. 2, Wiley, NY, ***1978***, pp. 1057–1303.

[425]For lists of some other reagents, with references, see Molina, P.; Alajarin, M.; Vilaplana, M.J. *Synthesis* ***1982***, 1016; Attanasi, O.; Palma, P.; Serra-Zanetti, F. *Synthesis* ***1983***, 741; Jurš ić, B. *Synth. Commun.* ***1989***, *19*, 689.

[426]Kim, J.N.; Chung, K.H.; Ryu, E.K. *Synth. Commun.* ***1990***, *20*, 2785.

[427]Shinozaki, H.; Imaizumi, M.; Tajima, M. *Chem. Lett.* ***1983***, 929.

[428]Ortiz-Marciales, M.; Piñero, L.; Ufret, L.; Algarín, W.; Morales, J. *Synth. Commun.* ***1998***, *28*, 2807.

[429]Desai, D.G.; Swami, S.S.; Mahale, G.D. *Synth. Commun.* ***2000***, *30*, 1623.

[430]Chaudhari, S.S.; Akamanchi, K.G. *Synth. Commun.* ***1999***, *29*, 1741.

[431]Iranpoor, N.; Zeynizadeh, B. *Synth. Commun.* ***1999***, *29*, 2747.

[432]Tamami, B.; Kiasat, A.R. *Synth. Commun.* ***2000***, *30*, 235.

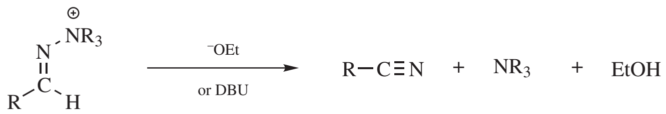
[433]Meshram, H.M. *Synthesis* ***1992***, 943.

[434]Khan, T.A.; Peruncheralathan, S.; Ila, H.; Junjappa, H. *Synlett* ***2004***, 2019.

[435]See Shono, T.; Matsumura, Y.; Tsubata, K.; Kamada, T.; Kishi, K. *J. Org. Chem.* ***1989***, *54*, 2249.

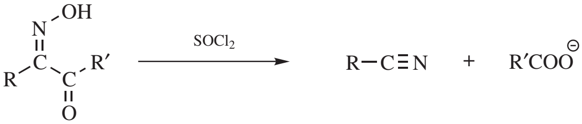
[436]Yang, S.H.; Chang, S. *Org. Lett.* ***2001***, *3*, 4209.

is effective for this transformation.[437] Microwave irradiation on EPZ-10[438] or sulfuric acid impregnated silica gel[439] gives the nitrile, as does microwave irradiation of an oxime with tetrachloropyridine on alumina.[440] Aldehydes can be converted to oximes *in situ* and microwave irradiation on alumina[441] or with ammonium acetate[442] gives the nitrile. Solvent-free reactions are known.[443] Electrochemical synthesis has also been used.[435] The reaction is most successful when the H and OH are anti. Various alkyl and acyl derivatives of aldoximes, for example, RCH=NOR, RCH=NOCOR, $RCH{=}NOSO_2Ar$, and so on, also give nitriles, as do chlorimines RCH=NCl (the latter with base treatment).[444] *N,N*-Dichloro derivatives of primary amines give nitriles on pyrolysis: $RCH_2NCl_2 \rightarrow RCN$.[445]



Quaternary hydrazonium salts (derived from aldehydes) give nitriles when treated with $^{-}$OEt[446] or DBU (p. 1132):[447] as do dimethylhydrazones, $RCH{=}NNMe_2$, when treated with Et_2NLi and HMPA.[448] All these are methods of converting aldehyde derivatives to nitriles. For the conversion of aldehydes directly to nitriles, without isolation of intermediates (see **16-16**).

Hydroxylamines that have an α-proton are converted to nitrones when treated with a manganese salen complex.[449]



Certain ketoximes can be converted to nitriles by the action of proton or Lewis acids.[450] Among these are oximes of α-diketones (illustrated above), α-keto acids,

[437]Miller, C.P.; Kaufman, D.H. *Synlett* ***2000***, 1169.

[438]Bandgar, B.P.; Sadavarte, V.S.; Sabu, K.R. *Synth. Commun.* ***1999***, *29*, 3409.

[439]Kumar, H.M.S.; Mohanty, P.K.; Kumar, M.S.; Yadav, J.S. *Synth. Commun.* ***1997***, *27*, 1327; Sarvari, M.H. *Synthesis* ***2005***, 787.

[440]Lingaiah, N.; Narender, R. *Synth. Commun.* ***2002***, *32*, 2391.

[441]Bose, D.S.; Narsaiah, A.V. *Tetrahedron Lett.* ***1998***, *39*, 6533.

[442]Das, B.; Ramesh, C.; Madhusudhan, P. *Synlett* ***2000***, 1599.

[443]See Sharghi, H.; Sarvari, M.H. *Synthesis* ***2003***, 243.

[444]Hauser, C.R.; Le Maistre, J.W.; Rainsford, A.E. *J. Am. Chem. Soc.* ***1935***, *57*, 1056.

[445]Roberts, J.T.; Rittberg, B.R.; Kovacic, P. *J. Org. Chem.* ***1981***, *46*, 4111.

[446]Smith, R.F.; Walker, L.E. *J. Org. Chem.* ***1962***, *27*, 4372; Grandberg, I.I. *J. Gen. Chem. USSR*, ***1964***, *34*, 570; Grundon, M.F.; Scott, M.D. *J. Chem. Soc.* ***1964***, 5674; Ioffe, B.V.; Zelenina, N.L. *J. Org. Chem. USSR*, ***1968***, *4*, 1496.

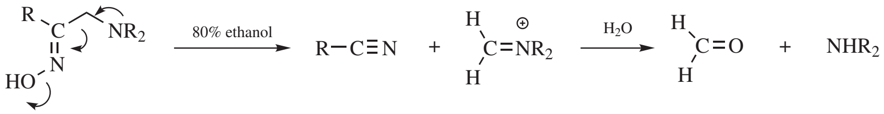
[447]Moore, J.S.; Stupp, S.I. *J. Org. Chem.* ***1990***, *55*, 3374.

[448]Cuvigny, T.; Le Borgne, J.F.; Larchevêque, M.; Normant, H. *Synthesis* ***1976***, 237.

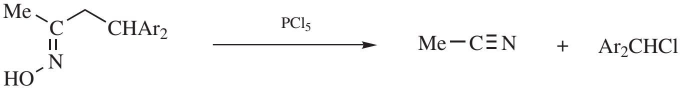
[449]Cicchi, S.; Cardona, F.; Brandi, A.; Corsi, M.; Goti, A. *Tetrahedron Lett.* ***1999***, *40*, 1989.

[450]For reviews, see Gawley, R.E. *Org. React.* ***1988***, *35*, 1; Conley, R.T.; Ghosh, S. *Mech. Mol. Migr.* ***1971***, *4*, 197, 197–251; McCarty, C.G., in Patai, S. *The Chemistry of the Carbon–Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 416–439; Casanova, J., in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 915–932.

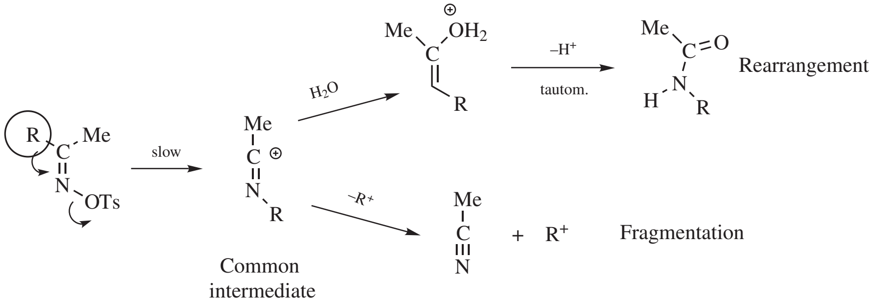
α-dialkylamino ketones, α-hydroxy ketones, β-keto ethers, and similar compounds.[451] These are fragmentation reactions, analogous to **17-25**. For example, α-dialkylamino ketoximes also give amines and aldehydes or ketones besides nitriles:[452]



The reaction that normally occurs on treatment of a ketoxime with a Lewis or proton acid is the Beckmann rearrangement (**18-17**); fragmentations are considered side reactions, often called "abnormal" or "second-order" Beckmann rearrangements.[453] Obviously, the substrates mentioned are much more susceptible to fragmentation than are ordinary ketoximes, since in each case an unshared pair is available to assist in removal of the group cleaving from the carbon. However, fragmentation is a side reaction even with ordinary ketoximes[454] and, in cases where a particularly stable carbocation can be cleaved, may be the main reaction:[455]



There are indications that the mechanism at least in some cases first involves a rearrangement and then cleavage. The ratio of fragmentation to Beckmann rearrangement of a series of oxime tosylates, RC(=NOTs)Me, was not related to the solvolysis rate but *was* related to the stability of R^+ (as determined by the solvolysis rate of the corresponding RCl), which showed that fragmentation did not take place in the rate-determining step.[456] It may be postulated then that the first step in the fragmentation and in the rearrangement is the same and that this is the rate-determining step. The product is determined in the second step:



[451]For more complete lists with references, see Olah, G.A.; Vankar, Y.D.; Berrier, A.L. *Synthesis* ***1980***, 45; Conley, R.T.; Ghosh, S. *Mech. Mol. Migr.* ***1971***, *4*, 197.

[452]Fischer, H.P.; Grob, C.A.; Renk, E. *Helv. Chim. Acta* ***1962***, *45*, 2539; Fischer, H.P.; Grob, C.A. *Helv. Chim. Acta* ***1963***, *46*, 936.

[453]See the discussion in Ferris, A.F. *J. Org. Chem.* ***1960***, *25*, 12.

[454]See, for example, Hill, R.K.; Conley, R.T. *J. Am. Chem. Soc.* ***1960***, *82*, 645.

[455]Hassner, A.; Nash, E.G. *Tetrahedron Lett.* ***1965***, 525.

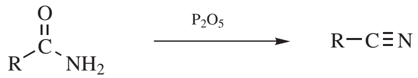
[456]Grob, C.A.; Fischer, H.P.; Raudenbusch, W.; Zergenyi, J. *Helv. Chim. Acta* ***1964***, *47*, 1003.

However, in other cases the simple E1 or E2 mechanisms operate.[457]

OS **V**, 266; **IX**, 281; OS **II**, 622; **III**, 690.

17-30 Dehydration of Unsubstituted Amides

***N,N*-Dihydro-*C*-oxo-bielimination**



Unsubstituted amides can be dehydrated to nitriles.[458] Phosphorous pentoxide is the most common dehydrating agent for this reaction, but many others, including $POCl_3$, PCl_5, CCl_4-Ph_3P,[459] HMPA,[460] LiCl with a zirconium catalyst,[461] $MeOOCNSO_2NEt_3$ (the Burgess reagent),[462] $Me_2N{=}CHCl^+$ Cl^-,[463] $AlCl_3$/KI/H_2O,[464] Bu_2SnO with microwave irradiation,[465] PPh_3/NCS,[466] triflic anhydride,[467] oxalyl chloride/DMSO/–78°C[468] (Swern conditions, see **19-3**), and $SOCl_2$ have also been used.[469] Heating an amide with paraformaldehyde and formic acid gives the nitrile.[470] Treatment with benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate converts amides to nitriles.[471] It is possible to convert an acid to the nitrile, without isolation of the amide, by heating its ammonium salt with the dehydrating agent,[472] or by other methods.[473] Acyl halides can also be directly converted to nitriles by heating with sulfamide $(NH_2)_2SO_2$.[474] The reaction may be formally looked on as a β-elimination from the enol form of the amide RC(OH)=NH, in which case it is like **17-29**, except that H and OH have changed

[457]Ahmad, A.; Spenser, I.D. *Can. J. Chem.* ***1961***, *39*, 1340; Ferris, A.F.; Johnson, G.S.; Gould, F.E. *J. Org. Chem.* ***1960***, *25*, 1813; Grob, C.A.; Sieber, A. *Helv. Chim. Acta* ***1967***, *50*, 2520; Green, M.; Pearson, S.C. *J. Chem. Soc. B* ***1969***, 593.

[458]For reviews, see Bieron J.F.; Dinan, F.J., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 274–283; Friedrich, K.; Wallenfels, K., in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 96–103; Friedrich, K., in Patai, S.; Rapoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 2, Wiley, NY, ***1978***, p. 1345.

[459]Yamato, E.; Sugasawa, S. *Tetrahedron Lett.* ***1970***, 4383; Appel, R.; Kleinstück, R.; Ziehn, K. *Chem. Ber.* ***1971***, *104*, 1030; Harrison, C.R.; Hodge, P.; Rogers, W.J. *Synthesis* ***1977***, 41.

[460]Monson, R.S.; Priest, D.N. *Can. J. Chem.* ***1971***, *49*, 2897.

[461]Ruck, R.T.; Bergman, R.G. *Angew. Chem. Int. Ed.* ***2004***, *43*, 5375.

[462]Claremon, D.A.; Phillips, B.T. *Tetrahedron Lett.* ***1988***, *29*, 2155.

[463]Barger, T.M.; Riley, C.M. *Synth. Commun.* ***1980***, *10*, 479.

[464]Boruah, M.; Konwar, D. *J. Org. Chem.* ***2002***, *67*, 7138.

[465]Bose, D.S.; Jayalakshmi, B. *J. Org. Chem.* ***1999***, *64*, 1713.

[466]Iranpoor, N.; Firouzabadi, H.; Aghapoor, G. *Synth. Commun.* ***2002***, *32*, 2535.

[467]Bose, D.S.; Jayalakshmi, B. *Synthesis* ***1999***, 64.

[468]Nakajima, N.; Ubukata, M. *Tetrahedron Lett.* ***1997***, *38*, 2099.

[469]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1983–1985.

[470]Heck, M.-P.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* ***1996***, *61*, 6486.

[471]Bose, D.S.; Narsaiah, A.V. *Synthesis* ***2001***, 373.

[472]See, for example, Imamoto, T.; Takaoka, T.; Yokoyama, M. *Synthesis* ***1983***, 142.

[473]For a list of methods, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1949–1950.

[474]Hulkenberg, A.; Troost, J.J. *Tetrahedron Lett.* ***1982***, *23*, 1505.

places. In some cases, for example, with $SOCl_2$, the mechanism probably *is* through the enol form, with the dehydrating agent forming an ester with the OH group, for example, RC(OSOCl)=NH, which undergoes elimination by the E1 or E2 mechanism.[475] *N,N*-Disubstituted ureas give cyanamides ($R_2N–CO–NH_2 \rightarrow R_2N–CN$) when dehydrated with $CHCl_3$–NaOH under phase-transfer conditions.[476] Treatment of an amide with aqueous NaOH and ultrasound leads to the nitrile.[477]

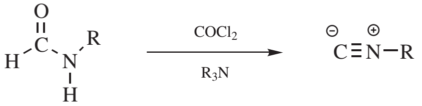
N-Alkyl-substituted amides can be converted to nitriles and alkyl chlorides by treatment with PCl_5. This is called the *von Braun reaction* (not to be confused with the other von Braun reaction, **10-54**).

$$R'CONHR + PCl_5 \longrightarrow R'CN + RCl$$

OS **I**, 428; **II**, 379; **III**, 493, 535, 584, 646, 768; **IV**, 62, 144, 166, 172, 436, 486, 706; **VI**, 304, 465.

17-31 Conversion of *N*-Alkylformamides to Isonitriles (Isocyanides)

CN-Dihydro-*C*-oxo-bielimination



Isocyanides (isonitriles) can be prepared by elimination of water from *N*-alkylformamides[478] with phosgene and a tertiary amine.[479] Other reagents, among them TsCl in quinoline, $POCl_3$ and a tertiary amine,[480] $Me_2N{=}CHCl^+\ Cl^-$,[481] triflic anhydride-(*i*Pr)$_2$NEt,[482] PhOC(=S)Cl,[483] and $Ph_3P–CCl_4$-Et_3N[484] have also been employed. Formamides react with thionyl chloride (two sequential treatments) to give an intermediate that gives an isonitrile upon electrolysis in DMF with $LiClO_4$.[485]

A variation of this process uses carbodiimides,[486] which can be prepared by the dehydration of *N,N'*-disubstituted ureas with various dehydrating agents,[487] among

[475]Rickborn, B.; Jensen, F.R. *J. Org. Chem.* ***1962***, *27*, 4608.

[476]Schroth, W.; Kluge, H.; Frach, R.; Hodek, W.; Schädler, H.D. *J. Prakt. Chem.* ***1983***, *325*, 787.

[477]Sivakumar, M.; Senthilkumar, P.; Pandit, A.B. *Synth. Commun.* ***2001***, *31*, 2583.

[478]For a new synthesis see Creedon, S.M.; Crowley, H.K.; McCarthy, D.G. *J. Chem. Soc. Perkin Trans. 1* ***1998***, 1015.

[479]For reviews, see Hoffmann, P.; Gokel, G.W.; Marquarding, D.; Ugi, I., in Ugi, I. *Isonitrile Chemistry*, Academic Press, NY, ***1971***, pp. 10–17; Ugi, I.; Fetzer, U.; Eholzer, U.; Knupfer, H.; Offermann, K. *Angew. Chem. Int. Ed.* ***1965***, *4*, 472; *Newer Methods Prep. Org. Chem.* ***1968***, *4*, 37.

[480]See Obrecht, R.; Herrmann, R.; Ugi, I. *Synthesis* ***1985***, 400.

[481]Walborsky, H.M.; Niznik, G.E. *J. Org. Chem.* ***1972***, *37*, 187.

[482]Baldwin, J.E.; O'Neil, I.A. *Synlett* ***1991***, 603.

[483]Bose, D.S.; Goud, P.R. *Tetrahedron Lett.* ***1999***, *40*, 747.

[484]Appel, R.; Kleinstück, R.; Ziehn, K. *Angew. Chem. Int. Ed.* ***1971***, *10*, 132.

[485]Guirado, A.; Zapata, A.; Gómez, J.L.; Trebalón, L.; Gálvez, J. *Tetrahedron* ***1999***, *55*, 9631.

[486]For a review of the reactions in this section, see Bocharov, B.V. *Russ. Chem. Rev.* ***1965***, *34*, 212. For a review of carbodiimide chemistry; see Williams, A.; Ibrahim, I.T. *Chem. Rev.* ***1981***, *81*, 589.

[487]For some others not mentioned here, see Sakai, S.; Fujinami, T.; Otani, N.; Aizawa, T. *Chem. Lett.* ***1976***, 811; Shibanuma, T.; Shiono, M.; Mukaiyama, T. *Chem. Lett.* ***1977***, 575; Kim, S.; Yi, K.Y. *J. Org. Chem.* ***1986***, *51*, 2613, *Tetrahedron Lett.* ***1986***, *27*, 1925.

which are TsCl in pyridine, $POCl_3$, PCl_5, P_2O_5–pyridine, TsCl (with phase-transfer catalysis),[488] and Ph_3PBr_2–Et_3N.[489] Hydrogen sulfide can be removed from the corresponding thioureas by treatment with HgO, NaOCl, or diethyl azodicarboxylate–triphenylphosphine.[490]

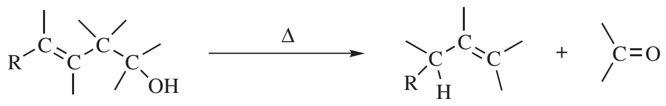
OS **V**, 300, 772; **VI**, 620, 751, 987. See also OS **VII**, 27. For the carbodiimide/thiourea dehydration, see OS **V**, 555; **VI**, 951.

REACTIONS IN WHICH C=O BONDS ARE FORMED

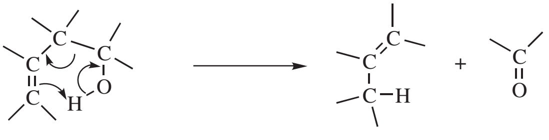
Many elimination reactions in which C=O bonds are formed were considered in Chapter 16, along with their more important reverse reactions (also see, **12-40** and **12-41**).

17-32 Pyrolysis of β-Hydroxy Alkenes

***O*-Hydro-*C*-allyl-elimination**



When pyrolyzed, β-hydroxy alkenes cleave to give alkenes and aldehydes or ketones.[491] Alkenes produced this way are quite pure, since there are no side reactions. The mechanism has been shown to be pericyclic, primarily by observations that the kinetics are first order[492] and that, for ROD, the deuterium appeared in the allylic position of the new alkene.[493] This mechanism is the reverse of that for the oxygen analog of the ene synthesis (**16-54**). β-Hydroxyacetylenes react similarly to give the corresponding allenes and carbonyl compounds.[494] The mechanism is the same despite the linear geometry of the triple bonds.



[488]Jászay, Z.M.; Petneházy, I.; Töke, L.; Szajáni, B. *Synthesis* ***1987***, 520.

[489]Bestmann, H.J.; Lienert, J.; Mott, L. *J.L. Liebigs Ann. Chem.* ***1968***, *718*, 24.

[490]Mitsunobu, O.; Kato, K.; Tomari, M. *Tetrahedron* ***1970***, *26*, 5731.

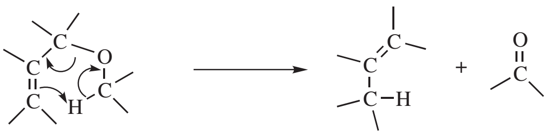
[491]Arnold, R.T.; Smolinsky, G. *J. Am. Chem. Soc.* ***1959***, *81*, 6643. For a review, see Marvell, E.N.; Whalley, W., in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 2, Wiley, NY, ***1971***, pp. 729–734.

[492]Voorhees, K.J.; Smith, G.G. *J. Org. Chem.* ***1971***, *36*, 1755.

[493]Arnold, R.T.; Smolinsky, G. *J. Org. Chem.* ***1960***, *25*, 128; Smith, G.G.; Taylor, R. *Chem. Ind. (London)* ***1961***, 949.

[494]Viola, A.; Proverb, R.J.; Yates, B.L.; Larrahondo, J. *J. Am. Chem. Soc.* ***1973***, *95*, 3609.

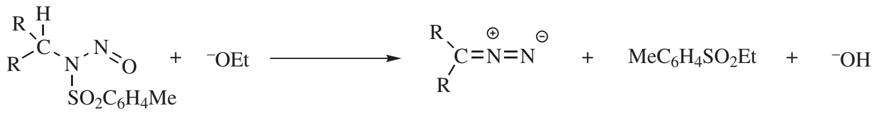
In a related reaction, pyrolysis of allylic ethers that contain at least one α hydrogen gives alkenes and aldehydes or ketones. The mechanism is also pericyclic[495]



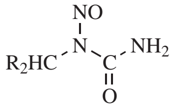
REACTIONS IN WHICH N=N BONDS ARE FORMED

17-33 Eliminations to Give Diazoalkanes

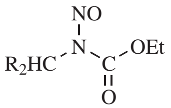
N-Nitrosoamine-diazoalkane transformation



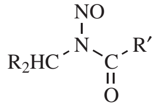
Various *N*-nitroso-*N*-alkyl compounds undergo elimination to give diazoalkanes.[496] One of the most convenient methods for the preparation of diazomethane involves base treatment of *N*-nitroso-*N*-methyl-*p*-toluenesulfonamide (illustrated above, with R = H).[497] However, other compounds commonly used are (base treatment is required in all cases):



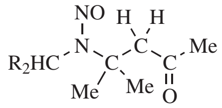
N-Nitroso-*N*-alkylureas



N-Nitroso-*N*-alkylcarbamates



N-Nitroso-*N*-alkyl amides



N-Nitroso-*N*-alkyl-4-amino-4-methyl-2-pentanone

All these compounds can be used to prepare diazomethane, although the sulfonamide, which is commercially available, is most satisfactory. *N*-Nitroso-*N*-methylcarbamate and *N*-nitroso-*N*-methylurea give good yields, but are highly irritating and carcinogenic.[498] For higher diazoalkanes the preferred substrates are nitrosoalkylcarbamates.

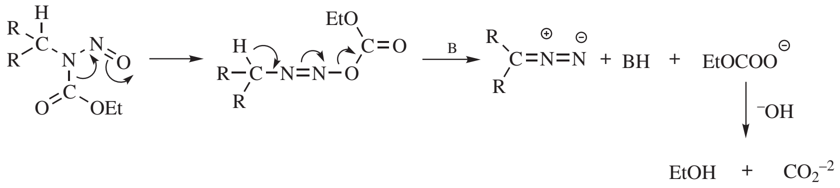
[495]Cookson, R.C.; Wallis, S.R. *J. Chem. Soc. B* ***1966***, 1245; Kwart, H.; Slutsky, J.; Sarner, S.F. *J. Am. Chem. Soc.* ***1973***, *95*, 5242; Egger, K.W.; Vitins, P. *Int. J. Chem. Kinet.* ***1974***, *6*, 429.

[496]For a review, see Regitz, M.; Maas, G. *Diazo Compounds*; Academic Press, NY, ***1986***, pp. 296–325. For a review of the preparation and reactions of diazomethane, see Black, T.H. *Aldrichimica Acta* ***1983***, *16*, 3. For discussions, see Cowell, G.W.; Ledwith, A. *Q. Rev. Chem. Soc.* ***1970***, *24*, 119, pp. 126–131; Smith, P.A.S. *Open-chain Nitrogen Compounds*; W. A. Benjamin, NY, ***1966***, especially pp. 257–258, 474–475, in Vol. 2.

[497]de Boer, T.J.; Backer, H.J. *Org. Synth.* ***IV***, 225, 250; Hudlicky, M. *J. Org. Chem.* ***1980***, *45*, 5377.

[498]Searle, C.E. *Chem. Br.* ***1970***, *6*, 5.

Most of these reactions probably begin with a 1,3 nitrogen-to-oxygen rearrangement, followed by the actual elimination (illustrated for the carbamate):



OS **II**, 165; **III**, 119, 244; **IV**, 225, 250; **V**, 351; **VI**, 981.

EXTRUSION REACTIONS

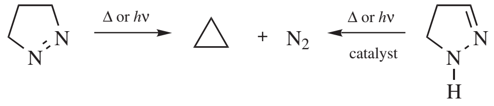
We consider an *extrusion reaction*[499] to be one in which an atom or group Y connected to two other atoms X and Z is lost from a molecule, leading to a product in which X is bonded directly to Z.

$$X{-}Y{-}Z \longrightarrow X{-}Z + Y$$

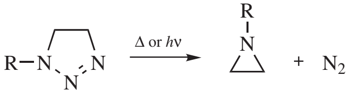
Reactions **14-32** and **17-20** also fit this definition. Reaction **17-28** does not fit the definition, but is often also classified as an extrusion reaction. An extrusibility scale has been developed, showing that the ease of extrusion of the common Y groups is in the order: –N=N– > –COO– > $-SO_2-$ > –CO–.[500]

17-34 Extrusion of N_2 from Pyrazolines, Pyrazoles, and Triazolines

Azo-extrusion



52 **53**



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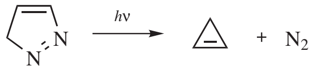
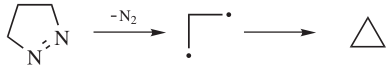


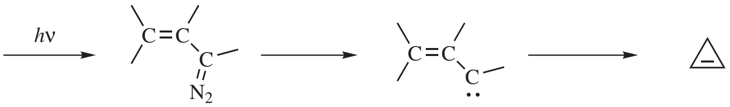
55

[499]For a monograph, see Stark, B.P.; Duke, A.J. *Extrusion Reactions*, Pergamon, Elmsford, NY, ***1967***. For a review of extrusions that are photochemically induced, see Givens, R.S. *Org. Photochem.* ***1981***, *5*, 227.
[500]Paine, A.J.; Warkentin, J. *Can. J. Chem.* ***1981***, *59*, 491.

1-Pyrazolines (**52**) can be converted to cyclopropane and N_2 on photolysis[501] or pyrolysis.[502] The tautomeric 2-pyrazolines (**53**), which are more stable than **52** also give the reaction, but in this case an acidic or basic catalyst is required, the function of which is to convert **53** to **52**.[503] In the absence of such catalysts, **53** do not react.[504] In a similar manner, triazolines (**54**) are converted to aziridines.[505] Side reactions are frequent with both **52** and **54**, and some substrates do not give the reaction at all. However, the reaction has proved synthetically useful in many cases. In general, photolysis gives better yields and fewer side reactions than pyrolysis with both **52** and **54**. 3*H*-Pyrazoles[506] (**55**) are stable to heat, but in some cases can be converted to cyclopropenes on photolysis,[507] although in other cases other types of products are obtained.



There is much evidence that the mechanism[508] of the 1-pyrazoline reactions generally involves diradicals, although the mode of formation and detailed structure (e.g., singlet vs. triplet) of these radicals may vary with the substrate and reaction conditions. The reactions of the 3*H*-pyrazoles have been postulated to proceed through a diazo compound that loses N_2 to give a vinylic carbene.[509]

55 

OS **V**, 96, 929. See also, OS **VIII**, 597.

[501]Van Auken, T.V.; Rinehart Jr., K.L. *J. Am. Chem. Soc.* ***1962***, *84*, 3736.

[502]For reviews of the reactions in this section, see Adam, W.; De Lucchi, O. *Angew. Chem. Int. Ed.* ***1980***, *19*, 762; Meier, H.; Zeller, K. *Angew. Chem. Int. Ed.* ***1977***, *16*, 835; Stark, B.P.; Duke, A.J. *Extrusion Reactions*, Pergamon, Elmsford, NY, ***1967***, pp. 116–151. For a review of the formation and fragmentation of cyclic azo compounds, see Mackenzie, K., in Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 1, Wiley, NY, ***1975***, pp. 329–442.

[503]For example, see Jones, W.M.; Sanderfer, P.O.; Baarda, D.G. *J. Org. Chem.* ***1967***, *32*, 1367.

[504]McGreer, D.E.; Wai, W.; Carmichael, G. *Can. J. Chem.* ***1960***, *38*, 2410; Kocsis K.; Ferrini, P.G.; Arigoni, D.; Jeger, O. *Helv. Chim. Acta* ***1960***, *43*, 2178.

[505]For a review, see Scheiner, P. *Sel. Org. Transform.* ***1970***, *1*, 327.

[506]For a review of 3*H*-pyrazoles, see Sammes, M.P.; Katritzky, A.R. *Adv. Heterocycl. Chem.* ***1983***, *34*, 2.

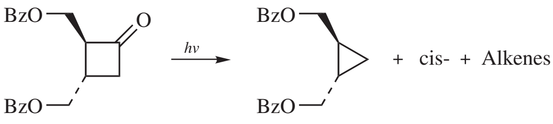
[507]Ege, G.*Tetrahedron Lett.* ***1963***, 1667; Closs, G.L.; Böll, W.A.; Heyn, H.; Dev, V. *J. Am. Chem. Soc.* ***1968***, *90*, 173; Franck-Neumann, M.; Buchecker, C. *Tetrahedron Lett.* ***1969***, 15; Pincock, J.A.; Morchat, R.; Arnold, D.R. *J. Am. Chem. Soc.* ***1973***, *95*, 7536.

[508]For a review of the mechanism; see Engel, P.S. *Chem. Rev.* ***1980***, *80*, 99. See also, Engel, P.S.; Nalepa, C.J. *Pure Appl. Chem.* ***1980***, *52*, 2621; Engel, P.S.; Gerth, D.B. *J. Am. Chem. Soc.* ***1983***, *105*, 6849; Reedich, D.E.; Sheridan, R.S. *J. Am. Chem. Soc.* ***1988***, *110*, 3697.

[509]Closs, G.L.; Böll, W.A.; Heyn, H.; Dev, V. *J. Am. Chem. Soc.* ***1968***, *90*, 173; Pincock, J.A.; Morchat, R.; Arnold, D.R. *J. Am. Chem. Soc.* ***1973***, *95*, 7536.

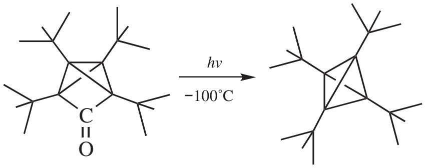
17-35 Extrusion of CO or CO_2

Carbonyl-extrusion



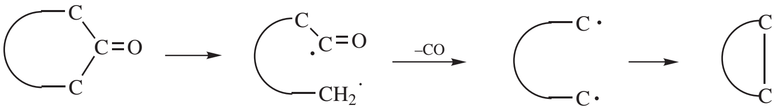
56 **57**

Although the reaction is not general, certain cyclic ketones can be photolyzed to give ring-contracted products.[510] In the example above, the cyclobutanone **56** was photolyzed to give **57**.[511] This reaction was used to synthesize tetra-*tert*-butyltetrahedrane, **58**.[512]

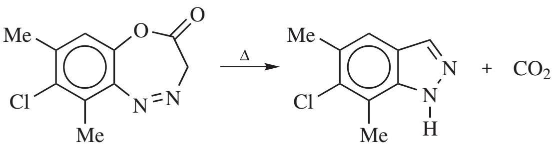


58

The mechanism probably involves a Norrish type I cleavage (p. 343), loss of CO from the resulting radical, and recombination of the radical fragments.



Certain lactones extrude CO_2 on heating or on irradiation, such as the pyrolysis of **59**.[513]



59

[510]For reviews of the reactions in this section, see Redmore, D.; Gutsche, C.D. *Adv. Alicyclic Chem.* ***1971***, *3*, 1, see pp. 91–107; Stark, B.P.; Duke, A.J. *Extrusion Reactions*, Pergamon, Elmsford, NY, ***1967***, pp. 47–71.

[511]Ramnauth, J.; Lee-Ruff, E. *Can. J. Chem.* ***1997***, *75*, 518. See also, Ramnauth, J.; Lee-Ruff, E. *Can. J. Chem.* ***2001***, *79*, 114.

[512]Maier, G.; Pfriem, S.; Schäfer, U.; Matusch, R. *Angew. Chem. Int. Ed.* ***1978***, *17*, 520.

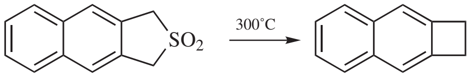
[513]Ried, W.; Wagner, K. *Liebigs Ann. Chem.* ***1965***, *681*, 45.

Decarboxylation of β-lactones (see **17-26**) may be regarded as a degenerate example of this reaction. Unsymmetrical diacyl peroxides RCO–OO–COR′ lose two molecules of CO_2 when photolyzed in the solid state to give the product RR′.[514] Electrolysis was also used, but yields were lower. This is an alternative to the Kolbe reaction (**11-34**) (see also **17-28** and **17-38**).

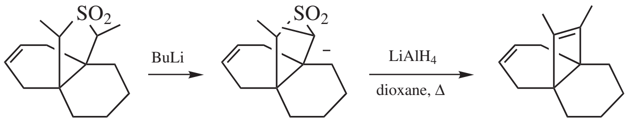
There are no OS references, but see OS **VI**, 418, for a related reaction.

17-36 Extrusion of SO_2

Sulfonyl-extrusion



In a reaction similar to **17-35**, certain sulfones, both cyclic and acyclic,[515] extrude SO_2 on heating or photolysis to give ring-contracted products.[516] An example is the preparation of naphtho(*b*)cyclobutene shown above.[517] In a different kind of reaction, five-membered cyclic sulfones can be converted to cyclobutenes by treatment with butyllithium followed by $LiAlH_4$,[518] for example,



This method is most successful when both the α and α' position of the sulfone bear alkyl substituents (see also **17-20**). Treating four-membered ring sultams with $SnCl_2$ led to aziridine products via loss of SO_2.[519]

OS **VI**, 482.

[514]Lomölder, R.; Schäfer, H.J. *Angew. Chem. Int. Ed.* ***1987***, *26*, 1253.

[515]See, for example, Gould, I.R.; Tung, C.; Turro, N.J.; Givens, R.S.; Matuszewski, B. *J. Am. Chem. Soc.* ***1984***, *106*, 1789.

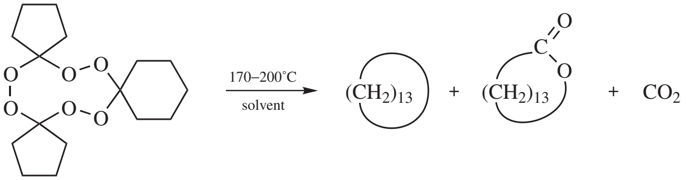
[516]For reviews of extrusions of SO_2, see Vögtle, F.; Rossa, L. *Angew. Chem. Int. Ed.* ***1979***, *18*, 515; Stark, B.P.; Duke, A.J. *Extrusion Reactions*, Pergamon, Elmsford, NY, ***1967***, pp. 72–90; Kice, J.L., in Kharasch, N.; Meyers, C.Y. *The Chemisry of Organic Sulfur Compounds*, Vol. 2, Pergamon, Elmsford, NY, ***1966***, pp. 115–136. For a review of extrusion reactions of S, Se, and Te compounds, see Guziec, Jr., F.S.; SanFilippo, L.J. *Tetrahedron* ***1988***, *44*, 6241.

[517]Cava, M.P.; Shirley, R.L. *J. Am. Chem. Soc.* ***1960***, *82*, 654.

[518]Photis, J.M.; Paquette, L.A. *J. Am. Chem. Soc.* ***1974***, *96*, 4715.

[519]Kataoka, T.; Iwama, T. *Tetrahedron Lett.* ***1995***, *36*, 5559.

17-37 The Story Synthesis



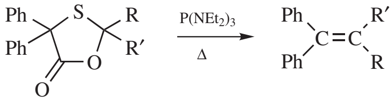
60

When cycloalkylidine peroxides (e.g., **60**) are heated in an inert solvent (e.g., decane), extrusion of CO_2 takes place; the products are the cycloalkane containing three carbon atoms less than the starting peroxide and the lactone containing two carbon atoms less[520] (the *Story synthesis*).[521] The two products are formed in comparable yields, usually ~15–25% each. Although the yields are low, the reaction is useful because there are not many other ways to prepare large rings. The reaction is versatile, having been used to prepare rings of every size from 8 to 33 members.

Both dimeric and trimeric cycloalkylidine peroxides can be synthesized[522] by treatment of the corresponding cyclic ketones with H_2O_2 in acid solution.[523] The trimeric peroxide is formed first and is subsequently converted to the dimeric compound.[524]

17-38 Alkene Synthesis by Twofold Extrusion

Carbon dioxide, thio-extrusion



61

4,4-Diphenyloxathiolan-5-ones (**61**) give good yields of the corresponding alkenes when heated with tris(diethylamino)phosphine.[525] This reaction is an

[520]Sanderson, J.R.; Story, P.R.; Paul, K. *J. Org. Chem.* ***1975***, *40*, 691; Sanderson, J.R.; Paul, K.; Story, P.R. *Synthesis* ***1975***, 275.

[521]For a review, see Story, P.R.; Busch, P. *Adv. Org. Chem.* ***1972***, *8*, 67, see pp. 79–94.

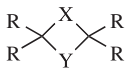
[522]For synthesis of mixed trimeric peroxides (e.g., **60**), see Sanderson, J.R.; Zeiler, A.G. *Synthesis* ***1975***, 388; Paul, K.; Story, P.R.; Busch, P.; Sanderson, J.R. *J. Org. Chem.* ***1976***, *41*, 1283.

[523]Kharasch, M.S.; Sosnovsky, G. *J. Org. Chem.* ***1958***, *23*, 1322; Ledaal, T. *Acta Chem. Scand.*, ***1967***, *21*, 1656. For another method, see Sanderson, J.R.; Zeiler, A.G. *Synthesis* ***1975***, 125.

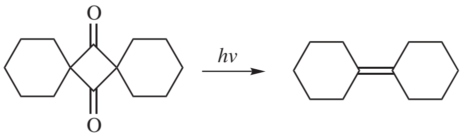
[524]Story, P.R.; Lee, B.; Bishop, C.E.; Denson, D.D.; Busch, P. *J. Org. Chem.* ***1970***, *35*, 3059. See also, Sanderson, J.R.; Wilterdink, R.J.; Zeiler, A.G. *Synthesis* ***1976***, 479.

[525]Barton, D.H.R.; Willis, B.J. *J. Chem. Soc. Perkin Trans. 1* ***1972***, 305.

example of a general type: alkene synthesis by twofold extrusion of X and Y from a molecule of the type **62**.[526] Other examples are photolysis of 1,4-diones[527] (e.g., **63**) and treatment of acetoxy sulfones [RCH(OAc)CH_2SO_2Ph] with Mg/EtOH and a catalytic amount of $HgCl_2$.[528] **61** can be prepared by the condensation of thiobenzilic acid Ph_2C(SH)COOH with aldehydes or ketones.



62



63

OS **V**, 297.

[526]For a review of those in which X or Y contains S, Se, or Te, see Guziec, Jr., F.S.; SanFilippo, L.J. *Tetrahedron* ***1988***, *44*, 6241.

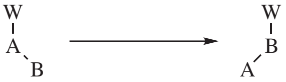
[527]Turro, N.J.; Leermakers, P.A.; Wilson, H.R.; Neckers, D.C.; Byers, G.W.; Vesley, G.F. *J. Am. Chem. Soc*. ***1965***, *87*, 2613.

[528]Lee, G.H.; Lee, H.K.; Choi, E.B.; Kim, B.T.; Pak, C.S. *Tetrahedron Lett*. ***1995***, *36*, 5607.

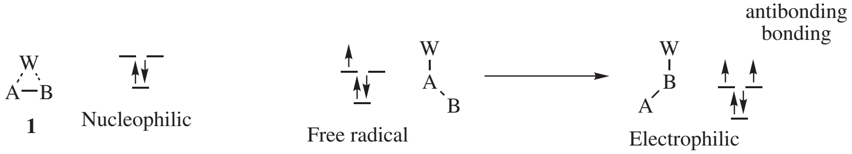
CHAPTER 18

Rearrangements

In a rearrangement reaction a group moves from one atom to another in the same molecule.[1] Most are migrations from an atom to an adjacent one (called 1,2-shifts), but some are over longer distances. The migrating group (W)



may move with its electron pair (these can be called *nucleophilic* or *anionotropic* rearrangements; the migrating group can be regarded as a nucleophile), without its electron pair (*electrophilic* or *cationotropic* rearrangements; in the case of migrating hydrogen, *prototropic* rearrangements), or with just one electron (free-radical rearrangements). The atom A is called the *migration origin* and B is the *migration terminus*. However, there are some rearrangements that do not lend themselves to neat categorization in this manner. Among these are those with cyclic transition states (**18-27–18-36**).



As we will see, nucleophilic 1,2-shifts are much more common than electrophilic or free-radical 1,2-shifts. The reason for this can be seen by a consideration of the transition states (or in some cases intermediates) involved. We represent the transition state or intermediate for all three cases by **1**, in which the two-electron

[1]For books, see de Mayo, P. *Rearrangements in Ground and Excited States*, 3 vols., Academic Press, NY, ***1980***; Stevens, T.S.; Watts, W.E. *Selected Molecular Rearrangements*, Van Nostrand-Reinhold, Princeton, NJ, ***1973***. For a review of many of these rearrangements, see Collins, C.J.; Eastham, J.F., in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 761–821. See also, the series *Mechanisms of Molecular Migrations.*

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A–W bond overlaps with the orbital on atom B, which contains zero, one, and two electrons, in the case of nucleophilic, free-radical, and electrophilic migration, respectively. The overlap of these orbitals gives rise to three new orbitals, which have an energy relationship similar to those on p. 72 (one bonding and two degenerate antibonding orbitals). In a nucleophilic migration, where only two electrons are involved, both can go into the bonding orbital and **1** is a low-energy transition state; but in a free-radical or electrophilic migration, there are, respectively, three or four electrons that must be accommodated, and antibonding orbitals must be occupied. It is not surprising therefore that, when 1,2-electrophilic or free-radical shifts are found, the migrating group W is usually aryl or some other group that can accommodate the extra one or two electrons and thus effectively remove them from the three-membered transition state or intermediate (see **41** on p. 1577).

In any rearrangement, we can in principle distinguish between two possible modes of reaction: In one of these, the group W becomes completely detached from A and may end up on the B atom of a different molecule (*intermolecular* rearrangement); in the other W goes from A to B in the *same* molecule (*intramolecular* rearrangement), in which case there must be some continuing tie holding W to the A–B system, preventing it from coming completely free. Strictly speaking, only the intramolecular type fits our definition of a rearrangement, but the general practice, which is followed here, is to include under the title "rearrangement" all net rearrangements whether they are inter- or intramolecular. It is usually not difficult to tell whether a given rearrangement is inter- or intramolecular. The most common method involves the use of *crossover* experiments. In this type of experiment, rearrangement is carried out on a mixture of W–A–B and V–A–C, where V is closely related to W (say, methyl vs. ethyl) and B to C. In an intramolecular process only A–B–W and A–C–V are recovered, but if the reaction is intermolecular, then not only will these two be found, but also A–B–V and A–C–W.

MECHANISMS

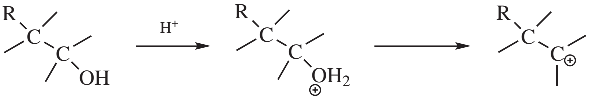
Nucleophilic Rearrangements[2]

Broadly speaking, such rearrangements consist of three steps, of which the actual migration is the second:

[2]For reviews, see Vogel, P. *Carbocation Chemistry*; Elsevier, NY, ***1985***, pp. 323–372; Shubin, V.G. *Top. Curr. Chem.* ***1984***, *116/117*, 267; Saunders, M.; Chandrasekhar, J.; Schleyer, P.v.R., in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 1, Academic Press, NY, ***1980***, pp. 1–53; Kirmse, W. *Top. Curr. Chem.* ***1979***, *80*, 89. For reviews of rearrangements in vinylic cations, see Shchegolev, A.A.; Kanishchev, M.I. *Russ. Chem. Rev.* ***1981***, *50*, 553; Lee, C.C. *Isot. Org. Chem.* ***1980***, *5*, 1.

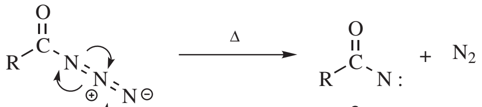
This process has been called the *Whitmore 1,2-shift*.[3] Since the migrating group carries the electron pair with it, the migration terminus B must be an atom with only six electrons in its outer shell (an open sextet). The first step therefore is creation of a system with an open sextet. Such a system can arise in various ways, but two of these are the most important:

1. *Formation of a Carbocation*. These can be formed in a number of ways (see p. 247), but one of the most common methods when a rearrangement is desired is the acid treatment of an alcohol to give **2** from an intermediate oxonium ion. These two steps are of course the same as the first two steps of the S_N1cA or the E1 reactions of alcohols.



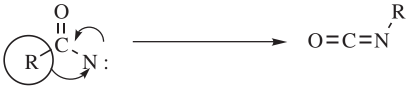
2

2. *Formation of a Nitrene*. The decomposition of acyl azides is one of several ways in which acyl nitrenes **3** are formed (see p. 293). After the migration has taken place, the atom at the migration origin (A) must necessarily have an open sextet. In the third step, this atom acquires an octet. In the case of carbocations, the most common third steps are combinations with a nucleophile (rearrangement with substitution) and loss of H^+ (rearrangement with elimination).



3

Although we have presented this mechanism as taking place in three steps, and some reactions do take place in this way, in many cases two or all three steps are simultaneous. For example, in the nitrene example above, as the R migrates, an electron pair from the nitrogen moves into the C–N bond to give a stable isocyanate, **4**.



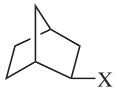
3 **4**

In this example, the second and third steps are simultaneous. It is also possible for the second and third steps to be simultaneous even when the "third" step involves more than just a simple motion of a pair of electrons. Similarly, there are many reactions in which the first two steps are simultaneous; that is, there is no actual formation of a species, such as **2** or **3**. In these instances, it may be said that

[3]It was first postulated by Whitmore, F.C. *J. Am. Chem. Soc.* ***1932***, *54*, 3274.

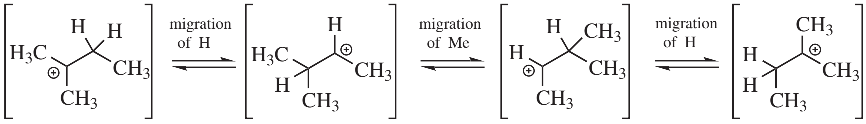
R assists in the removal of the leaving group, with migration of R and the removal of the leaving group taking place simultaneously. Many investigations have been carried out in attempts to determine, in various reactions, whether such intermediates as **2** or **3** actually form, or whether the steps are simultaneous (see, e.g., the discussions on pp. 1381, 1563), but the difference between the two possibilities is often subtle, and the question is not always easily answered.[4]

Evidence for this mechanism is that rearrangements of this sort occur under conditions where we have previously encountered carbocations: S_N1 conditions, Friedel–Crafts alkylation, and so on. Solvolysis of neopentyl bromide leads to rearrangement products, and the rate increases with increasing ionizing power of the solvent but is unaffected by concentration of base,[5] so that the first step is carbocation formation. The same compound under S_N2 conditions gave no rearrangement, but only ordinary substitution, though slowly. Thus with neopentyl bromide, formation of a carbocation leads only to rearrangement. Carbocations usually rearrange to more stable carbocations. Thus the direction of rearrangement is usually primary → secondary → tertiary. Neopentyl (Me_3CCH_2), neophyl ($PhCMe_2CH_2$), and norbornyl (e.g., **5**) type systems are especially prone to carbocation rearrangement reactions. It has been shown that the rate of migration increases with the degree of electron deficiency at the migration terminus.[6]



5

We have previously mentioned (p. 236) that stable tertiary carbocations can be obtained, in solution, at very low temperatures. The NMR studies have shown that when these solutions are warmed, rapid migrations of hydride and of alkyl groups take place, resulting in an equilibrium mixture of structures.[7] For example, the *tert*-pentyl cation (**5**)[8] equilibrates as follows:



6 **7** **7'** **6'**

[4]The IUPAC designations depend on the nature of the steps. For the rules, see Guthrie, R.D. *Pure Appl. Chem.* ***1989***, *61*, 23, 44–45.

[5]Dostrovsky, I.; Hughes, E.D. *J. Chem. Soc.* ***1946***, 166.

[6]Borodkin, G.I.; Shakirov, M.M.; Shubin, V.G.; Koptyug, V.A. *J. Org. Chem. USSR* ***1978***, *14*, 290, 924.

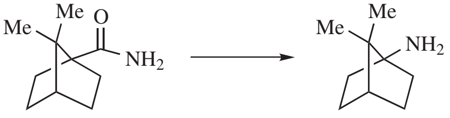
[7]For reviews, see Brouwer, D.M.; Hogeveen, H. *Prog. Phys. Org. Chem.* ***1972***, *9*, 179, see pp. 203–237; Olah, G.A.; Olah, J.A., in Olah, G.A.; Schleyer, P.V.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, pp. 751–760, 766–778. For a discussion of the rates of these reactions, see Sorensen, T.S. *Acc. Chem. Res.* ***1976***, *9*, 257.

[8]Brouwer, D.M. *Recl. Trav. Chim. Pays-Bas* ***1968***, *87*, 210; Saunders, M.; Hagen, E.L. *J. Am. Chem. Soc.* ***1968***, *90*, 2436.

Carbocations that rearrange to give products of identical structure (e.g., **6** ⇌ **6'**,**7** ⇌ **7'**) are called *degenerate carbocations* and such rearrangements are *degenerate rearrangements*. Many examples are known.[9]

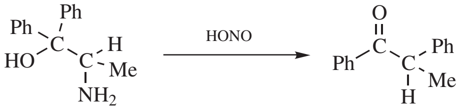
The Actual Nature of the Migration

Most nucleophilic 1,2-shifts are intramolecular. The W group does not become free, but always remains connected in some way to the substrate. Apart from the evidence from crossover experiments, the strongest evidence is that when the W group is chiral, the configuration is *retained* in the product. For example, (+)-PhCHMe-COOH was converted to (−)-$PhCHMeNH_2$ by the Curtius (**18-14**), Hofmann (**18-13**), Lossen (**18-15**), and Schmidt (**18-16**) reactions.[10] In these reactions, the extent of retention varied from 95.8 to 99.6%. Retention of configuration in the migrating group has been shown many times since.[11] Another experiment demonstrating retention was the



8 **9**

easy conversion of **8** to **9**.[11] Neither inversion nor racemization could take place at a bridgehead. There is much other evidence that retention of configuration usually occurs in W, and inversion never.[12] However, this is not the state of affairs at A and B. In many reactions, of course, the structure of W–A–B is such that the product has only one steric possibility at A or B or both, and in most of these cases nothing can be learned. But in cases where the steric nature of A or B can be investigated, the results are mixed. It has been shown that either inversion or racemization can occur at A or B. Thus the following conversion proceeded with inversion at B:[13]



(−) (+)

[9]For reviews, see Ahlberg, P.; Jonsäll, G.; Engdahl, C. *Adv. Phys. Org. Chem.* ***1983***, *19*, 223; Leone, R.E.; Barborak, J.C.; Schleyer, P.v.R., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 4, Wiley, NY, ***1970***, pp. 1837–1939; Leone, R.E.; Schleyer, P.v.R. *Angew. Chem. Int. Ed.* ***1970***, *9*, 860.

[10]Campbell, A.; Kenyon, J. *J. Chem. Soc.* ***1946***, 25, and references cited therein.

[11]For retention of migrating group configuration in the Wagner–Meerwein and pinacol rearrangements, see Beggs, J.J.; Meyers, M.B. *J. Chem. Soc. B* ***1970***, 930; Kirmse, W.; Gruber, W.; Knist, J. *Chem. Ber.* ***1973***, *106*, 1376; Shono, T.; Fujita, K.; Kumai, S. *Tetrahedron Lett.* ***1973***, 3123; Borodkin, G.I.; Panova, Y.B.; Shakirov, M.M.; Shubin, V.G. *J. Org. Chem. USSR* ***1983***, *19*, 103.

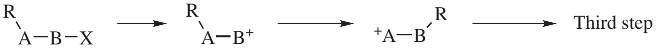
[12]See Cram, D.J., in Newman *Steric Effects in Organic Chemistry*, Wiley, NY, ***1956***; pp. 251–254; Wheland, G.W. *Advanced Organic Chemistry*, 3rd ed., Wiley, NY, ***1960***, pp. 597–604.

[13]Bernstein, H.I.; Whitmore, F.C. *J. Am. Chem. Soc.* ***1939***, *61*, 1324. For other examples, see Tsuchihashi, G.; Tomooka, K.; Suzuki, K. *Tetrahedron Lett.* ***1984***, *25*, 4253.

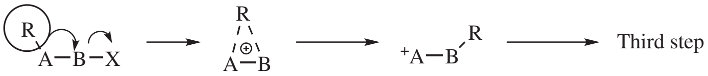
and inversion at A has been shown in other cases.[14] However, in many other cases, racemization occurs at A or B or both.[15] It is not always necessary for the product to have two steric possibilities in order to investigate the stereochemistry at A or B. Thus, in most Beckmann rearrangements (**18-17**), only the group trans (usually called *anti*) to the hydroxyl group migrates:

showing inversion at B.

This information tells us about the degree of concertedness of the three steps of the rearrangement. First consider the migration terminus B. If racemization is found at B, it is probable that the first step takes place before the second and that a positively charged carbon (or other sextet atom) is present at B:



With respect to B this is an S_N1-type process. If inversion occurs at B, it is likely that the first two steps are concerted, that a carbocation is *not* an intermediate, and that the process is S_N2-like:



10

In this case, participation by R assists in removal of X in the same way that neighboring groups do (p. 446). Indeed, R *is* a neighboring group here. The only difference is that, in the case of the neighboring-group mechanism of nucleophilic substitution, R never becomes detached from A, while in a rearrangement the bond between R and A is broken. In either case, the anchimeric assistance results in an increased rate of reaction. Of course, for such a process to take place, R must be in a favorable geometrical position (R and X antiperiplanar). Intermediate **10** may be a true intermediate or only a transition state, depending on what migrates. In certain cases of the S_N1-type process, it is possible for migration to take place with net retention of configuration at the migrating terminus because of conformational effects in the carbocation.[16]

We may summarize a few conclusions:

1. The S_N1-type process occurs mostly when B is a tertiary atom or has one aryl group and at least one other alkyl or aryl group. In other cases, the S_N2-type

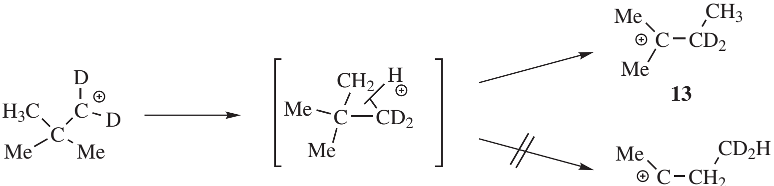
[14]See Meerwein, H.; van Emster, K. *Ber.* ***1920***, *53*, 1815; ***1922***, *55*, 2500; Meerwein, H.; Gérard, L. *Liebigs Ann. Chem.* ***1923***, *435*, 174.

[15]For example, see Winstein, S.; Morse, B.K. *J. Am. Chem. Soc.* ***1952***, *74*, 1133.

[16]Collins, C.J.; Benjamin, B.M. *J. Org. Chem.* ***1972***, *37*, 4358, and references cited therein.

process is more likely. Inversion of configuration (indicating an S_N2-type process) has been shown for a neopentyl substrate by the use of the chiral neopentyl-1-*d* alcohol.[17] On the other hand, there is other evidence that neopentyl systems undergo rearrangement by a carbocation (S_N1-type) mechanism.[18]

2. The question as to whether **10** is an intermediate or a transition state has been much debated. When R is aryl or vinyl, then **10** is probably an intermediate and the migrating group lends anchimeric assistance[19] (see p. 459 for resonance stabilization of this intermediate, when R is aryl). When R is alkyl, **10** is a protonated cyclopropane (edge- or corner-protonated; see p. 1026). There is much evidence that in simple migrations of a methyl group, the bulk of the products formed do not arise from protonated cyclopropane *intermediates*. Evidence for this statement has already been given (p. 467). Further evidence was obtained from experiments involving labeling.



11 **12** (hypothetical) **13** **14**

Rearrangement of the neopentyl cation labeled with deuterium in the 1 position (**11**) gave only *tert*-pentyl products with the label in the 3 position (derived from **13**), though if **12** were an intermediate, the cyclopropane ring could just as well cleave the other way to give *tert*-pentyl derivatives labeled in the 4 position (derived from **14**).[20] Another experiment that led to the same conclusion was the generation, in several ways, of $Me_3C^{13}CH_2^+$. In this case, the only *tert*-pentyl products isolated were labeled in C-3, that is, Me_2C^+–$^{13}CH_2CH_3$ derivatives; no derivatives of Me_2C^+–$CH_2{}^{13}CH_3$ were found.[21]

Although the bulk of the products are not formed from protonated cyclopropane intermediates, there is considerable evidence that at least in 1-propyl

[17]Sanderson, W.A.; Mosher, H.S. *J. Am. Chem. Soc.* ***1966***, *88*, 4185; Mosher, H.S. *Tetrahedron* ***1974***, *30*, 1733. See also, Guthrie, R.D. *J. Am. Chem. Soc.* ***1967***, *89*, 6718.

[18]Nordlander, J.E.; Jindal, S.P.; Schleyer, P.v.R.; Fort Jr., R.C.; Harper, J.J.; Nicholas, R.D. *J. Am. Chem. Soc.* ***1966***, *88*, 4475; Shiner, Jr., V.J.; Imhoff, M.A. *J. Am. Chem. Soc.* ***1985***, *107*, 2121.

[19]For example, see Rachon, J.; Goedkin, V.; Walborsky, H.M. *J. Org. Chem.* ***1989***, *54*, 1006. For an opposing view, see Kirmse, W.; Feyen, P. *Chem. Ber.* ***1975***, *108*, 71; Kirmse, W.; Plath, P.; Schaffrodt, H. *Chem. Ber.* ***1975***, *108*, 79.

[20]Skell, P.S.; Starer, I.; Krapcho, A.P. *J. Am. Chem. Soc.* ***1960***, *82*, 5257.

[21]Karabatsos, G.J.; Orzech Jr., C.E.; Meyerson, S. *J. Am. Chem. Soc.* ***1964***, *86*, 1994.

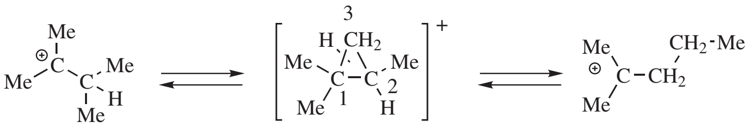
systems, a small part of the product can in fact arise from such intermediates.[22] Among this evidence is the isolation of 10–15% cyclopropanes (mentioned on p. 467). Additional evidence comes from propyl cations generated by diazotization of labeled amines ($CH_3CH_2CD_2^+$, $CH_3CD_2CH_2^+$, $CH_3CH_2{}^{14}CH_2^+$), where isotopic distribution in the products indicated that a small amount (~5%) of the product had to be formed from protonated cyclopropane intermediates, for example,[23]

$$CH_3CH_2CD_2NH_2 \xrightarrow{HONO} \sim 1\% \quad C_2H_4D\text{—}CHD\text{—}OH$$

$$CH_3CD_2CH_2NH_2 \xrightarrow{HONO} \sim 1\% \quad C_2H_4D\text{—}CHD\text{—}OH$$

$$CH_3CH_{2}{}_{14}CH_2NH_2 \xrightarrow{HONO} \sim 2\% \quad {}^{14}CH_3CH_2CH_2OH + \sim 2\% \quad CH_3{}^{14}CH_2CH_2OH$$

Even more scrambling was found in trifluoroacetolysis of 1-propyl-1-^{14}C-mercuric perchlorate.[24] However, protonated cyclopropane intermediates accounted for <1% of the products from diazotization of labeled isobutylamine[25] and from formolysis of labeled 1-propyl tosylate.[26]



15 16 17

It is likely that protonated cyclopropane transition states or intermediates are also responsible for certain non-1,2 rearrangements. For example, in super acid solution, the ions **15** and **17** are in equilibrium. It is not possible for these to interconvert solely by 1,2-alkyl or hydride shifts unless primary carbocations (which are highly unlikely) are intermediates. However, the reaction can be explained[27] by postulating that (in the forward reaction) it is the 1,2 bond

[22]For reviews, see Saunders, M.; Vogel, P.; Hagen, E.L.; Rosenfeld, J. *Acc. Chem. Res.* ***1973***, *6*, 53; Lee, C.C. *Prog. Phys. Org. Chem.* ***1970***, *7*, 129; Collins, C.J. *Chem. Rev.* ***1969***, *69*, 543. See also, Cooper, C.N.; Jenner, P.J.; Perry, N.B.; Russell-King, J.; Storesund, H.J.; Whiting, M.C. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 605.

[23]Lee, C.C.; Kruger, J.E. *Tetrahedron* ***1967***, *23*, 2539; Lee, C.C.; Wan, K. *J. Am. Chem. Soc.* ***1969***, *91*, 6416; Karabatsos, G.J.; Orzech, Jr., C.E.; Fry, J.L.; Meyerson, S. *J. Am. Chem. Soc.* ***1970***, *92*, 606.

[24]Lee, C.C.; Cessna, A.J.; Ko, E.C.F.; Vassie, S. *J. Am. Chem. Soc.* ***1973***, *95*, 5688. See also, Lee, C.C.; Reichle, R. *J. Org. Chem.* ***1977***, *42*, 2058, and references cited therein.

[25]Karabatsos, G.J.; Hsi, N.; Meyerson, S. *J. Am. Chem. Soc.* ***1970***, *92*, 621. See also, Karabatsos, G.J.; Anand, M.; Rickter, D.O.; Meyerson, S. *J. Am. Chem. Soc.* ***1970***, *92*, 1254.

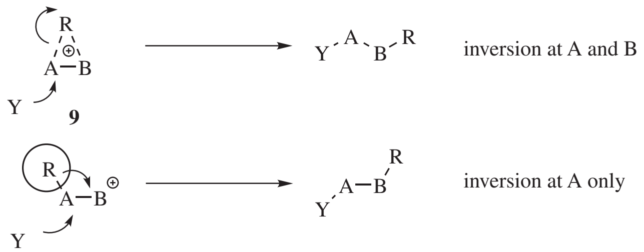
[26]Lee, C.C.; Kruger, J.E. *Can. J. Chem.* ***1966***, *44*, 2343; Shatkina, T.N.; Lovtsova, A.N.; Reutov, O.A. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1967***, 2616; Karabatsos, G.J.; Fry, J.L.; Meyerson, S. *J. Am. Chem. Soc.* ***1970***, *92*, 614. See also, Lee, C.C.; Zohdi, H.F. *Can. J. Chem.* ***1983***, *61*, 2092.

[27]Brouwer, D.M.; Oelderik, J.M. *Recl. Trav. Chim. Pays-Bas* ***1968***, *87*, 721; Saunders, M.; Jaffe, M.H.; Vogel, P. *J. Am. Chem. Soc.* ***1971***, *93*, 2558; Saunders, M.; Vogel, P. *J. Am. Chem. Soc.* ***1971***, *93*, 2559, 2561; Kirmse, W.; Loosen, K.; Prolingheuer, E. *Chem. Ber.* ***1980***, *113*, 129.

of the intermediate or transition state **16** that opens up rather than the 2,3 bond, which is the one that would open if the reaction were a normal 1,2-shift of a methyl group. In this case, opening of the 1,2 bond produces a tertiary cation, while opening of the 2,3 bond would give a secondary cation. (In the reaction **17** → **15**, it is of course the 1,3 bond that opens).

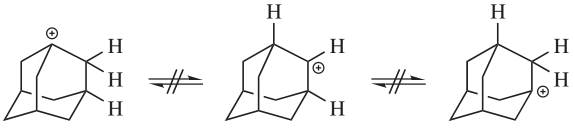
3. There has been much discussion of H as migrating group. There is no conclusive evidence that **10** in this case is or is not a true intermediate, although both positions have been argued (see p. 467).

The stereochemistry at the migration origin A is less often involved, since in most cases it does not end up as a tetrahedral atom; but when there is inversion here, there is an S_N2-type process at the beginning of the migration. This may or may not be accompanied by an S_N2 process at the migration terminus B:



In some cases, it has been found that, when H is the migrating species, the configuration at A may be *retained*.[28]

There is evidence that the configuration of the molecule may be important even where the leaving group is gone long before migration takes place. For example, the 1-adamantyl cation (**18**) does not equilibrate intramolecularly, even at temperatures up to 130°C,[29] though open-chain (e.g., **6** ⇄ **6'**) and cyclic tertiary



18 **18'**

carbocations undergo such equilibration at 0°C or below. On the basis of this and other evidence it has been concluded that for a 1,2-shift of hydrogen or methyl to proceed as smoothly as possible, the vacant *p* orbital of the carbon bearing the positive charge and the sp^3 orbital carrying the migrating group must be coplanar,[29] which is not possible for **18**.

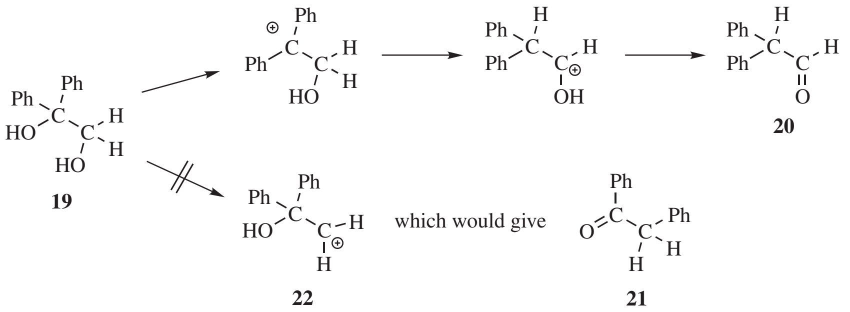
[28]Winstein, S.; Holness, N.J. *J. Am. Chem. Soc.* ***1955***, *77*, 5562; Cram, D.J.; Tadanier, J. *J. Am. Chem. Soc.* ***1959***, *81*, 2737; Bundel', Yu.G.; Pankratova, K.G.; Gordin, M.B.; Reutov, O.A. *Doklad. Chem.* ***1971***, *199*, 700; Kirmse, W.; Ratajczak, H.; Rauleder, G. *Chem. Ber.* ***1977***, *110*, 2290.

[29]Brouwer, D.M.; Hogeveen, H. *Recl. Trav. Chim. Pays-Bas* ***1970***, *89*, 211; Majerski, Z.; Schleyer, P.v.R.; Wolf, A.P. *J. Am. Chem. Soc.* ***1970***, *92*, 5731.

Migratory Aptitudes[30]

In many reactions, there is no question about which group migrates. For example, in the Hofmann, Curtius, and similar reactions there is only one possible migrating group in each molecule, and one can measure migratory aptitudes only by comparing the relative rearrangement rates of different compounds. In other instances, there are two or more potential migrating groups, but which migrates is settled by the geometry of the molecule. The Beckmann rearrangement (**18-17**) provides an example. As we have seen, only the group trans to the OH migrates. In compounds whose geometry is not restricted in this manner, there still may be eclipsing effects (see p. 1502), so that the choice of migrating group is largely determined by which group is in the right place in the most stable conformation of the molecule.[31] However, in some reactions, especially the Wagner–Meerwein (**18-1**) and the pinacol (**18-2**) rearrangements, the molecule may contain several groups that, geometrically at least, have approximately equal chances of migrating, and these reactions have often been used for the direct study of relative migratory aptitudes. In the pinacol rearrangement, there is the additional question of which OH group leaves and which does not, since a group can migrate only if the OH group on *the other* carbon is lost.

We deal with the second question first. To study this question, the best type of substrate to use is one of the form $R_2C(OH)-CR'_2(OH)$, since the only thing that determines migratory aptitude is which OH group comes off. Once the OH group is gone, the migrating group is determined. As might be expected, the OH that leaves is the one whose loss gives rise to the more stable carbocation. Thus 1,1-diphenylethanediol (**19**) gives diphenylacetaldehyde (**20**), not phenylacetophenone (**21**). Obviously, it does not matter in this case whether phenyl has a greater



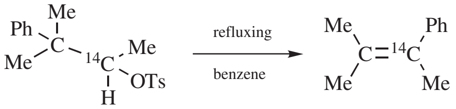
inherent migratory aptitude than hydrogen or not. Only the hydrogen can migrate because **22** is not formed. As we know, carbocation stability is enhanced by

[30]For discussions, see Koptyug, V.A.; Shubin, V.G. *J. Org. Chem. USSR* ***1980***, *16*, 1685; Wheland, G.W. *Advanced Organic Chemistry*, 3rd ed., Wiley, NY, ***1960***, pp. 573–597.

[31]For a discussion, see Cram, D.J., in Newman, M.S. *Steric Effects in Organic Chemistry*, Wiley, NY, ***1956***, pp. 270–276. For an interesting example, see Nickon, A.; Weglein, R.C. *J. Am. Chem. Soc.* ***1975***, *97*, 1271.

groups in the order aryl > alkyl > hydrogen, and this normally determines which side loses the OH group. However, exceptions are known, and which group is lost may depend on the reaction conditions (e.g., see the reaction of **53**, p. 1586).

In order to answer the question about inherent migratory aptitudes, the obvious type of substrate to use (in the pinacol rearrangement) is $R'RC(OH)-C(OH)RR'$, since the same carbocation is formed no matter which OH leaves, and it would seem that a direct comparison of the migratory tendencies of R and R′ is possible. On closer inspection, however, we can see that several factors are operating. Apart from the question of possible conformational effects, already mentioned, there is also the fact that whether the group R or R′ migrates is determined not only by the relative inherent migrating abilities of R and R′, but also by whether the group that does *not* migrate is better at stabilizing the positive charge that will now be found at the migration origin.[32] Thus, migration of R gives rise to the cation $R'C^+(OH)CR_2R'_2$, while migration of R' gives the cation $R^+C(OH)CRR'_2$, and these cations have different stabilities. It is possible that in a given case R might be found to migrate less than R′, not because it actually has a lower inherent migrating tendency, but because it is much better at stabilizing the positive charge. In addition to this factor,



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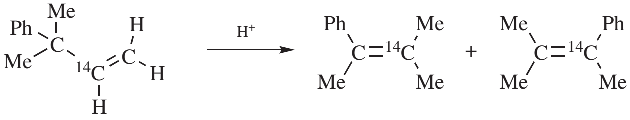


24

migrating ability of a group is also related to its capacity to render anchimeric assistance to the departure of the nucleofuge. An example of this effect is the finding that in the decomposition of tosylate **23** only the phenyl group migrates, while in acid treatment of the corresponding alkene **24**, there is competitive migration of both methyl and phenyl (in these reactions ^{14}C labeling is necessary to determine which group has migrated).[33] Both **23** and **24** give the same carbocation; the differing results must be caused by the fact that in **23** the phenyl group can assist the leaving group, while no such process is possible for **24**. This example clearly illustrates the difference between migration to a relatively

[32]For example, see McCall, M.J.; Townsend, J.M.; Bonner, W.A. *J. Am. Chem. Soc.* ***1975***, *97*, 2743; Brownbridge, P.; Hodgson, P.K.G.; Shepherd, R.; Warren, S. *J. Chem. Soc. Perkin Trans. 1* ***1976***, 2024.
[33]Grimaud, J.; Laurent, A. *Bull. Soc. Chim. Fr.* ***1967***, 3599.

free terminus and one that proceeds with the migrating group lending anchimeric assistance.[34]

It is not surprising therefore that clear-cut answers as to relative migrating tendencies are not available. More often than not migratory aptitudes are in the order aryl > alkyl, but exceptions are known, and the position of hydrogen in this series is often unpredictable. In some cases, migration of hydrogen is preferred to aryl migration; in other cases, migration of alkyl is preferred to that of hydrogen. Mixtures are often found and the isomer that predominates often depends on conditions. For example, the comparison between methyl and ethyl has been made many times in various systems, and in some cases methyl migration and in others ethyl migration has been found to predominate.[35] However, it can be said that among aryl migrating groups, electron-donating substituents in the para and meta positions increase the migratory aptitudes, while the same substituents in the ortho positions decrease them. Electron-withdrawing groups decrease migrating ability in all positions. The following are a few of the relative migratory aptitudes determined for aryl groups by Bachmann and Ferguson:[36] *p*-anisyl, 500; *p*-tolyl, 15.7; *m*-tolyl, 1.95; phenyl, 1.00; *p*-chlorophenyl, 0.7; *o*-anisyl, 0.3. For the *o*-anisyl group, the poor migrating ability probably has a steric cause, while for the others there is a fair correlation with activation or deactivation of electrophilic aromatic substitution, which is what the process is with respect to the benzene ring. It has been reported that at least in certain systems acyl groups have a greater migratory aptitude than alkyl groups.[37]

Memory Effects[38]

Solvolysis of the endo bicyclic compound **25** (X = ONs, p. 497, or Br) gave mostly the bicyclic allylic alcohol, **28**, along with a smaller amount of the tricyclic alcohol **32**, while solvolysis of the exo isomers, **29**, gave mostly **32**, with smaller amounts of **28**.[39] Thus the two isomers gave entirely different ratios of products, although

[34]A number of studies of migratory aptitudes in the dienone-phenol rearrangement (**18-5**) are in accord with the above. For a discussion, see Fischer, A.; Henderson, G.N. *J. Chem. Soc., Chem. Commun.* ***1979***, 279, and references cited therein. See also, Palmer, J.D.; Waring, A.J. *J. Chem. Soc. Perkin Trans. 2* ***1979***, 1089; Marx, J.N.; Hahn, Y.P. *J. Org. Chem.* ***1988***, *53*, 2866.

[35]For examples, see Cram, D.J.; Knight, J.D. *J. Am. Chem. Soc.* ***1952***, *74*, 5839; Stiles, M.; Mayer, R.P. *J. Am. Chem. Soc.* ***1959***, *81*, 1497; Heidke, R.L.; Saunders, Jr., W.H. *J. Am. Chem. Soc.* ***1966***, *88*, 5816; Dubois, J.E.; Bauer, P. *J. Am. Chem. Soc.* ***1968***, *90*, 4510, 4511; Bundel', Yu. G.; Levina, I.Yu.; Reutov, O.A. *J. Org. Chem. USSR* ***1970***, *6*, 1; Pilkington, J.W.; Waring, A.J. *J. Chem. Soc. Perkin Trans. 2* ***1976***, 1349; Korchagina, D.V.; Derendyaev, B.G.; Shubin, V.G.; Koptyug, V.A. *J. Org. Chem. USSR* ***1976***, *12*, 378; Wistuba, E.; Rüchardt, C. *Tetrahedron Lett.* ***1981***, *22*, 4069; Jost, R.; Laali, K.; Sommer, J. *Nouv. J. Chim.* ***1983***, *7*, 79

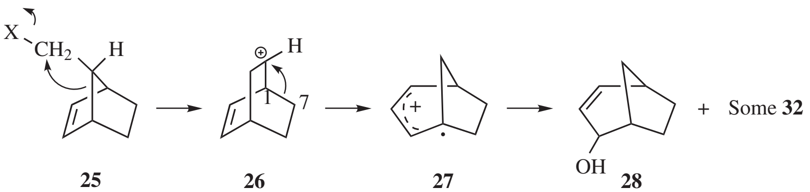
[36]Bachmann, W.E.; Ferguson, J.W. *J. Am. Chem. Soc.* ***1934***, *56*, 2081.

[37]Le Drian, C.; Vogel, P. *Helv. Chim. Acta* ***1987***, *70*, 1703; *Tetrahedron Lett.* ***1987***, *28*, 1523.

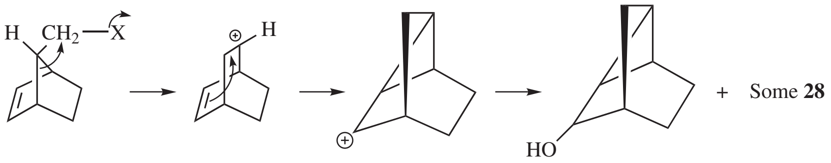
[38]For a review, see Berson, J.A. *Angew. Chem. Int. Ed.* ***1968***, *7*, 779.

[39]Berson, J.A.; Poonian, M.S.; Libbey, W.J. *J. Am. Chem. Soc.* ***1969***, *91*, 5567; Berson, J.A.; Donald, D.S.; Libbey, W.J. *J. Am. Chem. Soc.* ***1969***, *91*, 5580; Berson, J.A.; Wege, D.; Clarke, G.M.; Bergman, R.G. *J. Am. Chem. Soc.* ***1969***, *91*, 5594, 5601.

the carbocation initially formed (**26** or **30**) seems to be the same for each. In the case of **26**, a second rearrangement (a shift of the 1,7 bond) follows, while with **30** what follows is an intramolecular addition of the positive carbon to the double bond.

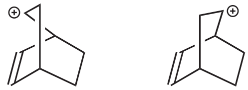


25 **26** **27** **28**



29 **30** **31** **32**

It seems as if **26** and **30** "remember" how they were formed before they go on to give the second step. Such effects are called *memory effects* and other such cases are known.[40] The causes of these effects are not well understood, though there has been much discussion. One possible cause is differential solvation of the apparently identical ions **26** and **30**. Other possibilities are (*1*) that the ions have geometrical structures that are twisted in opposite senses (e.g., a twisted **30** might have its positive carbon closer to the double



Twisted **30** Twisted **26**

bond than a twisted **26**); (*2*) that ion pairing is responsible;[41] and (*3*) that nonclassical carbocations are involved.[42] One possibility that has been ruled out is that the steps **25** → **26** → **27** and **29** → **30** → **31** are concerted, so that **26** and **30** never exist at all. This possibility has been excluded by several kinds of evidence, including the fact that **25** gives not only **28**, but also some **32**; and **29** gives some **28**

[40]For examples of memory effects in other systems, see Berson, J.A.; Luibrand, R.T.; Kundu, N.G.; Morris, D.G. *J. Am. Chem. Soc.* ***1971***, *93*, 3075; Collins, C.J. *Acc. Chem. Res.* ***1971***, *4*, 315; Collins, J.A.; Glover, I.T.; Eckart, M.D.; Raaen, V.F.; Benjamin, B.M.; Benjaminov, B.S. *J. Am. Chem. Soc.* ***1972***, *94*, 899; Svensson, T. *Chem. Scr.,* ***1974***, *6*, 22.

[41]See Collins, C.J. *Chem. Soc. Rev.* ***1975***, *4*, 251.

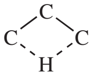
[42]See, for example, Seybold, G.; Vogel, P.; Saunders, M.; Wiberg, K.B. *J. Am. Chem. Soc.* ***1973***, *95*, 2045; Kirmse, W.; Günther, B. *J. Am. Chem. Soc.* ***1978***, *100*, 3619.

along with **32**. This means that some of the **26** and **30** ions interconvert, a phenomenon known as *leakage*.

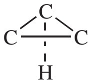
Longer Nucleophilic Rearrangements

The question as to whether a group can migrate with its electron pair from A to C in W–A–B–C or over longer distances has been much debated. Although claims have been made that alkyl groups can migrate in this way, the evidence is that such migration is extremely rare, if it occurs at all. One experiment that demonstrated this was the generation of the 3,3-dimethyl-1-butyl cation $Me_3CCH_2CH_2^+$. If 1,3-methyl migrations are possible, this cation would appear to be a favorable substrate, since such a migration would convert a primary cation into the tertiary 2-methyl-2-pentyl cation $Me_2CCH_2CH_2CH_3$, while the only possible 1,2 migration (of hydride) would give only a secondary cation. However, no products arising from the 2-methyl-2-pentyl cation were found, the only rearranged products being those formed by the 1,2 hydride migration.[43] 1,3 Migration of bromine has been reported.[44]

However, most of the debate over the possibility of 1,3 migrations has concerned not methyl or bromine, but 1,3 hydride shifts.[45] There is no doubt that *apparent* 1,3 hydride shifts take place (many instances have been found), but the question is whether they are truly direct hydride shifts or whether they occur by another



A



B

mechanism. There are at least two ways in which indirect 1,3-hydride shifts can take place: (*1*) by successive 1,2-shifts or (*2*) through the intervention of protonated cyclopropanes (see p. 1565). A direct 1,3-shift would have the transition state **A**, while the transition state for a 1,3-shift involving a protonated cyclopropane intermediate would resemble **B**. The evidence is that most reported 1,3 hydride shifts are actually the result of successive 1,2 migrations,[46] but that in some cases small amounts of products cannot be accounted for in this way. For example, the reaction of 2-methyl-1-butanol with KOH and bromoform gave a mixture of alkenes, nearly all of which could have arisen from simple

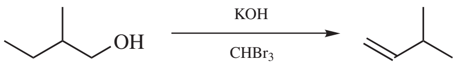
[43]Skell, P.S.; Reichenbacher, P.H. *J. Am. Chem. Soc.* ***1968***, *90*, 2309.

[44]Reineke, C.E.; McCarthy, Jr., J.R. *J. Am. Chem. Soc.* ***1970***, *92*, 6376; Smolina, T.A.; Gopius, E.D.; Gruzdneva, V.N.; Reutov, O.A. *Doklad. Chem.* ***1973***, *209*, 280.

[45]For a review, see Fry, J.L.; Karabatsos, G.J., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, p. 527.

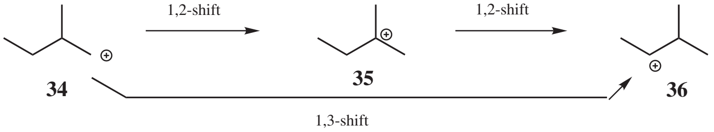
[46]For example, see Bundel', Yu.G.; Levina, I.Yu.; Krzhizhevskii, A.M.; Reutov, O.A. *Doklad. Chem.* ***1968***, *181*, 583; Fărcaşiu, D.; Kascheres, C.; Schwartz, L.H. *J. Am. Chem. Soc.* ***1972***, *94*, 180; Kirmse, W.; Knist, J.; Ratajczak, H. *Chem. Ber.* ***1976***, *109*, 2296.

elimination or 1,2-shifts of hydride or alkyl. However, 1.2% of the product was **33**:[47]



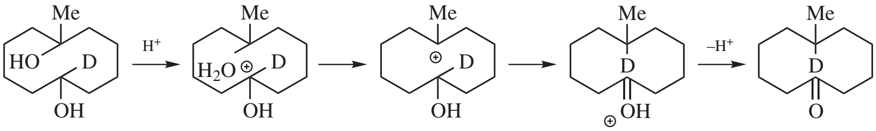
33

Hypothetically, **33** could have arisen from a 1,3-shift (direct or through a protonated cyclopropane) or from two successive 1,2-shifts:



34 **35** **36**

However, the same reaction applied to 2-methyl-2-butanol gave no **33**, which demonstrated that **36** was not formed from **35**. The conclusion made was that **36** was formed directly from **34**. This experiment does not answer the question as to whether **36** was formed by a direct shift or through a protonated cyclopropane, but from other evidence[48] it appears that 1,3 hydride shifts that do not result from successive 1,2 migrations usually take place through protonated cyclopropane intermediates (which, as we saw on p. 1565, account for only a small percentage of the product in any case). However, there is evidence that direct 1,3 hydride shifts by way of **A** may take place in super acid solutions.[49] Although direct nucleophilic rearrangements over distances >1,2 are rare (or perhaps nonexistent) when the migrating atom or group must move along a chain, this is not so for a shift across a ring of 8–11 members. Many such transannular rearrangements are known.[50] Several examples are given on p. 223. This is the mechanism of one of these:[51]



[47]Skell, P.S.; Maxwell, R.J. *J. Am. Chem. Soc.* ***1962***, *84*, 3963. See also, Skell, P.S.; Starer, I. *J. Am. Chem. Soc.* ***1962***, *84*, 3962.

[48]For example, see Brouwer, D.M.; van Doorn, J.A. *Recl. Trav. Chim. Pays-Bas* ***1969***, *8*, 573; Dupuy, W.E.; Goldsmith, E.A.; Hudson, H.R. *J. Chem. Soc. Perkin Trans. 2* ***1973***, 74; Hudson, H.R.; Koplick, A.J.; Poulton, D.J. *Tetrahedron Lett.* ***1975***, 1449; Fry, J.L.; Karabatsos, G.J., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, p. 527.

[49]Saunders, M.; Stofko Jr., J.J. *J. Am. Chem. Soc.* ***1973***, *95*, 252.

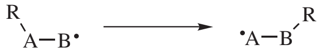
[50]For reviews, see Cope, A.C.; Martin, M.M.; McKervey, M.A. *Q. Rev. Chem. Soc.* ***1966***, *20*, 119. For many references, see Blomquist, A.T.; Buck, C.J. *J. Am. Chem. Soc.* ***1951***, *81*, 672.

[51]Prelog, V.; Küng, W. *Helv. Chim. Acta* ***1956***, *39*, 1394.

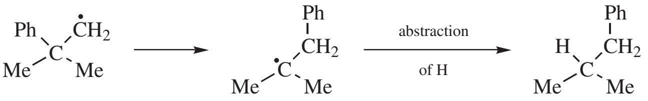
It is noteworthy that the *methyl* group does not migrate in this system. It is generally true that alkyl groups do not undergo transannular migration.[52] In most cases, it is hydride that undergoes this type of migration, though a small amount of phenyl migration has also been shown.[53]

Free-Radical Rearrangements[54]

1,2-Free-radical rearrangements are much less common than the nucleophilic type previously considered, for the reasons mentioned on p. 1559. Where they do occur, the general pattern is similar. There must first be generation of a free radical, and then the actual migration in which the migrating group moves with one electron:



Finally, the new free radical must stabilize itself by a further reaction. The order of radical stability leads us to predict that here too, as with carbocation rearrangements, any migrations should be in the order primary → secondary → tertiary, and that the logical place to look for them should be in neopentyl and neophyl systems. The most common way of generating free radicals for the purpose of detection of rearrangements is by decarbonylation of aldehydes (**14-32**). In this manner, it was found that neophyl radicals *do* undergo rearrangement. Thus, $PhCMe_2CH_2CHO$ treated with di-*tert*-butyl peroxide gave about equal amounts of the normal product $PhCMe_2CH_3$ and the product arising from migration of phenyl:[55]



[52]For an apparent exception, see Fărcaşiu, D.; Seppo, E.; Kizirian, M.; Ledlie, D.B.; Sevin, A. *J. Am. Chem. Soc.* ***1989***, *111*, 8466.

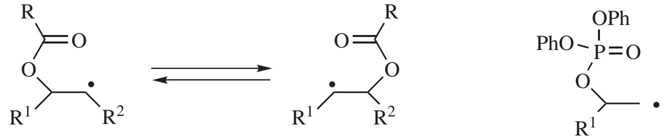
[53]Cope, A.C.; Burton, P.E.; Caspar, M.L. *J. Am. Chem. Soc.* ***1962***, *84*, 4855.

[54]For reviews, see Beckwith, A.L.J.; Ingold, K.U. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 1, Academic Press, NY, ***1980***, pp. 161–310; Wilt, J.W., in Kochi, J.K. *Free Radicals*, Vol. 1, Wiley, NY, ***1973***, pp. 333–501; Stepukhovich, A.D.; Babayan, V.I. *Russ. Chem. Rev.* ***1972***, *41*, 750; Nonhebel, D.C.; Walton, J.C. *Free-Radical Chemistry*, Cambridge University Press, London, ***1974***, pp. 498–552; Huyser, E.S. *Free-Radical Chain Reactions*, Wiley, NY, ***1970***, pp. 235–255; Freidlina, R.Kh. *Adv. Free-Radical Chem.* ***1965***, *1*, 211–278; Pryor, W.A. *Free Radicals*, McGraw-Hill, NY, ***1966***, pp. 266–284.

[55]Winstein, S.; Seubold, Jr., F.H. *J. Am. Chem. Soc.* ***1947***, *69*, 2916; Seubold, Jr., F.H. *J. Am. Chem. Soc.* ***1953***, *75*, 2532. For the observation of this rearrangement by esr, see Hamilton, Jr., E.J.; Fischer, H. *Helv. Chim. Acta* ***1973***, *56*, 795.

Many other cases of free-radical migration of aryl groups have been found.[56] Intramolecular radical rearrangements are known.[57] The C-4 radicals of α- and β-thujone undergo two distinct rearrangement reactions, and it has been proposed that these could serve as simultaneous, but independent radical clocks.[58]

A 1,2-shift has been observed in radicals bearing an OCOR group at the β-carbon where the oxygen group migrates as shown in the interconversion of **37** and **38**. This has been proven by ^{18}O isotopic labeling experiments[59] and other mechanistic explorations.[60] A similar rearrangement was observed with phosphatoxy alkyl radicals, such as **39**.[61] A 1,2-shift of hydrogen atoms has been observed in aryl radicals.[62]



37 **38** **39**

A C → N 1,2-aryl rearrangement was observed when alkyl azides were treated with *n*-Bu_3SnH, proceeding via an C–N•–$SnBu_3$ species to give an imine.[63]

It is noteworthy that the extent of migration is much less than with corresponding carbocations: Thus in the example given, there was only ~50% migration, whereas the carbocation would have given much more. Also noteworthy is that there was no migration of the methyl group. In general, it may be said that free-radical migration of alkyl groups does not occur at ordinary temperatures. Many attempts have been made to detect such migration on the traditional neopentyl and bornyl types of substrates. However, alkyl migration is not observed, even in substrates where the corresponding carbocations undergo facile rearrangement.[64] Another type of migration that is very common for carbocations, but not observed

[56]For example, see Curtin, D.Y.; Hurwitz, M.J. *J. Am. Chem. Soc.* ***1952***, *74*, 5381; Wilt, J.K.; Philip, H. *J. Org. Chem.* ***1959***, *24*, 441; ***1960***, *25*, 891; Pines, H.; Goetschel, C.T. *J. Am. Chem. Soc.* ***1964***, *87*, 4207; Goerner Jr., R.N.; Cote, P.N.; Vittimberga, B.M. *J. Org. Chem.* ***1977***, *42*, 19; Collins, C.J.; Roark, W.H.; Raaen, V.F.; Benjamin, B.M. *J. Am. Chem. Soc.* ***1979***, *101*, 1877; Walter, D.W.; McBride, J.M. *J. Am. Chem. Soc.* ***1981***, *103*, 7069, 7074. For a review, see Studer, A.; Bossart, M. *Tetrahedron* ***2001***, *57*, 9649.

[57]Prévost, N.; Shipman, M. *Org. Lett.* ***2001***, *3*, 2383.

[58]He, X.; Ortiz de Montellano, P.R. *J. Org. Chem.* ***2004***, *69*, 5684.

[59]Crich, D.; Filzen, G.F. *J. Org. Chem.* ***1995***, *60*, 4834.

[60]Beckwith, A.L.J.; Duggan, P.J. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 1777; ***1993***, 1673.

[61]Crich, D.; Yao, Q. *Tetrahedron Lett.* ***1993***, *34*, 5677. See Ganapathy, S.; Cambron R.T.; Dockery, K.P.; Wu, Y.-W.; Harris, J.M.; Bentrude, W.G. *Tetrahedron Lett.* ***1993***, *34*, 5987 for a related triplet sensitized rearrangement of allylic phosphites and phosphonates.

[62]Brooks, M.A.; Scott, L.T. *J. Am. Chem. Soc.* ***1999***, *121*, 5444.

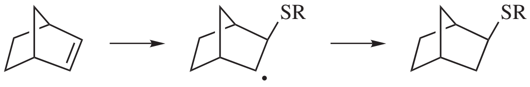
[63]Kim, S.; Do, J.Y. *J. Chem. Soc., Chem. Commun.* ***1995***, 1607.

[64]For a summary of unsuccessful attempts, see Slaugh, L.H.; Magoon, E.F.; Guinn, V.P. *J. Org. Chem.* ***1963***, *28*, 2643.

for free radicals, is 1,2 migration of hydrogen. We confine ourselves to a few examples of the lack of migration of alkyl groups and hydrogen:

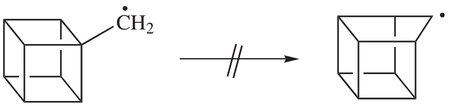
1. 3,3-Dimethylpentanal ($EtCMe_2CH_2CHO$) gave no rearranged products on decarbonylation.[65]

2. Addition of RSH to norbornene gave only *exo*-norbornyl sulfides, though **40** is an intermediate, and the corresponding carbocation cannot be formed without rearrangement.[66]



40

3. The cubylcarbinyl radical did not rearrange to the 1-homocubyl radical, though doing so would result in a considerable decrease in strain.[67]



Cubylcarbinyl radical   1-Homocubyl radical

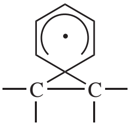
4. It was shown[68] that no rearrangement of isobutyl radical to *tert*-butyl radical (which would involve the formation of a more stable radical by a hydrogen shift) took place during the chlorination of isobutane.

However, 1,2 migration of alkyl groups has been shown to occur in certain *diradicals*.[69] For example, the following rearrangement has been established by tritium labeling.[70]

In this case, the fact that migration of the methyl group leads directly to a compound in which all electrons are paired undoubtedly contributes to the driving force of the reaction.

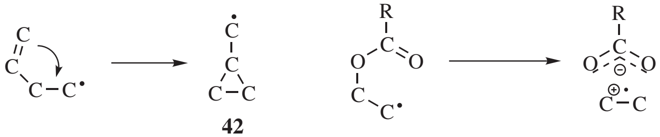
[65]Seubold, Jr., F.H. *J. Am. Chem. Soc.* ***1954***, *76*, 3732.
[66]Cristol, S.J.; Brindell, G.D. *J. Am. Chem. Soc.* ***1954***, *76*, 5699.
[67]Eaton, P.E.; Yip, Y. *J. Am. Chem. Soc.* ***1991***, *113*, 7692.
[68]Brown, H.C.; Russel, G.A. *J. Am. Chem. Soc.* ***1952***, *74*, 3995. See also, Desai, V.R.; Nechvatal, A.; Tedder, J.M. *J. Chem. Soc. B* ***1970***, 386.
[69]For a review, see Freidlina, R.Kh.; Terent'ev, A.B. *Russ. Chem. Rev.* ***1974***, *43*, 129.
[70]McKnight, C.; Rowland, F.S. *J. Am. Chem. Soc.* ***1966***, *88*, 3179. For other examples, see Greene, F.D.; Adam, W.; Knudsen Jr., G.A. *J. Org. Chem.* ***1966***, *31*, 2087; Gajewski, J.J.; Burka, L.T. *J. Am. Chem. Soc.* ***1972***, *94*, 8857, 8860, 8865; Adam, W.; Aponte, G.S. *J. Am. Chem. Soc.* ***1971***, *93*, 4300.

The fact that aryl groups migrate, but alkyl groups and hydrogen generally do not, leads to the proposition that **41**, in which the odd electron is not found in the three-membered ring, may be an intermediate. There has been much controversy on this point, but the bulk of the evidence indicates that **41** is a transition state, not an intermediate.[71] Among the evidence is the failure to observe **41** either by ESR[72] or CIDNP.[73] Both of these techniques can detect free radicals with extremely short lifetimes (pp. 266–268).[74]



41

Besides aryl, vinylic[75] and acetoxy groups[76] also migrate. Vinylic groups migrate by way of a cyclopropylcarbinyl radical intermediate (**42**),[77] while the migration of acetoxy groups may involve the charge-separated structure shown.[78] Thermal isomerization of 1-(3-butenyl)cyclopropane at 415°C leads to bicyclo[2.2.1]heptane.[79] Migration has been observed for chloro (and to a much lesser extent



bromo) groups. For example, in the reaction of $Cl_3CCH{=}CH_2$ with bromine under the influence of peroxides, the products were 47% $Cl_3CCHBrCH_2Br$

[71]For molecular-orbital calcualtions indicating that **41** is an intermediate, see Yamabe, S. *Chem. Lett.* ***1989***, 1523.

[72]Edge, D.J.; Kochi, J.K. *J. Am. Chem. Soc.* ***1972***, *94*, 7695.

[73]Shevlin, P.B.; Hansen, H.J. *J. Org. Chem.* ***1977***, *42*, 3011; Olah, G.A.; Krishnamurthy, V.V.; Singh, B.P.; Iyer, P.S. *J. Org. Chem.* ***1983***, *48*, 955. **37** has been detected as an intemediate in a different reaction: Effio, A.; Griller, D.; Ingold, K.U.; Scaiano, J.C.; Sheng, S.J. *J. Am. Chem. Soc.* ***1980***, *102*, 6063; Leardini, R.; Nanni, D.; Pedulli, G.F.; Tundo, A.; Zanardi, G.; Foresti, E.; Palmieri, P. *J. Am. Chem. Soc.* ***1989***, *111*, 7723.

[74]For other evidence, see Martin, M.M. *J. Am. Chem. Soc.* ***1962***, *84*, 1986; Rüchardt, C.; Hecht, R. *Chem. Ber.* ***1965***, *98*, 2460, 2471; Rüchardt, C.; Trautwein, H. *Chem. Ber.* ***1965***, *98*, 2478.

[75]For example, see Slaugh, L.H. *J. Am. Chem. Soc.* ***1965***, *87*, 1522; Newcomb, M.; Glenn, A.G.; Williams, W.G. *J. Org. Chem.* ***1989***, *54*, 2675.

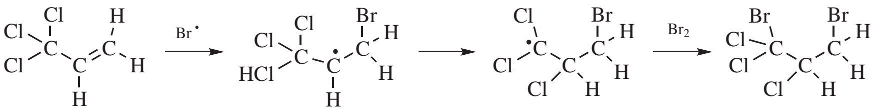
[76]Surzur, J.; Teissier, P. *Bull. Soc. Chim. Fr.* ***1970***, 3060; Tanner, D.D.; Law, F.C.P. *J. Am. Chem. Soc.* ***1969***, *91*, 7535; Julia, S.; Lorne, R. *C. R. Acad. Sci. Ser. C* ***1971***, *273*, 174; Lewis, S.N.; Miller, J.J.; Winstein, S. *J. Org. Chem.* ***1972***, *37*, 1478.

[77]For evidence for this species, see Montgomery, L.K.; Matt, J.W.; Webster, J.R. *J. Am. Chem. Soc.* ***1967***, *89*, 923; Montgomery, L.K.; Matt, J.W. *J. Am. Chem. Soc.* ***1967***, *89*, 934, 6556; Giese, B.; Heinrich, N.; Horler, H.; Koch, W.; Schwarz, H. *Chem. Ber.* ***1986***, *119*, 3528.

[78]Beckwith, A.L.J.; Thomas, C.B. *J. Chem. Soc. Perkin Trans. 2* ***1973***, 861; Barclay, L.R.C.; Lusztyk, J.; Ingold, K.U. *J. Am. Chem. Soc.* ***1984***, *106*, 1793.

[79]Baldwin, J.E.; Burrell, R.C.; Shukla, R. *Org. Lett.* ***2002***, *4*, 3305.

(the normal addition product) and 53% $BrCCl_2CHClCH_2Br$, which arose by rearrangement:

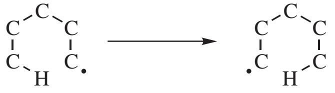


In this particular case, the driving force for the rearrangement is the particular stability of dichloroalkyl free radicals. Nesmeyanov, Freidlina, and co-workers have extensively studied reactions of this sort.[80] It has been shown that the 1,2 migration of Cl readily occurs if the migration origin is tertiary and the migration terminus primary.[81] Migration of Cl and Br could take place by a transition state in which the odd electron is accommodated in a vacant *d* orbital of the halogen.

Migratory aptitudes have been measured for the phenyl and vinyl groups, and for three other groups, using the system $RCMe_2CH_2\bullet \rightarrow Me_2\dot{C}\,CH_2R$. These were found to be in the order R = $H_2C{=}CH_2 > Me_3CC{=}O > Ph > Me_3C{\equiv}C > CN$.[82]

In summary then, 1,2 free-radical migrations are much less prevalent than the analogous carbocation processes, and are important only for aryl, vinylic, acetoxy, and halogen migrating groups. The direction of migration is normally toward the more stable radical, but "wrong-way" rearrangements are also known.[83]

Despite the fact that hydrogen atoms do not migrate 1,2, longer free-radical migrations of hydrogen are known.[84] The most common are 1,5-shifts, but 1,6 and longer shifts have also been found. The possibility of 1,3 hydrogen shifts has been much investigated, but it is not certain if any actually occur. If they do they are rare, presumably because the most favorable geometry for C•••H•••C in the transition state is linear and this geometry cannot be achieved in a 1,3-shift. 1,4-Shifts are definitely known, but are still not very common. These long shifts are best regarded as internal abstractions of hydrogen (for reactions involving them, see **14-6** and **18-40**):



Transannular shifts of hydrogen atoms have also been observed.[85]

[80]For reviews, see Freidlina, R.Kh.; Terent'ev, A.B. *Russ. Chem. Rev.* ***1979***, *48*, 828; Freidlina, R.Kh. *Adv. Free-Radical Chem.* ***1965***, *1*, 211, 231–249.

[81]See, for example, Skell, P.S.; Pavlis, R.R.; Lewis, D.C.; Shea, K.J. *J. Am. Chem. Soc.* ***1973***, *95*, 6735; Chen, K.S.; Tang, D.Y.H.; Montgomery, L.K.; Kochi, J.K. *J. Am. Chem. Soc.* ***1974***, *96*, 2201.

[82]Lindsay, D.A.; Lusztyk, J.L.; Ingold, K.U. *J. Am. Chem. Soc.* ***1984***, *106*, 7087.

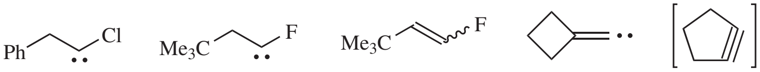
[83]Slaugh, L.H.; Raley, J.H. *J. Am. Chem. Soc.* ***1960***, *82*, 1259; Bonner, W.A.; Mango, F.D. *J. Org. Chem.* ***1964***, *29*, 29; Dannenberg, J.J.; Dill, K. *Tetrahedron Lett.* ***1972***, 1571.

[84]For a discussion, see Freidlina, R.Kh.; Terent'ev, A.B. *Acc. Chem. Res.* ***1977***, *10*, 9.

[85]Heusler, K.; Kalvoda, J. *Tetrahedron Lett.* ***1963***, 1001; Cope, A.C.; Bly, R.S.; Martin, M.M.; Petterson, R.C. *J. Am. Chem. Soc.* ***1965***, *87*, 3111; Fisch, M.; Ourisson, G. *Chem. Commun.* ***1965***, 407; Traynham, J.G.; Couvillon, T.M. *J. Am. Chem. Soc.* ***1967***, *89*, 3205.

Carbene Rearrangements[86]

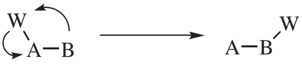
Carbenes can rearrange to alkenes in many cases.[87] A 1,2-hydrogen shift leads to an alkene, and this is often competitive with insertion reactions.[88] Benzylchlorocarbene (**43**) rearranges via a 1,2 hydrogen shift to give the alkene.[89] Similarly, carbene **44** rearranges to alkene **45**, and replacement of H on the α-carbon with D showed a deuterium isotope effect of ~5.[90] Vinylidene carbene ($H_2C{=}C{:}$) rearranges to acetylene.[91] Rearrangement of alkylidene carbene **46** has been calculated to give the highly unstable cyclopentyne (**47**), which cannot be isolated, but can give a [2 + 2]-cycloaddition product when generated in the presence of a simple alkene.[92] The spiro carbenes undergo rearrangement reactions.[93]



43 **44** **45** **46** **47**

Electrophilic Rearrangements[94]

Rearrangements in which a group migrates without its electrons are much rarer than the two kinds previously considered, but the general principles are the same. A carbanion (or other negative ion) is created first, and the actual rearrangement step involves migration of a group without its electrons:



The product of the rearrangement may be stable or may react further, depending on its nature (see also, pp. 1585). An *ab initio* study predicts that a [1,2]-alkyl shift in alkyne anions should be facile.[95]

[86]For a review of thermally induced cyclopropane–carbene rearrangements, see Baird, M.S. *Chem. Rev.* ***2003***, *103*, 1271.

[87]de Meijere, A.; Kozhushkov, S.I.; Faber, D.; Bagutskii, V.; Boese, R.; Haumann, T.; Walsh, R. *Eur. J. Org. Chem.* ***2001***, 3607.

[88]Nickon, A.; Stern, A.G.; Ilao, M.C. *Tetrahedron Lett.* ***1993***, *34*, 1391.

[89]Merrer, D.C.; Moss, R.A.; Liu, M.T.H.; Banks, J.-T.; Ingold, K.U. *J. Org. Chem.* ***1998***, *63*, 3010.

[90]Moss, R.A.; Ho, C.-J.; Liu, W.; Sierakowski, C. *Tetrahedron Lett.* ***1992***, *33*, 4287.

[91]Hayes, R.L.; Fattal, E.; Govind, N.; Carter, E.A. *J. Am. Chem. Soc.* ***2001***, *123*, 641.

[92]Gilbert, J.C.; Kirschner, S. *Tetrahedron Lett.* ***1993***, *34*, 599, 603.

[93]Moss, R.A.; Zheng, F.; Krough-Jespersen, K. *Org. Lett.* ***2001***, *3*, 1439.

[94]For reviews, see Hunter, D.H.; Stothers, J.B.; Warnhoff, E.W. in de Mayo, P. *Rearrangments in Ground and Excited States*, Vol. 1, Academic Press, NY, ***1980***, pp. 391–470; Grovenstein, Jr., E. *Angew. Chem. Int. Ed.* ***1978***, *17*, 313; *Adv. Organomet. Chem.* ***1977***, *16*, 167; Jensen, F.R.; Rickborn, B. *Electrophilic Substitution of Organomercurials*, McGraw-Hill, NY, ***1968***, pp. 21–30; Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, ***1965***, pp. 223–243.

[95]Borosky, G.L. *J. Org. Chem.* ***1998***, *63*, 3337.

REACTIONS

The reactions in this chapter are classified into three main groups and 1,2-shifts are considered first. Within this group, reactions are classified according to (*1*) the identity of the substrate atoms A and B and (*2*) the nature of the migrating group W. In the second group are the cyclic rearrangements. The third group consists of rearrangements that cannot be fitted into either of the first two categories.

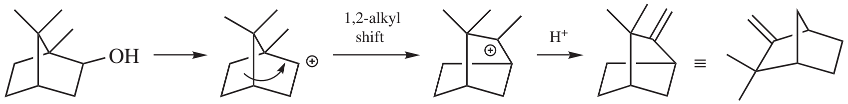
Reactions in which the migration terminus is on an aromatic ring have been treated under aromatic substitution. These are **11-27–11-32**, **11-36**, **13-30–13-32**, and, partially, **11-33**, **11-38**, and **11-39**. Double-bond shifts have also been treated in other chapters, though they may be considered rearrangements (p. $$$, p. $$$, and **12-2**). Other reactions that may be regarded as rearrangements are the Pummerer (**19-83**) and Willgerodt (**19-84**) reactions.

1,2-REARRANGEMENTS

A. Carbon-to-Carbon Migrations of R, H, and Ar

18-1 Wagner–Meerwein and Related Reactions

1/Hydro,1/hydroxy-(2/ → 1/alkyl)-*migro*-elimination, and so on



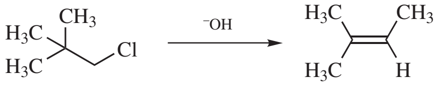
isoborneol **48** **49** camphene

Wagner–Meerwein rearrangements were first discovered in the bicyclic terpenes, and most of the early development of this reaction was with these compounds.[96] An example is the conversion of isoborneol to camphene. It fundamentally involves a 1,2 alkyl shift of an intermediate carbocation, such as **48** → **49**. When alcohols are treated with acids, simple substitution (e.g., **10-48**) or elimination (**17-1**) usually accounts for most or all of the products. But in many cases, especially where two or three alkyl or aryl groups are on the β carbon, some or all of the product is rearranged. These rearrangements have been called *Wagner–Meerwein rearrangements*, although this term is nowadays reserved for relatively specific transformations, such as isoborneol to camphene and related reactions. As pointed out previously, the carbocation that is a direct product of the rearrangement must stabilize itself, and most often it does this by the loss

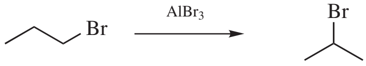
[96]For a review of rearrangements in bicyclic systems, see Hogeveen, H.; van Kruchten, E.M.G.A. *Top. Curr. Chem.* ***1979***, *80*, 89. For reviews concerning caranes and pinanes see, respectively, Arbuzov, B.A.; Isaeva, Z.G. *Russ. Chem. Rev.* ***1976***, *45*, 673; Banthorpe, D.V.; Whittaker, D. *Q. Rev. Chem. Soc.* ***1966***, *20*, 373.

of a hydrogen β to it, so the rearrangement product is usually an alkene.[97] If there is a choice of protons, Zaitsev's rule (p. 1482) governs the direction, as we might expect. Sometimes a different positive group is lost instead of a proton. Less often, the new carbocation stabilizes itself by combining with a nucleophile instead of losing a proton. The nucleophile may be the water that is the original leaving group, so that the product is a rearranged alcohol, or it may be some other species present (solvent, added nucleophile, etc.). Rearrangement is usually predominant in neopentyl and neophyl types of substrates, and with these types normal nucleophilic substitution is difficult (normal elimination is of course impossible). Under S_N2 conditions, substitution is extremely slow;[98] and under S_N1 conditions, carbocations are formed that rapidly rearrange. However, free-radical substitution, unaccompanied by rearrangement, can be carried out on neopentyl systems, though, as we have seen (p. 1574), neophyl systems undergo rearrangement as well as substitution.

Example *a*

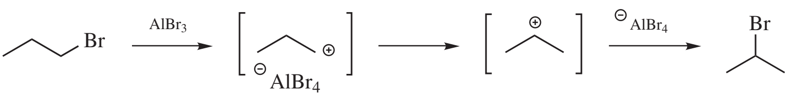


Example *b*



Examples of Wagner–Meerwein-type rearrangements are found in simpler systems, such as neopentyl chloride (example *a*) and even 1-bromopropane (example *b*). These two examples illustrate the following points:

1. Hydride ion can migrate. In example *b*, it was hydride that shifted, not bromine:



2. The leaving group does not have to be H_2O, but can be any departing species whose loss creates a carbocation, including N_2 from aliphatic diazonium ions[99] (see the section on leaving groups in nucleophilic substitution, p. 438). Also, rearrangement may follow when the carbocation is created by addition of a proton or other positive species to a double bond. Even alkanes give

[97]For a review of such rearrangements, see Kaupp, G. *Top. Curr. Chem.* ***1988***, *146*, 57.

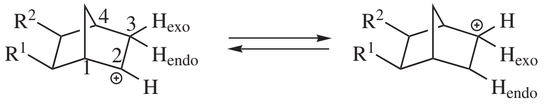
[98]See, however, Lewis, R.G.; Gustafson, D.H.; Erman, W.F. *Tetrahedron Lett.* ***1967***, 401; Paquette, L.A.; Philips, J.C. *Tetrahedron Lett.* ***1967***, 4645; Anderson, P.H.; Stephenson, B.; Mosher, H.S. *J. Am. Chem. Soc.* ***1974***, *96*, 3171.

[99]For reviews of rearrangements arising from diazotization of aliphatic amines, see, in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, the articles by White, E.H.; Woodcock, D.J. pp. 407–497 (473–483) and by Banthorpe, D.V. pp. 585–667 (586–612).

rearrangements when heated with Lewis acids, provided some species is initially present to form a carbocation from the alkane.

3. Example *b* illustrates that the last step can be substitution instead of elimination.
4. Example *a* illustrates that the new double bond is formed in accord with Zaitsev's rule.

2-Norbornyl cations (see **48**), besides displaying the 1,2-shifts of a CH_2 group previously illustrated for the isoborneol → camphene conversion, are also prone to rapid hydride shifts from the 3 to the 2 position (known as 3,2-shifts). These 3,2-shifts usually take place from the exo side;[100] that is, the 3-exo hydrogen migrates to the 2-exo position.[101] This stereoselectivity is analogous to the behavior we have previously seen for norbornyl



systems, namely, that nucleophiles attack norbornyl cations from the exo side (p. 461) and that addition to norbornenes is also usually from the exo direction (p. 1023).

For rearrangements of alkyl carbocations, the direction of rearrangement is usually toward the most stable carbocation (or radical), which is tertiary > secondary > primary, but rearrangements in the other direction have also been found,[102] and often the product is a mixture corresponding to an equilibrium mixture of the possible carbocations. In the Wagner–Meerwein rearrangement, the rearrangement has been observed for a secondary to a secondary carbocation rearrangement, leading to some controversy. Winstein[103] described norbornyl cations in terms of the resonance structures represented by the nonclassical ion **50**.[104] This view was questioned, primarily by Brown,[105] who suggested that the facile rearrangements could be explained by a series of fast 1,3-Wagner–Meerwein shifts.[106]

[100]For example, see Kleinfelter, D.C.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1961***, *83*, 2329; Collins, C.J.; Cheema, Z.K.; Werth, R.G.; Benjamin, B.M. *J. Am. Chem. Soc.* ***1964***, *86*, 4913; Berson, J.A.; Hammons, J.H.; McRowe, A.W.; Bergman, R.G.; Remanick, A.; Houston, D. *J. Am. Chem. Soc.* ***1967***, *89*, 2590.

[101]For examples of 3,2-endo shifts, see Bushell, A.W.; Wilder, Jr., P. *J. Am. Chem. Soc.* ***1967***, *89*, 5721; Wilder, Jr., P.; Hsieh, W. *J. Org. Chem.* ***1971***, *36*, 2552.

[102]See, for example, Cooper, C.N.; Jenner, P.J.; Perry, N.B.; Russell-King, J.; Storesund, H.J.; Whiting, M.C. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 605.

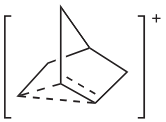
[103]Winstein, S. *Quart. Rev. Chem. Soc.* ***1969***, *23*, 141; Winstein, S.; Trifan, D.S. *J. Am. Chem. Soc.* ***1949***, *71*, 2953; Winstein, S.; Trifan, D.S. *J. Am. Chem. Soc.* ***1952***, *74*, 1154.

[104]Berson, J.A., in de Mayo, P. *Molecular Rearrangements*, Vol. 1, Academic Press, NY, ***1980***, p. 111; Sargent, G.D. *Quart. Rev. Chem. Soc.* ***1966***, *20*, 301; Olah, G.A. *Acc. Chem. Res.* ***1976***, *9*, 41; Scheppelle, S.E. *Chem. Rev.* ***1972***, *72*, 511.

[105]Brown, H.C. *The Non–Classical Ion Problem*, Plenum, New York, ***1977***; Brown, H.C. *Tetrahedron* ***1976***, *32*, 179; Brown, H.C.; Kawakami, J.H. *J. Am. Chem. Soc.* ***1970***, *92*, 1990. See also, Story, R.R.; Clark, B.C., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, New York, ***1972***, p. 1007.

[106]Brown, H.C.; Ravindranathan, M. *J. Am. Chem. Soc.* ***1978***, *100*, 1865.

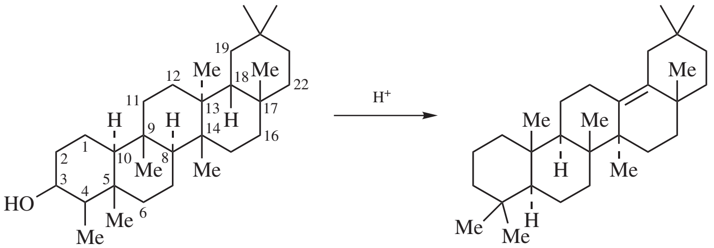
There is considerable evidence, however, that the norbornyl cation rearranges with σ-participation,[107] and there is strong NMR evidence for the nonclassical ion in super acids at low temperatures.[108]



50

As alluded to above, the term "Wagner–Meerwein rearrangement" is not precise. Some use it to refer to all the rearrangements in this section and in **18-2**. Others use it only when an alcohol is converted to a rearranged alkene. Terpene chemists call the migration of a methyl group the *Nametkin rearrangement.* The term *retropinacol rearrangement* is often applied to some or all of these. Fortunately, this disparity in nomenclature does not seem to cause much confusion.

Sometimes several of these rearrangements occur in one molecule, either simultaneously or in rapid succession. A spectacular example is found in the triterpene series. Friedelin is a triterpenoid ketone found in cork. Reduction gives 3β-friedelanol (**51**). When this compound is treated with acid, 13(18)-oleanene (**52**) is formed.[109] In this case, *seven* 1,2-shifts take place. On removal of H_2O from position 3 to leave a positive



51 **52**

charge, the following shifts occur: hydride from 4 to 3; methyl from 5 to 4; hydride from 10 to 5; methyl from 9 to 10; hydride from 8 to 9; methyl from 14 to 8; and methyl from 13 to 14. This leaves a positive charge at position 13, which is stabilized by loss of the proton at the 18 position to give **52**. All these shifts are stereospecific, the group always migrating on the side of the ring system on which it is located; that is, a group above the "plane" of the ring system (indicated by a solid line in **51**) moves above the plane, and a group below the plane (dashed line) moves

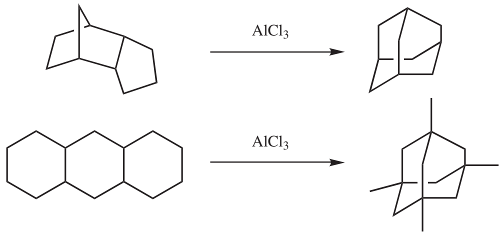
[107]Coates, R.M.; Fretz, E.R. *J. Am. Chem. Soc.* ***1977***, *99*, 297; Brown, H.C.; Ravindranathan, M. *J. Am. Chem. Soc.* ***1977***, *99*, 299.

[108]Olah, G.A. *Carbocations and Electrophilic Reactions*, Verlag Chemie/Wiley, New York, ***1974***, pp. 80–89; Olah, G.A.; White, A.M.; DeMember, J.R.; Commeyras, A.; Lui, C.Y. *J. Am. Chem. Soc.* ***1970***, *92*, 4627.

[109]Corey, E.J.; Ursprung, J.J. *J. Am. Chem. Soc.* ***1956***, *78*, 5041.

below it. It is probable that the seven shifts are not all concerted, although some of them may be, for intermediate products can be isolated.[110] As an illustration of point 2 (p. 1581), it may be mentioned that friedelene, derived from dehydration of **51**, also gives **52** on treatment with acid.[111]

It was mentioned above that even alkanes undergo Wagner–Meerwein rearrangements if treated with Lewis acids and a small amount of initiator. Catalytic asymmetric Wagner–Meerwein shifts have been observed.[112] An interesting application of this reaction is the conversion of tricyclic molecules to adamantane and its derivatives.[113] It has been found that *all* tricyclic alkanes containing 10 carbons are converted to adamantane by treatment with a Lewis acid, such as $AlCl_3$. If the substrate contains >10 carbons, alkyl-substituted adamantanes are produced. The IUPAC name for these reactions is *Schleyer adamantization*. Two examples are



If 14 or more carbons are present, the product may be diamantane or a substituted diamantane.[114] These reactions are successful because of the high thermodynamic stability of adamantane, diamantane, and similar diamond-like molecules. The most stable of a set of C_nH_m isomers (called the *stabilomer*) will be the end product if the reaction reaches equilibrium.[115] Best yields are obtained by the use of "sludge" catalysts[116] (i.e., a mixture of AlX_3 and *tert*-butyl bromide or *sec*-butyl bromide).[117] Though it is certain that these adamantane-forming reactions take place by nucleophilic 1,2-shifts, the exact pathways are not easy to unravel

[110]For a discussion, see Whitlock Jr., H.W.; Olson, A.H. *J. Am. Chem. Soc.* ***1970***, *92*, 5383.

[111]Dutler, H.; Jeger, O.; Ruzicka, L. *Helv. Chim. Acta* ***1955***, *38*, 1268; Brownlie, G.; Spring, F.S.; Stevenson, R.; Strachan, W.S. *J. Chem. Soc.* ***1956***, 2419; Coates, R.M. *Tetrahedron Lett.* ***1967***, 4143.

[112]Trost, B.M.; Yasukata, T. *J. Am. Chem. Soc.* ***2001***, *123*, 7162.

[113]For reviews, see McKervey, M.A.; Rooney, J.J., in Olah, G.A. *Cage Hydrocarbons*, Wiley, NY, ***1990***, pp. 39–64; McKervey, M.A. *Tetrahedron* ***1980***, *36*, 971; *Chem. Soc. Rev.* ***1974***, *3*, 479; Greenberg, A.; Liebman, J.F. *Strained Organic Molecules*, Academic Press, NY, ***1978***, pp. 178–202; Bingham, R.C.; Schleyer, P.v.R. *Fortschr. Chem. Forsch.* ***1971***, *18*, 1, 3–23.

[114]See Gund, T.M.; Osawa, E.; Williams, Jr., V.Z.; Schleyer, P.v.R. *J. Org. Chem.* ***1974***, *39*, 2979.

[115]For a method for the prediction of stabilomers, see Godleski, S.A.; Schleyer, P.v.R.; Ōsawa, E.; Wipke, W.T. *Prog. Phys. Org. Chem.* ***1981***, *13*, 63.

[116]Schneider, A.; Warren, R.W.; Janoski, E.J. *J. Org. Chem.* ***1966***, *31*, 1617; Williams, Jr., V.Z.; Schleyer, P.v.R.; Gleicher, G.J.; Rodewald, L.B. *J. Am. Chem. Soc.* ***1966***, *88*, 3862; Robinson, M.J.T.; Tarratt, H.J.F. *Tetrahedron Lett.* ***1968***, 5.

[117]For other methods, see Johnston, D.E.; McKervey, M.A.; Rooney, J.J. *J. Am. Chem. Soc.* ***1971***, *93*, 2798; Olah, G.A.; Wu, A.; Farooq, O.; Prakash, G.K.S. *J. Org. Chem.* ***1989***, *54*, 1450.

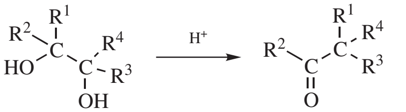
because of their complexity.[118] Treatment of adamantane-2-^{14}C with $AlCl_3$ results in total carbon scrambling on a statistical basis.[119]

As already indicated, the mechanism of the Wagner–Meerwein rearrangement is usually nucleophilic. Free-radical rearrangements are also known (see the mechanism section of this chapter), though virtually only with aryl migration. However, carbanion mechanisms (electrophilic) have also been found.[94] Thus Ph_3CCH_2Cl treated with sodium gave Ph_2CHCH_2Ph along with unrearranged products.[120] This is called the *Grovenstein–Zimmerman rearrangement*. The intermediate is Ph_3CCH_2-, and the phenyl moves without its electron pair. Only aryl and vinylic,[121] and not alkyl, groups migrate by the electrophilic mechanism (p. $$$) and transition states or intermediates analogous to **41** and **42** are likely.[122]

OS **V**, 16, 194; **VI**, 378, 845.

18-2 The Pinacol Rearrangement

1/*O*-Hydro,3/hydroxy-(2/ → 3/alkyl)-*migro*-elimination



R = alkyl, aryl, or hydrogen

When *vic*-diols (glycols) are treated with acids,[123] they can be rearranged to give aldehydes or ketones, although elimination without rearrangement can also be accomplished. This reaction is called the *pinacol rearrangement*; the reaction gets its name from a prototype compound pinacol ($Me_2COHCOHMe_2$), which is rearranged to pinacolone (Me_3CCOCH_3).[124] In this type of reaction, reduction can compete with rearrangement.[125] The reaction has been accomplished many times, with alkyl, aryl, hydrogen, and even ethoxycarbonyl (COOEt)[126] as migrating

[118]See, for example, Engler, E.M.; Fărcaşiu, M.; Sevin, A.; Cense, J.M.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1973***, *95*, 5769; Klester, A.M.; Ganter, C. *Helv. Chim. Acta* ***1983***, *66*, 1200; ***1985***, *68*, 734.

[119]Majerski, Z.; Liggero, S.H.; Schleyer, P.v.R.; Wolf, A.P. *Chem. Commun.* ***1970***, 1596.

[120]Grovenstein, Jr., E. *J. Am. Chem. Soc.* ***1957***, *79*, 4985; Grovenstein, Jr., E.; Williams Jr., L.P. *J. Am. Chem. Soc.* ***1961***, *83*, 412; Zimmerman, H.E.; Zweig, A. *J. Am. Chem. Soc.* ***1961***, *83*, 1196. See also, Crimmins, T.F.; Murphy, W.S.; Hauser, C.R. *J. Org. Chem.* ***1966***, *31*, 4273; Grovenstein, Jr., E.; Cheng, Y. *J. Am. Chem. Soc.* ***1972***, *94*, 4971.

[121]See Grovenstein, Jr., E.; Black, K.W.; Goel, S.C.; Hughes, R.L.; Northrop, J.H.; Streeter, D.L.; VanDerveer, D. *J. Org. Chem.* ***1989***, *54*, 1671, and references cited therein.

[122]Bertrand, J.A.; Grovenstein, Jr., E.; Lu, P.; VanDerveer, D. *J. Am. Chem. Soc.* ***1976***, *98*, 7835.

[123]For a reaction initiated by iminium salts, see Lopez, L.; Mele, G.; Mazzeo, C. *J. Chem. Soc. Perkin Trans. 1* ***1994***, 779. For reactions initiated by radical cations, see de Sanabia, J.A.; Carrión, A.E. *Tetrahedron Lett.* ***1993***, *34*, 7837. $SbCl_5$ has been used: see Harada, T.; Mukaiyama, T. *Chem. Lett.* ***1992***, 81.

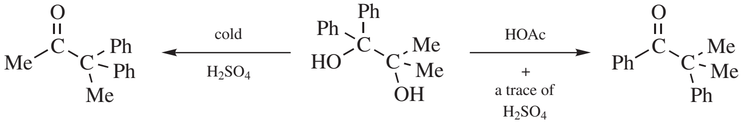
[124]For reviews, see Bartók, M.; Molnár, A., in Patai, S. *The Chemistry of Functional Groups, Supplement E*, Wiley, NY, ***1980***, pp. 722–732; Collins, C.J.; Eastham, J.F., in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 762–771.

[125]Grant, A.A.; Allukian, M.; Fry, A.J. *Tetrahedron Lett.* ***2002***, *43*, 4391.

[126]Kagan, J.; Agdeppa Jr., D.A.; Mayers, D.A.; Singh, S.P.; Walters, M.J.; Wintermute, R.D. *J. Org. Chem.* ***1976***, *41*, 2355. COOH has been found to migrate in a Wagner–Meerwein reaction: Berner, D.; Cox, D.P.; Dahn, H. *J. Am. Chem. Soc.* ***1982***, *104*, 2631.

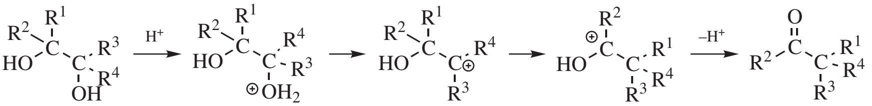
groups. In most cases, each carbon has at least one alkyl or aryl group, and the reaction is most often carried out with tri- and tetrasubstituted glycols. As mentioned earlier, glycols in which the four R groups are not identical can give rise to more than one product, depending on which group migrates (see p. 1568 for a discussion of migratory aptitudes). A noncatalytic reaction is possible in supercritical water.[127]

Stereodifferentiation is possible in this reaction.[128] When TMSOTf was used to initiate the reaction, it was shown to be highly regioselective.[129] Mixtures are often produced, and which group preferentially migrates may depend on the reaction conditions, as well as on the nature of the substrate. Thus the



54 53 55

action of cold, concentrated sulfuric acid on **53** produces mainly the ketone **54** (methyl migration), while treatment of **53** with acetic acid containing a trace of sulfuric acid gives mostly **55** (phenyl migration).[130] If at least one R is hydrogen, aldehydes can be produced as well as ketones. Generally, aldehyde formation is favored by the use of mild conditions (lower temperatures, weaker acids), because under more drastic conditions the aldehydes may be converted to ketones (**18-4**). The reaction has been carried out in the solid state, by treating solid substrates with HCl gas or with an organic solid acid.[131]



56

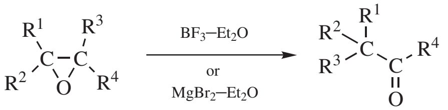
The mechanism involves a simple 1,2-shift. The ion **56** (where all four R groups are Me) has been trapped by the addition of tetrahydrothiophene.[132] It may seem odd that a migration takes place when the positive charge is already at a tertiary position, but carbocations stabilized by an oxygen atom are even more stable than tertiary alkyl cations (p. 242). There is also the driving force supplied by the fact that the new carbocation can immediately stabilize itself by losing a proton.

It is obvious that other compounds in which a positive charge can be placed on a carbon α to one bearing an OH group can also give this rearrangement. This is true for β-amino alcohols, which rearrange on treatment with nitrous acid (this is called

[127]Ikushima, Y.; Hatakeda, K.; Sato, O.; Yokoyama, T.; Arai, M. *J. Am. Chem. Soc.* ***2000***, *122*, 1908.
[128]Paquette, L.A.; Lanter, J.C.; Johnston, J.N. *J. Org. Chem.* ***1997***, *62*, 1702.
[129]Kudo, K.; Saigo, K.; Hashimoto, Y.; Saito, K.; Hasegawa, M. *Chem. Lett.* ***1992***, 1449.
[130]Ramart-Lucas, P.; Salmon-Legagneur, F. *C. R. Acad. Sci.* ***1928***, *188*, 1301.
[131]Toda, F.; Shigemasa, T. *J. Chem. Soc. Perkin Trans. 1* ***1989***, 209.
[132]Bosshard, H.; Baumann, M.E.; Schetty, G. *Helv. Chim. Acta* ***1970***, *53*, 1271.

the *semipinacol* rearrangement), iodohydrins, for which the reagent is mercuric oxide or silver nitrate, β-hydroxyalkyl selenides, $R^1R^2C(OH)C(SeR^5)R^3R^4$,[133] and allylic alcohols,[134] which can rearrange on treatment with a strong acid that protonates the double bond.

A similar rearrangement is given by epoxides,[135]



R = alkyl, aryl, or hydrogen

when treated with acidic[136] reagents, such as BF_3–etherate or $MgBr_2$–etherate, 5 *M* $LiClO_4$ in ether,[137] $InCl_3$,[138] $Al(OC_6F_3)_3$,[139] $Bi(OTf)_3$,[140] $VO(OEt)Cl_2$,[141] or sometimes by heat alone.[142] Epoxides are converted to aldehydes or ketones on treatment with certain metallic catalysts[143] including treatment with iron complexes in refluxing dioxane,[144] $IrCl_3$,[145] or with $BiOClO_4$ in dichloromethane.[146] A related rearrangement called the *Meinwald rearrangement* was induced by the enzyme pig liver esterase.[147] It has been shown that epoxides are intermediates in the pinacol rearrangements of certain glycols.[148] Among the evidence for the mechanism given is that $Me_2COHCOHMe_2$, $Me_2COHCNH_2Me_2$, and $Me_2COHCClMe_2$ gave the reaction at different rates (as expected), but yielded the *same mixture* of two products pinacol and pinacolone indicating a common intermediate.[149]

[133]For a review, see Krief, A.; Laboureur, J.L.; Dumont, W.; Labar, D. *Bull. Soc. Chim. Fr.* ***1990***, 681.

[134]See Wang, B.M.; Song, Z.L.; Fan, C.A.; Tu, Y.Q.; Chen, W.M. *Synlett* ***2003***, 1497; Hurley, P.B.; Dake, G.R. *Synlett* ***2003***, 2131.

[135]For a discussion of the mechanism, see Hodgson, D.M.; Robinson, L.A.; Jones, M.L. *Tetrahedron Lett.* ***1999***, *40*, 8637.

[136]Epoxides can also be rearranged with basic catalysts, though the products are usually different. For a review, see Yandovskii, V.N.; Ershov, B.A. *Russ. Chem. Rev.* ***1972***, *41*, 403, 410.

[137]Sudha, R.; Narashimhan, K.M.; Saraswathy, V.G.; Sankararaman, S. *J. Org. Chem.* ***1996***, *61*, 1877; Sankararaman, S.; Nesakumar, J.E. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 3173.

[138]Ranu, B.C.; Jana, U. *J. Org. Chem.* ***1998***, *63*, 8212.

[139]Kita, Y.; Furukawa, A.; Futamura, J.; Ueda, K.; Sawama, Y.; Hamamoto, H.; Fujioka, H. *J. Org. Chem.* ***2001***, *66*, 8779.

[140]Bhatia, K.A.; Eash, K.J.; Leonard, N.M.; Oswald, M.C.; Mohan, R.S. *Tetrahedron Lett.* ***2001***, *42*, 8129.

[141]Martínez, F.; del Campo., C.; Llama, E.F. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 1749.

[142]For a list of reagents that accomplish this transformation, with references, see Larock, R.C. *Comprehensive Organic Transformations*; 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1277–1280.

[143]For example, see Alper, H.; Des Roches, D.; Durst, T.; Legault, R. *J. Org. Chem.* ***1976***, *41*, 3611; Milstein, D.; Buchman, O.; Blum, J. *J. Org. Chem.* ***1977***, *42*, 2299; Prandi, J.; Namy, J.L.; Menoret, G.; Kagan, H.B. *J. Organomet. Chem.* ***1985***, *285*, 449; Miyashita, A.; Shimada, T.; Sugawara, A.; Nohira, H. *Chem. Lett.* ***1986***, 1323; Maruoka, K.; Nagahara, S.; Ooi, T.; Yamamoto, H. *Tetrahedron Lett.* ***1989***, *30*, 5607.

[144]Suda, K.; Baba, K.; Nakajima, S.-I.; Takanami, T. *Tetrahedron Lett.* ***1999***, *40*, 7243.

[145]Karamé, I.; Tommasino, M.L.; LeMaire, M. *Tetrahedron Lett.* ***2003***, *44*, 7687.

[146]Anderson, A.M.; Blazek, J.M.; Garg, P.; Payne, B.J.; Mohan, R.S. *Tetrahedron Lett.* ***2000***, *41*, 1527.

[147]Niwayama, S.; Noguchi, H.; Ohno, M.; Kobayashi, S. *Tetrahedron Lett.* ***1993***, *34*, 665.

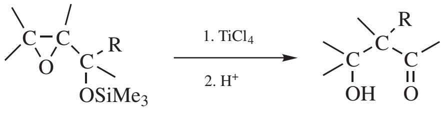
[148]See, for example, Matsumoto, K. *Tetrahedron* ***1968***, *24*, 6851; Pocker, Y.; Ronald, B.P. *J. Am. Chem. Soc.* ***1970***, *92*, 3385; *J. Org. Chem.* ***1970***, *35*, 3362; Tamura, K.; Moriyoshi, T. *Bull. Chem. Soc. Jpn.* ***1974***, *47*, 2942.

[149]Pocker, Y. *Chem. Ind.* (*London*), ***1959***, 332. See also, Herlihy, K.P. *Aust. J. Chem.* ***1981***, *34*, 107.

A good way to prepare β-diketones consists of heating α,β-epoxy ketones at 80–140°C in toluene with small amounts of $(Ph_3P)_4Pd$ and 1,2-bis(diphenylphosphino)ethane.[150] Epoxides are converted to 1,2-diketones with Bi, DMSO, O_2, and a catalytic amounts of $Cu(OTf)_2$ at 100°C.[151] α,β–Epoxy ketones are also converted to 1,2-diketones with a ruthenium catalyst[152] or an iron catalyst.[153] Epoxides with an α-hydroxyalkyl substituent give a pinacol rearrangement product in the presence of a $ZnBr_2$[154] or $Tb(OTf)_3$[155] catalyst to give a γ-hydroxy ketone.

Oxaziridines are converted to ring-expanded lactams under photochemical conditions.[156] *N*-Tosyl aziridines with an α-hydroxyalkyl substituent give a pinacol rearrangement product in the presence of Lewis acids, such as SmI_2, in this case a keto-*N*-tosyl amide.[157]

β-Hydroxy ketones can be prepared by treating the silyl ethers (**57**) of α,β-epoxy alcohols with $TiCl_4$.[158]

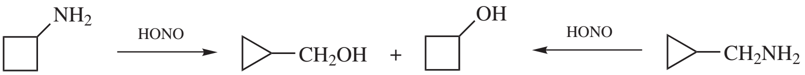


57

OS **I**, 462; **II**, 73, 408; **III**, 312; **IV**, 375, 957; **V**, 326, 647; **VI**, 39, 320; **VII**, 129. See also, OS **VII**, 456.

18-3 Expansion and Contraction of Rings

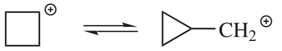
Demyanov ring contraction; Demyanov ring expansion



When a positive charge is formed on an alicyclic carbon, migration of an alkyl group can take place to give ring contraction, producing a ring that is one carbon smaller than the original, as in the interconversion of the cyclobutyl cation and the

[150]Suzuki, M.; Watanabe, A.; Noyori, R. *J. Am. Chem. Soc.* ***1980***, *102*, 2095.
[151]Antoniotti, S.; Duñach, E. *Chem. Commun.* ***2001***, 2566.
[152]Chang, C.-L.; Kumar, M.P.; Liu, R.-S. *J. Org. Chem.* ***2004***, *69*, 2793.
[153]Suda, K.; Baba, K.; Nakajima, S.; Takanami, T. *Chem. Commun.* ***2002***, 2570.
[154]Tu, Y.Q.; Fan, C.A.; Ren, S.K.; Chan, A.S.C. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 3791.
[155]Bickley, J.F.; Hauer, B.; Pena, P.C.A.; Roberts, S.M.; Skidmore, J. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 1253.
[156]Bourguet, E.; Baneres, J.-L.; Girard, J.-P.; Parello, J.; Vidal, J.-P.; Lusinchi, X.; Declerzq, J.-P. *Org. Lett.* ***2001***, *3*, 3067.
[157]Wang, B.M.; Song, Z.L.; Fan, C.A.; Tu, Y.Q.; Shi, Y. *Org. Lett.* ***2002***, *4*, 363.
[158]Maruoka, K.; Hasegawa, M.; Yamamoto, H.; Suzuki, K.; Shimazaki, M.; Tsuchihashi, G. *J. Am. Chem. Soc.* ***1986***, *108*, 3827. For a different rearrangement of **53**, see Maruoka, K.; Ooi, T.; Yamamoto, H. *J. Am. Chem. Soc.* ***1989***, *111*, 6431.

cyclopropylcarbinyl cation.



Note that this change involves conversion of a secondary to a primary carbocation. In a similar manner, when a positive charge is placed on a carbon a to an alicyclic ring, ring expansion can take place.[159] The new carbocation, and the old one, can then give products by combination with a nucleophile (e.g., the alcohols shown above), or by elimination, so that this reaction is a special case of **18-1**. Often, both rearranged and unrearranged products are formed, so that, for example, cyclobutylamine and cyclopropylmethylamine give similar mixtures of the two alcohols shown above on treatment with nitrous acid (a small amount of 3-buten-1-ol is also produced). When the carbocation is formed by diazotization of an amine, the reaction is called the *Demyanov rearrangement*,[160] but of course similar products are formed when the carbocation is generated in other ways. The expansion reaction has been performed on rings of C_3–C_8,[161] but yields are best with the smaller rings, where relief of small-angle strain provides a driving force for the reaction. The contraction reaction has been applied to four-membered rings and to rings of C_6–C_8, but contraction of a cyclopentyl cation to a cyclobutylmethyl system is generally not feasible because of the additional strain involved. Strain is apparently much less of a factor in the cyclobutyl–cyclopropylmethyl interconversion (for a discussion of this interconversion, see p. 450). The influence of substituents on this rearrangement has been examined.[162]

Ring expansions of certain hydroxyamines, such as **58**

58

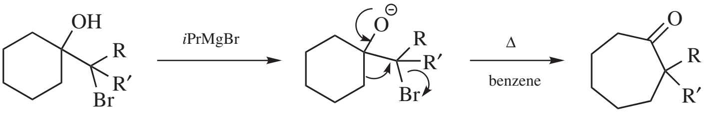
[159]For monographs on ring expansions, see Hesse, M. *Ring Enlargement in Organic Chemistry*, VCH, NY, ***1991***; Gutsche, C.D.; Redmore, D. *Carbocyclic Ring Expansion Reactions*, Academic Press, NY, ***1968***. For a review of ring contractions, see Redmore, D.; Gutsche, C.D. *Adv. Alicyclic Chem.* ***1971***, *3*, 1. For reviews of ring expansions in certain systems, see Baldwin, J.E.; Adlington, R.M.; Robertson, J. *Tetrahedron* ***1989***, *45*, 909; Stach, H.; Hesse, M. *Tetrahedron* ***1988***, *44*, 1573; Dolbier Jr., W.R. *Mech. Mol. Migr.* ***1971***, *3*, 1. For reviews of expansions and contractions of three- and four membered rings, see Salaün, J., in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 2, Wiley, NY, ***1987***, pp. 809–878; Conia, J.M.; Robson, M.J. *Angew. Chem. Int. Ed.* ***1975***, *14*, 473. For a list of ring expansions and contractions, with references, see Larock, R.C. *Comprehensive Organic Transformation*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1283–1302.

[160]For a review, see Smith, P.A.S.; Baer, D.R. *Org. React.* ***1960***, *11*, 157. See also, Chow, L.; McClure, M.; White, J. *Org. Biomol. Chem.* ***2004***, *2*, 648.

[161]For a review concerning three-membered rings, see Wong, H.N.C.; Hon, M.; Tse, C.; Yip, Y.; Tanko, J.; Hudlicky, T. *Chem. Rev.* ***1989***, *89*, 165, see pp. 182–186. For a review concerning three- and four-membered rings, see Breslow, R., in Mayo, P. *Molecular Rearrangements*, Vol. 1, Wiley, NY, ***1963***, pp. 233–294.

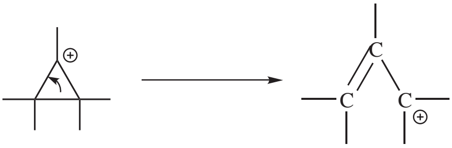
[162]Wiberg, K.B.; Shobe, D.; Nelson, G.C. *J. Am. Chem. Soc.* ***1993***, *115*, 10645.

are analogous to the semipinacol rearrangement (**18-2**). This reaction is called the *Tiffeneau–Demyanov ring expansion*. These have been performed on rings of C_4–C_8 and the yields are better than for the simple Demyanov ring expansion. A similar reaction has been used to expand rings of from five to eight members.[163] In this case, a cyclic bromohydrin of the form **59** is treated with a Grignard reagent which, acting as a base, removes the OH proton to give the alkoxide **60**. Refluxing of **60** brings about the ring enlargement. The reaction has been accomplished for **59** in which at least one R group is phenyl or methyl,[164] but fails when both R groups are hydrogen.[165]

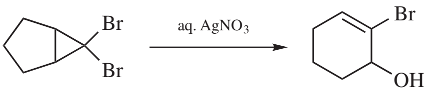


59 **60**

A positive charge generated on a three-membered ring gives "contraction" to an allylic cation.[166]



We have previously seen (p. 487) that this is the reason nucleophilic substitutions are not feasible at a cyclopropyl substrate. The reaction is often used to convert cyclopropyl halides and tosylates to allylic products, especially for the purpose of ring expansion, an example being the conversion of **61–62**.[167] The stereochemistry of these cyclopropyl cleavages is governed by the principle of orbital symmetry conservation (for a discussion, see p. 1644).



61 **62**

Three-membered rings can also be cleaved to unsaturated products in at least two other ways. (*1*) On pyrolysis, cyclopropanes can undergo "contraction" to

[163]Sisti, A.J. *Tetrahedron Lett.* ***1967***, 5327; *J. Org. Chem.* ***1968***, *33*, 453. See also, Sisti, A.J.; Vitale, A.C. *J. Org. Chem.* ***1972***, *37*, 4090.

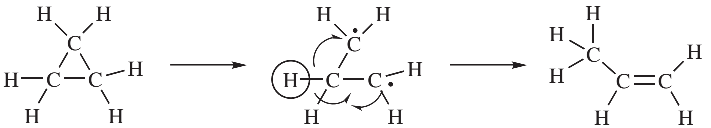
[164]Sisti, A.J.; Meyers, M. *J. Org. Chem.* ***1973***, *38*, 4431; Sisti, A.J.; Rusch, G.M. *J. Org. Chem.* ***1974***, *39*, 1182.

[165]Sisti, A.J. *J. Org. Chem.* ***1968***, *33*, 3953.

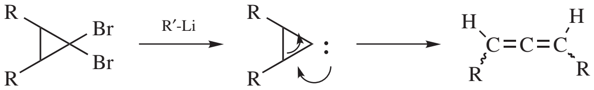
[166]For reviews, see Marvell, E.N. *Thermal Electrocylic Reactions*, Academic Press, NY, ***1980***, pp. 23–53; Sorensen, T.S.; Rauk, A., in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, ***1977***, pp. 1–78.

[167]Skell, P.S.; Sandler, S.R. *J. Am. Chem. Soc.* ***1958***, *80*, 2024.

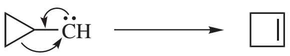
propenes.[168] In the simplest case, cyclopropane gives propene when heated to 400–500°C. The mechanism is generally regarded[169] as involving a diradical



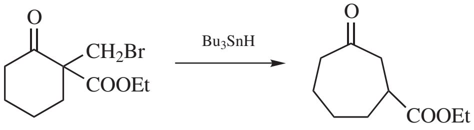
intermediate[170] (recall that free-radical 1,2 migration is possible for diradicals, p. 1574). (*2*) The generation of a carbene or carbenoid carbon in a three-membered ring can lead to allenes, and allenes are often prepared in this



way.[171] Flash vacuum pyrolysis of 1-chlorocyclopropene thermally rearranges to chloroallene.[172] One way to generate, such a species is treatment of a 1,1-dihalocyclopropane with an alkyllithium compound (**12-39**).[173] In contrast, the generation of a carbene or carbenoid at a cyclopropylmethyl carbon gives ring expansion.[174]



Some free-radical ring enlargements are also known, an example being:[175]



[168]For reviews, see Berson, J.A., in de Mayo, P. *Rearrangaements in Ground and Excited States*, Vol. 1, Academic Press, NY, ***1980***, pp. 324–352; *Ann. Rev. Phys. Chem.* ***1977***, *28*, 111; Bergman, R.G., in Kochi, J.K. *Free Radicals*, Vol. 1, Wiley, NY, ***1973***, pp. 191–237; Frey, H.M. *Adv. Phys. Org. Chem.* ***1966***, *4*, 147, see pp. 148–170.

[169]For evidence that diradical intermediates may not be involved, at least in some cases, see Fields, R.; Haszeldine, R.N.; Peter, D. *Chem. Commun.* ***1967***, 1081; Parry, K.A.W.; Robinson, P.J. *Chem. Commun.* ***1967***, 1083; Clifford, R.P.; Holbrook, K.A. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 1972; Baldwin, J.E.; Grayston, M.W. *J. Am. Chem. Soc.* ***1974***, *96*, 1629, 1630.

[170]We have seen before that such diradicals can close up to give cyclopropanes (**17-34**). Therefore, pyrolysis of cyclopropanes can produce not only propenes, but also isomerized (cis → trans or optically active → inactive) cyclopropanes. See, for example, Berson, J.A.; Balquist, J.M. *J. Am. Chem. Soc.* ***1968***, *90*, 7343; Bergman, R.G.; Carter, W.L. *J. Am. Chem. Soc.* ***1969***, *91*, 7411.

[171]For reviews, see Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis*, Wiley, NY, ***1984***, pp. 20–23; Kirmse, W. *Carbene Chemistry*, 2nd ed., Academic Press, NY, ***1971***, pp. 462–467.

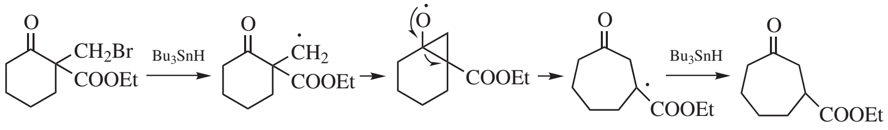
[172]Billups, W.E.; Bachman, R.E. *Tetrahedron Lett.* ***1992***, *33*, 1825.

[173]See Baird, M.S.; Baxter, A.G.W. *J. Chem. Soc. Perkin Trans. 1* ***1979***, 2317, and references cited therein.

[174]For a review, see Gutsche, C.D.; Redmore, D. *Carbocyclic Ring Expansion Reactions*, Academic Press, NY, ***1968***, pp. 111–117.

[175]Dowd, P.; Choi, S. *Tetrahedron Lett.* ***1991***, *32*, 565; *Tetrahedron* ***1991***, *47*, 4847. For a related ring expansion, see Baldwin, J.E.; Adlington, R.M.; Robertson, J. *J. Chem. Soc., Chem. Commun.* ***1988***, 1404.

This reaction has been used to make rings of 6, 7, 8, and 13 members. A possible mechanism is

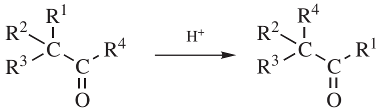


This reaction has been extended to the expansion of rings by three or four carbons, by the use of a substrate containing $(CH_2)_nX$ ($n = 3$ or 4) instead of CH_2Br.[176] By this means, 5-, 6-, and 7-membered rings were enlarged to 18–11-membered rings.

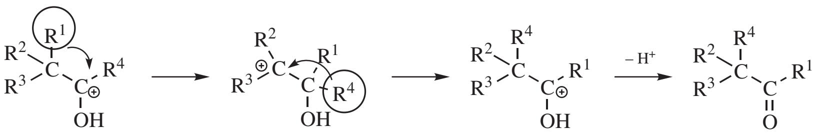
OS **III**, 276; **IV**, 221, 957; **V**, 306, 320; **VI**, 142, 187; **VII**, 12, 114, 117, 129, 135; **VIII**, 179, 467, 556, 578.

18-4 Acid-Catalyzed Rearrangements of Aldehydes and Ketones

1/Alkyl,2/alkyl-interchange, and so on

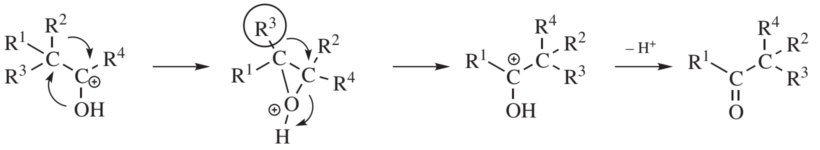


Rearrangements of this type, where a group α to a carbonyl "changes places" with a group attached to the carbonyl carbon, occur when migratory aptitudes are favorable.[177] The R^2, R^3, and R^4 groups may be alkyl or hydrogen. Certain aldehydes have been converted to ketones, and ketones to other ketones (though more drastic conditions are required for the latter), but no rearrangement of a ketone to an aldehyde ($R^1 = H$) has so far been reported. There are two mechanisms,[178] each beginning with protonation of the oxygen and each involving two migrations. In one pathway, the migrations are in opposite directions:[179]

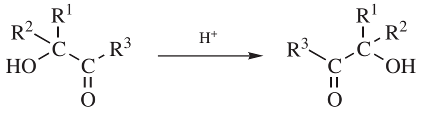


[176]Dowd, P.; Choi, S. *J. Am. Chem. Soc.* ***1987***, *109*, 6548; *Tetrahedron Lett.* ***1991***, *32*, 565.
[177]For reviews, see Fry, A. *Mech. Mol. Migr.* ***1971***, *4*, 113; Collins, C.J.; Eastham, J.F., in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 771–790.
[178]Favorskii, A.; Chilingaren, A. *C. R. Acad. Sci.* ***1926***, *182*, 221.
[179]Kendrick Jr., L.W.; Benjamin, B.M.; Collins, C.J. *J. Am. Chem. Soc.* ***1958***, *80*, 4057; Rothrock, T.S.; Fry, A. *J. Am. Chem. Soc.* ***1958***, *80*, 4349; Collins, C.J.; Bowman, N.S. *J. Am. Chem. Soc.* ***1959***, *81*, 3614.

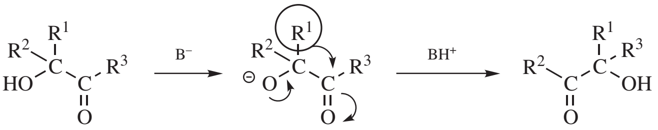
In the other pathway, the migrations are in the same direction. The actual mechanism of this pathway is not certain, but an epoxide (protonated) intermediate[180] is one possibility:[181]



If the reaction is carried out with ketone labeled in the C=O group with ^{14}C, the first pathway predicts that the product will contain all the ^{14}C in the C=O carbon, while in the second pathway the label will be in the α carbon (demonstrating migration of oxygen). The results of such experiments[182] have shown that in some cases only the C=O carbon was labeled, in other cases only the a carbon, while in still others both carbons bore the label, indicating that in these cases both pathways were in operation. With α-hydroxy aldehydes and ketones, the process may stop after only one migration (this is called the *α-ketol* rearrangement).

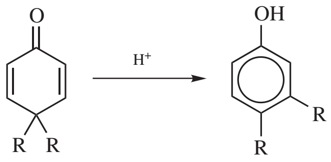


The α-ketol rearrangement can also be brought about by base catalysis, but only if the alcohol is tertiary, since if R^1 or R^2 = hydrogen, enolization of the substrate is more favored than rearrangement.



18-5 The Dienone–Phenol Rearrangement

2/*C* → 5/*O*-Hydro,1/*C* → 2/*C*-alkyl-bis-migration

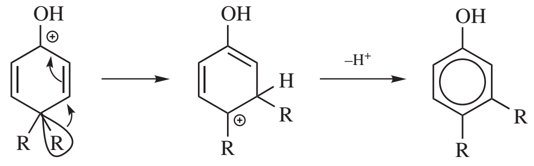


[180]Zook, H.D.; Smith, W.E.; Greene, J.L. *J. Am. Chem. Soc.* ***1957***, *79*, 4436.

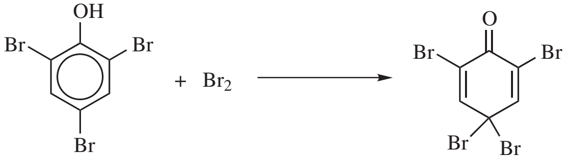
[181]Some such pathway is necessary to account for the migration of oxygen that is found. It may involve a protonated epoxide, a 1,2-diol, or simply a [1,2]-shift of an OH group.

[182]See, for example, Barton, S.; Porter, C.R. *J. Chem. Soc.* ***1956***, 2483; Zalesskaya, T.E.; Remizova, T.B. *J. Gen. Chem. USSR* ***1965***, *35*, 29; Fry, A.; Oka, M. *J. Am. Chem. Soc.* ***1979***, *101*, 6353.

Cyclohexadienone derivatives that have two alkyl groups in the 4 position undergo, on acid treatment,[183] 1,2 migration of one of these groups from **64** to give the phenol. Note that a photochemical version of this reaction has been observed.[184]

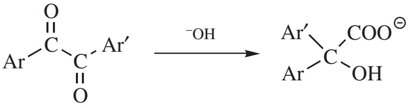


The driving force in the overall reaction (the *dienone–phenol rearrangement*) is of course creation of an aromatic system.[185] Note that **63** and **64** are arenium ions (p. 240), the same as those generated by attack of a phenol on an electrophile.[186] Sometimes, in the reaction of a phenol with an electrophile, a kind of reverse rearrangement (called the *phenol–dienone rearrangement)* takes place, though without an actual migration.[187] An example is



18-6 The Benzil–Benzilic Acid Rearrangement

1/*O*-Hydro,3/oxido-(1/ → 2/aryl)-*migro*-addition



When treated with base, α-diketones rearrange to give the salts of α-hydroxy acids, a reaction known as the *benzil-benzilic acid rearrangement* (benzil is

[183]For a reagent that greatly accelerates this reaction, see Chalais, S.; Laszlo, P.; Mathy, A. *Tetrahedron Lett.* ***1986***, *27*, 2627.

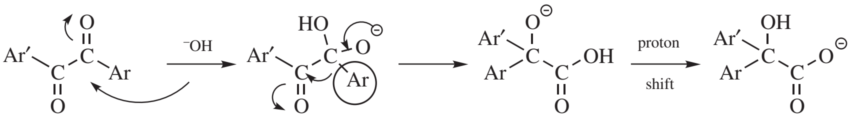
[184]Guo, Z.; Schultz, A.G. *Org. Lett.* ***2001***, *3*, 1177.

[185]For reviews, see Perkins, M.J.; Ward, P. *Mech. Mol. Migr.* ***1971***, *4*, 55, 90–103; Miller, B. *Mech. Mol. Migr.* ***1968***, *1*, 247; Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 55–68; Waring, A.J. *Adv. Alicyclic Chem.* ***1966***, *1*, 129, 207–223. For a review of other rearrangements of cyclohexadienones, see Miller, B. *Acc. Chem. Res.* ***1975***, *8*, 245.

[186]For evidence that these ions are indeed intermediates in this rearrangement, see Vitullo, V.P.; Grossman, N. *J. Am. Chem. Soc.* ***1972***, *94*, 3844; Planas, A.; Tomás, J.; Bonet, J. *Tetrahedron Lett.* ***1987***, *28*, 471.

[187]For a review, see Ershov, V.V.; Volod'kin, A.A.; Bogdanov, G.N. *Russ. Chem. Rev.* ***1963***, *32*, 75.

PhCOCOPh; benzilic acid is $Ph_2COHCOOH$).[188] A rhodium catalyzed version of this reaction has also been reported.[189] Though the reaction is usually illustrated with aryl groups, it can also be applied to aliphatic diketones[190] and to α-keto aldehydes. The use of an alkoxide instead of hydroxide gives the corresponding ester directly,[191] though alkoxide ions that are readily oxidized (e.g., OEt^- or $OCHMe_2^-$) are not useful here, since they reduce the benzil to a benzoin. The mechanism is similar to the rearrangements in **18-1–18-4**, but there is a difference: The migrating group does not move to a carbon with an open sextet. The carbon makes room for the migrating group by releasing a pair of π electrons from the C=O bond to the oxygen. The first step is attack of the base at the carbonyl group, the same as the first step of the tetrahedral mechanism of nucleophilic substitution (p. 1254) and of many additions to the C=O bond (Chapter 16):

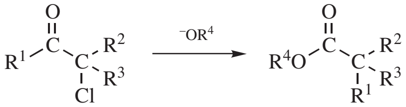


The mechanism has been intensely studied,[188] and there is much evidence for it.[192] The reaction is irreversible.

OS **I**, 89.

18-7 The Favorskii Rearrangement

2/Alkoxy-de-chloro(2/ → 1/alkyl)-*migro*-substitution



The reaction of α-halo ketones (chloro, bromo, or iodo) with alkoxide ions[193] to give rearranged esters is called the *Favorskii rearrangement*.[194] The use of

[188]For a review, see Selman, S.; Eastham, J.F. *Q. Rev. Chem. Soc.* ***1960***, *14*, 221.

[189]Shimizu, I.; Tekawa, M.; Maruyama, Y.; Yamamoto, A. *Chem. Lett.* ***1992***, 1365.

[190]For an example, see Schaltegger, A.; Bigler, P. *Helv. Chim. Acta* ***1986***, *69*, 1666.

[191]Doering, W. von E.; Urban, R.S. *J. Am. Chem. Soc.* ***1956***, *78*, 5938.

[192]However, some evidence for an SET pathway has been reported: Screttas, C.G.; Micha-Screttas, M.; Cazianis, C.T. *Tetrahedron Lett.* ***1983***, *24*, 3287.

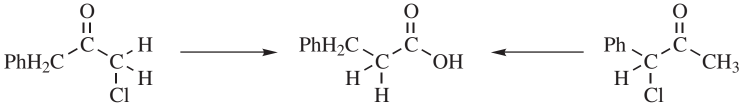
[193]The reaction has also been reported to take place with BF_3–MeOH and Ag^+: Giordano, C.; Castaldi, G.; Casagrande, F.; Abis, L. *Tetrahedron Lett.* ***1982***, *23*, 1385.

[194]For reviews, see Boyer, L.E.; Brazzillo, J.; Forman, M.A.; Zanoni, B. *J. Org. Chem.* ***1996***, *61*, 7611; Hunter, D.H.; Stothers, J.B.; Warnhoff, E.W., in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 1, Academic Press, NY, ***1980***, pp. 437–461; Chenier, P.J. *J. Chem. Educ.* ***1978***, *55*, 286; Rappe, C., in Patai, S. *The Chemistry of the Carbon–Halogen Bond*, pt. 2, Wiley, NY, ***1973***, pp. 1084–1101; Redmore, D.; Gutsche, C.D. *Carbocylcic Ring Expansion Reactions*, Academic Press, NY, ***1968***, pp.46–69; Akhrem, A.A.; Ustynyuk, T.K.; Titov, Yu.A. *Russ. Chem. Rev.* ***1970***, *39*, 732. For an asymmetric version, see Satoh, T.; Motohashi, S.; Kimura, S.; Tokutake, N.; Yamakawa, K. *Tetrahedron Lett.* ***1993***, *34*, 4823.

hydroxide ions or amines as bases leads to the free carboxylic acid (salt) or amide, respectively, instead of the ester. Cyclic α-halo ketones give ring contraction, as in the conversion of **65–66**.

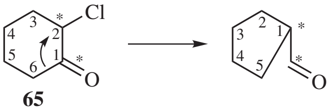
65 **66**

The reaction has also been carried out on α-hydroxy ketones[195] and on α,β-epoxy ketones, which give β-hydroxy acids.[196] The fact that an epoxide gives a reaction analogous to a halide indicates that the oxygen and halogen are leaving groups in a nucleophilic substitution step.



67 **68** **69**

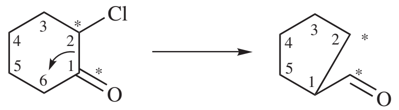
Through the years, the mechanism[197] of the Favorskii rearrangement has been the subject of much investigation; at least five different mechanisms have been proposed. However, the finding[198] that **67** and **68** *both* give **69** (this behavior is typical) shows that any mechanism where the halogen leaves and R^1 takes its place is invalid, since in such a case **67** would be expected to give **69** (with $PhCH_2$ migrating), but **68** should give PhCHMeCOOH (with CH_3 migrating). That is, in the case of **68**, it was PhCH that migrated and not methyl. Another important result was determined by radioactive labeling. **65**, in which C-1 and C-2 were equally labeled with ^{14}C, was converted to **66**. The product was found to contain 50% of the label on the carbonyl carbon, 25% on C-1, and 25% on C-2.[199] Now the carbonyl carbon, which originally carried half of the radioactivity, still had this much, so the rearrangement did not directly affect *it*. However, if the C-6 carbon had migrated to C-2, the other half of the radioactivity would be only on C-1 of the product:



65

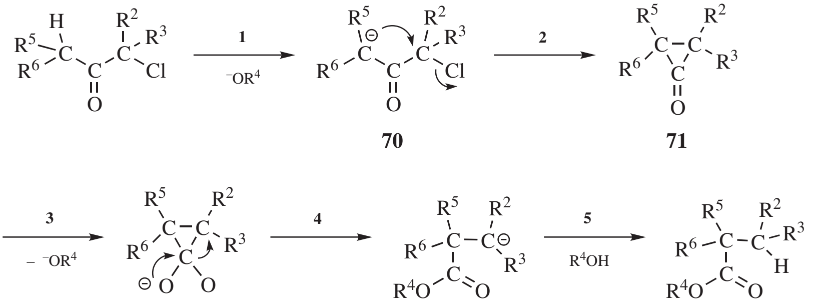
[195]Craig, J.C.; Dinner, A.; Mulligan, P.J. *J. Org. Chem.* ***1972***, *37*, 3539.
[196]See, for example, House, H.O.; Gilmor, W.F. *J. Am. Chem. Soc.* ***1961***, *83*, 3972; Mouk, R.W.; Patel, K.M.; Reusch, W. *Tetrahedron* ***1975***, *31*, 13.
[197]For a review of the mechanism, see Baretta, A.; Waegell, B. *React. Intermed. (Plenum)* ***1982***, *2*, 527.
[198]McPhee, W.D.; Klingsberg, E. *J. Am. Chem. Soc.* ***1944***, *66*, 1132; Bordwell, F.G.; Scamehorn, R.G.; Springer, W.R. *J. Am. Chem. Soc.* ***1969***, *91*, 2087.
[199]Loftfield, R.B. *J. Am. Chem. Soc.* ***1951***, *73*, 4707.

On the other hand, if the migration had gone the other way: If the C-2 carbon had migrated to C-6–then this half of the radioactivity would be found solely on C-2 of the product:



65

The fact that C-1 and C-2 were found to be equally labeled showed that *both migrations occurred*, with equal probability. Since C-2 and C-6 of **65** are not equivalent, this means that there must be a symmetrical intermediate.[200] The type of intermediate that best fits the circumstances is a cyclopropanone,[201] and the mechanism (for the general case) is formulated (replacing R^1 of our former symbolism with CHR^5R^6, since it is obvious that for this mechanism an α hydrogen is required on the non-halogenated side of the carbonyl):



70 **71**

The intermediate corresponding to **71** in the case of **65** is a symmetrical compound, and the three-membered ring can be opened with equal probability on either side of the carbonyl, accounting for the results with ^{14}C. In the general case, **71** is not symmetrical and should open on the side that gives the more stable carbanion.[202] This accounts for the fact that **67** and **68** give the same product. The intermediate in both cases is **70**, which always opens to give the carbanion stabilized by resonance. The cyclopropanone intermediate (**71**) has been isolated in the case where $R^2 = R^5 = t$-Bu and $R^3 = R^6 = H$,[203] and it

[200]A preliminary migration of the chlorine from C-2 to C-6 was ruled out by the fact that recovered **65** had the same isotopic distribution as the starting **65**.

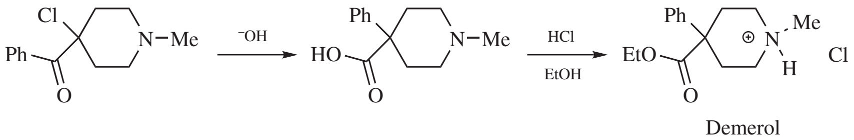
[201]Although cyclopropanones are very reactive compounds, several of them have been isolated. For reviews of cyclopropanone chemistry, see Wasserman, H.H.; Clark, G.M.; Turley, P.C. *Top. Curr. Chem.* ***1974***, *47*, 73; Turro, N.J. *Acc. Chem. Res.* ***1969***, *2*, 25.

[202]Factors other than carbanion stability (including steric factors) may also be important in determining which side of an unsymmetrical **71** is preferentially opened. See, for example, Rappe, C.; Knutsson, L. *Acta Chem. Scand.*, ***1967***, *21*, 2205; Rappe, C.; Knutsson, L.; Turro, N.J.; Gagosian, R.B. *J. Am. Chem. Soc.* ***1970***, *92*, 2032.

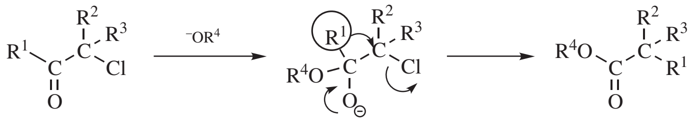
[203]Pazos, J.F.; Pacifici, J.G.; Pierson, G.O.; Sclove, D.B.; Greene, F.D. *J. Org. Chem.* ***1974***, *39*, 1990.

has also been trapped.[204] Also, cyclopropanones synthesized by other methods have been shown to give Favorskii products on treatment with NaOMe or other bases.[205]

The mechanism discussed is in accord with all the facts when the halo ketone contains an α hydrogen on the other side of the carbonyl group. However, ketones that do not have a hydrogen there also rearrange to give the same type of product. This is usually called the *quasi-Favorskii rearrangement*. An example is found in the preparation of Demerol:[206]



The quasi-Favorskii rearrangement obviously cannot take place by the cyclopropanone mechanism. The mechanism that is generally accepted (called the *semibenzilic mechanism*[207]) is a base-catalyzed pinacol



rearrangement-type mechanism similar to that of **18-6**. This mechanism requires inversion at the migration terminus and this has been found.[208] It has been shown that even where there *is* an appropriately situated a hydrogen, the semibenzilic mechanism may still operate.[209]

An interesting analog of the Favorskii rearrangement treats a ketone, such as 4-*tert*-butylcyclohexanone, without an α-halogen with $Tl(NO_3)_3$ to give 3-*tert*-butylcyclopentane-1-carboxylic acid.[210]

OS **IV**, 594; **VI**, 368, 711.

[204]Fort, A.W. *J. Am. Chem. Soc.* ***1962***, *84*, 4979; Cookson, R.C.; Nye, M.J. *Proc. Chem. Soc.* ***1963***, 129; Breslow, R.; Posner, J.; Krebs, A. *J. Am. Chem. Soc.* ***1963***, *85*, 234; Baldwin, J.E.; Cardellina, J.H.I. *Chem. Commun.* ***1968***, 558.

[205]Crandall, J.K.; Machleder, W.H. *J. Org. Chem.* ***1968***, *90*, 7347; Turro, N.J.; Gagosian, R.B.; Rappe, C.; Knutsson, L. *Chem. Commun.* ***1969***, 270; Wharton, P.S.; Fritzberg, A.R. *J. Org. Chem.* ***1972***, *37*, 1899.

[206]Smissman, E.E.; Hite, G. *J. Am. Chem. Soc.* ***1959***, *81*, 1201.

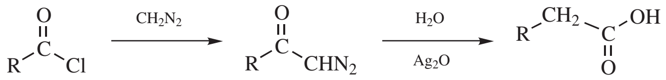
[207]Tchoubar, B.; Sackur, O. *C. R. Acad. Sci.* ***1939***, *208*, 1020.

[208]Baudry, D.; Bégué, J.; Charpentier-Morize, M. *Bull. Soc. Chim. Fr.* ***1971***, 1416; *Tetrahedron Lett.* ***1970***, 2147.

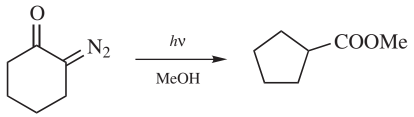
[209]For example, see Salaun, J.R.; Garnier, B.; Conia, J.M. *Tetrahedron* ***1973***, *29*, 2895; Rappe, C.; Knutsson, L. *Acta Chem. Scand.*, ***1967***, *21*, 163; Warnhoff, E.W.; Wong, C.M.; Tai, W.T. *J. Am. Chem. Soc.* ***1968***, *90*, 514.

[210]Ferraz, H.M.; Silva, Jr., J.F. *Tetrahedron Lett.* ***1997***, *38*, 1899.

18-8 The Arndt–Eistert Synthesis



In the *Arndt–Eistert synthesis*, an acyl halide is converted to a carboxylic acid with one additional carbon.[211] The first step of this process is reaction **16-89**. The actual rearrangement occurs in the second step on treatment of the diazo ketone with water and silver oxide or with silver benzoate and triethylamine. This rearrangement is called the *Wolff rearrangement*.[212] It is the best method of increasing a carbon chain by one if a *carboxylic acid* is available (**10-75** and **16-30** begin with alkyl halides). If an alcohol R'OH is used instead of water, the ester RCH_2COOR' is isolated directly.[213] Similarly, ammonia gives the amide. Other catalysts are sometimes used (e.g., colloidal platinum, copper, etc.), but occasionally the diazo ketone is simply heated or photolyzed in the presence of water, an alcohol, or ammonia, with no catalyst at all.[214] The photolysis method[215] often gives better results than the silver catalysis method. Of course, diazo ketones prepared in any other way also give the rearrangement.[216] The reaction is of wide scope. The R group may be alkyl or aryl and may contain many functional groups including unsaturation, but not including groups acidic enough to react with CH_2N_2 or diazo ketones (e.g., **10-5** and **10-19**). Sometimes the reaction is performed with other diazoalkanes (i.e., $R'CHN_2$) to give RCHR'COOH. The reaction has often been used for ring contraction of cyclic diazo ketones,[217] such as **72**.[218]



72

[211]For reviews, see Meier, H.; Zeller, K. *Angew. Chem. Int. Ed.* ***1975***, *14*, 32; Kirmse, W. *Carbene Chemistry*, 2nd ed., Academic Press, NY, ***1971***, pp. 475–493; Rodina, L.L.; Korobitsyna, I.K. *Russ. Chem. Rev.* ***1967***, *36*, 260; For a review of rearrangements of diazo and diazonium compounds, see Whittaker, D., in Patai, S. *The Chemistry of Diazonium and Diazo Compounds*, pt. 2, Wiley, NY, ***1978***, pp. 593–644.

[212]For a review, see Kirmse, W. *Eur. J. Org. Chem.* ***2002***, 2193. For a microwave-induced Wolff rearrangement, see Sudrik, S.G.; Chavan, S.P.; Chandrakumar, K.R.S.; Pal, S.; Date, S.K.; Chavan, S.P.; Sonawane, H.R. *J. Org. Chem.* ***2002***, *67*, 1574.

[213]For an ultrasound-induced version of this variation, see Winum, J.-Y.; Kamal, M.; Leydet, A.; Roque, J.-P.; Montero, J.-L. *Tetrahedron Lett.* ***1996***, *37*, 1781.

[214]For a list of methods, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1850–1851.

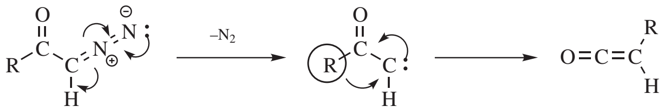
[215]For reviews of the photolysis method, see Regitz, M.; Maas, G. *Diazo Compounds*, Academic Press, NY, ***1986***, pp. 185–195; Ando, W., in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***,78, pp. 458–475.

[216]For a method of conducting the reaction with trimethylsilyldiazomethane instead of CH_2N_2, see Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* ***1980***, *21*, 4461.

[217]For a review, see Redmore, D.; Gutsche, C.D. *Carbocyclic Ring Expansion Reactions*, Academic Press, NY, ***1968***, pp. 125–136.

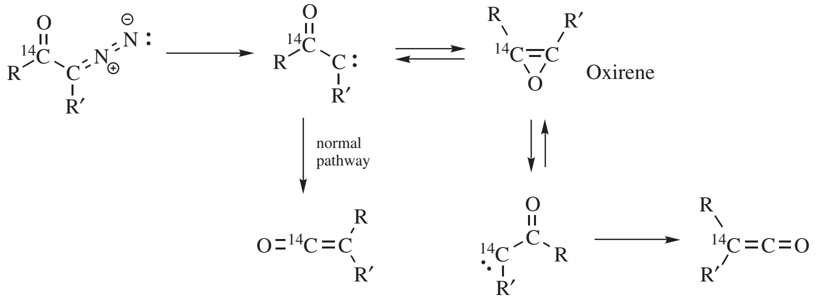
[218]Korobitsyna, I.K.; Rodina, L.L.; Sushko, T.P. *J. Org. Chem. USSR* ***1968***, *4*, 165; Jones, Jr., M.; Ando, W. *J. Am. Chem. Soc.* ***1968***, *90*, 2200. See Lee, Y.R.; Suk, J.Y.; Kim, B.S. *Tetrahedron Lett.* ***1999***, *40*, 8219.

The mechanism is generally regarded as involving formation of a carbene.[219] It is the divalent carbon that has the open sextet and to which the migrating group brings its electron pair:



The actual product of the reaction is thus the ketene, which then reacts with water (**15-3**), an alcohol (**15-5**), or ammonia or an amine (**15-8**). Particularly stable ketenes[220] (e.g., $Ph_2C{=}C{=}O$) have been isolated and others have been trapped in other ways (e.g., as β-lactams,[221] **16-96**). The purpose of the catalyst is not well understood, though many suggestions have been made. This mechanism is strictly analogous to that of the Curtius rearrangement (**18-14**). Although the mechanism as shown above involves a free carbene and there is much evidence to support this,[222] it is also possible that at least in some cases the two steps are concerted and a free carbene is absent.

When the Wolff rearrangement is carried out photochemically, the mechanism is basically the same,[215] but another pathway can intervene. Some of the ketocarbene originally formed can undergo a carbene–carbene rearrangement, through an oxirene intermediate.[223] This was shown by ^{14}C labeling experiments, where



diazo ketones labeled in the carbonyl group gave rise to ketenes that bore the label at both C=C carbons.[224] In general, the smallest degree of scrambling (and thus of

[219]See Scott, A.P.; Platz, M.S.; Radom, L. *J. Am. Chem. Soc.* ***2001***, *123*, 6069.

[220]In some cases, ketenes are subject to rearrangement, see Farlow, R.A.; Thamatloor, D.A.; Sunoj, R.B.; Hadad, C.M. *J. Org. Chem.* ***2002***, *67*, 3257.

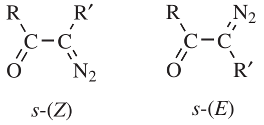
[221]Kirmse, W.; Horner, L. *Chem. Ber.* ***1956***, *89*, 2759; also see, Horner, L.; Spietschka, E. *Chem. Ber.* ***1956***, *89*, 2765.

[222]For a summary of evidence on both sides of the question, see Kirmse, W. *Carbene Chemistry*, 2nd ed., Academic Press, NY, ***1971***, pp. 476–480. See also, Torres, M.; Ribo, J.; Clement, A.; Strausz, O.P. *Can. J. Chem.* ***1983***, *61*, 996; Tomoika, H.; Hayashi, N.; Asano, T.; Izawa, Y. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 758.

[223]For a review of oxirenes, see Lewars, Y. *Chem. Rev.* ***1983***, *83*, 519.

[224]Fenwick, J.; Frater, G.; Ogi, K.; Strausz, O.P. *J. Am. Chem. Soc.* ***1973***, *95*, 124; Zeller, K. *Chem. Ber.* ***1978***, *112*, 678. See also, Thornton, D.E.; Gosavi, R.K.; Strausz, O.P. *J. Am. Chem. Soc.* ***1970***, *92*, 1768; Russell, R.L.; Rowland, F.S. *J. Am. Chem. Soc.* ***1970***, *92*, 7508; Majerski, Z.; Redvanly, C.S. *J. Chem. Soc., Chem. Commun.* ***1972***, 694.

the oxirene pathway) was found when R′ = H. An intermediate believed to be an oxirene has been detected by laser spectroscopy.[225] The oxirene pathway is not found in the thermal Wolff rearrangement. It is likely that an excited singlet state of the carbene is necessary for the oxirene pathway to intervene.[226] In the photochemical process, ketocarbene intermediates, in the triplet state, have been isolated in an Ar matrix at 10–15 K, where they have been identified by UV–visible, IR, and esr spectra.[227] These intermediates went on to give the rearrangement via the normal pathway, with no evidence for oxirene intermediates.

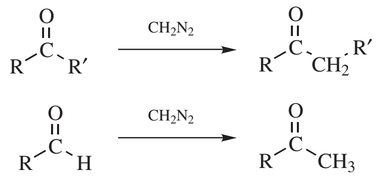


The diazo ketone can exist in two conformations, called *s*-(*E*) and *s*-(*Z*). Studies have shown that Wolff rearrangement takes place preferentially from the *s*-(*Z*) conformation.[228]

OS **III**, 356; **VI**, 613, 840.

18-9 Homologation of Aldehydes and Ketones

Methylene-insertion



Aldehydes and ketones[229] can be converted to their homologs with diazomethane.[230] Several other reagents[231] are also effective, including Me_3SiI, and then silica gel,[232] or $LiCH(B–OCH_2CH_2O–)_2$.[233] With the diazomethane reaction,

[225]Tanigaki, K.; Ebbesen, T.W. *J. Am. Chem. Soc.* ***1987***, *109*, 5883. See also, Bachmann, C.; N'Guessan, T.Y.; Debû, F.; Monnier, M.; Pourcin, J.; Aycard, J.; Bodot, H. *J. Am. Chem. Soc.* ***1990***, *112*, 7488.

[226]Csizmadia, I.G.; Gunning, H.E.; Gosavi, R.K.; Strausz, O.P. *J. Am. Chem. Soc.* ***1973***, *95*, 133.

[227]McMahon, R.J.; Chapman, O.L.; Hayes, R.A.; Hess, T.C.; Krimmer, H. *J. Am. Chem. Soc.* ***1985***, *107*, 7597.

[228]Kaplan, F.; Mitchell, M.L. *Tetrahedron Lett.* ***1979***, 759; Tomioka, H.; Okuno, H.; Izawa, Y. *J. Org. Chem.* ***1980***, *45*, 5278.

[229]For a homologation of carboxylic esters RCOOEt → RCH_2COOEt, which goes by an entirely different pathway, see Kowalski, C.J.; Haque, M.S.; Fields, K.W. *J. Am. Chem. Soc.* ***1985***, *107*, 1429. Also see, Yamamoto, M.; Nakazawa, M.; Kishikawa, K.; Kohmoto, S. *Chem. Commun.* ***1996***, 2353.

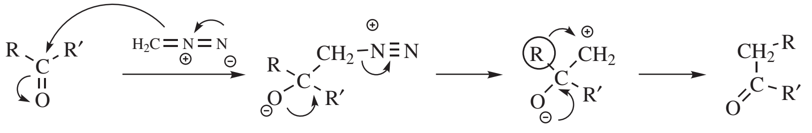
[230]For a review, see Gutsche, C.D. *Org. React.* ***1954***, *8*, 364.

[231]See Taylor, E.C.; Chiang, C.; McKillop, A. *Tetrahedron Lett.* ***1977***, 1827; Villieras, J.; Perriot, P.; Normant, J.F. *Synthesis* ***1979***, 968; Aoyama, T.; Shioiri, T. *Synthesis* ***1988***, 228.

[232]Lemini, C.; Ordoñez, M.; Pérez-Flores, J.; Cruz-Almanza, R. *Synth. Commun.* ***1995***, *25*, 2695.

[233]Schummer, D.; Höfle, G. *Tetrahedron* ***1995***, *51*, 11219.

formation of an epoxide (**16-46**) is a side reaction. Although this reaction appears superficially to be similar to the insertion of carbenes into C–H bonds, **12-21** (and IUPAC names it as an insertion), the mechanism is quite different. This is a true rearrangement and no free carbene is involved. The first step is an addition to the C=O bond:



The betaine **73** can sometimes be isolated. As shown in **16-46**, intermediate **73** can also go to the epoxide. The evidence for this mechanism is summarized in the review by Gutsche.[230] Note that this mechanism is essentially the same as in the apparent "insertions" of oxygen (**18-19**) and nitrogen (**18-16**) into ketones.

Aldehydes give fairly good yields of methyl ketones; that is, hydrogen migrates in preference to alkyl. The most abundant side product is not the homologous aldehyde, but the epoxide. However, the yield of aldehyde at the expense of methyl ketone can be increased by the addition of methanol. If the aldehyde contains electron-withdrawing groups, the yield of epoxides is increased and the ketone is formed in smaller amounts, if at all. Ketones give poorer yields of homologous ketones. Epoxides are usually the predominant product here, especially when one or both R groups contain an electron-withdrawing group. The yield of ketones also decreases with increasing length of the chain. The use of a Lewis acid increases the yield of ketone.[234] Cyclic ketones,[235] three-membered[236] and larger, behave particularly well and give good yields of ketones with the ring expanded by one.[237] Aliphatic diazo compounds ($RCHN_2$ and R_2CN_2) are sometimes used instead of diazomethane, with the expected results.[238] Ethyl diazoacetate can be used analogously, in the presence of a Lewis acid or of triethyloxonium fluoroborate,[239] to

[234]For a review of homologations catalyzed by Lewis acids, see Müller, E.; Kessler, H.; Zeeh, B. *Fortschr. Chem. Forsch.* ***1966***, *7*, 128, see pp. 137–150.

[235]For other methods for the ring enlargement of cyclic ketones, see Krief, A.; Laboureur, J.L. *Tetrahedron Lett.* ***1987***, *28*, 1545; Krief, A.; Laboureur, J.L.; Dumont, W. *Tetrahedron Lett.* ***1987***, *28*, 1549; Abraham, W.D.; Bhupathy, M.; Cohen, T. *Tetrahedron Lett.* ***1987***, *28*, 2203; Trost, B.M.; Mikhail, G.K. *J. Am. Chem. Soc.* ***1987***, *109*, 4124.

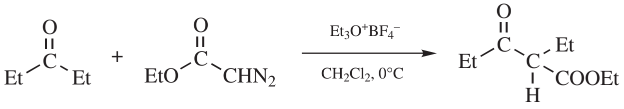
[236]For example, see Turro, N.J.; Gagosian, R.B. *J. Am. Chem. Soc.* ***1970***, *92*, 2036.

[237]For a review, see Gutsche, C.D.; Redmore, D. *Carbocyclic Ring Expansion Reactions*, Academic Press, NY, ***1968***, pp. 81–98. For a review pertaining to bridged bicyclic ketones, see Krow, G.R. *Tetrahedron* ***1987***, *43*, 3.

[238]For example, see Smith, R.F. *J. Org. Chem.* ***1960***, *25*, 453; Warner, C.R.; Walsh, Jr., E.J.; Smith, R.F. *J. Chem. Soc.* ***1962***, 1232; Loeschorn, C.A.; Nakajima, M.; Anselme, J. *Bull. Soc. Chim. Belg.* ***1981***, *90*, 985.

[239]Mock, W.L.; Hartman, M.E. *J. Org. Chem.* ***1977***, *42*, 459, 466; Baldwin, S.W.; Landmesser, N.G. *Synth. Commun.* ***1978***, *8*, 413.

give a β-keto ester, such as **74**.



74

When unsymmetrical ketones were used in this reaction (with BF_3 as catalyst), the less highly substituted carbon preferentially migrated.[240] The reaction can be made regioselective by applying this method to the α-halo ketone, in which case only the other carbon migrates.[241] The ethyl diazoacetate procedure has also been applied to the acetals or ketals of α,β-unsaturated aldehydes and ketones.[242]

Bicyclic ketones can be expanded to form monocyclic ketones in the presence of certain reagents. Treatment of a bicyclo[4.1.0]hexan-4-one derivative with SmI_2 led to a cyclohexanone.[243] The SmI_2 also converts α-halomethyl cyclic ketones to the next larger ring ketone[244] and cyclic ketones to the next larger ring ketone in the presence of CH_2I_2.[245] α-Chloro-α-3-iodopropylcyclobutanones were converted to cycloheptanones using radical conditions (Bu_3SnH/AIBN).[246]

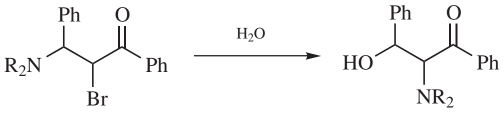
Another homologation reaction converts an aldehyde to its tosyl hydrazone, and subsequent reaction with an aldehyde and NaOEt/EtOH give a ketone.[247] The reaction of an aldehyde with vinyl acetate and barium hydroxide gives the homologated conjugated aldehyde.[248]

OS **IV**, 225, 780. For homologation of carboxyl acid derivatives, see OS **IX**, 426

B. Carbon-to-Carbon Migrations of Other Groups

18-10 Migrations of Halogen, Hydroxyl, Amino, and so on

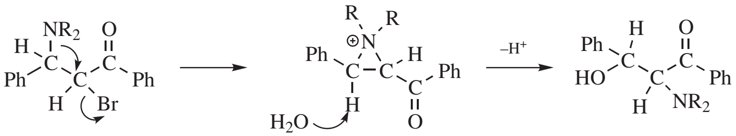
Hydroxy-de-bromo-*cine*-substitution, and so on



When a nucleophilic substitution is carried out on a substrate that has a neighboring group (p. 446) on the adjacent carbon, a cyclic intermediate can be generated

[240]Liu, H.J.; Majumdar, S.P. *Synth. Commun.* ***1975***, *5*, 125.
[241]Dave, V.; Warnhoff, E.W. *J. Org. Chem.* ***1983***, *48*, 2590.
[242]Doyle, M.P.; Trudell, M.L.; Terpstra, J.W. *J. Org. Chem.* ***1983***, *48*, 5146.
[243]Lee, P.H.; Lee, J. *Tetrahedron Lett.* ***1998***, *39*, 7889.
[244]Hasegawa, E.; Kitazume, T.; Suzuki, K.; Tosaka, E. *Tetrahedron Lett.* ***1998***, *39*, 4059.
[245]Fukuzawa, S.; Tsuchimoto, T. *Tetrahedron Lett.* ***1995***, *36*, 5937.
[246]Zhang, W.; Dowd, P. *Tetrahedron Lett.* ***1992***, *33*, 3285. For an example generating larger rings, see Dowd, P.; Choi, S.-C. *Tetrahedron* ***1992***, *48*, 4773.
[247]Angle, S.R.; Neitzel, M.L. *J. Org. Chem.* ***2000***, *65*, 6458.
[248]Mahata, P.K.; Barun, O.; Ila, H.; Junjappa, H. *Synlett* ***2000***, 1345.

that is opened on the opposite side, resulting in migration of the neighboring group. In the example shown above (NR_2 = morpholino),[249] the reaction took place via an aziridinium salt **75** to give an α-amino-β-hydroxy ketone.



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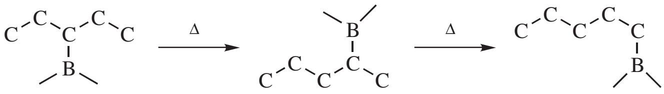
Sulfonate esters and halides can also migrate in this reaction.[250] α-Halo and α-acyloxy epoxides undergo ready rearrangement to α-halo and α-acyloxy ketones, respectively.[251] These substrates are very prone to rearrange, and often do so on standing without a catalyst, though in some cases an acid catalyst is necessary. The reaction is essentially the same as the rearrangement of epoxides shown in **18-2**, except that in this case halogen or acyloxy is the migrating group (as shown above; however, it is also possible for one of the R groups (alkyl, aryl, or hydrogen) to migrate instead, and mixtures are sometimes obtained).

18-11 Migration of Boron

Hydro,dialkylboro-interchange, and so on



Boranes are prepared by the reaction of $BH_3(B_2H_6)$ or an alkylborane with an alkene (**15-16**). When a nonterminal borane is heated at temperatures ranging from 100 to 200°C, the boron moves toward the end of the chain.[252] The reaction is catalyzed by small amounts of borane or other species containing B–H bonds.

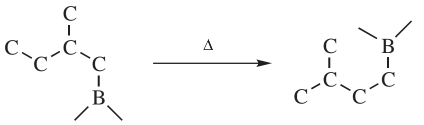
[249]Southwick, P.L.; Walsh, W.L. *J. Am. Chem. Soc.* ***1955***, *77*, 405. See also, Suzuki, K.; Okano, K.; Nakai, K.; Terao, Y.; Sekiya, M. *Synthesis* ***1983***, 723.

[250]For a review of Cl migrations, see Peterson, P.E. *Acc. Chem. Res.* ***1971***, *4*, 407. See also, Loktev, V.F.; Korchagina, D.V.; Shubin, V.G.; Koptyug, V.A. *J. Org. Chem. USSR* ***1977***, *13*, 201; Dobronravov, P.N.; Shteingarts, V.D. *J. Org. Chem. USSR* ***1977***, *13*, 420. For examples of Br migration, see Gudkova, A.S.; Uteniyazov, K.; Reutov, O.A. *Doklad. Chem.* ***1974***, *214*, 70; Brusova, G.P.; Gopius, E.D.; Smolina, T.A.; Reutov, O.A. *Doklad. Chem.* ***1980***, *253*, 334. For a review of F migration (by several mechanisms) see Kobrina, L.S.; Kovtonyuk, V.N. *Russ. Chem. Rev.* ***1988***, *57*, 62. For an example OH migration, see Cathcart, R.C.; Bovenkamp, J.W.; Moir, R.Y.; Bannard, R.A.B.; Casselman, A.A. *Can. J. Chem.* ***1977***, *55*, 3774. For a review of migrations of ArS and $Ar_2P(O)$, see Warren, S. *Acc. Chem. Res.* ***1978***, *11*, 403. See also, Aggarwal, V.K.; Warren, S. *J. Chem. Soc. Perkin Trans. 1* ***1987***, 2579.

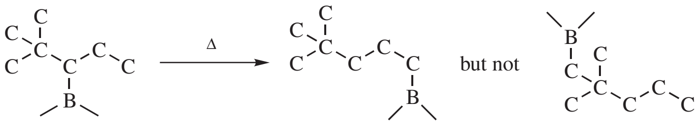
[251]For a review, see McDonald, R.N. *Mech. Mol. Migr.* ***1971***, *3*, 67.

[252]Brown, H.C. *Hydroboration*, W. A. Benjamin, NY, ***1962***, pp. 136–149, Brown, H.C.; Zweifel, G. *J. Am. Chem. Soc.* ***1966***, *88*, 1433. See also, Brown, H.C.; Racherla, U.S. *J. Organomet. Chem.* ***1982***, *241*, C37.

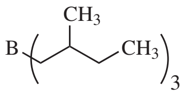
The boron can move past a branch, for example,



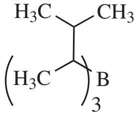
but not past a double branch, for example,



The reaction is an equilibrium: **76**, **77**, and **78** each gave a mixture containing ~40% **76**, 1% **77**, and 59% **78**. The migration can go quite a long distance. Thus $(C_{11}H_{23}CHC_{11}H_{23})_3B$ was completely converted to $(C_{23}H_{47})_3B$, involving a migration of 11 positions.[253] If the boron is on a cycloalkyl ring, it can move around



76



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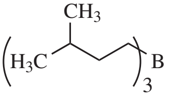
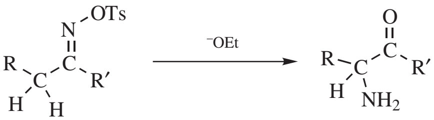


78

the ring; if any alkyl chain is also on the ring, the boron may move from the ring to the chain, ending up at the end of the chain.[254] The reaction is useful for the migration of double bonds in a controlled way (see **12-2**). The mechanism may involve a π complex, at least partially.[255]

18-12 The Neber Rearrangement

Neber oxime tosylate-amino ketone rearrangement



α-Amino ketones can be prepared by treatment of ketoxime tosylates with a base, such as ethoxide ion or pyridine.[256] This reaction is called the *Neber rearrangement*. The R group is usually aryl, though the reaction has been carried out with

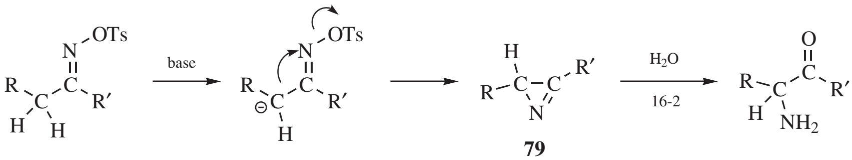
[253]Logan, T.J. *J. Org. Chem.* ***1961***, *26*, 3657.

[254]Brown, H.C.; Zweifel, G. *J. Am. Chem. Soc.* ***1967***, *89*, 561.

[255]See Wood, S.E.; Rickborn, B. *J. Org. Chem.* ***1983***, *48*, 555; Field, L.D.; Gallagher, S.P. *Tetrahedron Lett.* ***1985***, *26*, 6125.

[256]For a review, see Conley, R.T.; Ghosh, S. *Mech. Mol. Migr.* ***1971***, *4*, 197, pp. 289–304.

R = alkyl or hydrogen. The R′ group may be alkyl, or aryl but not hydrogen. The Beckmann rearrangement (**18-17**) and the abnormal Beckmann reaction (elimination to the nitrile, **17-30**) may be side reactions, although these generally occur in acid media. A similar rearrangement is given by *N,N*-dichloroamines of the type $RCH_2CH(NCl_2)R'$, where the product is also $RCH(NH_2)COR'$.[257] The mechanism of the Neber rearrangement is via an azirine intermediate **79**.[258]

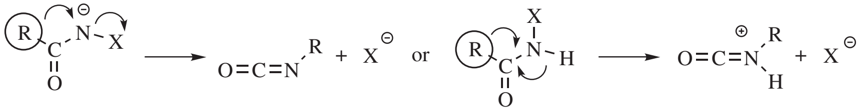


The best evidence for this mechanism is that the azirine intermediate has been isolated.[258,259] In contrast to the Beckmann rearrangement, this one is sterically indiscriminate:[260] Both a syn and an anti ketoxime give the same product. The mechanism as shown above consists of three steps. However, it is possible that the first two steps are concerted, and it is also possible that what is shown as the second step is actually two steps: loss of OTs to give a nitrene, and formation of the azirine. In the case of the dichloroamines, HCl is first lost to give $RCH_2C(=NCl)R'$, which then behaves analogously.[261] *N*-Chloroimines prepared in other ways also give the reaction.[262]

OS **V**, 909; **VII**, 149.

C. Carbon-to-Nitrogen Migrations of R and AR

The reactions in this group are nucleophilic migrations from a carbon to a nitrogen atom. In each case the nitrogen atom either has six electrons in its outer shell (and thus invites the migration of a group carrying an electron pair) or else loses a nucleofuge concurrently with the migration (p. 1560). Reactions **18-13–18-16** are used to prepare amines from acid derivatives. Reactions **18-16** and **18-17** are used to prepare amines from ketones. The mechanisms of **18-13–18-16** (with carboxylic acids) are very similar and follow one of two patterns:



[257]Baumgarten, H.E.; Petersen, H.E. *J. Am. Chem. Soc.* ***1960***, *82*, 459, and references cited therein.

[258]Cram, D.J.; Hatch, M.J. *J. Am. Chem. Soc.* ***1953***, *75*, 33; Hatch, M.J.; Cram, D.J. *J. Am. Chem. Soc.* ***1953***, *75*, 38.

[259]Neber, P.W.; Burgard, A. *Liebigs Ann. Chem.* ***1932***, *493*, 281; Parcell, R.F. *Chem. Ind. (London)* ***1963***, 1396.

[260]House, H.O.; Berkowitz, W.F. *J. Org. Chem.* ***1963***, *28*, 2271.

[261]For example, see Nakai, M.; Furukawa, N.; Oae, S. *Bull. Chem. Soc. Jpn.* ***1969***, *42*, 2917.

[262]Baumgarten, H.E.; Petersen, J.M.; Wolf, D.C. *J. Org. Chem.* ***1963***, *28*, 2369.

Some of the evidence[263] is (*1*) configuration is retained in R (p. 1563); (*2*) the kinetics are first order; (*3*) intramolecular rearrangement is shown by labeling; and (*4*) no rearrangement occurs *within* the migrating group, for example, a neopentyl group on the carbon of the starting material is still a neopentyl group on the nitrogen of the product.

In many cases, it is not certain whether the nucleofuge X is lost first, creating an intermediate nitrene[264] or nitrenium ion, or whether migration and loss of the nucleofuge are simultaneous, as shown above.[265] It is likely that both possibilities can exist, depending on the substrate and reaction conditions.

18-13 The Hofmann Rearrangement

Bis(hydrogen)-(2/ 1/*N*-alkyl)-*migro*-detachment (formation of isocyanate)

$$RCONH_2 + NaOBr \longrightarrow R{-}N{=}C{=}O \xrightarrow[\textbf{16-2}]{\text{hydrolysis}} RNH_2$$

In the *Hofmann rearrangement*, an unsubstituted amide is treated with sodium hypobromite (or sodium hydroxide and bromine, which is essentially the same thing) to give a primary amine that has one carbon fewer than the starting amide.[266] The actual product is the isocyanate, but this compound is seldom isolated[267] since it is usually hydrolyzed under the reaction conditions. The R group may be alkyl or aryl, but if it is an alkyl group of more than about six or seven carbons, low yields are obtained unless Br_2 and NaOMe are used instead of Br_2 and NaOH.[268] Another modification uses NBS/NaOMe.[269] Under these conditions the product of addition to the isocyanate is the carbamate RNHCOOMe (**16-8**), which is easily isolated or can be hydrolyzed to the amine. Side reactions when NaOH is the base are formation of ureas RNHCONHR and acylureas RCONHCONHR by addition, respectively, of RNH_2 and $RCONH_2$ to RNCO (**16-20**). If acylureas are desired, they can be made the main products by using only one-half of the usual quantities of Br_2 and NaOH. Another side product, but only from primary R, is the nitrile derived from oxidation of RNH_2 (**19-5**). Imides react to give amino acids, for example, phthalimide gives *o*-aminobenzoic acid. α-Hydroxy and α-halo amides give aldehydes and ketones by way of the unstable α-hydroxy- or α-haloamines. However, a side product with an α-halo amide is a *gem*-dihalide. Ureas analogously give hydrazines.

[263]For a discussion of this mechanism and the evidence for it, see Smith, P.A.S., in de Mayo, P. *Molecular Rearrangements*, Vol. 1, Wiley, NY, ***1963***, Vol. 1, pp. 258–550.

[264]For a review of rearrangements involving nitrene intermediates, see Boyer, J.H. *Mech. Mol. Migr.* ***1969***, *2*, 267. See also, Ref. 282.

[265]The question is discussed by Lwowski, W., in Lwowski *Nitrenes*, Wiley, NY, ***1970***, pp. 217–221.

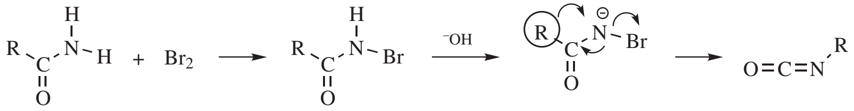
[266]For a review, see Wallis, E.S.; Lane, J.F. *Org. React.* ***1946***, *3*, 267.

[267]If desired, the isocyanate can be isolated by the use of phase-transfer conditions: see Sy, A.O.; Raksis, J.W. *Tetrahedron Lett.* ***1980***, *21*, 2223.

[268]For an example of the use of this method at low temperatures, see Radlick, P.; Brown, L.R. *Synthesis* ***1974***, 290.

[269]Huang, X.; Keillor, J.W. *Tetrahedron Lett.* ***1997***, *38*, 313.

The mechanism follows the pattern outlined on p. 1606.



80

The first step is an example of **12-52** and intermediate *N*-halo amides (**80**) have been isolated. In the second step, **80** lose a proton to the base. Compound **80** is acidic because of the presence of two electron-withdrawing groups (acyl and halo) on the nitrogen. It is possible that the third step is actually two steps: loss of bromide to form a nitrene, followed by the actual migration, but most of the available evidence favors the concerted reaction.[270] A similar reaction can be effected by the treatment of amides with lead tetraacetate.[271] Among other reagents that convert $RCONH_2$ to RNH_2 (R = alkyl, but not aryl) are phenyliodosyl bis(trifluoroacetate) $PhI(OCOCF_3)_2$[272] and hydroxy(tosyloxy)iodobenzene PhI(OH)OTs.[273] A mixture of NBS, $Hg(OAc)_2$, and R'OH is one of several reagent mixtures that convert an amide $RCONH_2$ to the carbamate RNHCOOR' (R = primary, secondary, or tertiary alkyl or aryl) in high yield.[274] A mixture of NBS and DBU (p. 1132) in methanol gives the carbamate,[275] as does electrolysis in methanol.[276]

A variation of the Hofmann rearrangement treated a β-hydroxy primary amide with $PhI(O_2CCF_3)_2$ in aqueous acetonitrile, giving an isocyanate via –CON–I, which reacts with the hydroxyl group intramolecularly to give a cyclic carbamate.[277] Note that carbamates are converted to isocyanates by heating with Montmorillonite K10.[278]

OS **II**, 19, 44, 462; **IV**, 45; **VIII**, 26, 132.

18-14 The Curtius Rearrangement

Dinitrogen-(2/ → 1/*N*-alkyl)-*migro*-detachment

$$RCON_3 \xrightarrow{\Delta} R\text{—}N{=}C{=}O$$

[270]See, for example, Imamoto, T.; Tsuno, Y.; Yukawa, Y. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 1632, 1639, 1644; Imamoto, T.; Kim, S.; Tsuno, Y.; Yukawa, Y. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 2776.

[271]Acott, B.; Beckwith, A.L.J.; Hassanali, A. *Aust. J. Chem.* ***1968***, *21*, 185, 197; Baumgarten, H.E.; Smith, H.L.; Staklis, A. *J. Org. Chem.* ***1975***, *40*, 3554.

[272]Loudon, G.M.; Radhakrishna, A.S.; Almond, M.R.; Blodgett, J.K.; Boutin, R.H. *J. Org. Chem.* ***1984***, *49*, 4272; Boutin, R.H.; Loudon, G.M. *J. Org. Chem.* ***1984***, *49*, 4277; Pavlides, V.H.; Chan, E.D.; Pennington, L.; McParland, M.; Whitehead, M.; Coutts, I.G.C. *Synth. Commun.* ***1988***, *18*, 1615.

[273]Vasudevan, A.; Koser, G.F. *J. Org. Chem.* ***1988***, *53*, 5158.

[274]Jew, S.; Park, H.G.; Park, H.; Park, M.; Cho, Y. *Tetrahedron Lett.* ***1990***, *31*, 1559.

[275]Huang, X.; Seid, M.; Keillor, J.W. *J. Org. Chem.* ***1997***, *62*, 7495.

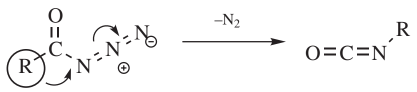
[276]Matsumura, Y.; Maki, T. ; Satoh, Y. *Tetrahedron Lett.* ***1997***, *38*, 8879.

[277]Yu, C.; Jiang, Y.; Liu, B.; Hu, L. *Tetrahedron Lett.* ***2001***, *42*, 1449.

[278]Uriz, P.; Serra, M.; Salagre, P.; Castillon, S.; Claver, C.; Fernandez, E. *Tetrahedron Lett.* ***2002***, *43*, 1673.

The *Curtius rearrangement* involves the pyrolysis of acyl azides to yield isocyanates.[279] The reaction gives good yields of isocyanates, since no water is present to hydrolyze them to the amine. Of course, they can be subsequently hydrolyzed, and indeed the reaction *can* be carried out in water or alcohol, in which case the products are amines, carbamates, or acylureas, as in **18-13**.[280] This is a very general reaction and can be applied to almost any carboxylic acid: aliphatic, aromatic, alicyclic, heterocyclic, unsaturated, and containing many functional groups. Acyl azides can be prepared as in **10-43** or by treatment of acylhydrazines (hydrazides) with nitrous acid (analogous to **12-49**). The Curtius rearrangement is catalyzed by Lewis or protic acids, but these are usually not necessary for good results.

The mechanism is similar to that in **18-13** to give an isocyanate. Also note the exact analogy between this reaction and **18-8**. However, in this case, there is no evidence for a free nitrene and it is probable that the steps are concerted.[281]



Alkyl azides can be similarly pyrolyzed to give imines, in an analogous reaction:[282]

$$R_3CN_3 \xrightarrow{\Delta} R_2C{=}NR$$

The R groups may be alkyl, aryl, or hydrogen, though if hydrogen migrates, the product is the unstable $R_2C{=}NH$. The mechanism is essentially the same as that of the Curtius rearrangement. However, in pyrolysis of tertiary alkyl azides, there is evidence that free alkyl nitrenes are intermediates.[283] The reaction can also be carried out with acid catalysis, in which case lower temperatures can be used, though the acid may hydrolyze the imine (**16-2**). Cycloalkyl azides give

[279]For a review, see Banthorpe, D.V., in Patai, S. *The Chemistry of the Azido Group*, Wiley, NY, ***1971***, pp. 397–405.

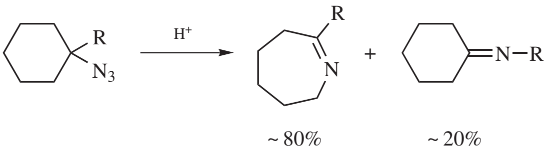
[280]For a variation that conveniently produces the amine directly, see Pfister, J.R.; Wyman, W.E. *Synthesis* ***1983***, 38. See also, Capson, T.L.; Poulter, C.D. *Tetrahedron Lett.* ***1984***, *25*, 3515.

[281]See, for example, Lwowski, W. *Angew. Chem. Int. Ed.* ***1967***, *6*, 897; Linke, S.; Tissue, G.T.; Lwowski, W. *J. Am. Chem. Soc.* ***1967***, *89*, 6308; Smalley, R.K.; Bingham, T.E. *J. Chem. Soc. C* ***1969***, 2481.

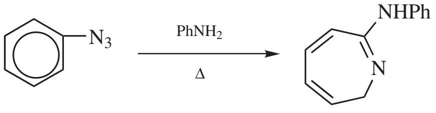
[282]For a treatise on azides, which includes discussion of rearrangement reactions, see Scriven, E.F.V. *Azides and Nitrenes*, Academic Press, NY, ***1984***. For a review of rearrangements of alkyl and aryl azides, see Stevens, T.S.; Watts, W.E. *Selected Molecular Rearrangements*, Van Nostrand-Reinhold, Princeton, NJ, ***1973***, pp. 45–52. For reviews of the formation of nitrenes from alkyl and aryl azides, see, in Lwowski, W. *Nitrenes*, Wiley, NY, ***1970***, the chapters by Lewis, F.D.; Saunders, Jr., W.H. pp. 47–97, 47–78 and by Smith, P.A.S. pp. 99–162.

[283]Abramovitch, R.A.; Kyba, E.P. *J. Am. Chem. Soc.* ***1974***, *96*, 480; Montgomery, F.C.; Saunders, Jr., W.H. *J. Org. Chem.* ***1976***, *41*, 2368.

ring expansion.[284]



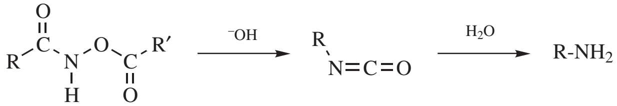
Aryl azides also give ring expansion on heating, for example,[285]



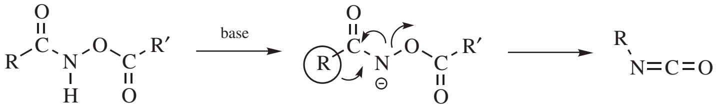
OS **III**, 846; **IV**, 819; **V**, 273; **VI**, 95, 910. Also see, OS **VI**, 210.

18-15 The Lossen Rearrangement

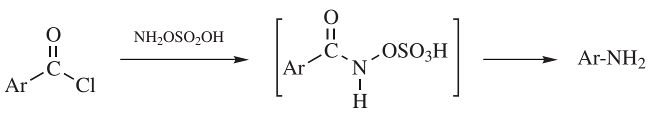
Hydro,acetoxy-(2/ → 1*N*-alkyl)-*migro*-detachment



The *O*-acyl derivatives of hydroxamic acids[286] give isocyanates when treated with bases or sometimes even just on heating, in a reaction known as the *Lossen rearrangement*.[287] The mechanism is similar to that of **18-13** and **18-14**:



In a similar reaction, aromatic acyl halides are converted to amines in one laboratory step by treatment with hydroxylamine-*O*-sulfonic acid.[288]



A chiral Lossen rearrangement is known.[289]

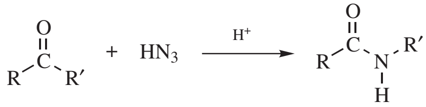
[284]Smith, P.A.S.; Lakritz, J. cited in Smith, P.A.S., in de Mayo, P. *Molecular Rearrangments*, Vol. 1, Wiley, NY, ***1963***, p. 474.
[285]Huisgen, R.; Vossius, D.; Appl, M. *Chem. Ber.* ***1958***, *91*, 1,12.
[286]For a review of hydroxamic acids, see Bauer, L.; Exner, O. *Angew. Chem. Int. Ed.* ***1974***, *13*, 376.
[287]For an example, see Salomon, C.J.; Breuer, E. *J. Org. Chem*, ***1997***, *62*, 3858.
[288]Wallace, R.G.; Barker, J.M.; Wood, M.L. *Synthesis* ***1990***, 1143.
[289]Chandrasekhar, S.; Sridhar, M. *Tetrahedron Asymmetry* ***2000***, *11*, 3467.

18-16 The Schmidt Reaction

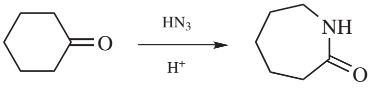
$$RCOOH + HN_3 \xrightarrow{H^+} R{-}N{=}C{=}O \xrightarrow{H_2O} RNH_2$$

There are actually three reactions called by the name *Schmidt reaction*, involving the addition of hydrazoic acid to carboxylic acids, aldehydes and ketones, and alcohols and alkenes.[290] The most common is the reaction with carboxylic acids, illustrated above.[291] Sulfuric acid is the most common catalyst, but Lewis acids have also been used. Good results are obtained for aliphatic R, especially for long chains. When R is aryl, the yields are variable, being best for sterically hindered compounds like mesitoic acid. This method has the advantage over **18-13** and **18-14** in that there is just one laboratory step from the acid to the amine, but conditions are more drastic.[292] Under the acid conditions employed, the isocyanate is virtually never isolated.

The reaction between a ketone and hydrazoic acid is a method for "insertion" of NH between the carbonyl group and one R group, converting a ketone into an amide.[293]



Either or both of the R groups may be aryl. In general, dialkyl ketones and cyclic ketones react more rapidly than alkyl aryl ketones, and these more rapidly than diaryl ketones. The latter require sulfuric acid and do not react in concentrated HCl, which is strong enough for dialkyl ketones. Dialkyl and cyclic ketones react sufficiently faster than diaryl or aryl alkyl ketones or carboxylic acids or alcohols so that these functions may be present in the same molecule without interference. Cyclic ketones give lactams:[294]



[290]For a review, see Banthorpe, D.V., in Patai, S. *The Chemistry of the Azido Group*, Wiley, NY, ***1971***, pp. 405–434.

[291]For a review, see Koldobskii, G.I.; Ostrovskii, V.A.; Gidaspov, B.V. *Russ. Chem. Rev.* ***1978***, *47*, 1084.

[292]For a comparision of reactions **18-13–18-16** as methods for converting an acid to an amine, see Smith, P.A.S. *Org. React.* ***1946***, *3*, 337, 363–366.

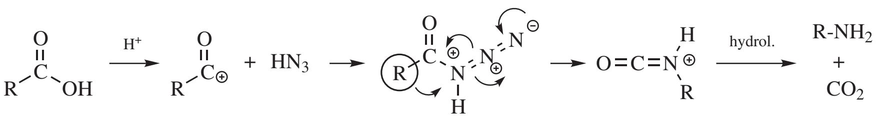
[293]For reviews, see Koldobskii, G.I.; Tereschenko, G.F.; Gerasimova, E.S.; Bagal, L.I. *Russ. Chem. Rev.* ***1971***, *40*, 835; Beckwith, A.L.J., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 137–145.

[294]For a review with respect to bicyclic ketones, see Krow, G.R. *Tetrahedron* ***1981***, *37*, 1283.

With alkyl aryl ketones, it is the aryl group that generally migrates to the nitrogen, except when the alkyl group is bulky.[295] The reaction has been applied to a few aldehydes, but rarely. With aldehydes the product is usually the nitrile (**16-16**). Even with ketones, conversion to the nitrile is often a side reaction, especially with the type of ketone that gives **17-30**. A useful variation of the Schmidt reaction treats a cyclic ketone with an alkyl azide (RN_3)[296] in the presence of $TiCl_4$, generating a lactam.[297] An intramolecular Schmidt reaction gives bicyclic amines by treatment of a cyclic alkene having a pendant azidoalkyl group with $Hg(ClO_4)_2$, and then $NaBH_4$.[298] Another variation treats a silyl enol ether of a cyclic ketone with $TMSN_3$ and photolyzes the product with UV light to give a lactam.[299] αAzido cyclic ketones rearrangement to lactams under radical conditions (Bu_3SnH/AIBN).[300]

Alcohols and alkenes react with HN_3 to give alkyl azides,[301] which in the course of reaction rearrange in the same way as discussed in reaction **18-14**.[282] The Mitsunobu reaction (**10-17**) can be used to convert alcohols to alkyl azides, and an alternative reagent for azides, $(PhO)_2PON_3$, for use in the Mitsunobu is now available.[302]

There is evidence that the mechanism with carboxylic acids[293] is similar to that of **18-14**, except that it is the protonated azide that undergoes the rearrangement:[303]



The first step is the same as that of the $A_{AC}1$ mechanism (**16-59** which explains why good results are obtained with hindered substrates. The mechanism with ketones

[295]Exceptions to this statement have been noted in the case of cyclic aromatic ketones bearing electron-donating groups in ortho and para positions: Bhalerao, U.T.; Thyagarajan, G. *Can. J. Chem.* ***1968***, *46*, 3367; Tomita, M.; Minami, S.; Uyeo, S. *J. Chem. Soc. C* ***1969***, 183.

[296]See Furness, K.; Aubé, J. *Org. Lett.* ***1999***, *1*, 495.

[297]Desai, P.; Schildknegt, K.; Agrios, K.A.; Mossman, C.; Milligan, G.L.; Aubé, J. *J. Am. Chem. Soc.* ***2000***, *122*, 7226; Sahasrabudhe, K.; Gracias, V.; Furness, K.; Smith, B.T.; Katz, C.E.; Reddy, D.S.; Aubé, J. *J. Am. Chem. Soc.* ***2003***, *125*, 7914. For a variation using a ketal with TMSOTf see Mossman, C.J.; Aubé, J. *Tetrahedron*, ***1996***, *52*, 3403.

[298]Pearson, W.H.; Hutta, D.A.; Fang, W.-k. *J. Org. Chem.* ***2000***, *65*, 8326. See also, Wrobleski, A.; Aubé, J. *J. Org. Chem.* ***2001***, *66*, 886.

[299]Evans, P.A.; Modi, D.P. *J. Org. Chem.* ***1995***, *60*, 6662.

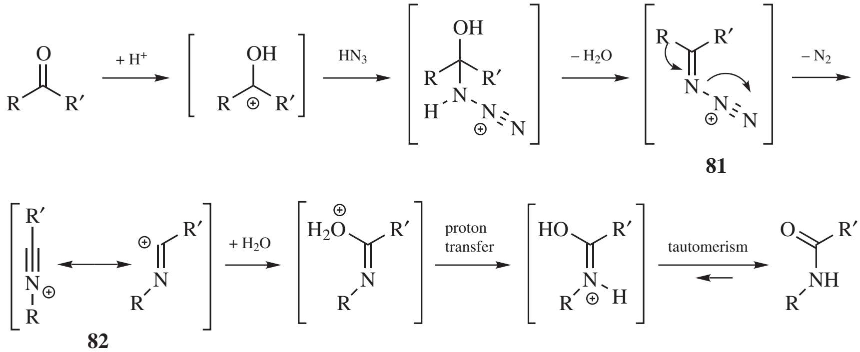
[300]Benati, L.; Nanni, D.; Sangiorgi, C.; Spagnolo, P. *J. Org. Chem.* ***1999***, *64*, 7836.

[301]For an example, see Kumar, H.M.S.; Reddy, B.V.S.; Anjaneyulu, S.; Yadav, J.S. *Tetrahedron Lett.* ***1998***, *39*, 7385. Also see, Saito, A.; Saito, K.; Tanaka, A.; Oritani, T. *Tetrahedron Lett.* ***1997***, *38*, 3955.

[302]Thompson, A.S.; Humphrey, G.R.; DeMarco, A.M.; Mathre, D.J.; Grabowski, E.J.J. *J. Org. Chem.* ***1993***, *58*, 5886.

[303]There has been some controversy about this mechanism. For a discussion, see Vogler, E.A.; Hayes, J.M. *J. Org. Chem.* ***1979***, *44*, 3682.

involves formation of a nitrilium ion **82**, which reacts with water.

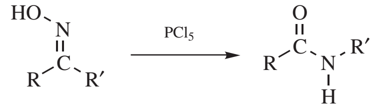


The intermediates **81** have been independently generated in aqueous solution.[304] Note the similarity of this mechanism to those of "insertion" of CH_2 (**18-9**) and of O (**18-19**). The three reactions are essentially analogous, both in products and in mechanism.[293,305] Also note the similarity of the latter part of this mechanism to that of the Beckmann rearrangement (**18-17**).

OS **V**, 408; **VI**, 368; **VII**, 254; **X**, 207. See also, OS **V**, 623.

18-17 The Beckmann Rearrangement

Beckmann oxime-amide rearrangement



When oximes are treated with PCl_5 or a number of other reagents, they rearrange to substituted amides in a reaction called the *Beckmann rearrangement*.[306] Among other reagents used have been concentrated H_2SO_4, formic acid, liquid SO_2, $SOCl_2$,[307] silica gel,[308] MoO_3 on silica gel,[309] $RuCl_3$,[310] $Y(OTf)_3$,[311]

[304]Amyes, T.L.; Richard, J.P. *J. Am. Chem. Soc.* ***1991***, *113*, 1867.

[305]For evidence for this mechanism, see Ostrovskii, V.A.; Koshtaleva, T.M.; Shirokova, N.P.; Koldobskii, G.I.; Gidaspov, B.V. *J. Org. Chem. USSR* ***1974***, *10*, 2365, and references cited therein.

[306]For reviews, see Gawley, R.E. *Org. React.* ***1988***, *35*, 1; McCarty, C.G., in Patai, S. *The Chemistry of the Carbon-Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 408–439. Also see, Nguyen, M.T.; Raspoet, G.; Vanquickenborne, L.G. *J. Am. Chem. Soc.* ***1997***, *119*, 2552.

[307]Butler, R.N.; O'Donoghue, D.A. *J. Chem. Res. (S)*, ***1983***, 18.

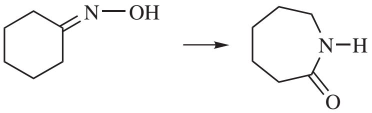
[308]Costa, A.; Mestres, R.; Riego, J.M. *Synth. Commun.* ***1982***, *12*, 1003. On silica with microwave irradiation, see Loupy, A.; Régnier, S. *Tetrahedron Lett.* ***1999***, *40*, 6221.

[309]Dongare, M.K.; Bhagwat, V.V.; Ramana, C.V.; Gurjar, M.K. *Tetrahedron Lett.* ***2004***, *45*, 4759.

[310]De, S.K. *Synth. Commun.* ***2004***, *34*, 3431.

[311]De, S.K. *Org. Prep. Proceed. Int.* ***2004***, *36*, 383.

HCl–HOAc-Ac_2O, $POCl_3$,[312] $BiCl_3$,[313] neat with $FeCl_3$,[314] and polyphosphoric acid.[315] The reaction has been done in supercritical water[316] and in ionic liquids.[317] A polymer-bound Beckman rearrangement has been reported.[318] Simply heating the oxime of benzophenone neat leads to *N*-phenyl benzamide.[319] The oximes of cyclic ketones give ring enlargement and form the lactam,[320] as in the formation of caprolactam (**83**) from the oxime of cyclohexanone. Heating an oxime of a cyclic ketone, *neat*, with $AlCl_3$ also leads to the lactam,[321] as does microwave irradiation of an oxime on Montmorillonite K10 clay.[322] Other solvent-free reactions are known.[323] Treatment of a cyclic ketone with NH_2OSO_3H on silica gel followed by microwave irradiation also gives the lactam.[324] Cyclic ketones can be converted directly to lactams in one laboratory step by treatment with NH_2OSO_2OH and formic acid (**16-14** takes place first, then the Beckmann rearrangement).[325] Heating a ketone with hydroxylamine HCl and oxalic acid also gives the amide.[326] Note that the reaction of an imine with BF_3•OEt_2 and *m*-chloroperoxybenzoic acid leads to a formamide.[327]



83

Of the groups attached to the carbon of the C=N unit, the one that migrates in the Beckman rearrangement is generally the one anti to the hydroxyl, and this is

[312]Majo, V.J.; Venugopal, M.; Prince, A.A.M.; Perumal, P.T. *Synth. Commun.* ***1995***, *25*, 3863.

[313]With microwave irradiation, see Thakur, A.J.; Boruah, A.; Prajapati, D.; Sandhu, J.S. *Synth. Commun.* ***2000***, *30*, 2105.

[314]Khodaei, M.M.; Meybodi, F.A.; Rezai, N.; Salehi, P. *Synth. Commun.* ***2001***, *31*, 2047.

[315]For a review of Beckmann rearrangements with polyphosphoric acid, see Beckwith, A.L.J., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 131–137.

[316]Ikushima, Y.; Hatakeda, K.; Sato, O.; Yokoyama, T.; Arai, M. *J. Am. Chem. Soc.* ***2000***, *122*, 1908; Boero, M.; Ikeshoji, T.; Liew, C.C.; Terakura, K.; Parrinello, M. *J. Am. Chem. Soc.* ***2004***, *126*, 6280.

[317]In BPy BF_4, butylpyridinium tetrafluoroborate: Peng, J.; Deng, Y. *Tetrahedron Lett.* ***2001***, *42*, 403. In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Ren, R.X.; Zueva, L.D.; Ou, X. *Tetrahedron Lett.* ***2001***, *42*, 8441.

[318]His, S.; Meyer, C.; Cossy, J.; Emeric, G.; Greiner, A. *Tetrahedron Lett.* ***2003***, *44*, 8581.

[319]Chandrasekhar, S.; Gopalaiah, K. *Tetrahedron Lett.* ***2001***, *42*, 8123.

[320]For a review of such ring enlargements, see Vinnik, M.I.; Zarakhani, N.G. *Russ. Chem. Rev.* ***1967***, *36*, 51. For a review with respect to bicyclic oximes, see Krow, G.R. *Tetrahedron* ***1981***, *37*, 1283.

[321]Ghiaci, M.; Imanzadeh, G.H. *Synth. Commun.* ***1998***, *28*, 2275. See Moghaddam, F.M.; Rad, A.A.R.; Zali-Boinee, H. *Synth. Commun.* ***2004***, *34*, 2071.

[322]Bosch, A.I.; de la Cruz, P.; Diez-Barra, E.; Loupy, A.; Langa, F. *Synlett* ***1995***, 1259.

[323]Sharghi, H.; Hosseini, M. *Synthesis* ***2002***, 1057; Eshghi, H.; Gordi, Z. *Synth. Commun.* ***2003***, *33*, 2971.

[324]Laurent, A.; Jacquault, P.; DiMarino, J.-L.; Hamelin, J. *J. Chem. Soc., Chem. Commun.* ***1995***, 1101.

[325]Olah, G.A.; Fung, A.P. *Synthesis* ***1979***, 537. See also, Novoselov, E.F.; Isaev, S.D.; Yurchenko, A.G.; Vodichka, L.; Trshiska, Ya. *J. Org. Chem. USSR* ***1981***, *17*, 2284.

[326]Chandrassekhar, S.; Gopalaiah, K. *Tetrahedron Lett.* ***2003***, *44*, 7437.

[327]An, G.-i.; Kim, M.; Kim. J.Y.; Rhee, H. *Tetrahedron Lett.* ***2003***, *44*, 2183.

often used as a method of determining the configuration of the oxime. However, it is not unequivocal. It is known that with some oximes the syn group migrates and that with others, especially where R and R′ are both alkyl, mixtures of the two possible amides are obtained. However, this behavior does not necessarily mean that the syn group actually undergoes migration. In most cases, the oxime undergoes isomerization under the reaction conditions *before* migration takes place.[328] The scope of the reaction is quite broad and R and R′ may be alkyl, aryl, or hydrogen. However, hydrogen very seldom *migrates*, so the reaction is not generally a means of converting aldoximes to unsubstituted amides ($RCONH_2$). This latter conversion can be accomplished, however, by treatment of the aldoxime with nickel acetate under neutral conditions[329] or by heating the aldoxime for 60 h at 100°C after it has been adsorbed onto silica gel.[330] As in the case of the Schmidt rearrangement, when the oxime is derived from an alkyl aryl ketone, it is generally the aryl group that preferentially migrates.[331]

Not only do oximes undergo the Beckmann rearrangement, but so also do esters of oximes with many acids, organic and inorganic. A side reaction with many substrates is the formation of nitriles (the "abnormal" Beckmann rearrangement, **17-30**). The other reagents convert OH to an ester leaving group (e.g., $OPCl_4$ from PCl_5 and OSO_2OH from concentrated H_2SO_4[332]). The *O*-carbonates of imines, such as $Ph_2C{=}N{-}OCO_2Et$, react with $BF_3{\bullet}OEt_2$ to give the corresponding amide, in this case *N*-phenyl benzamide.[333]

In the first step of the mechanism, the OH group is converted by the reagent to a better leaving group, for example, proton acids convert it to OH_2^+. After that, the mechanism[334] follows a course analogous to that for the Schmidt reaction of ketones (**18-16**) from the formation of nitrilium ion **82** on:[335] Alternatively, the attack on **82** can be by the leaving group, if different from H_2O. For example, when PCl_5 is used to induce the reaction, a $N{-}O{-}PCl_4$ species is formed, which generates **82**. Intermediates of the form **82** have been detected by nmr and uv spectroscopy.[336] The rearrangement has also been found to take place by a different mechanism, involving formation of a nitrile by fragmentation, and then addition by

[328]Lansbury, P.T.; Mancuso, N.R. *Tetrahedron Lett.* ***1965***, 2445 have shown that some Beckmann rearrangements are *authentically* nonstereospecific.

[329]Field, L.; Hughmark, P.B.; Shumaker, S.H.; Marshall, W.S. *J. Am. Chem. Soc.* ***1961***, *83*, 1983. See also, Leusink, A.J.; Meerbeek, T.G.; Noltes, J.G. *Recl. Trav. Chim. Pays-Bas* ***1976***, *95*, 123; ***1977***, *96*, 142.

[330]Chattopadhyaya, J.B.; Rama Rao, A.V. *Tetrahedron* ***1974***, *30*, 2899.

[331]See Arisawa, M.; Yamaguchi, M. *Org. Lett.* ***2001***, *3*, 311.

[332]Gregory, B.J.; Moodie, R.B.; Schofield, K. *J. Chem. Soc. B* ***1970***, 338; Kim, S.; Kawakami, T.; Ando, T.; Yukawa, Y. *Bull. Chem. Soc. Jpn.* ***1979***, *52*, 1115.

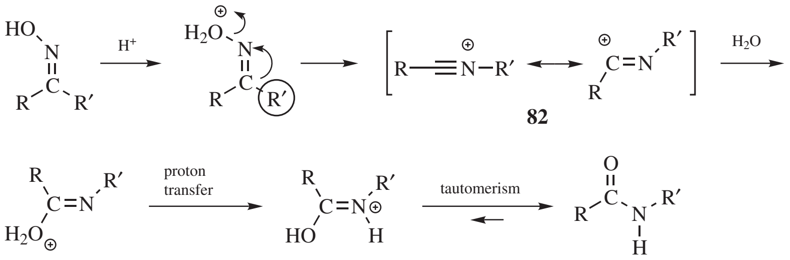
[333]Anilkumar, R.; Chandrasekhar, S. *Tetrahedron Lett.* ***2000***, *41*, 5427.

[334]For a discussion of the gas-phase reaction mechanism, see Nguyen, M.T.; Vanquickenborne, L.G. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 1969.

[335]For summaries of the considerable evidence for this mechanism, see Donaruma, L.G.; Heldt, W.Z. *Org. React.* ***1960***, *11*, 1, 5–14; Smith, P.A.S., in de Mayo, P. *Molecular Rearrangments*, Vol. 1, Wiley, NY, ***1963***, 483–507, p. 488–493.

[336]Gregory, B.J.; Moodie, R.B.; Schofield, K. *J. Chem. Soc. B* ***1970***, 338.

a Ritter reaction (**16-91**).[337] Beckmann rearrangements have also been carried out photochemically.[338]



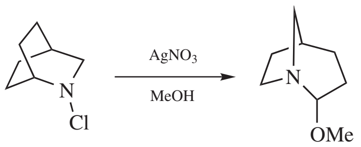
If the rearrangement of oxime sulfonates is induced by organoaluminum reagents,[339] the nitrilium ion intermediate **82** is captured by the nucleophile originally attached to the Al. By this means an oxime can be converted to an imine, an imino thioether (R–N=C–SR), or an imino nitrile (R–N=C–CN).[340] In the last case, the nucleophile comes from added trimethylsilyl cyanide. The imine-producing reaction can also be accomplished with a Grignard reagent in benzene or toluene.[341]

In a related reaction, treatment of spirocyclic oxaziridines with MnCl(TPP)[342] or photolysis[343] leads to a lactam.

OS **II**, 76, 371; **VIII**, 568.

18-18 Stieglitz and Related Rearrangements

Methoxy-de-*N*-chloro-(2/ → 1/*N*-alkyl)-*migro*-substitution, and so on



Besides the reactions discussed at **18-13–18-17**, a number of other rearrangements are known in which an alkyl group migrates from C to N. Certain bicyclic *N*-haloamines, for example *N*-chloro-2-azabicyclo[2.2.2]octane (above), undergo

[337]Hill, R.K.; Conley, R.T.; Chortyk, O.T. *J. Am. Chem. Soc.* ***1965***, *87*, 5646; Palmere, R.M.; Conley, R.T.; Rabinowitz, J.L. *J. Org. Chem.* ***1972***, *37*, 4095.

[338]See, for example, Izawa, H.; de Mayo, P.; Tabata, T. *Can. J. Chem.* ***1969***, *47*, 51; Cunningham, M.; Ng Lim, L.S.; Just, T. *Can. J. Chem.* ***1971***, *49*, 2891; Suginome, H.; Yagihashi, F. *J. Chem. Soc. Perkin Trans. 1* ***1977***, 2488.

[339]For a review, see Maruoka, K.; Yamamoto, H. *Angew. Chem. Int. Ed.* ***1985***, *24*, 668.

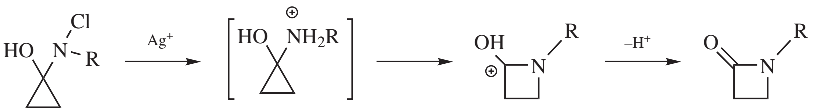
[340]Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* ***1983***, *105*, 2831; Maruoka, K.; Nakai, S.; Yamamoto, H. *Org. Synth. 66*, 185.

[341]Hattori, K.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* ***1982***, *23*, 3395.

[342]Suda, K.; Sashima, M.; Izutsu, M.; Hino, F. *J. Chem. Soc., Chem. Commun.* ***1994***, 949.

[343]Post, A.J.; Nwaukwa, S.; Morrison, H. *J. Am. Chem. Soc.* ***1994***, *116*, 6439.

rearrangement when solvolyzed in the presence of silver nitrate.[344] This reaction is similar to the Wagner–Meerwein rearrangement (**18-1**) and is initiated by the silver-catalyzed departure of the chloride ion.[345] Similar reactions have been used for ring expansions and contractions, analogous to those discussed for reaction **18-3**.[346] An example is the conversion of 1-(*N*-chloroamino)cyclopropanols to β-lactams.[347] Methyl prolinate was converted to the lactam 2-piperidone upon treatment with SmI_2 and pivalic acid–THF.[348]



The name *Stieglitz rearrangement* is generally applied to the rearrangements of trityl *N*-haloamines and

$$Ar_3CNHX \xrightarrow{\text{base}} Ar_2C{=}NAr$$

$$Ar_3CNHOH \xrightarrow{PCl_5} Ar_2C{=}NAr$$

hydroxylamines. These reactions are similar to the rearrangements of alkyl azides (**18-14**), and the name Stieglitz rearrangement is also given to the rearrangement of trityl azides. Another similar reaction is the rearrangement undergone by tritylamines when treated with lead tetraacetate:[349]

$$Ar_3CNH_2 \xrightarrow{Pb(OAc)_4} Ar_2C{=}NAr$$

D. Carbon-to-Oxygen Migrations of R and AR

18-19 The Baeyer–Villiger Rearrangement[350]

Oxy-insertion

[344]Gassman, P.G.; Fox, B.L. *J. Am. Chem. Soc.* ***1967***, *89*, 338. See also, Schell, F.M.; Ganguly, R.N. *J. Org. Chem.* ***1980***, *45*, 4069; Davies, J.W.; Malpass, J.R.; Walker, M.P. *J. Chem. Soc., Chem. Commun.* ***1985***, 686; Hoffman, R.V.; Kumar, A.; Buntain, G.A. *J. Am. Chem. Soc.* ***1985***, *107*, 4731.

[345]For C → N rearrangements induced by $AlCl_3$, see Kovacic, P.; Lowery, M.K.; Roskos, P.D. *Tetrahedron* ***1970***, *26*, 529.

[346]Gassman, P.G.; Carrasquillo, A. *Tetrahedron Lett.* ***1971***, 109; Hoffman, R.V.; Buntain, G.A. *J. Org. Chem.* ***1988***, *53*, 3316.

[347]Wasserman, H.H.; Adickes, H.W.; Espejo de Ochoa, O. *J. Am. Chem. Soc.* ***1971***, *93*, 5586; Wasserman, H.H.; Glazer, E.A.; Hearn, M.J. *Tetrahedron Lett.* ***1973***, 4855.

[348]Honda, T.; Ishikawa, F. *Chem. Commun.* ***1999***, 1065.

[349]Sisti, A.J.; Milstein, S.R. *J. Org. Chem.* ***1974***, *39*, 3932.

[350]For a review, see Renz, M.; Meunier, B. *Eur. J. Org. Chem.* ***1999***, 737. For a review of green procedures, see Ten Brink, G.-J.; Arends, W.C.E.; Sheldon, R.A. *Chem. Rev.* ***2004***, *104*, 4105.

The treatment of ketones with peroxyacids, such as peroxybenzoic or peroxyacetic acid, or with other peroxy compounds in the presence of acid catalysts, gives carboxylic esters by "insertion" of oxygen[351] and the carboxylic acid parent of the peroxyacid as a by-product. The reaction is called the *Baeyer–Villiger rearrangement*.[352] A particularly good reagent is peroxytrifluoroacetic acid. Reactions with this reagent are rapid and clean, giving high yields of product, though it is often necessary to add a buffer, such as Na_2HPO_4, to prevent transesterification of the product with trifluoroacetic acid that is also formed during the reaction. The reaction is often applied to cyclic ketones to give lactones.[353] Hydrogen peroxide has been used to convert cyclic ketones to lactones using a catalytic amount of $MeReO_3$[354] or a diselenide catalyst.[355] Hydrogen peroxide and a $MeReO_3$ catalyst has been used in an ionic liquid.[356] Transition-metal catalysts have been used with peroxyacids to facilitate the oxidation.[357] Hydrogen peroxide and $PhAsO_3H_2$ in hexafluoro-1-propanol can be used.[358] Polymer-supported peroxy acids have been used,[359] and solvent-free Bayer–Villiger reactions are known.[360] Enantioselective synthesis[361] of chiral lactones from achiral ketones has been achieved by the use of enzymes[362]

[351]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*; 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1665–1667.

[352]For reviews, see Hudlický, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, pp. 186–195; Plesničar, B., in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. C, Academic Press, NY, ***1978***, pp. 254–267; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 321–329; Lewis, S.N., in Augustine, R.L. *Oxidation*, Vol. 1, Marcel Dekker, NY, ***1969***, pp. 237–244; Lee, J.B.; Uff, B.C. *Q. Rev. Chem. Soc.* ***1967***, *21*, 429, see pp. 449–453. Also see, Mino, T.; Masuda, S.; Nishio, M.; Yamashita, M. *J. Org. Chem.* ***1997***, *62*, 2633. For a discussion of uncatalyzed versus BF_3-assisted reactions, see Carlqvist, P.; Eklund, R.; Brinck, T. *J. Org. Chem.* ***2001***, *66*, 1193.

[353]For a review of the reaction as applied to bicyclic ketones, see Krow, G.R. *Tetrahedron* ***1981***, *37*, 2697.

[354]Phillips, A.M.F.; Romão, C. *Eur. J. Org. Chem.* ***1999***, 1767.

[355]ten Brink, G.-J.; Vis, J.-M.; Arends, I.W.C.E.; Sheldon, R.A. *J. Org. Chem.* ***2001***, *66*, 2429.

[356]In bmim BF_4, 1-butyl-3-methylimidazoliuum tetrafluoroborate: Bernini, R.; Coratti, A.; Fabrizi, G.; Goggiamani, A. *Tetrahedron Lett.* ***2003***, *44*, 8991.

[357]Kotsuki, H.; Arimura, K.; Araki, T.; Shinohara, T. *Synlett* ***1999***, 462; Alam, M.M.; Varala, R.; Adapa, S.R. *Synth. Commun.* ***2003***, *33*, 3035.

[358]Berkessel, A.; Andreae, M.R.M. *Tetrahedron Lett.* ***2001***, *42*, 2293.

[359]Lambert, A.; Elings, J.A.; Macquarrie, D.J.; Carr, G.; Clark, J.H. *Synlett* ***2000***, 1052. For a discussion of selectivity in solid-state Bayer-Villiger reactions, see Hagiwara, H.; Nagatomo, H.; Yoshii, F.; Hoshi, T.; Suzuki, T.; Ando, M. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 2645.

[360]Yakura, T.; Kitano, T.; Ikeda, M.; Uenishi, J. *Tetrahedron Lett.* ***2002***, *43*, 6925.

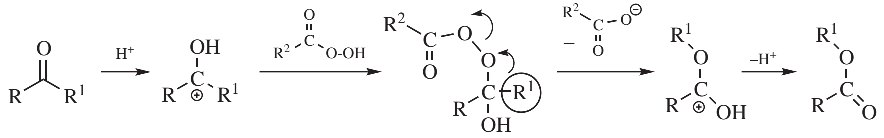
[361]See Bolm, C.; Beckmann, O.; Kühn, T.; Palazzi, C.; Adam, W.; Rao, P.B.; Saha-Möller, C.R. *Tetrahedron Asymmetry* ***2001***, *12*, 2441; Bolm, C.; Frison J.-C.; Zhang, Y.; Wulff, W.D. *Synlett* ***2004***, 1619.

[362]See Taschner, M.J.; Black, D.J. *J. Am. Chem. Soc.* ***1988***, *110*, 6892; Taschner, M.J.; Peddada, L. *J. Chem. Soc., Chem. Commun.* ***1992***, 1384; Pchelka, B.K.; Gelo Pujic, M.; Guibé-Jampel, E. *J. Chem. Soc. Perkin Trans. 1* ***1998***, 2625; Stewart, J.D.; Reed, K.W.; Martinez, C.A.; Zhu, J.; Chen, G.; Kayser, M.M. *J. Am. Chem. Soc.* ***1998***, *120*, 3541; Lemoult, S.C.; Richardson, P.F.; Roberts, S.M. *J. Chem. Soc. Perkin Trans. 1* ***1995***, 89; Mihovilovic, M.D.; Müller, B.; Kayser, M.M.; Stewart, J.D.; Stanetty, P. *Synlett* ***2002***, 703. For a review of enzyme-catalyzed Baeyer–Villiger rearrangements, see Walsh, C.T.; Chen, Y.J. *Angew. Chem. Int. Ed.* ***1988***, *27*, 333. For a review of monooxygenase-mediated Baeyer–Villiger rearrangements, see Mihovilovic, M.D.; Müller, B.; Stanetty, P. *Eur. J. Org. Chem.* ***2002***, 3711. For a reaction using engineered *E. coli* cells, see Mihovilovic, M.D.; Chen, G.; Wang, S.; Kyte, B.; Rochon, F.; Kayser, M.M.; Stewart, J.D. *J. Org. Chem.* ***2001***, *66*, 733.

and other asymmetric reactions are known.[363] Oxidation of chiral substrates with *m*-chloroperoxybenzoic acid (mcpba) also leads to chiral lactones.[364]

For acyclic compounds, R′ must usually be secondary, tertiary, or vinylic, although primary R′ has been rearranged with peroxytrifluoroacetic acid,[365] with BF_3–H_2O_2,[366] and with $K_2S_2O_8$–H_2SO_4.[367] For unsymmetrical ketones the approximate order of migration is tertiary alkyl > secondary alkyl, aryl > primary alkyl > methyl. Since the methyl group has a low migrating ability, the reaction provides a means of cleaving a methyl ketone R'COMe to produce an alcohol or phenol (R'OH) (by hydrolysis of the ester R'OCOMe). The migrating ability of aryl groups is increased by electron-donating and decreased by electron-withdrawing substituents.[368] There is a preference of anti over gauche migration.[369] Enolizable β-diketones do not react. α-Diketones can be converted to anhydrides.[370] With aldehydes, migration of hydrogen gives the carboxylic acid, and this is a way of accomplishing **19-23**. Migration of the other group would give formates, but this seldom happens, though aryl aldehydes have been converted to formates with H_2O_2 and a selenium compound[371] (see also the Dakin reaction in **19-11**).

The mechanism[372] is similar to those of the analogous reactions with hydrazoic acid (**18-16** with ketones) and diazomethane (**18-8**):



One important piece of evidence for this mechanism was that benzophenone–^{18}O gave ester entirely labeled in the carbonyl oxygen, with none in the alkoxyl oxygen.[373] Carbon-14 isotope-effect studies on acetophenones have shown that

[363]For example, see Sugimura, T.; Fujiwara, Y.; Tai, A. *Tetrahedron Lett.* ***1997***, *38*, 6019; Bolm, C.; Schlingloff, G.; Weickhardt, K. *Angew. Chem. Int. Ed.* ***1994***, *33*, 1848; Bolm, C.; Schlingloff, G. *J. Chem. Soc., Chem. Commun.* ***1995***, 1247; Bolm, C.; Beckmann, O.; Cosp, A.; Palazzi, C. *Synlett* ***2001***, 1461; Bolm, C.; Beckmann, O.; Palazzi, C. *Can. J. Chem.* ***2001***, *79*, 1593; Shinohara, T.; Fujioka, S.; Kotsuki, H. *Heterocycles* ***2001***, *55*, 237; Watanabe, A.; Uchida, T.; Ito, K.; Katsuki, T. *Tetrahedron Lett.* ***2002***, *43*, 4481; Murhashi, S.-I.; Ono, S.; Imada, Y. *Angew. Chem. Int. Ed.* ***2002***, *41*, 2366.

[364]Hunt, KW.; Grieco, P.A. *Org. Lett.* ***2000***, *2*, 1717.

[365]Emmons, W.D.; Lucas, G.B. *J. Am. Chem. Soc.* ***1955***, *77*, 2287.

[366]McClure, J.D.; Williams, P.H. *J. Org. Chem.* ***1962***, *27*, 24.

[367]Deno, N.C.; Billups, W.E.; Kramer, K.E.; Lastomirsky, R.R. *J. Org. Chem.* ***1970***, *35*, 3080.

[368]For as report of substituent effects in the α, β, and γ position of alkyl groups, see Noyori, R.; Sato, T.; Kobayashi, H. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 2661.

[369]Snowden, M.; Bermudez, A.; Kelly, D.R.; Radkiewicz-Poutsma, J.L. *J. Org. Chem.* ***2004***, *69*, 7148.

[370]For a study of the mechanism of this conversion, see Cullis, P.M.; Arnold, J.R.P.; Clarke, M.; Howell, R.; DeMira, M.; Naylor, M.; Nicholls, D. *J. Chem. Soc., Chem. Commun.* ***1987***, 1088.

[371]Syper, L. *Synthesis* ***1989***, 167. See also, Godfrey, I.M.; Sargent, M.V.; Elix, J.A. *J. Chem. Soc. Perkin Trans. 1* ***1974***, 1353.

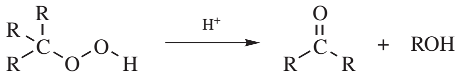
[372]Proposed by Criegee, R. *Liebigs Ann. Chem.* ***1948***, *560*, 127.

[373]Doering, W. von E.; Dorfman, E. *J. Am. Chem. Soc.* ***1953***, *75*, 5595. For summaries of the other evidence, see Smith, P.A.S., in de Mayo, P. *Molecular Rearrangements*, Vol. 1, Wiley, NY, ***1963***, pp. 578–584.

migration of aryl groups takes place in the rate-determining step,[374] demonstrating that migration of Ar is concerted with departure of $OCOR^2$.[375] It is hardly likely that migration would be the slow step if the leaving group departed first to give an ion with a positive charge on an oxygen atom, which would be a highly unstable species.

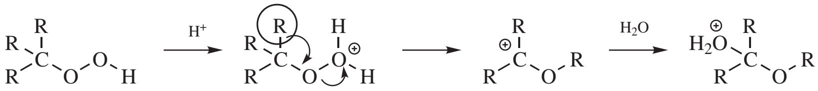
18-20 Rearrangement of Hydroperoxides

C-Alkyl-*O*-hydroxy-elimination



Hydroperoxides (R = alkyl, aryl, or hydrogen) can be cleaved by proton or Lewis acids in a reaction whose principal step is a rearrangement.[376] The reaction has also been applied to peroxy esters ($R_3COOCOR'$), but less often. When aryl and alkyl groups are both present, migration of aryl dominates. It is not necessary actually to prepare and isolate hydroperoxides. The reaction takes place when the alcohols are treated with H_2O_2 and acids. Migration of an alkyl group of a primary hydroperoxide provides a means for converting an alcohol to its next lower homolog ($RCH_2OOH \rightarrow CH_2{=}O + ROH$).

The mechanism is as follows:[377]



72 84

The last step is hydrolysis of the unstable hemiacetal. Alkoxycarbocation intermediates (**84**, R = alkyl) have been isolated in super acid solution[378] at

[374]Palmer, B.W.; Fry, A. *J. Am. Chem. Soc.* ***1970***, *92*, 2580. See also, Mitsuhashi, T.; Miyadera, H.; Simamura, O. *Chem. Commun.* ***1970***, 1301. For secondary isotope-effect studies, see Winnik, M.A.; Stoute, V.; Fitzgerald, P. *J. Am. Chem. Soc.* ***1974***, *96*, 1977.

[375]In some cases, the rate-determining step has been shown to be the addition of peracid to the substrate (see, e.g., Ogata, Y.; Sawaki, Y. *J. Org. Chem.* ***1972***, *37*, 2953). Even in these cases it is still highly probable that migration is concerted with departure of the nucleofuge.

[376]For reviews, see Yablokov, V.A. *Russ. Chem. Rev.* ***1980***, *49*, 833; Lee, J.B.; Uff, B.C. *Q. Rev. Chem. Soc.* ***1967***, *21*, 429, 445–449.

[377]For a discussion of the transition state involved in the migration step, see Wistuba, E.; Rüchardt, C. *Tetrahedron Lett.* ***1981***, *22*, 3389.

[378]For a review of peroxy compounds in super acids, see Olah, G.A.; Parker, D.G.; Yoneda, N. *Angew. Chem. Int. Ed.* ***1978***, *17*, 909.

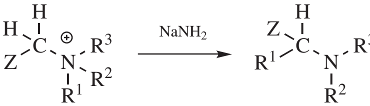
low temperatures, and their structures proved by nmr.[379] The protonated hydroperoxides could not be observed in these solutions, evidently reacting immediately on formation.

OS **V**, 818.

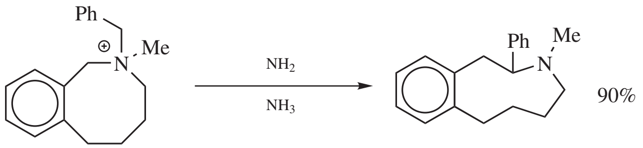
E. Nitrogen-to-Carbon, Oxygen-to-Carbon, and Sulfur-to-Carbon Migration

18-21 The Stevens Rearrangement

Hydron-(2/*N* → 1/alkyl)-*migro*-detachment



In the *Stevens rearrangement*, a quaternary ammonium salt containing an electron-withdrawing group Z on one of the carbons attached to the nitrogen is treated with a strong base (e.g., NaOR or $NaNH_2$) to give a rearranged tertiary amine. The Z group may be RCO, ROOC, or phenyl.[380] The most common migrating groups are allylic, benzylic, benzhydryl, 3-phenylpropargyl, and phenacyl, though even methyl migrates to a sufficiently negative center.[381] When an allylic group migrates, it may or may not involve an allylic rearrangement within the migrating group (see **18-35**), depending on the substrate and reaction conditions. The reaction has been used for ring enlargement,[382] for example:



The mechanism has been the subject of much study.[383] That the rearrangement is intramolecular was shown by crossover experiments, by ^{14}C labeling,[384] and by the

[379]Sheldon, R.A.; van Doorn, J.A. *Tetrahedron Lett.* ***1973***, 1021.

[380]For reviews of the Stevens rearrangement, see Lepley, A.R.; Giumanini, A.G. *Mech. Mol. Migr.* ***1971***, *3*, 297; Pine, S.H. *Org. React.* ***1970***, *18*, 403. For reviews of the Stevens and the closely related Wittig rearrangement (**18-22**), see Stevens, T.S.; Watts, W.E. *Selected Molecular Rearrangements*, Van Nostrand-Reinhold, Princeton, NJ, ***1973***, pp. 81–116; Wilt, J.W., in Kochi, J.K. *Free Radicals*, Vol. 1, Wiley, NY, ***1973***, pp. 448–458; Iwai, I. *Mech. Mol. Migr.* ***1969***, *2*, 73, see pp. 105–113; Stevens, T.S. *Prog. Org. Chem.* ***1968***, *7*, 48.

[381]Migration of aryl is rare, but has been reported: Heaney, H.; Ward, T.J. *Chem. Commun.* ***1969***, 810; Truce, W.E.; Heuring, D.L. *Chem. Commun.* ***1969***, 1499.

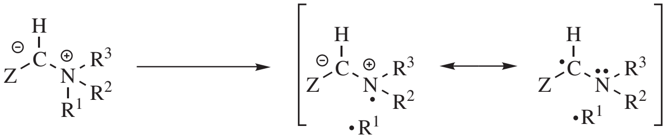
[382]Elmasmodi, A.; Cotelle, P.; Barbry, D.; Hasiak, B.; Couturier, D. *Synthesis* ***1989***, 327.

[383]For example, see Pine, S.H. *J. Chem. Educ.* ***1971***, *48*, 99; Heard, G.L.; Yates, B.F. *Aust. J. Chem.* ***1994***, *47*, 1685.

[384]Stevens, T.S. *J. Chem. Soc.* ***1930***, 2107; Johnstone, R.A.W.; Stevens, T.S. *J. Chem. Soc.* ***1955***, 4487.

fact that retention of configuration is found at R^1.[385] The first step is loss of the acidic proton to give the ylid **85**, which has been isolated.[386] The finding[387] that CIDNP spectra[388] could be obtained in many instances shows that in these cases the product is formed directly from a free-radical precursor. The following radical pair mechanism was proposed:[389]

Mechanism *a*

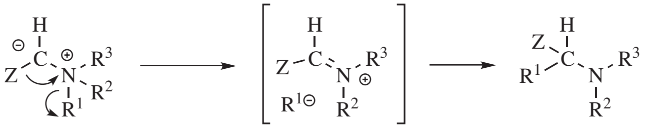


85

Solvent cage

The radicals do not drift apart because they are held together by the solvent cage. According to this mechanism, the radicals must recombine rapidly in order to account for the fact that R^1 does not racemize. Other evidence in favor of mechanism *a* is that in some cases small amounts of coupling products (R^1–R^1) have been isolated,[390] which would be expected if some •R^1 leaked from the solvent cage. However, not all the evidence is easily compatible with mechanism *a*.[391] It is possible that another mechanism (*b*) similar to mechanism *a*, but involving

Mechanism *b*



85

Solvent cage

ion pairs in a solvent cage instead of radical pairs, operates in some cases. A third possible mechanism would be a concerted 1,2-shift,[392] but the orbital symmetry

[385]Brewster, J.H.; Kline, M.W. *J. Am. Chem. Soc.* ***1952***, *74*, 5179; Schöllkopf, U.; Ludwig, U.; Ostermann, G.; Patsch, M. *Tetrahedron Lett.* ***1969***, 3415.

[386]Jemison, R.W.; Mageswaran, S.; Ollis, W.D.; Potter, S.E.; Pretty, A.J.; Sutherland, I.O.; Thebtaranonth, Y. *Chem. Commun.* ***1970***, 1201.

[387]Lepley, A.R.; Becker, R.H.; Giumanini, A.G. *J. Org. Chem.* ***1971***, *36*, 1222; Baldwin, J.E.; Brown, J.E. *J. Am. Chem. Soc.* ***1969***, *91*, 3646; Jemison, R.W.; Morris, D.G. *Chem. Commun.* ***1969***, 1226; Schöllkopf, U.; Ludwig, U.; Ostermann, G.; Patsch, M. *Tetrahedron Lett.* ***1969***, 3415.

[388]For a review of the application of CIDNP to rearrangement reactions, see Lepley, A.R., in Lepley, A.R.; Closs, G.L. *Chemically Induced Magnetic Polarization*, Wiley, NY, ***1973***, pp. 323–384.

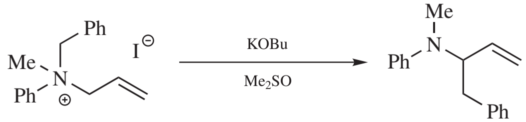
[389]Schöllkopf, U.; Ludwig, U. *Chem. Ber.* ***1968***, *101*, 2224; Ollis, W.D.; Rey, M.; Sutherland, I.O. *J. Chem. Soc. Perkin Trans. 1* ***1983***, 1009, 1049.

[390]Schöllkopf, U.; Ludwig, U.; Ostermann, G.; Patsch, M. *Tetrahedron Lett.* ***1969***, 3415; Hennion, G.F.; Shoemaker, M.J. *J. Am. Chem. Soc.* ***1970***, *92*, 1769.

[391]See, for example, Pine, S.H.; Catto, B.A.; Yamagishi, F.G. *J. Org. Chem.* ***1970***, *35*, 3663.

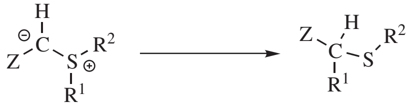
[392]For evidence against this mechanism, see Jenny, E.F.; Druey, J. *Angew. Chem. Int. Ed.* ***1962***, *1*, 155.

principle requires that this take place with inversion at R^1.[393] (see p. 1654.) Since the actual migration takes place with retention, it cannot, according to this argument, proceed by a concerted mechanism. However, in the case where the migrating group is allylic, a concerted mechanism can also operate (**18-35**). An interesting finding compatible with all three mechanisms is that optically active allylbenzylmethylphenylammonium iodide (asymmetric nitrogen, see p. 142) gave an optically active product:[394]

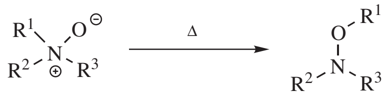


The *Sommelet–Hauser rearrangement* competes when Z is an aryl group (see **13-31**). *Hofmann elimination* competes when one of the R groups contains a β hydrogen atom (**17-7** and **17-8**).

Sulfur ylids containing a Z group give an analogous rearrangement, often also referred to as a Stevens



rearrangement.[395] In this case too, there is much evidence (including CIDNP) that a radical-pair cage mechanism is operating,[396] except that when the migrating group is allylic, the mechanism may be different (see **18-35**). Another reaction with a similar mechanism[397] is the *Meisenheimer rearrangement*,[398] in which certain tertiary



[393]Woodward, R.B.; Hoffmann, R. *The Conservation of Orbital Symmetry*, Academic Press, NY, ***1970***, p. 131.

[394]Hill, R.K.; Chan, T. *J. Am. Chem. Soc.* ***1966***, *88*, 866.

[395]For a review, see Olsen, R.K.; Currie, Jr., J.O., in Patai, S. *The Chemistry of The Thiol Group*, pt. 2, Wiley, NY, ***1974***, pp. 561–566.

[396]See, for example, Baldwin, J.E.; Erickson, W.F.; Hackler, R.E.; Scott, R.M. *Chem. Commun.* ***1970***, 576; Schöllkopf, U.; Schossig, J.; Ostermann, G. *Liebigs Ann. Chem.* ***1970***, *737*, 158; Iwamura, H.I.; Iwamura, M.; Nishida, T.; Yoshida, M.; Nakayama, T. *Tetrahedron Lett.* ***1971***, 63.

[397]For some of the evidence, see Ostermann, G.; Schöllkopf, U. *Liebigs Ann. Chem.* ***1970***, *737*, 170; Lorand, J.P.; Grant, R.W.; Samuel, P.A.; O'Connell, E.; Zaro, J. *Tetrahedron Lett.* ***1969***, 4087.

[398]For a review, see Johnstone, R.A.W. *Mech. Mol. Migr.* ***1969***, *2*, 249. See Buston, J.E.H.; Coldham, I.; Mulholland, K.R. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 2327.

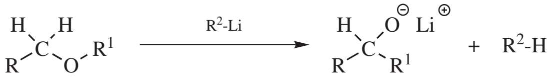
amine oxides rearrange on heating to give substituted hydroxylamines.[399] The migrating group R^1 is almost always allylic or benzilic.[400] R^2 and R^3 may be alkyl or aryl, but if one of the R groups contains a β hydrogen, Cope elimination (**17-9**) often competes. In a related reaction, when 2-methylpyridine *N*-oxides are treated with trifluoroacetic anhydride, the *Boekelheide reaction* occurs to give 2-hydroxymethylpyridines.[401]

Certain tertiary benzylic amines, when treated with BuLi, undergo a rearrangement analogous to the Wittig rearrangement (**18-22**), for example, $PhCH_2NPh_2 \rightarrow Ph_2CHNHPh$.[402] Only aryl groups migrate in this reaction.

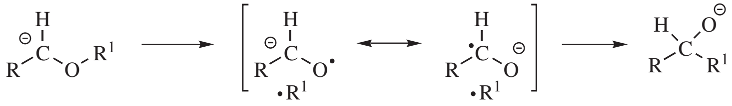
Isocyanides, when heated in the gas phase or in nonpolar solvents, undergo a 1,2-intramolecular rearrangement to nitriles: RNC → RCN.[403] In polar solvents the mechanism is different.[404]

18-22 The Wittig Rearrangement[405]

Hydron-(2/*O* → 1/alkyl)-*migro*-detachment



The rearrangement of ethers with alkyllithium reagents is called the *Wittig rearrangement* (not to be confused with the Wittig reaction, **16-44**) and is similar to **18-21**.[380] However, a stronger base is required (e.g., phenyllithium or sodium amide). The R and R′ groups, may be alkyl,[406] aryl, or vinylic.[407] Also, one of the hydrogens may be replaced by an alkyl or aryl group, in which case the product is the salt of a tertiary alcohol. Migratory aptitudes



[399]For example, see Buston, J.E.H.; Coldham, I.; Mulholland, K.R. *Tetrahedron Asymmetry*, ***1998***, *9*, 1995.
[400]Migration of aryl and of certain alkyl groups has also been reported. See Khuthier, A.; Al-Mallah, K.Y.; Hanna, S.Y.; Abdulla, N.I. *J. Org. Chem.* ***1987***, *52*, 1710, and references cited therein.
[401]Fontenas, C.; Bejan, E.; Haddon, H.A.; Balavoine, G.G.A. *Synth. Commun.* ***1995***, *25*, 629.
[402]Eisch, J.J.; Kovacs, C.A.; Chobe, P. *J. Org. Chem.* ***1989***, *54*, 1275.
[403]See Pakusch, J.; Rüchardt, C. *Chem. Ber.* ***1991***, *124*, 971, and references cited therein.
[404]Meier, M.; Rüchardt, C. *Chimia* ***1986***, *40*, 238.
[405]See Hiersemann, M.; Abraham, L.; Pollex, A. *Synlett* ***2003***, 1088.
[406]See Bailey, W.F.; England, M.D.; Mealy, M.J.; Thongsornkleeb, C.; Teng, L. *Org. Lett.* ***2000***, *2*, 489.
[407]For migration of vinyl, see Rautenstrauch, V.; Büchi, G.; Wüest, H. *J. Am. Chem. Soc.* ***1974***, *96*, 2576. For rearrangment of an α-trimethylsilyl allyl ether, see Maleczka, Jr., R.E.; Geng, F. *Org. Lett.* ***1999***, *1*, 1115.

here are allylic, benzylic > ethyl > methyl > phenyl.[408] The stereospecificity of the 1,2-Wittig rearrangement has been discussed.[409] The following radical-pair mechanism[410] (similar to mechanism *a* of **18-21**) is likely, after removal of the proton by the base. One of the radicals in the radical pair is a ketyl. Among the evidence for this mechanism is (*1*) the rearrangement is largely intramolecular; (*2*) migratory aptitudes are in the order of free-radical stabilities, not of carbanion stabilities[411] (which rules out an ion-pair mechanism similar to mechanism *b* of **18-21**); (*3*) aldehydes are obtained as side products;[412] (*4*) partial racemization of R' has been observed[413] (the remainder of the product retained its configuration); (*5*) crossover products have been detected;[414] and (*6*) when ketyl radicals and R radicals from different precursors were brought together, similar products resulted.[415] However, there is evidence that at least in some cases the radical-pair mechanism accounts for only a portion of the product, and some kind of concerted mechanism can also take place.[416] Most of the above investigations were carried out with systems where R' is alkyl, but a radical-pair mechanism has also been suggested for the case where R' is aryl.[417] When R' is allylic a concerted mechanism can operate (**18-35**).

When R is vinylic it is possible, by using a combination of an alkyllithium and *t*-BuOK, to get migration to the γ carbon (as well as to the α carbon), producing an enolate that, on hydrolysis, gives an aldehyde:[418]

$$CH_2{=}CH{-}CH_2{-}OR' \longrightarrow R'CH_2{-}CH{=}CH{-}OLi \longrightarrow R'CH_2CH_2CHO$$

An aza-Wittig rearrangement is also known.[419]

There are no OS references, but see OS **VIII**, 501, for a related reaction.

[408]Wittig, G. *Angew. Chem.* ***1954***, *66*, 10; Solov'yanov, A.A.; Ahmed, E.A.A.; Beletskaya, I.P.; Reutov, O.A. *J. Chem. Soc., Chem. Commun.* ***1987***, *23*, 1232.

[409]Maleczka Jr., R.E.; Geng, F. *J. Am. Chem. Soc.* ***1998***, *120*, 8551.

[410]For a review of the mechanism, see Schöllkopf, U. *Angew. Chem. Int. Ed.* ***1970***, *9*, 763.

[411]Lansbury, P.T.; Pattison, V.A.; Sidler, J.D.; Bieber, J.B. *J. Am. Chem. Soc.* ***1966***, *88*, 78; Schäfer, H.; Schöllkopf, U.; Walter, D. *Tetrahedron Lett.* ***1968***, 2809.

[412]For example, see Hauser, C.R.; Kantor, S.W. *J. Am. Chem. Soc.* ***1951***, *73*, 1437; Cast, J.; Stevens, T.S.; Holmes, J. *J. Chem. Soc.* ***1960***, 3521.

[413]Schöllkopf, U.; Schäfer, H. *Liebigs Ann. Chem.* ***1963***, *663*, 22; Felkin, H.; Frajerman, C. *Tetrahedron Lett.* ***1977***, 3485; Hebert, E.; Welvart, Z. *J. Chem. Soc., Chem. Commun.* ***1980***, 1035; *Nouv. J. Chim.* ***1981***, *5*, 327.

[414]Lansbury, P.T.; Pattison, V.A. *J. Org. Chem.* ***1962***, *27*, 1933; *J. Am. Chem. Soc.* ***1962***, *84*, 4295.

[415]Garst, J.F.; Smith, C.D. *J. Am. Chem. Soc.* ***1973***, *95*, 6870.

[416]Garst, J.F.; Smith, C.D. *J. Am. Chem. Soc.* ***1976***, *98*, 1526. For evidence against this, see Hebert, E.; Welvart, Z.; Ghelfenstein, M.; Szwarc, H. *Tetrahedron Lett.* ***1983***, *24*, 1381.

[417]Eisch, J.J.; Kovacs, C.A.; Rhee, S. *J. Organomet. Chem.* ***1974***, *65*, 289.

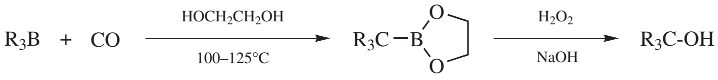
[418]Schlosser, M.; Strunk, S. *Tetrahedron* ***1989***, *45*, 2649.

[419]Coldham, I. *J. Chem. Soc. Perkin Trans. 1* ***1993***, 1275; Anderson, J.C.; Siddons, D.C.; Smith, S.C.; Swarbrick, M.E. *J. Chem. Soc., Chem. Commun.* ***1995***, 1835; Ahman, J.; Somfai, P. *J. Am. Chem. Soc.* ***1994***, *116*, 9781.

F. Boron-to-Carbon Migrations[420]

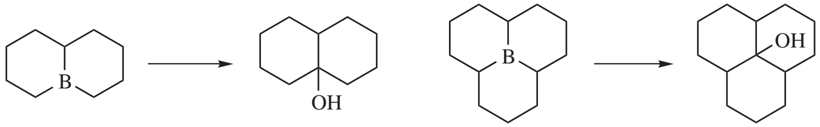
For another reaction involving boron-to-carbon migration, see **10-73**.

18-23 Conversion of Boranes to Alcohols



86

Trialkylboranes (which can be prepared from alkenes by **15-16**) react with carbon monoxide[421] at 100–125°C in the presence of ethylene glycol to give the 2-bora-1,3-dioxolanes (**86**), which are easily oxidized (**12-27**) to tertiary alcohols.[422] The R groups may be primary, secondary, or tertiary, and may be the same or different.[423] Yields are high and the reaction is quite useful, especially for the preparation of sterically hindered alcohols, such as tricyclohexylcarbinol (**87**) and tri-2-norbornylcarbinol (**88**), which are difficult to prepare by **16-24**. Heterocycles in which boron is a ring atom react similarly (except that high CO pressures are required), and cyclic alcohols can be obtained from these substrates.[424] The preparation of such heterocyclic boranes was discussed at **15-16**. The overall conversion of a diene or triene to a cyclic alcohol has been described by H.C. Brown as "stitching" with boron and "riveting" with carbon.



87 **88**

[420]For reviews, see Matteson, D.S., in Hartley, F.R. *The Chemistry of the Metal-Carbon Bond*, Vol. 4, Wiley, NY, ***1984***, pp. 307–409, 346–387; Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, pp. 256–301; Negishi, E.; Idacavage, M.J. *Org. React.* ***1985***, *33*, 1; Suzuki, A *Top. Curr. Chem.* ***1983***, *112*, 67; Pelter, A., in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 2, Academic Press, NY, ***1980***, pp. 95–147; *Chem. Soc. Rev.* ***1982***, *11*, 191; Cragg, G.M.L.; Koch, K.R. *Chem. Soc. Rev.* ***1977***, *6*, 393; Weill-Raynal, J. *Synthesis* ***1976***, 633; Cragg, G.M.L. *Organoboranes in Organic Synthesis*; Marcel Dekker, NY, ***1973***, pp. 249–300; Paetzold, P.I.; Grundke, H. *Synthesis* ***1973***, 635.

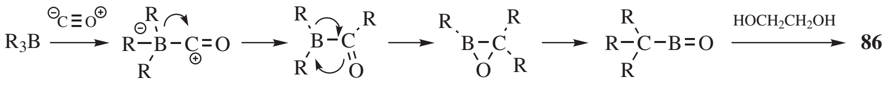
[421]For discussions of the reaction of boranes with CO, see Negishi, E. *Intra-Sci. Chem. Rep.* ***1973***, *7(1)*, 81; Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithica, NY, ***1972***, pp. 343–371; *Acc. Chem. Res.* ***1969***, *2*, 65.

[422]Hillman, M.E.D. *J. Am. Chem. Soc.* ***1962***, *84*, 4715; ***1963***, *85*, 982; Brown, H.C.; Rathke, M.W. *J. Am. Chem. Soc.* ***1967***, *89*, 2737; Puzitskii, K.V.; Pirozhkov, S.D.; Ryabova, K.G.; Pastukhova, I.V.; Eidus, Ya.T. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1972***, *21*, 1939; ***1973***, *22*, 1760; Brown, H.C.; Cole, T.E.; Srebnik, M.; Kim, K. *J. Org. Chem.* ***1986***, *51*, 4925.

[423]Brown, H.C.; Gupta, S.K. *J. Am. Chem. Soc.* ***1971***, *93*, 1818; Negishi, E.; Brown, H.C. *Synthesis* ***1972***, 197.

[424]Brown, H.C.; Negishi, E.; Dickason, W.C. *J. Org. Chem.* ***1985***, *50*, 520, and references cited therein.

Though the mechanism has not been investigated thoroughly, it has been shown to be intramolecular by the failure to find crossover products when mixtures of boranes are used.[425] The following scheme, involving three boron-to-carbon migrations, has been suggested.



89 **90**

The purpose of the ethylene glycol is to intercept the boronic anhydride **90**, which otherwise forms polymers that are difficult to oxidize. As we will see in **18-23** and **18-24**, it is possible to stop the reaction after only one or two migrations have taken place.

Method 1 $$R_3B + CHCl_2OMe \xrightarrow[\text{2. } H_2O_2\text{—NaOH}]{\text{1. LiOCEt}_3\text{—THF}} R_3COH$$

Method 2 $$R_3B + {}^{\ominus}CN \xrightarrow{\text{THF}} \underset{\mathbf{91}}{R_3\overset{\ominus}{B}\text{—}CN} \xrightarrow[\text{2. NaOH—}H_2O_2]{\text{1. excess }(CF_3CO)_2O} R_3COH$$

There are two other methods for achieving the conversion $R_3B \rightarrow R_3COH$, which often give better results: (*1*) treatment with α,α-dichloromethyl methyl ether and the base lithium triethylcarboxide[426] (*2*) treatment with a suspension of sodium cyanide in THF followed by reaction of the resulting trialkylcyanoborate **91** with an excess (>2 equivalents) of trifluoroacetic anhydride.[427] All the above migrations take place with retention of configuration at the migrating carbon.[428]

Several other methods for the conversion of boranes to tertiary alcohols are also known.[429]

If the reaction between trialkylboranes and carbon monoxide (**18-23**) is carried out in the presence of water followed by addition of NaOH, the product is a secondary alcohol. If H_2O_2 is added along with the NaOH, the corresponding ketone is obtained instead.[430] Various functional groups (e.g., OAc, COOR, CN) may be

[425]Brown, H.C.; Rathke, M.W. *J. Am. Chem. Soc.* ***1967***, *89*, 4528.

[426]Brown, H.C.; Carlson, B.A. *J. Org. Chem.* ***1973***, *38*, 2422; Brown, H.C.; Katz, J.; Carlson, B.A. *J. Org. Chem.* ***1973***, *38*, 3968.

[427]Pelter, A.; Hutchings, M.G.; Smith, K.; Williams, D.J. *J. Chem. Soc. Perkin Trans. 1* ***1975***, 145, and references cited therein.

[428]See however Pelter, A.; Maddocks, P.J.; Smith, K. *J. Chem. Soc., Chem. Commun.* ***1978***, 805.

[429]See, for example, Brown, H.C.; Lane, C.F. *Synthesis* ***1972***, 303; Yamamoto, Y.; Brown, H.C. *J. Org. Chem.* ***1974***, *39*, 861; Zweifel, G.; Fisher, R.P. *Synthesis* ***1974***, 339; Midland, M.M.; Brown, H.C. *J. Org. Chem.* ***1975***, *40*, 2845; Levy, A.B.; Schwartz, S.J. *Tetrahedron Lett.* ***1976***, 2201; Baba, T.; Avasthi, K.; Suzuki, A. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 1571; Pelter, A.; Rao, J.M. *J. Organomet. Chem.* ***1985***, *285*, 65; Junchai, B.; Hongxun, D. *J. Chem. Soc., Chem. Commun.* ***1990***, 323.

[430]Brown, H.C.; Rathke, M.W. *J. Am. Chem. Soc.* ***1967***, *89*, 2738.

present in R without being affected,[431] though if they are in the α or β position relative to the boron atom, difficulties may

$$\overset{\ominus}{R_3B{-}CN} \xrightarrow[\text{2. } H_2O_2{-}OH^-]{\text{1. } (CF_3CO)_2O} RCOR$$

91

be encountered. The use of an equimolar amount of trifluoroacetic anhydride leads to the ketone rather than the tertiary alcohol.[427,432] By this procedure, thexylboranes (RR'R^2B, where R^2 = thexyl) can be converted to unsymmetrical ketones (RCOR').[433] Variations of this methodology have been used to prepare optically active alcohols.[434]

For another conversion of trialkylboranes to ketones (see **18-26**).[435] Other conversions of boranes to secondary alcohols are also known.[436]

OS **VII**, 427. Also see, OS **VI**, 137.

18-24 Conversion of Boranes to Primary Alcohols, Aldehydes, or Carboxylic Acids

$$R_3B + CO \xrightarrow[\text{2. } H_2O_2\text{-}OH^-]{\text{1. } LiBH_4} RCH_2OH$$

$$R_3B + CO \xrightarrow[\text{2. } H_2O_2\text{-}NaH_2PO_4\text{-}Na_2HPO_4]{\text{1. } LiAlH(OMe)_3} RCHO$$

When the reaction between a trialkylborane and carbon monoxide (**18-23**) is carried out in the presence of a reducing agent such as lithium borohydride or potassium triisopropoxyborohydride, the reduction agent intercepts the intermediate **89**, so that only one boron-to-carbon migration takes place, and the product is hydrolyzed to a primary alcohol or oxidized to an aldehyde.[437] This procedure wastes two of the three R groups, but this problem can be avoided by the use of

[431] Brown, H.C.; Kabalka, G.W.; Rathke, M.W. *J. Am. Chem. Soc.* ***1967***, *89*, 4530.

[432] Pelter, A.; Smith, K.; Hutchings, M.G.; Rowe, K. *J. Chem. Soc. Perkin Trans. 1* ***1975***, 129; See also, Mallison, P.R.; White, D.N.J.; Pelter, A.; Rowe, K.; Smith, K. *J. Chem. Res. (S)*, ***1978***, 234.

[433] This has been done enantioselectively: Brown, H.C.; Bakshi, R.K.; Singaram, B. *J. Am. Chem. Soc.* ***1988***, *110*, 1529.

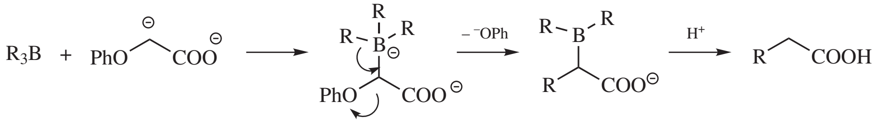
[434] For reviews, see Matteson, D.S. *Mol. Struct. Energ.* ***1988***, *5*, 343; *Acc. Chem. Res.* ***1988***, *21*, 294; *Synthesis* ***1986***, 973, 980–983.

[435] For still other methods, see Brown, H.C.; Levy, A.B.; Midland, M.M. *J. Am. Chem. Soc.* ***1975***, *97*, 5017; Ncube, S.; Pelter, A.; Smith, K. *Tetrahedron Lett.* ***1979***, 1893; Pelter, A.; Rao, J.M. *J. Organomet. Chem.* ***1985***, *285*, 65; Yogo, T.; Koshino, J.; Suzuki, A. *Chem. Lett.* ***1981***, 1059; Brown. H.C.; Bhat, N.G.; Basavaiah, D. *Synthesis* ***1983***, 885; Narayana, C.; Periasamy, M. *Tetrahedron Lett.* ***1985***, *26*, 6361.

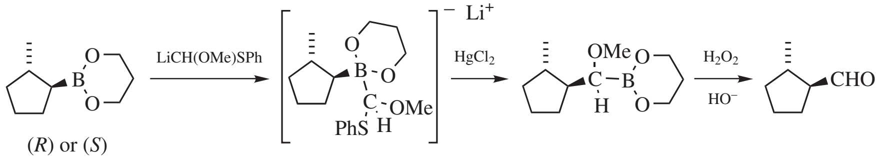
[436] See, for example, Zweifel, G.; Fisher, R.P. *Synthesis* ***1974***, 339; Brown, H.C.; DeLue, N.R. *J. Am. Chem. Soc.* ***1974***, *96*, 311; Hubbard, J.L.; Brown, H.C. *Synthesis* ***1978***, 676; Uguen, D. *Bull. Soc. Chim. Fr.* ***1981***, II-99.

[437] Brown, H.C.; Hubbard, J.L.; Smith, K. *Synthesis* ***1979***, 701, and references cited therein. For discussions of the mechanism, see Brown, H.C.; Hubbard, J.L. *J. Org. Chem.* ***1979***, *44*, 467; Hubbard, J.L.; Smith, K. *J. Organomet. Chem.* ***1984***, *276*, C41.

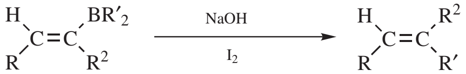
B-alkyl-9-BBN derivatives (p. 1077). Since only the 9-alkyl group migrates, this method permits the conversion in high yield of an alkene to a primary alcohol or aldehyde containing one more carbon.[438] When B-alkyl-9-BBN derivatives are treated with CO and lithium tri-*tert*-butoxyaluminum hydride,[439] other functional groups (e.g., CN and ester) can be present in the alkyl group without being reduced.[440] Boranes can be directly converted to carboxylic acids by reaction with the dianion of phenoxyacetic acid.[441]



Boronic esters $RB(OR')_2$ react with methoxy(phenylthio)methyllithium LiCH(OMe)SPh to give salts, which, after treatment with $HgCl_2$, and then H_2O_2, yield aldehydes.[442] This synthesis has been made enantioselective, with high ee values (>99%), by the use of an optically pure boronic ester,[443] for example:



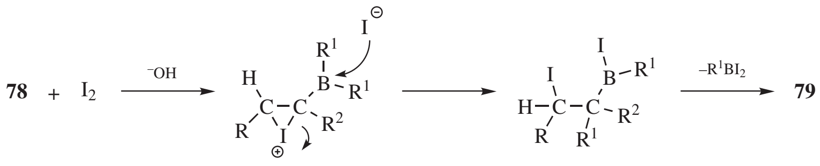
18-25 Conversion of Vinylic Boranes to Alkenes



The reaction between trialkylboranes and iodine to give alkyl iodides was mentioned at **12-31**. When the substrate contains a vinylic group, the reaction takes a different course,[444] with one of the R' groups migrating to the carbon, to give alkenes.[445] The reaction is stereospecific in two senses: (*1*) if the groups

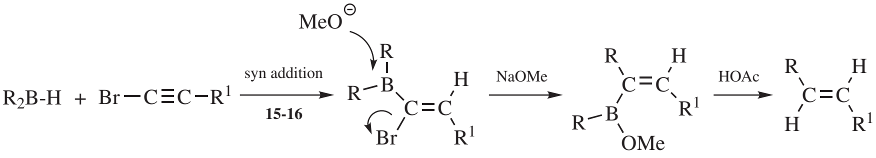
[438]Brown, H.C.; Knights, E.F.; Coleman, R.A. *J. Am. Chem. Soc.* ***1969***, *91*, 2144.
[439]Brown, H.C.; Coleman, R.A. *J. Am. Chem. Soc.* ***1969***, *91*, 4606.
[440]For other methods of converting boranes to aldehydes, see Yamamoto, S.; Shiono, M.; Mukaiyama, T. *Chem. Lett.* ***1973***, 961; Negishi, E.; Yoshida, T.; Silveira, Jr., A.; Chiou, B.L. *J. Org. Chem.* ***1975***, *40*, 814.
[441]Hara, S.; Kishimura, K.; Suzuki, A.; Dhillon, R.S. *J. Org. Chem.* ***1990***, *55*, 6356. See also, Brown, H.C.; Imai, T. *J. Org. Chem.* ***1984***, *49*, 892.
[442]Brown, H.C.; Imai, T. *J. Am. Chem. Soc.* ***1983***, *105*, 6285. For a related method that produces primary alcohols, see Brown, H.C.; Imai, T.; Perumal, P.T.; Singaram, B. *J. Org. Chem.* ***1985***, *50*, 4032.
[443]Brown, H.C.; Imai, T.; Desai, M.C.; Singaram, B. *J. Am. Chem. Soc.* ***1985***, *107*, 4980.
[444]Zweifel, G.; Fisher, R.P. *Synthesis* ***1975***, 376; Brown, H.C.; Basavaiah, D.; Kulkarni, S.U.; Bhat, N.G.; Vara Prasad, J.V.N. *J. Org. Chem.* ***1988***, *53*, 239.
[445]For a list of methods of preparing alkenes using boron reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 421–427.

R and R″ are cis in the starting compound, they will be trans in the product; (*2*) there is retention of configuration within the migrating group R′.[446] Since vinylic boranes can be prepared from alkynes (**15-16**), this is a method for the addition of R′ and H to a triple bond. If $R^2 = H$, the product is a (*Z*)-alkene. The mechanism is believed to involve an iodonium intermediate, such as **92**, and attack by iodide on boron. When R′ is vinylic, the product is a conjugated diene.[447]



92

In another procedure, the addition of a dialkylborane to a 1-haloalkyne produces an α-halo vinylic borane (**93**).[448] Treatment of this with NaOMe gives the rearrangement shown, and protonolysis of the product



93

produces the (*E*)-alkene.[446] If R is a vinylic group the product is a 1,3-diene.[449] If one of the groups is thexyl, the other migrates.[450] This extends the scope of the synthesis, since dialkylboranes where one R group is thexyl are easily prepared. A combination of both of the procedures described above results in the preparation of trisubstituted alkenes.[451] The entire conversion of haloalkyne to alkene can be carried out in one reaction vessel, without isolation of intermediates. An aluminum counterpart of the α-halo vinylic borane procedure has been reported.[452]

[446]Zweifel, G.; Fisher, R.P.; Snow, J.T.; Whitney, C.C. *J. Am. Chem. Soc.* ***1971***, *93*, 6309.

[447]Zweifel, G.; Polston, N.L.; Whitney, C.C. *J. Am. Chem. Soc.* ***1968***, *90*, 6243; Brown, H.C.; Ravindran, N. *J. Org. Chem.* ***1973***, *38*, 1617; Hyuga, S.; Takinami, S.; Hara, S.; Suzuki, A. *Tetrahedron Lett.* ***1986***, *27*, 977.

[448]For improvements in this method, see Brown, H.C.; Basavaiah, D.; Kulkarni, S.U.; Lee, H.D.; Negishi, E.; Katz, J. *J. Org. Chem.* ***1986***, *51*, 5270.

[449]Negishi, E.; Yoshida, T. *J. Chem. Soc. Chem. Commun.* ***1973***, 606; See also, Negishi, E.; Yoshida, T.; Abramovitch, A.; Lew, G.; Williams, R.H. *Tetrahedron* ***1991***, *47*, 343.

[450]Corey, E.J.; Ravindranathan, T. *J. Am. Chem. Soc.* ***1972***, *94*, 4013; Negishi, E.; Katz, J.; Brown, H.C. *Synthesis* ***1972***, 555.

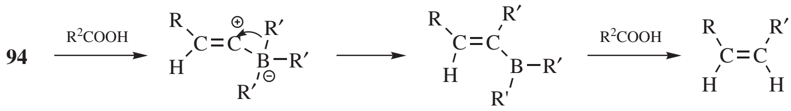
[451]Zweifel, G.; Fisher, R.P. *Synthesis* ***1972***, 557.

[452]Miller, J.A. *J. Org. Chem.* ***1989***, *54*, 998.

18-26 Formation of Alkynes, Alkenes, and Ketones from Boranes and Acetylides

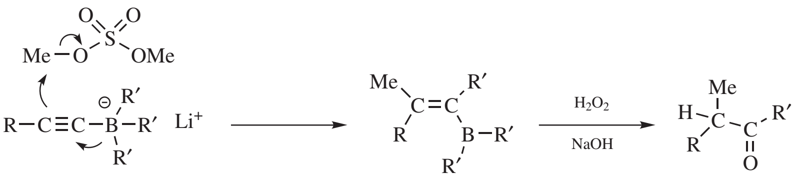
94

A hydrogen directly attached to a triple-bond carbon can be replaced in high yield by an alkyl or an aryl group, by treatment of the lithium acetylide with a trialkyl- or triarylborane, followed by reaction of the lithium alkynyltrialkylborate **94** with iodine.[453] The R′ group may be primary or secondary alkyl as well as aryl, so the reaction has a broader scope than the older reaction **10-74**.[454] The R group may be alkyl, aryl, or hydrogen, though in the last-mentioned case satisfactory yields are obtained only if lithium acetylide–ethylenediamine is used as the starting



compound.[455] Optically active alkynes can be prepared by using optically active thexylborinates (RR^{2}BOR', R^2 = thexyl), where R is chiral, and LiC≡CSiMe$_3$.[456] The reaction can be adapted to the preparation of alkenes[414] by treatment of **94** with an electrophile such as propanoic acid[457] or tributyltin chloride.[458] The reaction with Bu$_3$SnCl produces the (*Z*)-alkene stereoselectively.

Treatment of **94** with an electrophile, such as methyl sulfate, allyl bromide, or triethyloxonium borofluoride, followed by oxidation of the resulting vinylic borane gives a ketone (illustrated for methyl sulfate):[459]



[453]Suzuki, A.; Miyaura, N.; Abiko, S.; Itoh, M.; Brown, H.C.; Sinclair, J.A.; Midland, M.M. *J. Org. Chem.* ***1986***, *51*, 4507; Sikorski, J.A.; Bhat, N.G.; Cole, T.E.; Wang, K.K.; Brown, H.C. *J. Org. Chem.* ***1986***, *51*, 4521. For a review of reactions of organoborates, see Suzuki, A. *Acc. Chem. Res.* ***1982***, *15*, 178.

[454]For a study of the relative migratory aptitudes of R', see Slayden, S.W. *J. Org. Chem.* ***1981***, *46*, 2311.

[455]Midland, M.M.; Sinclair, J.A.; Brown, H.C. *J. Org. Chem.* ***1974***, *39*, 731.

[456]Brown, H.C.; Mahindroo, V.K.; Bhat, N.G.; Singaram, B. *J. Org. Chem.* ***1991***, *56*, 1500.

[457]Miyaura, N.; Yoshinari, T.; Itoh, M.; Suzuki, A. *Tetrahedron Lett.* ***1974***, 2961; Pelter, A.; Gould, K.J.; Harrison, C.R. *Tetrahedron Lett.* ***1975***, 3327.

[458]Hooz, J.; Mortimer, R. *Tetrahedron Lett.* ***1976***, 805; Wang, K.K.; Chu, K. *J. Org. Chem.* ***1984***, *49*, 5175.

[459]Pelter, A.; Drake, R.A. *Tetrahedron Lett.* ***1988***, *29*, 4181.

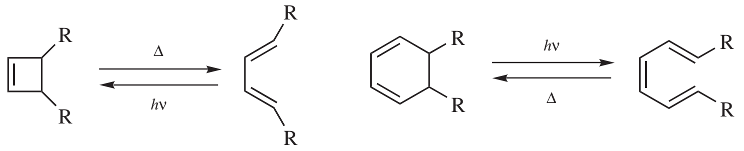
Note that there are reactions that involve N → O rearrangements, including those mediated by silicon.[460]

NON-1,2 REARRANGEMENTS

A. Electrocyclic Rearrangements

18-27 Electrocyclic Rearrangements of Cyclobutenes and 1,3-Cyclohexadienes

(4)*seco*-1/4/Detachment; (4)*cyclo*-1/4/Attachment
(6)*seco*-1,6/Detachment; (6)*cyclo*-1/6/Attachment



Cyclobutenes and 1,3-dienes can be interconverted by treatment with uv light or with heat.[461] The thermal reaction is generally not reversible (although exceptions[462] are known), and many cyclobutenes have been converted to 1,3-dienes by heating at temperatures between 100 and 200°C. The photochemical conversion can in principle be carried out in either direction, but most often 1,3-dienes are converted to cyclobutenes rather than the reverse, because the dienes are stronger absorbers of light at the wavelengths used.[463] In a similar reaction, 1,3-cyclohexadienes interconvert with 1,3,5-trienes, but in this case the ring-closing process is generally favored thermally and the ring-opening process photochemically, though exceptions are known in both directions.[464] Substituent effects can lead to acceleration of the electrocyclization process.[465] Torquoselectivity in cyclobutene ring opening reaction has been examined.[466]

[460]Talami, S.; Stirling, C.J.M. *Can. J. Chem.* ***1999***, *77*, 1105.

[461]See Dolbier Jr., W.R.; Koroniak, H.; Houk, K.N.; Sheu, C. *Acc. Chem. Res.* ***1996***, *29*, 471; Niwayama, S.; Kallel, E.A.; Spellmeyer, D.C.; Sheu, C.; Houk, K.N. *J. Org. Chem.* ***1996***, *61*, 2813. The effect of pressure on this reaction has been discussed, see Jenner, G. *Tetrahedron* ***1998***, *54*, 2771.

[462]For example; see Shumate, K.M.; Neuman, P.N.; Fonken, G.J. *J. Am. Chem. Soc.* ***1965***, *87*, 3996; Gil-Av, E.; Herling, J. *Tetrahedron Lett.* ***1967***, 1; Doorakian, G.A.; Freedman, H.H. *J. Am. Chem. Soc.* ***1968***, *90*, 3582; Brune, H.A.; Schwab, W. *Tetrahedron* ***1969***, *25*, 4375; Steiner, R.P.; Michl, J. *J. Am. Chem. Soc.* ***1978***, *100*, 6413.

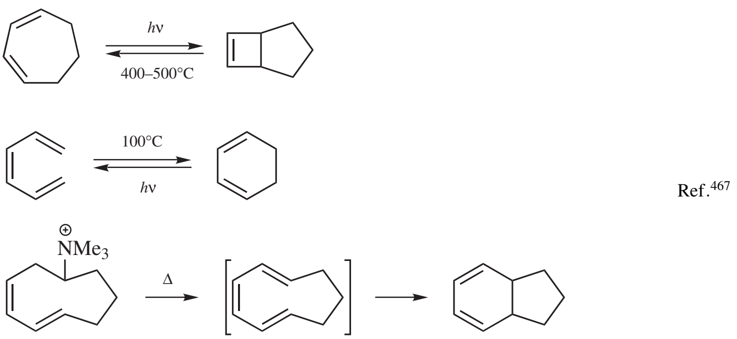
[463]For examples of photochemical conversion of a cylcobutene to a 1,3-diene, see Scerer, Jr., K.V. *J. Am. Chem. Soc.* ***1968***, *90*, 7352; Saltiel, J.; Lim, L.N. *J. Am. Chem. Soc.* ***1969***, *91*, 5404; Adam, W.; Oppenländer, T.; Zang, G. *J. Am. Chem. Soc.* ***1985***, *107*, 3921; Dauben, W.G.; Haubrich, J.E. *J. Org. Chem.* ***1988***, *53*, 600.

[464]For a review of photochemical rearrangements in trienes, see Dauben, W.G.; McInnis, E.L.; Michno, D.M., in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, ***1980***, pp. 91–129. For an *ab initio* study see Rodríguez-Otero, J. *J. Org. Chem.* ***1999***, *64*, 6842.

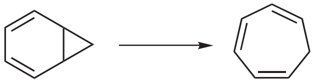
[465]Tanaka, K.; Mori, H.; Yamamoto, M.; Katsumura, S. *J. Org. Chem.* ***2001***, *66*, 3099.

[466]Yasui, M.; Naruse, Y.; Inagaki, S. *J. Org. Chem.* ***2004***, *69*, 7246.

Some examples are



An interesting example of 1,3-cyclohexadiene–1,3,5-triene interconversion is the reaction of norcaradienes to give cycloheptatrienes.[468] Norcaradienes give this reaction so readily (because they are *cis*-1,2-divinylcyclopropanes, see p. 1661) that they cannot generally be isolated, though some exceptions are known[469,470] (see also, p. 1239).



Norcaradiene

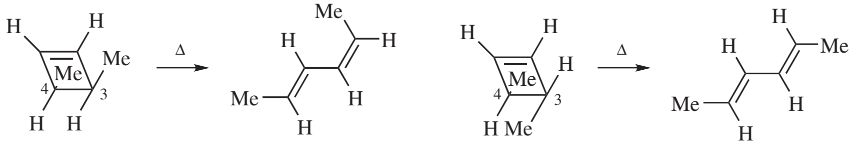
[467]Dauben, W.G.; Cargill, R.L. *Tetrahedron* ***1961***, *12*, 186; Chapman, O.L.; Pasto, D.J.; Borden, G.W.; Griswold, A.A. *J. Am. Chem. Soc.* ***1962***, *84*, 1220.

[468]For reviews of the norcaradiene-cycloheptatriene interconversion and the analogous benzene oxide–oxepin interconversion, see Maier, G. *Angew. Chem. Int. Ed.* ***1967***, *6*, 402; Vogel, E.; Günther, H. *Angew. Chem. Int. Ed.* ***1967***, *6*, 385; Vogel, E. *Pure Appl. Chem.* ***1969***, *20*, 237.

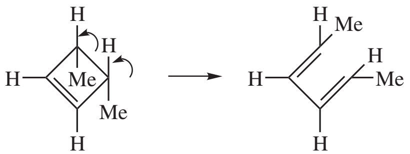
[469]Ciganek, E. *J. Am. Chem. Soc.* ***1967***, *89*, 1454; Mukai, T.; Kubota, H.; Toda, T. *Tetrahedron Lett.* ***1967***, 3581; Maier, G.; Heep, U. *Chem. Ber.* ***1968***, *101*, 1371; Ciganek, E. *J. Am. Chem. Soc.* ***1971***, *93*, 2207; Dürr, H.; Kober, H. *Tetrahedron Lett.* ***1972***, 1255, 1259; Vogel, E.; Wiedemann, W.; Roth, H.D.; Eimer, J.; Günther, H. *Liebigs Ann. Chem.* ***1972***, *759*, 1; Bannerman, C.G.F.; Cadogan, J.I.G.; Gosney, I.; Wilson, N.H. *J. Chem. Soc., Chem. Commun.* ***1975***, 618; Takeuchi, K.; Kitagawa, T.; Senzaki, Y.; Okamoto, K. *Chem. Lett.* ***1983***, 73; Kawase, T.; Iyoda, M.; Oda, M. *Angew. Chem. Int. Ed.* ***1987***, *26*, 559.

[470]See, for example, Ciganek, E. *J. Am. Chem. Soc.* ***1967***, *89*, 1454; Mukai, T.; Kubota, H.; Toda, T. *Tetrahedron Lett.* ***1967***, 3581; Maier, G.; Heep, U. *Chem. Ber.* ***1968***, *101*, 1371; Ciganek, E. *J. Am. Chem. Soc.* ***1971***, *93*, 2207; Dürr, H.; Kober, H. *Tetrahedron Lett.* ***1972***, 1255, 1259; Vogel, E.; Wiedemann, W.; Roth, H.D.; Eimer, J.; Günther, H. *Liebigs Ann. Chem.* ***1972***, *759*, 1; Bannerman, C.G.F.; Cadogan, J.I.G.; Gosney, I.; Wilson, N.H. *J. Chem. Soc., Chem. Commun.* ***1975***, 618; Takeuchi, K.; Kitagawa, T.; Senzaki, Y.; Okamoto, K. *Chem. Lett.* ***1983***, 73; Kawase, T.; Iyoda, M.; Oda, M. *Angew. Chem. Int. Ed.* ***1987***, *26*, 559.

These reactions, called *electrocyclic rearrangements*,[471] take place by pericyclic mechanisms. The evidence comes from stereochemical studies, which show a remarkable stereospecificity whose direction depends on whether the reaction is induced by heat or light. For example, it was found for the thermal reaction that *cis*-3,4-dimethylcyclobutene gave only *cis*,*trans*-2,4-hexadiene, while the trans isomer gave only the trans–trans diene:[472]



This is evidence for a four-membered cyclic transition state and arises from conrotatory motion about the C-3–C-4 bond.[473] It is called conrotatory because both movements are clockwise (or both counterclockwise). Because both rotate in the same direction, the cis isomer gives the cis–trans diene:[474]



The other possibility (*disrotatory* motion) would have one moving clockwise while the other moves counterclockwise; the cis isomer would have given the cis–cis

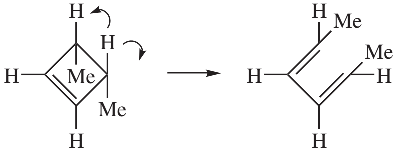
[471]For a monograph on thermal isomerizations, which includes electrocyclic and sigmatropic rearrangements, as well as other types, see Gajewski, J.J. *Hydrocarbon Thermal Isomerizations*, Academic Press, NY, ***1981***. For a monograph on electrocyclic reactions, see Marvell, E.N. *Thermal Electrocyclic Reactions*, Academic Press, NY, ***1980***. For reviews, see Dolbier, W.R.; Koroniak, H. *Mol. Struct. Energ.*, ***1988***, *8*, 65; Laarhoven, W.H. *Org. Photochem.* ***1987***, *9*, 129; George, M.V.; Mitra, A.; Sukumaran, K.B. *Angew. Chem. Int. Ed.* ***1980***, *19*, 973; Jutz, J.C. *Top. Curr. Chem.* ***1978***, *73*, 125; Gilchrist, T.L.; Storr, R.C. *Organic Reactions and Orbital Symmetry*, Cambridge University Press, Cambridge, ***1972***, pp. 48–72; DeWolfe, R.H. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***; pp. 461–470; Crowley, K.J.; Mazzocchi, P.H., in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, ***1970***, pp. 284–297; Criegee, R. *Angew. Chem. Int. Ed.* ***1968***, *7*, 559; Vollmer, J.J.; Servis, K.L. *J. Chem. Educ.* ***1968***, *45*, 214. For a review of isotope effects in these reactions, see Gajewski, J.J. *Isot. Org. Chem.* ***1987***, *7*, 115. For a related review, see Schultz, A.G.; Motyka, L. *Org. Photochem.* ***1983***, *6*, 1.

[472]Winter, R.E.K. *Tetrahedron Lett.* ***1965***, 1207. Also see, Vogel, E. *Liebigs Ann. Chem.* ***1958***, *615*, 14; Criegee, R.; Noll, K. *Liebigs Ann. Chem.* ***1959***, *627*, 1.

[473]The mechanism of cyclobutene thermal isomerization has been examined. See Baldwin, J.E.; Gallagher, S.S.; Leber, P.A.; Raghavan, A.S.; Shukla, R. *J. Org. Chem.* ***2004***, *69*, 7212.

[474]This picture is from Woodward, R.B.; Hoffmann, R. *J. Am. Chem. Soc.* ***1965***, *87*, 395, who coined the terms, *conrotatory* and *disrotatory*.

diene (shown) or the trans–trans diene:



If the motion had been disrotatory, this would still have been evidence for a cyclic mechanism. If the mechanism were a diradical or some other kind of noncyclic process, it is likely that no stereospecificity of either kind would have been observed. The reverse reaction is also conrotatory. In contrast, the photochemical cyclobutene: 1,3-Diene interconversion is *disrotatory* in either direction.[475] On the other hand, the cyclohexadiene: 1,3,5-Triene interconversion shows precisely the opposite behavior. The thermal process is *disrotatory*, while the photochemical process is *conrotatory* (in either direction). These startling results are a consequence of the symmetry rules mentioned in Chapter 15 (p. 1208).[476] As in the case of cycloaddition reactions, we will use the frontier orbital and Möbius–Hückel approaches.[477]

The Frontier Orbital Method[478]

As applied to these reactions, the frontier orbital method may be expressed: *A σ bond will open in such a way that the resulting p orbitals will have the symmetry of the highest occupied π orbital of the product.* In the case of cyclobutenes, the HOMO of the product in the thermal reaction is the χ_2 orbital (Fig. 18.1).

[475]Photochemical ring opening of cyclobutenes can also be nonstereospecific. See Leigh, W.J.; Zheng, K. *J. Am. Chem. Soc.* ***1991***, *113*, 4019; Leigh, W.J.; Zheng, K.; Nguyen, N.; Werstiuk, N.H.; Ma, J. *J. Am. Chem. Soc.* ***1991***, *113*, 4993, and references cited therein.

[476]Woodward, R.B.; Hoffmann, R. *J. Am. Chem. Soc.* ***1965***, *87*, 395. Also see, Longuet-Higgins, H.C.; Abrahamson, E.W. *J. Am. Chem. Soc.* ***1965***, *87*, 2045; Fukui, K. *Tetrahedron Lett.* ***1965***, 2009.

[477]For the correlation diagram method, see Jones, R.A.Y. *Physical and Mechanistic Organic Chemistry*, 2nd ed., Cambridge University Press, Cambridge, ***1984***, pp. 352–359; Yates, K. *Hückel Molecular Orbital Theory*, Academic Press, NY, ***1978***, pp. 250–263. Also see, Zimmerman, H.E., in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, ***1977***, pp. 53–107; *Acc. Chem. Res.* ***1971***, *4*, 272; *J. Am. Chem. Soc.* ***1966***, *88*, 1564, 1566; Dewar, M.J.S. *Angew. Chem. Int. Ed.* ***1971***, *10*, 761; Jefford, C.W.; Burger, U. *Chimia* ***1971***, *25*, 297; Herndon, W.C. *J. Chem. Educ.* ***1981***, *58*, 371.

[478]Fukui, K.; Fujimoto, H. *Bull. Chem. Soc. Jpn.* ***1967***, *40*, 2018; ***1969***, *42*, 3399; Fukui, K. *Fortschr. Chem. Forsch.* ***1970***, *15*, 1; *Acc. Chem. Res.* ***1971***, *4*, 57; Houk, K.N. *Acc. Chem. Res.* ***1975***, *8*, 361. See also, Chu, S. *Tetrahedron* ***1978***, *34*, 645. For a monograph on frontier orbitals see Fleming, I. *Pericyclic Reactions*, Oxford University Press, Oxford, ***1999***. For reviews, see Fukui, K. *Angew. Chem. Int. Ed.* ***1982***, *21*, 801; Houk, K.N., in Marchand, A.P.; Lehr, R.F. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, ***1977***, pp. 181–271.

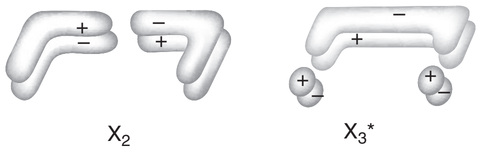


Fig. 18.1. Symmetries of the X_2 and X_3* orbitals of a conjugated diene.

Therefore, in a thermal process, the cyclobutene must open so that on one side the positive lobe lies above the plane, and on the other side below it. Thus the substituents are forced into conrotatory motion (Fig. 18.2). On the other hand, in the photochemical process, the HOMO of the product is now the χ_3 orbital (Fig. 18.1), and in order for the *p* orbitals to achieve this symmetry (the two plus lobes on the same side of the plane), the substituents are forced into disrotatory motion.

We may also look at this reaction from the opposite direction (ring closing). For this direction, the rule is that *those lobes of orbitals that overlap (in the HOMO) must be of the same sign*. For thermal cyclization of butadienes, this requires conrotatory motion (Fig. 18.3). In the photochemical process the HOMO is the χ_3 orbital, so that disrotatory motion is required for lobes of the same sign to overlap.

The Möbius–Hückel Method[481]

As we saw on p. 1210, in this method we choose a basis set of *p* orbitals and look for sign inversions in the transition state. Figure 18.4 shows a basis set for a 1,3-diene. It is seen that disrotatory ring closing (Fig. 18.4*a*) results in overlap of plus lobes only, while in conrotatory closing (Fig. 18.4*b*) there is one overlap of a plus

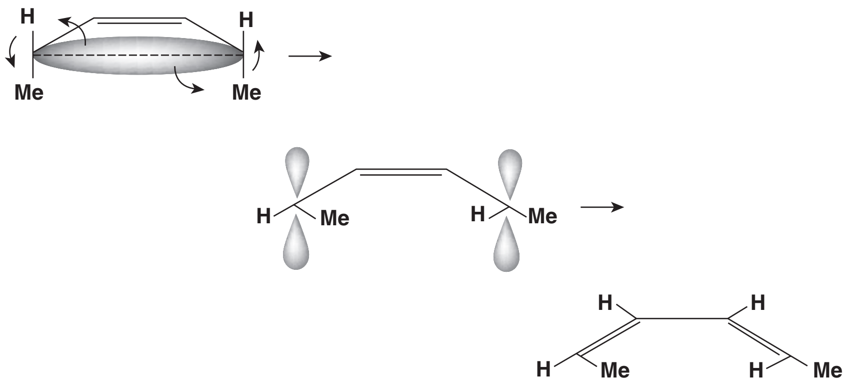


Fig. 18.2. Thermal opening of 1,2-dimethylcyclobutene. The two hydrogens and two methyls are forced into conrotatory motion so that the resulting *p* orbitals have the symmetry of the HOMO of the diene.

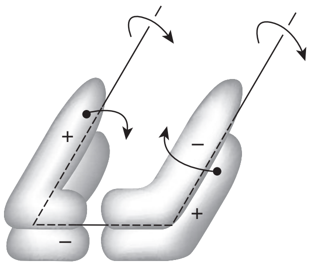


Fig. 18.3. Thermal ring closing of a 1,3-diene. Conrotatory motion is required for two + lobes to overlap.

with a minus lobe. In the first case, we have zero sign inversions, while in the second there is one sign inversion. With zero (or an even number of) sign inversions, the disrotatory transition state is a Hückel system, and so is allowed thermally only if the total number of electrons is $4n + 2$ (p. 1211). Since the total here is 4, the

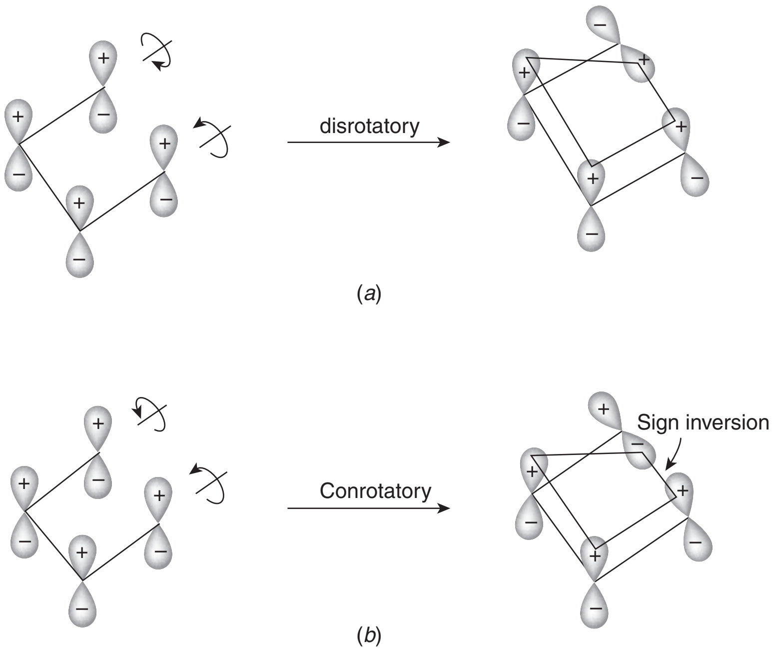
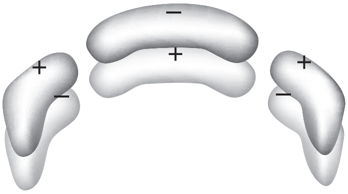


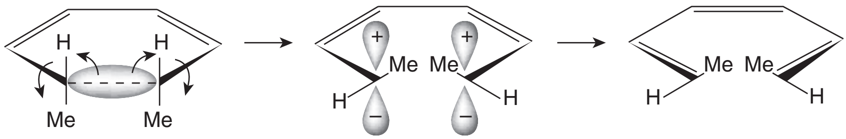
Fig. 18.4. The 1,3-diene–cyclobutene interconversion. The orbitals shown are *not* molecular orbitals, but a basis set of *p*-atomic orbitals. (*a*) Disrotatory ring closure gives zero sign inversion. (*b*) Conrotatory ring closure gives one sign inversion. We could have chosen to show any other basis set (e.g., another basis set would have two plus lobes above the plane and two below, etc.). This would change the number of sign inversion, but the disrotatory mode would still have an even number of sign inversions, and the conrotatory mode an odd number, whichever basis set was chosen.

disrotatory process is not allowed. On the other hand, the conrotatory process, with one sign inversion, is a Möbius system, which is thermally allowed if the total number is $4n$. The conrotatory process is therefore allowed thermally. For the photochemical reactions, the rules are reversed: A reaction with $4n$ electrons requires a Hückel system, so only the disrotatory process is allowed.

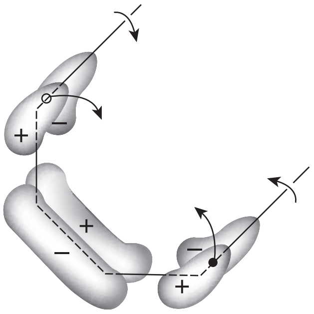
Both the frontier orbital and the Möbius–Hückel methods can also be applied to the cyclohexadiene: 1,3,5-triene reaction;[479] in either case the predicted result is that for the thermal process, only the disrotatory pathway is allowed, and for the photochemical process, only the conrotatory. For example, for a 1,3,5-triene, the symmetry of the HOMO is



In the thermal cleavage of cyclohexadienes, then, the positive lobes must lie on the same side of the plane, requiring disrotatory motion:



Disrotatory motion is also necessary for the reverse reaction, in order that the orbitals that overlap may be of the same sign:

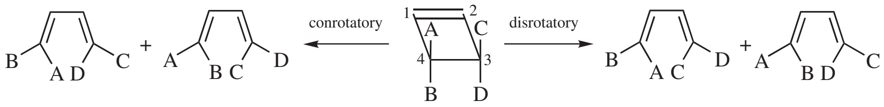


[479]For a discussion of the transition structures and energy, see Zora, M. *J. Org. Chem.* ***2004***, *69*, 1940.

All these directions are reversed for photochemical processes, because in each case a higher orbital, with inverted symmetry, is occupied.

In the Möbius–Hückel approach, diagrams similar to Fig. 18.4 can be drawn for this case. Here too, the disrotatory pathway is a Hückel system and the conrotatory pathway a Möbius system, but since six electrons are now involved, the thermal reaction follows the Hückel pathway and the photochemical reaction the Möbius pathway.

In the most general case, there are four possible products that can arise from a given cyclobutene or cyclohexadiene: two from the conrotatory and two from the disrotatory pathway. For example, conrotatory ring opening of **95** gives either **96** or **97**, while disrotatory opening gives either **98** or **99**. The orbital-symmetry rules tell us when a given reaction will operate by the conrotatory and when by the disrotatory mode, but they do not say which of the two possible conrotatory or disrotatory pathways will be followed. It is often possible,



96 **97** **95** **98** **99**

however, to make such predictions on steric grounds. For example, in the opening of **95** by the disrotatory pathway, **98** arises when groups A and C swing in toward each other (clockwise motion around C-4, counterclockwise around C-3), while **99** is formed when groups B and D swing in and A and C swing out (clockwise motion around C-3, counterclockwise around C-4). We therefore predict that when A and C are larger than B and D, the predominant or exclusive product will be **99**, rather than **98**. Predictions of this kind have largely been borne out.[480] There is evidence, however, that steric effects[481] are not the only factor, and that electronic effects also play a role, which may be even greater.[482] An electron-donating group stabilizes the transition state when it rotates *outward*, because it mixes with the LUMO; if it rotates *inward*, it mixes with the HOMO, destabilizing the transition state.[483] The compound 3-formylcyclobutene provided a test. Steric factors would cause the CHO

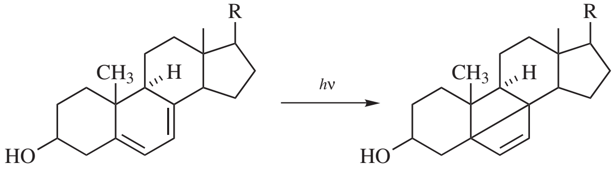
[480]For example, see Baldwin, J.E.; Krueger, S.M. *J. Am. Chem. Soc.* ***1969***, *91*, 6444; Spangler, C.W.; Hennis, R.P. *J. Chem. Soc., Chem. Commun.* ***1972***, 24; Gesche, P.; Klinger, F.; Riesen, A.; Tschamber, T.; Zehnder, M.; Streith, J. *Helv. Chim. Acta* ***1987***, *70*, 2087.

[481]Leigh, W.J.; Postigo, J.A. *J. Am. Chem. Soc.* ***1995***, *117*, 1688.

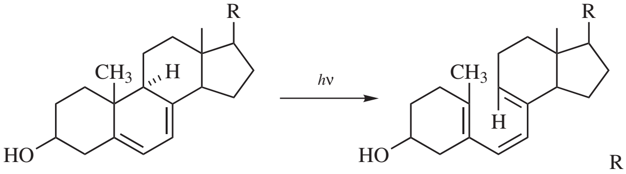
[482]Kirmse, W.; Rondan, N.G.; Houk, K.N. *J. Am. Chem. Soc.* ***1984***, *106*, 7989; Dolbier, Jr., W.R.; Gray, T.A.; Keaffaber, J.J.; Celewicz, L.; Koroniak, H. *J. Am. Chem. Soc.* ***1990***, *112*, 363; Hayes, R.; Ingham, S.; Saengchantara, S.T.; Wallace, T.W. *Tetrahedron Lett.* ***1991***, *32*, 2953.

[483]For theoretical studies, see Buda, A.B.; Wang, Y.; Houk, K.N. *J. Org. Chem.* ***1989***, *54*, 2264; Kallel, E.A.; Wang, Y.; Spellmeyer, D.C.; Houk, K.N. *J. Am. Chem. Soc.* ***1990***, *112*, 6759.

(an electron-withdrawing group) to rotate outward; electronic effects would cause it to rotate inward. The experiment showed inward rotation.[484]



100



101 **102**

R = C_9H_{17}

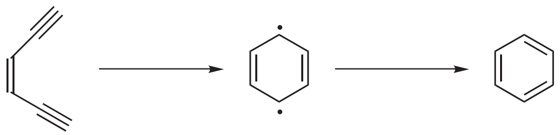
Cyclohexadienes are of course 1,3-dienes, and in certain cases it is possible to convert them to cyclobutenes instead of to 1,3,5-trienes.[485] An interesting example is found in the pyrocalciferols. Photolysis of the syn isomer **100** (or of the other syn isomer, not shown) leads to the corresponding cyclobutene,[486] while photolysis of the anti isomers (one of them is **101**) gives the ring-opened 1,3,5-triene, **102**. This difference in behavior is at first sight remarkable, but is easily explained by the orbital-symmetry rules. Photochemical ring opening to a 1,3,5-triene must be conrotatory. If **100** were to react by this pathway, the product would be the triene **102**, but this compound would have to contain a *trans*-cyclohexene ring (either the methyl group or the hydrogen would have to be directed inside the ring). On the other hand, photochemical conversion to a cyclobutene must be disrotatory, but if **101** were to give this reaction, the product would have to have a trans-fused ring junction. Compounds with such ring junctions are known (p. 188), but are very strained. Stable *trans*-cyclohexenes are unknown (p. 226). Thus, **100** and **101** give the products they do owing to a combination of orbital-symmetry rules and steric influences.

[484]Rudolf, K.; Spellmeyer, D.C.; Houk, K.N. *J. Org. Chem.* ***1987***, *52*, 3708; Piers, E.; Lu, Y.-F. *J. Org. Chem.* ***1989***, *54*, 2267.

[485]For a discussion of the factors favoring either direction, see Dauben, W.G.; Kellogg, M.S.; Seeman, J.I.; Vietmeyer, N.D.; Wendschuh, P.H. *Pure Appl. Chem.* ***1973***, *33*, 197.

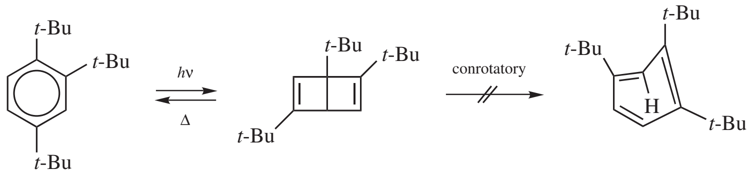
[486]Dauben, W.G.; Fonken, G.J. *J. Am. Chem. Soc.* ***1959***, *81*, 4060. This was the first reported example of the conversion of a 1,3-diene to a cyclobutene.

A variation of this process is the *Bergmann cyclization*,[487] where an ene-diyne cyclizes to a biradical (**103**) and then aromatizes as shown.



103

Simply heating the en-diyne will usually lead to aromatization via this pathway.[488] Quinones can be formed via Bergman cyclization[489] and there are other synthetic applications.[490] The role of vinyl substitution has been examined.[491] An aza-Bergman cyclization is known.[492]



104 **105** **106**

The 1,3-diene-cyclobutene interconversion can even be applied to benzene rings. For example,[493] photolysis of 1,2,4-tri-*tert*-butylbenzene (**104**) gives

[487]Bergman, R.G. *Accts. Chem. Res.* ***1973***, *6*, 25; Darby, N.; Kim, C.U.; Shelton, K.W.; Takada, S.; Masamune, S. *J. Chem. Soc. (D)*, ***1971***, *23*, 1516; Adam, W.; Krebs, O. *Chem. Rev.* ***2003***, *103*, 4131. For a discussion of electronic and stereoelectronic effects see Pourde II, G.W.; Warner, P.M.; Parrish, D.A.; Jones, G.B. *J. Org. Chem.* ***2002***, *67*, 5369; Jones, G.B.; Wright, J.M.; Hynd, G.; Wyatt, J.K.; Warner, P.M.; Huber, R.S.; Li, A.; Kilgore, M.W.; Sticca, R.P.; Pollenz, R.S. *J. Org. Chem.* ***2002***, *67*, 5727. For polar effects, see Schmittel, M.; Kiau, S. *Chem. Lett*, ***1995***, 953; Grissom, J.W.; Calkins, T.L.; McMillen, H.A.; Jiang, Y. *J. Org. Chem.* ***1994***, *59*, 5833. For free-energy relationships see Choy, N.; Kim, C.-S.; Ballestero, C.; Artigas, L.; Diez, C.; Lichtenberger, F.; Shapiro, J.; Russell, K.C. *Tetrahedron Lett.* ***2000***, *41*, 6955.

[488]For examples, see Grissom, J.W.; Klingberg, D. *Tetrahedron Lett.* ***1995***, *36*, 6607; Danheiser, R.L.; Gould, A.E.; de la Pradilla, R.F.; Helgason, A.L. *J. Org. Chem.* ***1994***, *59*, 5514; Grissom, J.W.; Calkins, T.L.; McMillen, H.A. *J. Org. Chem.* ***1993***, *58*, 6556; Tanaka, H.; Yamada, H.; Matsuda, A.; Takahashi, T. *Synlett* ***1997***, 381.

[489]Jones, G.B.; Warner, P.M. *J. Org. Chem.* ***2001***, *66*, 8669.

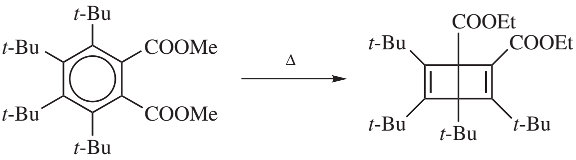
[490]Bowles, D.M.; Palmer, G.J.; Landis, C.A.; Scott, J.L.; Anthony, J.E. *Tetrahedron* ***2001***, *57*, 3753.

[491]Jones, G.B.; Warner, P.M. *J. Am. Chem. Soc.* ***2001***, *123*, 2134.

[492]Feng, L.; Kumar, D.; Kerwin, S.M. *J. Org. Chem.* ***2003***, *68*, 2234.

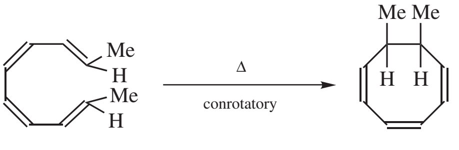
[493]Unsubstituted Dewar benzene has been obtained, along with other photoproducts, by photolysis of benzene: Ward, H.R.; Wishnok, J.S. *J. Am. Chem. Soc.* ***1968***, *90*, 1085; Bryce-Smith, D.; Gilbert, A.; Robinson, D.A. *Angew. Chem. Int. Ed.* ***1971***, *10*, 745. For other examples, see Arnett, E.M.; Bollinger, J.M. *Tetrahedron Lett.* ***1964***, 3803; Camaggi, G.; Gozzo, F.; Cevidalli, G. *Chem. Commun.* ***1966***, 313; Haller, I. *J. Am. Chem. Soc.* ***1966***, *88*, 2070; *J. Chem. Phys.* ***1967***, *47*, 1117; Barlow, M.G.; Haszeldine, R.N.; Hubbard, R. *Chem. Commun.* ***1969***, 202; Lemal, D.M.; Staros, J.V.; Austel, V. *J. Am. Chem. Soc.* ***1969***, *91*, 3373.

1,2,5-tri-*tert*-butyl[2.2.0]hexadiene (**105**, a Dewar benzene).[494] The reaction owes its success to the fact that once **105** is formed, it cannot, under the conditions used, revert to **104** by either a thermal or a photochemical route. The orbital-symmetry rules prohibit thermal conversion of **105** to **104** by a pericyclic mechanism, because thermal conversion of a cyclobutene to a 1,3-diene must be conrotatory, and conrotatory reaction of **105** would result in a 1,3,5-cyclohexatriene containing one trans double bond (**106**), which is of course too strained to exist. Compound **105** cannot revert to **104** by a photochemical pathway either, because light of the frequency used to excite **104** would not be absorbed by **105**. This is thus another example of a molecule that owes its stability to the orbital-symmetry rules (see p. 1232). Pyrolysis of **105** does give **104** , probably by a diradical mechanism.[495] In the case of **107** and **108**, the Dewar benzene is actually more stable than the benzene. Compound **107** rearranges to **108** in 90% yield at 120°C.[496] In this case, thermolysis of the benzene gives the Dewar benzene (rather than the reverse), because of the strain of four adjacent *tert*-butyl groups on the ring.



107 **108**

A number of electrocyclic reactions have been carried out with systems of other sizes, for example, conversion of the 1,3,5,7-octatetraene **109** to the cyclooctatriene **110**.[497] The stereochemistry of these reactions can be predicted in a



109 **110**

[494]Wilzbach, K.E.; Kaplan, L. *J. Am. Chem. Soc.* ***1965***, *87*, 4004; van Tamelen, E.E.; Pappas, S.P.; Kirk, K.L. *J. Am. Chem. Soc.* ***1971***, *93*, 6092; van Tamelen, E.E. *Acc. Chem. Res.* ***1972***, *5*, 186. As mentioned on p. $$$ (Lemal, D.M.; Lokensgard, J.P. *J. Am. Chem. Soc.* ***1966***, *88*, 5934; Schäfer, W.; Criegee, R.; Askani, R.; Grüner, H. *Angew. Chem. Int. Ed.* ***1967***, *6*, 78), Dewar benzenes can be photolyzed further to give prismanes.

[495]See, for example, Oth, J.F.M. *Recl. Trav. Chim. Pays-Bas* ***1968***, *87*, 1185; Adam, W.; Chang, J.C. *Int. J. Chem. Kinet.*, ***1969***, *1*, 487; Lechtken, P.; Breslow, R.; Schmidt, A.H.; Turro, N.J. *J. Am. Chem. Soc.* ***1973***, *95*, 3025; Wingert, H.; Irngartinger, H.; Kallfass, D.; Regitz, M. *Chem. Ber.* ***1987***, *120*, 825.

[496]Maier, G.; Schneider, K. *Angew. Chem. Int. Ed.* ***1980***, *19*, 1022. See also, Wingert, H.; Maas, G.; Regitz, M. *Tetrahedron* ***1986***, *42*, 5341.

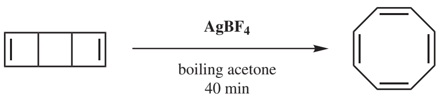
[497]Marvell, E.N.; Seubert, J. *J. Am. Chem. Soc.* ***1967***, *89*, 3377; Huisgen, R.; Dahmen, A.; Huber, H. *J. Am. Chem. Soc.* ***1967***, *89*, 7130, *Tetrahedron Lett.* ***1969***, 1461; Dahmen, A.; Huber, H. *Tetrahedron Lett.* ***1969***, 1465.

similar manner. The results of such predictions can be summarized according to whether the number of electrons involved in the cyclic process is of the form 4*n* or 4*n* + 2 (where *n* is any integer including zero).

	Thermal Reaction	Photochemical Reaction
4*n*	Conrotatory	Disrotatory
4*n* + 2	Disrotatory	Conrotatory

Although the orbital-symmetry rules predict the stereochemical results in almost all cases, it is necessary to recall (p. 1210) that they only say what is allowed and what is forbidden, but the fact that a reaction is allowed does not necessarily mean that the reaction takes place, and if an allowed reaction does take place, it does not *necessarily* follow that a concerted pathway is involved, since other pathways of lower energy may be available.[498] Furthermore, a "forbidden" reaction might still be made to go, if a method of achieving its high activation energy can be found. This was, in fact, done for the cyclobutene butadiene interconversion (*cis*-3,4-dichlorocyclobutene gave the forbidden *cis*,-*cis*- and *trans*,*trans*-1,4-dichloro-1,3-butadienes, as well as the allowed cis, trans isomer) by the use of ir laser light.[499] This is a thermal reaction. The laser light excites the molecule to a higher vibrational level (p. 330), but not to a higher electronic state.

As is the case for [2+2]-cycloaddition reactions (**15-63**), certain forbidden electrocyclic reactions can be made to take place by the use of metallic catalysts.[500] An example is the silver ion-catalyzed conversion of tricyclo[4.2.0.0^{2,5}]octa-3,7-diene to cyclooctatetraene:[501]



This conversion is very slow thermally (i.e., without the catalyst) because the reaction must take place by a disrotatory pathway, which is disallowed thermally.[502] In another example, the major thermal product from the barrelene anion is a

[498]For a discussion, see Baldwin, J.E.; Andrist, A.H.; Pinschmidt Jr., R.K. *Acc. Chem. Res.* ***1972***, *5*, 402.

[499]Mao, C.; Presser, N.; John, L.; Moriarty, R.M.; Gordon, R.J. *J. Am. Chem. Soc.* ***1981***, *103*, 2105.

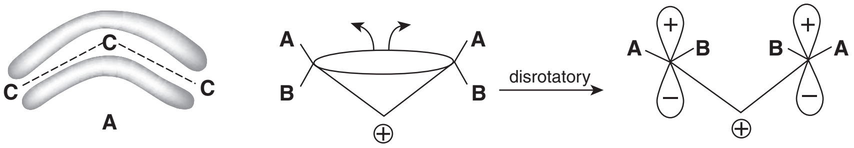
[500]For a review, see Pettit, R.; Sugahara, H.; Wristers, J.; Merk, W. *Discuss. Faraday Soc.* ***1969***, *47*, 71. See also, Labunskaya, V.I.; Shebaldova, A.D.; Khidekel', M.L. *Russ. Chem. Rev.* ***1974***, *43*, 1; Mango, F.D. *Top. Curr. Chem.* ***1974***, *45*, 39; *Tetrahedron Lett.* ***1973***, 1509; *Intra-Sci. Chem. Rep.* ***1972***, *6 (3)*, 171; *CHEMTECH* ***1971***, *1*, 758; *Adv. Catal.* ***1969***, *20*, 291; Mango, F.D.; Schachtschneider, J.H. *J. Am. Chem. Soc.* ***1971***, *93*, 1123; ***1969***, *91*, 2484; van der Lugt, W.T.A.M. *Tetrahedron Lett.* ***1970***, 2281; Wristers, J.; Brener, L.; Pettit, R. *J. Am. Chem. Soc.* ***1970***, *92*, 7499.

[501]Merk, W.; Pettit, R. *J. Am. Chem. Soc.* ***1967***, *89*, 4788.

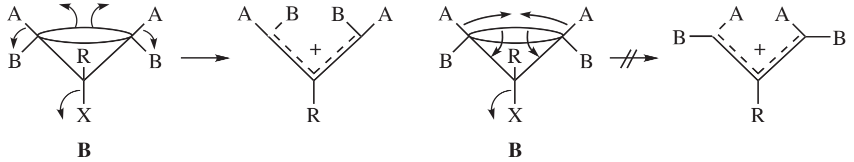
[502]For discussions of how these reactions take place, see Slegeir, W.; Case, R.; McKennis, J.S.; Pettit, R. *J. Am. Chem. Soc.* ***1974***, *96*, 287; Pinhas, A.R.; Carpenter, B.K. *J. Chem. Soc., Chem. Commun.* ***1980***, 15.

rearranged allyl anion that is formed by disrotatory cleavage of the cyclopropyl ring, a formally Woodward–Hoffmann-forbidden process.[503]

The ring opening of cyclopropyl cations (pp. 486, 1591) is an electrocyclic reaction and is governed by the orbital symmetry rules.[504] For this case, we invoke the rule that the *s* bond opens in such a way that the resulting *p* orbitals have the symmetry of the highest occupied orbital of the product, in this case, an allylic cation. We may recall that an allylic system has three molecular orbitals (p. 42). For the cation, with only two electrons, the highest occupied orbital is the one of the lowest energy (A). Thus, the cyclopropyl cation must undergo a



disrotatory ring opening in order to maintain the symmetry. (Note that, in contrast, ring opening of the cyclopropyl *anion* must be conrotatory,[505] since in this case it is the next orbital of the allylic system that is the highest occupied, and this has the opposite symmetry.[506]) However, it is very difficult to generate a free cyclopropyl cation (p. 487), and it is likely that in most cases, cleavage of the σ bond is concerted with departure of the leaving group in the original cyclopropyl substrate. This, of course, means that the σ bond provides anchimeric assistance to the removal of the leaving group (an S_N2-type process), and we would expect that such assistance should come from the back side. This has an important effect on the direction of ring opening. The orbital-symmetry rules require that the ring opening be disrotatory, but as we have seen, there are two disrotatory pathways and the rules do not tell us which is preferred. But the fact that the *s* orbital provides assistance from the backside means that the two substituents that are trans to the leaving group must move *outward*, not inward.[507] Thus, the disrotatory pathway that is followed is the one shown in B, not the one shown in C, because the former puts the electrons of the σ bond on the



[503]Leivers, M.; Tam, I.; Groves, K.; Leung, D.; Xie, Y.; Breslow, R. *Org. Lett.* ***2003***, *5*, 3407.

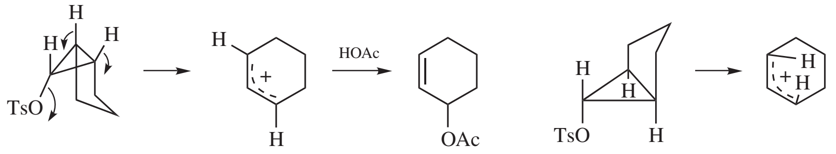
[504]For discussions, see DePuy, C.H. *Acc. Chem. Res.* ***1968***, *1*, 33; Schöllkopf, U. *Angew. Chem. Int. Ed.* ***1968***, *7*, 588.

[505]For a review of ring opening of cyclopropyl anions and related reactions, see Boche, G. *Top. Curr. Chem.* ***1988***, *146*, 1.

[506]For evidence that this is so, see Newcomb, M.; Ford, W.T. *J. Am. Chem. Soc.* ***1974***, *96*, 2968; Boche, G.; Buckl, K.; Martens, D.; Schneider, D.R.; Wagner, H. *Chem. Ber.* ***1979***, *112*, 2961; Coates, R.M.; Last, L.A. *J. Am. Chem. Soc.* ***1983***, *105*, 7322. For a review of the analogous ring opening of epoxides, see Huisgen, R. *Angew. Chem. Int. Ed.* ***1977***, *16*, 572.

[507]This was first proposed by DePuy, C.H.; Schnack, L.G.; Hausser, J.W.; Wiedemann, W. *J. Am. Chem. Soc.* ***1965***, *87*, 4006.

side opposite that of the leaving group.[508] Strong confirmation of this picture[509] comes from acetolysis of *endo*- (**111**) and *exo*-bicyclo[3,1,0]hexyl-6-tosylate (**112**). The groups trans to the tosylate must move outward. For **111**, this means that the two hydrogens can go outside the framework of the six-membered ring, but for **112** they



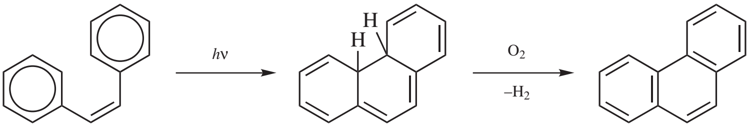
111 **112**

are forced to go inside. Consequently, it is not surprising that the rate ratio for solvolysis of **111/112** was found to be >2.5 × 10^6 and that at 150°C **112** did not solvolyze at all.[510] This evidence is kinetic. Unlike the cases of the cyclobutene (1,3-diene and cyclohexadiene) 1,3,5-triene interconversions, the direct product here is a cation, which is not stable but reacts with a nucleophile and loses some of its steric integrity in the process, so that much of the evidence has been of the kinetic type rather than from studies of product stereochemistry. However, it has been shown by investigations in superacids, where it is possible to keep the cations intact and to study their structures by NMR, that in all cases studied the cation that is predicted by these rules is in fact formed.[511]

OS **V**, 235, 277, 467; **VI**, 39, 145, 196, 422, 427, 862; **IX**, 180.

18-28 Conversion of One Aromatic Compound to Another

(6)*cyclo*-de-hydrogen-coupling (Overall transformation)



Stilbenes can be converted to phenanthrenes by irradiation with UV light[512] in the presence of an oxidizing agent, such as dissolved molecular oxygen, $FeCl_3$,

[508]It has been suggested that the pathway shown in **C** is possible in certain cases: Hausser, J.W.; Grubber, M.J. *J. Org. Chem.* ***1972***, *37*, 2648; Hausser, J.W.; Uchic, J.T. *J. Org. Chem.* ***1972***, *37*, 4087.

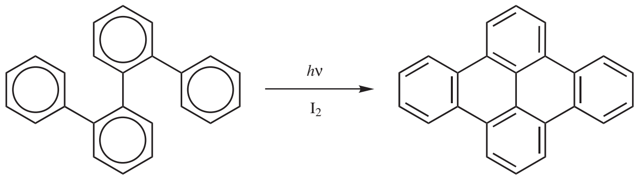
[509]There is much other evidence. For example, see Jefford, C.W.; Medary, R. *Tetrahedron Lett.* ***1966***, 2069; Jefford, C.W.; Wojnarowski, W. *Tetrahedron Lett.* ***1968***, 199; Sliwinski, W.F.; Su, T.M.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1972***, *94*, 133; Sandler, S.R. *J. Org. Chem.* ***1967***, *32*, 3876; Ghosez, L.; Slinckx, G.; Glineur, M.; Hoet, P.; Laroche, P. *Tetrahedron Lett.* ***1967***, 2773; Parham, W.E.; Yong, K.S. *J. Org. Chem.* ***1968***, *33*, 3947; Reese, C.B.; Shaw, A. *J. Am. Chem. Soc.* ***1970***, *92*, 2566; Dolbier, Jr., W.R.; Phanstiel, O. *Tetrahedron Lett.* ***1988***, *29*, 53.

[510]Schöllkopf, U.; Fellenberger, K.; Patsch, M.; Schleyer, P.v.R.; Su, T.M.; Van Dine, G.W. *Tetrahedron Lett.* ***1967***, 3639.

[511]Schleyer, P.v.R.; Su, T.M.; Saunders, M.; Rosenfeld, J.C. *J. Am. Chem. Soc.* ***1969***, *91*, 5174.

[512]For reviews, see Mallory, F.B.; Mallory, C.W. *Org. React.* ***1984***, *30*, 1; Laarhoven, W.H. *Recl. Trav. Chim. Pays-Bas* ***1983***, *102*, 185, 241; Blackburn, E.V.; Timmons, C.J. *Q. Rev. Chem. Soc.* ***1969***, *23*, 482; Stermitz, L.F. *Org. Photochem.* ***1967***, *1*, 247. For a review of electrocyclizations of conjugated aryl olefins in general, see Laarhoven, W.H. *Org. Photochem.* ***1989***, *10*, 163.

Pd–C,[513] or iodine.[514] The reaction is a photochemically allowed conrotatory[515] conversion of a 1,3,5-hexatriene to a cyclohexadiene, followed by removal of two hydrogen atoms by the oxidizing agent. The intermediate dihydrophenanthrene has been isolated.[516] The use of substrates containing heteroatoms (e.g., PhN=NPh) allows the formation of heterocyclic ring systems. The actual reacting species must be the *cis*-stilbene, but *trans*-stilbenes can often be used, because they are isomerized to the cis isomers under the reaction conditions. The reaction can be extended to the preparation of many fused aromatic systems, for example,[517]



though not all such systems give reaction.[518]

Isomerization of biphenylene to benzo[*a*]pentalene[519] is a well-known benzene ring contraction rearrangement,[520] driven by relief of strain in the four-membered ring. Related to this process is the FVP of the alternant polycyclic aromatic hydrocarbon benzo[*b*]biphenylene at 1100°C, which gives fluoranthene, a nonalternant polycyclic aromatic hydrocarbon, as the major product at 1100°C in the gas phase.[521] The mechanism used explain that this isomerization involves equilibrating diradicals of 2-phenylnaphthalene, which rearrange by the net migration of a phenyl group to give equilibrating diradicals of 1-phenylnaphthalene, one isomer of which then cyclizes to fluoranthene.

Another transformation of one aromatic compound to another is the *Stone–Wales rearrangement* of pyracyclene (**113**),[522] which is a bond-switching reaction. The rearrangement of bifluorenylidene (**114**) to dibenzo[*g,p*]chrysene (**115**) occurs at temperatures as low as 400°C and is accelerated in the presence of decomposing iodomethane, a convenient source of methyl radicals.[523] This result suggested a

[513]Rawal, V.H.; Jones, R.J.; Cava, M.P. *Tetrahedron Lett.* ***1985***, *26*, 2423.

[514]For the use of iodine plus propylene oxide in the absence of air, see Liu, L.; Yang, B.; Katz, T.J.; Poindexter, M.K. *J. Org. Chem.* ***1991***, *56*, 3769.

[515]Cuppen, T.J.H.M.; Laarhoven, W.H. *J. Am. Chem. Soc.* ***1972***, *94*, 5914.

[516]Doyle, T.D.; Benson, W.R.; Filipescu, N. *J. Am. Chem. Soc.* ***1976***, *98*, 3262.

[517]Sato, T.; Shimada, S.; Hata, K. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 2484.

[518]For a discussion and lists of photocyclizing and nonphotocyclizing compounds, see Laarhoven, W.H. *Recl. Trav. Chim. Pays-Bas* ***1983***, *102*, 185, 185–204.

[519]Wiersum, U.E.; Jenneskens, L.W. *Tetrahedron Lett.* ***1993***, *34*, 6615; Brown, R.F.C.; Choi, N.; Coulston, K.J.; Eastwood, F.W.; Wiersum, U.E.; Jenneskens, L.W. *Tetrahedron Lett.* ***1994***, *35*, 4405.

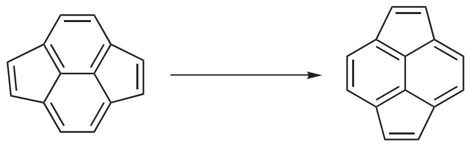
[520]Scott, LT.; Roelofs, N.H. *J. Am. Chem. Soc.* ***1987***, *109*, 5461; Scott, L.T.; Roelofs, N.H. *Tetrahedron Lett.* ***1988***, *29*, 6857; Anderson, M.R.; Brown, R.F.C.; Coulston, K.J.; Eastwood, F.W.; Ward, A. *Aust. J. Chem.* ***1990***, *43*, 1137; Brown, R F.C.; Eastwood, F.W.; Wong, N.R. *Tetrahedron Lett.* ***1993***, *34*, 3607.

[521]Preda, D.V.; Scott, L.T. *Org. Lett.* ***2000***, *2*, 1489.

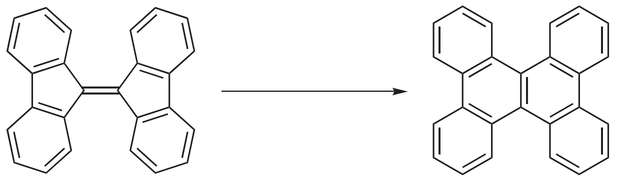
[522]Stone, A.J.; Wales, D.J. *Chem. Phys. Lett.* ***1986***, *128*, 501.

[523]Alder, R.W.; Whittaker, G. *J. Chem. Soc., Perkin Trans. 2* ***1975***, 712

radical rearrangement. This rearrangement is believed to occur by a radical-promoted mechanism consisting of a sequence of homoallyl–cyclopropylcarbinyl rearrangement steps.[524]



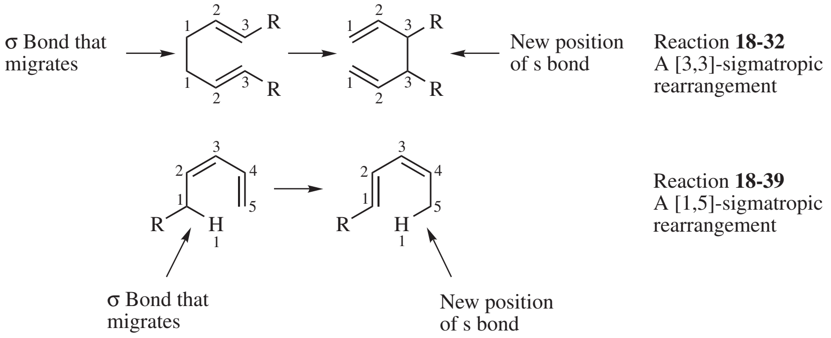
113



114 **115**

B. Sigmatropic Rearrangements

A sigmatropic rearrangement is defined[525] as migration, in an uncatalyzed intramolecular process, of a σ bond, adjacent to one or more π systems, to a new position in a molecule, with the π systems becoming reorganized in the process. Examples are



The *order* of a sigmatropic rearrangement is expressed by two numbers set in brackets: [*i*,*j*]. These numbers can be determined by counting the atoms over which each end of the σ bond has moved. Each of the original termini is given the number 1. Thus in the first example above, each terminus of the σ bond has

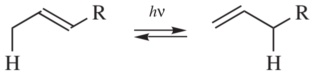
[524]Alder, R.W.; Harvey, J. N. *J. Am. Chem. Soc.* ***2004***, *126*, 2490.

[525]Woodward, R.B.; Hoffmann, R. *The Conservation of Orbital Symmetry*, Academic Press, NY, ***1970***, p. 114.

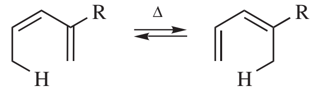
migrated from C-1 to C-3, so the order is [3,3]. In the second example, the carbon terminus has moved from C-1 to C-5, but the hydrogen terminus has not moved at all, so the order is [1,5].

18-29 [1,*j*]-Sigmatropic Migrations of Hydrogen

1/ → 3/Hydrogen-migration; 1/ → 5/Hydrogen-migration



[1,3]



[1,5]

Many examples of thermal or photochemical rearrangements in which a hydrogen atom migrates from one end of a system of π bonds to the other have been reported,[526] although the reaction is subject to geometrical conditions. Isotope effects play a role in sigmatropic rearrangements, and there is evidence for a kinetic silicon isotope effect.[527] Pericyclic mechanisms are involved,[528] and the hydrogen must, in the transition state, be in contact with both ends of the chain at the same time. This means that for [1,5] and longer rearrangements, the molecule must be able to adopt the cisoid conformation. Furthermore, there are two geometrical pathways by which any sigmatropic rearrangement can take place, which we illustrate for the case of a [1,5]-sigmatropic rearrangement,[529] starting with a substrate of the form **116**, where the migration origin is an asymmetric carbon atom and U ≠ V. In one of the two pathways, the hydrogen moves along the top or bottom face of the π system. This is called *suprafacial migration*. In the other pathway, the hydrogen moves *across* the π system, from top to bottom, or vice versa. This is *antarafacial* migration. Altogether, a single isomer like **116** (different rotamers) can give four products. In a suprafacial migration, H can move across the top of the π system (as drawn above) to give the (*R*,*Z*) isomer, or it can rotate 180° and move across the bottom of the π system to give the (*S*,*E*) isomer.[530] The antarafacial migration can similarly lead to two diastereomers, in

[526]For a monograph, see Gajewski, J.J. *Hydrocarbon Thermal Isomerizations*, Academic Press, NY, ***1981***. For reviews, see Mironov, V.A.; Fedorovich, A.D.; Akhrem, A.A. *Russ. Chem. Rev.* ***1981***, *50*, 666; Spangler, C.W. *Chem. Rev.* ***1976***, *76*, 187; DeWolfe, R.H., in Bamford, C.H.; Tipper, C.F.H. *Comprehensieve Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 474–480; Woodward, R.B.; Hoffmann, R. *The Conservation of Orbital Symmetry*, Academic Press, NY, ***1970***, pp. 114–140; Hansen, H.; Schmid, H. *Chimia*, ***1970***, *24*, 89; Roth, W.R. *Chimia*, ***1966***, *20*, 229.

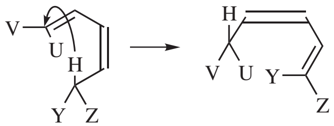
[527]Lin, Y.-L.; Turos, E. *J. Am. Chem. Soc.* ***1999***, *121*, 856.

[528]For a discussion of catalysts that induce pericyclic rearrangements, see Moss, S.; King, B.T.; de Meijere, A.; Kozhushkov, S.I.; Eaton, P.E.; Michl, J. *Org. Lett.* ***2001***, *3*, 2375.

[529]Note that a [1,5]-sigmatropic rearrangement of hydrogen is also an internal ene synthesis (**15-20**).

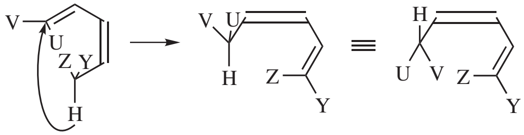
[530]Since we are using the arbitrary designations U, V, Y, and Z, we have been arbitrary in which isomer to call (*R*,*Z*) and which to call (*S*,*E*).

this case the (*S*,*Z*) and (*R*,*E*) isomers.



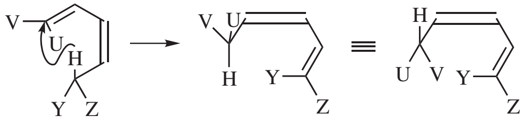
Suprafacial

116 (*R*, *Z*) Isomer



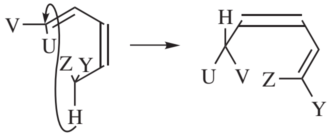
Suprafacial

116 (*S*,*E*) Isomer



Antarafacial

116 (*S*, *Z*) Isomer



Antarafacial

116 (*R*,*E*) Isomer

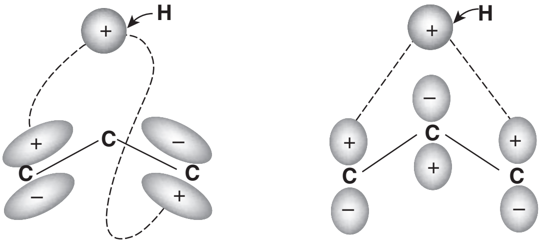
In any given sigmatropic rearrangement, only one of the two pathways is allowed by the orbital-symmetry rules; the other is forbidden. To analyze this situation, first we use a modified frontier orbital approach.[531] We will imagine that in the transition state **C**, the migrating H atom breaks away from the rest of the system, which we may treat as if it were a free radical.

C

Imaginary
transition state
for a [1,3]-
sigmatropic
rearrangement

[531]See Woodward, R.B.; Hoffmann, R. *The Conservation of Orbital Symmetry*, Academic Press, NY, ***1970***, pp. 114–140.

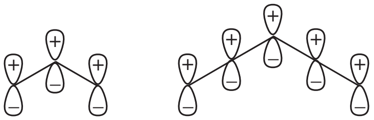
Note that this is not what actually takes place; we merely imagine it in order to be able to analyze the process. In a [1,3]-sigmatropic rearrangement, the imaginary transition state consists of a hydrogen atom and an allyl radical. The latter species (p. 42) has three π orbitals, but the only one that concerns us here is the HOMO which, in a thermal rearrangement is **D**. The electron of the hydrogen atom is of course in a 1*s* orbital, which has only one lobe. The rule governing sigmatropic migration of hydrogen is *the H must move from a plus to a plus or from a minus to a minus*



D E

lobe, of the HOMO; it cannot move to a lobe of opposite sign.[532] Obviously, the only way this can happen in a thermal [1,3]-sigmatropic rearrangement is if the migration is antarafacial. Consequently, the rule predicts that antarafacial thermal [1,3]-sigmatropic rearrangements are allowed, but the suprafacial pathway is forbidden. However, in a photochemical reaction, promotion of an electron means that **E** is now the HOMO; the suprafacial pathway is now allowed and the antarafacial pathway forbidden.

A similar analysis of [1,5]-sigmatropic rearrangements shows that in this case the thermal reaction must be suprafacial and the photochemical process antarafacial. For the general case, with odd-numbered *j*, we can say that [1,*j*]-suprafacial migrations are allowed thermally when *j* is of the form $4n + 1$, and photochemically when *j* has the form $4n - 1$; the opposite is true for antarafacial migrations.



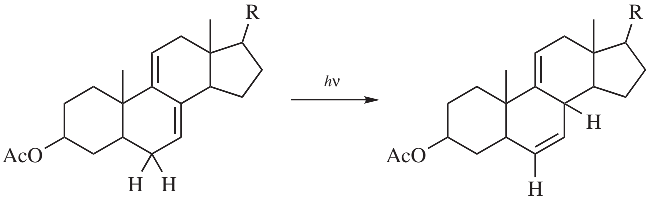
F G

As expected, the Möbius–Hückel method leads to the same predictions. Here, we look at the basis set of orbitals shown in **F** and **G** for [1,3]- and [1,5]-rearrangements, respectively. A [1,3]-shift involves four electrons, so an allowed thermal pericyclic reaction must be a Möbius system (p. 1210) with one or an odd number

[532]This follows from the principle that bonds are formed only by overlap of orbitals of the same sign. Since this is a concerted reaction, the hydrogen orbital in the transition state must overlap simultaneously with one lobe from the migration origin and one from the terminus. It is obvious that both of these lobes must have the same sign.

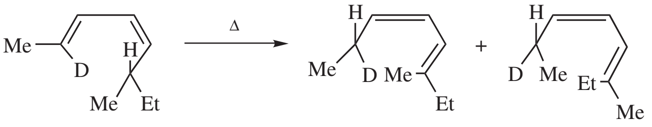
of sign inversions. As can be seen in **F**, only an antarafacial migration can achieve this. A [1,5]-shift, with six electrons, is allowed thermally only when it is a Hückel system with zero or an even number of sign inversions; hence it requires a suprafacial migration.[533]

The actual reported results bear out this analysis. Thus a thermal [1,3] migration is allowed to take place only antarafacially, but such a transition state would be extremely strained, and thermal [1,3]-sigmatropic migrations of hydrogen are unknown.[534] On the other hand, the photochemical pathway allows suprafacial [1,3]-shifts, and a few such reactions are known, an example being the photochemical rearrangement of **117** to **118**.[535] Substituents influence the efficacy of the [1,3]-hydrogen shift.[536]

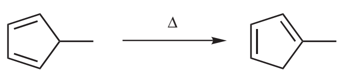


117 **118**

The situation is reversed for [1,5]-hydrogen shifts. In this case the thermal rearrangements, being suprafacial, are quite common, while photochemical rearrangements are rare.[537] Two examples of the thermal reaction are



Ref. [538]



Ref. [539]

[533]For a discussion of the origins for the preference for orbital-symmetry forbidden reactions and the stereochemistry of [1,5]-sigmatropic shifts, see Kless, A.; Nendel, M.; Wilsey, S.; Houk, K.N. *J. Am. Chem. Soc.* ***1999***, *121*, 4524.

[534]A possible [1,3]-migration of hydrogen has been reported. See Yeh, M.; Linder, L.; Hoffman, D.K.; Barton, T.J. *J. Am. Chem. Soc.* ***1986***, *108*, 7849. See also, Pasto, D.J.; Brophy, J.E. *J. Org. Chem.* ***1991***, *56*, 4554.

[535]Dauben, W.G.; Wipke, W.T. *Pure Appl. Chem.* ***1964***, *9*, 539, 546. For another example, see Kropp, P.J.; Fravel, Jr., H.G.; Fields, T.R. *J. Am. Chem. Soc.* ***1976***, *98*, 840.

[536]Hudson, C.E.; McAdoo, D.J. *J. Org. Chem.* ***2003***, *68*, 2735.

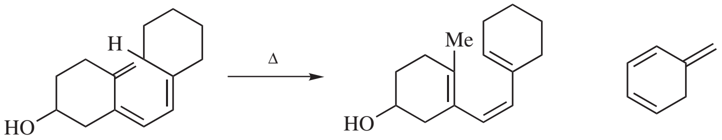
[537]For examples of photochemical [1,5]-antarafacial reactions, see Kiefer, E.F.; Tanna, C.H. *J. Am. Chem. Soc.* ***1969***, *91*, 4478; Kiefer, E.F.; Fukunaga, J.Y. *Tetrahedron Lett.* ***1969***, 993; Dauben, W.G.; Poulter, C.D.; Suter, C. *J. Am. Chem. Soc.* ***1970***, *92*, 7408.

[538]Roth, W.R.; König, J.; Stein, K. *Chem. Ber.* ***1970***, *103*, 426.

[539]McLean, S.; Haynes, P. *Tetrahedron* ***1965***, *21*, 2329. For a review of such rearrangements, see Klärner, F. *Top. Stereochem.* ***1984***, *15*, 1. For a discussion of [1,5]-sigmatropic hydrogen shifts in cyclic 1,3-dienes, see Hess, Jr., B.A.; Baldwin, J.E. *J. Org. Chem.* ***2002***, *67*, 6025.

Note that the first example bears out the stereochemical prediction made earlier. Only the two isomers shown were formed. In the second example, migration can continue around the ring. Migrations of this kind are called *circumambulatory rearrangements*.[540] Such migrations are known for cyclopentadiene, pyrrole, and phosphole derivatives.[541] Geminal bond participation has been observed in pentadienes,[542] the effects of phenyl substituents have been studied,[543] and the kinetics and activation parameters of [1,5] hydrogen shifts have been examined.[544] The [1,5] hydrogen shifts are also known with vinyl aziridines.[545]

The rare [1,4]-hydrogen transfer has been observed in radical cyclizations.[546] With respect to [1,7]-hydrogen shifts, the rules predict the thermal reaction to be antarafacial.[547] Unlike the case of [1,3]-shifts, the transition state is not too greatly strained, and an example of such rearrangements is the formation of **119** and **120**.[548] Photochemical [1,7]-shifts are suprafacial and, not surprisingly, many of these have been observed.[549]



119 **120**

The orbital symmetry rules also help us to explain, as on pp. 1232 and 1642, the unexpected stability of certain compounds. Thus, **120** could, by a thermal [1,3]-sigmatropic rearrangement, easily convert to toluene, which of course is far more stable because it has an aromatic sextet. Yet, **120** has been prepared and is stable at dry ice temperature and in dilute solutions.[550]

[540]For a review, see Childs, R.F. *Tetrahedron* ***1982***, *38*, 567. See also, Minkin, V.I.; Mikhailov, I.E.; Dushenko, G.A.; Yudilevich, J.A.; Minyaev, R.M.; Zschunke, A.; Mügge, K. *J. Phys. Org. Chem.* ***1991***, *4*, 31. For a study of [1,5]-sigmatropic shiftamers, see Tantillo, D.J.; Hoffmann, R. *Eur. J. Org. Chem.* ***2004***, 273.

[541]Bachrach, S.M. *J. Org. Chem.* ***1993***, *58*, 5414.

[542]Ikeda, H.; Ushioda, N.; Inagaki, S. *Chem. Lett.* ***2001***, 166.

[543]Hayase, S.; Hrovat, D.A.; Borden, W.T. *J. Am. Chem. Soc.* ***2004***, *126*, 10028.

[544]Baldwin, J.E.; Raghavan, A.S. *J. Org. Chem.* ***2004***, *69*, 8128.

[545]Åhman, J.; Somfai, P.; Tanner, D. *J. Chem. Soc., Chem. Commun.* ***1994***, 2785; Somfai, P.; Åhman, J. *Tetrahedron Lett.* ***1995***, *36*, 1953.

[546]Journet, M.; Malacria, M. *Tetrahedron Lett.* ***1992***, *33*, 1893.

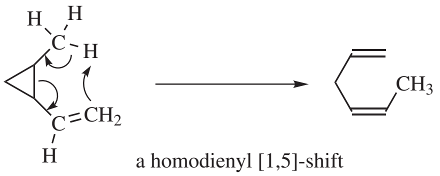
[547]For a computational study that supports tunneling in thermal [1,7]-hydrogen shifts see Hess, Jr., B.A. *J. Org. Chem.* ***2001***, *66*, 5897.

[548]Gurskii, M.E.; Gridnev, I.D.; Il'ichev, Y.V.; Ignatenko, A.V.; Bubnov, Y.N. *Angew. Chem. Int. Ed.* ***1992***, *31*, 781; Baldwin, J.E.; Reddy, V.P. *J. Am. Chem. Soc.* ***1987***, *109*, 8051; ***1988***, *110*, 8223.

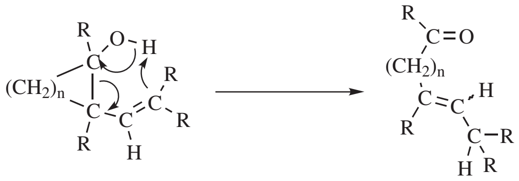
[549]See Murray, R.W.; Kaplan, M.L. *J. Am. Chem. Soc.* ***1966***, *88*, 3527; ter Borg, A.P.; Kloosterziel, H. *Recl. Trav. Chim. Pays-Bas* ***1969***, *88*, 266; Tezuka, T.; Kimura, M.; Sato, A.; Mukai, T. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 1120.

[550]Bailey, W.J.; Baylouny, R.A. *J. Org. Chem.* ***1962***, *27*, 3476.

Analogs of sigmatropic rearrangements in which a cyclopropane ring replaces one of the double bonds are also known, for example,[551]

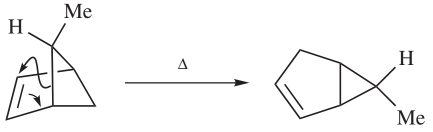


The reverse reaction has also been reported.[552] 2-Vinylcycloalkanols[553] undergo an analogous reaction, as do cyclopropyl ketones (see p. 1673 for this reaction).



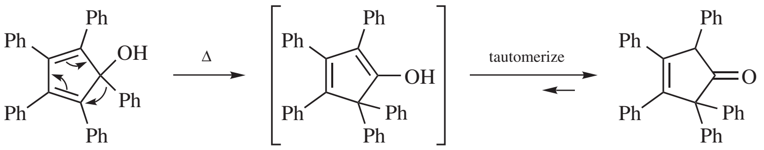
18-30 [1,*j*]-Sigmatropic Migrations of Carbon

[1,3] migration of alkyl



Ref. [554]

[1,5] migration of phenyl



Ref. [555]

[551]Frey, H.M.; Solly, R.K. *Int. J. Chem. Kinet.*, ***1969***, *1*, 473; Roth, W.R.; König, J. *Liebigs Ann. Chem.* ***1965***, *688*, 28; Ohloff, G. *Tetrahedron Lett.* ***1965***, 3795; Jorgenson, M.J.; Thacher, A.F. *Tetrahedron Lett.* ***1969***, 4651; Corey, E.J.; Yamamoto, H.; Herron D.K.; Achiwa, K. *J. Am. Chem. Soc.* ***1970***, *92*, 6635; Loncharich, R.J.; Houk, K.N. *J. Am. Chem. Soc.* ***1988***, *110*, 2089; Parziale, P.A.; Berson, J.A. *J. Am. Chem. Soc.* ***1990***, *112*, 1650; Pegg, G.G.; Meehan, G.V. *Aust. J. Chem.* ***1990***, *43*, 1009, 1071.

[552]Roth, W.R.; König, J. *Liebigs Ann. Chem.* ***1965***, *688*, 28. Also see, Grimme, W. *Chem. Ber.* ***1965***, *98*, 756.

[553]Arnold, R.T.; Smolinsky, G. *J. Am. Chem. Soc.* ***1960***, *82*, 4918; Leriverend, P.; Conia, J.M. *Tetrahedron Lett.* ***1969***, 2681; Conia, J.M.; Barnier, J.P. *Tetrahedron Lett.* ***1969***, 2679.

[554]Roth, W.R.; Friedrich, A. *Tetrahedron Lett.* ***1969***, 2607.

[555]Youssef, A.K.; Ogliaruso, M.A. *J. Org. Chem.* ***1972***, *37*, 2601.

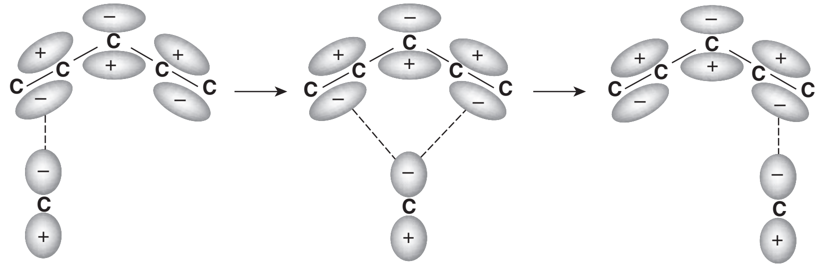


Fig. 18.5. Hypothetical orbital movement for a thermal [1,5]-sigmatropic migration of carbon. To move from one negative lobe, the migrating carbon uses only its own negative lobe, retaining its configuration.

Sigmatropic migrations of alkyl or aryl groups[556] are less common than the corresponding hydrogen migrations.[557] When they do take place, there is an important difference. Unlike a hydrogen atom, whose electron is in a 1*s* orbital with only one lobe, a carbon free radical has its odd electron in a *p* orbital that has *two lobes of opposite sign*. Therefore, if we draw the imaginary transition states for this case (see p. 1650), we see that in a thermal suprafacial [1,5] process (Fig. 18.5), symmetry can be conserved only if the migrating carbon moves in such a way that the lobe which was originally attached to the π system remains attached to the π system.

This can happen only if configuration is *retained within the migrating group*. On the other hand, thermal suprafacial [1,3] migration (Fig. 18.6) *can* take place if the migrating carbon switches lobes. If the migrating carbon was originally bonded by its minus lobe, it must now use its plus lobe to form the new C–C bond. Thus, configuration in the migrating group will be *inverted*. From these considerations we predict that suprafacial [1,*j*]-sigmatropic rearrangements in which carbon is the migrating group are always allowed, both thermally and photochemically, but that thermal [1,3] migrations will proceed with inversion and thermal [1,5]

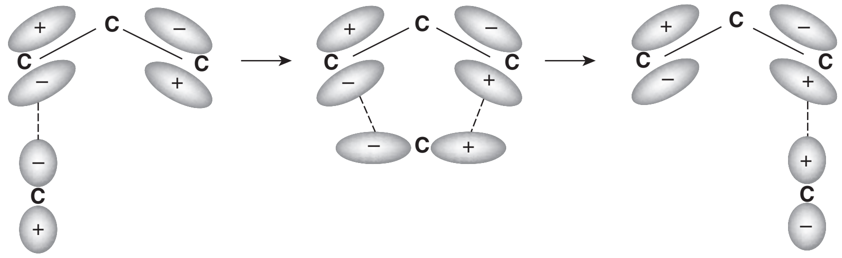
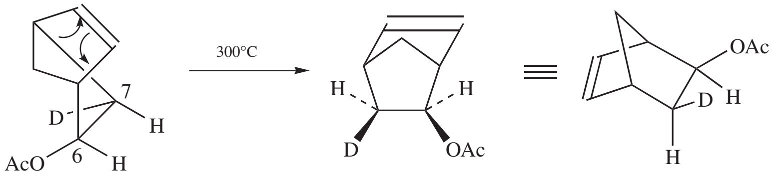


Fig. 18.6. Hypothetical orbital movement for a thermal [1,3]-sigmatropic migration of carbon. The migrating carbon moves a negative to a positive lobe, requiring it to switch its own bonding lobe from negative to positive, inverting its configuration.

[556]For reviews, see Mironov, V.A.; Fedorovich, A.D.; Akhrem, A.A. *Russ. Chem. Rev.* ***1981***, *50*, 666; Spangler, C.W. *Chem. Rev.* ***1976***, *76*, 187

[557]It has been shown that methyl and phenyl have lower migratory aptitudes than hydrogen in thermal sigmatropic rearrangements: Shen, K.; McEwen, W.E.; Wolf, A.P. *Tetrahedron Lett.* ***1969***, 827; Miller, L.L.; Greisinger, R.; Boyer, R.F. *J. Am. Chem. Soc.* ***1969***, *91*, 1578.

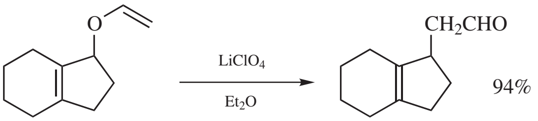
migrations with retention of configuration within the migrating group. More generally, we can say that suprafacial [1,*j*] migrations of carbon in systems where $j = 4n - 1$ proceed with inversion thermally and retention photochemically, while systems where $j = 4n + 1$ show the opposite behavior. Where antarafacial migrations take place, all these predictions are of course reversed.



121 **122**

The first laboratory test of these predictions was the pyrolysis of deuterated *endo*-bicyclo[3.2.0]hept-2-en-6-yl acetate (**121**), which gave the *exo*-deuterio-*exo*-norbornyl acetate **122**.[558] Thus, as predicted by the orbital symmetry rules, this thermal suprafacial [1,3]-sigmatropic reaction took place with complete inversion at C-7. Similar results have been obtained in a number of other cases.[559] However, similar studies of the pyrolysis of the parent hydrocarbon of **121**, labeled with D at C-6 and C-7, showed that while most of the product was formed with inversion at C-7, a significant fraction (11–29%) was formed with retention.[560] Other cases of lack of complete inversion are also known.[561] A diradical mechanism has been invoked to explain such cases.[562] There is strong evidence for a radical mechanism for some [1,3]-sigmatropic rearrangements.[563] Photochemical suprafacial [1,3] migrations of carbon have been shown to proceed with retention, as predicted.[564]

Although allylic vinylic ethers generally undergo [3,3]-sigmatropic rearrangements (**18-33**), they can be made to give the [1,3] kind, to give aldehydes, for example,



[558]Berson, J.A.; Nelson, G.L. *J. Am. Chem. Soc.* ***1967***, *89*, 5503; Berson, J.A. *Acc. Chem. Res.* ***1968***, *1*, 152.

[559]See Roth, W.R.; Friedrich, A. *Tetrahedron Lett.* ***1969***, 2607; Berson, J.A. *Acc. Chem. Res.* ***1972***, *5*, 406; Bampfield, H.A.; Brook, P.R.; Hunt, K. *J. Chem. Soc., Chem. Commun.* ***1976***, 146; Franzus, B.; Scheinbaum, M.L.; Waters, D.L.; Bowlin, H.B. *J. Am. Chem. Soc.* ***1976***, *98*, 1241; Klärner, F.; Adamsky, F. *Angew. Chem. Int. Ed.* ***1979***, *18*, 674.

[560]Baldwin, J.E.; Belfield, K.D. *J. Am. Chem. Soc.* ***1988***, *110*, 296; Klärner, F.; Drewes, R.; Hasselmann, D. *J. Am. Chem. Soc.* ***1988***, *110*, 297.

[561]See, for example, Berson, J.A.; Holder, R.W. *J. Am. Chem. Soc.* ***1973***, *95*, 2037; Pikulin, S.; Berson, J.A. *J. Am. Chem. Soc.* ***1988***, *110*, 8500.

[562]See Newman-Evans, R.H.; Carpenter, B.K. *J. Am. Chem. Soc.* ***1984***, *106*, 7994; Pikulin, S.; Berson, J.A. *J. Am. Chem. Soc.* ***1988***, *110*, 8500. See also, Berson, J.A. *Chemtracts: Org. Chem.* ***1989***, *2*, 213.

[563]See, for example, Bates, G.S.; Ramaswamy, S. *Can. J. Chem.* ***1985***, *63*, 745; Dolbier, W.B.; Phanstiel IV, O. *J. Am. Chem. Soc.* ***1989***, *111*, 4907.

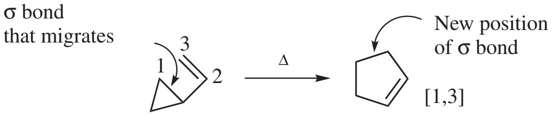
[564]Cookson, R.C.; Hudec, J.; Sharma, M. *Chem. Commun.* ***1971***, 107, 108.

by treatment with $LiClO_4$ in diethyl ether.[565] In this case, the C–O bond undergoes a 1,3 migration from the O to the end vinylic carbon. When the vinylic ether is of the type ROCR'=CH_2, ketones RCH_2COR' are formed. There is evidence that this [1,3]-sigmatropic rearrangement is not concerted, but involves dissociation of the substrate into ions.[565]

Thermal suprafacial [1,5] migrations of carbon have been found to take place with retention,[566] but also with inversion.[567] A diradical mechanism has been suggested for the latter case.[567]

Simple nucleophilic, electrophilic, and free-radical 1,2-shifts can also be regarded as sigmatropic rearrangements (in this case, [1,2]-rearrangements). We have already (p. $$$) applied similar principles to such rearrangements to show that nucleophilic 1,2-shifts are allowed, but the other two types are forbidden unless the migrating group has some means of delocalizing the extra electron or electron pair. The mechanism of the forbidden [3s,5s]-sigmatropic shift has been examined.[568]

18-31 Conversion of Vinylcyclopropanes to Cyclopentenes



The thermal expansion of a vinylcyclopropane to a cyclopentene ring[569] is a special case of a [1,3]-sigmatropic migration of carbon, although it can also be considered an internal $[_{\pi}2 + _{\sigma}2]$-cycloaddition reaction (see **15-63**). It is known as a *vinylcyclopropane rearrangement*.[570] The reaction has been carried out on many vinylcyclopropanes bearing various substituents in the ring[571] or

[565]Grieco, P.A.; Clark, J.D.; Jagoe, C.T. *J. Am. Chem. Soc.* ***1991***, *113*, 5488; Palani, N.; Balasubramanian, K.K. *Tetrahedron Lett.* ***1995***, *36*, 9527.

[566]Boersma, M.A.M.; de Haan, J.W.; Kloosterziel, H.; van de Ven, L.J.M. *Chem. Commun.* ***1970***, 1168.

[567]Klärner, F.; Yaslak, S.; Wette, M. *Chem. Ber.* ***1979***, *112*, 1168; Klärner, F.; Brassel, B. *J. Am. Chem. Soc.* ***1980***, *102*, 2469; Gajewski, J.J.; Gortva, A.M.; Borden, J.E. *J. Am. Chem. Soc.* ***1986***, *108*, 1083; Baldwin, J.E.; Broline, B.M. *J. Am. Chem. Soc.* ***1982***, *104*, 2857.

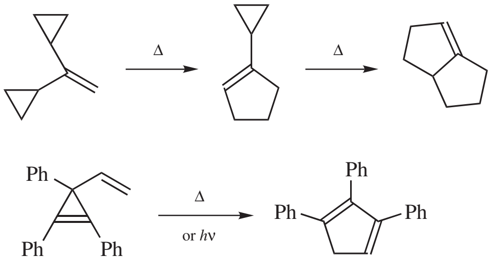
[568]Leach, A.G.; Catak, S.; Houk, K.N. *Chem. Eur. J.* ***2002***, *8*, 1290.

[569]For reviews, see Baldwin, J.E. *Chem. Rev.* ***2003***, *103*, 1197; Wong, H.N.C.; Hon, M.; Tse, C.; Yip, Y.; Tanko, J.; Hudlicky, T. *Chem. Rev.* ***1989***, *89*, 165, see pp. 169–172; Hudlicky, T.; Kutchan, T.M.; Naqvi, S.M. *Org. React.* ***1985***, *33*, 247; DeWolfe, R.H., in Bamford, C.H.; Tipper, C.F.H. *Comprehenseive Chemical Kintetics*, Vol. 9, Elseiver, NY, ***1973***, pp. 470–474; Gutsche, C.D.; Redmore, D. *Carbocyclic Ring Expansion Reactions*, Academic Press, NY, ***1968***, pp. 163–170.

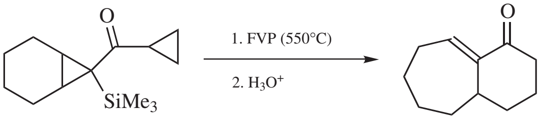
[570]For a novel vinylcyclopropane rearrangement, see Armesto, D.; Ramos, A.; Mayoral, E.P.; Ortiz, M.J.; Agarrabeitia, A.R. *Org. Lett.* ***2000***, *2*, 183.

[571]For a study of substituent effects, see McGaffin, G.; Grimm, B.; Heinecke, U.; Michaelsen, H.; de Meijere, A.; Walsh, R. *Eur. J. Org. Chem.* ***2001***, 3559.

on the vinyl group and has been extended to 1,1-dicyclopropylethene[572]

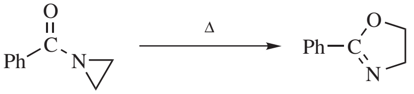


and (both thermally[573] and photochemically[574]) to vinylcyclopropenes. This rearrangement can be catalyzed by rhodium and silver compounds, and has been used to form rings.[575] Another variation converts α-trimethylsilylcyclopropyl ketones to ring-expanded ketones, such as **123**, via FVP at 550°C.[576] Flash vacuum pyrolysis of the trimethylsilyl ether of cyclopropylcarbinyl alcohols gives similar results.[577] A variation uses flash vacuum pyrolysis at 600°C to convert α-trimethylsilyloxy-α-vinyl cyclic ketones to ring expanded ketones.[578]



123

Various heterocyclic analogs[579] are also known, as in the rearrangement of aziridinyl amides (**124**).[580] Cyclopropyl ketones can be treated with tosylamine and a zirconium catalyst, which converts the imine formed *in situ* to a pyrroline.[581]



124

[572]Ketley, A.D. *Tetrahedron Lett.* ***1964***, 1687; Branton, G.R.; Frey, H.M. *J. Chem. Soc. A* ***1966***, 1342.
[573]Small, A.; Breslow, R. cited in Breslow, R. in de Mayo, P. *Molecular Rearrangments*, Vol. 1, Wiley, NY, ***1963***, p. 236.
[574]Padwa, A.; Blacklock, T.J.; Getman, D.; Hatanaka, N.; Loza, R. *J. Org. Chem.* ***1978***, *43*, 1481; Zimmerman, H.E.; Kreil, D.J. *J. Org. Chem.* ***1982***, *47*, 2060.
[575]Wender, P.A.; Husfeld, C.O.; Langkopf, E.; Love, J.A. *J. Am. Chem. Soc.* ***1998***, *120*, 1940.
[576]Liu, H.; Shook, C.A.; Jamison, J.A.; Thiruvazhi, M.; Cohen, T. *J. Am. Chem. Soc.* ***1998***, *120*, 605.
[577]Rüedi, G.; Nagel, M.; Hansen, H.-J. *Org. Lett.* ***2004***, *6*, 2989.
[578]Rüedi, G.; Oberli, M.A.; Nagel, M.; Hansen, H.-J. *Org. Lett.* ***2004***, *6*, 3179.
[579]For a review of a nitrogen analog, see Boeckman, Jr., R.K.; Walters, M.A. *Adv. Heterocycl. Nat. Prod. Synth.* ***1990***, *1*, 1.
[580]For reviews of ring expansions of aziridines, see Heine, H.W. *Mech. Mol. Migr.* ***1971***, *3*, 145; Dermer, O.C.; Ham, G.E. *Ethylenimine and Other Aziridines*, Academic Press, NY, ***1969***, pp. 282–290. See also, Wong, H.N.C.; Hon, M.; Tse, C.; Yip, Y.; Tanko, J.; Hudlicky, T. *Chem. Rev.* ***1989***, *89*, 165, 190–192.
[581]Shi, M.; Yang, Y.-H.; Xu, B. *Synlett* ***2004***, 1622.

Two competing reactions are the homodienyl [1,5]-shift (if a suitable H is available, see **18-29**), and simple cleavage of the cyclopropane ring, leading in this case to a diene (see **18-3**).

Vinylcyclobutanes can be similarly converted to cyclohexenes,[582] but larger ring compounds do not generally give the reaction.[583] Bicyclo[2.1.0]pentane derivatives undergo this reaction, and tricyclo[4.1.0.0^{2,5}]heptanes rearrange to give nonconjugated cycloheptadienes.[584] Though high temperatures (as high as 500°C) are normally required for the thermal reaction, the lithium salts of 2-vinylcyclopropanols rearrange to the lithium salt of cyclopent-3-enols at 25°C.[585] Salts of 2-vinylcyclobutanols behave analogously.[586]

The reaction rate has also been greatly increased by the addition of a one-electron oxidant tris-(4-bromophenyl)aminium hexafluoroantimonate $Ar_3N^{\bullet +}$ SbF_6^- (Ar = *p*-bromophenyl).[587] This reagent converts the substrate to a cation radical, which undergoes ring expansion much faster.[588]

The mechanisms of these ring expansions are not certain. Both concerted[589] and diradical[590] pathways have been proposed,[591] and it is possible that both pathways operate, in different systems.

For the conversion of a vinylcyclopropane to a cyclopentene in a different way, see OS **68**, 220.

[582]See, for example, Overberger, C.G.; Borchert, A.E. *J. Am. Chem. Soc.* ***1960***, *82*, 1007; Gruseck, U.; Heuschmann, M. *Chem. Ber.* ***1990***, *123*, 1911. The kinetics of gas-phase fragmentation of propenylmethyl cyclobutanes has been examined, see Baldwin, J.E.; Burrell, R.C. *J. Org. Chem.* ***2002***, *67*, 3249. Thermal [1,3]-carbon sigmatropic rearrangements of vinylcyclobutanes have been reviewed. See Leber, P.A.; Baldwin, J.E. *Acc. Chem. Res.* ***2002***, *35*, 279.

[583]For an exception, see Thies, R.W. *J. Am. Chem. Soc.* ***1972***, *94*, 7074.

[584]Deak, H.L.; Stokes, S.S.; Snapper, M.L. *J. Am. Chem. Soc.* ***2001***, *123*, 5152.

[585]Danheiser, R.L.; Bronson, J.J.; Okano, K. *J. Am. Chem. Soc.* ***1985***, *107*, 4579.

[586]Danheiser, R.L.; Martinez-Davila, C.; Sard, H. *Tetrahedron* ***1981***, *37*, 3943.

[587]Dinnocenzo, J.P.; Conlan, D.A. *J. Am. Chem. Soc.* ***1988***, *110*, 2324.

[588]For a review of ring expansion of vinylcyclobutane cation radicals, see Bauld, N.L. *Tetrahedron* ***1989***, *45*, 5307.

[589]For evidence favoring the concerted mechanism, see Billups, W.E.; Leavell, K.H.; Lewis, E.S.; Vanderpool, S. *J. Am. Chem. Soc.* ***1973***, *95*, 8096; Berson, J.A.; Dervan, P.B.; Malherbe, R.; Jenkins, J.A. *J. Am. Chem. Soc.* ***1976***, *98*, 5937; Andrews, G.D.; Baldwin, J.E. *J. Am. Chem. Soc.* ***1976***, *98*, 6705, 6706; Dolbier, Jr., W.R.; Al-Sader, B.H.; Sellers, S.F.; Koroniak, H. *J. Am. Chem. Soc.* ***1981***, *103*, 2138; Gajewski, J.J.; Olson, L.P. *J. Am. Chem. Soc.* ***1991***, *113*, 7432.

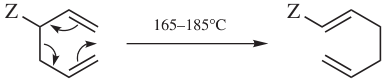
[590]For evidence favoring the diradical mechanism, see Willcott, M.R.; Cargle, V.H. *J.Am.Chem.Soc.* ***1967***, *89*, 723; Doering, W. von E.; Schmidt, E.K.G. *Tetrahedron* ***1971***, *27*, 2005; Roth, W.R.; Schmidt, E.K.G. *Tetrahedron Lett.* ***1971***, 3639; Simpson, J.M.; Richey Jr., H.G. *Tetrahedron Lett.* ***1973***, 2545; Gilbert, J.C.; Higley, D.P. *Tetrahedron Lett.* ***1973***, 2075; Caramella, P.; Huisgen, R.; Schmolke, B. *J.Am.Chem.Soc.* ***1974***, *96*, 2997, 2999; Mazzocchi, P.H.; Tamburin, H.J. *J.Am.Chem. Soc.* ***1975***, *97*, 555; Zimmerman, H.E.; Fleming, S.A. *J. Am. Chem. Soc.* ***1983***, *105*, 622; Klumpp, G.W.; Schakel, M. *Tetrahedron Lett.* ***1983***, *24,* 4595; McGaffin, G.; de Meijere, A.; Walsh, R. *Chem. Ber.* ***1991***, *124*, 939. A "continuous diradical transition state" has also been proposed: Roth, W.R.; Lennartz, H.; Doering, W. von E.; Birladeanu, L.; Guyton, C.A.; Kitagawa, T. *J. Am. Chem. Soc.* ***1990***, *112*, 1722, and references cited therein.

[591]For a discussion concerning whether or not this [1,3]-shift is a concerted reaction, see Gajewski, J.J.; Olson, L.P.; Willcott III, M.R. *J. Am. Chem. Soc.* ***1996***, *118*, 299. For a discussion of the mechanism of this reaction, see Su, M.-D. *Tetrahedron* ***1995***, *51*, 5871.

N-Cyclopropylimines undergo rearrangement to cyclic imines (pyrrolines) under photochemical conditions.[592] P-Vinyl phosphiranes (the P analog of cyclopropanes with P in the ring) under a similar rearrangement, and the mechanism has been studied.[593]

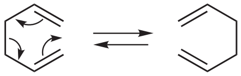
18-32 The Cope Rearrangment

(3/4/) → (1/6/)-*sigma*-Migration

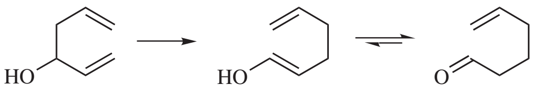


Z = Ph, RCO, and so on.

When 1,5-dienes are heated, a [3,3] sigmatropic rearrangement known as the *Cope rearrangement* (not to be confused with the Cope elimination reaction, **17-9**) occurs to generate an isomeric 1,5-diene.[594] When the diene is symmetrical about the 3,4 bond, we have the unusual situation where a reaction gives a product identical with the starting material:[595]



Therefore, a Cope rearrangement can be detected only when the diene is not symmetrical about this bond. Any 1,5-diene gives the rearrangement; for example, 3-methyl-1,5-hexadiene heated to 300°C gives 1,5-heptadiene.[596] However, the reaction takes place more easily (lower temperature required) when there is a group on the 3- or 4-carbon with leads to the new double bond being substituted. The reaction is obviously reversible[597] and produces an equilibrium mixture of the two 1,5-dienes, which is richer in the thermodynamically more stable isomer. However, the equilibrium can be shifted to the right for 3-hydroxy-1,5-dienes,[598] because the product tautomerizes to the ketone or aldehyde:



[592]Campos, P.J.; Soldevilla, A.; Sampedro, D.; Rodrguez, M.A. *Org. Lett.* ***2001***, *3*, 4087.

[593]Mátrai, J.; Dransfeld, A.; Veszprém, T.; Nguyen, M.T. *J. Org. Chem.* ***2001***, *66*, 5671.

[594]For reviews, see Bartlett, P.A. *Tetrahedron* ***1980***, *36*, 2, 28–39; Rhoads, S.J.; Raulins, N.R. *Org. React.* ***1975***, *22*, 1; Smith, G.G.; Kelly, F.W. *Prog. Phys. Org. Chem.* ***1971***, *8*, 75, 153–201; DeWolfe, R.H., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 455–461.

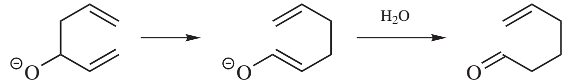
[595]Note that the same holds true for [1,*j*]-sigmatropic reactions of symmetrical substrates (**18-28**, **18-29**).

[596]Levy, H.; Cope, A.C. *J. Am. Chem. Soc.* ***1944***, *66*, 1684.

[597]For a review of the reverse Cope cyclization, see Cooper, N.J.; Knight, D.W. *Tetrahedron* ***2004***, *60*, 243.

[598]For an exception, see Elmore, S.W.; Paquette, L.A. *Tetrahedron Lett.* ***1991***, *32*, 319.

The reaction of 3-hydroxy-1,5-dienes is called the *oxy-Cope rearrangement*,[599] and has proved highly useful in synthesis.[600] The oxy-Cope rearrangement is greatly accelerated (by factors of 10^{10}–10^{17}) if the alkoxide is used rather than the alcohol (the *anionic oxy-Cope rearrangement*),[601] where the direct product is the enolate ion, which is hydrolyzed to the ketone. A metal free reaction using a phosphazene base has been reported.[602] The silyloxy-Cope rearrangement has proven to be quite useful.[603] An antibody-catalyzed oxy-Cope reaction is known,[604] and the mechanism and origins of catalysis for this reaction have been studied.[605] Sulfur substitution also leads to rate enhancement of the oxy-Cope rearrangement.[606] Note that 2-oxonia Cope rearrangements have been implicated in Prins cyclization reactions (**16-54**).[607]



aza-Cope rearrangements are also known.[608] In amino-Cope rearrangements, the solvent plays a role in the regioselectivity of the reaction.[609] It has been suggested that this latter reaction does not proceed solely by a concerted [3.3]-sigmatropic rearrangement.[610]

[599]Berson, J.A.; Walsh, Jr., E.J. *J. Am. Chem. Soc.* ***1968***, *90*, 4729; Warrington, J.M.; Yap, G.P.A.; Barriault, L. *Org. Lett.* ***2000***, *2*, 663; Ovaska, T.V.; Roses, J.B. *Org. Lett.* ***2000***, *2*, 2361. For reviews, see Paquette, L.A. *Angew. Chem. Int. Ed.* ***1990***, *29*, 609; Marvell, E.N.; Whalley, W., in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 2, Wiley, NY, ***1971***, pp. 738–743.

[600]For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1306–1307.

[601]Evans, D.A.; Nelson, J.V. *J. Am. Chem. Soc.* ***1980***, *102*, 774; Miyashi, T.; Hazato, A.; Mukai, T. *J. Am. Chem. Soc.* ***1978***, *100*, 1008; Paquette, L.A.; Pegg, N.A.; Toops, D.; Maynard, G.D.; Rogers, R.D. *J. Am. Chem. Soc.* ***1990***, *112*, 277; Gajewski, J.J.; Gee, K.R. *J. Am. Chem. Soc.* ***1991***, *113*, 967. See also, Wender, P.A.; Ternansky, R.J.; Sieburth, S.M. *Tetrahedron Lett.* ***1985***, *26*, 4319. For a study of isomerization of the parent substrate in the gas phase, see Schulze, S.M.; Santella, N.; Grabowski, J.J.; Lee, J.K. *J. Org. Chem.* ***2001***, *66*, 7247.

[602]Mamdani, H.T.; Hartley, R.C. *Tetrahedron Lett.* ***2000***, *41*, 747.

[603]For a review, see Schneider, C. *Synlett* ***2001***, 1079.

[604]Braisted, A.C.; Schultz, P.G. *J. Am. Chem. Soc.* ***1994***, *116*, 2211.

[605]Black, K.A.; Leach, A.G.; Kalani, Y.S.; Houk, K.N. *J. Am. Chem. Soc.* ***2004***, *126*, 9695.

[606]Paquette, L.A.; Reddy, Y.R.; Vayner, G.; Houk, K.N. *J. Am. Chem. Soc.* ***2000***, *122*, 10788.

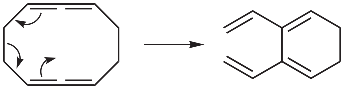
[607]See Rychnovsky, S.D.; Marumoto, S.; Jaber, J.J. *Org. Lett.* ***2001***, *3*, 3815.

[608]Beholz, L.G.; Stille, J.R. *J. Org. Chem.* ***1993***, *58*, 5095; Sprules, T.J.; Galpin, J.D.; Macdonald, D. *Tetrahedron Lett.* ***1993***, *34*, 247; Cook, G.R.; Barta, N.S.; Stille, J.R. *J. Org. Chem.* ***1992***, *57*, 461. See Yadav, J.S.; Reddy, B.V.S.; Rasheed, M.A.; Kumar, H.M.S. *Synlett* ***2000***, 487.

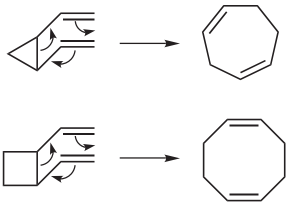
[609]Dobson, H.K.; LeBlanc, R.; Perrier, H.; Stephenson, C.; Welch, T.R.; Macdonald, D. *Tetrahedron Lett.* ***1999***, *40*, 3119.

[610]Allin, S.M.; Button, M.A.C. *Tetrahedron Lett.* ***1999***, *40*, 3801.

The 1,5-diene system may be inside a ring or part of an allenic system[611] (this example illustrates both of these situations):[612]



but the reaction does not take place when one of the double bonds is part of an aromatic system (e.g., 4-phenyl-1-butene).[613] When the two double bonds are in vinylic groups attached to adjacent ring positions, the product is a ring four carbons larger. This has been applied to divinylcyclopropanes and divinylcyclobutanes:[614]



Indeed, *cis*-1,2-divinylcyclopropanes give this rearrangement so rapidly that they generally cannot be isolated at room temperature,[615] though exceptions are known.[616] When heated, 1,5-diynes are converted to 3,4-dimethylenecyclobutenes **125**.[617] A rate-determining Cope rearrangement is followed by a very rapid electrocyclic (**18-27**) reaction. The interconversion of 1,3,5-trienes and cyclohexadienes

[611]Duncan, J.A.; Azar, J.K.; Beatle, J.C.; Kennedy, S.R.; Wulf, C.M. *J. Am. Chem. Soc.* ***1999***, *121*, 12029.

[612]Harris, Jr., J.F. *Tetrahedron Lett.* ***1965***, 1359.

[613]See, for example, Lambert, J.B.; Fabricius, D.M.; Hoard, J.A. *J. Org. Chem.* ***1979***, *44*, 1480; Marvell, E.N.; Almond, S.W. *Tetrahedron Lett.* ***1979***, 2777, 2779; Newcomb, M.; Vieta, R.S. *J. Org. Chem.* ***1980***, *45*, 4793. For exceptions in certain systems, see Doering, W. von E.; Bragole, R.A. *Tetrahedron* ***1966***, *22*, 385; Jung, M.E.; Hudspeth, J.P. *J. Am. Chem. Soc.* ***1978***, *100*, 4309; Yasuda, M.; Harano, K.; Kanematsu, K. *J. Org. Chem.* ***1980***, *45*, 2368.

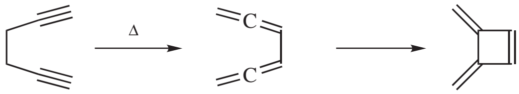
[614]Vogel, E.; Ott, K.H.; Gajek, K. *Liebigs Ann. Chem.* ***1961***, *644*, 172. For reviews, see Wong, H.N.C.; Hon, M.; Tse, C.; Yip, Y.; Tanko, J.; Hudlicky, T. *Chem. Rev.* ***1989***, *89*, 165, see pp. 172–174; Mil'vitskaya, E.M; Tarakanova, A.V.; Plate, A.F. *Russ. Chem. Rev.* ***1976***, *45*, 469, see pp. 475–476.

[615]Unsubstituted *cis*-1,2-divinylcyclopropane is fairly stable at −20°C: Brown, J.M.; Golding, B.T.; Stofko, Jr., J.J. *J. Chem. Soc., Chem. Commun.* ***1973***, 319; Schneider, M.P.; Rebell, J. *J. Chem. Soc., Chem. Commun.* ***1975***, 283.

[616]See, for example, Brown, J.M. *Chem. Commun.* ***1965***, 226; Schönleber, D. *Chem. Ber.* ***1969***, *102*, 1789; Bolesov, I.G.; Ii-hsein, U.; Levina, R.Ya. *J. Org. Chem. USSR* ***1970***, *6*, 1791; Schneider, M.P.; Rau, A. *J. Am. Chem. Soc.* ***1979***, *101*, 4426.

[617]For reviews of Cope rearrangements involving triple bonds, see Viola, A.; Collins, J.J.; Filipp, N. *Tetrahedron* ***1981***, *37*, 3765; Théron F.; Verny, M.; Vessière, R., in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, pt. 1, Wiley, NY, ***1978***, pp. 381–445, pp. 428–430; Huntsman, W.D. *Intra-Sci. Chem. Rep.* ***1972***, *6*, 151.

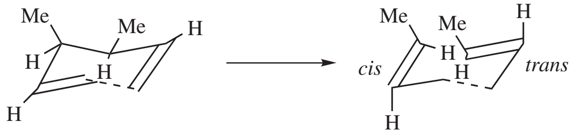
(in **18-27**) is very similar to the Cope rearrangement, but in **18-27**, the 3,4 bond goes from a double bond to a single bond rather than from a single bond to no bond.



125

Like [2 + 2]-cycloadditions (p. 1220), Cope rearrangements of simple 1,5-dienes can be catalyzed by certain transition-metal compounds. For example, the addition of $PdCl_2(PhCN)_2$ causes the reaction to take place at room temperature.[618] This can be quite useful synthetically, because of the high temperatures required in the uncatalyzed process.

As we have indicated with our arrows, the mechanism of the uncatalyzed Cope rearrangement is a simple six-centered pericyclic process.[619] Since the mechanism is so simple, it has been possible to study some rather subtle points, among them the question of whether the six-membered transition state is in the boat or the chair form.[620] For the case of 3,4-dimethyl-1,5-hexadiene, it was demonstrated conclusively that the transition state is in the chair form. This was shown by the stereospecific nature of the reaction: The meso isomer gave the cis–trans product, while the (±) diastereomer gave the trans–trans diene.[621] If the transition state is in the chair form (taking the meso isomer, e.g.), one methyl must be "axial" and the other "equatorial" and the product must be the cis–trans alkene:



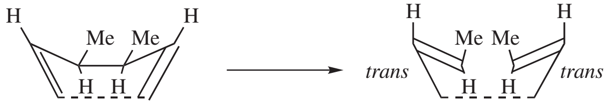
[618]Overman, L.E.; Knoll, F.M. *J. Am. Chem. Soc.* ***1980***, *102*, 865; Hamilton, R.; Mitchell, T.R.B.; Rooney, J.J. *J. Chem. Soc., Chem. Commun.* ***1981***, 456. For reviews of catalysis of Cope and Claisen rearrangements, see Overman, L.E. *Angew. Chem. Int. Ed.* ***1984***, *23*, 579; Lutz, R.P. *Chem. Rev.* ***1984***, *84*, 205. For a study of the mechanism, see Overman, L.E.; Renaldo, A.F. *J. Am. Chem. Soc.* ***1990***, *112*, 3945.

[619]For a mechanistic discussion, see Poupko, R.; Zimmermann, H.; Müller, K.; Luz, Z. *J. Am. Chem. Soc.* ***1996***, *118*, 7995.

[620]For a discussion showing a preference for the chair conformation, see Shea, K.J.; Stoddard, G.J.; England, W.P.; Haffner, C.D. *J. Am. Chem. Soc*, ***1992***, *114*, 2635. See also, Tantillo, D.J.; Hoffmann, R. *J. Org. Chem.* ***2002***, *67*, 1419.

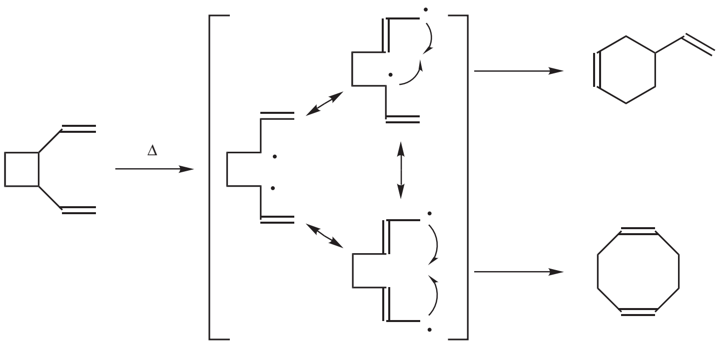
[621]Doering, W. von E.; Roth, W.R.*Tetrahedron* ***1962***, *18*, 67. See also, Hill, R.K.; Gilman, N.W. *Chem. Commun.* ***1967***, 619; Goldstein, M.J.; DeCamp, M.R. *J. Am. Chem. Soc.* ***1974***, *96*, 7356; Hansen, H.; Schmid, H. *Tetrahedron* ***1974***, *30*, 1959; Gajewski, J.J.; Benner, C.W.; Hawkins, C.M. *J. Org. Chem.* ***1987***, *52*, 5198; Paquette, L.A.; DeRussy, D.T.; Cottrell, C.E. *J. Am. Chem. Soc.* ***1988***, *110*, 890.

There are two possible boat forms for the transition state of the meso isomer. One leads to a trans–trans product;



the other to a cis–cis alkene. For the (±) pair the predictions are just the opposite: There is just one boat form, and it leads to the cis–trans alkene, while one chair form ("diaxial" methyls) leads to the cis–cis product and the other ("diequatorial" methyls) predicts the trans–trans product. Thus the nature of the products obtained demonstrates that the transition state is a chair and not a boat.[622] While 3,4-dimethyl-1,5-hexadiene is free to assume either the chair or boat (it prefers the chair), other compounds are not so free. Thus 1,2-divinylcyclopropane (p. 1661) can react *only* in the boat form, demonstrating that such reactions are not impossible.[623]

Because of the nature of the transition state[624] in the pericyclic mechanism, optically active substrates with a stereogenic carbon at C-3 or C-4 transfer the chirality to the product (see p. 1673 for an example in the mechanistically similar Claisen rearrangement).[625] There are many examples of asymmetric [3,3]-sigmatropic rearrangements.[626]



[622]Preference for the chair transition state is a consequence of orbital-symmetry relationships: Hoffmann, R.; Woodward, R.B. *J. Am. Chem. Soc.* ***1965***, *87*, 4389; Fukui, K.; Fujimoto, H. *Tetrahedron Lett.* ***1966***, 251.

[623]For other examples of Cope rearrangements in the boat form, see Goldstein, M.J.; Benzon, M.S. *J. Am. Chem. Soc.* ***1972***, *94*, 7147; Shea, K.J.; Phillips, R.B. *J. Am. Chem. Soc.* ***1980***, *102*, 3156; Wiberg, K.B.; Matturro, M.; Adams, R. *J. Am. Chem. Soc.* ***1981***, *103*, 1600; Gajewski, J.J.; Jiminez, J.L. *J. Am. Chem. Soc.* ***1986***, *108*, 468.

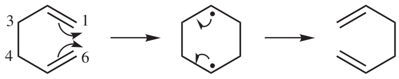
[624]See Jiao, H.; Schleyer, P.v.R. *Angew. Chem. Int. Ed.* ***1995***, *34*, 334; Özkan, I.; Zora, M. *J. Org. Chem.* ***2003***, *68*, 9635.

[625]For a review of Cope and Claisen reactions as enantioselective syntheses, see Hill, R.K., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 3, Academic Press, NY, ***1984***, pp. 503–572, 503–545.

[626]For a review, see Nubbemeyer, U. *Synthesis* ***2003***, 961.

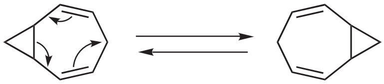
Not all Cope rearrangements proceed by the cyclic six-centered mechanism.[627] Thus *cis*-1,2-divinylcyclobutane (p. 1661) rearranges smoothly to 1,5-cyclooctadiene, since the geometry is favorable. The trans isomer also gives this product, but the main product is 4-vinylcyclohexene (resulting from **18-31**). This reaction can be rationalized as proceeding by a diradical mechanism,[628] although it is possible that at least part of the cyclooctadiene produced comes from a prior epimerization of the *trans*- to the *cis*-divinylcyclobutane followed by Cope rearrangement of the latter.[629]

It has been suggested that another type of diradical two-step mechanism may be preferred by some substrates.[630] Indeed, a nonconcerted Cope rearrangement has been reported.[631] In this pathway,[632] the 1,6 bond is formed before the 3,4 bond breaks:



This is related to the *Bergman cyclization* that was introduced in **18-27**.

It was pointed out earlier that a Cope rearrangement of the symmetrical 1,5-hexadiene gives 1,5-hexadiene. This is a *degenerate Cope rearrangement* (p. 1563). Another molecule that undergoes it is bicyclo[5.1.0]octadiene



126 **126**

[627]The diradical character of the Cope rearrangement transition state has been studied. See Staroverov, V.B.; Davidson, E.R. *J. Am. Chem. Soc.* ***2000***, *122*, 186; Navarro-Vázquez, A.; Prall, M.; Schreiner, P.R. *Org. Lett.* ***2004***, *6*, 2981.

[628]Hammond, G.S.; De Boer, C.D. *J. Am. Chem. Soc.* ***1964***, *86*, 899; Trecker, D.J.; Henry, J.P. *J. Am. Chem. Soc.* ***1964***, *86*, 902. Also see, Dolbier, Jr., W.R.; Mancini, G.J. *Tetrahedron Lett.* ***1975***, 2141; Kessler, H.; Ott, W. *J. Am. Chem. Soc.* ***1976***, *98*, 5014. For a discussion of diradical mechanisms in Cope rearrangements, see Berson, J.A., in de Mayo, P. *Rearrangements in Ground and Excited States*, Academic Press, NY, ***1980***, pp. 358–372.

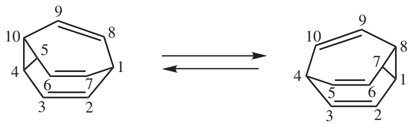
[629]See, for example, Berson, J.A.; Dervan, P.B. *J. Am. Chem. Soc.* ***1972***, *94*, 8949; Baldwin, J.E.; Gilbert, K.E. *J. Am. Chem. Soc.* ***1976***, *98*, 8283. For a similar result in the 1,2-divinylcyclopropane series, see Baldwin, J.E.; Ullenius, C. *J. Am. Chem. Soc.* ***1984***, *96*, 1542.

[630]Doering, W. von E.; Toscano, V.G.; Beasley, G.H. *Tetrahedron* ***1971***, *27*, 5299; Dewar, M.J.S.; Wade, Jr., L.E. *J. Am. Chem. Soc.* ***1977***, *99*, 4417; Padwa, A.; Blacklock, T.J. *J. Am. Chem. Soc.* ***1980***, *102*, 2797; Dollinger, M.; Henning, W.; Kirmse, W. *Chem. Ber.* ***1982***, *115*, 2309; Kaufmann, D.; de Meijere, A. *Chem. Ber.* ***1984***, *117*, 1128; Dewar, M.J.S.; Jie, C. *J. Am. Chem. Soc.* ***1987***, *109*, 5893; *J. Chem. Soc., Chem. Commun.* ***1989***, 98. For evidence against this view, see Gajewski, J.J. *Acc. Chem. Res.* ***1980***, *13*, 142; Morokuma, K.; Borden, W.T.; Hrovat, D.A. *J. Am. Chem. Soc.* ***1988***, *110*, 4474; Halevi, E.A.; Rom, R. *Isr. J. Chem.* ***1989***, *29*, 311; Owens, K.A.; Berson, J.A. *J. Am. Chem. Soc.* ***1990***, *112*, 5973.

[631]Roth, W.R.; Gleiter, R.; Paschmann, V.; Hackler, U.E.; Fritzsche, G.; Lange, H. *Eur. J. Org. Chem.* ***1998***, 961; Roth, W.R.; Schaffers, T.; Heiber, M. *Chem. Ber.* ***1992***, *125*, 739.

[632]For a report of still another mechanism, featuring a diionic variant of the diradical, see Gompper, R.; Ulrich, W. *Angew. Chem. Int. Ed.* ***1976***, *15*, 299.

(**126**).[633] At room temperature, the NMR spectrum of this compound is in accord with the structure shown on the left. At 180°C, it is converted by a Cope reaction to a compound equivalent to itself. The interesting thing is that at 180°C the NMR spectrum shows that what exists is an equilibrium mixture of the two structures. That is, at this temperature the molecule rapidly (faster than 10^3 times per second) changes back and forth between the two structures. This is called *valence tautomerism* and is quite distinct from resonance, even though only electrons shift.[634] The positions of the nuclei are not the same in the two structures. Molecules like **126** that exhibit valence tautomerism (in this case, at 180°C) are said to have *fluxional* structures. It may be recalled that *cis*-1,2- divinylcyclopropane does not exist at room temperature because it rapidly rearranges to 1,4-cycloheptadiene (p. 1661), but in **126** the *cis*-divinylcyclopropane structure is frozen into the molecule in both structures. Several other compounds with this structural feature are also known. Of these, *bullvalene* (**127**) is especially interesting.



127

The Cope rearrangement shown changes the position of the cyclopropane ring from 4,5,10 to 1,7,8. But the molecule could also have undergone rearrangements to put this ring at 1,2,8 or 1,2,7. Any of these could then undergo several Cope rearrangements. In all, there are $\frac{10!}{3}$ or >1.2 million tautomeric forms, and the cyclopropane ring can be at any three carbons that are adjacent. Since each of these tautomers is equivalent to all the others, this has been called an infinitely degenerate Cope rearrangement. Bullvalene has been synthesized and its ^{1}H NMR spectrum determined.[635] At −25°C, there are two peaks with an area ratio of 6:4. This is in accord with a single non-tautomeric structure. The six are the vinylic protons and the four are the allylic ones. But at 100°C the compound shows only one NMR peak, indicating that we have here a truly unusual situation where the compound rapidly interchanges its structure among 1.2 million equivalent forms.[636] The ^{13}C NMR spectrum of bullvalene also shows

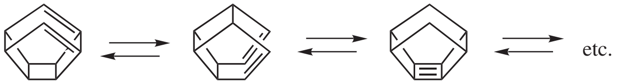
[633]Doering, W. von E.; Roth, W.R. *Tetrahedron* ***1963***, *19*, 715.

[634]For reviews of valence tautomerizations, see Decock-Le Révérend, B.; Goudmand, P. *Bull. Soc. Chim. Fr.* ***1973***, 389; Gajewski, J.J. *Mech. Mol. Migr.* ***1971***, *4*, 1, see pp. 32–49; Paquette, L.A. *Angew. Chem. Int. Ed.* ***1971***, *10*, 11; Domareva-Mandel'shtam, T.V.; D'yakonov, I.A. *Russ. Chem. Rev.* ***1966***, *35*, 559, 568; Schröder, G.; Oth, J.F.M.; Merényi, R. *Angew. Chem. Int. Ed.* ***1965***, *4*, 752.

[635]Schröder, G. *Chem. Ber.* ***1964***, *97*, 3140; Merényi, R.; Oth, J.F.M.; Schröder, G. *Chem. Ber.* ***1964***, *97*, 3150. For a review of bullvalenes, see Schröder, G.; Oth, J.F.M. *Angew. Chem. Int. Ed.* ***1967***, *6*, 414.

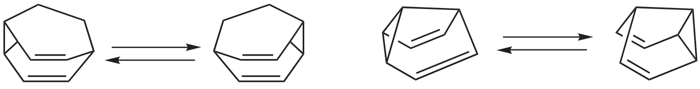
[636]A number of azabullvalenes (**127** containing heterocyclic nitrogen) have been synthesized. They also have fluxional structures when heated, though with fewer tautomeric forms than bullvalene itself: Paquette, L.A.; Malpass, J.R.; Krow, G.R.; Barton, T.J. *J. Am. Chem. Soc.* ***1969***, *91*, 5296.

only one peak at 100°C.[637]



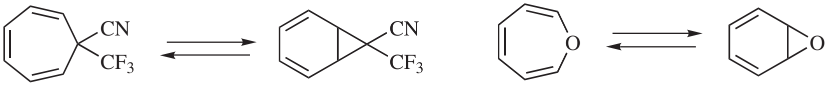
128

Another compound for which degenerate Cope rearrangements result in equivalence for all the carbons is *hypostrophene* (**128**).[638] In the case of the compound *barbaralane* (**129**)[639] (bullvalene in which one CH=CH has been replaced by a CH_2):



129 **130**

there are only 2 equivalent tautomers.[640] However, NMR spectra indicate that even at room temperature a rapid interchange of both tautomers is present, although by about −100°C this has slowed to the point where the spectrum is in accord with a single structure. In the case of *semibullvalene* (**130**) (barbaralane in which the CH_2 has been removed), not only is there a rapid interchange at room temperature, but even at −110°C.[641] Compound **130** has the lowest energy barrier of any known compound capable of undergoing the Cope rearrangement.[642]



131 **132** Oxepin Benzene oxide

[637]Oth, J.F.M.; Müllen, K.; Gilles, J.; Schröder, G. *Helv. Chim. Acta* ***1974***, *57*, 1415; Nakanishi, H.; Yamamoto, O. *Tetrahedron Lett.* ***1974***, 1803; Günther, H.; Ulmen, J. *Tetrahedron* ***1974***, *30*, 3781. For deuterium nmr spectra, see Poupko, R.; Zimmermann, H.; Luz, Z. *J. Am. Chem. Soc.* ***1984***, *106*, 5391. For a crystal structure study, see Luger, P.; Buschmann, J.; McMullan, R.K.; Ruble, J.R.; Matias, P.; Jeffrey, G.A. *J. Am. Chem. Soc.* ***1986***, *108*, 7825.

[638]McKennis, J.S.; Brener, L.; Ward, J.S.; Pettit, R. *J. Am. Chem. Soc.* ***1971***, *93*, 4957; Paquette, L.A.; Davis, R.F.; James, D.R. *Tetrahedron Lett.* ***1974***, 1615.

[639]For a study of sigmatropic shiftamers in extended barbaralanes, see Tantillo, D.J.; Hoffmann, R.; Houk, K.N.; Warner, P.M.; Brown, E.C.; Henze, D.K. *J. Am. Chem. Soc.* ***2004***, *126*, 4256.

[640]Barbaralane was synthesized by Biethan, U.; Klusacek, H.; Musso, H. *Angew. Chem. Int. Ed.* ***1967***, *6*, 176; by Tsuruta, H.; Kurabayashi, K.; Mukai, T. *Tetrahedron Lett.* ***1965***, 3775; by Doering, W. von E.; Ferrier, B.M.; Fossel, E.T.; Hartenstein, J.H.; Jones Jr., M.; Klumpp, G.W.; Rubin, R.M.; Saunders, M. *Tetrahedron* ***1967***, *23*, 3943; and by Henkel, J.G.; Hane, J.T. *J. Org. Chem.* ***1983***, *48*, 3858.

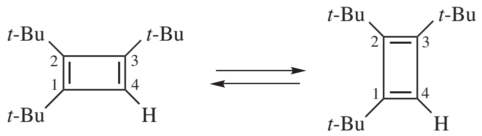
[641]Meinwald, J.; Schmidt, D. *J. Am. Chem. Soc.* ***1969***, *91*, 5877; Zimmerman, H.E.; Binkley, R.W.; Givens, R.S.; Grunewald, G.L.; Sherwin, M.A. *J. Am. Chem. Soc.* ***1969***, *91*, 3316.

[642]Cheng, A.K.; Anet, F.A.L.; Mioduski, J.; Meinwald, J. *J. Am. Chem. Soc.* ***1974***, *96*, 2887; Moskau, D.; Aydin, R.; Leber, W.; Günther, H.; Quast, H.; Martin, H.-D.; Hassenrück, K.; Miller, L.S.; Grohmann, K. *Chem. Ber.* ***1989***, *122*, 925. For a discussion concerning whether or not semibullvalenes are homoaromatic, see Williams, R.V.; Gadgil, V.R.; Chauhan, K.; Jackman, L.M.; Fernandes, E. *J. Org. Chem.* ***1998***, *63*, 3302.

The molecules taking part in a valence tautomerization need not be equivalent. Thus, NMR spectra indicate that a true valence tautomerization exists at room temperature between the cycloheptatriene **131** and the norcaradiene **132**.[643] In this case, one isomer (**132**) has the *cis*-1,2-divinylcyclopropane structure, while the other does not. In an analogous interconversion, benzene oxide[644] and oxepin exist in a tautomeric equilibrium at room temperature.[645]

Bullvalene and hypostrophene are members of a group of compounds all of whose formulas can be expressed by the symbol $(CH)_{10}$.[646] Many other members of this group are known. Similar groups of $(CH)_n$ compounds exist for other even-numbered values of "*n*".[646] For example, there are 20 possible $(CH)_8$[647] compounds,[648] and five possible $(CH)_6$ compounds,[649] all of which are known: benzene, prismane (p. 220), Dewar benzene (p. 1641), bicyclopropenyl,[650] and benzvalene.[651]

An interesting example of a valence tautomerism is the case of 1,2,3-tri-*tert*-butylcyclobutadiene (p. 74). There are two isomers, both rectangular, and ^{13}C NMR spectra show that they exist in a dynamic equilibrium, even at −185°C.[652]



[643]Ciganek, E. *J. Am. Chem. Soc.* ***1965***, *87*, 1149. For other examples of norcaradiene–cycloheptatriene valence tautomerizations, see Görlitz, M.; Günther, H. *Tetrahedron* ***1969***, *25*, 4467; Ciganek, E. *J. Am. Chem. Soc.* ***1965***, *93*, 2207; Dürr, H.; Kober, H. *Chem. Ber.* ***1973***, *106*, 1565; Betz, W.; Daub, J. *Chem. Ber.* ***1974***, *107*, 2095; Maas, G.; Regitz, M. *Chem. Ber.* ***1976***, *109*, 2039; Warner, P.M.; Lu, S. *J. Am. Chem. Soc.* ***1980***, *102*, 331; Neidlein, R.; Radke, C.M. *Helv. Chim. Acta* ***1983***, *66*, 2626; Takeuchi, K.; Kitagawa, T.; Ueda, A.; Senzaki, Y.; Okamoto, K. *Tetrahedron* ***1985***, *41*, 5455.

[644]For a review of arene oxides, see Shirwaiker, G.S.; Bhatt, M.V. *Adv. Heterocycl. Chem.* ***1984***, *37*, 67.

[645]For reviews, see Maier, G. *Angew. Chem. Int. Ed.* ***1967***, *6*, 402; Vogel, E.; Günther, H. *Angew. Chem. Int. Ed.* ***1967***, *6*, 385; Vogel, E. *Pure Appl. Chem.* ***1969***, *20*, 237. See also, Boyd, D.R.; Stubbs, M.E. *J. Am. Chem. Soc.* ***1983***, *105*, 2554.

[646]For reviews of rearrangements and interconversions of $(CH)_n$ compounds, see Balaban, A.T.; Banciu, M. *J. Chem. Educ.* ***1984***, *61*, 766; Greenberg, A.; Liebman, J.F. *Strained Organic Molecules*, Academic Press, NY, ***1978***, pp. 203–215; Scott, L.T.; Jones, Jr., M. *Chem. Rev.* ***1972***, *72*, 181. See also, Maier, G.; Wiegand, N.H.; Baum, S.; Wüllner, R. *Chem. Ber.* ***1989***, *122*, 781.

[647]For a review of strain in $(CH)_8$ compounds, see Hassenrück, K.; Martin, H.; Walsh, R. *Chem. Rev.* ***1989***, *89*, 1125.

[648]The structures of all possible $(CH)_n$ compounds, for $n = 4$, 6, 8, and 10, are shown in Balaban, A.T; Banziu, M. *J. Chem. Educ.* ***1984***, *61*, 766. For a review of $(CH)_{12}$ compounds, see Banciu, M.; Popa, C.; Balaban, A.T. *Chem. Scr.*, ***1984***, *24*, 28.

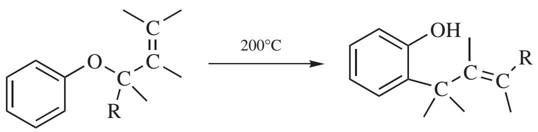
[649]For reviews of valence isomers of benzene and some related compounds, see Kobayashi, Y.; Kumadaki, I. *Top. Curr. Chem.* ***1984***, *123*, 103; Bickelhaupt, F.; de Wolf, W.H. *Recl. Trav. Chim. Pays-Bas* ***1988***, *107*, 459.

[650]For a study of how this compound isomerizes to benzene, see Davis, J.H.; Shea, K.J.; Bergman, R.G. *J. Am. Chem. Soc.* ***1977***, *99*, 1499.

[651]For reviews of benzvalenes, see Christl, M. *Angew. Chem. Int. Ed.* ***1981***, *20*, 529; Burger, U. *Chimia*, ***1979***, 147.

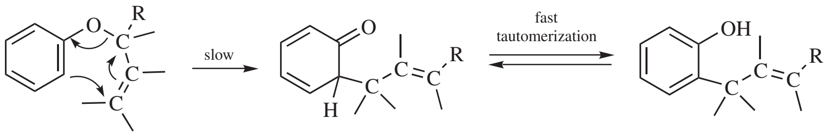
[652]Maier, G.; Kalinowski, H.; Euler, K. *Angew. Chem. Int. Ed.* ***1982***, *21*, 693.

18-33 The Claisen Rearrangement[653]



Allylic aryl ethers, when heated, rearrange to *o*-allylphenols in a reaction called the *Claisen rearrangement*.[654] If both ortho positions are filled, the allylic group migrates to the para position (this is often called the *para-Claisen rearrangement*).[655] There is no reaction when the para and both ortho positions are filled. Migration to the meta position has not been observed. In the ortho migration, the allylic group always undergoes an allylic shift. That is, as shown above, a substituent α to the oxygen is now γ to the ring (and vice versa). On the other hand, in the para migration there is never an allylic shift: The allylic group is found exactly as it was in the original ether. Compounds with propargylic groups (i.e., groups with a triple bond in the appropriate position) do not generally give the corresponding products.

The mechanism is a concerted pericyclic [3,3]-sigmatropic rearrangement[656] and accounts for all these facts. For the ortho rearrangement:



Evidence is the lack of a catalyst, the fact that the reaction is first order in the ether, the absence of crossover products when mixtures are heated, and the presence of the allylic shift, which is required by this mechanism. A *retro*-Claisen rearrangement is known and its mechanism has been examined.[657] The allylic

[653]For a reiview of the Claisen rearrangment since about 1910, see Castro, A.M.M. *Chem. Rev.* ***2004***, *104*, 2939.

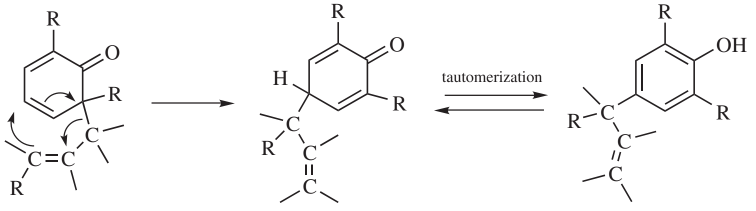
[654]For reviews, see Fleming, I. *Pericyclic Reactions*, Oxford University Press, Oxford, ***1999***, pp. 71–83; Moody, C.J. *Adv. Heterocycl. Chem.* ***1987***, *42*, 203; Bartlett, P.A. *Tetrahedron* ***1980***, *36*, 2, see pp. 28–39; Ziegler, F.E. *Acc. Chem. Res.* ***1977***, *10*, 227; Bennett, G.B. *Synthesis* ***1977***, 589; Rhoads, S.J.; Raulins, N.R. *Org. React.* ***1975***, *22*, 1; Shine, H.J. *Aromatic Rearrangements*; Elsevier, NY, ***1969***, pp. 89–120; Smith, G.G.; Kelly, F.W. *Prog. Phys. Org. Chem.* ***1971***, *8*, 75, 153–201; Hansen, H.; Schmid, H. *Chimia,* ***1970***, *24*, 89, *Chem. Br.* ***1969***, *5*, 111; Jefferson, A.; Scheinmann, F. *Q. Rev. Chem. Soc.* ***1968***, *22*, 391; Thyagarajan, B.S. *Adv. Heterocycl. Chem.* ***1967***, *8*, 143; Dalrymplem D.L.; Kruger, T.L.; White, W.N., in Patai *The Chemistry of the Ether Linkage*, Wiley, NY, ***1967***, pp. 635–660.

[655]For a discussion of regioselectivity, see Gozzo, F.C.; Fernandes, S.A.; Rodrigues, D.C.; Eberlin, M.N.; Marsaioli, A.J. *J. Org. Chem.* ***2003***, *68*, 5493.

[656]For isotope effect evidence regarding the nature of the concerted transition state, see McMichael, K.D.; Korver, G.L. *J. Am. Chem. Soc.* ***1979***, *101*, 2746; Gajewski, J.J.; Conrad, N.D. *J. Am. Chem. Soc.* ***1979***, *101*, 2747; Kupczyk-Subotkowska, L.; Saunders, Jr., W.H.; Shine, H.J. *J. Am. Chem. Soc.* ***1988***, *110*, 7153.

[657]Boeckman, Jr., R.K.; Shair, M.D.; Vargas, J.R.; Stolz, L.A. *J. Org. Chem.* ***1993***, *58*, 1295.

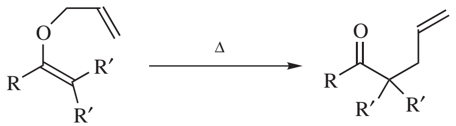
shift for the ortho rearrangement (and the absence of one for the para) has been demonstrated by ^{14}C labeling, even when no substituents are present. Studies of the transition-state geometry have shown that, like the Cope rearrangement, the Claisen rearrangement usually prefers a chair-like transition state.[658] When the ortho positions have no hydrogen, a second [3,3]-sigmatropic migration (a Cope reaction) follows:



133

and the migrating group is restored to its original structure. Intermediates of structure **133** have been trapped by means of a Diels–Alder reaction.[659] The rearrangement of aryl allyl ethers is facilitated by Ag–KI in hot acetic acid,[660] and by $AlMe_3$ in water.[661] A solid-phase reaction of polymer-bound substrate undergoes the Claisen rearrangement with microwave irradiation.[662]

Allylic ethers of enols (allylic vinylic ethers) also undergo the Claisen rearrangement;[663] in fact, it was discovered with these compounds first:[664]



In these cases of course, the final tautomerization does not take place even when R' = H, since there is no aromaticity to restore, and ketones are more stable than enols.[665] Catalytic Claisen rearrangements of allyl vinyl ethers are well known.[666]

[658]Wunderli, A.; Winkler, T.; Hansen, H. *Helv. Chim. Acta* ***1977***, *60*, 2436; Copley, S.D.; Knowles, J.R. *J. Am. Chem. Soc.* ***1985***, *107*, 5306. Also see, Yoo, H.Y.; Houk, K.N. *J. Am. Chem. Soc.* ***1994***, *116*, 12047; Kupczyk-Subotkowska, L.; Saunders, Jr., W.H.; Shine, H.J.; Subotkowski, W. *J. Am. Chem. Soc.* ***1993***, *115*, 5957; Kupczyk-Subotkowska, L.; Subotkowski, W.; Saunders, Jr., W.H.; Shine, H.J.; *J. Am. Chem. Soc.* ***1992***, *114*, 3441.

[659]Conroy, H.; Firestone, R.A. *J. Am. Chem. Soc.* ***1956***, *78*, 2290.

[660]Sharghi, H.; Aghapour, G. *J. Org. Chem.* ***2000***, *65*, 2813.

[661]Wipf, P.; Ribe, S. *Org. Lett.* ***2001***, *3*, 1503.

[662]Kumar, H.M.S.; Anjaneyulu, S.; Reddy, B.V.S.; Yadav, J.C. *Synlett* ***2000***, 1129.

[663]For a review, see Ziegler, F.E. *Chem. Rev.* ***1988***, *88*, 1423.

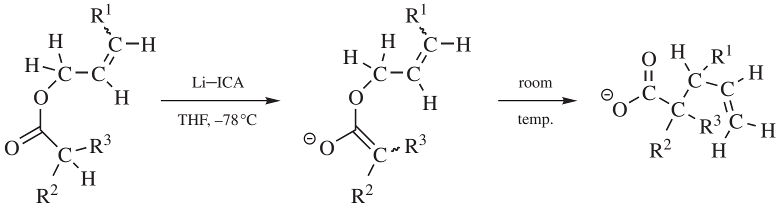
[664]Claisen, L. *Berchte.* ***1912***, *45*, 3157.

[665]However, it has proved possible to reverse the reaction, with a Lewis acid catalyst. See Boeckman Jr., R.K.; Flann, C.J.; Poss, K.M. *J. Am. Chem. Soc.* ***1985***, *107*, 4359.

[666]For a review, see Hiersemann, M.; Abraham, L. *Eur. J. Org. Chem.* ***2002***, 1461.

The use of water as solvent accelerates the reaction.[667] A microwave induced reaction on silica gel is known[668]. The mechanism is similar to that with allylic aryl ethers.[669] Allyl allene ethers undergo a Claisen rearrangement when heated in DMF to give the expected diene with a conjugated aldehyde unit.[670] Butenolides with a β-allylic ether unit undergo Claisen rearrangement–Conia reaction[671] cascade to give an oxaspiro heptane with β-keto lactone comprising the five-membered ring.[672] Allylic esters of β-keto acids undergo a Claisen rearrangement in what is known as the *Carroll rearrangement*[673] (also called the *Kimel–Cope rearrangement*[674]), and the reaction can be catalyzed by a ruthenium complex.[675]

It is possible to treat ketones with allyl alcohol and an acid catalyst to give γ,δ-unsaturated ketones directly, presumably by initial formation of the vinylic ethers, and then Claisen rearrangement.[676] In an analogous procedure, the enolates (**134**) of allylic esters [formed by treatment of the esters with lithium isopropylcyclohexylamide (LICA)] rearrange to γ,δ-unsaturated acids.[677] Allylic alcohols can be treated with a catalytic amount of mercuric acetate, and in the presence of an excess of allyl vinyl ethers give an alkene–aldehyde via a Claisen rearrangement.[678]



134

[667]Grieco, P.A.; Brandes, E.B.; McCann, S.; Clark, J.D. *J. Org. Chem.* ***1989***, *54*, 5849. The effect of water on the transition state has been examined; see Guest, J.M.; Craw, J.S.; Vincent, M.A.; Hillier, I.H. *J. Chem. Soc. Perkin Trans. 2* ***1997***, 71; Sehgal, A.; Shao, L.; Gao, J. *J. Am. Chem. Soc.* ***1995***, *117*, 11337.

[668]Kotha, S.; Mandal, K.; Deb, A.C.; Banerjee, S. *Tetrahedron Lett.* ***2004***, *45*, 9603.

[669]For discussions of the transition state, see Gajewski, J.J.; Jurayj, J.; Kimbrough, D.R.; Gande, M.E.; Ganem, B.; Carpenter, B.K. *J. Am. Chem. Soc.* ***1987***, *109*, 1170. For MO calculations, see Vance, R.L.; Rondan, N.G.; Houk, K.N.; Jensen, F.; Borden, W.T.; Komornicki, A.; Wimmer, E. *J. Am. Chem. Soc.* ***1988***, *110*, 2314; Dewar, M.J.S.; Jie, C. *J. Am. Chem. Soc.* ***1989***, *111*, 511.

[670]Parsons, P.J.; Thomson, P.; Taylor, A.; Sparks, T. *Org. Lett.* ***2000***, *2*, 571.

[671]For a review of the Conia-ene reaction, see Conia, J.M.; Le Perchec, P. *Synthesis* ***1975***, 1.

[672]Schobert, R.; Siegfried, S.; Gordon, G.; Nieuwenhuyzen, M.; Allenmark, S. *Eur. J. Org. Chem.* ***2001***, 1951.

[673]Carroll, M.F. *J. Chem. Soc.* ***1940***, 704, 1266; Carroll, M.F. *J. Chem. Soc.* ***1941***, 507; Ziegler, F.E. *Chem. Rev.* ***1988***, *88*, 1423.

[674]Kimel, W.; Cope, A.C. *J. Am. Chem. Soc.* ***1943***, *65*, 1992.

[675]Burger, E.C.; Tunge, J.A. *Org. Lett.* ***2004***, *6*, 2603.

[676]Lorette, N.B. *J. Org. Chem.* ***1961***, *26*, 4855. See also, Saucy, G.; Marbet, R. *Helv. Chim. Acta* ***1967***, *50*, 2091; Marbet, R.; Saucy, G. *Helv. Chim. Acta* ***1967***, *50*, 2095; Thomas, A.F. *J. Am. Chem. Soc.* ***1969***, *91*, 3281; Johnson, W.S.; Werthemann, L.; Bartlett, W.R.; Brocksom, T.J.; Li, T.; Faulkner, D.J.; Petersen, M.R. *J. Am. Chem. Soc.* ***1970***, *92*, 741; Pitteloud, R.; Petrzilka, M. *Helv. Chim. Acta* ***1979***, *62*, 1319; Daub, G.W.; Sanchez, M.G.; Cromer, R.A.; Gibson, L.L. *J. Org. Chem.* ***1982***, *47*, 743; Bartlett, P.A.; Tanzella, D.J.; Barstow, J.F. *J. Org. Chem.* ***1982***, *47*, 3941.

[677]Ireland, R.E.; Mueller, R.H.; Willard, A.K. *J. Am. Chem. Soc.* ***1976***, *98*, 2868; Gajewski, J.J.; Emrani, J. *J. Am. Chem. Soc.* ***1984***, *106*, 5733; Cameron A.G.; Knight, D.W. *J. Chem. Soc. Perkin Trans. 1* ***1986***, 161. See also, Wilcox, C.S.; Babston, R.E. *J. Am. Chem. Soc.* ***1986***, *108*, 6636.

[678]Tokuyama, H.; Makido, T.; Ueda, T.; Fukuyama, T. *Synth. Commun.* ***2002***, *32*, 869.

Alternatively, the silylketene acetal $R^3R^2C{=}C(OSiR_3)OCH_2CH{=}CHR^1$ is often used instead of **134**.[677,679] This rearrangement also proceeds at room temperature. By either procedure, the reaction is called the *Ireland–Claisen rearrangement*.[680] Note the presence of the negative charge in **134**. As with the oxy-Cope rearrangement (in **18-34**), negative charges generally accelerate the Claisen reaction,[681] although the extent of the acceleration can depend on the identity of the positive counterion.[682] The reaction proceeds with good syn selectivity in many cases.[683] The Ireland–Claisen rearrangement has been made enantioselective by converting **134** to an enol borinate in which the boron is attached to a chiral group.[684] The Ireland–Claisen rearrangement can be done with amide derivatives also.[685]

A number of expected analogs of the Claisen rearrangement are known, for example, rearrangement of $ArNHCH_2CH{=}CH_2$,[686] of *N*-allylic enamines ($R_2C{=}CRNRCR_2CR{=}CR_2$),[687] of allylic imino esters, $RC(OCH_2CH{=}CH_2){=}NR$[688] (these have often been rearranged with transition-metal catalysts[689]), and of $RCH{=}NRCHRCH_2CH{=}CH_2$. These rearrangements of nitrogen-containing compounds can be called *aza-Claisen rearrangements*,[690] but are often called

[679]Ireland, R.E.; Wipf, P.; Armstrong III, J.D. *J. Org. Chem.* ***1991***, *56*, 650.

[680]For a recent example, see Dell, C.P.; Khan, K.M.; Knight, D.W. *J. Chem. Soc. Perkin Trans. 1* ***1994***, 341. For a review, see Chai, Y.; Hong, S.-p.; Lindsay, H.A.; McFarland, C.; McIntosh, M.C. *Tetrahedron* ***2002***, *58*, 2905.

[681]See, for example, Denmark, S.E.; Harmata, M.A.; White, K.S. *J. Am. Chem. Soc.* ***1989***, *111*, 8878.

[682]Koreeda, M.; Luengo, J.I. *J. Am. Chem. Soc.* ***1985***, *107*, 5572; Kirchner, J.J.; Pratt, D.V.; Hopkins, P.B. *Tetrahedron Lett.* ***1988***, *29*, 4229.

[683]Mohamed, M.; Brook, M.A. *Tetrahedron Lett.* ***2001***, *42*, 191. For a discussion of boat or chair preferences, see Khaledy, M.M.; Kalani, M.Y.S.; Khuong, K.S.; Houk, K.N.; Aviyente, V.; Neier, R.; Soldermann, N.; Velker, J. *J. Org. Chem.* ***2003***, *68*, 572.

[684]Corey, E.J.; Lee, D. *J. Am. Chem. Soc.* ***1991***, *113*, 4026.

[685]Tsunoda, T.; Tatsuki, S.; Shiraishi, Y.; Akasaka, M.; Itô, S. *Tetrahedron Lett.* ***1993***, *34*, 3297. Also see, Walters, M.A.; Hoem, A.B.; Arcand, H.R.; Hegeman, A.D.; McDonough, C.S. *Tetrahedron Lett.* ***1993***, *34*, 1453.

[686]Marcinkiewicz, S.; Green, J.; Mamalis, P. *Tetrahedron* ***1961***, *14*, 208; Inada, S.; Ikado, S.; Okazaki, M. *Chem. Lett.* ***1973***, 1213; Schmid, M.; Hansen, H.; Schmid, H. *Helv. Chim. Acta* ***1973***, *56*, 105; Jolidon, S.; Hansen, H. *Helv. Chim. Acta* ***1977***, *60*, 978.

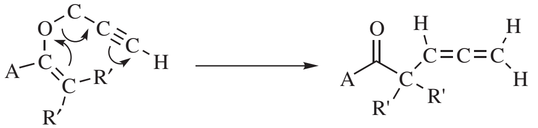
[687]Ficini, J.; Barbara, C. *Tetrahedron Lett.* ***1966***, 6425; Ireland, R.E.; Willard, A.K. *J. Org. Chem.* ***1974***, *39*, 421; Hill, R.K.; Khatri, H.N. *Tetrahedron Lett.* ***1978***, 4337; Anderson, J.C.; Flaherty, A.; Swarbrick, M.E. *J. Org. Chem.* ***2000***, *65*, 9152. For the reverse of this rearrangement, see Wu, P.; Fowler, F.W. *J. Org. Chem.* ***1988***, *53*, 5998.

[688]For examples, see Synerholm, M.E.; Gilman, N.W.; Morgan, J.W.; Hill, R.K. *J. Org. Chem.* ***1968***, *33*, 1111; Black, D.S.; Eastwood, F.W.; Okraglik, R.; Poynton, A.J.; Wade, A.M.; Welker, C.H. *Aust. J. Chem.* ***1972***, *25*, 1483; Overman, L.E. *J. Am. Chem. Soc.* ***1974***, *96*, 597; Metz, P.; Mues, C. *Tetrahedron* ***1988***, *44*, 6841. See Gradl, S.N.; Kennedy-Smith, J.J.; Kim, J.; Trauner, D. *Synlett* ***2002***, 411.

[689]See Schenck, T.G.; Bosnich, B. *J. Am. Chem. Soc.* ***1985***, *107*, 2058, and references cited therein. Palladium catalyzed: Jiang, Y.; Longmire, J.M.; Zhang, X. *Tetrahedron Lett.* ***1999***, *40*, 1449; Donde, Y.; Overman, L.E. *J. Am. Chem. Soc.* ***1999***, *121*, 2933; Anderson, C.E.; Overman, L.E. *J. Am. Chem. Soc.* ***2003***, *125*, 12412.

[690]See Majumdar, K.C.; Samanta, S.K. *Tetrahedron* ***2001***, *57*, 4955; Kirsch, S.F.; Overman, L.F.; Watson, M.P. *J. Org. Chem.* ***2004***, *69*, 8101.

aza-Cope rearrangements[691] as described in **18-34**. However, a palladium catalyzed aza-Claisen has been reported.[692] A so-called amine-Claisen rearrangement was reported for *N*-allyl indoles, when heated in the presence of $BF_3{\bullet}OEt_2$.[693] An *azo-Cope* rearrangement: $CH_2{=}CHCR^1_2\ CR^2_2\ N{=}NAr \rightarrow R^1_2C{=}CHCH_2NArN{=}CR^2_2$ has been reported.[694] Propargylic vinylic compounds give allenic aldehydes, ketones, esters, or amides:[695]



The conversion of allylic aryl thioethers $ArSCH_2CH{=}CH_2$ to *o*-allylic thiophenols is not feasible, because the latter are not stable,[696] but react to give bicyclic compounds.[697] However, many allylic vinylic sulfides do give the rearrangement (the *thio-Claisen rearrangement*).[698] Allylic vinylic sulfones, for example, $H_2C{=}CRCH_2{-}SO_2{-}CH{=}CH_2$, rearrange, when heated in the presence of ethanol and pyridine, to unsaturated sulfonate salts $CH_2{=}CRCH_2CH_2CH_2SO_3^-$, produced by reaction of the reagents with the unstable sulfene intermediates $CH_2{=}CRCH_2CH_2CH{=}SO_2$.[699] Allylic vinylic sulfoxides rapidly rearrange at room temperature or below.[700]

As mentioned for the Ireland–Claisen rearrangement, asymmetric Claisen rearrangement reactions are well known.[701] Chiral Lewis acids have been designed for

[691]For a review, see Przheval'skii, N.M.; Grandberg, I.I. *Russ. Chem. Rev.* ***1987***, *56*, 477. For reviews of [3,3]-sigmatropic rearrangements with heteroatoms present, see Blechert, S. *Synthesis* ***1989***, 71; Winterfeldt, E. *Fortschr. Chem. Forsch.* ***1970***, *16*, 75. For a review of [3,3]-rearrangements of iminium salts, see Heimgartner, H.; Hansen, H.; Schmid, H. *Adv. Org. Chem.* ***1979***, *9*, pt. 2, 655.

[692]Uozumi, Y.; Kato, K.; Hayashi, T. *Tetrahedron Asymmetry*, ***1998***, *9*, 1065; Mehmandoust, M.; Petit, Y.; Larchevêque, M. *Tetrahedron Lett.* ***1992***, *33*, 4313. For a 3-aza-Claisen rearrangement, see Gilbert, J.C.; Cousins, K.R. *Tetrahedron* ***1994***, *50*, 10671.

[693]Anderson, W.K.; Lai, G. *Synthesis* ***1995***, 1287.

[694]Mitsuhashi, T. *J. Am. Chem. Soc.* ***1986***, *108*, 2400.

[695]For reviews of Claisen rearrangements involving triple bonds, see Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis*, Wiley, NY, ***1984***, pp. 337–343; Viola, A.; Collins, J.J.; Filipp, N. *Tetrahedron* ***1981***, *37*, 3765; Théron F.; Verny, M.; Vessière, R., in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, pt. 1, Wiley, NY, ***1978***, pp. 421–428. See also, Henderson, M.A.; Heathcock, C.H. *J. Org. Chem.* ***1988***, *53*, 4736.

[696]They have been trapped: See, for example, Mortensen, J.Z.; Hedegaard, B.; Lawesson, S. *Tetrahedron* ***1971***, *27*, 3831; Kwart, H.; Schwartz, J.L. *J. Org. Chem.* ***1974***, *39*, 1575.

[697]Meyers, C.Y.; Rinaldi, C.; Banoli, L. *J. Org. Chem.* ***1963***, *28*, 2440; Kwart, H.; Cohen, M.H. *J. Org. Chem.* ***1967***, *32*, 3135; *Chem. Commun.* ***1968***, 319; Makisumi, Y.; Murabayashi, A. *Tetrahedron Lett.* ***1969***, 1971, 2449.

[698]For a review, see Majumdar, K.C.; Ghosh, S.; Ghosh, M. *Tetrahedron* ***2003***, *59*, 7251.

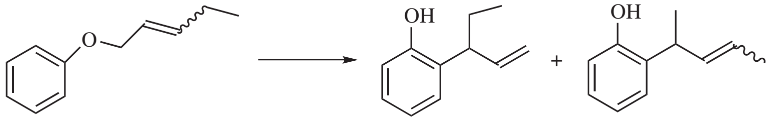
[699]King, J.F.; Harding, D.R.K. *J. Am. Chem. Soc.* ***1976***, *98*, 3312.

[700]Block, E.; Ahmad, S. *J. Am. Chem. Soc.* ***1985***, *107*, 6731.

[701]For example, see Zumpe, F.L.; Kazmaier, U. *Synlett* ***1998***, 434; Ito, H.; Sato, A.; Taguchi, T. *Tetrahedron Lett.* ***1997***, *38*, 4815; Kazmaier, U.; Krebs, A. *Angew. Chem. Int. Ed.* ***1995***, *34*, 2012. For asymmetric induction in the thio-Claisen rearrangement, see Reddy, K.V.; Rajappa, S. *Tetrahedron Lett.* ***1992***, *33*, 7957.

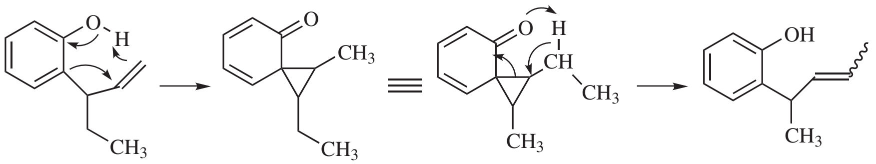
this purpose.[702] In general, asymmetric [3,3]-sigmatropic rearrangements are well known.[703]

Ethers with an alkyl group in the γ position (ArO–C–C=C–R systems) sometimes give abnormal products, with the β carbon becoming attached to the ring:[704]

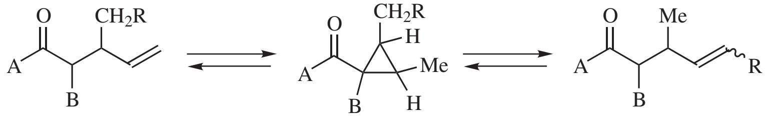


Normal product Abnormal product

It has been established that these abnormal products do not arise directly from the starting ether, but are formed by a further rearrangement of the normal product:[705]



This rearrangement, which has been called an *enolene rearrangement*, a *homodienyl* [1,5]-*sigmatropic hydrogen shift* (see **18-29**), and a [1,5]-*homosigmatropic rearrangement*, involves a shift of three electron pairs over *seven* atoms. It has been found that this "abnormal" Claisen rearrangement is general and can interconvert the enol forms of systems of the types **135** and **136** through the cyclopropane intermediate **137**.[706]



135 **136** **137**

A = H, R, Ar, OR, and so on
B = H, R, Ar, COR, COAr, COOR, and so on

[702]Maruoka, K.; Saito, S.; Yamamoto, J. *J. Am. Chem. Soc.* ***1995***, *117*, 1165. See Sharma, G.V.M.; Ilangovan, A.; Sreevivas, P.; Mahalingam, A.K. *Synlett* ***2000***, 615. **Yb**: Hiersemann, M.; Abraham, L. *Org. Lett.* ***2001***, *3*, 49. **Rh**: Miller, S.P.; Morken, J.P. *Org. Lett.* ***2002***, *4*, 2743.

[703]For a review, see Enders, D.; Knopp, M.; Schiffers, R. *Tetrahedron Asymmetry*, ***1996***, *7*, 1847.

[704]For reviews of these abnormal Claisen rearrangements, see Hansen, H. *Mech. Mol. Migr.* ***1971***, *3*, 177; Marvell, E.N.; Whalley, W., in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 2, Wiley, NY, ***1971***, pp. 743–750.

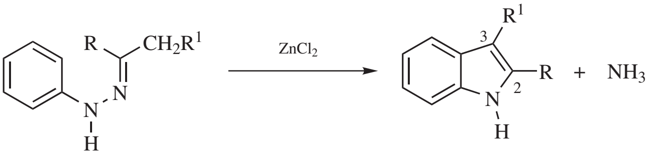
[705]Habich, A.; Barner, R.; Roberts, R.; Schmid, H. *Helv. Chim. Acta* ***1962***, *45*, 1943; Lauer, W.M.; Johnson, T.A. *J. Org. Chem.* ***1963***, *28*, 2913; Fráter, G.; Schmid, H. *Helv. Chim. Acta* ***1966***, *49*, 1957; Marvell, E.N.; Schatz, B. *Tetrahedron Lett.* ***1967***, 67.

[706]Watson, J.M.; Irvine, J.L.; Roberts, R.M. *J. Am. Chem. Soc.* ***1973***, *95*, 3348.

Since the Claisen rearrangement mechanism does not involve ions, it should not be greatly dependent on the presence or absence of substituent groups on the ring.[707] This is the case. Electron-donating groups increase the rate and electron-withdrawing groups decrease it, but the effect is small, with the *p*-amino compound reacting only ~10–20 times faster than the *p*-nitro compound.[708] However, solvent effects[709] are greater: Rates varied over a 300-fold range when the reaction was run in 17 different solvents.[710] An especially good solvent is trifluoroacetic acid, in which the reaction can be carried out at room temperature.[711] Most Claisen rearrangements are performed without a catalyst, but $AlCl_3$ or BF_3 are sometimes used.[712] In this case, it may become a Friedel–Crafts reaction, with the mechanism no longer cyclic,[713] and ortho, meta, and para products may be obtained.

OS **III**, 418; **V**, 25; **VI**, 298, 491, 507, 584, 606; **VII**, 177; **VIII**, 251, 536.

18-34 The Fischer Indole Synthesis



When arylhydrazones of aldehydes or ketones are treated with a catalyst, elimination of ammonia takes place and an indole is formed, in the *Fischer indole synthesis*.[714] Zinc chloride is the catalyst most frequently employed, but dozens of others, including other metal halides, proton and Lewis acids, and certain transition

[707]However, there are substituent effects, see Aviyente, V.; Yoo, H.Y.; Houk, K.N. *J. Org. Chem.* ***1997***, *62*, 6121.

[708]Goering, H.L.; Jacobson, R.R. *J. Am. Chem. Soc.* ***1958***, *80*, 3277; White, W.N.; Gwynn, D.; Schlitt, R.; Girard, C.; Fife, W.K. *J. Am. Chem. Soc.* ***1958***, *80*, 3271; White, W.N.; Slater, C.D. *J. Org. Chem.* ***1962***, *27*, 2908; Zahl, G.; Kosbahn, W.; Kresze, G. *Liebigs Ann. Chem.* ***1975***, 1733. See also, Desimoni, G.; Faita, G.; Gamba, A.; Righetti, P.P.; Tacconi, G.; Toma, L. *Tetrahedron* ***1990***, *46*, 2165; Gajewski, J.J.; Gee, K.R.; Jurayj, J. *J. Org. Chem.* ***1990***, *55*, 1813.

[709]For a discussion of the role played by solvent and substituents, see Gajewski, J.J. *Acc. Chem. Res.* ***1997***, *30*, 219. For solvent effects, see Davidson, M.M.; Hillier, I.H.; Hall, R.J.; Burton, N.A. *J. Am. Chem. Soc.* ***1994***, *116*, 9294.

[710]White, W.N.; Wolfarth, E.F. *J. Org. Chem.* ***1970***, *35*, 2196. See also Brandes, E.; Greico, P.A.; Gajewski, J.J. *J. Org. Chem.* ***1989***, *54*, 515.

[711]Svanholm, U.; Parker, V.D. *J. Chem. Soc. Perkin Trans. 2* ***1974***, 169.

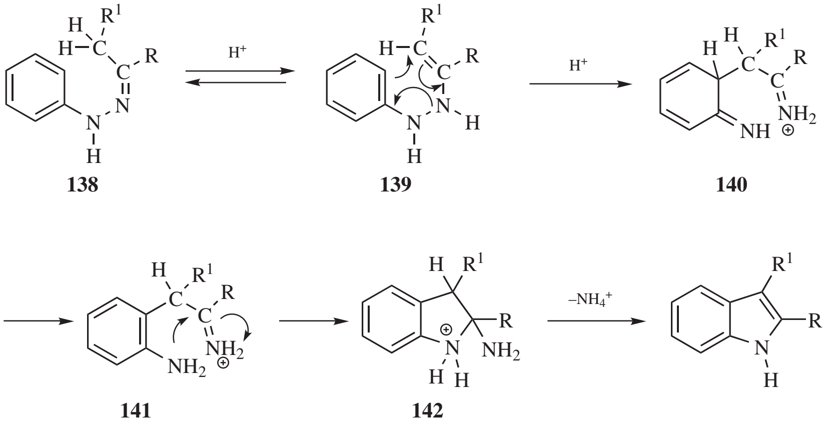
[712]For a review, see Lutz, R.P. *Chem. Rev.* ***1984***, *84*, 205.

[713]For example, crossover experiments have demonstrated that the $ZnCl_2$-catalyzed reaction is intermolecular: Yagodin, V.G.; Bunina-Krivorukova, L.I.; Bal'yan, Kh.V. *J. Org. Chem. USSR* ***1971***, *7*, 1491.

[714]For a monograph, see Robinson, B. *The Fischer Indole Synthesis*, Wiley, NY, ***1983***. For reviews, see Grandberg, I.I.; Sorokin, V.I. *Russ. Chem. Rev.* ***1974***, *43*, 115; Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1969***, pp. 190–207; Sundberg, R.J. *The Chemistry of Indoles*, Academic Press, NY, ***1970***, pp. 142–163; Robinson, B. *Chem. Rev.* ***1969***, *69*, 227. For reviews of some abnormal Fischer indole syntheses, see Ishii, H. *Acc. Chem. Res.* ***1981***, *14*, 275; Fusco, R.; Sannicolo, F. *Tetrahedron* ***1980***, *36*, 161.

metals have also been used. Microwave irradiation has been used to facilitate this reaction.[715] The reaction has been done using an $AlCl_3$ complex as an ionic liquid,[716] and solid-phase Fischer-indole syntheses are known.[717] Aniline derivatives react with α-diazoketones, in the presence of a rhodium catalyst, to give indoles as well.[718] Arylhydrazones are easily prepared by the treatment of aldehydes or ketones with phenylhydrazine (**16-2**) or by aliphatic diazonium coupling (**12-7**). However, it is not necessary to isolate the arylhydrazone. The aldehyde or ketone can be treated with a mixture of phenylhydrazine and the catalyst; this is now common practice. In order to obtain an indole, the aldehyde or ketone must be of the form $RCOCH_2R'$ (R = alkyl, aryl, or hydrogen). Vinyl ethers, such as dihydrofuran, serves as an aldehyde surrogate when treated with phenylhydrazine and a catalytic amount of aqueous sulfuric acid to give an 3-substituted indole.[719]

At first glance, the reaction does not seem to be a rearrangement. However, the key step of the mechanism[720] is a [3,3]-sigmatropic rearrangement:[721]



There is much evidence for this mechanism, for example, (*1*) the isolation of **142**,[722] (*2*) the detection of **141** by ^{13}C and ^{15}N NMR,[723] (*3*) the isolation of side products that could only have come from **140**,[724] and (*4*) ^{15}N labeling experiments that showed

[715]Abramovitch, R.A.; Bulman, A. *Synlett* ***1992***, 795; Lipińska, T.; Guibé-Jampel, E.; Petit, A.; Loupy, A. *Synth. Commun.* ***1999***, *29*, 1349.
[716]In $AlCl_3$–*N*-butylpyridinium: Rebeiro, G.LO.; Khadilkar, B.M. *Synthesis* ***2001***, 370.
[717]Rosenbaum, C.; Katzka, C.; Marzinzik, A.; Waldmann, H. *Chem. Commun.* ***2003***, 1822.
[718]Moody, C.J.; Swann, E. *Synlett* ***1998***, 135.
[719]Campos, K.R.; Woo, J.C.S.; Lee, S.; Tillyer, R.D. *Org. Lett.* ***2004***, *6*, 79.
[720]For a mechanistic study, see Hughes, D.L.; Zhao, D. *J. Org. Chem.* ***1993***, *58*, 228.
[721]This mechanism was proposed by Robinson, G.M.; Robinson, R. *J. Chem. Soc.* ***1918***, *113*, 639.
[722]Southwick, P.L.; Vida, J.A.; Fitzgerald, B.M.; Lee, S.K. *J. Org. Chem.* ***1968***, *33*, 2051; Forrest, T.P.; Chen, F.M.F. *J. Chem. Soc., Chem. Commun.* ***1972***, 1067.
[723]Douglas, A.W. *J. Am. Chem. Soc.* ***1978***, *100*, 6463; ***1979***, *101*, 5676.
[724]Bajwa, G.S.; Brown, R.K. *Can. J. Chem.* ***1969***, *47*, 785; ***1970***, *48*, 2293, and references cited therein.

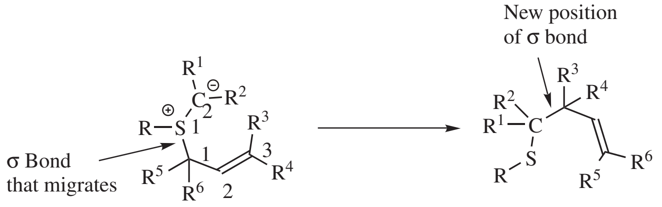
that it was the nitrogen farther from the ring that is eliminated as ammonia.[725] The main function of the catalyst seems to be to speed the conversion of **138** to **139**. The reaction can be performed without a catalyst.

There are alternative methods to produce indoles. Acetophenone reacts with 2-chloro nitrobenzene derivatives in the presence of a phenol and a palladium catalyst to give an indole.[726]

OS **III**, 725; **IV**, 884. Also see, OS **IV**, 657.

18-35 [2,3]-Sigmatropic Rearrangements

(2/*S*-3/) → (1/5/)-*sigma*-Migration



Sulfur ylids bearing an allylic group are converted on heating to unsaturated sulfides.[727] This is a concerted [2,3]-sigmatropic rearrangement[728] and has also been demonstrated for the analogous cases of nitrogen ylids[729] and the conjugate bases of allylic ethers (in the last case it is called the *[2,3]-Wittig rearrangement*).[730] It has been argued that the [2,3]-Wittig rearrangement demands severe deformation of the molecule in order to proceed.[731] The SmI_2 compound has been shown to induce

[725]Clausius, K.; Weisser, H.R. *Helv. Chim. Acta* ***1952***, *35*, 400.

[726]Rutherford, J.L.; Rainka, M.P.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2002***, *124*, 15168.

[727]For example, see Blackburn, G.M.; Ollis, W.D.; Plackett, J.D.; Smith, C.; Sutherland, I.O. *Chem. Commun.* ***1968***, 186; Trost, B.M.; LaRochelle, R. *Tetrahedron Lett.* ***1968***, 3327; Baldwin, J.E.; Hackler, R.E.; Kelly, D.P. *Chem. Commun.* ***1968***, 537, 538, 1083; Bates, R.B.; Feld, D. *Tetrahedron Lett.* ***1968***, 417; Kirmse, W.; Kapps, M. *Chem. Ber.* ***1968***, *101*, 994, 1004; Biellmann, J.F.; Ducep, J.B. *Tetrahedron Lett.* ***1971***, 33; Ceré, V.; Paolucci, C.; Pollicino, S.; Sandri, E.; Fava, A. *J. Org. Chem.* ***1981***, *46*, 3315; Kido, F.; Sinha, S.C.; Abiko, T.; Yoshikoshi, A. *Tetrahedron Lett.* ***1989***, *30*, 1575. For a review as applied to ring expansions, see Vedejs, E. *Acc. Chem. Res.* ***1984***, *17*, 358.

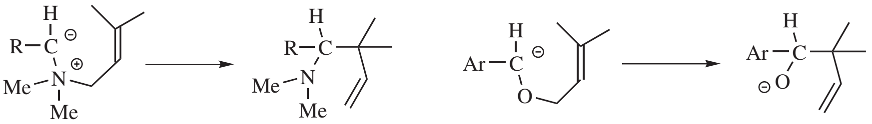
[728]For a review of the stereochemistry of these reactions, see Hoffmann, R.W. *Angew. Chem. Int. Ed.* ***1979***, *18*, 563.

[729]For example, see Jemison, R.W.; Ollis, W.D. *Chem. Commun.* ***1969***, 294; Rautenstrauch, V. *Helv. Chim. Acta* ***1972***, *55*, 2233; Mageswaran, S.; Ollis, W.D.; Sutherland, I.O.; Thebtaranonth, Y. *J. Chem. Soc., Chem. Commun.* ***1973***, 651; Ollis, W.D.; Sutherland, I.O.; Thebtaranonth, Y. *J. Chem. Soc., Chem. Commun.* ***1973***, 657; Mander, L.N.; Turner, J.V. *J. Org. Chem.* ***1973***, *38*, 2915; Stévenart-De Mesmaeker, N.; Merényi, R.; Viehe, H.G. *Tetrahedron Lett.* ***1987***, *28*, 2591; Honda, K.; Inoue, S.; Sato, K. *J. Am. Chem. Soc.* ***1990***, *112*, 1999.

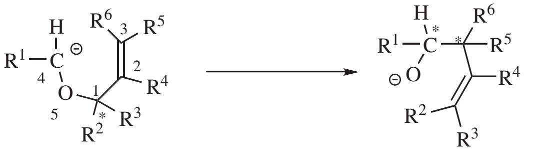
[730]See, for example, Makisumi, Y.; Notzumoto, S. *Tetrahedron Lett.* ***1966***, 6393; Schöllkopf, U.; Fellenberger, K.; Rizk, M. *Liebigs Ann. Chem.* ***1970***, *734*, 106; Rautenstrauch, V. *Chem. Commun.* ***1970***, 4. For a review, see Nakai, T.; Mikami, K. *Chem. Rev.* ***1986***, *86*, 885. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1063–1067.

[731]You, Z.; Koreeda, M. *Tetrahedron Lett.* ***1993***, *34*, 2597.

a [2,3]-Wittig rearrangement.[732] The reaction has been extended to certain other systems,[733] even to an all-carbon system.[734]



Since the reactions involve migration of an allylic group from a sulfur, nitrogen, or oxygen atom to an adjacent negatively charged carbon atom, they are special cases of the Stevens or Wittig rearrangements (**18-21**, **18-22**). However, in this case the migrating group *must* be allylic (in **18-21** and **18-22** other groups can also migrate). Thus, when the migrating group is allylic, there are two possible pathways: (*1*) the radical-ion or ion-pair mechanisms (**18-21**, **18-22**) and (*2*) the concerted pericyclic [2,3]-sigmatropic rearrangement. These can easily be told apart, since the latter always involves an allylic shift (as in the Claisen rearrangement), while the former pathway does not.



Of these reactions, the [2,3]-Wittig rearrangement in particular has often been used as a means of transferring chirality. The product of this reaction has potential stereogenic centers at C-3 and C-4 (if $R^5 \neq R^6$), and if the starting ether is optically active because of a stereogenic center at C-1, the product may be optically active as well. Many examples are known in which an optically active ether was converted to a product that was optically active because of chirality at C-3, C-4, or both.[735] If a

[732]Kunishima, M.; Hioki, K.; Kono, K.; Kato, A.; Tani, S. *J. Org. Chem.* ***1997***, *62*, 7542. Also see, Hioki, K.; Kono, K.; Tani, S.; Kunishima, M. *Tetrahedron Lett.* ***1998***, *39*, 5229. For an enantioselective [2,3]-Wittig rearrangment, see Fujimoto, K.; Nakai, T. *Tetrahedron Lett.* ***1994***, *35*, 5019.

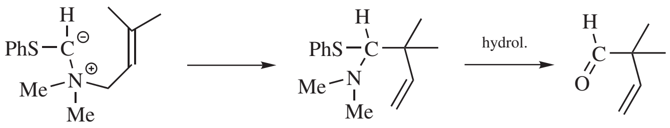
[733]See, for example, Baldwin, J.E.; Brown, J.E.; Höfle, G. *J. Am. Chem. Soc.* ***1971***, *93*, 788; Yamamoto, Y.; Oda, J.; Inouye, Y. *J. Chem. Soc., Chem. Commun.* ***1973***, 848; Ranganathan, S.; Ranganathan, D.; Sidhu, R.S.; Mehrotra, A.K. *Tetrahedron Lett.* ***1973***, 3577; Murata, Y.; Nakai, T. *Chem. Lett.* ***1990***, 2069. For reviews with respect to selenium compounds, see Reich, H.J., in Liotta, D.C. *Organoselenium Chemistry*, Wiley, NY, ***1987***, pp. 365–393; Reich, H.J., in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. C, Academic Press, NY, ***1978***, pp. 102–111.

[734]Baldwin, J.E.; Urban, F.J. *Chem. Commun.* ***1970***, 165.

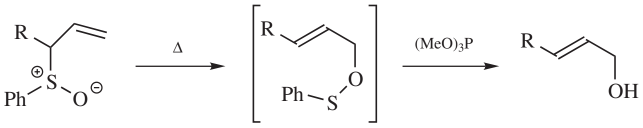
[735]For reviews of stereochemistry in this reaction, see Mikami, K.; Nakai, T. *Synthesis* ***1991***, 594; Nakai, T.; Mikami, K. *Chem. Rev.* ***1986***, *86*, 885, 888–895. See also, Nakai, T.; Nakai, E. *Tetrahedron Lett.* ***1988***, *29*, 4587; Balestra, M.; Kallmerten, J. *Tetrahedron Lett.* ***1988***, *29*, 6901; Brückner, R. *Chem. Ber.* ***1989***, *122*, 193, 703; Scheuplein, S.W.; Kusche, A.; Brückner, R.; Harms, K. *Chem. Ber.* ***1990***, *123*, 917; Wu, Y.; Houk, K.N.; Marshall, J.A. *J. Org. Chem.* ***1990***, *55*, 1421; Marshall, J.A.; Wang, X. *J. Org. Chem.* ***1990***, *55*, 2995.

suitable stereogenic center is present in R^1 (or if a functional group in R^1 can be so converted), then stereocontrol over three contiguous stereogenic centers can be achieved. Stereocontrol of the new double bond (*E* or *Z*) has also been accomplished.

If an OR or SR group is attached to the negative carbon, the reaction becomes a method for the preparation of β,γ-unsaturated aldehydes, because the product is easily hydrolyzed.[736]

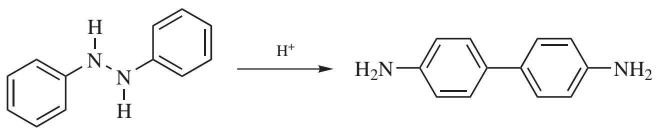


Another [2,3]-sigmatropic rearrangement converts allylic sulfoxides to allylically rearranged alcohols by treatment with a thiophilic reagent, such as trimethyl phosphite.[737] This is often called the *Mislow–Evans rearrangement*. In this case, the migration is from sulfur to oxygen. [2,3]-Oxygen-to-sulfur migrations are also known.[738] The Sommelet–Hauser rearrangement (**13-31**) is also a [2,3]-sigmatropic rearrangement.



OS **VIII**, 427.

18-36 The Benzidine Rearrangement



Hydrazobenzene **143**

[736]Huynh, C.; Julia, S.; Lorne, R.; Michelot, D. *Bull. Soc. Chim. Fr.* ***1972***, 4057.

[737]Tang, R.; Mislow, K. *J. Am. Chem. Soc.* ***1970***, *92*, 2100; Evans, D.A.; Andrews, G.C. *Acc. Chem. Res.* ***1974***, *7*, 147; Hoffmann, R.W. *Angew. Chemie. Int. Ed., Engl.*, ***1979***, *18*, 563; Sato, T.; Otera, J.; Nozaki, H. *J. Org. Chem.* ***1989***, *54*, 2779; Bickart, P.; Carson, F.W.; Jacobus, J.; Miller, E.G.; Mislow, K. *J. Am. Chem. Soc.* ***1968***, *90*, 4869.

[738]Braverman, S.; Mechoulam, H. *Isr. J. Chem.* ***1967***, *5*, 71, Braverman, S.; Stabinsky, Y. *Chem. Commun.* ***1967***, 270; Rautenstrauch, V. *Chem. Commun.* ***1970***, 526; Smith, G.; Stirling, C.J.M. *J. Chem. Soc. C* ***1971***, 1530; Tamaru, Y.; Nagao, K.; Bando, T.; Yoshida, Z. *J. Org. Chem.* ***1990***, *55*, 1823.

When hydrazobenzene is treated with acids, it rearranges to give ~70% 4,4′-diaminobiphenyl (**143**, benzidine) and ~30% 2,4′-diaminobiphenyl. This reaction is called the *benzidine rearrangement* and is general for *N,N′*-diarylhydrazines.[739] Usually, the major product is the 4,4′-diaminobiaryl, but four other products may also be produced. These are the 2,4′-diaminobiaryl, already referred to, the 2,2′-diaminobiaryl, and the *o*- and *p*-arylaminoanilines (called *semidines*). The 2,2′- and *p*-arylaminoaniline compounds are formed less often and in smaller amounts than the other two side products. Usually, the 4,4′-diaminobiaryl predominates, except when one or both para positions of the diarylhydrazine are occupied. However, the 4,4′-diamine may still be produced even if the para positions are occupied. If SO_3H, COOH, or Cl (but not R, Ar, or NR_2) is present in the para position, it may be ejected. With dinaphthylhydrazines, the major products are not the 4,4′-diaminobinaphthyls, but the 2,2′ isomers. Another side reaction is disproportionation to $ArNH_2$ and ArN=NAr. For example, *p,p′*-$PhC_6H_4NHNHC_6H_4Ph$ gives 88% disproportionation products at 25°C.[740]

The mechanism has been exhaustively studied and several mechanisms have been proposed.[741] At one time, it was believed that NHAr broke away from ArNHNHAr and became attached to the para position to give the semidine, which then went on to product. The fact that semidines could be isolated lent this argument support, as did the fact that this would be analogous to the rearrangements considered in Chapter 11 (**11-28–11-32**). However, this theory was killed when it was discovered that semidines could not be converted to benzidines under the reaction conditions. Cleavage into two independent pieces (either ions or radicals) has been ruled out by many types of crossover experiments, which always showed that the two rings of the starting material are in the product; that is, ArNHNHAr′ gives no molecules (of any of the five products) containing two Ar groups or two Ar′ groups, and mixtures of ArNHNHAr and Ar′NHNHAr′ give no molecules containing both Ar and Ar′. An important discovery was the fact that, although the reaction is always first order in substrate, it can be either

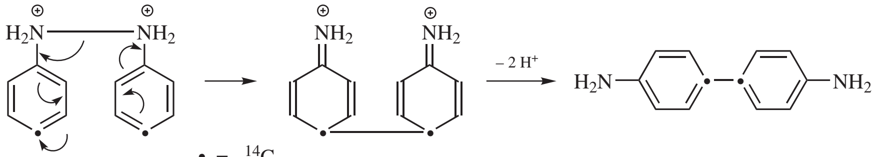
[739]For reviews, see, in Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 2, Wiley, NY, ***1975***, the reviews by Cox, R.A.; Buncel, E. pp. 775–807; Koga, G.; Koga, N.; Anselme, J. pp. 914–921; Williams, D.L.H., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, Vol. 13, 1972, pp. 437–448; Shine, H.J. *Mech. Mol. Migr.* ***1969***, *2*, 191; *Aromatic Rearrangements*, Elsevier, NY, ***1969***, pp. 126–179; Banthorpe, D.V. *Top. Carbocyclic Chem.* ***1969***, *1*, 1; Lukashevich, V.O. *Russ. Chem. Rev.* ***1967***, *36*, 895.

[740]Shine, H.J.; Stanley, J.P. *J. Org. Chem.* ***1967***, *32*, 905. For investigations of the mechanism of the disproportionation reactions, see Rhee, E.S.; Shine, H.J. *J. Am. Chem. Soc.* ***1986***, *108*, 1000; ***1987***, *109*, 5052.

[741]For a history of the mechanistic investigations and controversies, see Shine, H.J. *J. Phys. Org. Chem.* ***1989***, *2*, 491.

first[742] or second[743] order in [H^+]. With some substrates the reaction is entirely first order in [H^+], while with others it is entirely second order in [H^+], regardless of the acidity. With still other substrates, the reaction is first order in [H^+] at low acidities and second order at higher acidities. With the latter substrates fractional orders can often be observed,[744] because at intermediate acidities, both processes take place simultaneously. These kinetic results seem to indicate that the actual reacting species can be either the monoprotonated substrate $ArNHNH_2Ar$ or the diprotonated $ArNH_2NH_2Ar$.

Most of the proposed mechanisms[745] attempted to show how all five products could be produced by variations of a single process. An important breakthrough was the discovery that the two main products are formed in entirely different ways, as shown by isotope-effect studies.[746] When the reaction was run with hydrazobenzene labeled with ^{15}N at both nitrogen atoms, the isotope effect was 1.022 for formation of **143**, but 1.063 for formation of 2,4′-diaminobiphenyl. This showed that the N–N bond is broken in the rate-determining step in both cases, but the steps themselves are obviously different. When the reaction was run with hydrazobenzene labeled with ^{14}C at a para position, there was an isotope effect of 1.028 for formation of **143**, but essentially no isotope effect (1.001) for formation of 2,4′-diaminobiphenyl. This can only mean that for **143** formation of the new C–C bond *and* breaking of the N–N bond both take place in the rate-determining step; in other words, the mechanism is concerted. The following [5.5]-sigmatropic rearrangement accounts for this:[745,747]



• = ^{14}C

144

[742]Banthorpe, D.V.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1962***, 2386, 2402, 2407, 2413, 2418, 2429; Shine, H.J.; Chamness, J.T. *J. Org. Chem.* ***1963***, *28*, 1232; Banthorpe, D.V.; O'Sullivan, M. *J. Chem. Soc. B* ***1968***, 627.

[743]Hammond, G.S.; Shine, H.J. *J. Am. Chem. Soc.* ***1950***, *72*, 220; Banthorpe, D.V.; Cooper, A. *J. Chem. Soc. B* ***1968***, 618; Banthorpe, D.V.; Cooper, A.; O'Sullivan, M. *J. Chem. Soc. B* ***1971***, 2054.

[744]Carlin, R.B.; Odioso, R.C. *J. Am. Chem. Soc.* ***1954***, *76*, 100; Banthorpe, D.V.; Ingold, C.K.; Roy, J. *J. Chem. Soc. B* ***1968***, 64; Banthorpe, D.V.; Ingold, C.K.; O'Sullivan, M. *J. Chem. Soc. B* ***1968***, 624.

[745]For example, see the "polar-transition-state mechanism:" Banthorpe, D.V.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1964***, 2864, and the "π-complex mechanism:" Dewar, M.J.S., in de Mayo, P. *Molecular Rearrangments*, Vol. 1, Wiley, NY, ***1963***, pp. 323–344.

[746]Shine, H.J.; Zmuda, H.; Park, K.H.; Kwart, H.; Horgan, A.J.; Collins, C.; Maxwell, B.E. *J. Am. Chem. Soc.* ***1981***, *103*, 955; Shine, H.J.; Zmuda, H.; Park, K.H.; Kwart, H.; Horgan, A.J.; Brechbiel, M. *J. Am. Chem. Soc.* ***1982***, *104*, 2501.

[747]This step was also part of the "polar-transition-state mechanism".

The diion **144** was obtained as a stable species in super acid solution at −78°C by treatment of hydrazobenzene with $FSO_3H–SO_2$ (SO_2ClF).[748] Though the results just given were obtained with hydrazobenzene, which reacts by the diprotonated pathway, monoprotonated substrates have been found to react by the same [5,5]-sigmatropic mechanism.[749] Some of the other rearrangements in this section are also sigmatropic. Thus, formation of the *p*-semidine takes place by a [1,5]-sigmatropic rearrangement,[750] and the conversion of 2,2′-hydrazonaphthalene to 2,2′-diamino-1,1′-binaphthyl by a [3,3]-sigmatropic rearrangement.[751]

2,4′-Diaminobiphenyl is formed by a completely different mechanism, though the details are not known. There is rate-determining breaking of the N–N bond, but the C–C bond is not formed during this step.[752] The formation of the *o*-semidine also takes place by a nonconcerted pathway.[753] Under certain conditions, benzidine rearrangements have been found to go through radical cations.[754]

C. Other Cyclic Rearrangements

18-37 Metathesis of Alkenes (Alkene or Olefin Metathesis)[755]

Alkene metathesis

$$CH_3CH{=}CHCH_2CH_3 \xrightarrow[WCl_6–EtOH]{EtAlCl_2} CH_3CH{=}CHCH_3 + CH_3CH_2CH{=}CHCH_2CH_3$$

When alkenes are treated with certain catalysts they are converted to other alkenes in a reaction in which the alkylidene groups ($R^1R^2C{=}$) have become interchanged by a process schematically illustrated by the equation:

[748]Olah, G.A.; Dunne, K.; Kelly, D.P.; Mo, Y.K. *J. Am. Chem. Soc.* ***1972***, *94*, 7438.

[749]Shine, H.J.; Park, K.H.; Brownawell, M.L.; San Filippo, Jr., J. *J. Am. Chem. Soc.* ***1984***, *106*, 7077.

[750]Heesing, A.; Schinke, U. *Chem. Ber.* ***1977***, *110*, 3319; Shine, H.J.; Zmuda, H.; Kwart, H.; Horgan, A.G.; Brechbiel, M. *J. Am. Chem. Soc.* ***1982***, *104*, 5181.

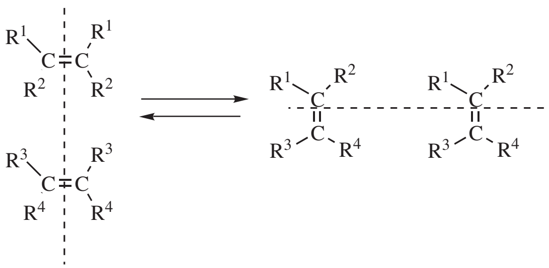
[751]Shine, H.J.; Gruszecka, E.; Subotkowski, W.; Brownawell, M.; San Filippo, Jr., J. *J. Am. Chem. Soc.* ***1985***, *107*, 3218.

[752]See Rhee, E.S.; Shine, H.J. *J. Am. Chem. Soc.* ***1986***, *108*, 1000; ***1987***, *109*, 5052.

[753]Rhee, E.S.; Shine, H.J. *J. Org. Chem.* ***1987***, *52*, 5633.

[754]See, for example, Nojima, M.; Ando, T.; Tokura, N. *J. Chem. Soc. Perkin Trans. 1* ***1976***, 1504.

[755]For reviews, see Grubbs, R.H. *Tetrahedron* ***2004***, *60*, 7117; Wakamatsu, H.; Blechert, S. *Angew. Chem. Int. Ed.* ***2002***, *41*, 2403; Schrock, R.R.; Hoveyda, A.H. *Angew. Chem. Int. Ed.* ***2003***, *42*, 4592.



The reaction is called *metathesis* of alkenes or *alkene metathesis* (*olefin metathesis*).[756] In the example shown above, 2-pentene (either cis, trans, or a cis–trans mixture) is converted to a mixture of ~50% 2-pentene, 25% 2-butene, and 25% 3-hexene. The reaction is reversible[757] and the alkene starting material and products exist in an equilibrium, so the same mixture can be obtained by starting with equimolar quantities of 2-butene and 3-hexene.[758] In general, the reaction can be applied to a single unsymmetrical alkene, giving a mixture of itself and two other alkenes, or to a mixture of two alkenes, in which case the number of different molecules in the product depends on the symmetry of the reactants. As in the case above, a mixture of $R^1R^2C{=}CR^1R^2$ and $R^3R^4C{=}CR^3R^4$ gives rise to only one new alkene ($R^1R^2C{=}CR^3R^4$), while in the most general case, a mixture of $R^1R^2C{=}CR^3R^4$ and $R^5R^6C{=}CR^7R^8$ gives a mixture of 10 alkenes: the original $2 + 8$ new ones. In early work, tungsten, molybdenum,[759] or rhenium complexes were used, and with simple alkenes the proportions of products are generally statistical,[760] which limited the synthetic utility of the reaction

[756]For monographs, see Drăguţn, V.; Balaban, A.T.; Dimonie, M. *Olefin Metathesis and Ring-Opening Polymerization of Cyclo-Olefins*, Wiley, NY, ***1985***; Ivin, K.J. *Olefin Metathesis*, Academic Press, NY, ***1983***. For reviews, see Feast, W.J.; Gibson, V.C., in Hartley, F.R. *The Chemistry of the Metal-Carbon Bond*, Vol. 5, Wiley, NY, 1989, pp. 199–228; Streck, R. *CHEMTECH* ***1989*** , 498; Schrock, R.R. *J. Organomet. Chem.* ***1986***, *300*, 249; Grubbs, R.H., in Wilkinson, G. *Comprehensive Organometallic Chemistry*, Vol. 8, Pergamon, Elmsford, NY, ***1982***, pp. 499–551; Basset, J.M.; Leconte, M. *CHEMTECH* ***1980***, 762; Banks, R.L. *CHEMTECH* ***1979***, 494; *Fortschr. Chem. Forsch.* ***1972***, *25*, 39; Calderon N.; Lawrence, J.P.; Ofstead, E.A. *Adv. Organomet. Chem.* ***1979***, *17*, 449; Grubbs, R.H. *Prog. Inorg. Chem.* ***1978***, *24*, 1; Calderon N., in Patai, S. *The Chemistry of Functional Groups: Supplement A* pt. 2, Wiley, NY, ***1977***, pp. 913–964; *Acc. Chem. Res.* ***1972***, *5*, 127; Katz, T.J. *Adv. Organomet. Chem.* ***1977***, *16*, 283; Haines, R.J.; Leigh, G.J. *Chem. Soc. Rev.* ***1975***, *4*, 155; Hocks, L. *Bull. Soc. Chim. Fr.* ***1975***, 1893; Mol, J.C.; Moulijn, J.A. *Adv. Catal.* ***1974***, *24*, 131; Hughes, W.B. *Organomet. Chem. Synth.* ***1972***, *1*, 341; Khidekel', M.L.; Shebaldova, A.D.; Kalechits, I.V. *Russ. Chem. Rev.* ***1971***, *40*, 669; Bailey, G.C. *Catal. Rev.* ***1969***, *3*, 37.

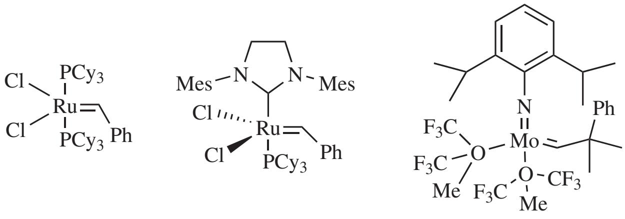
[757]Smith III, A.B.; Adams, C.M.; Kozmin, S.A. *J. Am. Chem. Soc.* ***2001***, *123*, 990.

[758]Calderon N.; Chen, H.Y.; Scott, K.W. *Tetrahedron Lett.* ***1967***, 3327; Wang, J.; Menapace, H.R. *J. Org. Chem.* ***1968***, *33*, 3794; Hughes, W.B. *J. Am. Chem. Soc.* ***1970***, *92*, 532.

[759]For an example, see Crowe, W.E.; Zhang, Z.J. *J. Am. Chem. Soc.* ***1993***, *115*, 10998.; Fu, G.C.; Grubbs, R.H. *J. Am. Chem. Soc.* ***1993***, *115*, 3800.

[760]Calderon N.; Ofstead, E.A.; Ward, J.P.; Judy, W.A.; Scott, K.W. *J. Am. Chem. Soc.* ***1968***, *90*, 4133.

since the yield of any one product is low. However, in some cases one alkene may be more or less thermodynamically stable than the rest, so that the proportions are not statistical. Furthermore, it may be possible to shift the equilibrium. For example, 2-methyl-1-butene gives rise to ethylene and 3,4-dimethyl-3-hexene. By allowing the gaseous ethylene to escape, the yield of 3,4-dimethyl-3-hexene can be raised to 95%.[761]



145 **146** **147**

The development of new catalysts have revolutionized this reaction, making it one of the most important methods available for synthesis. Tailoring the substrate to include two terminal alkenes leads to ethylene as a product, whose escape from the reaction drives the equilibrium to product. Many catalysts, both homogeneous[762] and heterogeneous,[763] have been used for this reaction. Although there are several examples of the former, ruthenium complexes are the most important,[764] while among the latter are oxides of Mo, W, and Re deposited on alumina or silica gel.[765] The major breakthrough in these catalysts was the development of catalysts that are relatively air stable. The three most used catalysts are carbene complexes **145**[766] and **146**[767] (Grubbs catalysts I and II, respectively), and **147** (the Shrock catalyst).[768] Catalyst **146** can be generated *in situ* from air stable

[761]Knoche, H. Ger. Pat.(Offen.) 2024835, 1970 [*Chem. Abstr.*, ***1971***, *74*, 44118b]. See also Chevalier, P.; Sinou, D.; Descotes, G. *Bull. Soc. Chim. Fr.* ***1976***, 2254; Bespalova, N.B.; Babich, E.D.; Vdovin, V.M.; Nametkin, N.S. *Doklad. Chem.* ***1975***, *225*, 668; Ichikawa, K.; Fukuzumi, K. *J. Org. Chem.* ***1976***, *41*, 2633; Baker, R.; Crimmin, M.J. *Tetrahedron Lett.* ***1977***, 441.

[762]First reported by Calderon N.; Chen, H.Y.; Scott, K.W. *Tetrahedron Lett.* ***1967***, 3327. For a lengthy list, see Hughes, W.B. *Organomet. Chem. Synth.* ***1972***, *1*, 341, see pp. 362–368. For a homogeneous rhenium catalyst, see Toreki, R.; Schrock, R.R. *J. Am. Chem. Soc.* ***1990***, *112*, 2448.

[763]First reported by Banks, R.L.; Bailey, G.C. *Ind. Eng. Chem. Prod. Res. Dev.*, ***1964***, *3*, 170. See also, Banks, R.L. *CHEMTECH* ***1986***, 112.

[764]Gilbertson, S.R.; Hoge, G.S.; Genov, D.G. *J. Org. Chem.* ***1998***, *63*, 10077; Maier, M.E.; Bugl, M. *Synlett* ***1998***, 1390; Stefinovic, M.; Snieckus, V. *J. Org. Chem.* ***1998***, *63*, 2808.

[765]For a list of heterogeneous catalysts, see Banks, R.L. *Fortschr. Chem. Forsch.* ***1972***, *25*, 39, 41–46.

[766]Schwab, P.; Grubbs, R.H.; Ziller, J.W. *J. Am. Chem. Soc.* ***1996***, *118*, 100.

[767]Scholl, M.; Ding, S.; Lee, C.W.; Grubbs, R.H. *Org. Lett.* ***1999***, *1*, 953.

[768]Bazan, G.C.; Oskam, J.H.; Cho, H.-N.; Park, L.Y.; Schrock, R.R. *J. Am. Chem. Soc.* ***1991***, *113*, 6899, and references cited therein.

precursors. [769] Recyclable catalyst have been developed,[770] and the reaction has been done in ionic liquids,[771] as well as supercritical CO_2[772] (p. 414). Microwave-induced ring-closing metathesis reactions are known.[773] Polymer-bound ruthenium catalysts[774] and molybdenum catalysts[775] have been used, and the **146** has been immobilized on polyethylene glycol, PEG).[776] Efficient methods have been developed for the removal of ruthenium by-products from metathesis reactions.[777] By choice of the proper catalyst, the reaction has been applied to terminal and internal alkenes, straight chain or branched. The effect of substitution on the ease of reaction is $CH_2{=} > RCH_2CH{=} > R_2CHCH{=} > R_2C{=}$.[778] Note that isomerization of the C=C unit can occur after metathesis.[779] Cross-metathesis[780,781] (or symmetrical homo-metathesis[782]) of alkenes to give new alkenes

[769]Louie, J.; Grubbs, R.H. *Angew. Chem. Int. Ed.* ***2001***, *40*, 247.

[770]Kingsbury, J.S.; Harrity, J.P.A.; Bonitatebus Jr., P.J.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***1999***, *121*, 791.

[771]In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Buijsman, R.C.; van Vuuren, E.; Sterrenburg, J.G. *Org. Lett.* ***2001***, *3*, 3785. See Clavier, H.; Audic, N.; Mauduit, M.; Guillemin, J.-C. *Chem. Commun.* ***2004***, 2282.

[772]Fürstner, A.; Ackerman, L.; Beck, K.; Hori, H.; Koch, D.; Langemann, K.; Liebl, M.; Six, C.; Leitner, W. *J. Am. Chem. Soc.* ***2001***, *123*, 9000.

[773]Grabacia, S.; Desai, B.; Lavastre, O.; Kappe, C.O. *J. Org. Chem.* ***2003***, *68*, 9136; Mayo, K.G.; Nearhoof, E.H.; Kiddle, J.J. *Org. Lett.* ***2002***, *4*, 1567; Balan, D.; Adolfsson, H. *Tetrahedron Lett.* ***2004***, *45*, 3089. For a solvent-free microwave-induced reaction, see Thanh, G.V.; Loupy, A. *Tetrahedron Lett.* ***2003***, *44*, 9091.

[774]Yao, Q. *Angew. Chem. Int. Ed.* ***2000***, *39*, 3896; Schürer, S.C.; Gessler, S.; Buschmann, N.; Blechert, S. *Angew. Chem. Int. Ed.* ***2000***, *39*, 3898.

[775]Hultzsch, K.C.; Jernelius, J.A.; Hoveyda, A.H.; Schrock, R.R. *Angew. Chem. Int. Ed.* ***2002***, *41*, 589.

[776]A recyclable catalyst, see Yao, Q.; Motta, A.R. *Tetrahedron Lett.* ***2004***, *45*, 2447.

[777]Ahn, Y.M.; Yang, K.; Georg, G.I. *Org. Lett.* ***2001***, *3*, 1411; Cho, J.H.; Kim, B.M. *Org. Lett.* ***2003***, *5*, 531. A scavenger resin has been developed, see Westhus, M.; Gonthier, E.; Brohm, D.; Breinbauer, R. *Tetrahedron Lett.* ***2004***, *45*, 3141.

[778]For an explanation for this order, see McGinnis, J.; Katz, T.J.; Hurwitz, S. *J. Am. Chem. Soc.* ***1976***, *98*, 605; Casey, C.J.; Tuinstra, H.E.; Saeman, M.C. *J. Am. Chem. Soc.* ***1976***, *98*, 608. A model for selectivity has been proposed, see Chatterjee, A.K.; Choi, T.-L.; Sanders, D.P.; Grubbs, R.H. *J. Am. Chem. Soc.* ***2003,*** *125*, 11360.

[779]For example, see Schmidt, B. *J. Org. Chem.* ***2004***, *69*, 7672; Sutton, A.E.; Seigal, B.A.; Finnegan, D.F.; Snapper, M.L. *J. Am. Chem. Soc.* ***2002***, *124*, 13390.

[780]See La, D.S.; Sattely, E.S.; Ford, J.G.; Schrock, R.R.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2001***, *123*, 7767.

[781]Chatterjee, A.K.; Grubbs, R.H. *Org. Lett.* ***1999***, *1*, 1751; Chatterjee, A.K.; Morgan, J.P.; Scholl, M.; Grubbs, R.H. *J. Am. Chem. Soc.* ***2000***, *122*, 3783; Fassina, V.; Ramminger, C.; Seferin, M.; Monteiro, A.L. *Tetrahedron* ***2000***, *56*, 7403; Randl, S.; Buschmann, N.; Connon, S.J.; Blechert, S. *Synlett* ***2001***, 1547; Grela, K.; Bieniek, M. *Tetrahedron Lett.* ***2001***, *42, 6*425; Choi, T.-L.; Chatterjee, A.K.; Grubbs, R.H. *Angew. Chem. Int. Ed.* ***2001***, *40*, 1277; Arjona, O.; Csákÿ, A.G.; Medel, R.; Plumet, J. *J. Org. Chem.* ***2002***, *67*, 1380; Chatterjee, A.K.; Sanders, D.P.; Grubbs, R.H. *Org. Lett.* ***2002***, *4*, 1939; Hansen, E.C.; Lee, D. *Org. Lett.* ***2004***, *6*, 2035; BouzBouz, S.; Simmons, R.; Cossy, J. *Org. Lett.* ***2004,*** *6*, 3465.

[782]Blanco, O.M.; Castedo, L. *Synlett* ***1999***, 557.

can be accomplished with the modern metathesis catalysts. Monosubstiuted alkenes react faster than disubstituted alkenes.[783] A double metathesis reaction of a diene (also called domino metathesis[784] or tandem metathesis[785]) with conjugated aldehydes has been reported,[786] and a triple-metathesis was reported to for a dihydropyran with two dihydropyran substituents.[787] Cross-metathesis of a terminal alkyne and a terminal alkenes (en-ynes)[788] to give a diene has also been reported.[789] Cross-metathesis of vinylcyclopropanes leads to an alkene with two cyclopropyl substituents.[790] Vinylcyclopropane-alkyne metathesis reactions have been reported.[791]Cyclic alkenes can be opened, usually with polymerization using metathesis catalysts. Ring-opening metathesis generates dienes from cyclic alkenes.[792] Allenes undergo a metathesis reaction to give symmetrical allenes.[793] The Grubbs catalyst is compatible with forming cyclic alkenes by ring-closing metathesis followed by treatment with hydrogen to give the saturated cyclic compound.[794] An interesting variation reacts an α,ω-diene with a cyclic alkene. The combination of ring-opening metathesis and ring-closing cross-metathesis leads to ring expansion to give a macrocyclic nonconjugated diene.[795]

Dienes can react intermolecularly or intramolecularly.[796] Intramolecular reactions generate rings, usually alkenes or dienes. Alkene metathesis can be

[783]For an example with a styrene derivative versus a terminal alkene in the same molecule, see Lautens, M.; Maddess, M.L. *Org. Lett.* ***2004***, *6*, 1883.

[784]Rückert, A.; Eisele, D.; Blechert, S. *Tetrahedron Lett.* ***2001***, *42*, 5245.

[785]Choi, T.-L.; Grubbs, R.H. *Chem. Commun.* ***2001***, *26* 48.

[786]BouzBouz, S.; Cossy, J. *Org. Lett.* ***2001***, *3*, 1451; van Otterlo, W.A.L.; Ngidi, E.L.; de Koning, C.D.; Fernandes, M.A. *Tetrahedron Lett.* ***2004***, *45*, 659.

[787]Sundararajan, G.; Prabagaran, N.; Varghese, B. *Org. Lett.* ***2001***, *3*, 1973.

[788]For a discussion of (Z/E) selectivity and substituent effects, see Kang, B.; Lee, J.M.; Kwak, J.; Lee, Y.S.; Chang, S. *J. Org. Chem.* ***2004***, *69*, 7661. For a review, see Diver, S.T.; Giessert, A.J. *Chem. Rev.* ***2004***, *104*, 1317.

[789]For a review, see Poulsen, C.S.; Madsen, R. *Synthesis* ***2003***, 1. See Stragies, R.; Voigtmann, U.; Blechert, S. *Tetrahedron Lett.* ***2000***, *41*, 5465; Yao, Q. *Org. Lett.* ***2001***, *3*, 2069; Lee, H.-Y.; Kim, B.G.; Snapper, M.L. *Org. Lett.* ***2003***, *5*, 1855; Giessert, A.J.; Brazis, N.J.; Diver, S.T. *Org. Lett.* ***2003***, *5*, 3819; Kim, M.; Park, S.; Maifeld, S.V.; Lee, D. *J. Am. Chem. Soc.* ***2004***, *126*, 10242; Tonogaki, K.; Mori, M. *Tetrahedron Lett.* ***2002***, *43*, 2235. See also, Kang, B.; Kim, D.-h.; Do, Y.; Chang, S. *Org. Lett.* ***2003***, *5*, 3041.

[790]Verbicky, C.A.; Zercher, C.K. *Tetrahedron Lett.* ***2000***, *41*, 8723.

[791]López, F.; Delgado, A.; Rodríguez, J.R.; Castedo, L.; Mascareñas, J.L. *J. Am. Chem. Soc.* ***2004***, *126*, 10262.

[792]See La, D.S.; Ford, J.G.; Sattely, E.S.; Bonitatebus, P.J.; Schrock, R.R.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***1999***, *121*, 11603; Wright, D.L.; Usher, L.C.; Estrella-Jimenez, M. *Org. Lett.* ***2001***, *3*, 4275; Randl, S.; Connon, S.J.; Blechert, S. *Chem. Commun.* ***2001***, 1796; Morgan, J.P.; Morrill, C.; Grubbs, R.H. *Org. Lett.* ***2002***, *4*, 67.

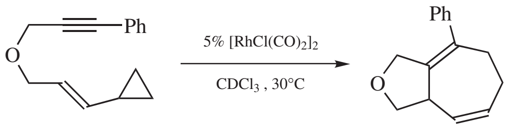
[793]Ahmed, M.; Arnauld, T.; Barrett, A.G.M.; Braddock, D.C.; Flack, K.; Procopiou, P.A. *Org. Lett.* ***2000***, *2*, 551.

[794]Louie, J.; Bielawski, C.W.; Grubbs, R.H. *J. Am. Chem. Soc.* ***2001***, *123*, 11312.

[795]Lee, C.W.; Choi, T.-L.; Grubbs, R.H. *J. Am. Chem. Soc.* ***2002***, *124*, 3224.

[796]Kroll, W.R.; Doyle, G. *Chem. Commun.* ***1971***, 839. For a review see Grubbs, R.H.; Miller, S.J.; Fu, G.C. *Acc. Chem. Res.* ***1995***, *28*, 446.

used to form very large rings, including 21-membered lactone rings.[797] Diynes can also react intramolecularly to give large-ring alkynes.[798] Metathesis with vinyl-cyclopropyl-alkynes is also known, producing a ring expanded product (see **148**).[799]



148

The synthetic importance of ring-closing and ring-opening metathesis reactions has led to the development of several new catalysts.[800] Catalysts have been developed that are compatible with both water and methanol.[801] The reaction is compatible with the presence of other functional groups,[802] such as other alkene units,[803] carbonyl units,[804] the alkene unit of conjugated esters,[805] butenolides[806] and other lactones,[807] amines,[808] amides,[809] sulfones,[810] phosphine oxides,[811] sulfonate esters,[812] and sulfonamides[813]

[797]Fürstner, A.; Langemann, K. *J. Org. Chem.* ***1996***, *61*, 3942. Also see, Goldring, W.P.D.; Hodder, A.S.; Weiler, L. *Tetrahedron Lett.* ***1998***, *39*, 4955; Ghosh, A.K.; Hussain, K.A. *Tetrahedron Lett.* ***1998***, *39*, 1881.

[798]Chen, F.-E.; Kuang, Y.-Y.; Dai, H.-F.; Lu, L.; Huo, M. *Synthesis* ***2003***, 2629.

[799]Wender, P.A.; Sperandio, D. *J. Org.Chem.* ***1998***, *63*, 4164.

[800]Schrock, R.R.; Hoveyda, A.H. *Angew. Chem. Int. Ed.* ***2003***. *42*, 4592; Garber, S.B.; Kingsbury, J.S.; Gray, B.L.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2000***, *122*, 8168; Grela, K.; Kim, M. *Eur. J. Org. Chem.* ***2003***, 963; Conon, S.J.; Dunne, A.M.; Blechert, S. *Angew. Chem. Int. Ed.* ***2002***, *41*, 3835; Zhang, W.; Kraft, S.; Moore, J.S. *J. Am. Chem. Soc.* ***2004***, *126*, 329; Aggarwal, V.K.; Alonso, E.; Fang, G.; Ferrara, M.; Hynd, G.; Porcelloni, M. *Angew. Chem. Int. Ed.* ***2001***, *40*, 1433. Also see, references cited therein.

[801]Kirkland, T.A.; Lynn, D.M.; Grubbs, R.H. *J. Org. Chem.* ***1998***, *63*, 9904.

[802]Oxygen and nitrogen-containing heterocycles can be prepared. For a review, see Deiter, S.A.; Martin, S.F. *Chem. Rev.* ***2004***, *104*, 2199.

[803]Takahashi, T.; Kotora, M.; Kasai, K. *J. Chem. Soc., Chem. Commun.* ***1994***, 2693.

[804]Schneider, M.F.; Junga, H.; Blechert, S. *Tetrahedron* ***1995***, *51*, 13003; Junga, H.; Blechert, S. *Tetrahedron Lett.* ***1993***, *34*, 3731; Llebaria, A.; Camps, F.; Moretó, J.M. *Tetrahedron Lett.* ***1992***, *33*, 3683.

[805]Lee, C.W.; Grubbs, R.H. *J. Org. Chem.* ***2001***, *66*, 7155.

[806]Paquette, L.A.; Méndez-Andino, J. *Tetrahedron Lett.* ***1999***, *40*, 4301.

[807]Brimble, M.A.; Trzoss, M. *Tetrahedron* ***2004***, *60*, 5613.

[808]Wright, D.L.; Schulte II, J.P.; Page, M.A. *Org. Lett.* ***2000***, *2*, 1847; Dolman, S.J.; Sattely, E.S.; Hoveyda, A.H.; Schrock, R.R. *J. Am. Chem. Soc.* ***2002***, *124*, 6991.

[809]Vo-Thanh, G.; Boucard, V.; Sauriat-Dorizon, H.; Guibé, F. *Synlett* ***2001***, 37; Ma, S.; Ni, B.; Liang, Z. *J. Org. Chem.* ***2004***, *69*, 6305.

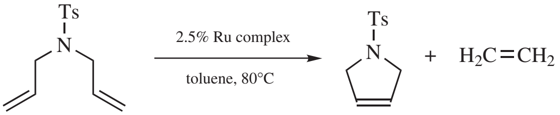
[810]Yao, Q. *Org. Lett.* ***2002***, *4*, 427.

[811]Demchuk, O.M.; Pietrusiewicz, K.M.; Michrowska, A.; Grela, K. *Org. Lett.* ***2003***, *5*, 3217.

[812]LeFlohic, A. ;Meyer, C.; Cossy, J.; Desmurs, J.-R.; Galland, J.-C. *Synlett* ***2003***, 667.

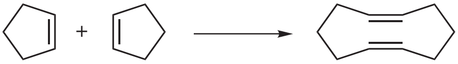
[813]Hanson, P.R.; Probst, D.A.; Robinson, R.E.; Yau, M. *Tetrahedron Lett.* ***1999***, *40*, 4761; Kinderman, S.S.; Van Maarseveen, J.H.; Schoemaker, H.E.; Hiemstra, H.; Rutjes, F.P.J.T. *Org. Lett.* ***2001***, *3*, 2045.

(see **149**).[814] Ether groups,[815] including vinyl ethers,[816] vinyl halides,[817] vinyl silanes,[818] vinyl sulfones,[819] allylic ethers,[820] and thioethers[821] are also compatible. Asymmetric ring-closing metathesis reactions have been reported.[822] Asymmetric ring-opening metathesis has also been reported.[823]



149

Two cyclic alkenes react to give dimeric dienes,[824] for example,



However, the products can then react with additional monomers and with each other, so that polymers are generally produced, and the cyclic dienes are obtained only in low yield. The reaction between a cyclic and a linear alkene can give an ring-opened diene:[825]

[814]Fürstner, A.; Picquet, M.; Bruneau, C.; Dixneuf, P.H. *Chem. Commun.* ***1998***, 1315; Maier, M.E.; Lapeva, T. *Synlett* ***1998***, 891; Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* ***1998***, *63*, 6082; O'Mahony, D.J.R.; Belanger, D.B.; Livinghouse, T. *Synlett* ***1998***, 443; Visser, M.S.; Heron N.M.; Didiuk, M.T.; Sagal, J.F.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***1996***, *118*, 4291.

[815]Edwards, S.D.; Lewis, T.; Taylor, R.J.K. *Tetrahedron Lett.* ***1999***, *40*, 4267.

[816]Sturino, C.F.; Wong, J.C.Y. *Tetrahedron Lett.* ***1998***, *39*, 9623; Rainier, J.D.; Cox, J.M.; Allwein, S.P. *Tetrahedron Lett.* ***2001***, *42*, 179.

[817]Chao, W.; Weinreb, S.M. *Org. Lett.* ***2003***, *5*, 2505.

[818]Schuman, M.; Gouverneur, V. *Tetrahedron Lett.* ***2002***, *43*, 3513.

[819]Kim, S.; Lim, C.J. *Angew. Chem. Int. Ed.* ***2002***, *41*, 3265.

[820]Delgado, M.; Martín, J.D. *Tetrahedron Lett.* ***1997***, *38*, 6299; Miller, S.J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R.H. *J. Am. Chem. Soc.* ***1995***, *117*, 2108.

[821]Leconte, M.; Pagano, S.; Mutch, A.; Lefebvre, F.; Basset, J.M. *Bull. Soc. Chim. Fr.* ***1995***, *132*, 1069.

[822]Cefalo, D.R.; Kiely, A.F.; Wuchrer, M.; Jamieson, J.Y. ; Schrock, R.R.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2001***, *123*, 3139.

[823]Gillingham, D.G.; Kataoka, O.; Garber, S.B.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2004***, *126*, 12288.

[824]Calderon N.; Ofstead, E.A.; Judy, W.A. *J. Polym. Sci. Part A-1* ***1967***, *5*, 2209; Wasserman, E.; Ben-Efraim, D.A.; Wolovsky, R. *J. Am. Chem. Soc.* ***1968***, *90*, 3286; Wolovsky, R.; Nir, Z. *Synthesis* ***1972***, 134.

[825]Wasserman, E.; Ben-Efraim, D.A.; Wolovsky, R. *J. Am. Chem. Soc.* ***1968***, *90*, 3286; Ray, G.C.; Crain, D.L. Fr. Pat. 1511381, 1968 [*Chem. Abstr.*, ***1969***, *70*, 114580q]; Mango, F.D. U.S. Pat. 3424811, 1969 [*Chem. Abstr.*, ***1969***, *70*, 106042a]; Rossi, R.; Diversi, P.; Lucherini, A.; Porri, L. *Tetrahedron Lett.* ***1974***, 879; Lal, J.; Smith, R.R. *J. Org. Chem.* ***1975***, *40*, 775.

Alkenes containing functional groups[826] do not give the reaction with most of the common catalysts, but some success has been reported with WCl_6–$SnMe_4$[827] and with certain other catalysts.

The reaction has also been applied to internal triple bonds:[828]

$$2\,RC{\equiv}CR' \rightleftharpoons RC{\equiv}CR + R'C{\equiv}CR'$$

but it has not been successful for terminal triple bonds,[829] although as noted above, molecules with a terminal alkene and a terminal alkyne react quite well. Ring-closing metathesis of alkene–alkynes leads to a cyclic alkene with a pendant vinyl unit (a diene).[830] Intramolecular reactions of a double bond with a triple bond are known[831] and a tetracyclic tetraene has been prepared from a poly-yne-diene.[832]

The generally accepted mechanism is a chain mechanism,[833] involving the intervention of a metal–carbene complex (**150** and **151**)[834] and a four-membered ring

[826]For a review, see Mol, J.C. *CHEMTECH* ***1983***, 250. See also, Bosma, R.H.A.; van den Aardweg, G.C.N.; Mol, J.C. *J. Organomet. Chem.* ***1983***, *255*, 159; ***1985***, *280*, 115; Xiaoding, X.; Mol, J.C. *J. Chem. Soc., Chem. Commun.* ***1985***, 631; Crisp, C.T.; Collis, M.P. *Aust. J. Chem.* ***1988***, *41*, 935.

[827]First shown by van Dam, P.B.; Mittelmeijer, M.C.; Boelhouwer, C. *J. Chem. Soc., Chem. Commun.* ***1972***, 1221.

[828]Pennella, F.; Banks, R.L.; Bailey, G.C. *Chem. Commun.* ***1968***, 1548; Villemin, D.; Cadiot, P. *Tetrahedron Lett.* ***1982***, *23*, 5139; McCullough, L.G.; Schrock, R.R. *J. Am. Chem. Soc.* ***1984***, *106*, 4067; Fürstner, A.; Mathes, C. *Org. Lett.* ***2001***, *3*, 221; Fürstner, A.; Mathes, C.; Lehmann, C.W. *J. Am. Chem. Soc.* ***1999***, *121*, 9453; Fürstner, A.; Guth, O.; Rumbo, A.; Seidel, G. *J. Am. Chem. Soc.* ***1999***, *121*, 11108; Brizius, G.; Bunz, U.H.F. *Org. Lett.* ***2002***, *4*, 2829; Grela, K.; Ignatonska, J. *Org. Lett.* ***2002***, *4*, 3747. For a review, see Tamao, K.; Kobayashi, K.; Ito, Y. *Synlett* ***1992***, 539.

[829]McCullough, L.G.; Listemann, M.L.; Schrock, R.R.; Churchill, M.R.; Ziller, J.W. *J. Am. Chem. Soc.* ***1983***, *105*, 6729.

[830]Mori, M.; Kitamura, T.; Sakakibara, N.; Sato, Y. *Org. Lett.* ***2000***, *2*, 543; Kitamura, T.; Mori, M. *Org. Lett.* ***2001***, *3*, 1161.

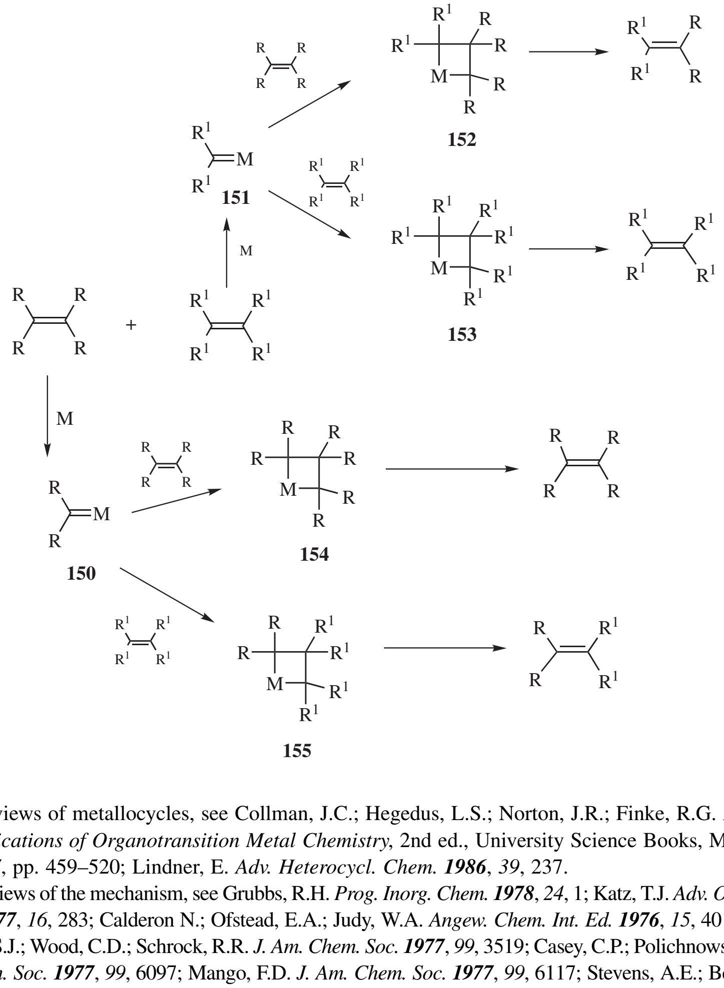
[831]Trost, B.M.; Trost, M.K. *J. Am. Chem. Soc.* ***1991***, *113*, 1850; Gilbertson, S.R.; Hoge, G.S. *Tetrahedron Lett.* ***1998***, *39*, 2075.

[832]Zuercher, W.J.; Scholl, M.; Grubbs, R.H. *J. Org. Chem.* ***1998***, *63*, 4291.

[833]For a discussion of the mechanism of ring-closing meththesis, see Sanford, M.S.; Ulman, M.; Grubbs, R.H. *J. Am. Chem. Soc.* ***2001***, *123*, 749; Sanford, M.S.; Love, J.A.; Grubbs, R.H. *J. Am. Chem. Soc.* ***2001***, *123*, 6543; Cavallo, L. *J. Am. Chem. Soc.* ***2002***, *124*, 8965; Adlhart, C.; Chen, P. *J. Am. Chem. Soc.* ***2004***, *126*, 3496.

[834]For a review of these complexes and their role in this reaction, see Crabtree, R.H. *The Organometallic Chemistry of the Transition Metals*, Wiley, NY, ***1988***, pp. 244–267.

containing a metal[835] (**152–155**).[836] In the cross-metathesis reaction shown as an example, $R_2C{=}CR_2$ reacts with $R^1{}_2C{=}CR^1{}_2$ in the presence of a metal catalyst, M. Initial reaction with the catalyst leads to the two expected metal carbenes, **150** and **151**. Metal carbene **151** can react with both alkenes to form metallocyclobutanes **152** and **153**. Each of these intermediates loses the metal to form the alkenes, the product of metathesis $R_2C{=}CR^1{}_2$ and the one of the original alkenes. In a likewise manner, **150** reacts with each alkene to form metallocyclobutanes **154** and **155**, which decomposes to $R_2C{=}CR_2$ and the metathesis product.

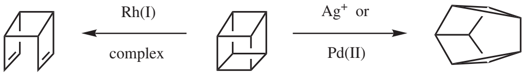


[835]For reviews of metallocycles, see Collman, J.C.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed., University Science Books, Mill Valley, CA; ***1987***, pp. 459–520; Lindner, E. *Adv. Heterocycl. Chem.* ***1986***, *39*, 237.

[836]For reviews of the mechanism, see Grubbs, R.H. *Prog. Inorg. Chem.* ***1978***, *24*, 1; Katz, T.J. *Adv. Organomet. Chem.* ***1977***, *16*, 283; Calderon N.; Ofstead, E.A.; Judy, W.A. *Angew. Chem. Int. Ed.* ***1976***, *15*, 401. See also McLain, S.J.; Wood, C.D.; Schrock, R.R. *J. Am. Chem. Soc.* ***1977***, *99*, 3519; Casey, C.P.; Polichnowski, S.W. *J. Am. Chem. Soc.* ***1977***, *99*, 6097; Mango, F.D. *J. Am. Chem. Soc.* ***1977***, *99*, 6117; Stevens, A.E.; Beauchamp, J.L. *J. Am. Chem. Soc.* ***1979***, *101*, 6449; Lee, J.B.; Ott, K.C.; Grubbs, R.H. *J. Am. Chem. Soc.* ***1982***, *104*, 7491; Levisalles, J.; Rudler, H.; Villemin, D. *J. Organomet. Chem.* ***1980***, *193*, 235; Iwasawa, Y.; Hamamura, H. *J. Chem. Soc., Chem. Commun.* ***1983***, 130; Rappé, A.K.; Upton, T.H. *Organometallics*, ***1984***, *3*, 1440; Kress, J.; Osborn, J.A.; Greene, R.M.E.; Ivin, K.J.; Rooney, J.J. *J. Am. Chem. Soc.* ***1987***, *109*, 899; Feldman, J.; Davis, W.M.; Schrock, R.R. *Organometallics*, ***1989***, *8*, 2266.

OS **80**, 85; **81**, 1.

18-38 Metal-Ion-Catalyzed σ-Bond Rearrangements



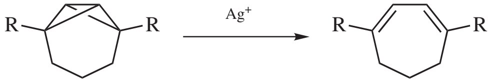
156 Cubane Cuneane

Many highly strained cage molecules undergo rearrangement when treated with metallic ions, such as Ag^+, Rh(I), or Pd(II).[837] The bond rearrangements observed can be formally classified into two main types: (*1*) [2+2]-ring

Type 1 Type 2

openings of cyclobutanes and (*2*) conversion of a bicyclo[2.2.0] system to a bicyclopropyl system. The molecule cubane supplies an example of each type (see above). Treatment with Rh(I) complexes converts cubane to tricyclo[4.2.0.0^{2,5}]octa-3,7-diene (**156**),[838] an example of type 1, while Ag^+ or Pd(II) causes the second type of reaction, producing cuneane.[839] Other examples are

Type 1



157 **158**

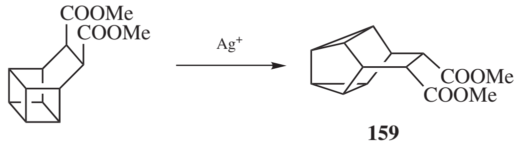
Ref. [840]

[837]For reviews, see Halpern, J., in Wender, I.; Pino, P. *Organic Syntheses via Metal Carbonyls*, Vol. 2, Wiley, NY, ***1977***, pp. 705–721; Bishop III, K.C. *Chem. Rev.* ***1976***, *76*, 461; Cardin, D.J.; Cetinkaya, B.; Doyle, M.J.; Lappert, M.F. *Chem. Soc. Rev.* ***1973***, *2*, 99, 132–139; Paquette, L.A. *Synthesis* ***1975***, 347; *Acc. Chem. Res.* ***1971***, *4*, 280.

[838]Eaton, P.E.; Chakraborty, U.R. *J. Am. Chem. Soc.* ***1978***, *100*, 3634.

[839]Cassar, L.; Eaton, P.E.; Halpern, J. *J. Am. Chem. Soc.* ***1970***, *92*, 6336.

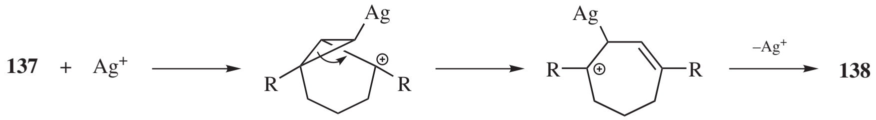
[840]Gassman, P.G.; Atkins, T.J. *J. Am. Chem. Soc.* ***1971***, *93*, 4579; ***1972***, *94*, 7748; Sakai, M.; Westberg, H.H.; Yamaguchi, H.; Masamune, S. *J. Am. Chem. Soc.* ***1972***, *93*, 4611; Paquette, L.A.; Wilson, S.E.; Henzel, R.P. *J. Am. Chem. Soc.* ***1972***, *94*, 7771.

Type 2 [841]  Ref. [842]

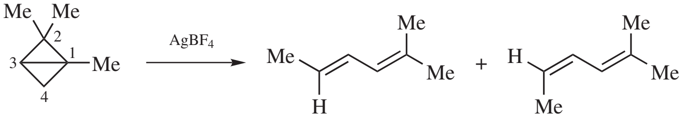
159

159 is the 9,10-dicarbomethyoxy derivative of *snoutane* (pentacyclo[3.3.2.0^{2,4}.0^{3,7}.0^{6,8}] decane).

The mechanisms of these reactions are not completely understood, although relief of strain undoubtedly supplies the driving force. The reactions are thermally forbidden by the orbital-symmetry rules, and the role of the catalyst is to provide low-energy pathways so that the reactions can take place. The type 1 reactions are the reverse of the catalyzed [2 + 2] ring closures discussed at **15-63**. The following mechanism, in which Ag^+ attacks one of the edge bonds, has been suggested for the conversion of **157** to **158**.[843]



Simpler bicyclobutanes can also be converted to dienes, but in this case the products usually result from cleavage of the central bond and one of the edge bonds.[844] For example, treatment of **160** with $AgBF_4$,[845]



160

[841]The starting compound here is a derivative of basketane, or 1,8-bishomocubane. For a review of homo-, bishomo-, and trishomocubanes, see Marchand, A.P. *Chem. Rev.* ***1989***, *89*, 1011.

[842]See, for example, Furstoss, R.; Lehn, J.M. *Bull. Soc. Chim. Fr.* ***1966***, 2497; Dauben, W.G.; Kielbania Jr., A.J. *J. Am. Chem. Soc.* ***1971***, *93*, 7345; Paquette, L.A.; Beckley, R.S.; Farnham, W.B. *J. Am. Chem. Soc.* ***1975***, *97*, 1089.

[843]Gassman, P.G.; Atkins, T.J. *J. Am. Chem. Soc.* ***1971***, *93*, 4579; Sakai, M.; Westberg, H.H.; Yamaguchi, H.; Masamune, S. *J. Am. Chem. Soc.* ***1972***, *93*, 4611.

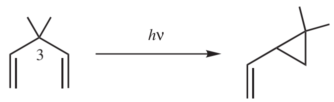
[844]Compound **157** can also be cleaved in this manner, giving a 3-methylenecyclohexene. See, for example, Dauben, W.G.; Kielbania Jr., A.J. *J. Am. Chem. Soc.* ***1972***, *94*, 3669; Gassman, P.G.; Reitz, R.R. *J. Am. Chem. Soc.* ***1973***, *95*, 3057; Paquette, L.A.; Zon, G. *J. Am. Chem. Soc.* ***1974***, *96*, 203, 224.

[845]Paquette, L.A.; Henzel, R.P.; Wilson, S.E. *J. Am. Chem. Soc.* ***1971***, *93*, 2335.

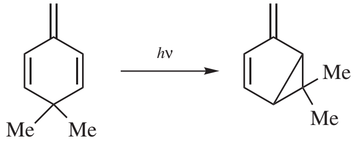
or [(π-allyl)PdCl]$_2$[846] gives a mixture of the two dienes shown, resulting from a formal cleavage of the C_1–C_3 and C_1–C_2 bonds (note that a hydride shift has taken place). Dienes can also be converted to bicyclobutanes under photochemical conditions.[847]

18-39 The Di-π-methane and Related Rearrangements

Di-π-methane rearrangement



1,4-Dienes carrying alkyl or aryl substituents on C-3[848] can be photochemically rearranged to vinylcyclopropanes in a reaction called the *di-π-methane rearrangement*.[849] An example is conversion of **161** to **162**.[850] For most



161 **162**

1,4-dienes it is only the singlet excited states that give the reaction; triplet states generally take other pathways.[851] For unsymmetrical dienes, the reaction is regioselective. For example, **163** gave **164**, not **165**:[852]

[846]Gassman, P.G.; Meyer, R.G.; Williams, F.J. *Chem. Commun.* ***1971***, 842.

[847]Garavelli, M.; Frabboni, B.; Fato, M.; Celani, P.; Bernardi, F.; Robb, M.A.; Olivucci, M. *J. Am. Chem. Soc.* ***1999***, *121*, 1537.

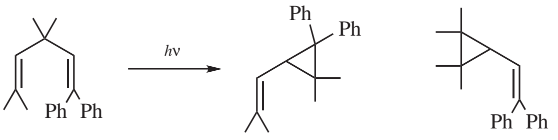
[848]Zimmerman, H.E.; Pincock, J.A. *J. Am. Chem. Soc.* ***1973***, *95*, 2957.

[849]For reviews, see Zimmerman, H.E. *Org. Photochem.* ***1991***, *11*, 1; Zimmerman, H.E., in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, ***1980***, pp. 131–166; Hixson, S.S.; Mariano, P.S.; Zimmerman, H.E. *Chem. Rev.* ***1973***, *73*, 531. See also: Roth, W.R.; WIldt, H.; Schlemenat, A. *Eur. J. Org. Chem.* **2001**, 4081.

[850]Zimmerman, H.E.; Hackett, P.; Juers, D.F.; McCall, J.M.; Schröder, B. *J. Am. Chem. Soc.* ***1971***, *93*, 3653.

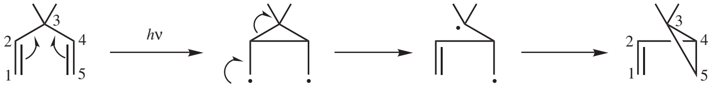
[851]However, some substrates, generally rigid bicyclic molecules, (e.g., barrelene, p. 152, which is converted to semi-bullvalene) give the di-π-methane rearrangement only from triplet states.

[852]Zimmerman, H.E.; Baum, A.A. *J. Am. Chem. Soc.* ***1971***, *93*, 3646. See also, Zimmerman, H.E.; Welter, T.R. *J. Am. Chem. Soc.* ***1978***, *100*, 4131; Alexander, D.W.; Pratt, A.C.; Rowley, D.H.; Tipping, A.E. *J. Chem. Soc., Chem. Commun.* ***1978***, 101; Paquette, L.A.; Bay, E.; Ku, A.Y.; Rondan, N.G.; Houk, K.N. *J. Org. Chem.* ***1982***, *47*, 422.

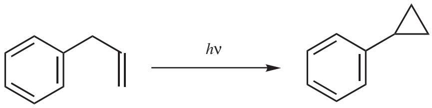


163 **164** **165** Not formed

The mechanism can be described by the diradical pathway given[853] (the C-3 substituents act to stabilize the radical), though the species shown are not necessarily intermediates, but may be transition states. It has been shown, for the case of certain substituted substrates, that configuration is retained at C-1 and C-5 and inverted at C-3.[854]



The reaction has been extended to allylic benzenes[855] (in this case C-3 substituents are not required), to β,γ-unsaturated ketones[856] (the latter reaction, which is called the *oxa-di-π-methane rearrangement*,[857] generally occurs only from the triplet state), to β,γ-unsaturated imines,[858] and to triple-bond systems.[859]



[853]See Zimmerman, H.E.; Little, R.D. *J. Am. Chem. Soc.* ***1974***, *96*, 5143; Zimmerman, H.E.; Boettcher, R.J.; Buehler, N.E.; Keck, G.E. *J. Am. Chem. Soc.* ***1975***, *97*, 5635. For an argument against the intermediacy of the •CH_2–cyclopropyl–CH_2• intermediate, see Adam, W.; De Lucchi, O.; Dörr, M. *J. Am. Chem. Soc.* ***1989***, *111*, 5209.

[854]Zimmerman, H.E.; Robbins, J.D.; McKelvey, R.D.; Samuel, C.J.; Sousa, L.R. *J. Am. Chem. Soc.* ***1989***, *111*, 5209.

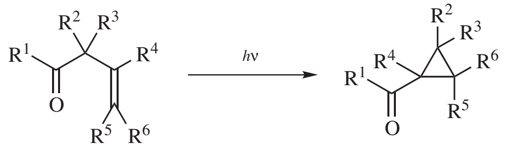
[855]For example, see Griffin, G.W.; Covell, J.; Petterson, R.C.; Dodson, R.M.; Klose, G. *J. Am. Chem. Soc.* ***1965***, *87*, 1410; Hixson, S.S. *J. Am. Chem. Soc.* ***1972***, *94*, 2507; Cookson, R.C.; Ferreira, A.B.; Salisbury, K. *J. Chem. Soc., Chem. Commun.* ***1974***, 665; Fasel, J.; Hansen, H. *Chimia*, ***1982***, *36*, 193; Paquette, L.A.; Bay, E. *J. Am. Chem. Soc.* ***1984***, *106*, 6693; Zimmerman, H.E.; Swafford, R.L. *J. Org. Chem.* ***1984***, *49*, 3069.

[856]For reviews of photochemical rearrangements of unsaturated ketones, see Schuster, D.I., in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, ***1980***, pp. 167–279; Houk, K.N. *Chem. Rev.* ***1976***, *76*, 1; Schaffner, K. *Tetrahedron* ***1976***, *32*, 641; Dauben, W.G.; Lodder, G.; Ipaktschi, J. *Top. Curr. Chem.* ***1975***, *54*, 73.

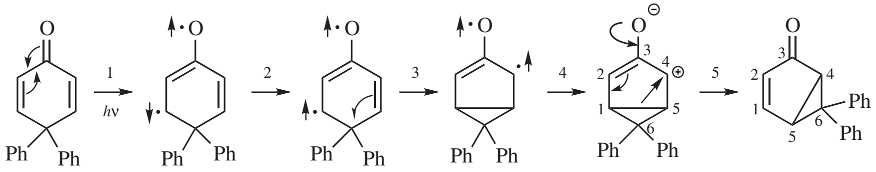
[857]For a review, see Demuth, M. *Org. Photochem.* ***1991***, *11*, 37.

[858]See Armesto, D.; Horspool, W.M.; Langa, F.; Ramos, A. *J. Chem. Soc. Perkin Trans. 1* ***1991***, 223.

[859]See Griffin, G.W.; Chihal, D.M.; Perreten, J.; Bhacca, N.S. *J. Org. Chem.* ***1976***, *41*, 3931.



When photolyzed, 2,5-cyclohexadienones can undergo a number of different reactions, one of which is formally the same as the di-π-methane rearrangement.[860] In this reaction, photolysis of the substrate **166** gives the bicyclo[3.1.0]hexenone (**171**). Although the reaction is formally the same (note the conversion of **161** to **162**



166 **167** **168** **169** **170** **171**

Singlet Triplet Triplet

above), the mechanism is different from that of the di-π-methane rearrangement, because irradiation of a ketone can cause an $n \rightarrow \pi^*$ transition, which is of course not possible for a diene lacking a carbonyl group. The mechanism[861] in this case has been formulated as proceeding through the excited triplet states **168** and **169**. In step 1, the molecule undergoes an $n \rightarrow \pi^*$ excitation to the singlet species **167**, which cross to the triplet **168**. Step 3 is a rearrangement from one excited state to another. Step 4 is a $\pi^* \rightarrow n$ electron demotion (an intersystem crossing from $T_1 \rightarrow S_0$, see p. 339). The conversion of **170** to **171** consists of two 1,2 alkyl migrations (a one-step process would be a 1,3-migration of alkyl to a carbocation center, see p. $$$): The old C_6–C_5 bond becomes the new C_6–C_4 bond and the old C_6–C_1 bond becomes the new C_6–C_5 bond.[862]

2,4-Cyclohexadienones also undergo photochemical rearrangements, but the products are different, generally involving ring opening.[863]

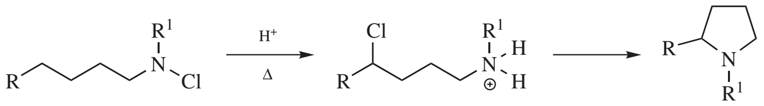
[860]For reviews of the photochemistry of 2,5-cyclohexadienones and related compounds, see Schaffner, K.; Demuth, M., in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, ***1980***, pp. 281–348; Zimmerman, H.E. *Angew. Chem. Int. Ed.* ***1969***, *8*, 1; Kropp, P.J. *Org. Photochem.* ***1967***, *1*, 1; Schaffner, K. *Adv. Photochem.* ***1966***, *4*, 81. For synthetic use, see Schultz, A.G.; Lavieri, F.P.; Macielag, M.; Plummer, M. *J. Am. Chem. Soc.* ***1987***, *109*, 3991, and references cited therein.

[861]Schuster, D.I. *Acc. Chem. Res.* ***1978***, *11*, 65; Zimmerman, H.E.; Pasteris, R.J. *J. Org. Chem.* ***1980***, *45*, 4864, 4876; Schuster, D.I.; Liu, K. *Tetrahedron* ***1981***, *37*, 3329.

[862]Zimmerman, H.E.; Crumine, D.S.; Döpp, D.; Huyffer, P.S. *J. Am. Chem. Soc.* ***1969***, *91*, 434.

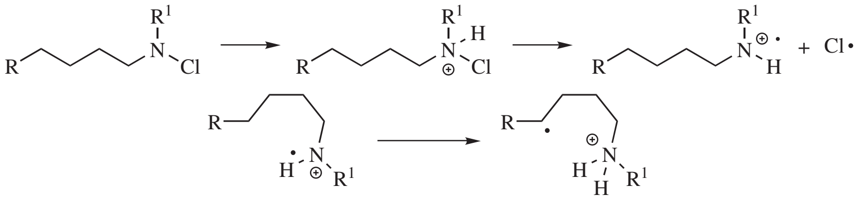
[863]For reviews, see Schaffner, K.; Demuth, M., in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, ***1980***, p. 281; Quinkert, G. *Angew. Chem. Int. Ed.* ***1972***, *11*, 1072; Kropp, P.J. *Org. Photochem.* ***1967***, *1*, 1.

18-40 The Hofmann–Löffler and Related Reactions

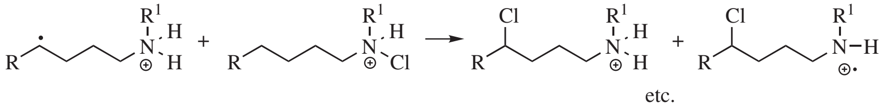


A common feature of the reactions in this section[864] is that they serve to introduce functionality at a position remote from functional groups already present. As such, they have proved very useful in synthesizing many compounds, especially in the steroid field (see also, **19-2** and **19-17**). When *N*-haloamines in which one alkyl group has a hydrogen in the 4 or 5 position are heated with sulfuric acid, pyrrolidines, or piperidines are formed, in a reaction known as the *Hofmann–Löffler reaction* (also called the *Hofmann–Löffler–Freytag reaction*).[865] The R′ group is normally alkyl, but the reaction has been extended to R′ = H by the use of concentrated sulfuric acid solution and ferrous salts.[866] The first step of the reaction is a rearrangement, with the halogen migrating from the nitrogen to the 4 or 5 position of the alkyl group. It is possible to isolate the resulting haloamine salt, but usually this is not done, and the second step, the ring closure (**10-31**), takes place. Though the reaction is most often induced by heat, this is not necessary, and irradiation and chemical initiators (e.g., peroxides) have been used instead. The mechanism is of a free-radical type, with the main step involving an internal hydrogen abstraction.[867]

Initiation



Propagation



etc.

A similar reaction has been carried out on *N*-halo amides, which give γ-lactones:[868]

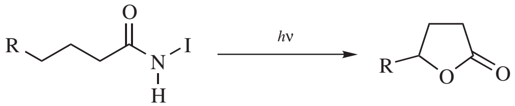
[864]For a review of the reactions in this section, see Carruthers, W. *Some Modern Methods of Organic Synthesis* 3rd ed.; Cambridge University Press: Cambridge, ***1986***, pp. 263–279.

[865]For reviews, see Stella, L. *Angew. Chem. Int. Ed.* ***1983***, *22*, 337; Sosnovsky, G.; Rawlinson, D.J. *Adv. Free-Radical Chem.* ***1972***, *4*, 203, see pp. 249–259; Deno, N.C. *Methods Free-Radical Chem.* ***1972***, *3*, 135, see pp. 136–143.

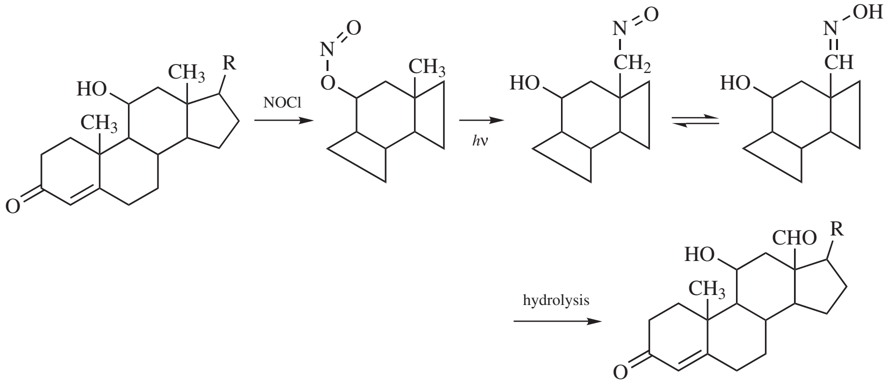
[866]Schmitz, E.; Murawski, D. *Chem. Ber.* ***1966***, *99*, 1493.

[867]Wawzonek, S.; Thelan, P.J. *J. Am. Chem. Soc.* ***1950***, *72*, 2118.

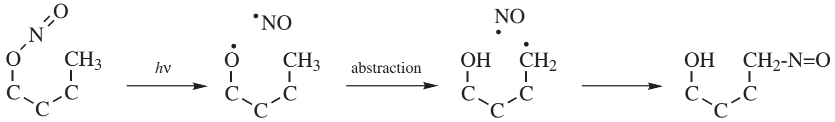
[868]Barton, D.H.R.; Beckwith, A.L.J.; Goosen, A. *J. Chem. Soc.* ***1965***, 181; Petterson, R.C.; Wambsgans, A. *J. Am. Chem. Soc.* ***1964***, *86*, 1648; Neale, R.S.; Marcus, N.L.; Schepers, R.G. *J. Am. Chem. Soc.* ***1966***, *88*, 3051. For a review of *N*-halo amide rearrangements, see Neale, R.S. *Synthesis* ***1971***, 1.



Another related reaction is the *Barton reaction*,[869] by which a methyl group in the ∂ position to an OH group can be oxidized to a CHO group. The alcohol is first converted to the nitrite ester. Photolysis of the nitrite results in conversion of the nitrite group to the OH group and nitrosation of the methyl group. Hydrolysis of the oxime tautomer gives the aldehyde, for example,[870]



This reaction takes place only when the methyl group is in a favorable steric position.[871] The mechanism is similar to that of the Hofmann–Löffler reaction.[872]



[869]For reviews, see Hesse, R.H. *Adv. Free-Radical Chem.* ***1969***, *3*, 83; Barton, D.H.R. *Pure Appl. Chem.* ***1968***, *16*, 1.

[870]Barton, D.H.R.; Beaton, J.M. *J. Am. Chem. Soc.* ***1961***, *83*, 4083. Also see, Barton, D.H.R.; Beaton, J.M.; Geller, L.E.; Pechet, M.M. *J. Am. Chem. Soc.* ***1960***, *82*, 2640.

[871]For a discussion of which positions are favorable, see Burke, S.D.; Silks III, L.A.; Strickland, S.M.S. *Tetrahedron Lett.* ***1988***, *29*, 2761.

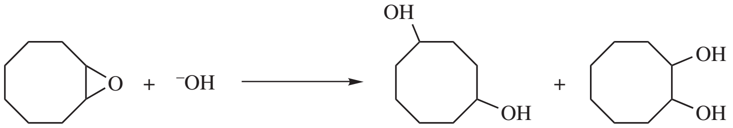
[872]Kabasakalian, P.; Townley, E.R. *J. Am. Chem. Soc.* ***1962***, *84*, 2711; Akhtar, M.; Barton, D.H.R.; Sammes, P.G. *J. Am. Chem. Soc.* ***1965***, *87*, 4601. See also, Nickon, A.; Ferguson, R.; Bosch, A.; Iwadare, T. *J. Am. Chem. Soc.* ***1977***, *99*, 4518; Barton, D.H.R.; Hesse, R.H.; Pechet, M.M.; Smith, L.C. *J. Chem. Soc. Perkin Trans. 1* ***1979***, 1159; Green, M.M.; Boyle, B.A.; Vairamani, M.; Mukhopadhyay, T.; Saunders, Jr., W.H.; Bowen, P.; Allinger, N.L. *J. Am. Chem. Soc.* ***1986***, *108*, 2381.

This is one of the few known methods for effecting substitution at an angular methyl group. Not only CH_3 groups, but also alkyl groups of the form RCH_2 and R_2CH can give the Barton reaction if the geometry of the system is favorable. An RCH_2 group is converted to the oxime R(C=NOH) (which is hydrolyzable to a ketone) or to a nitroso dimer, while an R_2CH group gives a nitroso compound $R_2C(NO)$. With very few exceptions, the only carbons that become nitrosated are those in the position δ to the original OH group, indicating that a six-membered transition state is necessary for the hydrogen abstraction.[873]

OS **III**, 159.

D. Noncyclic Rearrangements

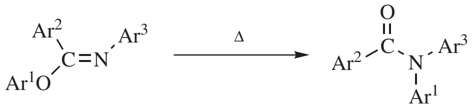
18-41 Hydride Shifts



The above is a typical example of a transannular hydride shift. The 1,2-diol is formed by a normal epoxide hydrolysis reaction (**10-7**). For a discussion of 1,3 and longer hydride shifts (see p. 1572).

18-42 The Chapman Rearrangement

1/*O* → 3/*N*-Aryl-migration

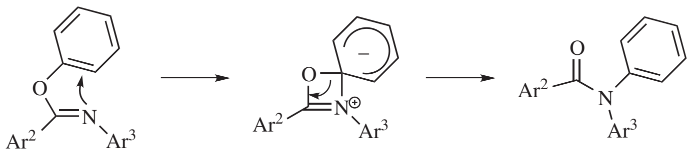


In the *Chapman rearrangement*, *N,N*-diaryl amides are formed when aryl imino esters are heated.[874] Best yields are obtained in refluxing tetraethylene glycol dimethyl ether (tetraglyme),[875] although the reaction can also be carried out without any solvent at all. Many groups may be present in the rings, for example, alkyl, halo, OR, CN, and COOR. Aryl migrates best when it contains electron-withdrawing groups. On the other hand, electron-withdrawing groups in Ar^2 or Ar^3 decrease the reactivity. The products can be hydrolyzed to diarylamines, and

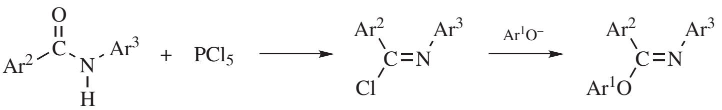
[873]For a discussion, see Nickon, A.; Ferguson, R.; Bosch, A.; Iwadare, T. *J. Am. Chem. Soc.* ***1977***, *99*, 4518.

[874]For reviews, see Schulenberg, J.W.; Archer, S. *Org. React.* ***1965***, *14*, 1; McCarty, C.G., in Patai, S. *The Chemistry of the Carbon-Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 439–447; McCarty, C.G.; Garner, L.A., in Patai, S. *The Chemistry of Amidines and Imidates*, Wiley, NY, ***1975***, pp. 189–240. For a review of 1,3 migrations of R in general, see Landis, P.S. *Mech. Mol. Migr.* ***1969***, *2*, 43.

[875]Wheeler, O.H.; Roman, F.; Santiago, M.V.; Quiles, F. *Can. J. Chem.* ***1969***, *47*, 503.

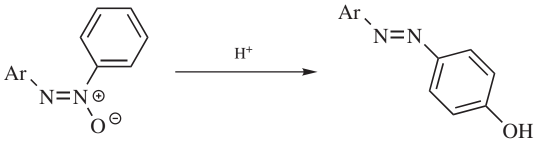


this is a method for preparing these compounds. The mechanism probably involves an intramolecular[876] aromatic nucleophilic substitution, resulting in a 1,3 oxygen-to-nitrogen shift. Aryl imino esters can be prepared from *N*-aryl amides by reaction with PCl_5, followed by treatment of the resulting imino chloride with an aroxide ion.[877]



Imino esters with any or all of the three groups being alkyl also rearrange, but they require catalysis by H_2SO_4 or a trace of methyl iodide or methyl sulfate.[878] The mechanism is different, involving an intermolecular process.[879] This is also true for derivatives for formamide (Ar^2 = H).

18-43 The Wallach Rearrangement



172 **173**

The conversion of azoxy compounds, on acid treatment, to *p*-hydroxy azo compounds (or sometimes the *o*-hydroxy isomers[880]) is called the *Wallach rearrangement*.[881] When both para positions are occupied, the *o*-hydroxy product may be

[876]For evidence for the intramolecular character of the reaction, see Wiberg, K.B.; Rowland, B.I. *J. Am. Chem. Soc.* ***1955***, *77*, 2205; Wheeler, O.H.; Roman, F.; Rosado, O. *J. Org. Chem.* ***1969***, *34*, 966; Kimura, M. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 205.

[877]For a review of the formation and reactions of imino chlorides, see Bonnett, R., in Patai, S. *The Chemistry of the Carbon–Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 597–662.

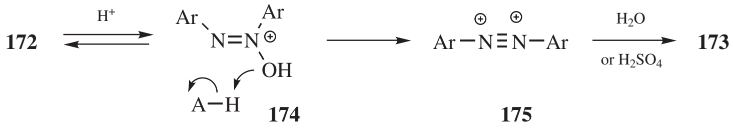
[878]Landis, P.S. *Mech. Mol. Migr.* ***1969***, *2*, 43.

[879]See Challis, B.C.; Frenkel, A.D. *J. Chem. Soc. Perkin Trans. 2* ***1978***, 192.

[880]For example, see Dolenko, A.; Buncel, E. *Can. J. Chem.* ***1974***, *52*, 623; Yamamoto, J.; Nishigaki, Y.; Umezu, M.; Matsuura, T. *Tetrahedron* ***1980***, *36*, 3177.

[881]For reviews, see Buncel, E. *Mech. Mol. Migr.* ***1968***, *1*, 61; Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1969***, pp. 272–284, 357–359; Cox, R.A.; Buncel, E., in Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 2, Wiley, NY, ***1975***, pp. 808–837.

obtained, but ipso substitution at one of the para positions is also possible.[882] Although the mechanism[883] is not completely settled, the following facts are known: (*1*) The para rearrangement is intermolecular.[884] (*2*) When the reaction was carried out with an azoxy compound in which the N–O nitrogen was labeled with ^{15}N, *both* nitrogens of the product carried the label equally,[885] demonstrating that the oxygen did not have a preference for migration to either the near or the far ring. This shows that there is a symmetrical intermediate. (*3*) Kinetic studies show that two protons are normally required for the reaction.[886] The following mechanism,[887] involving the symmetrical intermediate **175**, has been proposed to explain the facts.[888]



It has proved possible to obtain **174** and **175** as stable species in super acid solutions.[748] Another mechanism, involving an intermediate with only one positive charge, has been proposed for certain substrates at low acidities.[889]

A photochemical Wallach rearrangement[890] is also known: The product is the *o*-hydroxy azo compound, the OH group is found in the farther ring, and the rearrangement is intramolecular.[891]

[882]See, for example, Shimao, I.; Oae, S. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 643.

[883]For reviews, see Furin, G.G. *Russ. Chem. Rev.* ***1987***, *56*, 532; Williams, D.L.H.; Buncel, E. *Isot. Org. Chem.* ***1980***, *5*, 184; Buncel, E. *Acc. Chem. Res.* ***1975***, *8*, 132.

[884]See, for example, Oae, S.; Fukumoto, T.; Yamagami, M. *Bull. Chem. Soc. Jpn.* ***1963***, *36*, 601.

[885]Shemyakin, M.M.; Maimind, V.I.; Vaichunaite, B.K. *Chem. Ind.* (*London*) ***1958***, 755; *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1960***, 808. Also see Behr, L.C.; Hendley, E.C. *J. Org. Chem.* ***1966***, *31*, 2715.

[886]Buncel, E.; Lawton, B.T. *Chem. Ind. (London)* ***1963***, 1835; Hahn, C.S.; Lee, K.W.; Jaffé, H.H. *J. Am. Chem. Soc.* ***1967***, *89*, 4975; Cox, R.A. *J. Am. Chem. Soc.* ***1974***, *96*, 1059.

[887]Buncel, E.; Strachan, W.M.J. *Can. J. Chem.* ***1970***, *48*, 377; Cox, R.A. *J. Am. Chem. Soc.* ***1974***, *96*, 1059; Buncel, E.; Keum, S. *J. Chem. Soc., Chem. Commun.* ***1983***, 578.

[888]For other proposed mechanisms, see Shemyakin, M.M.; Agadzhanyan, Ts.E.; Maimind, V.I.; Kudryavtsev, R.V. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1963***, 1216; Hahn, C.S.; Lee, K.W.; Jaffé, H.H. *J. Am. Chem. Soc.* ***1967***, *89*, 4975; Hendley, E.C.; Duffey, D. *J. Org. Chem.* ***1970***, *35*, 3579.

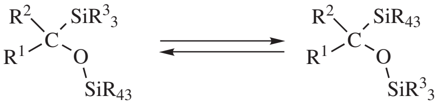
[889]Cox, R.A.; Dolenko, A.; Buncel, E. *J. Chem. Soc. Perkin Trans. 2* ***1975***, 471; Cox, R.A.; Buncel, E. *J. Am. Chem. Soc.* ***1975***, *97*, 1871.

[890]For a thermal rearrangement (no catalyst), see Shimao, I.; Hashidzume, H. *Bull. Chem. Soc. Jpn.* ***1976***, *49*, 754.

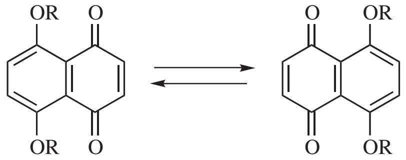
[891]For discussions of the mechanism of the photochemical reaction, see Goon, D.J.W.; Murray, N.G.; Schoch, J.; Bunce, N.J. *Can. J. Chem.* ***1973***, *51*, 3827; Squire, R.H.; Jaffé, H.H. *J. Am. Chem. Soc.* ***1973***, *95*, 8188; Shine, H.J.; Subotkowski, W.; Gruszecka, E. *Can. J. Chem.* ***1986***, *64*, 1108.

18-44 Dyotropic Rearrangements

1/*C*-Trialkylsilyl,2/*O*-trialkylsilyl-interchange

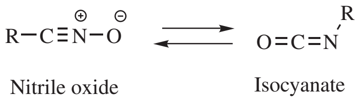


A *dyotropic rearrangement*[892] is an uncatalyzed process in which two σ bonds simultaneously migrate intramolecularly.[893] There are two types. The above is an example of type 1, which consists of reactions in which the two σ bonds interchange positions. In type 2, the two σ bonds do not interchange positions. An example is



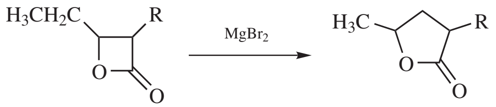
Some other examples are

Type 1



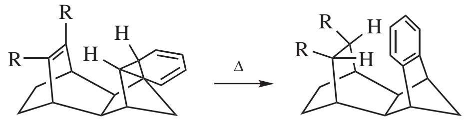
Ref. [894]

Type 1



Ref. [895]

Type 2



Ref. [896]

A useful type 1 example is the *Brook rearrangement*,[897] a stereospecific intramolecular migration of silicon from carbon to oxygen that occurs for

[892]Reetz, M.T. *Angew. Chem. Int. Ed.* ***1972***, *11*, 129, 130.

[893]For reviews, see Minkin, V.I.; Olekhnovich, L.P.; Zhdanov, Yu.A. *Molecular Design of Tautomeric Compounds*, D. Reidel Publishing Co., Dordrecht, ***1988***, pp. 221–246; Minkin, V.I. *Sov. Sci. Rev. Sect. B* ***1985***, *7*, 51; Reetz, M.T. *Adv. Organomet. Chem.* ***1977***, *16*, 33. Also see Mackenzie, K.; Gravaatt, E.C.; Gregory, R.J.; Howard, J.A.K.; Maher, J.P. *Tetrahedron Lett.* ***1992***, *33*, 5629.

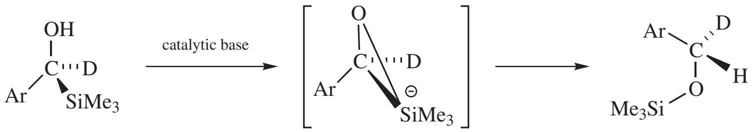
[894]See, for example, Taylor, G.A. *J. Chem. Soc. Perkin Trans. 1* ***1985***, 1181.

[895]See Black, T.H.; Hall, J.A.; Sheu, R.G. *J. Org. Chem.* ***1988***, *53*, 2371; Black, T.H.; Fields, J.D. *Synth. Commun.* ***1988***, *18*, 125.

[896]See Mackenzie, K.; Proctor, G.; Woodnutt, D.J. *Tetrahedron* ***1987***, *43*, 5981, and references cited therein.

[897]For a review, see Moser, W.H. *Tetrahedron* ***2001***, *57*, 2065.

(α-hydroxybenzyl)trialkylsilanes (**176**) in the presence of a catalytic amount of base.[898] Formation of a Si–O bond rather than the Si–C bond drives the rearrangement, which is believed to proceed via formation of **177**, and does proceed with inversion of configuration at carbon and retention of configuration at silicon.[899] A reverse Brook rearrangement is also known.[900] The reaction has been extended to other systems. A homo-Brook rearrangement has also been reported.[901] Another variation is the aza-Brook rearrangement of α-silylallyl)amines.[902] The Brook rearrangement has been used in synthesis involving silyl dithianes.[903] A Brook rearrangement mediated [6 + 2]-annulation has been used for the construction of eight-membered carbocycles.[904]



176 **177**

The Brook rearrangement has been used in two important synthetic applications, a multicomponent coupling protocol initiated by a Brook rearrangement involving silyl dithianes as mentioned, and anion relay chemistry (ARC) involving a Brook rearrangement. An example of the former is the conversion of the 2-silyl dithiane **178** to the anion with *tert*-butyllithium followed by ring opening of an epoxide to give **179**.[905] Treatment with HMPA triggers a solvent-controlled Brook rearrangement that gives a new dithiane anion (**180**), which then reacts with a different epoxide to give the final product, **181**. An example of the anion relay chemistry treats dithiane (**182**) with *n*-butyllithium, and then **183** to give **184**.[906] Subsequent treatment with a variety of electrophiles, such as allyl bromide, in HMPA, leads to **185** via a Brook rearrangement, and then alkylation of the resultant dithian anion. This reaction can be initiated by nucleophiles other

[898]Brook, A.G. *Acc. Chem. Res.* ***1974***, *7*, 77; Brook, A.G.; Bassendale, A.R., in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 2, Academic Press, NY, ***1980***, pp. 149–227.

[899]Brook, A. G.; Pascoe, J. D. *J. Am. Chem. Soc.* ***1971*** *93*, 6224.

[900]Wright, A.: West, R. *J. Am. Chem. Soc.* ***1974***, *96*,3214; Wright, A.; West, R. *J. Am. Chem. Soc.* ***1974***, *96*, 3227; Linderman, J.J.; Ghannam, A. *J. Am. Chem. Soc.* ***1990***, *112*, 2392.

[901]Wilson, S.R.; Georgiadis, G.M. *J. Org. Chem.* ***1983***, *48*, 4143.

[902]Honda, T.; Mori, M. *J. Org. Chem.* ***1996***, *61*, 1196.

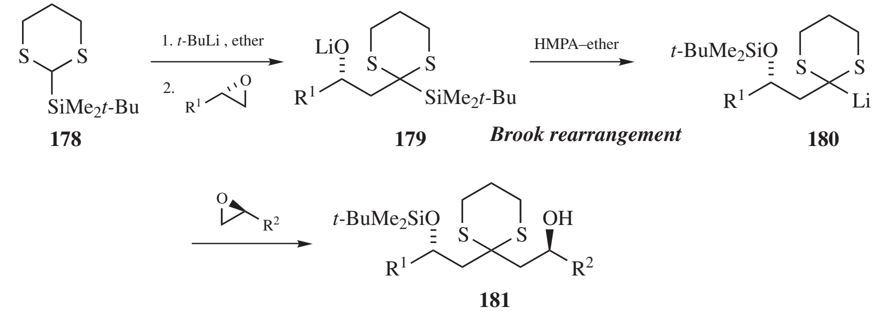
[903]For examples, see Smith III, A.B.; Adams, C. M. *Acc. Chem. Res.* ***2004***, *37*, 365; Smith III, A.B.; Kim, D.-S. *Org. Lett.* ***2005***, *7*, 3247.

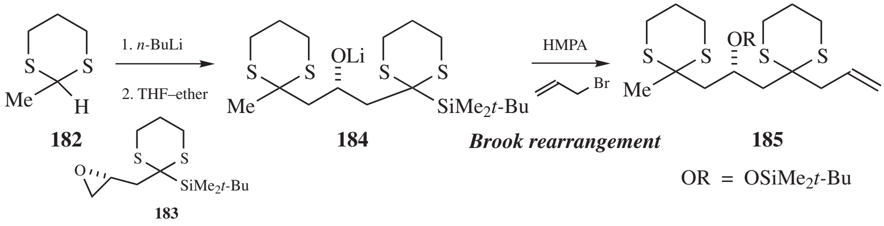
[904]Takeda, K.; Haraguchi, H.; Okamoto, Y. *Org. Lett.* ***2003***, *5*, 3705; Sawada, Y.; Sasaki, M.; Takeda, K. *Org. Lett.* ***2004***, *6*, 2277.

[905]Smith III, A.B.; Boldi, A.M. *J. Am. Chem. Soc.* ***1997***, *119*, 6925; Smith III, A.B.; Pitram, S.M. ; Boldi, A.M.; Gaunt, M.J.; Sfouggatakis, C.; Moser, W.H. *J. Am. Chem. Soc.* ***2003***, *125*, 14435.

[906]Smith III, A.B.; Xian, M. *J. Am. Chem. Soc.* ***2006***, *128*, 66.

than dithiane anion. Organocuprates can be used, and the anion stabilizing group can be a nitrile.[907]





[907]Private communication, Professor Amos B. Smith III, University Pennsylvania.

CHAPTER 19

Oxidations and Reductions

First, we must examine what we mean when we speak of oxidation and reduction. Inorganic chemists define oxidation in two ways: loss of electrons and increase in oxidation number. In organic chemistry, these definitions, while still technically correct, are not easy to apply. While electrons are directly transferred in some organic oxidations and reductions, the mechanisms of most of these reactions do not involve a direct electron transfer. As for oxidation number, while this is easy to apply in some cases, (e.g., the oxidation number of carbon in CH_4 is -4), in most cases attempts to apply the concept lead to fractional values or to apparent absurdities. Thus carbon in propane has an oxidation number of -2.67 and in butane of -2.5, although organic chemists seldom think of these two compounds as being in different oxidation states. An improvement could be made by assigning different oxidation states to different carbon atoms in a molecule, depending on what is bonded to them (e.g., the two carbons in acetic acid are obviously in different oxidation states), but for this a whole set of arbitrary assumptions would be required, since the oxidation number of an atom in a molecule is assigned on the basis of the oxidation numbers of the atoms attached to it. There would seem little to be gained by such a procedure. The practice in organic chemistry has been to set up a series of functional groups, in a qualitative way, arranged in order of increasing oxidation state, and then to define oxidation as *the conversion of a functional group in a molecule from one category to a higher one*. Reduction is the opposite. For the simple functional groups this series is shown in Table 19.1.[1] Note that this classification applies only to a single carbon atom or to two adjacent carbon atoms. Thus 1,3-dichloropropane is in the same oxidation state as chloromethane, but 1,2-dichloropropane is in a higher one. Obviously, such distinctions are somewhat arbitrary, and if we attempt to carry them too far, we will find ourselves painted into a corner. Nevertheless, the basic idea has served organic chemistry well. Note that

[1]For more extensive tables, with subclassifications, see Soloveichik, S.; Krakauer, H. *J. Chem. Educ.* ***1966***, *43*, 532.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Sixth Edition, by Michael B. Smith and Jerry March
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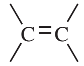
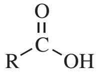
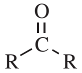
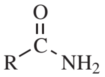
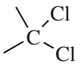
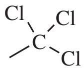
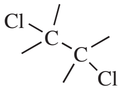
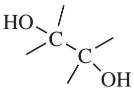
TABLE 19.1. Categories of Simple Functional Groups Arranged According to Oxidation State[a]

RH		—C≡C—		CO_2
	ROH			CCl_4
	RCl RNH_2			
	and so on			
			and so on	
		 and so on		
		Approximate Oxidation Number		
−4	−2	0	+2	+4

[a]Oxidation is the conversion of a functional group in a molecule to a higher category; reduction is conversion to a lower one. Conversions within a category are neither oxidations nor reductions. The numbers given at the bottom are only approximations.

conversion of any compound to another in the same category is not an oxidation or a reduction. Most oxidations in organic chemistry involve a gain of oxygen and/or a loss of hydrogen (Lavoisier's original definition of oxidation). The reverse is true for reductions.

Of course, there is no oxidation without a concurrent reduction. However, we classify reactions as oxidations or reductions depending on whether the *organic compound* is oxidized or reduced. In some cases, both the oxidant and reductant are organic; those reactions are treated separately at the end of the chapter.

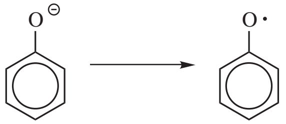
MECHANISMS

Noted that our definition of oxidation has nothing to do with mechanism. Thus the conversion of bromomethane to methanol with KOH (**10-1**) and to methane with $LiAlH_4$ (**19-53**) have the same S_N2 mechanisms, but one is a reduction (according to our definition) and the other is not. It is impractical to consider the mechanisms

of oxidation and reduction reactions in broad categories in this chapter as we have done for the reactions considered in Chapters 10–18.[2] The main reason is that the mechanisms are too diverse, and this in turn is because the bond changes are too different. For example, in Chapter 15, most reactions involved the bond change C=C → W—C—C—Y yet a relatively few mechanisms covered those reactions. But for oxidations and reductions the bond changes are far more diverse. Another reason is that the mechanism of a given oxidation or reduction reaction can vary greatly with the oxidizing or reducing agent employed. Very often the mechanism has been studied intensively for only one or a few of many possible agents.

Although we do not cover oxidation and reduction mechanisms in the same way as we have covered other mechanisms, it is still possible to list a few broad mechanistic categories. In doing this, we follow the scheme of Wiberg.[3]

1. *Direct Electron Transfer.*[4] We have already met some reactions in which the reduction is a direct gain of electrons or the oxidation a direct loss of them. An example is the Birch reduction (**15-13**), where sodium directly transfers an electron to an aromatic ring. An example from this chapter is found in the bimolecular reduction of ketones (**19-76**), where again it is a metal that supplies the electrons. This kind of mechanism is found largely in three types of reaction:[5] (a) the oxidation or reduction of a free radical (oxidation to a positive or reduction to a negative ion), (b) the oxidation of a negative ion or the reduction of a positive ion to a comparatively stable free radical, and (c) electrolytic oxidations or reductions (an example is the Kolbe reaction, **14-29**). An important example of (b) is oxidation of amines and phenolate ions:



[2]For monographs on oxidation mechanisms, see Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 16, Elsevier, NY, ***1980***; *Oxidation in Organic Chemistry*, Academic Press, NY, pt. A [Wiberg, K.B.], ***1965***, pts. B, C, and D [Trahanovsky, W.S.], ***1973, 1978, 1982***; Waters, W.A. *Mechanisms of Oxidation of Organic Compounds*, Wiley, NY, ***1964***; Stewart, R. *Oxidation Mechanisms*, W. A. Benjamin, NY, ***1964***. For a review, see Stewart, R. *Isot. Org. Chem.* ***1976***, *2*, 271.

[3]Wiberg, K.B. *Surv. Prog. Chem.* ***1963***, *1*, 211.

[4]For a monograph on direct electron-transfer mechanisms, see Eberson, L. *Electron Transfer Reactions in Organic Chemistry*, Springer, NY, ***1987***. For a review, see Eberson, L. *Adv. Phys. Org. Chem.* ***1982***, *18*, 79. For a review of multistage electron-transfer mechanisms, see Deuchert, K.; Hünig, S. *Angew. Chem. Int. Ed.* ***1978***, *17*, 875.

[5]Littler, J.S.; Sayce, I.G. *J. Chem. Soc.* ***1964***, 2545.

These reactions occur easily because of the relative stability of the radicals involved.[6] The single electron-transfer mechanism (SET), which we have met several times (e.g., p. 264) is an important case.

2. *Hydride Transfer.*[7] In some reactions, a hydride ion is transferred to or from the substrate. The reduction of epoxides with $LiAlH_4$ is an example (**19-35**). Another is the Cannizzaro reaction (**19-81**). Reactions in which a carbocation abstracts a hydride ion belong in this category:[8]

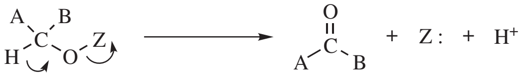
$$R^{+} + R'H \longrightarrow RH + R'^{+}$$

3. *Hydrogen-Atom Transfer.* Many oxidation and reduction reactions are free-radical substitutions and involve the transfer of a hydrogen atom. For example, one of the two main propagation steps of **14-1** involves abstraction of hydrogen:

$$RH + Cl\bullet \longrightarrow R\bullet + HCl$$

This is the case for many of the reactions of Chapter 14.

4. *Formation of Ester Intermediates.* A number of oxidations involve the formation of an ester intermediate (usually of an inorganic acid), and then the cleavage of this intermediate:



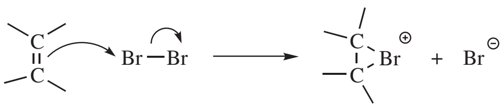
Z is usually CrO_3H, MnO_3, or a similar inorganic acid moiety. One example of this mechanism will be seen in **19-23**, where A was an alkyl or aryl group, B was OH, and Z was CrO_3H. Another is the oxidation of a secondary alcohol to a ketone (**19-3**), where A and B are alkyl or aryl groups and Z is also CrO_3H. In the lead tetraacetate oxidation of glycols (**19-7**) the mechanism also follows this pattern, but the positive leaving group is carbon instead of hydrogen. Note that the cleavage shown is an example of an E2 elimination.

5. *Displacement Mechanisms.* In these reactions, the organic substrate uses its electrons to cause displacement on an electrophilic oxidizing agent. One example is the addition of bromine to an alkene (**15-39**).

[6]For a review of the oxidation of phenols, see Mihailović, M.Lj.; Čeković, Z., in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, ***1971***, pp. 505–592.

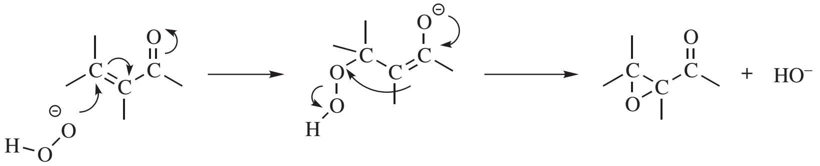
[7]For a review, see Watt, C.I.F. *Adv. Phys. Org. Chem.* ***1988***, *24*, 57.

[8]For a review of these reactions, see Nenitzescu, C.D., in Olah, G.A.; Schleyer, P.V.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, pp. 463–520.



An example from this chapter is found in **19-29**:

6. *Addition–Elimination Mechanisms*. In the reaction between α,β-unsaturated ketones and alkaline peroxide (**15-50**), the oxidizing agent adds to the substrate and then part of it is lost:



In this case, the oxygen of the oxidizing agent is in oxidation state −1 and the hydroxide ion departs with its oxygen in the −2 state, so it is reduced and the substrate oxidized. There are several reactions that follow this pattern of addition of an oxidizing agent and the loss of part of the agent, usually in a different oxidation state. Another example is the oxidation of ketones with SeO_2 (**19-17**). This reaction is also an example of category 4, since it involves formation and E2 cleavage of an ester. This example shows that these six categories are not mutually exclusive.

REACTIONS

In this chapter, the reactions are classified by the type of bond change occurring to the organic substrate, in conformity with our practice in the other chapters.[9] This means that there is no discussion in any one place of the use of a particular oxidizing or reducing agent, for example, acid dichromate or $LiAlH_4$ (except for a discussion of selectivity of reducing agents, p. 1787). Some oxidizing or reducing agents are fairly specific in their action, attacking only one or a few types of substrate.

[9]For a table of oxidation and reduction reactions, and the oxidizing and reducing agents for each, see Hudlický, M. *J. Chem. Educ.* ***1977***, *54*, 100.

Others, like acid dichromate, permanganate, $LiAlH_4$, and catalytic hydrogenation, are much more versatile.[10,9,11]

OXIDATIONS[11,2]

In some cases, oxidations have been placed in another chapter. The oxidation of an alkene to a diol (**15-48**), and aromatic compound to a diol (**15-49**), or oxidation to an epoxide (**15-50**) are placed in Chapter 15, for consistency with the concept of addition to a π-bond. Diamination of an alkene (**15-53**) and formation of aziridines (**15-54**) are in Chapter 15 for the same reason. Most other oxidations have been placed here. The reactions in this section are classified into groups depending on

[10]For books on certain oxidizing agents, see Mijs, W.J.; de Jonge, C.R.J.I. *Organic Synthesis by Oxidation with Metal Compounds*, Plenum, NY, ***1986***; Cainelli, G.; Cardillo, G. *Chromium Oxidations in Organic Chemistry*, Springer, NY, ***1984***; Arndt, D. *Manganese Compounds as Oxidizing Agents in Organic Chemistry*, Open Court Publishing Company, La Salle, IL, ***1981***; Lee, D.G. *The Oxidation of Organic Compounds by Permanganate Ion and Hexavalent Chromium*, Open Court Publishing Company, La Salle, IL, ***1980***. For some reviews, see Curci, R. *Adv. Oxygenated Processes* ***1990***, *2*, 1 (dioxiranes); Adam, W.; Curci, R.; Edwards, J.O. *Acc. Chem. Res.* ***1989***, *22*, 205 (dioxiranes); Murray, R.W. *Chem. Rev.* ***1989***, *89*, 1187; *Mol. Struc. Energ.* ***1988***, *5*, 311 (dioxiranes); Kafafi, S.A.; Martinez, R.I.; Herron J.T. *Mol. Struc. Energ.* ***1988***, *5*, 283 (dioxiranes); Krief, A.; Hevesi, L. *Organoselenium Chemistry I*; Springer, NY, ***1988***, pp. 76–103 (seleninic anhydrides and acids); Ley, S.V., in Liotta, D.C. *Organoselenium Chemistry*, Wiley, NY, ***1987***, pp. 163–206 (seleninic anhydrides and acids); Barton, D.H.R.; Finet, J. *Pure Appl. Chem.* ***1987***, *59*, 937 [bismuth(V)]; Fatiadi, A.J. *Synthesis* ***1987***, 85 (KMnO4); Rubottom, G.M., in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. D, Academic Press, NY, ***1982***, pp. 1–145 (lead tetraacetate); Fatiadi, A.J., in Pizey, J.S. *Synthetic Reagents*, Vol. 4, Wiley, NY, ***1981***, pp. 147–335; *Synthesis* ***1974***, 229 (HIO_4); Fatiadi, A.J. *Synthesis* ***1976***, 65, 133 (MnO_2); Ogata, Y., in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. C, Academic Press, NY, ***1978***, pp. 295–342 (nitric acid and nitrogen oxides); McKillop, A. *Pure Appl. Chem.* ***1975***, *43*, 463 (thallium nitrate); Pizey, J.S. *Synthetic Reagents*, Vol. 2, Wiley, NY, ***1974***, pp. 143–174 (MnO_2); George, M.V.; Balachandran, K.S. *Chem. Rev.* ***1975***, *75*, 491 (nickel peroxide); Courtney, J.L.; Swansborough, K.F. *Rev. Pure Appl. Chem.* ***1972***, *22*, 47 (ruthenium tetroxide); Ho, T.L. *Synthesis* ***1973***, 347 (ceric ion); Aylward, J.B. *Q. Rev. Chem. Soc.* ***1971***, *25*, 407 (lead tetraacetate); Meth-Cohn, O.; Suschitzky, H. *Chem. Ind. (London)* ***1969***, 443 (MnO_2); Sklarz, B. *Q. Rev. Chem. Soc.* ***1967***, *21*, 3 (HIO_4); Korshunov, S.P.; Vereshchagin, L.I. *Russ. Chem. Rev.* ***1966***, *35*, 942 (MnO_2); Weinberg, N.L.; Weinberg, H.R. *Chem. Rev.* ***1968***, *68*, 449 (electrochemical oxidation). For reviews of the behavior of certain reducing agents, see Keefer, L.K.; Lunn, G. *Chem. Rev.* ***1989***, *89*, 459 (Ni—Al alloy); Málek, J. *Org. React.* ***1988***, *36*, 249; ***1985***, *34*, 1–317 (metal alkoxyaluminum hydrides); Alpatova, N.M.; Zabusova, S.E.; Tomilov, A.P. *Russ. Chem. Rev.* ***1986***, *55*, 99 (solvated electrons generated electrochemically); Caubère, P. *Angew. Chem. Int. Ed.* ***1983***, *22*, 599 (modified sodium hydride); Nagai, Y. *Org. Prep. Proced. Int.* ***1980***, *12*, 13 (hydrosilanes); Pizey, J.S. *Synthetic Reagents*, Vol. 1, Wiley, NY, ***1974***, pp. 101–294 ($LiAlH_4$); Winterfeldt, E. *Synthesis* ***1975***, 617 (diisobutylaluminum hydride and triisobutylaluminum), Hückel, W. *Fortschr. Chem. Forsch.* ***1966***, *6*, 197 (metals in ammonia or amines). For books on reductions with metal hydrides, see Seyden-Penne, J. *Reductions by the Alumino- and Borohydrides*, VCH, NY, ***1991***; Štrouf, O.; Čásenský, B.; Kubánek, V. *Sodium Dihydrido-bis(2-methoxyethoxo)aluminate (SDMA)*, Elsevier, NY, ***1985***; Hajós, A. *Complex Hydrides*, Elsevier, NY, ***1979***. Also see, House, H.O. *Modern Synthetic Reactions*, 2nd ed., W. A. Benjamin, NY, ***1972***.

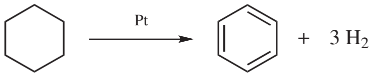
[11]For books on oxidation reactions, see Hudlický, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***; Haines, A.H. *Methods for the Oxidation of Organic Compounds*, 2 vols., Academic Press, NY, ***1985, 1988*** [The first volume pertains to hydrocarbon substrates; the second mostly to oxygen- and nitrogen-containing substrates]; Chinn, L.J. *Selection of Oxidants in Synthesis*, Marcel Dekker, NY, ***1971***; Augustine, R.L.; Trecker, D.J. *Oxidation*, 2 vols., Marcel Dekker, NY, ***1969, 1971***.

the type of bond change involved. These groups are (A) eliminations of hydrogen, (B) oxidations involving cleavage of carbon–carbon bonds, (C) reactions involving replacement of hydrogen by oxygen, (D) reactions in which oxygen is added to the substrate, and (E) oxidative coupling.

A. Eliminations of Hydrogen

19-1 Aromatization of Six-Membered Rings

Hexahydro-terelimination



Six-membered alicyclic rings can be aromatized in a number of ways.[12] Aromatization is accomplished most easily if there are already one or two double bonds in the ring or if the ring is fused to an aromatic ring. The reaction can also be applied to heterocyclic five - and six-membered rings. Many groups may be present on the ring without interference, and even *gem*-dialkyl substitution does not always prevent the reaction: In such cases, one alkyl group often migrates or is eliminated. However, more drastic conditions are usually required for this. In some cases OH and COOH groups are lost from the ring. Cyclic ketones are converted to phenols. Seven-membered and larger rings are often isomerized to six-membered aromatic rings, although this is not the case for partially hydrogenated azulene systems (which are frequently found in Nature); these are converted to azulenes.

There are three types of reagents most frequently used to effect aromatization.

1. Hydrogenation catalysts,[13] such as platinum, palladium,[14] and nickel. In this case, the reaction is the reverse of double-bond hydrogenation (**15-11** and **15-15**), and presumably the mechanism is also the reverse, although not much is known.[15] Cyclohexene has been detected as an intermediate in the conversion of cyclohexane to benzene, using Pt.[16] The substrate is heated with the catalyst at ~ 300–350°C. The reactions can often be carried out under milder

[12]For reviews, see Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Academic Press, NY, **1985**, pp. 16–22, 217–222; Fu, P.P.; Harvey, R.G. *Chem. Rev.* ***1978***, *78*, 317; Valenta, Z., in Bentley, K.W.; Kirby, G.W. *Elucidation of Chemical Structures by Physical and Chemical Methods* (Vol. 4 of Weissberger, A. *Techniques of Chemistry*), 2nd ed., pt. 2, Wiley, NY, ***1973***, pp. 1–76; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 34–44.

[13]For a review, see Rylander, P.N. *Organic Synthesis with Noble Metal Catalysts*, Academic Press, NY, ***1973***, pp. 1–59.

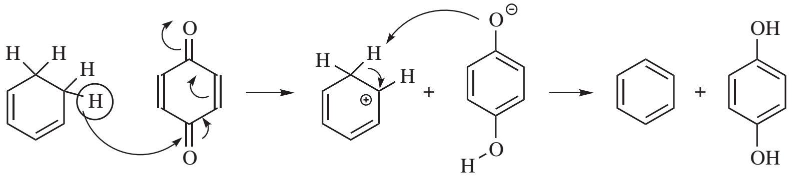
[14]Ishikawa, T.; Uedo, E.; Tani, R.; Saito, S. *J. Org. Chem.* ***2001***, *66*, 186; Cossy, J.; Belotti, D. *Org. Lett.* ***2002***, *4*, 2557.

[15]For a discussion, see Tsai, M.; Friend, C.M.; Muetterties, E.L. *J. Am. Chem. Soc.* ***1982***, *104*, 2539. See also, Augustine, R.L.; Thompson, M.M. *J. Org. Chem.* ***1987***, *52*, 1911.

[16]Land, D.P.; Pettiette-Hall, C.L.; McIver, Jr., R.T.; Hemminger, J.C. *J. Am. Chem. Soc.* ***1989***, *111*, 5970.

conditions if a hydrogen acceptor, such as maleic acid, cyclohexene, or benzene, is present to remove hydrogen as it is formed. The acceptor is reduced to the saturated compound. Other transition metals can be used, including $TiCl_4$-NEt_3.[17] It has been reported that dehydrogenation of 1-methylcyclohexene-1-^{13}C over an alumina catalyst gave toluene with the label partially scrambled throughout the aromatic ring.[18] For polycylic systems, heating with oxygen on activated carbon generates the aromatic compound, as in the conversion of dihydroanthracene to anthracene.[19]

2. The elements sulfur and selenium, which combine with the hydrogen evolved to give, respectively, H_2S and H_2Se. Little is known about this mechanism either.[20]
3. Quinones,[21] which become reduced to the corresponding hydroquinones. Two important quinones often used for aromatizations are chloranil (2,3,5,6-tetrachloro-1,4-benzoquinone) and DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone).[22] The latter is more reactive and can be used in cases where the substrate is difficult to dehydrogenate. It is likely that the mechanism involves a transfer of hydride to the quinone oxygen, followed by the transfer of a proton to the phenolate ion:[23,21]



Among other reagents[24] that have been used for aromatization of six-membered rings are atmospheric oxygen, MnO_2,[25] $KMnO_4$-Al_2O_3,[26] SeO_2, various strong bases,[27]

[17]Srinivas, G.; Periasamy, M. *Tetrahedron Lett.* ***2002***, *43*, 2785.

[18]Marshall, J.L.; Miiller, D.E.; Ihrig, A.M. *Tetrahedron Lett.* ***1973***, 3491.

[19]Nakamichi, N.; Kawabata, H.; Hiyashi, M. *J. Org. Chem.* ***2003***, *68*, 8272.

[20]House, H.O.; Orchin, M. *J. Am. Chem. Soc.* ***1960***, *82*, 639; Silverwood, H.A.; Orchin, M. *J. Org. Chem.* ***1962***, *27*, 3401.

[21]For reviews, see Becker, H.; Turner, A.B., in Patai, S.; Rappoport, Z. *The Chemistry of the Quinonoid Compounds*, Vol. 2, pt. 2, Wiley, NY, ***1988***, pp. 1351–1384; Becker, H., in Patai, S. *The Chemistry of the Quinonoid Compounds*, Vol. 1, pt. 1, Wiley, NY, ***1974***, pp. 335–423.

[22]For reviews of DDQ, see Turner, A.B., in Pizey, J.S. *Synthetic Reagents*, Vol. 3, Wiley, NY, ***1977***, pp. 193–225; Walker, D.; Hiebert, J.D. *Chem. Rev.* ***1967***, *67*, 153.

[23]Braude, E.A.; Jackman, L.M.; Linstead, R.P.; Lowe, G. *J. Chem. Soc.* ***1960***, 3123, 3133; Trost, B.M. *J. Am. Chem. Soc.* ***1967***, *89*, 1847. See also, Stoos, F.; Roč ek, J. *J. Am. Chem. Soc.* ***1972***, *94*, 2719; Hashish, Z.M.; Hoodless, I.M. *Can. J. Chem.* ***1976***, *54*, 2261; Müller, P.; Joly, D.; Mermoud, F. *Helv. Chim. Acta* ***1984***, *67*, 105; Radtke, R.; Hintze, H.; Rösler, K.; Heesing, A. *Chem. Ber.* ***1990***, *123*, 627. Also see, Höfler, C.; Rüchardt, C. *Liebigs Ann. Chem.* ***1996***, 183.

[24]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 187–191.

[25]See, for example, Leffingwell, J.C.; Bluhm, H.J. *Chem. Commun.* ***1969***, 1151.

[26]McBride, C.M.; Chrisman, W.; Harris, C.E.; Singaram, B. *Tetrahedron Lett.* ***1999***, *40*, 45.

[27]For a review, see Pines, H.; Stalick, W.M. *Base-Catalyzed Reactions of Hydrocarbons and Related Compounds*, Academic Press, NY, ***1977***, pp. 483–503. See also, Reetz, M.T.; Eibach, F. *Liebigs Ann. Chem.* ***1978***, 1598; Trost, B.M.; Rigby, J.H. *Tetrahedron Lett.* ***1978***, 1667.

chromic acid,[28] H_2SO_4 and a ruthenium catalyst,[29] and SeO_2 on $P_2O_5/Me_3SiOSiMe_3$.[30] The last-mentioned reagent also dehydrogenates cyclopentanes to cyclopentadienes. In some instances, the hydrogen is not released as H_2 or transferred to an external oxidizing agent, but instead serves to reduce another molecule of substrate. This is a disproportionation reaction and can be illustrated by the conversion of cyclohexene to cyclohexane and benzene. Quinones react with allylic silanes and a $Bi(OTf)_3$ catalyst to give 2-allyl hydroquinone.[31] Similar reaction with acetic anhydride rather than an allylic silane leads to a 2-acetoxy hydroquinone.[32]

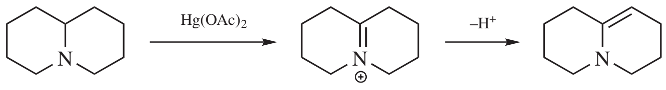
Heteroatom rings, as found in quinoline derivatives, for example, can be generated from amino-ketones with [hydroxy(tosyloxy)iodo]benzene and perchloric acid[33] or with $NaHSO_4$—$Na_2Cr_2O_7$ on wet silica.[34] Dihydropyridines are converted to pyridines with $NaNO_2$–oxalic acid and wet silica[35] $BaMnO_4$,[36] $FeCl_3$–acetic acid,[37] $Mg(HSO_4)_2$—$NaNO_2$,[38] NO^+-18-crown-6-$H(NO_3)_2^-$,[39] or with nicotinium dichromate.[40] Cyclic imines are converted to pyridine derivatives with NCS, and then excess sodium methoxide.[41]

Note that hydrogenolysis of cyclohexane leads to *n*-hexane with hydrogen and an iridium catalyst.[42]

OS **II**, 214, 423; **III**, 310, 358, 729, 807; **IV**, 536; **VI**, 731. Also see, OS **III**, 329.

19-2 Dehydrogenations Yielding Carbon–Carbon Double Bonds

Dihydro-elimination



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[28]Müller, P.; Pautex, N.; Hagemann, H. *Chimia* ***1988***, *42*, 414.

[29]Tanaka, H.; Ikeno, T.; Yamada, T. *Synlett* ***2003***, 576.

[30]Lee, J.G.; Kim, K.C. *Tetrahedron Lett.* ***1992***, *33*, 6363.

[31]Yadav, J.S.; Reddy, B.V.S.; Swamy, T. *Tetrahedron Lett.* ***2003***, *44*, 4861.

[32]Yadav, J.S.; Reddy, B.V.S.; Swamy, T.; Rao, K.R. *Tetrahedron Lett.* ***2004***, *45*, 6037.

[33]Varma, R.S.; Kumar, D. *Tetrahedron Lett.* ***1998***, *39*, 9113.

[34]Damavandi, J.A.; Zolfigol, M.A.; Karami, B. *Synth. Commun.* ***2001***, *31*, 3183.

[35]Zolfigol, M.A.; Kiany-Borazjani, M.; Sadeghi, M.M.; Mohammadpoor-Baltork, I.; Memarian, H.R. *Synth. Comm.* ***2000***, *30*, 551.

[36]Memarian, H.R.; Sadeghi, M.M.; Momeni, A.R. *Synth. Commun.* ***2001***, *31*, 2241.

[37]Lu, J.; Bai, Y.; Wang, Z.; Yang, B.Q.; Li, W. *Synth. Commun.* ***2001***, *31*, 2625.

[38]Zolfigol, M.A.; Kiany-Borazjani, M.; Sadeghi, M.M.; Mohammadpoor-Baltork, I.; Memarian, H.R. *Synth. Commun.* ***200***, *30*, 3919.

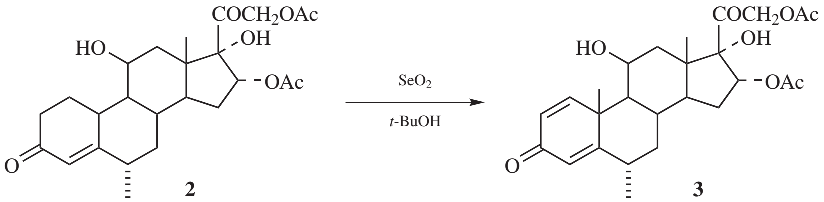
[39]Zolfigol, M.A.; Zebarjadian, M.H.; Sadeghi, M.M.; Mohammadpoor-Baltork, I. Memarian, H.R.; Shamsipur, M. *Synth. Commun.* ***2001***, *31*, 929.

[40]Sadeghi, M.M.; Mohammadpoor-Baltork, I.; Memarian, H.R.; Sobhani, S. *Synth. Commun.* ***2000***, *30*, 1661.

[41]DeKimpe, N.; Keppens, M.; Fonck, G. *Chem. Commun.* ***1996***, 635.

[42]Locatelli, F.; Candy, J.-P.; Didillon, B.; Niccolai, G.P.; Uzio, D.; Basset, J.-M. *J. Am. Chem. Soc.* ***2001***, *123*, 1658.

Dehydrogenation of an aliphatic compound to give a double bond in a specific location is not usually a feasible process, although industrially mixtures of alkenes are obtained in this way from mixtures of alkanes (generally by heating with chromia–alumina catalysts). There are, however, some notable exceptions. Heating cyclooctane with an iridium catalyst leads to cyclooctene.[43] Treating alkenes that have an allylic hydrogen with $CrCl_2$ converts them to allenes.[44] It is not surprising, however, that most of the exceptions generally involve cases where the new double bond can be in conjugation with a double bond or with an unshared pair of electrons already present.[45] One example is the synthesis developed by Leonard and co-workers,[46] in which tertiary amines give enamines (**10-69**) when treated with mercuric acetate[47] (see the example above). In this case the initial product is the iminium ion **1** which loses a proton to give the enamine. In another example, the oxidizing agent SeO_2 can in certain cases convert a carbonyl compound to an α,β-unsaturated carbonyl compound by removing H_2[48] (though this reagent more often gives **19-17**). This reaction has been most often applied in the steroid series, an example being formation of **2** from **3**.[49] In a similar manner, Hünig's base, diisopropylethylamine, was converted to the enamine *N,N*-diisopropyl-*N*-vinylamine by heating with an iridium catalyst.[50]



2 **3**

Similarly, SeO_2 has been used to dehydrogenate 1,4-diketones[51] ($RCOCH_2CH_2$-$COR \rightarrow RCOCH{=}CHCOR$) and 1,2-diarylalkanes ($ArCH_2CH_2Ar \rightarrow ArCH{=}CHAr$). These conversions can also be carried out by certain quinones, most notably DDQ (see **19-1**).[22] Ketones have been converted to conjugated ketones with

[43]Göttker-Schnetmann, I.; White, P.; Brookhart, M. *J. Am. Chem. Soc.* ***2004***, *126*, 1804.

[44]Takai, K.; Kokumai, R.; Toshikawa, S. *Synlett* ***2002***, 1164.

[45]For a review, see Haines, A.J. *Methods for the Oxidation of Organic Compounds*, Vol. 1, Academic Press, NY, ***1985***, pp. 6–16, 206–216. For lists of examples, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 251–256.

[46]For example, see Leonard, N.J.; Musker, W.K. *J. Am. Chem. Soc.* ***1959***, *81*, 5631; ***1960***, *82*, 5148.

[47]For reviews, see Haynes, L.W.; Cook, A.G., in Cook, A.G. *Enamines*, 2nd ed. Marcel Dekker, NY, ***1988***, pp. 103–163; Lee, D.G., in Augustine, R.L.; Trecker, D.J. *Oxidation*, Vol. 1, Marcel Dekker, NY, ***1969***, pp. 102–107.

[48]For reviews, see Back, T.G., in Patai, S. *The Chemistry of Organic Selenium and Tellurium Compounds*, pt. 2, Wiley, NY, ***1987***, pp. 91–213, 110–114; Jerussi, R.A. *Sel. Org. Transform.* ***1970***, *1*, 301, see pp. 315–321.

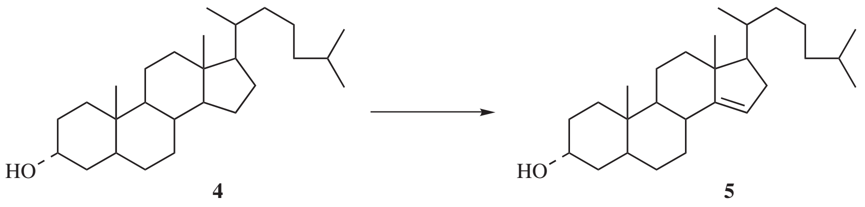
[49]Bernstein, S.; Littell, R. *J. Am. Chem. Soc.* ***1960***, *82*, 1235.

[50]Zhang, X.; Fried, A.; Knapp,S.; Goldman, A.S. *Chem. Commun.* ***2003***, 2060.

[51]For example, see Barnes, C.S.; Barton, D.H.R. *J. Chem. Soc.* ***1953***, 1419.

Ph(S=O)OMe and KH,[52] and also with (pyridyl)S(=O)OMe/KH, and then $CuSO_4$.[53] Silyl enol ethers also give the conjugated ketone upon treatment with ceric ammonium nitrate in DMF[54] or with $Pd(OAc)_2/NaOAc/O_2$.[55] Simple aldehydes and ketones have been dehydrogenated (e.g., cyclopentanone → cyclopentenone) by $PdCl_2$,[56] by $FeCl_3$,[57] and by benzeneseleninic anhydride[58] (this reagent also dehydrogenates lactones in a similar manner), among other reagents.

In an indirect method of achieving this conversion, the silyl enol ether of a simple ketone is treated with DDQ[59] or with triphenylmethyl cation[60] (for another indirect method, see **17-12**). Simple linear alkanes have been converted to alkenes by treatment with certain transition-metal compounds.[61]



An entirely different approach to specific dehydrogenation has been reported by R. Breslow[62] and by J.E. Baldwin.[63] By means of this approach it was possible, for example, to convert 3α-cholestanol (**4**) to 5α-cholest-14-en-3α-ol (**5**), thus introducing a double bond at a specific site remote from any functional group.[64] This was

[52]Resek, J.E.; Meyers, A.I. *Tetrahedron Lett.* ***1995***, *36*, 7051.

[53]Trost, B.M.; Parquette, J.R. *J. Org. Chem.* ***1993***, *58*, 1579.

[54]Evans, P.A.; Longmire, J.M.; Modi, D.P. *Tetrahedron Lett.* ***1995***, *36*, 3985.

[55]Larock, R.C.; Hightower, T.R.; Kraus, G.A.; Hahn, P.; Zheng, O. *Tetrahedron Lett.* ***1995***, *36*, 2423.

[56]Bierling, B.; Kirschke, K.; Oberender, H.; Schultz, M. *J. Prakt. Chem.* ***1972***, *314*, 170; Kirschke, K.; Müller, H.; Timm, D. *J. Prakt. Chem.* ***1975***, *317*, 807; Mincione, E.; Ortaggi, G.; Sirna, A. *Synthesis* ***1977***, 773; Mukaiyama, T.; Ohshima, M.; Nakatsuka, T. *Chem. Lett.* ***1983***, 1207. See also, Heck, R.F. *Palladium Reagents in Organic Synthesis*, Academic Press, NY, ***1985***, pp. 103–110.

[57]Cardinale, G.; Laan, J.A.M.; Russell, S.W.; Ward, J.P. *Recl. Trav. Chim. Pays-Bas* ***1982***, *101*, 199.

[58]Barton, D.H.R.; Hui, R.A.H.F.; Ley, S.V.; Williams, D.J. *J. Chem. Soc. Perkin Trans. 1* ***1982***, 1919; Barton, D.H.R.; Godfrey, C.R.A.; Morzycki, J.W.; Motherwell, W.B.; Ley, S.V. *J. Chem. Soc. Perkin Trans. 1* ***1982***, 1947.

[59]Jung, M.E.; Pan, Y.; Rathke, M.W.; Sullivan, D.F.; Woodbury, R.P. *J. Org. Chem.* ***1977***, *42*, 3961.

[60]Ryu, I.; Murai, S.; Hatayama, Y.; Sonoda, N. *Tetrahedron Lett.* ***1978***, 3455. For another method, which can also be applied to enol acetates, see Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* ***1983***, *24*, 5635, 5639.

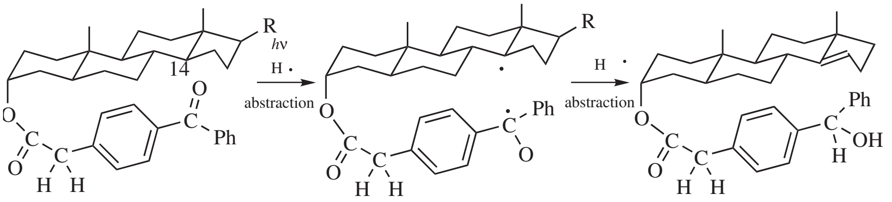
[61]See Burchard, T.; Felkin, H. *Nouv. J. Chim.* ***1986***, *10*, 673; Burk, M.J.; Crabtree, R.H. *J. Am. Chem. Soc.* ***1987***, *109*, 8025; Renneke, R.F.; Hill, C.L. *New J. Chem.* ***1987***, *11*, 763; *Angew. Chem. Int. Ed.* ***1988***, *27*, 1526; *J. Am. Chem. Soc.* ***1988***, *110*, 5461; Maguire, J.A.; Boese, W.T.; Goldman, A.S. *J. Am. Chem. Soc.* ***1989***, *111*, 7088; Sakakura, T.; Ishida, K.; Tanaka, M. *Chem. Lett.* ***1990***, 585; and references cited therein.

[62]Breslow, R.; Baldwin, S.W. *J. Am. Chem. Soc.* ***1970***, *92*, 732. For reviews, see Breslow, R. *Chemtracts: Org. Chem.* ***1988***, *1*, 333; *Acc. Chem. Res.* ***1980***, *13*, 170; *Isr. J. Chem.* ***1979***, *18*, 187; *Chem. Soc. Rev.* ***1972***, *1*, 553.

[63]Baldwin, J.E.; Bhatnagar, A.K.; Harper, R.W. *Chem. Commun.* ***1970***, 659.

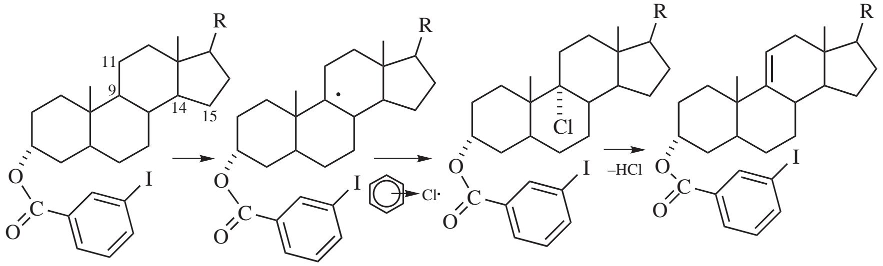
[64]For other methods of introducting a remote double bond, see Čeković, Z.; Cvetković, M. *Tetrahedron Lett.* ***1982***, *23*, 3791; Czekay, G.; Drewello, T.; Schwarz, H. *J. Am. Chem. Soc.* ***1989***, *111*, 4561. See also, Bégué, J. *J. Org. Chem.* ***1982***, *47*, 4268; Nagata, R.; Saito, I. *Synlett* ***1990***, 291.

accomplished by conversion of **4** to the ester **6**, followed by irradiation of **6**, which gave 55% **8**, which was then



6 **7** **8**

hydrolyzed to **5**. The radiation excites the benzophenone portion of **6** (p. $$$), which then abstracts hydrogen from the 14 position to give the diradical **7**, which undergoes another internal abstraction to give **8**. In other cases, diradicals like **7** can close to a macrocyclic lactone (**19-17**). In an alternate approach,[65] a 9(11) double bond was introduced into a steroid nucleus by reaction of the *m*-iodo ester **9** with $PhICl_2$ and uv light, which results in hydrogen being abstracted regioselectively from the 9 position, resulting in chlorination at that position. Dehydrohalogenation of **10** gives the 9(11)-unsaturated steroid **11**. In contrast, use of the para isomer of **7** results in chlorination at the 14 position and loss of HCl gives the 14-unsaturated steroid. These reactions are among the very few ways to introduce functionality at a specific site remote from any functional group (see also, **19-17**).

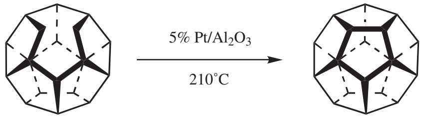


9 **10** **11**

Certain 1,2-diarylalkenes ArCH=CHAr' have been converted to the corresponding alkynes ArC≡CAr' by treatment with *t*-BuOK in DMF.[66] Dihydroindoles are converted to indoles with *N,N′,N″*-trichloro-1,3,5-triazin-2,4,6-trione and DBU.[67]

[65]Breslow, R.; Corcoran, R.J.; Snider, B.B.; Doll, R.J.; Khanna, P.L.; Kaleya, R. *J. Am. Chem. Soc.* ***1977***, *99*, 905. For related approaches, see Wolner, D. *Tetrahedron Lett.* ***1979***, 4613; Breslow, R.; Brandl, M.; Hunger, J.; Adams, A.D. *J. Am. Chem. Soc.* ***1987***, *109*, 3799; Batr, R.; Breslow, R. *Tetrahedron Lett.* ***1989***, *30*, 535; Orito, K.; Ohto, M.; Suginome, H. *J. Chem. Soc. Chem. Commun.* ***1990***, 1076.
[66]Akiyama, S.; Nakatsuji, S.; Nomura, K.; Matsuda, K.; Nakashima, K. *J. Chem. Soc. Chem. Commun.* ***1991***, 948.
[67]Tilstam, U.; Harre, M.; Heckrodt, T.; Weinmann, H. *Tetrahedron Lett.* ***2001***, *42*, 5385.

A different kind of dehydrogenation was used in the final step of Paquette's synthesis of dodecahedrane:[68]



dodecahedrane

OS **V**, 428, **VII**, 4, 473.

19-3 Oxidation or Dehydrogenation of Alcohols to Aldehydes and Ketones

***C,O*-Dihydro-elimination**

$$RCH_2OH \xrightarrow[\text{chromite}]{\text{copper}} RCHO$$

$$RCHOHR' \xrightarrow[H_2SO_4]{K_2Cr_2O_7} RCOR'$$

Primary alcohols can be converted to aldehydes and secondary alcohols to ketones in seven main ways:[69]

1. *With Strong Oxidizing Agents*.[70] Secondary alcohols are easily oxidized to ketones by acid dichromate[71] at room temperature or slightly above. Many

[68]Paquette, L.A.; Weber, J.C.; Kobayashi, T.; Miyahara, Y. *J. Am. Chem. Soc.* ***1988***, *110*, 8591. For a monograph on dodecahedrane and related compounds, see Paquette, L.A.; Doherty, A.M. *Polyquinane Chemistry*; Springer, NY, ***1987***. For reviews, see, in Olah, G.A. *Cage Hydrocarbons*, Wiley, NY, ***1990***, the reviews by Paquette, L.A. pp. 313–352, and by Fessner, W.; Prinzbach, H. pp. 353–405; Paquette, L.A. *Chem. Rev.* ***1989***, *89*, 1051; *Top. Curr. Chem.* ***1984***, *119*, 1, in Lindberg, T. *Strategies and Tactics in Organic Synthesis*, Academic Press, NY, ***1984***, pp. 175–200.

[69]For reviews, see Hudlický, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, pp. 114–126, 132–149; Haines, A.M. *Methods for the Oxidation of Organic Compounds*, Vol. 2, Academic Press, NY, ***1988***, pp. 5–148, 326–390; Müller, P., in Patai, S. *The Chemistry of Functional Groups, Supplement E*, Wiley, NY, ***1980***, pp. 469–538; Cullis, C.F.; Fish, A., in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 129–157. For a lengthy list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1234–1250.

[70]For thorough discussions, see Lee, D.G., in Augustine, R.L.; Trecker, D.J. *Oxidation*, Vol. 2, Marcel Dekker, NY, ***1971***, pp. 56–81; and (with respect to chromium and managanese reagents) House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 257–273.

[71]Various forms of H2CrO4 and of CrO3 are used for this reaction. For a review, see Cainelli, G.; Cardillo, G. *Chromium Oxidations in Organic Chemistry*, Open Court Publishers Co., La Salle, IL, ***1981***, pp. 118–216. For discussions, see Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis*, Vol. 1, Wiley, NY, ***1967***, pp. 142–147, 1059–1064, and subsequent volumes in this series.

other strong oxidizing agents ($KMnO_4$,[72] ruthenium tetroxide,[73] etc.) have also been employed. A solution of chromic acid and sulfuric acid in water is known as the *Jones reagent*.[74] When secondary alcohols are dissolved in acetone, titration with the Jones reagent oxidizes them to ketones rapidly and in high yield without disturbing any double or triple bonds that may be present (see **19-10**) and without epimerizing an adjacent stereogenic center.[75] The Jones reagent can also oxidize primary allylic alcohols to the corresponding aldehydes,[76] although overoxidation to the carboxylic acid is a problem. Oxidative cleavage of primary alcohols has been observed in the presence of molecular sieve 3 Å.[77] Indeed, for the oxidation of allylic alcohols three other Cr(VI) reagents are commonly used,[78] dipyridine Cr(VI) oxide (*Collins' reagent*),[79] pyridinium chlorochromate (PCC),[80] and pyridinium dichromate (PDC).[81] The PCC is somewhat acidic, and acid-catalyzed rearrangements have been observed.[82] A variety of amines and diamines have been converted to tetraalkylammonium halochromates or dichromates. Examples include *N*-benzyl 1,4-diazabicyclo[2.2.2]octane ammonium dichromate with microwave irradiation,[83] γ-picolinium chlorochromate,[84] and quinolinium

[72]For oxidation with $KMnO_4$ on alumina with no solvent, see Hajipour, A.R.; Mallakpour, S.E.; Imanzadeh, G. *Chem. Lett.* ***1999***, 99. For oxidation with silica-supported KMnO4, see Takemoto, T.; Yasuda, K.; Ley, S.V. *Synlett* ***2001***, 1555. For oxidation in the ionic liquid bmim BF4, 1-butyl-3-methylimidazolium tetrafluoroborate: Kumar, A.; Jain, N.; Chauhan, S.M.S. *Synth. Commun.* ***2004***, *34*, 2835.

[73]For a review, see Lee, D.G.; van den Engh, M. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B Academic Press, NY, ***1973***, pp. 197–222.

[74]Bowden, K.; Heilbron I.M.; Jones, E.R.H.; Weedon, B.C.L. *J. Chem. Soc.* ***1946***, 39; Bowers, A.; Halsall, T.G.; Jones, E.R.H.; Lemin, A.J. *J. Chem. Soc.* ***1953***, 2548. Also see, Scott, S.L.; Bakac, A.; Espenson, J.H. *J. Am. Chem. Soc.* ***1992***, *114*, 4605. For an oxidation with Jones reagent on silica in dichloromethane, see Ali, M.H.; Wiggin, C.J. *Synth. Commun.* ***2001***, *31*, 1389; Ali, M.H.; Wiggin, C.J. *Synth. Commun.* ***2001***, *31*, 3383.

[75]For example, see Djerassi, C.; Hart, P.A.; Warawa, E.J. *J. Am. Chem. Soc.* ***1964***, *86*, 78.

[76]Harding, K.E.; May, L.M.; Dick, K.F. *J. Org. Chem.* ***1975***, *40*, 1664.

[77]Fernandes, R.A.; Kumar, P. *Tetrahedron Lett.* ***2003***, *44*, 1275.

[78]For a comparative study of Jones's, Collins's, and Corey's reagents, see Warrener, R.N.; Lee, T.S.; Russell, R.A.; Paddon-Row, M.N. *Aust. J. Chem.* ***1978***, *31*, 1113.

[79]Collins, J.C.; Hess, W.W.; Frank, F.J. *Tetrahedron Lett.* ***1968***, 3363; Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* ***1970***, *35*, 4000; Stensiö, K. *Acta Chem. Scand.* ***1971***, *25*, 1125; Collins, J.C.; Hess, W.W. *Org. Synth.* ***VI***, 644; Sharpless, K.B.; Akashi, K. *J. Am. Chem. Soc.* ***1975***, *97*, 5927.

[80]Corey, E.J.; Suggs, J.W. *Tetrahedron Lett.* ***1975***, 2647. For reviews of this and related reagents, see Luzzio, F.A.; Guziec, Jr., F.S. *Org. Prep. Proced. Int.* ***1988***, *20*, 533; Piancatelli, G.; Scettri, A.; D'Auria, M. *Synthesis* ***1982***, 245. For an improved method of preparing this reagent, see Agarwal, S.; Tiwari, H.P.; Sharma, J.P. *Tetrahedron* ***1990***, *46*, 4417. For a PCC oxidation with no solvent, see Salehi, P.; Firouzabadi, H.; Farrokhi, A.; Gholizadeh, M. *Synthesis* ***2001***, 2273.

[81]Coates, W.M.; Corrigan, J.R. *Chem. Ind. (London)* ***1969***, 1594; Corey, E.J.; Schmidt, G. *Tetrahedron Lett.* ***1979***, 399; Czernecki, S.; Georgoulis, C.; Stevens, C.L.; Vijayakumaran, K. *Tetrahedron Lett.* ***1985***, *26*, 1699.

[82]See Ren, S.-K.; Wang, F.; Dou, H.-N.; Fan, C.-A.; He, L.; Song, Z.-L.; Xia, W.-J.; Li, D-R.; Jia, Y.-X.; Li, X.; Tu, Y.-Q. *Synthesis* ***2001***, 2384.

[83]Hajipour, A.R.; Mallakpour, S.E.; Khoee, S. *Synlett* ***2000***, 740.

[84]Khodaei, M.M.; Salehi, P.; Goodarzi, M. *Synth. Commun.* ***2001***, *31*, 1253.

fluorochromate.[85] benzyltriphenylphosphonium chlorochromate has been used in a similar manner.[86] Ammonium dichromate with HIO_3 on wet silica gel[87] or ammonium chlorochromate on Montmorillonite K10[88] have also been used. The MnO_2[89] reagent is also a fairly specific reagent for oxidation of allylic and benzylic OH groups in preference to aliphatic substrates. For acid-sensitive compounds, CrO_3 in HMPA[90] or trimethylsilyl chromates[91] can be used. Benzylic alcohols are oxidized to aldehydes with $BaCr_2O_7$ in acetonitrile.[92] Both CrO_3[93] and MnO_2[94] have been used to oxidized primary and benzylic alcohols, respectively, under solvent-free conditions. A catalytic mixture of *N*-hydroxyphthalimide, $Co(OAc)_2$ and mcpba oxidizes secondary alcohols to ketones.[95] Chromium trioxide with aqueous *tert*-butylhydroperoxide oxidizes benzylic alcohols with microwave irradiation.[96] Oxidizing agents have been supported on a polymer,[97] including chromic acid[98] and permanganate,[99] as well as poly[vinyl(pyridinium fluorochromate)].[100] Microwave induced oxidation of benzylic alcohols was reported using zeolite-supported ferric nitrate.[101] Microwave irradiation of CrO_3 with various co-reagents oxidizes alcohols.[102] Phase-transfer catalysis has also been used with permanganate,[103] chromic acid,[104] and

[85]Rajkumar, G.A.; Arabindoo, B.; Murugesan, V. *Synth. Commun.* ***1999***, *29*, 2105.

[86]Hajipour, A.R.; Mallakpour, S.E.; Backnejad, H. *Synth. Commun.* ***2000***, *30*, 3855.

[87]Shirini, F.; Zolfigol, M.A.; Azadbar, M.R. *Russ. J. Org. Chem.* ***2001***, *37*, 1600.

[88]Heravi, M.M.; Kiakojoori, R.; Tabar-Hydar, K. *Monat. Chem.* ***1999***, *130*, 581.

[89]For the use of MnO_2 on silica gel with microwave irradiation, see Varma, R.S.; Saini, R.K.; Dahiya, R. *Tetrahedron Lett.* ***1997***, *38*, 7823. For an example on bentonite clay with microwave irradiation, see Martinez, L.A.; García, O.; Delgado, F.; Alvarez, C.; Patiño, R. *Tetrahedron Lett.* ***1993***, *34*, 5293.

[90]Cardillo, G.; Orena, M.; Sandri, S. *Synthesis* ***1976***, 394.

[91]Moiseenkov, A.M.; Cheskis, B.A.; Veselovskii, A.B.; Veselovskii, V.V.; Romanovich, A.Ya.; Chizhov, B.A. *J. Org. Chem. USSR* ***1987***, *23*, 1646.

[92]Mottaghinejad, E.; Shaafi, E.; Ghasemzadeh, Z. *Tetrahedron Lett.* ***2004***, *45*, 8823.

[93]Lou, J.-D.; Xu, Z.-N. *Tetrahedron Lett.* ***2002***, *43*, 6095.

[94]Lou, J.D.; Xu, Z.-N. *Tetrahedron Lett.* ***2002***, *43*, 6149.

[95]Iwahama, T.; Yoshino, Y.; Keitoku, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* ***2000***, *65*, 6502.

[96]Singh, J.; Sharma, M.; Chhibber, M.; Kaur, J.; Kad, G.L. *Synth. Commun.* ***2000***, *30*, 3941.

[97]For a review of oxidations and other reactions with supported reagents, see McKillop, A.; Young, D.W. *Synthesis* ***1979***, 401.

[98]Cainelli, G.; Cardillo, G.; Orena, M.; Sandri, S. *J. Am. Chem. Soc.* ***1976***, *98*, 6737; Santaniello, E.; Ponti, F.; Manzocchi, A. *Synthesis* ***1978***, 534. See also, San Filippo, Jr., J.; Chern, C. *J. Org. Chem.* ***1977***, *42*, 2182.

[99]Regen, S.L.; Koteel, C. *J. Am. Chem. Soc.* ***1977***, *99*, 3837; Noureldin, N.A.; Lee, D.G. *Tetrahedron Lett.* ***1981***, *22*, 4889. See also, Menger, F.M.; Lee, C. *J. Org. Chem.* ***1979***, *44*, 3446.

[100]Srinivasan, R.; Balasubramanian, K. *Synth. Commun.* ***2000***, *30*, 4397.

[101]Heravi, M.M.; Ajami, D.; Aghapoor, K.; Ghassemzadeh, M. *Chem. Commun.* ***1999***, 833.

[102]With TMS-O-TMS: Heravi, M.M.; Ajami, D.; Tabar-Hydar, K. *Synth. Commun.* ***1999***, *29*, 163. With HY zeolite: Mirza-Ayhayan, M.; Heravi, M.M. *Synth. Commun.* ***1999***, *29*, 785.

[103]For a review of phase-transfer assisted permanganate oxidations, see Lee, D.G., in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. D Academic Press, NY, ***1982***, pp. 147–206.

[104]See, for example, Hutchins, R.O.; Natale, N.R.; Cook, W.J. *Tetrahedron Lett.* ***1977***, 4167; Landini, D.; Montanari, F.; Rolla, F. *Synthesis* ***1979***, 134; Pletcher, D.; Tait, S.J.D. *J. Chem. Soc. Perkin Trans. 2*, ***1979***, 788.

ruthenium tetroxide.[105] Phase-transfer catalysis is particularly useful because the oxidizing agents are insoluble in most organic solvents, while the substrates are generally insoluble in water (see p. 508). Ultrasound has been used for $KMnO_4$ oxidations.[106] A catalytic amount of $Cr(acac)_3$ in conjunction with H_5IO_5 oxidizes benzylic alcohols to aldehydes.[107]

Most of these oxidizing agents have also been used to convert primary alcohols to aldehydes, but precautions must be taken that the aldehyde is not further oxidized to the carboxylic acid (**19-22**).[108] When powerful oxidants, such as chromic acid, are used, one way to halt oxidation is by distillation of the aldehyde as it is formed. The following are among the oxidizing agents that have been used to convert at least some primary alcohols to aldehydes:[109] Collins' reagent, pyridinium chlorochromate and pyridinium dichromate, pyridinium dichromate, $Na_2Cr_2O_7$ in water,[110] $K_2Cr_2O_7$ in DMF at 100°C,[111] CrO_3 on silica gel,[112] wet CrO_3 on alumina with microwave irradiation,[113] $MeReO_3$,[114] HNO_3 with a $Yb(OTf)_3$ catalyst,[115] $FeBr_3$-H_2O_2,[116] a catalytic amount of $AuSiO_2$,[117] cerium (IV) immobilized on silica with $NaBrO_3$,[118] a bismuth catalyst,[119] O_2 with transition metal

[105]Morris, Jr., P.E.; Kiely, D.E. *J. Org. Chem.* ***1987***, *52*, 1149.

[106]Yamawaki, J.; Sumi, S.; Ando, T.; Hanfusa, T. *Chem. Lett.* ***1983***, 379.

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catalysts,[120] RuO_2 with a zeolite catalyst,[121] and CuCl–phenanthroline.[122]

Tetrapropylammonium perruthenate (Pr_4N^+ RuO_4^-; also called TPAP; the *Ley reagent*)[123] has become an important oxidizing agent. This reagent has been bound to a polymer.[124] In the presence of molecular oxygen, it is catalytic in TPAP.[125] A polymer-bound morpholine *N*-oxide has been used in conjunction with a catalytic amount of TPAP.[126] Propargylic alcohols are oxidized to propargylic aldehydes with $TiCl_4/NEt_3$.[127] Methods have been developed for recovery of the catalyst and reuse of TPAP.[128]

Most of these reagents also oxidize secondary alcohols to ketones. Reagents that can be used specifically to oxidize a secondary OH group in the presence of a primary OH group[129] are H_2O_2–ammonium molybdate,[130] $NaBrO_3$–CAN,[131] and NaOCl in HOAc,[132] while $RuCl_2(PPh_3)_3$–benzene,[133]

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osmium tetroxide,[134] and $Br_2Ni(OBz)_2$[135] oxidize primary OH groups in the presence of a secondary OH group.[136] Benzylic and allylic alcohols have been selectively oxidized to the aldehydes in the presence of saturated alcohols by the use of potassium manganate $KMnO_4$ under phase-transfer conditions.[137] On the other hand, Fremy's salt (see **19-4**) selectively oxidizes benzylic alcohols and not allylic or saturated ones.[138] Certain zirconocene complexes can selectively oxidize only one OH group of a diol, even if both are primary.[139] α-Hydroxy ketones are oxidized to 1,2-diketones with $Bi(NO_3)_3$ and a $Cu(OAc)_2$ catalyst,[140] ferric chloride (solid state),[141] or O_2 and a vanadium catalyst.[142] Tetrabutylammonium periodate oxidizes primary alcohols to aldehydes,[143] as does benzyltriphenylphosphonium periodate.[144] α-Hydroxyl phosphonate esters are oxidized to the α-keto phosphonate ester with zinc dichromate, without solvent[145] or with CrO_3 on alumina with microwave irradiation.[146]

O-Trimethylsilyl ethers of benzylic alcohols are oxidized to the corresponding aldehyde with CrO_3 on wet alumina.[147] Treatment with $MnO_2/AlCl_3$ leads to similar oxidation,[148] as does $NaBrO_3$ in aq. MeCN[149] or K_2FeO_4 on clay.[150] Oxidation of trimethylsilyl ethers with O_2, a catalytic amount of *N*-hydroxyphthalimide and a cobalt catalyst give an aldehyde.[151] Microwave irradiation with $BiCl_3$ oxidizes benzylic TMS ethers to the aldehyde.[152] Microwave irradiation on zeolite supported ferric nitrate has been used.[153] *O*-Tetrahydropyranyl ethers (*O*-THP) have been oxidized to the aldehyde with ferric nitrate on zeolites.[154]

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2. *The Oppenauer Oxidation*. When a ketone in the presence of an aluminum alkoxide is used as the oxidizing agent (it is reduced to a secondary alcohol), the reaction is known as the *Oppenauer oxidation*.[155] This is the reverse of the Meerwein–Ponndorf–Verley reaction (**19-36**) and the mechanism is also the reverse. The ketones most commonly used are acetone, butanone, and cyclohexanone. The most common base is aluminum *tert*-butoxide. The chief advantage of the method is its high selectivity. Although the method is most often used for the preparation of ketones, it has also been used for aldehydes. An iridium catalyst[156] has been developed for the Oppenauer oxidation, and also a water-soluble iridium catalyst[157] An uncatalyzed reaction under supercritical conditions was reported.[158]
3. *With DMSO-Based Reagents*. An alcohol is treated with DMSO, DCC,[159] and anhydrous phosphoric acid[160] in what is called *Moffatt oxidation*. In this way, a primary alcohol can be converted to the aldehyde with no carboxylic acid being produced. The strong acid conditions are sometimes a problem, and complete removal of the dicyclohexylurea by-product can be difficult. The use of oxalyl chloride and DMSO at low temperature, the Swern oxidation,[161] is generally more practical and widely used. Maintaining the low reaction temperature is essential in this reaction however, since the reagent generated *in situ* decomposes at temperatures significantly below ambient.

   Similar oxidation of alcohols has been carried out with DMSO and other reagents[162] in place of DCC: acetic anhydride,[163] SO_3–pyridine–triethylamine,[164] trifluoroacetic anhydride,[165] tosyl chloride,[166] $Ph_3P^+Br^-$,[167]

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4. *TEMPO and Related Reagents*. The nitroxyl radical TEMPO has been used in conjunction with coreagents, including mcpba[179] Br_2—$NaNO_2$,[180] O_2 with transition-metal catalysts,[181] CuBr•SMe_2—$C_8F_{17}Br$,[182] $CuBr_2$(bpy)-air (bpy=2, 2′-bipyridyl),[183] Oxone®,[184] CuBr•SMe_2 in perfluorous solvents,[185] 2,4,6-trichlorotriazine,[186] enzymes,[187] H_5IO_6,[188] and NCS.[189] Silica-supported TEMPO,[190] polymer-bound TEMPO,[191] and PEG–TEMPO[192] (where PEG is polyethylene glycol) have been used. The TEMPO compound has also been used with a polymer-bound hypervalent iodine reagent[193] (see below). A catalytic reaction using 5% TEMPO and 5% CuCl with O_2 in an

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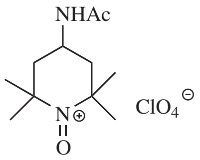
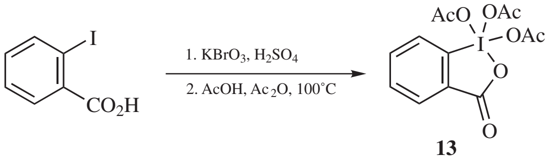
ionic liquid oxidizes benzylic alcohols to the corresponding aldehyde.[194] Other nitroxyl radical oxidizing agents are known.[195] A related oxidizing agent is oxoammonium salt **12** (*Bobbitt's reagent)*, a stable and nonhygroscopic salt that oxidizes primary and secondary alcohols in dichloromethane.[196]

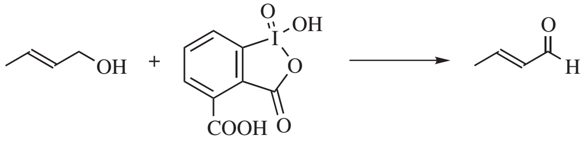


12

5. *With Hypervalent Iodine Reagents.*[197] Treatment of 2-iodobenzoic acid with $KBrO_3$ in sulfuric acid and heating the resulting product to 100°C with acetic anhydride and acetic acid gives hypervalent iodine reagent **13**, the so-called *Dess–Martin Periodinane.*[198] This reagent reacts with alcohols at ambient temperature to give the corresponding aldehyde or ketone.[199] The reaction is accelerated by water[200] and a water-soluble periodinane (*o*-iodoxybenzoic acid, **14**) has been prepared that oxidized allylic alcohols to conjugated aldehydes.[201]



13



14

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[196]Bobbitt, J.M. *J. Org. Chem.* ***1998***, *63*, 9367; Kernag, C.A.; Bobbitt, J.M.; McGrath, D.V. *Tetrahedron Lett.* ***1999***, *40*, 1635; Kernag, C.A.. For a review, see Merbouh, N.; Bobbitt, J.M.; Brückner, C. *Org. Prep. Proceed. Int.* ***2004***, *36*, 1.

[197]For a review of hypervalent iodine compounds, see Wirth, T.; Hirt, U.S. *Synthesis* ***1999***, 1271.

[198]Dess, D.B.; Martin, J.C. *J. Org. Chem.* ***1983***, *48*, 4155; Dess, D.B.; Martin, J.C. *J. Am. Chem. Soc.* ***1991***, *113*, 7277. For a synthesis of the requisite precursor, see Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* ***1999***, *64*, 4537.

[199]For example, see Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* ***1994***, *35*, 8019.

[200]Meyer, S.D.; Schreiber, S.L. *J. Org. Chem.* ***1994***, *59*, 7549. In aqueous β-cyclodextrin-acetone solution, see Surendra, K.; Krishnaveni, N.S.; Reddy, M.A.; Nageswar, Y.V.D.; Rao, K.R. *J. Org. Chem.* ***2003***, *68*, 2058.

[201]Thottumkara, A.P.; Vinod, T.K. *Tetrahedron Lett* ***2001***, *43*, 569.

The reagent has an indefinite shelf-life in a sealed container, but hydrolysis occurs upon long-term exposure to atmospheric moisture. A note of CAUTION! The Dess–Martin reagent can be shock sensitive under some conditions and explode >200°C.[202] Other hypervalent iodine oxidizing reagents are known,[203] including $PhI(OAc)_2$/TEMPO,[204] $PhI(OAc)_2$–chromium salen,[205] stabilized iodoxybenzoic acid,[206] and $PhI(OAc)_2$ supported on alumina with microwave irradiation.[207] Microwave irradiation of benzylic alcohols with PhI(OH)OTs gave the corresponding aldehyde.[208] Hypervalent iodine compounds have been used in ionic liquids.[209] Heating benzylic alcohols with *o*-iodoxybenzoic acid under solvent-free conditions gave the aldehyde.[210] Cyclopropylcarbinyl alcohols are oxidized to the corresponding cyclopropyl ketone or aldehyde with PhIO and a chromium–salen catalyst.[211] The Dess–Martin reagent oxidized aryl aldoximes to aryl aldehydes.[212]

6. *By Catalytic Dehydrogenation*. For the conversion of primary alcohols to aldehydes, dehydrogenation catalysts have the advantage over strong oxidizing agents that further oxidation to the carboxylic acid is prevented. Copper chromite is the agent most often used, but other catalysts (e.g., silver and copper) have also been employed. Many ketones were prepared in this manner. Catalytic dehydrogenation is more often used industrially than as a laboratory method. However, procedures using copper oxide,[213] copper(II) complexes,[214] rhodium complexes,[215] ruthenium complexes,[216] Raney nickel,[217] and palladium complexes[218] (under phase-transfer conditions)[219]

[202]Plumb, J.B.; Harper, D.J. *Chem. Eng. News*, ***1990***, July 16, p. 3. For an improved procedure, see Ireland, R.E.; Liu, L. *J. Org. Chem.* ***1993***, *58*, 2899.

[203]Moriarty, R.M.; Prakash, O. *Accts. Chem. Res.* ***1986***, *19*, 244; Moriarty, R.M.; John, L.S.; Du, P.C. *J. Chem. Soc. Chem. Commun.* ***1981***, 641; Moriarty, R.M.; Gupta, S.; Hu, H.; Berenschot, D.R.; White, K.B. *J. Am. Chem. Soc.* ***1981***, *103*, 686; Moriarty, R.M.; Hu, H.; Gupta, S.C. *Tetrahedron Lett.* ***1981***, *22*, 1283.

[204]DeMico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* ***1997***, *62*, 6974.

[205]Adam, W.; Hajra, S.; Herderich, M.; Saha-Möller, C.R. *Org. Lett.* ***2000***, *2*, 2773.

[206]Khan, T.A.; Tripoli, R.; Crawford, J.T.; Martin, C.G.; Murphy, J.A. *Org. Lett.* ***2003***, *5*, 2971.

[207]Varma, R.S.; Saini, R.K.; Dahiya, R. *J. Chem. Res. (S)* ***1998***, 120.

[208]Lee, J.C.; Lee, J.Y.; Lee, S.J. *Tetrahedron Lett.* ***2004***, *45*, 4939.

[209]In bmim Cl, 1-butyl-3-methylimidazolium chloride: Liu, Z.; Chen, Z.-C.; Zheng, Q.-C. *Org. Lett.* ***2003***, *5*, 3321; Karthikeyan, G.; Perumal, P.T. *Synlett* ***2003***, 2249.

[210]Moorthy, J.N.; Singhal, N.; Venkatakrishnan, P. *Tetrahedron Let.* ***2004***, *45*, 5419.

[211]Adam, W.; Gelalcha, F.G.; Saha-Möller, C.R.; Stegmann, V.R. *J. Org. Chem.* ***2000***, *65*, 1915.

[212]Bose, D.S.; Narsaiah, A.V. *Synth. Commun.* ***1999***, *29*, 937.

[213]Sheikh, M.Y.; Eadon, G. *Tetrahedron Lett.* ***1972***, 257.

[214]Muldoon, J.; Brown, S.N. *Org. Lett.* ***2002***, *4*, 1043.

[215]Takahashi, M.; Oshima, K.; Matsubara, S. *Tetrahedron Lett.* ***2003***, *44*, 9201.

[216]Meijer, R.H.; Ligthart, G.B.W.L.; Meuldijk, J.; Vekemans, J.A.J.M.; Hulshof, L.A.; Mills, A.M.; Kooijman, H.; Spek, A.L. *Tetrahedron* ***2004***, *60*, 1065.

[217]Krafft, M.E.; Zorc, B. *J. Org. Chem.* ***1986***, *51*, 5482.

[218]For a discussion of the enantioselective palladium(II) oxidation, see Mandal, S.K.; Jensen, D.R.; Pugsley, J.S.; Sigman, M.S. *J. Org. Chem.* ***2003***, *68*, 4600. See also Mandal, S.K.; Sigman, M.S. *J. Org. Chem.* ***2003***, *68*, 7535; Guram, A.S.; Bei, X.; Turner, H.W. *Org. Lett.* ***2003***, *5*, 2485; Ganchegui, B.; Bouquillon, S.; Hénin, F.; Muzart, J. *Tetrahedron Lett.* ***2002***, *43*, 6641. For a review, see Muzart, J. *Tetrahedron* ***2003***, *59*, 5789.

[219]Choudary, B.M.; Reddy, N.P.; Kantam, M.L.; Jamil, Z. *Tetrahedron Lett.* ***1985***, *26*, 6257.

have been reported. Allylic alcohols[220] are oxidized to the corresponding saturated aldehyde or ketone by heating with a rhodium catalyst, and benzylic alcohols are converted to the aldehyde with a rhodium catalyst.[221] Photolysis with an iron catalyst gives similar results.[222] Propargylic alcohols are oxidized by heating with a vanadium catalyst.[223] Secondary alcohols are oxidized with $Bi(NO_3)_3$ on Montmorillonite.[224]

7. *Miscellaneous Reagents*.[225] Nitric acid in dichloromethane oxidizes benzylic alcohols to the corresponding ketone. [226] Bromine is an effective oxidant, and iodine under photochemical conditions has been used.[227] Heating a 1,2-diol with NBS in CCl_4 gave the 1,2-diketone.[228] *N*-Bromosuccinimide with β-cyclodextrin oxidizes tetrahydropyranyl ethers in water.[229] Iodine has been used in conjunction with DMSO and hydrazine.[230] Sodium bromate (NaOBr) in conjunction with HCl oxidizes α-hydroxy esters to α-keto esters.[231] Enzymatic oxidations have been reported.[232] Dimethyl dioxirane[233] oxidizes benzylic alcohols to the corresponding aldehyde,[234] and dioxirane reagents are sufficiently mild that an α,β-epoxy alcohol was oxidized to the corresponding ketone, without disturbing the epoxide, using methyl trifluoromethyl dioxirane.[235] Hydrogen peroxide with urea oxidizes aryl aldehydes in formic acid.[236] Potassium monoperoxysulfate in the presence of a

[220]Tanaka, K.; Fu, G.C. *J. Org. Chem.* ***2001***, *66*, 8177.

[221]Miyata, A.; Murakami, M.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* ***2001***, *42*, 7067; Kölle, U.; Fränzl, H. *Monat. Chem.* ***2000***, *131*, 1321; Csjernyik, G.; Ell, A.H.; Fadini, L.; Pugin, B.; Bäckvall, J.-E. *J. Org. Chem.* ***2002***, *67*, 1657.

[222]Cherkaoui, H.; Soufiaoui, M.; Grée, R. *Tetrahedron* ***2001***, *57*, 2379.

[223]Maeda, Y.; Kakiuchi, N.; Matsumura, S.; Nishimura, T.; Uemura, S. *Tetrahedron Lett.* ***2001***, *42*, 8877.

[224]Samajdar, S.; Becker, F.F.; Banik, B.K. *Synth. Commun.* ***2001***, *31*, 2691.

[225]For a review of green, catalytic oxidations of alcohols, see Sheldon, R.A.; Arends, I.W.C.E.; ten Brink, G.-J.; Dijksman, A. *Acc. Chem. Res.* ***2002***, *35*, 774.

[226]Strazzolini, P.; Runcio, A. *Eur. J. Org. Chem.* ***2003***, 526.

[227]Itoh, A.; Kodama, T.; Masaki, Y. *Chem. Lett.* ***2001***, 686.

[228]Khurana, J.M.; Kandpal, B.M. *Tetrahedron Lett.* ***2003***, *44*, 4909.

[229]Narender, M.; Reddy, M.S.; Rao, K.R. *Synthesis* ***2004***, 1741. See Reddy, M.S.; Narender, M.; Nageswar, Y.V.D.; Rao, K.R. *Synthesis* ***2005***, 714.

[230]Gogoi, P.; Sarmah, G.K.; Konwar, D. *J. Org. Chem.* ***2004***, *69*, 5153.

[231]Chang, H.S.; Woo, J.C.; Lee, K.M.; Ko, Y.K.; Moon, S.-S.; Kim, D.-W. *Synth. Commun.* ***2002***, *32*, 31.

[232]*Bacilus stearothermophilus*: Fantin, G.; Fogagnolo, M.; Giovannini, P.P.; Medici, A.; Pedrini, P.; Poli, S. *Tetrahedron Lett.* ***1995***, *36*, 441. *Gluconobaccter oxydans* DSM 2343: Villa, R.; Romano, A.; Gandolfi, R.; Gargo, J.V.S.; Molinari, F. *Tetrahedron Lett.* ***2002***, *43*, 6059. Chloroperoxidase: Hu, S.; Dordick, J.S. *J. Org. Chem.* ***2002***, *67*, 314.

[233]For a discussion of whether dioxirane oxidation is electrophilic or nucleophilic, see Deubel, D.V. *J. Org. Chem.* ***2001***, *66*, 3790.

[234]Baumstark, A.L.; Kovac, F.; Vasquez, P.C. *Can. J. Chem.* ***1999***, *77*, 308. For a discussion of the mechanism, see Angelis, Y.S.; Hatzakis, N.S.; Smonou, I.; Orfanoupoulos, M. *Tetrahedron Lett.* ***2001***, *42*, 3753.

[235]D'Accolti, L.; Fusco, C.; Annese, C.; Rella, M.R.; Turteltaub, J.S.; Williard, P.G.; Curci, R. *J. Org. Chem.* ***2004***, *69*, 8510.

[236]Balicki, R. *Synth. Commun.* ***2001***, *31*, 2195.

chiral ketone oxidizes 1,2-diols to α-hydroxy ketones enantioselectively.[237] Potassium monoperoxysulfate also oxidizes secondary alcohols in the presence of O_2.[238] air in the presence of a zeolite oxidizes benzylic alcohols. [239] The reagent $Br^+(collidine)_2PF_6$ oxidizes benzylic alcohols to the corresponding aldehyde.[240] Sodium hypochlorite in acetic acid is useful for oxidizing larger amounts of secondary alcohols.[241] Calcium hypochlorite on moist alumina with microwave irradiation has been used to oxidize benzylic alcohols.[242] Chlorosulfimines, Ar(Cl)S=N—*t*-Bu, oxidize primary alcohols to aldehydes.[243] This latter reagent is generated from ArS—NH*t*-Bu and NCS.[244] Benzylic alcohols are converted to aldehydes with DBU (p. $$$) and Ar_3BCl_2.[245] Microwave irradiation of benzylic alcohols with $Co(CO_3)_2$ on silica gel generates the aryl aldehyde.[246]

Primary and secondary alcohols can also be oxidized, indirectly, through their esters (see **19-21**). In some cases, isolation of the ester is not required and the alcohol can then be oxidized to the aldehyde or ketone in one step.

The mechanism of oxidation with acid dichromate has been intensely studied.[247] The currently accepted mechanism is essentially that proposed by Westheimer.[248] The first two steps constitute an example of category 4 (p. 1706).

[237]Adam, W.; Saha-Möller, C.R.; Zhao, C.-G. *J. Org. Chem.* ***1999***, *64*, 7492.

[238]Döbler, C.; Mehltretter, G.M.; Sundermeier, U.; Eckert, M.; Militzer, H.-C.; Beller, M. *Tetrahedron Lett.* ***2001***, *42*, 8447.

[239]Son, Y.-C.; Makwana, V.D.; Howell, A.R.; Suib, S.L. *Angew. Chem. Int. Ed.* ***2001***, *40*, 4280.

[240]Rousseau, G.; Robin, S. *Tetrahedron Lett* ***2000***, *41*, 8881.

[241]Stevens, R.V.; Chapman, K.T.; Weller, H.N. *J. Org. Chem.* ***1980***, *45*, 2030. See also, Schneider, M.; Weber, J.; Faller, P. *J. Org. Chem.* ***1982***, *47*, 364; Mohrig, J.R.; Nienhuis, D.M.; Linck, C.F.; van Zoeren, C.; Fox, B.G.; Mahaffy, P.G. *J. Chem. Educ.* ***1985***, *62*, 519. For a reaction with aqueous NaOCl and a guanidinium salt, see Xie, H.; Zhang, S.; Duan, H. *Tetrahedron Lett.* ***2004***, *45*, 2013.

[242]Mojtahedi, M.M.; Saidi, M.R.; Bolourtchian, M.; Shirzi, J.S. *Monat. Chem.* ***2001***, *132*, 655.

[243]Mukaiyama, T.; Matsuo, J.-i.; Yanagisawa, M. *Chem Lett.* ***2000***, 1072; Matsuo, J.-i.; Kitgawa, H.; Iida, D.; Mukaiyama, T. *Chem. Lett.* ***2001***, 150.

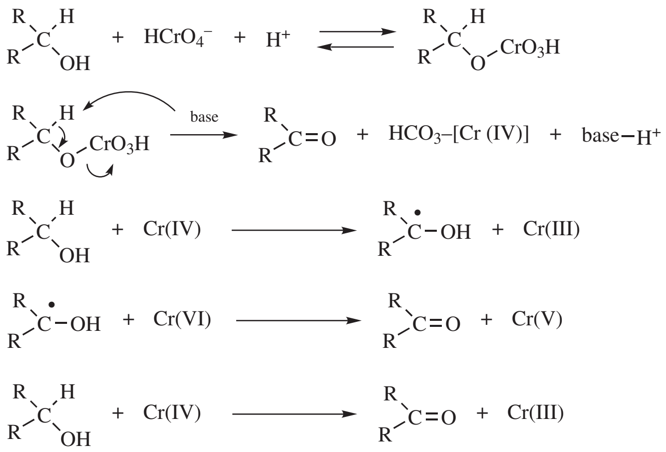
[244]Mukaiyama, T.; Matsuo, J.-i.; Iida, D.; Kitagawa, H. *Chem. Lett.* ***2001***, 846; Matsuo, J.-i.; Iida, D.; Yamanaka, H.; Mukaiyama, T. *Tetrahedron* ***2003***, *59*, 6739.

[245]Mantano, Y.; Nomura, H. *Angew. Chem. Int. Ed.* ***2002***, *41*, 3028.

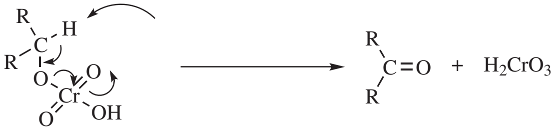
[246]Kiasat, A.R.; Kazemi, F.; Rafati, M. *Synth. Commun.* ***2003***, *33*, 601.

[247]See Müller, P. *Chimia* ***1977***, *31*, 209; Wiberg, K.B., in Wiberg, K.B. *Oxidation in Organic Chemistry*, pt. A, Academic Press, NY, ***1965***, pp. 142–170; Venkatasubramanian, N. *J. Sci. Ind. Res.* ***1963***, *22*, 397; Waters, W.A. *Mechanisms of Oxidation of Organic Compounds*, Wiley, NY, ***1964***, pp. 49–71; Stewart, R. *Oxidation Mechanisms*, W.A. Benjamin, NY, ***1964***, pp. 37–48; Durand, R.; Geneste, P.; Lamaty, G.; Moreau, C.; Pomarès, O.; Roque, J.P. *Recl. Trav. Chim. Pays-Bas* ***1978***, *97*, 42; Sengupta, K.K.; Samanta, T.; Basu, S.N. *Tetrahedron* ***1985***, *41*, 205.

[248]Westheimer, F.H. *Chem. Rev.* ***1949***, *45*, 419, see p. 434; Holloway, F.; Cohen, M.; Westheimer, F.H. *J. Am. Chem. Soc.* ***1951***, *73*, 65.



The base in the second step may be water, although it is also possible[249] that in some cases no external base is involved and that the proton is transferred directly to one of the CrO_3H oxygens in which case the Cr(IV) species



produced would be H_2CrO_3. Part of the evidence for this mechanism was the isotope effect of ~ 6 found on use of MeCDOHMe, showing that the a hydrogen is removed in the rate-determining step.[250] Note that, as in **19-23** the substrate is oxidized by three different oxidation states of chromium.[251]

With other oxidizing agents, mechanisms are less clear.[252] It seems certain that some oxidizing agents operate by a hydride-shift mechanism,[253] for example,

[249]Stewart, R.; Lee, D.G. *Can. J. Chem.* ***1964***, *42*, 439; Awasthy, A.; Roek, J.; Moriarty, R.M. *J. Am. Chem. Soc.* ***1967***, *89*, 5400; Kwart, H.; Nickle, J.H. *J. Am. Chem. Soc.* ***1979***, *98*, 2881 and cited rererences; Sengupta, K.K.; Samanta, T.; Basu, S.N. *Tetrahedron* ***1986***, *42*, 681. See also Müller, P.; Perlberger, J. *Helv. Chim. Acta* ***1974***, *57*, 1943; Agarwal, S.; Tiwari, H.P.; Sharma, J.P. *Tetrahedron* ***1990***, *46*, 1963.

[250]Westheimer, F.H.; Nicolaides, N. *J. Am. Chem. Soc.* ***1949***, *71*, 25. For other evidence, see Brownell, R.; Leo, A.; Chang, Y.W.; Westheimer, F.H. *J. Am. Chem. Soc.* ***1960***, *82*, 406; Roč ek, J.; Westheimer, F.H.; Eschenmoser, A.; Moldoványi, L.; Schreiber, J. *Helv. Chim. Acta* ***1962***, *45*, 2554; Lee, D.G.; Stewart, R. *J. Org. Chem.* ***1967***, *32*, 2868; Wiberg, K.B.; Schäfer, H. *J. Am. Chem. Soc.* ***1967***, *89*, 455; ***1969***, *91*, 927, 933; Müller, P. *Helv. Chim. Acta* ***1970***, *53*, 1869; ***1971***, *54*, 2000, Lee, D.G.; Raptis, M. *Tetrahedron* ***1973***, *29*, 1481.

[251]Rahman, M.; Roč ek, J. *J. Am. Chem. Soc.* ***1971***, *93*, 5455, 5462; Doyle, M.P.; Swedo, R.J.; Roč ek, J. *J. Am. Chem. Soc.* ***1973***, *95*, 8352; Wiberg, K.B.; Mukherjee, S.K. *J. Am. Chem. Soc.* ***1974***, *96*, 1884, 6647.

[252]For a review, see Cockerill, A.F.; Harrison, R.G., in Patai, S. *The Chemistry of Functional Groups, Supplement A* pt. 1, Wiley, NY, ***1977***, pp. 264–277.

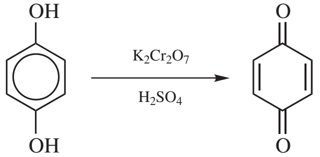
[253]See Barter, R.M.; Littler, J.S. *J. Chem. Soc. B* ***1967***, 205. For evidence that oxidation by HNO_2 involves a hydride shift, see Moodie, R.B.; Richards, S.N. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 1833; Ross, D.S.; Gu, C.; Hum, G.P.; Malhotra, R. *Int. J. Chem. Kinet.* ***1986***, *18*, 1277.

dehydrogenation with triphenylmethyl cation[254] and the Oppenauer oxidation, and some by a free-radical mechanism, (e.g., oxidation with $S_2O_8^{2-}$[255] and with VO_2^+.[256]). A summary of many proposed mechanisms is given by Littler.[257]

OS **I**, 87, 211, 241, 340; **II**, 139, 541; **III**, 37, 207; **IV**, 189, 192, 195, 467, 813, 838; **V**, 242, 310, 324, 692, 852, 866; **VI**, 218, 220, 373, 644, 1033; **VII**, 102, 112, 114, 177, 258, 297; **VIII**, 43, 367, 386; **IX**, 132, 432. Also see, OS **IV**, 283; **VIII**, 363, 501.

19-4 Oxidation of Phenols and Aromatic Amines to Quinones

1/*O*,6/*O*-Dihydro-elimination



Ortho and para diols are easily oxidized to ortho- and para-quinones, respectively.[258] Either or both OH groups can be replaced by NH_2 groups to give the same products, although for the preparation of ortho-quinones only OH groups are normally satisfactory. The reaction has been successfully carried out with other groups para to OH or NH_2; halogen, OR, Me, *t*-Bu, and even H, although with the last yields are poor. Many oxidizing agents have been used: acid dichromate,[259] silver oxide, silver carbonate, lead tetraacetate, HIO_4, NBS—H_2O—H_2SO_4,[260] MnO_2 on Bentonite with microwave irradiation,[261] dimethyl dioxirane,[262] and atmospheric oxygen,[263] to name a few. Substituted phenols, such as 4-($CH_2CH_2CH_2COOH$) phenol, are oxidized with a polymer-bound hypervalent iodine reagent to give a quinone with a spirocyclic lactone unit at C-4.[264] Oxidation

[254]Bonthrone, W.; Reid, D.H. *J. Chem. Soc.* ***1959***, 2773.

[255]Ball, D.L.; Crutchfield, M.M.; Edwards, J.O. *J. Org. Chem.* ***1960***, *25*, 1599; Bida, G.; Curci, R.; Edwards, J.O. *Int. J. Chem. Kinet.* ***1973***, *5*, 859; Snook, M.E.; Hamilton, G.A. *J. Am. Chem. Soc.* ***1974***, *96*, 860; Walling, C.; Camaioni, D.M. *J. Org. Chem.* ***1978***, *43*, 3266; Clerici, A.; Minisci, F.; Ogawa, K.; Surzur, J. *Tetrahedron Lett.* ***1978***, 1149; Beylerian, N.M.; Khachatrian, A.G. *J. Chem. Soc. Perkin Trans. 2* ***1984***, 1937.

[256]Littler, J.S.; Waters, W.A. *J. Chem. Soc.* ***1959***, 4046.

[257]Littler, J.S. *J. Chem. Soc.* ***1962***, 2190.

[258]For reviews, see Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Vol. 2, Academic Press, NY, ***1988***, pp. 305–323, 438–447; Naruta, Y.; Maruyama, K., in Patai, S.; Rappoport, Z. *The Chemistry of the Quinoid Compounds*, Vol. 2, pt. 1, Wiley, NY, ***1988***, pp. 247–276; Thomson, R.H., in Patai, S. *The Chemistry of the Quinoiid Compounds*, Vol. 1, pt. 1, Wiley, NY, ***1974***, pp. 112–132.

[259]For a review of this oxidation with chromium reagents, see Cainelli, G.; Cardillo, G. *Chromium Oxiations in Organic Chemistry*, Open Court Pub. Co., La Salle, IL, ***1981***, pp. 92–117.

[260]Kim, D.W.; Choi, H.Y.; Lee, K.Y.; Chi, D.Y. *Org. Lett.* ***2001***, *3*, 445.

[261]Gómez-Lara, J.; Gutiérrez-Perez, R.; Penieres-Carrillo, G.; López-Cortés, J.G.; Escudero-Salas, A.; Alvarez-Toledano, C. *Synth. Commun.* ***2000***, *30*, 2713.

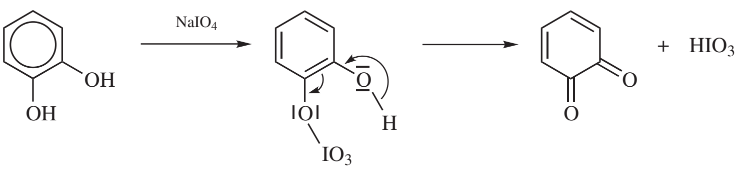
[262]Adam, W.; Schönberger, A. *Tetrahedron Lett.* ***1992***, *33*, 53.

[263]For an example on activated silica gel, see Hashemi, M.M.; Beni, Y.A. *J. Chem. Res. (S)* ***1998***, 138.

[264]Ley, S.V.; Thomas, A.W.; Finch, H. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 669.

has been done photochemically with O_2 and tetraphenylporphine.[265] A particularly effective reagent for rings with only one OH or NH_2 group is $(KSO_3)_2N$—O• (dipotassium nitrosodisulfonate; *Fremy's salt*), which is a stable free radical.[266] Phenols, even some whose para positions are unoccupied, can be oxidized to ortho-quinones with diphenylseleninic anhydride.[267] Quinoid coupling products are obtained from substituted phenol treated with O_2, a dicopper complex, and mushroom tyrosinase.[268]

Less is known about the mechanism than is the case for **19-3**, but, as in that case, it seems to vary with the oxidizing agent. For oxidation of catechol with $NaIO_4$, it was found that the reaction conducted in $H_2{}^{18}O$ gave unlabeled quinone,[269] so the following mechanism[270] was proposed:



When catechol was oxidized with MnO_4^- under aprotic conditions, a semiquinone radical ion intermediate was involved.[271] For autoxidations[272] (i.e., with atmospheric oxygen) a free-radical mechanism is known to operate.[273]

OS **I**, 383, 482, 511; **II**, 175, 254, 430, 553; **III**, 663, 753; **IV**, 148; **VI**, 412, 480, 1010.

19-5 Dehydrogenation of Amines

1/1/*N*,2/2/*C*-Tetrahydro-bielimination

$$RCH_2NH_2 \longrightarrow RCN$$

Primary amines at a primary carbon can be dehydrogenated to nitriles. The reaction has been carried out with a variety of reagents, among others, lead tetraacetate,[274] NaOCl,[275]

[265]Cossy, J.; Belotti, S. *Tetrahedron Lett.* ***2001***, *42*, 4329.

[266]For a review of oxidation with this salt, see Zimmer, H.; Lankin, D.C.; Horgan, S.W. *Chem. Rev.* ***1971***, *71*, 229.

[267]Barton, D.H.R.; Brewster, A.G.; Ley, S.V.; Rosenfeld, M.N. *J. Chem. Soc. Chem. Commun.* ***1976***, 985; Barton, D.H.R.; Ley, S.V., in *Further Perspectives in Organic Chemistry*, North-Holland Publishing Co., Amsterdam, The Netherlands, ***1979***, pp. 53–66. For another way of accomplishing this, see Krohn, K.; Rieger, H.; Khanbabaee, K. *Chem. Ber.* ***1989***, *122*, 2323.

[268]Gupta, R.; Mukherjee, R. *Tetrahedron Lett.* ***2000***, *41*, 7763.

[269]Adler, E.; Falkehag, I.; Smith, B. *Acta Chem. Scand.* ***1962***, *16*, 529.

[270]This mechanism is an example of category 4 (p. $$$).

[271]Bock, H.; Jaculi, D. *Angew. Chem. Int. Ed.* ***1984***, *23*, 305.

[272]For an example, see Rathore, R.; Bosch, E.; Kochi, J.K. *Tetrahedron Lett.* ***1994***, *35*, 1335.

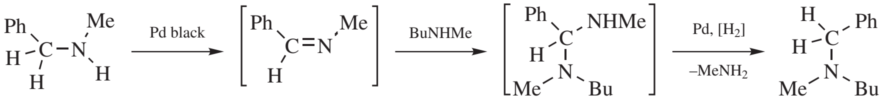
[273]Sheldon, R.A.; Kochi, J.K. *Metal-Catalyzed Oxidations of Organic Compounds*, Academic Press, NY, ***1981***, pp. 368–381; Walling, C. *Free Radicals in Solution*, Wiley, NY, ***1957***, pp. 457–461.

[274]Stojiljković, A.; Andrejević, V.; Mihailović, M.Lj. *Tetrahedron* ***1967***, *23*, 721.

[275]Yamazaki, S. *Synth. Commun.* ***1997***, *27*, 3559; Juršic, B. *J. Chem. Res. (S)* ***1988***, 168.

$K_2S_2O_8/NiSO_4$,[276] $Me_3N/O/OsO_4$,[277] $Ru/Al_2O_3/O_2$,[278] and $CuCl/O_2$/pyridine.[279] Several methods have been reported for the dehydrogenation of secondary amines to imines.[280] Among them[281] are treatment with (*1*) iodosylbenzene (PhIO) alone or in the presence of a ruthenium complex,[282] (*2*) DMSO and oxalyl chloride,[283] and (*3*) *t*-BuOOH and a rhenium catalyst.[284] *N*-Tosyl aziridines are converted to *N*-tosyl imines when heated with a palladium catalyst.[285] An interesting variation treats pyrrolidine with iodobenzene and a rhodium catalyst to give 2-phenylpyrroline.[286]

A reaction that involves dehydrogenation to an imine that then reacts further is the reaction of primary or secondary amines[287] with palladium black.[288] The imine initially formed by the dehydrogenation reacts with another molecule of the same or a different amine to give an aminal, which loses NH_3 or RNH_2 to give a secondary or tertiary amine. An example is the reaction between *N*-methylbenzylamine and butylmethylamine, which produces 95% *N*-methyl-*N*-butylbenzylamine.



19-6 Oxidation of Hydrazines, Hydrazones, and Hydroxylamines

1/*N*,2/*N*-Dihydro-elimination

$$\text{Ar—NH—NH—Ar} \xrightarrow{\text{NaOBr}} \text{Ar—N=N—Ar}$$

N,N'-Diarylhydrazines (hydrazo compounds) are oxidized to azo compounds by several oxidizing agents, including NaOBr, HgO,[289] $K_3Fe(CN)_6$ under phase-transfer

[276]Yamazaki, S.; Yamazaki, Y. *Bull. Chem. Soc. Jpn.* ***1990***, *63*, 301.
[277]Gao, S.; Herzig, D.; Wang, B. *Synthesis* ***2001***, 544.
[278]Yamaguchi, K.; Mizuno, N. *Angew. Chem. Int. Ed.* ***2003***, *42*, 1480.
[279]Kametani, T.; Takahashi, K.; Ohsawa, T.; Ihara, M. *Synthesis* ***1977***, 245; Capdevielle, P.; Lavigne, A.; Maumy, M. *Synthesis* ***1989***, 453; *Tetrahedron* ***1990***, 2835; Capdevielle, P.; Lavigne, A.; Sparfel, D.; Baranne-Lafont, J.; Cuong, N.K.; Maumy, M. *Tetrahedron Lett.* ***1990***, *31*, 3305.
[280]For a review, see Dayagi, S.; Degani, Y., in Patai, S. *The Chemistry of the Carbon-Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 117–124.
[281]For other methods, see Cornejo, J.J.; Larson, K.D.; Mendenhall, G.D. *J. Org. Chem.* ***1985***, *50*, 5382; Nishinaga, A.; Yamazaki, S.; Matsuura, T. *Tetrahedron Lett.* ***1988***, *29*, 4115.
[282]Müller, P.; Gilabert, D.M. *Tetrahedron* ***1988***, *44*, 7171.
[283]Keirs, D.; Overton, K. *J. Chem. Soc. Chem. Commun.* ***1987***, 1660.
[284]Murahashi, S.; Naot, T.; Taki, H. *J. Chem. Soc. Chem. Commun.* ***1985***, 613.
[285]Wolfe, J.P.; Ney, J.E. *Org. Lett.* ***2003***, *5*, 4607.
[286]Sezen, B.; Sames, D. *J. Am. Chem. Soc.* ***2004***, *126*, 13244.
[287]See Larsen, J.; Jørgensen, K.A. *J. Chem. Soc. Perkin Trans. 2*, ***1992***, 1213. Also see, Yamaguchi, J.; Takeda, T. *Chem. Lett.* ***1992***, 1933; Yamazaki, S. *Chem. Lett.* ***1992***, 823.
[288]Murahashi, S.; Yoshimura, N.; Tsumiyama, T.; Kojima, T. *J. Am. Chem. Soc.* ***1983***, *105*, 5002. See also, Wilson, Jr., R.B.; Laine, R.M. *J. Am. Chem. Soc.* ***1985***, *107*, 361.
[289]For a review of HgO, see Pizey, J.S. *Synthetic Reagents*, Vol. 1, Wiley, NY, ***1974***, pp. 295–319.

conditions[290] or with galvinoxyl,[291] $FeCl_3$,[292] MnO_2 (this reagent yields cis-azobenzenes),[293] $CuCl_2$, and air and NaOH.[294] The reaction is also applicable to *N,N′*-dialkyl- and *N,N′*-diacylhydrazines. Hydrazines (both alkyl and aryl) substituted on only one side also give azo compounds,[295] but these are unstable and decompose to nitrogen and the hydrocarbon:

$$\text{Ar—NH—NH}_2 \longrightarrow [\text{Ar—N=NH}] \longrightarrow \text{ArH} + \text{N}_2$$

Aniline derivatives are converted to azo compounds by heating with cetyltrimethylammonium dichromate in chloroform.[296] When hydrazones are oxidized with HgO, Ag_2O, MnO_2, lead tetraacetate, or certain other oxidizing agents, diazo compounds are obtained:[297]

$$\text{R}_2\text{C=N—NH}_2 \xrightarrow{\text{HgO}} \text{R}_2\text{C=}\overset{\oplus}{\text{N}}\text{=}\overset{\ominus}{\text{N}}$$

Hydrazones of the form $ArCH{=}NNH_2$ react with HgO in solvents, such as diglyme or ethanol, to give nitriles ArCN.[298] It is possible to oxidize dimethylhydrazones ($R{-}C{=}N{-}NMe_2$) to the corresponding nitrile ($R{-}C{\equiv}N$) with $MeReO_3$/H_2O_2[299] magnesium monoperoxyphthalate (MMPP),[300] or with dimethyl dioxirane.[301] Oxone® on wet alumina also converts hydrazones to nitriles with microwave irradiation.[302]

In a related reaction, primary aromatic amines have been oxidized to azo compounds by a variety of oxidizing agents, among them MnO_2, lead tetraacetate, O_2 and a base, barium permanganate,[303] and sodium perborate in acetic acid. *tert*-Butyl hydroperoxide has been used to oxidize certain primary amines to azoxy compounds.[304] Aromatic hydroxylamines (Ar—NH—OH) are easily oxidized to nitroso compounds (Ar—N=O), most commonly by acid dichromate.[305] Oximes of

[290]Dimroth, K.; Tüncher, W. *Synthesis* ***1977***, 339.

[291]Wang, X.-Y.; Wang, Y.-L.; Li, J.-P.; Duan, Z.F.; Zhang, Z.-Y. *Synth. Commun.* ***1999***, *29*, 2271.

[292]Wang, C.-L.; Wang, X.-X.; Wang, X.-Y.; Xiao, J.-P.; Wang, Y.-L. *Synth. Commun.* ***1999***, *29*, 3435.

[293]Hyatt, J.A. *Tetrahedron Lett.* ***1977***, 141.

[294]For a review, see Newbold, B.T., in Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 1, Wiley, NY, ***1975***, pp. 543–557, 564–573.

[295]See Mannen, S.; Itano, H.A. *Tetrahedron* ***1973***, *29*, 3497.

[296]Patel, S.; Mishra, B.K. *Tetrahedron Lett.* ***2004***, *45*, 1371.

[297]For a review, see Regitz, M.; Maas, G. *Diazo Compounds*, Academic Press, NY, ***1986***, pp. 233–256.

[298]Mobbs, D.B.; Suschitzky, H. *Tetrahedron Lett.* ***1971***, 361.

[299]Stanković, S.; Espenson, J.H. *Chem. Commun.* ***1998***, 1579.

[300]Fernández, R.; Gasch, C.; Lassaletta, J.-M.; Llera, J.-M.; Vázquez, J. *Tetrahedron Lett.* ***1993***, *34*, 141.

[301]Altamura, A.; D'Accolti, L.; Detomaso, A.; Dinoi, A.; Fiorentino, M.; Fusco, C.; Curci, R. *Tetrahedron Lett.* ***1998***, *39*, 2009.

[302]Ramalingam, T.; Reddy, B.V.S.; Srinivas, R.; Yadav, J.S. *Synth. Commun.* ***2000***, *30*, 4507.

[303]Firouzabadi, H.; Mostafavipoor, Z. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 914.

[304]Kosswig, K. *Liebigs Ann. Chem.* ***1971***, *749*, 206.

[305]For a review, see Hudlický, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, pp. 231–232.

aromatic aldehydes are converted to aryl nitriles with $InCl_3$[306] (ketoximes give a Beckmann rearrangement, **18-17**).

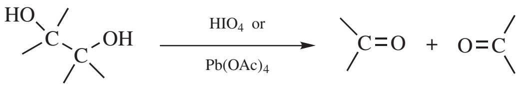
Nitrones, $C{=}N^+(R){=}O^-$, are generated by the oxidation of *N*-hydroxyl secondary amines with 5% aq. NaOCl.[307] Secondary amines, such as dibenzylamine, can be converted to the corresponding nitrone by heating with cumyl hydroperoxide in the presence of a titanium catalyst.[308] Imines are oxidized to amides with mcpba and BF_3•OEt_2.[309]

OS **II**, 496; **III**, 351, 356, 375, 668; **IV**, 66, 411; **V**, 96, 160, 897; **VI**, 78, 161, 334, 392, 803, 936; **VII**, 56. Also see, OS **V**, 258. For oxidation of primary amines, see OS **V**, 341.

B. Oxidations Involving Cleavage of Carbon–Carbon Bonds[310]

19-7 Oxidative Cleavage of Glycols and Related Compounds

2/*O*-De-hydrogen-uncoupling



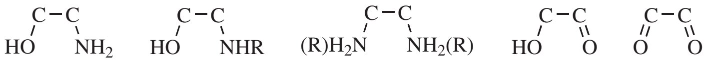
1,2-Glycols are easily cleaved under mild conditions and in good yield with periodic acid or lead tetraacetate.[311] The products are 2 equivalents of aldehyde, or 2 equivalents of ketone, or 1 equivalent of each, depending on the groups attached to the two carbons. The yields are so good that alkenes are often converted to glycols (**15-48**), and then cleaved with HIO_4 or $Pb(OAc)_4$ rather than being cleaved directly with ozone (**19-9**) or dichromate or permanganate (**19-10**). The diol can be generated and cleaved *in situ* from an alkene to give the carbonyl compounds.[312]

[306]Barman, D.C.; Thakur, A.J.; Prajapati, D.; Sandhu, J.S. *Chem. Lett.* ***2000***, 1196.
[307]Cicchi, S.; Corsi, M.; Goti, A. *J. Org. Chem.* ***1999***, *64*, 7243.
[308]Forcato, M.; Nugent, W.A.; Licini, G. *Tetrahedron Lett.* ***2003***, *44*, 49.
[309]An, G.-i.; Rhee, H. *Synlett* ***2003***, 876.
[310]For a review, see Bentley, K.W., in Bentley, K.W.; Kirby, G.W. *Elucidation of Chemical Structures by Physical and Chemical Methods* (Vol. 4 of Weissberger, A. *Techniques of Chemistry*), 2nd ed., pt. 2, Wiley, NY, ***1973***, pp. 137–254.
[311]For reviews covering both reagents, see Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Vol. 2, Academic Press, NY, ***1988***, pp. 277–301, 432–437; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 3353–363; Perlin, A.S., in Augustine, R.L. *Oxidation*, Vol. 1, Marcel Dekker, NY, ***1969***, pp. 189–212; Bunton, C.A., in Wiberg, K.B., in Wiberg, K.B. *Oxidation in Organic Chemistry*, pt. A, Academic Press, NY, ***1965***, pp. 367–407. For reviews of lead tetraacetate, see Rubottom, G.M., in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. D, Academic Press, NY, ***1982***, p. 1; Aylward, J.B. *Q. Rev. Chem. Soc.* ***1971***, *25*, 407. For reviews of HIO_4, see Fatiadi, A.J. *Synthesis* ***1976***, 65,133; Sklarz, B. *Q. Rev. Chem. Soc.* ***1967***, *21*, 3.
[312]Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* ***2004***, *6*, 3217.

A number of other oxidizing agents also give the same products, among them[313] activated MnO_2,[314] O_2 and a ruthenium catalyst,[315] PPh_3–DEAD,[316] and pyridinium chlorochromate.[317] Permanganate, dichromate, and several other oxidizing agents[318] also cleave glycols, giving carboxylic acids rather than aldehydes, but these reagents are seldom used synthetically. Electrochemical oxidation is an efficient method, and is useful not only for diols, but also for their mono- and dimethoxy derivatives.[319]

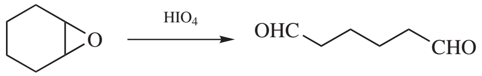
The two reagents (periodic acid and lead tetraacetate) are complementary, since periodic acid is best used in water and lead tetraacetate in organic solvents. Chiral lead carboxylates have been prepared for the oxidative cleavage of 1,2-diols.[320] When three or more OH groups are located on adjacent carbons, the middle one (or ones) is converted to formic acid.

Other compounds that contain oxygens or nitrogens on adjacent carbons undergo similar cleavage:



β-Amino alcohols | 1,2-Diamines | α-Hydroxy aldehydes and ketones | α-Diketones a-keto aldehydes Glyoxal

Cyclic 1,2-diamines are cleaved to diketones with dimethyl dioxirane.[321] α-Diketones and α-hydroxy ketones are also cleaved by alkaline H_2O_2.[322] The HIO_4 has been used to cleave epoxides to aldehydes,[323] for example,



α-Hydroxy acids and α-keto acids are not cleaved by HIO_4, but are cleaved by $NaIO_4$ in methanol in the presence of a crown ether,[324] $Pb(OAc)_4$, alkaline H_2O_2,

[313]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1250–1255.

[314]Adler, E.; Becker, H. *Acta Chem. Scand.* ***1961***, *15*, 849; Ohloff, G.; Giersch, W. *Angew. Chem. Int. Ed.* ***1973***, *12*, 401.

[315]Takezawa, E.; Sakaguchi, S.; Ishii, Y. *Org. Lett.* ***1999***, *1*, 713.

[316]Barrero, A.F.; Alvarez-Manzaneda, E.J.; Chahboun, R. *Tetrahedron Lett.* ***2000***, *41*, 1959.

[317]Cisneros, A.; Fernández, S.; Hernández, J.E. *Synth. Commun.* ***1982***, *12*, 833.

[318]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1650–1652.

[319]For a review, see Shono, T. *Electroorganic Chemistry as a New Tool in Organic Synthesis*, Springer, NY, ***1984***, pp. 31–37. See also, Ruholl, H.; Schäfer, H.J. *Synthesis* ***1988***, 54.

[320]Lena, J.I.C.; Sesenoglu, Ö.; Birlirakis, N.; Arseniyadis, S. *Tetrahedron Lett.* ***2001***, *42*, 21.

[321]Gagnon, J.L.; Zajac, Jr., W.W. *Tetrahedron Lett.* ***1995***, *36*, 1803.

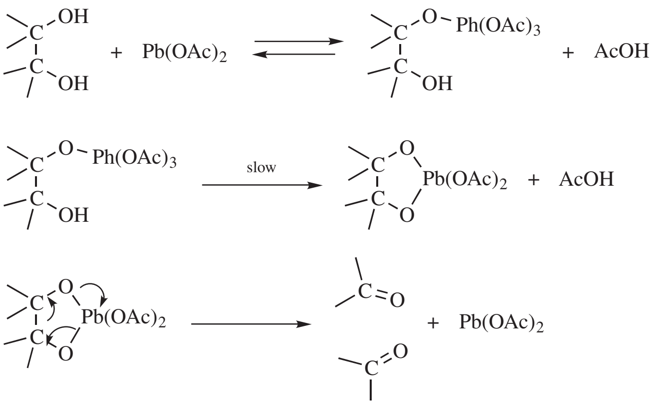
[322]See, for example, Ogata, Y.; Sawaki, Y.; Shiroyama, M. *J. Org. Chem.* ***1977***, *42*, 4061.

[323]Nagarkatti, J.P.; Ashley, K.R. *Tetrahedron Lett.* ***1973***, 4599.

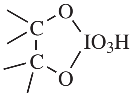
[324]Kore, A.R.; Sagar, A.D.; Salunkhe, M.M. *Org. Prep. Proceed. Int.* ***1995***, *27*, 373.

and other reagents. These are oxidative decarboxylations. α-Hydroxy acids give aldehydes or ketones, and α-keto acids give carboxylic acids. Also see, **19-12** and **19-13**.

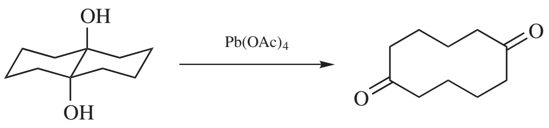
The mechanism of glycol oxidation with $Pb(OAc)_4$ was proposed by Criegee:[325]



This mechanism is supported by these facts: (*1*) the kinetics are second order (first order in each reactant); (*2*) added acetic acid retards the reaction (drives the equilibrium to the left); and (*3*) cis-glycols react much more rapidly than trans-glycols.[326] For periodic acid, the mechanism is similar, with the intermediate[327]



However, the cyclic-intermediate mechanism cannot account for all glycol oxidations, since some glycols that cannot form such an ester (e.g., **15**) are nevertheless cleaved by lead tetraacetate



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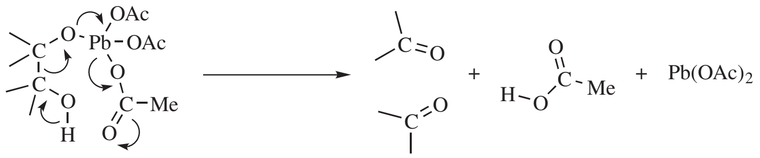
[325]Criegee, R.; Kraft, L.; Rank, B. *Liebigs Ann. Chem.* ***1933***, *507*, 159. For reviews, see Waters, W.A. *Mechanisms of Oxidation of Organic Compounds*, Wiley, NY, ***1964***, pp. 72–81; Stewart, R. *Oxidation Mechanisms*, W.A. Benjamin, NY, ***1964***, pp. 97–106.

[326]For example, see Criegee, R.; Höger, E.; Huber, G.; Kruck, P.; Marktscheffel, F.; Schellenberger, H. *Liebigs Ann. Chem.* ***1956***, *599*, 81.

[327]Buist, G.J.; Bunton, C.A.; Hipperson, W.C.P. *J. Chem. Soc. B* ***1971***, 2128.

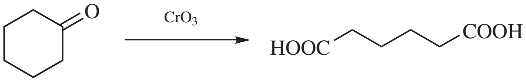
(though other glycols that cannot form cyclic esters are *not* cleaved, by either reagent[328]). To account for cases like **15**, a cyclic transition state has been proposed:[326]



OS **IV**, 124; **VII**, 185; **VIII**, 396.

19-8 Oxidative Cleavage of Ketones, Aldehydes, and Alcohols

Cycloalkanone oxidative ring opening



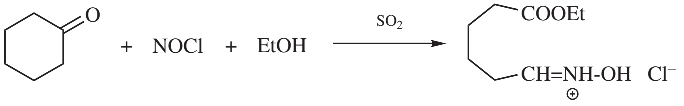
Oxidative cleavage of open-chain ketones or alcohols[329] is seldom a useful preparative procedure, not because these compounds do not undergo oxidation (they do, except for diaryl ketones), but because the result is generally a hopeless mixture. Aryl methyl ketones, such as acetophenone, however, are readily oxidized to aryl carboxylic acids with Re_2O_7 and 70% aqueous *tert*-butyl hydroperoxide.[330] Oxygen with a mixture of manganese and cobalt catalysts give similar oxidative cleavage,[331] and do hypervalent iodine compounds.[332] 1,3-Diketones, such as 1,3-diphenyl-1,3-propanedione, are oxidatively cleaved with aqueous Oxone® to give benzoic acid.[333] Noted that in the presence of benzaldehyde, aliphatic ketones are cleaved to give aliphatic carboxylic acids by treatment with BF_3(g) in refluxing hexane.[334] Aldehydes, such as $PhCH_2CHO$, are cleaved to benzaldehyde with phosphonium dichromate in refluxing acetonitrile.[335]

Despite problems with acyclic ketones, the reaction is quite useful for cyclic ketones and the corresponding secondary alcohols, the dicarboxylic acid being prepared in good yield. The formation of adipic acid from cyclohexanone (shown above) is an important industrial procedure. Acid dichromate and permanganate are the most common oxidizing agents, although autoxidation (oxidation with

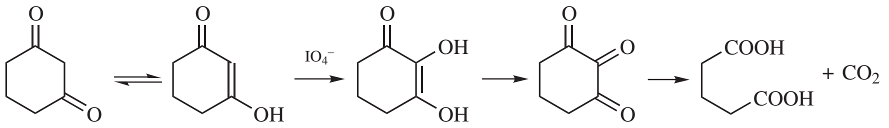
[328]Angyal, S.J.; Young, R.J. *J. Am. Chem. Soc.* ***1959***, *81*, 5251.
[329]For a review of metal ion-catalyzed oxidative cleavage of alcohols, see Trahanovsky, W.S. *Methods Free-Radical Chem.* ***1973***, *4*, 133–169. For a review of the oxidation of aldehydes and ketones, see Verter, H.S., in Zabicky, J. *The Chemistry of the Carbonyl Group*, pt. 2, Wiley, NY, ***1970***, pp. 71–156.
[330]Gurunath, S.; Sudalai, A. *Synlett* ***1999***, 559.
[331]Minisci, F.; Recupero, F.; Fontana, F.; Bjørsvik, H.-R.; Liguori, L. *Synlett* ***2002***, 610.
[332]Lee, J.C.; Choi, J.-H.; Lee, Y.C. *Synlett* ***2001***, 1563.
[333]Ashford, S.W.; Grega, K.C. *J. Org. Chem.* ***2001***, *66*, 1523.
[334]Kabalka, G.W.; Li, N.-S.; Tejedor, D.; Malladi, R.R.; Gao, X.; Trotman, S. *Synth. Commun.* ***1999***, *29*, 2783.
[335]Hajipour, A.R.; Mohammadpoor-Baltork, I.; Niknam, K. *Org. Prep. Proceed. Int.* ***1999***, *31*, 335.

atmospheric oxygen) in alkaline solution[336] and potassium superoxide under phase-transfer conditions[337] have also been used. Other reagents include LiOCl/Chlorox[338] and $MeOCO_2Me$ at 195°C.[339] Silyl-ketones have been cleaved to esters using electrolysis in alcohol solvents.[340] Cyclic 1,3-diketones are converted to α,ω-diesters with an excess of $KHSO_5$ in methanol.[341] Cyclic α-chloro ketones are cleaved to give an α,ω-functionalized compound (acetal-ester) when treated with cerium (IV) sulfate tetrahydrate and O_2.[342]

Cyclic ketones can also be cleaved by treatment with NOCl and an alcohol in liquid SO_2 to give an ω-oximinocarboxylic ester, for example,[343]



Cyclic 1,3-diketones, which exist mainly in the mono-enolic form, can be cleaved with sodium periodate with loss of one carbon, for example,[344]

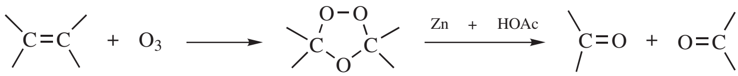


The species actually undergoing the cleavage is the triketone, so this is an example of **19-7**.

OS **I**, 18; **IV**, 19; **VI**, 690. See also, OS **VI**, 1024.

19-9 Ozonolysis

Oxo-uncoupling



16

[336]Wallace, T.J.; Pobiner, H.; Schriesheim, A. *J. Org. Chem.* ***1965***, *30*, 3768; Bjørsvik, H.-R.; Liguori, L.; González, R.R.; Merinero, J.A.V. *Tetrahedron Lett.* ***2002***, *43*, 4985. See also, Osowska-Pacewicka, K.; Alper, H. *J. Org. Chem.* ***1988***, *53*, 808.

[337]Lissel, M.; Dehmlow, E.V. *Tetrahedron Lett.* ***1978***, 3689; Sotiriou, C.; Lee, W.; Giese, R.W. *J. Org. Chem.* ***1990***, *55*, 2159.

[338]Madler, M.M.; Klucik, J.; Soell, P.S.; Brown, C.W.; Liu, S.; Berlin, K.D.; Benbrook, D.M.; Birckbichler, P.J.; Nelson, E.C. *Org. Prep. Proceed. Int.* ***1998***, *30*, 230.

[339]Selva, M.; Marques, C.A.; Tundo, P. *Gazz. Chim. Ital.* ***1993***, *123*, 515.

[340]Yoshida, J.; Itoh, M.; Matsunaga, S.; Isoe, S. *J. Org. Chem.* ***1992***, *57*, 4877.

[341]Yan, J.; Travis, B.R.; Borhan, B. *J. Org. Chem.* ***2004***, *69*, 9299.

[342]He, L.; Horiuchi, C.A. *Bull. Chem. Soc. Jpn.* ***1999***, *72*, 2515.

[343]Rogić, M.M.; Vitrone, J.; Swerdloff, M.D. *J. Am. Chem. Soc.* ***1977***, *99*, 1156; Moorhoff, C.M.; Paquette, L.A. *J. Org. Chem.* ***1991***, *56*, 703.

[344]Wolfrom, M.L.; Bobbitt, J.M. *J. Am. Chem. Soc.* ***1956***, *78*, 2489.

When compounds containing double bonds are treated with ozone, usually at low temperatures, they are converted to compounds called *ozonides* (**16**) that can be isolated but, because some of them are explosive, are more often decomposed with zinc and acetic acid, or catalytic hydrogenation to give 2 equivalents of aldehyde, or 2 equivalents of ketone, or 1 equivalent of each, depending on the groups attached to the alkene.[345] The decomposition of **16** has also been carried out with triethylamine[346] and with reducing agents, among them trimethyl phosphite,[347] thiourea,[348] and dimethyl sulfide.[349] However, ozonides can also be *oxidized* with oxygen, peroxyacids, or H_2O_2 to give ketones and/or carboxylic acids or *reduced* with $LiAlH_4$, $NaBH_4$, BH_3, or catalytic hydrogenation with excess H_2 to give 2 equivalents alcohol.[350] Ozonides can also be treated with ammonia, hydrogen, and a catalyst to give the corresponding amines,[351] or with an alcohol and anhydrous HCl to give the corresponding carboxylic esters.[352] Ozonolysis is therefore an important synthetic reaction.

A wide variety of alkenes undergo ozonolysis, including cyclic ones, where cleavage gives rise to one bifunctional product. Alkenes in which the double bond is connected to electron-donating groups react many times faster than those in which it is connected to electron-withdrawing groups.[353] The reaction has often been carried out on compounds containing more than one double bond; generally all the bonds are cleaved. In some cases, especially when bulky groups are present, conversion of the substrate to an epoxide (**15-50**) becomes an important side reaction and can be the main reaction.[354] Rearrangement is possible in some cases.[355] Ozonolysis of triple bonds[356] is less common and the reaction proceeds less easily,

[345]For monographs, see Razumovskii, S.D.; Zaikov, G.E. *Ozone and its Reactions with Organic Compounds*; Elsevier, NY, ***1984***; Bailey, P.S. *Ozonation in Organic Chemistry*, 2 vols., Academic Press, NY, ***1978, 1982***. For reviews, see Odinokov, V.N.; Tolstikov, G.A. *Russ. Chem. Rev.* ***1981***, *50*, 636; Belew, J.S., in Augustine, R.L.; Trecker, D.J. *Oxidation*, Vol. 1, Marcel Dekker, NY, ***1969***, pp. 259–335; Menyailo, A.T.; Pospelov, M.V. *Russ. Chem. Rev.* ***1967***, *36*, 284. For a review with respect to vinylic ethers, see Kuczkowski, R.L. *Adv. Oxygenated Processes* ***1991***, *3*, 1. For a review with respect to haloalkenes, see Gillies, C.W.; Kuczkowski, R.L. *Isr. J. Chem.* ***1983***, *23*, 446.

[346]Hon, Y.-S.; Lin, S.-W.; Chen, Y.-J. *Synth. Commun.* ***1993***, *23*, 1543.

[347]Knowles, W.S.; Thompson, Q.E. *J. Org. Chem.* ***1960***, *25*, 1031.

[348]Gupta, D.; Soman, R.; Dev, S. *Tetrahedron* ***1982***, *38*, 3013.

[349]Pappas, J.J.; Keaveney, W.P.; Gancher, E.; Berger, M. *Tetrahedron Lett.* ***1966***, 4273.

[350]Sousa, J.A.; Bluhm, A.L. *J. Org. Chem.* ***1960***, *25*, 108; Diaper, D.G.M.; Strachan, W.M.J. *Can. J. Chem.* ***1967***, *45*, 33; White, R.W.; King, S.W.; O'Brien, J.L. *Tetrahedron Lett.* ***1971***, 3587; Flippin, L.A.; Gallagher, D.W.; Jalali-Araghi, K. *J. Org. Chem.* ***1989***, *54*, 1430.

[351]Diaper, D.G.M.; Mitchell, D.L. *Can. J. Chem.* ***1962***, *40*, 1189; Benton, F.L.; Kiess, A.A. *J. Org. Chem.* ***1960***, *25*, 470; Pollart, K.A.; Miller, R.E. *J. Org. Chem.* ***1962***, *27*, 2392; White, R.W.; King, S.W.; O'Brien, J.L. *Tetrahedron Lett.* ***1971***, 3591.

[352]Neumeister, J.; Keul, H.; Saxena, M.P.; Griesbaum, K. *Angew. Chem. Int. Ed.* ***1978***, *17*, 939. See also, Schreiber, S.L.; Claus, R.E.; Reagan, J. *Tetrahedron Lett.* ***1982***, *23*, 3867; Cardinale, G.; Grimmelikhuysen, J.C.; Laan, J.A.M.; Ward, J.P. *Tetrahedron* ***1984***, *40*, 1881.

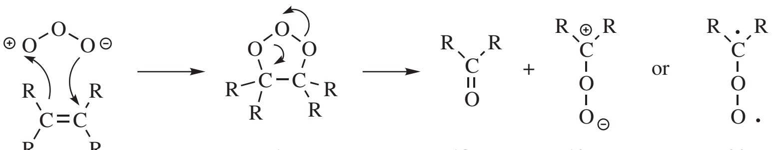
[353]Pryor, W.A.; Giamalva, D.; Church, D.F. *J. Am. Chem. Soc.* ***1985***, *107*, 2793.

[354]See, for example, Bailey, P.S.; Lane, A.G. *J. Am. Chem. Soc.* ***1967***, *89*, 4473; Gillies, C.W. *J. Am. Chem. Soc.* ***1975***, *97*, 1276; Bailey, P.S.; Hwang, H.H.; Chiang, C. *J. Org. Chem.* ***1985***, *50*, 231.

[355]For an example, see Barrero, A.F.; Alvarez-Manzaneda, E.J.; Chahboun, R.; Cuerva, J.M.; Segovia, A. *Synlett.* ***2000***, *1*269.

[356]For a discussion of the mechanism of ozonolysis of triple bonds, see Pryor, W.A.; Govindan, C.K.; Church, D.F. *J. Am. Chem. Soc.* ***1982***, *104*, 7563.

since ozone is an electrophilic agent[357] and prefers double to triple bonds (p. 1017). Compounds that contain triple bonds generally give carboxylic acids, although sometimes ozone oxidizes them to α-diketones (**19-26**). Aromatic compounds are also attacked less readily than alkenes, but have often been cleaved. Aromatic compounds behave as if the double bonds in the Kekulé structures were really there. Thus benzene gives three equivalents of glyoxal (HCOCHO), and *o*-xylene gives a glyoxal/MeCOCHO/MeCOCOMe ratio of 3:2:1, which shows that in this case cleavage is statistical. With polycyclic aromatic compounds the site of attack depends on the structure of the molecule and on the solvent.[358]



17 **18** **19** **20**

Although a large amount of work has been done on the mechanism of ozonization (formation of **16**), not all the details are known. The basic mechanism was formulated by Criegee.[359] The first step of the Criegee mechanism[360] is a 1,3-dipolar addition (**15-58**) of ozone to the substrate to give the "initial" or "primary" ozonide, the structure of which has been shown to be the 1,2,3-trioxolane, **17**, by microwave and other spectral methods.[361] A primary ozonide has been trapped.[362] However, **17** is highly unstable and cleaves to an aldehyde or ketone (**18**) and an intermediate,[363] which Criegee showed as a zwitterion (**19**), but which may be a diradical (**20**). This compound is usually referred to as a carbonyl oxide.[364] The carbonyl oxide (which we will represent as **19**) can then undergo various reactions, three of which lead to normal products. One is a recombination with **18**, the second

[357]See, for example, Wibaut, J.P.; Sixma, F.L.J. *Recl. Trav. Chim. Pays-Bas* ***1952***, *71*, 761; Williamson, D.G.; Cvetanovi, R.J. *J. Am. Chem. Soc.* ***1968***, *90*, 4248; Razumovskii, S.D.; Zaikov, G.E. *J. Org. Chem. USSR* ***1972***, *8*, 468, 473; Klutsch, G.; Fliszár, S. *Can. J. Chem.* ***1972***, *50*, 2841.

[358]Dobinson, F.; Bailey, P.S. *Tetrahedron Lett.* ***1960*** (No. 13) 14; O'Murchu, C. *Synthesis* ***1989***, 880.

[359]For reviews, see Kuczkowski, R.L. *Acc. Chem. Res.* ***1983***, *16*, 42; Razumovskii, S.D.; Zaikov, G.E. *Russ. Chem. Rev.* ***1980***, *49*, 1163; Criegee, R. *Angew. Chem. Int. Ed.* ***1975***, *14*, 745; Murray, R.W. *Acc. Chem. Res.* ***1968***, *1*, 313.

[360]For a modified-Criegee mechanism, see Ponec, R.; Yuzhakov, G.; Haas, Y.; Samuni, U. *J. Org. Chem.* ***1997***, *62*, 2757.

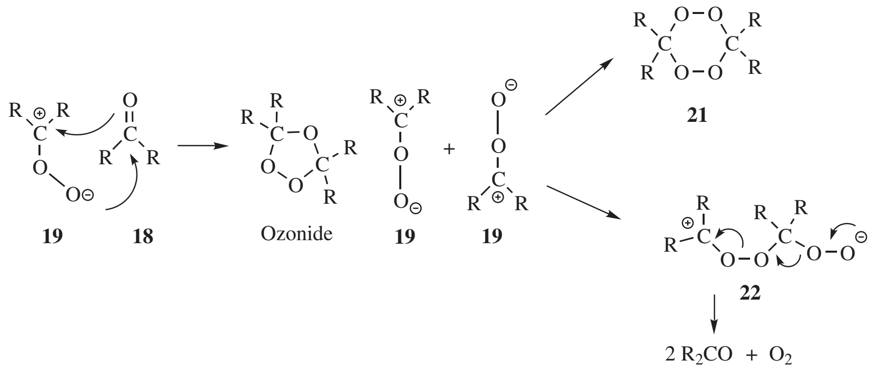
[361]Gillies, J.Z.; Gillies, C.W.; Suenram, R.D.; Lovas, F.J. *J. Am. Chem. Soc.* ***1988***, *110*, 7991. See also, Criegee, R.; Schröder, G. *Chem. Ber.* ***1960***, *93*, 689; Durham, L.J.; Greenwood, F.L. *J. Org. Chem.* ***1968***, *33*, 1629; Bailey, P.S.; Carter, Jr., T.P.; Fischer, C.M.; Thompson, J.A. *Can. J. Chem.* ***1973***, *51*, 1278; Hisatsune, I.C.; Shinoda, K.; Heicklen, J. *J. Am. Chem. Soc.* ***1979***, *101*, 2524; Mile, B.; Morris, G.W.; Alcock, W.G. *J. Chem. Soc. Perkin Trans. 2* ***1979***, 1644; Kohlmiller, C.K.; Andrews, L. *J. Am. Chem. Soc.* ***1981***, *103*, 2578; McGarrity, J.F.; Prodolliet, J. *J. Org. Chem.* ***1984***, *49*, 4465.

[362]Jung, M.E.; Davidov, P. *Org. Lett.* ***2001***, *3*, 627.

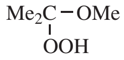
[363]A Criegee intermediate has been detected for the ozonolysis of 2-butene; see Fajgar, R.; Vítek, J.; Haas, Y.; Pola, J. *Tetrahedron Lett.* ***1996***, *37*, 3391.

[364]For reviews of carbonyl oxides, see Sander, W. *Angew. Chem. Int. Ed.* ***1990***, *29*, 344; Brunelle, W.H. *Chem. Rev.* ***1991***, *91*, 335.

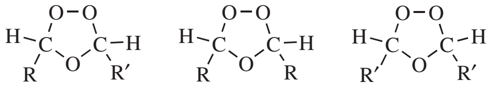
a dimerization to the bis(peroxide) **21**, and the third a kind of dimerization to **22**.[365] If the first path is taken (this is normally



possible only if **15** is an aldehyde; most ketones do not do this[366]) the product is an ozonide (a 1,2,4-trioxolane),[367] and hydrolysis of the ozonide gives the normal products. If **21** is formed, hydrolysis of it gives one of the products, and, of course, **18**, which then does not undergo further reaction, is the other. Intermediate **22**, if formed, can decompose directly, as shown, to give the normal products and oxygen. In protic solvents, **19** is converted to a hydroperoxide, and these have been isolated, for example,



from $Me_2C{=}CMe_2$ in methanol. Further evidence for the mechanism is that **21** can be isolated in some cases, for example, from $Me_2C{=}CMe_2$. But perhaps the most impressive evidence comes from the detection of cross-products. In the Criegee mechanism, the two parts of the original alkene break apart and then recombine to form the ozonide. In the case of an unsymmetrical alkene, RCH=CHR′, there should be three ozonides:

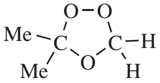


[365]Fliszár, S.; Chyliń ska, J.B. *Can. J. Chem.* ***1967***, *45*, 29; ***1968***, *46*, 783.

[366]It follows that tetrasubstituted alkenes do not normally give ozonides. However, they do give the normal cleavage products (ketones) by the other pathways. For the preparation of ozonides from tetrasubstituted alkenes by ozonolysis on polyethylene, see Griesbaum, K.; Volpp, W.; Greinert, R.; Greunig, H.; Schmid, J.; Henke, H. *J. Org. Chem.* ***1989***, *54*, 383.

[367]Kamata, M.; Komatsu, K.i.; Akaba, R. *Tetrahedron Lett.* ***2001***, *42*, 9203. For a report of an isolable ozonide, see dos Santos, C.; de Rosso, C.R.S.; Imamura, P.M. *Synth. Commun.* ***1999***, *29*, 1903.

since there are two different aldehydes **18** and two different species **19**, and these can recombine in the three ways shown. Actually *six* ozonides, corresponding to the cis and trans forms of these three, were isolated and characterized for methyl oleate.[368] Similar results have been reported for smaller alkenes, for example, 2-pentene, 4-nonene, and even 2-methyl-2-pentene.[369] The last-mentioned case is especially interesting, since it is quite plausible that this compound would cleave in only one way, so that only one ozonide (in cis and trans versions) would be found; but this is not so, and three were found for this case too. However, terminal alkenes give little or no cross-ozonide formation.[370] In general, the less alkylated end of the alkene tends to go to **18** and the other to **19**. Still other evidence[371] for the Criegee mechanism is (*1*) When $Me_2C{=}CMe_2$ was ozonized in the presence of



23

HCHO, the ozonide **23** could be isolated;[372] (*2*) **19** prepared in an entirely different manner (photooxidation of diazo compounds), reacted with aldehydes to give ozonides;[373] and (*3*) cis- and trans-alkenes generally give the same ozonide, which would be expected if they cleave first.[374] However, this was not true for $Me_3CCH{=}CHCMe_3$, where the cis-alkene gave the cis-ozonide (chiefly), and the trans gave the trans.[375] The latter result is not compatible with the Criegee mechanism. Also incompatible with the Criegee mechanism was the finding that the cis/trans ratios of symmetrical (cross) ozonides obtained from *cis*- and *trans*-4-methyl-2-pentene were not the same.[376]

[368]Riezebos, G.; Grimmelikhuysen, J.C.; van Dorp, D.A. *Recl. Trav. Chim. Pays-Bas* ***1963***, *82*, 1234; Privett, O.S.; Nickell, E.C. *J. Am. Oil Chem. Soc.* ***1964***, *41*, 72.

[369]Loan, L.D.; Murray, R.W.; Story, P.R. *J. Am. Chem. Soc.* ***1965***, *87*, 737; Lorenz, O.; Parks, C.R. *J. Org. Chem.* ***1965***, *30*, 1976.

[370]Murray, R.W.; Williams, G.J. *J. Org. Chem.* ***1969***, *34*, 1891.

[371]For further evidence, see Mori, M.; Nojima, M.; Kusabayashi, S. *J. Am. Chem. Soc.* ***1987***, *109*, 4407; Pierrot, M.; El Idrissi, M.; Santelli, M. *Tetrahedron Lett.* ***1989***, *30*, 461; Wojciechowski, B.J.; Chiang, C.; Kuczkowski, R.L. *J. Org. Chem.* ***1990***, *55*, 1120; Paryzek, Z.; Martynow, J.; Swoboda, W. *J. Chem. Soc. Perkin Trans. 1* ***1990***, 1220; Murray, R.W.; Morgan, M.M. *J. Org. Chem.* ***1991***, *56*, 684, 6123.

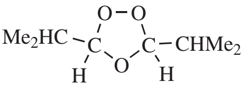
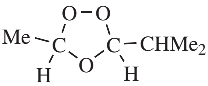
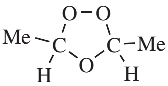
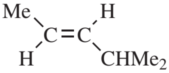
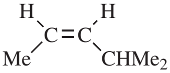
[372]Even ketones can react with **19** to form ozonides, provided they are present in large excess: Criegee, R.; Korber, H. *Chem. Ber.* ***1971***, *104*, 1812.

[373]Murray, R.W.; Suzui, A. *J. Am. Chem. Soc.* ***1973***, *95*, 3343; Higley, D.P.; Murray, R.W. *J. Am. Chem. Soc.* ***1974***, *96*, 3330.

[374]See, for example, Murray, R.W.; Williams, G.J. *J. Org. Chem.* ***1969***, *34*, 1896.

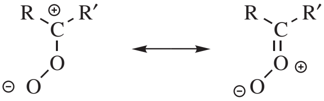
[375]Schröder, G. *Chem. Ber.* ***1962***, *95*, 733; Kolsaker, P. *Acta Chem. Scand. Ser. B* ***1978***, *32*, 557.

[376]Murray, R.W.; Youssefyeh, R.D.; Story, P.R. *J. Am. Chem. Soc.* ***1966***, *88*, 3143, 3655; Story, P.R.; Murray, R.W.; Youssefyeh, R.D. *J. Am. Chem. Soc.* ***1966***, *88*, 3144. Also see, Greenwood, F.L. *J. Am. Chem. Soc.* ***1966***, *88*, 3146; Choe, J.; Srinivasan, M.; Kuczkowski, R.L. *J. Am. Chem. Soc.* ***1983***, *105*, 4703.

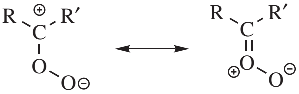
			
	50-50 cis–trans	48-52 cis–trans	38-62 cis–trans
	66-34 cis–trans	49-51 cis–trans	49-51 cis–trans

If the Criegee mechanism operated as shown above, the cis/trans ratio for each of the two cross-ozonides would have to be identical for the cis- and trans-alkenes, since in this mechanism they are completely cleaved.

The above stereochemical results have been explained[377] on the basis of the Criegee mechanism with the following refinements: (*1*) The formation of **17** is stereospecific, as expected from a 1,3-dipolar cycloaddition. (*2*) Once they are formed, **19** and **18** remain attracted to each other, much like an ion pair. (*3*) Intermediate **19** exists in syn and anti forms, which are produced in different amounts and can hold their shapes, at least for a time. This is



syn-**16**



anti-**16**

plausible if we remember that a C=O canonical form contributes to the structure of **19**. (*4*) The combination of **19** and **18** is also a 1,3-dipolar cycloaddition, so configuration is retained in this step too.[378]

Evidence that the basic Criegee mechanism operates even in these cases comes from ^{18}O labeling experiments, making use of the fact, mentioned above, that mixed ozonides (e.g., **23**) can be isolated when an external aldehyde is added. Both the normal and modified Criegee mechanisms predict that if ^{18}O-labeled aldehyde is added to the ozonolysis mixture, the label will appear in the ether oxygen (see the reaction between **19** and **18**), and this is what is found.[379] There is evidence that the *anti*-**19** couples much more readily than the *syn*-**19**. [380]

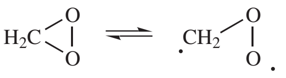
[377]Bauld, N.L.; Thompson, J.A.; Hudson, C.E.; Bailey, P.S. *J. Am. Chem. Soc.* ***1968***, *90*, 1822; Bailey, P.S.; Ferrell, T.M. *J. Am. Chem. Soc.* ***1978***, *100*, 899; Keul, H.; Kuczkowski, R.L. *J. Am. Chem. Soc.* ***1985***, *50*, 3371.

[378]For isotope-effect evidence that this step is concerted in some cases, see Choe, J.; Painter, M.K.; Kuczkowski, R.L. *J. Am. Chem. Soc.* ***1984***, *106*, 2891. However, there is evidence that it may not always be concerted: See, for example, Murray, R.W.; Su, J. *J. Org. Chem.* ***1983***, *48*, 817.

[379]Bishop, C.E.; Denson, D.D.; Story, P.R. *Tetrahedron Lett.* ***1968***, 5739; Fliszár, S.; Carles, J. *J. Am. Chem. Soc.* ***1969***, *91*, 2637; Gillies, C.W.; Kuczkowski, R.L. *J. Am. Chem. Soc.* ***1972***, *94*, 7609; Higley, D.P.; Murray, R.W. *J. Am. Chem. Soc.* ***1976***, *98*, 4526; Mazur, U.; Kuczkowski, R.L. *J. Org. Chem.* ***1979***, *44*, 3185.

[380]Mile, B.; Morris, G.M. *J. Chem. Soc. Chem. Commun.* ***1978***, 263.

The ozonolysis of ethylene[381] in the liquid phase (without a solvent) was shown to take place by the Criegee mechanism.[382] This reaction has been used to study the structure of the intermediate **19** or **20**. The compound dioxirane (**24**) was identified in the reaction mixture[383] at low temperatures and is probably in equilibrium with the biradical **20** (R = H). Dioxirane has been produced in solution, but it oxidatively cleaves dialkyl ethers (e.g., Et—O—Et) via a chain radical process, [384] so the choice of solvent is important.



24 **20** (R = H)

Ozonolysis in the gas phase is not generally carried out in the laboratory. However, the reaction is important because it takes place in the atmosphere and contributes to air pollution.[385] There is much evidence that the Criegee mechanism operates in the gas phase too, although the products are more complex because of other reactions that also take place.[386]

OS **V**, 489, 493; **VI**, 976; **VII**, 168; **IX**, 314. Also see OS **IV**, 554. For the preparation of ozone, see OS **III**, 673.

19-10 Oxidative Cleavage of Double Bonds and Aromatic Rings

Oxo-de-alkylidene-bisubstitution, and so on.

$$R_2C{=}CHR \xrightarrow{CrO_3} R_2C{=}O \ + \ RCOOH$$

Carbon–carbon double bonds can be cleaved by many oxidizing agents,[387] the most common of which are neutral or acid permanganate and acid dichromate. The

[381]For a discussion of intermediates in the formation of the ozonide in this reaction, see Samuni, U.; Fraenkel, R.; Haas, Y.; Fajgar, R.; Pola, J. *J. Am. Chem. Soc.* ***1996***, *118*, 3687.

[382]Fong, G.D.; Kuczkowski, R.L. *J. Am. Chem. Soc.* ***1980***, *102*, 4763.

[383]Suenram, R.D.; Lovas, F.J. *J. Am. Chem. Soc.* ***1978***, *100*, 5117. See, however, Ishiguro, K.; Hirano, Y.; Sawaki, Y. *J. Org. Chem.* ***1988***, *53*, 5397.

[384]Ferrer, M.; Sánchez-Baeza, F.; Casas, J.; Messeguer, A. *Tetrahedron Lett.* ***1994***, *35*, 2981.

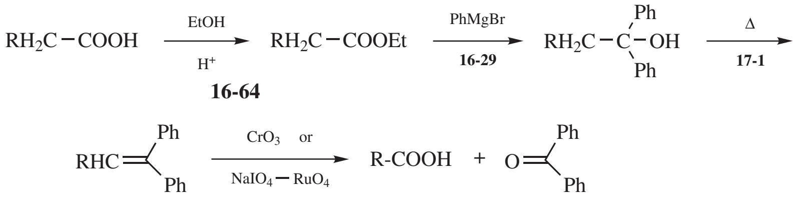
[385]For a review of the mechanisms of reactions of organic compounds with ozone in the gas phase, see Atkinson, R.; Carter, W.P.L. *Chem. Rev.* ***1984***, *84*, 437.

[386]See Atkinson, R.; Carter, W.P.L. *Chem. Rev.* ***1984***, *84*, 437, 452–454; Kühne, H.; Forster, M.; Hulliger, J.; Ruprecht, H.; Bauder, A.; Günthard, H. *Helv. Chim. Acta* ***1980***, *63*, 1971; Martinez, R.I.; Herron J.T. *J. Phys. Chem.* ***1988***, *92*, 4644.

[387]For a review of the oxidation of C=C and C=N bonds, see Henry, P.M.; Lange, G.L., in Patai, S. *The Chemistry of Functional Groups, Supplement A* pt. 1, Wiley, NY, ***1977***, pp. 965–1098. For a review of oxidative cleavages of C=C double bonds and aromatic rings, see Hudlický, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, pp. 77–84, 96–98. For reviews with respect to chromium reagents, see Badanyan, Sh.O.; Minasyan, T.T.; Vardapetyan, S.K. *Russ. Chem. Rev.* ***1987***, *56*, 740; Cainelli, G.; Cardillo, G. *Chromium Oxiations in Organic Chemistry*, Open Court Pub. Co., La Salle, IL, ***1981***, pp. 59–92. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, p. 1634.

products are generally 2 equivalents of ketone, 2 equivalents of carboxylic acid, or 1 equivalent of each, depending on what groups are attached to the alkene. With ordinary solutions of permanganate or dichromate yields are generally low, and the reaction is seldom a useful synthetic method; but high yields can be obtained by oxidizing with $KMnO_4$ dissolved in benzene containing the crown ether dicyclohexano-18-crown-6 (see p. 120).[388] The crown ether coordinates with K^+, permitting the $KMnO_4$ to dissolve in benzene. A mixture of aq. $KMnO_4$ and $NaIO_4$ on sand is also effective.[389] Another reagent frequently used for synthetic purposes is the *Lemieux–von Rudloff reagent*: HIO_4 containing a trace of MnO_4^-.[390] The MnO_4^- is the actual oxidizing agent, being reduced to the manganate stage, and the purpose of the HIO_4 is to reoxidize the manganate back to MnO_4^-. Another reagent that behaves similarly is $NaIO_4$–ruthenium tetroxide.[391] Cyclic alkenes are cleaved to α,ω-diketones, keto-acids or dicarboxylic acids. Cyclic alkenes are cleaved to dialdehydes with $KMnO_4$•$CuSO_4$ in dichloromethane.[392] Hydrogen peroxide on supported heteropolyacid cleaves cyclic alkenes.[393] A combination of $RuCl_3/HIO_5$ oxidatively cleaves cyclic alkenes to dicarboxylic acids.[394]

The *Barbier–Wieland procedure* for decreasing the length of a chain by one carbon involves oxidative cleavage by acid dichromate ($NaIO_4$–ruthenium tetroxide has also been used), but this is cleavage of a 1,1-diphenyl alkene, which generally gives good yields:



Addition of a catalytic amount of OsO_4 to Jones reagent (**19-3**) leads to good yields of the carboxylic acid from simple alkenes.[395] A combination of Oxone® and OsO_4 in DMF cleaves alkenes to carboxylic acids.[396] With certain reagents, the oxidation of double bonds can be stopped at the aldehyde stage, and in these cases the products are the same as in the ozonolysis procedure. Among these reagents are

[388]Sam, D.J.; Simmons, H.E. *J. Am. Chem. Soc.* ***1972***, *94*, 4024. See also, Lee, D.G.; Chang, V.S. *J. Org. Chem.* ***1978***, *43*, 1532.

[389]Huang, B.; Gupton, J.T.; Hansen, K.C.; Idoux, J.P. *Synth. Commun.* ***1996***, *26*, 165.

[390]Lemieux, R.U.; Rudloff, E. von *Can. J. Chem.* ***1955***, *33*, 1701, 1710; Rudloff, E. von *Can. J. Chem.* ***1955***, *33*, 1714; ***1956***, *34*, 1413; ***1965***, *43*, 1784.

[391]For a review, see Lee, D.G.; van den Engh, M., in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B, Academic Press, NY, ***1973***, pp. 186–192. For the use of $NaIO_4$–OsO_4, see Cainelli, G.; Contento, M.; Manescalchi, F.; Plessi, L. *Synthesis* ***1989***, 47.

[392]Göksu, S.; Altudda, R.; Sütbeyaz, Y. *Synth. Commun.* ***2000***, *30*, 1615.

[393]Brooks, C.D.; Huang, L.-c.; McCarron, M.; Johnstone, R.A.W. *Chem. Commun.* ***1999***, 37.

[394]Griffith, W.P.; Shoair, A.G.; Suriaatmaja, M. *Synth. Commun.* ***2000***, *30*, 3091.

[395]Henry, J.R.; Weinreb, S.M. *J. Org. Chem.* ***1993***, *58*, 4745.

[396]Travis, B.R.; Narayan, R.S.; Borhan, B. *J. Am. Chem. Soc.* ***2002***, *124*, 3824.

tert-butyl iodoxybenzene,[397] $KMnO_4$ in THF–H_2O,[398] and $NaIO_4$–OsO_4.[399] Electrolysis with $LiClO_4$ in aqueous acetonitrile also cleaves alkenes to give the aldehyde.[400] Enol ethers, RC(OR′)=CH_2, have been cleaved to carboxylic esters, RC(OR′)=O, by atmospheric oxygen.[401]

Cleavage of alkynes is generally rather difficult, but treatment of internal alkynes with an excess of Oxone® with a ruthenium catalyst leads to aliphatic carboxylic acids.[402]

The mechanism of oxidation probably involves in most cases the initial formation of a glycol (**15-29**) or cyclic ester,[403] and then further oxidation as in **19-7**.[404] In line with the electrophilic attack on the alkene, triple bonds are more resistant to oxidation than double bonds. Terminal triple-bond compounds can be cleaved to carboxylic acids ($RC{\equiv}CH \longrightarrow RCOOH$) with thallium(III) nitrate[405] or with [bis-(trifluoroacetoxy)iodo]pentafluorobenzene [i.e., $C_6F_5I(OCOCF_3)_2$],[406] among other reagents.

Aromatic rings can be cleaved with strong enough oxidizing agents. An important laboratory reagent for this purpose is ruthenium tetroxide along with a co-oxidant, such as $NaIO_4$ or NaOCl (household bleach can be used).[407] Examples[408] are the oxidation of naphthalene to phthalic acid[409] and, even more remarkably, of cyclohexylbenzene to cyclohexanecarboxylic acid[410] (note the contrast with **19-11**). The latter conversion was also accomplished with ozone.[411] Another reagent that oxidizes aromatic rings is air catalyzed by V_2O_5. The oxidations of naphthalene to phthalic anhydride and of benzene to maleic anhydride by this reagent are

[397]Ranganathan, S.; Ranganathan, D.; Singh, S.K. *Tetrahedron Lett.* ***1985***, *26*, 4955.

[398]Viski, P.; Szeverényi, Z.; Simándi, L.I. *J. Org. Chem.* ***1986***, *51*, 3213.

[399]Pappo, R.; Allen Jr., D.S.; Lemieux, R.U.; Johnson, W.S. *J. Org. Chem.* ***1956***, *21*, 478.

[400]Maki, S.; Niwa, H.; Hirano, T. *Synlett* ***1997***, 1385.

[401]Taylor, R. *J. Chem. Res. (S)* ***1987***, 178. For a similar oxidation with RuO4, see Torii, S.; Inokuchi, T.; Kondo, K. *J. Org. Chem.* ***1985***, *50*, 4980.

[402]Yang, D.; Chen, F.; Dong, Z.-M.; Zhang, D.-W. *J. Org. Chem.* ***2004***, *69*, 2221.

[403]See, for example, Lee, D.G.; Spitzer, U.A. *J. Org. Chem.* ***1976***, *41*, 3644; Lee, D.G.; Chang, V.S.; Helliwell, S. *J. Org. Chem.* ***1976***, *41*, 3644, 3646.

[404]There is evidence that oxidation with Cr(VI) in aqueous acetic acid involves an epoxide intermediate: Roč ek, J.; Drozd, J.C. *J. Am. Chem. Soc.* ***1970***, *92*, 6668.

[405]McKillop, A.; Oldenziel, O.H.; Swann, B.P.; Taylor, E.C.; Robey, R.L. *J. Am. Chem. Soc.* ***1973***, *95*, 1296.

[406]Moriarty, R.M.; Penmasta, R.; Awasthi, A.K.; Prakash, I. *J. Org. Chem.* ***1988***, *53*, 6124.

[407]Ruthenium tetroxide is an expensive reagent, but the cost can be greatly reduced by the use of an inexpensive cooxidant, such as NaOCl, the function of which is to oxidize RuO2 back to ruthenium tetroxide.

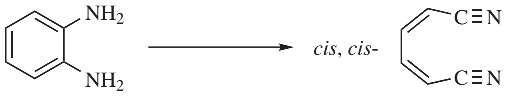
[408]For other examples, see Piatak, D.M.; Herbst, G.; Wicha, J.; Caspi, E. *J. Org. Chem.* ***1969***, *34*, 116; Wolfe, S.; Hasan, S.K.; Campbell, J.R. *Chem. Commun.* ***1970***, 1420; Ayres, D.C.; Hossain, A.M.M. *Chem. Commun.* ***1972***, 428; Nuñez, M.T.; Martín, V.S. *J. Org. Chem.* ***1990***, *55*, 1928.

[409]Spitzer, U.A.; Lee, D.G. *J. Org. Chem.* ***1974***, *39*, 2468.

[410]Caputo, J.A.; Fuchs, R. *Tetrahedron Lett.* ***1967***, 4729.

[411]Klein, H.; Steinmetz, A. *Tetrahedron Lett.* ***1975***, 4249. For other reagents that convert an aromatic ring to COOH and leave alkyl groups untouched, see Deno, N.C.; Greigger, B.A.; Messer, L.A.; Meyer, M.D.; Stroud, S.G. *Tetrahedron Lett.* ***1977***, 1703; Liotta, R.; Hoff, W.S. *J. Org. Chem.* ***1980***, *45*, 2887; Chakraborti, A.K.; Ghatak, U.R. *J. Chem. Soc. Perkin Trans. 1* ***1985***, 2605.

important industrial procedures.[412] *o*-Diamines have been oxidized with nickel peroxide, with lead tetraacetate,[413] and with O_2 catalyzed by CuCl:[414]



The last-named reagent also cleaves *o*-dihydroxybenzenes (catechols) to give, in the presence of MeOH, the mono-methylated dicarboxylic acids .[415]

$$\mathrm{HOOC{-}C{=}C{-}C{=}C{-}COOMe}$$

Enamines ($R'_2C{=}NR_2$) are oxidatively cleaved with potassium dichromate in sulfuric acid to the ketone ($R'_2C{=}O$).[416]

OS **II**, 53, 523; **III**, 39, 234, 449; **IV**, 136, 484, 824; **V**, 393; **VI**, 662, 690; **VII**, 397; **VIII**, 377, 490; **IX**, 530. Also see, OS **II**, 551.

19-11 Oxidation of Aromatic Side Chains

Oxo,hydroxy-de-dihydro,methyl-tersubstitution

$$\mathrm{ArR} \xrightarrow{\mathrm{KMnO_4}} \mathrm{ArCOOH}$$

Alkyl chains on aromatic rings can be oxidized to COOH groups by many oxidizing agents, including permanganate, nitric acid, and acid dichromate.[417] The method is most often applied to the methyl group, although longer side chains can also be cleaved. However, tertiary alkyl groups are resistant to oxidation, and when they *are* oxidized, ring cleavage usually occurs too.[418] It is usually difficult to oxidize an R group on a fused aromatic system without cleaving the ring or oxidizing it to a quinone (**19-19**). However, this has been done (e.g., 2-methylnaphthalene was converted to 2-naphthoic acid) with aqueous $Na_2Cr_2O_7$.[419] Aryl methyl groups are oxidized to aryl COOH with NaOCl in acetonitrile,[420] or with NBS in aq. NaOH under photochemical conditions.[421] Functional groups can be present anywhere on the side chain and, if in the α position, greatly increase the ease of oxidation. An exception is an a phenyl group. In such cases, the reaction stops at the diaryl ketone stage. Molecules containing aryl groups on different carbons cleave so that each

[412]For a review, see Pyatnitskii, Yu.I. *Russ. Chem. Rev.* ***1976***, *45*, 762.

[413]Nakagawa, K.; Onoue, H. *Tetrahedron Lett.* ***1965***, 1433; *Chem. Commun.* ***1966***, 396.

[414]Kajimoto, T.; Takahashi, H.; Tsuji, J. *J. Org. Chem.* ***1976***, *41*, 1389.

[415]Tsuji, J.; Takayanag, H.i *Tetrahedron* ***1978***, *34*, 641; Bankston, D. *Org. Synth. 66*, 180.

[416]Harris, C.E.; Lee, L.Y.; Dorr, H.; Singaram, B. *Tetrahedron Lett.* ***1995***, *36*, 2921.

[417]For many examples, see Hudlický, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, pp. 105-109; Lee, D.G. *The Oxidation of Organic Compounds by Permanganate Ion and Hexavalent Chromium*, Open-Court Pub. Co., La Salle, IL, ***1980***, pp. 43–64. For a review with chromium oxidizing agents, see Cainelli, G.; Cardillo, G. *Chromium Oxidations in Organic Chemistry*, Open Court Publishing Co., La Salle, IL, ***1981***, pp. 23–33.

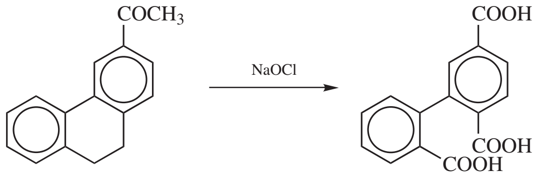
[418]Brandenberger, S.G.; Maas, L.W.; Dvoretzky, I. *J. Am. Chem. Soc.* ***1961***, *83*, 2146.

[419]Friedman, L.; Fishel, D.L.; Shechter, H. *J. Org. Chem.* ***1965***, *30*, 1453.

[420]Yamazaki, S. *Synth. Commun.* ***1999***, *29*, 2211.

[421]Itoh, A.; Kodama, T.; Hashimoto, S.; Masaki, Y. *Synthesis* ***2003***, 2289.

ring gets one carbon atom, as in the clevvage of the 9,10-bond of dihydrophenanthrenes **25** to **26**.



25 **26**

It is possible to oxidize only one alkyl group of a ring that contains more than one. The order of reactivity[422] toward most reagents is $CH_2Ar > CHR_2 > CH_2R > CH_3$.[423] Groups on the ring susceptible to oxidation (OH, NHR, NH_2, etc.) must be protected. The oxidation can be performed with oxygen, in which case it is autoxidation, and the mechanism is like that in **14-7**, with a hydroperoxide intermediate. With this procedure it is possible to isolate ketones from $ArCH_2R$, and this is often done.[424]

The mechanism has been studied for the closely related reaction: $Ar_2CH_2 + CrO_3 \rightarrow Ar_2C{=}O$.[425] A deuterium isotope effect of 6.4 was found, indicating that the rate-determining step is either $Ar_2CH_2 \rightarrow Ar_2CH\bullet$ or $Ar_2CH_2 \rightarrow Ar_2CH^+$. Either way this explains why tertiary groups are not converted to COOH and why the reactivity order is $CHR_2 > CH_2R > CH_3$, as mentioned above. Both free radicals and carbocations exhibit this order of stability (Chapter 5). The two possibilities are examples of categories 2 and 3 (p. 1706). Just how the radical or the cation goes on to the product is not known.

When the alkyl group is one oxidizable to COOH (**19-11**), cupric salts are oxidizing agents, and the OH group is found in a position ortho to that occupied by the alkyl group.[426] This reaction is used industrially to convert toluene to phenol.

In another kind of reaction, an aromatic aldehyde ArCHO or ketone ArCOR′ is converted to a phenol ArOH on treatment with alkaline H_2O_2,[427] but there must be an OH or NH_2 group in the ortho or para position. This is called the *Dakin reaction*.[428] The mechanism may be similar to that of the Baeyer–Villiger reaction (**18-19**):[429]

[422]Oxidation with Co(III) is an exception. The methyl group is oxidized in preference to the other alkyl groups: Onopchenko, A.; Schulz, J.G.D.; Seekircher, R. *J. Org. Chem.* ***1972***, *37*, 1414.

[423]For example, see Foster, G.; Hickinbottom, W.J. *J. Chem. Soc.* ***1960***, 680; Ferguson, L.N.; Wims, A.I. *J. Org. Chem.* ***1960***, *25*, 668.

[424]For a review, see Pines, H.; Stalick, W.M. *Base-Catalyzed Reactions of Hydrocarbons and Related Compounds*, Academic Press, NY, ***1977***, pp. 508–543.

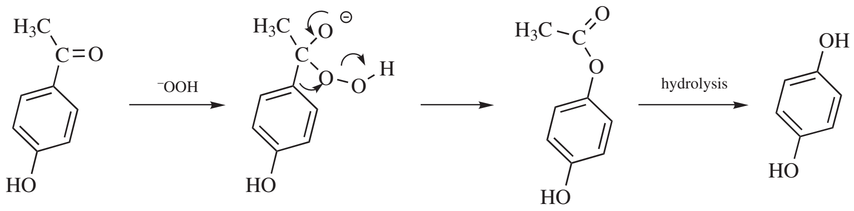
[425]Wiberg, K.B.; Evans, R.J. *Tetrahedron* ***1960***, *8*, 313.

[426]Kaeding, W.W. *J. Org. Chem.* ***1961***, *26*, 3144. For a discussion, see Lee, D.G.; van den Engh, M., in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B, Academic Press, NY, ***1973***, pp. 91–94.

[427]For a convenient procedure, see Hocking, M.B. *Can. J. Chem.* ***1973***, *51*, 2384.

[428]See Schubert, W.M.; Kintner, R.R., in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 749–752.

[429]For a discussion, see Hocking, M.B.; Bhandari, K.; Shell, B.; Smyth, T.A. *J. Org. Chem.* ***1982***, *47*, 4208.



27

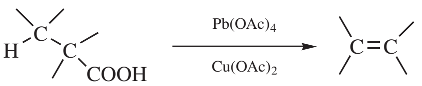
The intermediate **27** has been isolated.[430] The reaction has been performed on aromatic aldehydes with an alkoxy group in the ring, and no OH or NH_2. In this case, acidic H_2O_2 was used.[431] The Dakin reaction has been done in ionic liquids.[432]

OS **I**, 159, 385, 392, 543; **II**, 135, 428; **III**, 334, 420, 740, 791, 820, 822; **V**, 617, 810. Also see, OS **I**, 149; **III**, 759.

19-12 Oxidative Decarboxylation
Acetoxy-de-carboxy-substitution

$$\text{RCOOH} \xrightarrow{\text{Pb(OAc)}_4} \text{ROAc}$$

Hydro-carboxyl-elimination



Carboxylic acids can be decarboxylated[433] with lead tetraacetate to give a variety of products, among them the ester ROAc (formed by replacement of COOH by an acetoxy group), the alkane RH (see **12-40**), and, if α,β hydrogen is present, the alkene formed by elimination of H and COOH, as well as numerous other products arising from rearrangements, internal cyclizations,[434] and reactions with solvent molecules. When R is tertiary, the chief product is usually the alkene, which is often obtained in good yield. High yields of alkenes can also be obtained when R is primary or secondary, in this case by the use of $Cu(OAc)_2$ along with the $Pb(OAc)_4$.[435] In the absence of $Cu(OAc)_2$, primary acids give mostly alkanes (though yields are

[430]Hocking, M.B.; Ko, M.; Smyth, T.A. *Can. J. Chem.* ***1978***, *56*, 2646.

[431]Matsumoto, M.; Kobayashi, H.; Hotta, Y. *J. Org. Chem.* ***1984***, *49*, 4740.

[432]In bmim PF6, 1-butyl-3-methylimidazolium hexafluorophosphate: Zambrano, J.L.; Dorta, R. *Synlett* ***2003***, 1545.

[433]For reviews, see Serguchev, Yu.A.; Beletskaya, I.P. *Russ. Chem. Rev.* ***1980***, *49*, 1119; Sheldon, R.A.; Kochi, J.K. *Org. React.* ***1972***, *19*, 279.

[434]For examples, see Moriarty, R.M.; Walsh, H.G.; Gopal, H. *Tetrahedron Lett.* ***1966***, 4363; Davies, D.I.; Waring, C. *J. Chem. Soc. C* ***1968***, 1865, 2337.

[435]Bacha, J.D.; Kochi, J.K. *Tetrahedron* ***1968***, *24*, 2215; Ogibin, Yu.N.; Katzin, M.I.; Nikishin, G.I. *Synthesis* ***1974***, 889.

generally low) and secondary acids may give carboxylic esters or alkenes. Carboxylic esters have been obtained in good yields from some secondary acids, from β,γ-unsaturated acids, and from acids in which R is a benzylic group. Other oxidizing agents,[436] including Co(III), Ag(II), Mn(III), and Ce(IV), have also been used to effect oxidative decarboxylation.[437]

The mechanism with lead tetraacetate is generally accepted to be of the free-radical type.[438] First, there is an interchange of ester groups:

$$Pb(OAc)_4 + RCOOH \longrightarrow \underset{\textbf{28}}{Rb(OAc)_3OCOR} \quad \text{or} \quad \underset{\textbf{29}}{Pb(OAc)_2(OCOR)_2}$$

There follows a free-radical chain mechanism (shown for **28** although **29** and other lead esters can behave similarly)

$$\underset{\textbf{23}}{Pb(OAc)_3OCOR} \longrightarrow \bullet Pb(OAc)_3 + R\bullet + CO_2$$

Initiation

$$R\bullet + Pb(OAc)_3OCOR \longrightarrow R^+ + \bullet Pb(OAc)_2OCOR + OAc^-$$

$$\bullet Pb(OAc)_2OCOR \longrightarrow Pb(OAc)_2 + R\bullet + CO_2$$

Propagation

Products can then be formed either from R• or R^+. Primary R• abstract H from solvent molecules to give RH. R^+ can lose H^+ to give an alkene, react with HOAc to give the carboxylic ester, react with solvent molecules or with another functional group in the same molecule, or rearrange, thus accounting for the large number of possible products. The R• group can also dimerize to give RR. The effect of Cu^{2+} ions[439] is to oxidize the radicals to alkenes, thus producing good yields of alkenes from primary and secondary substrates. The Cu^{2+} ion has no effect on tertiary radicals, because these are efficiently oxidized to alkenes by lead tetraacetate.

$$H{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}\bullet + Cu^{2+} \longrightarrow >C{=}C< + H^+ + Cu^+$$

[436]For references, see Trahanovsky, W.S.; Cramer, J.; Brixius, D.W. *J. Am. Chem. Soc.* ***1974***, *96*, 1077; Kochi, J.K. *Organometallic Mechanisms and Catalysis*, Academic Press, NY, ***1978***, pp. 99–106. See also, Dessau, R.M.; Heiba, E.I. *J. Org. Chem.* ***1975***, *40*, 3647; Fristad, W.E.; Fry, M.A.; Klang, J.A. *J. Org. Chem.* ***1983***, *48*, 3575; Barton, D.H.R.; Crich, D.; Motherwell, W.B. *J. Chem. Soc. Chem. Commun.* ***1984***, 242; Toussaint, O.; Capdevielle, P.; Maumy, M. *Tetrahedron Lett.* ***1984***, *25*, 3819.

[437]For another method, see Barton, D.H.R.; Bridon, D.; Zard, S.Z. *Tetrahedron* ***1989***, *45*, 2615.

[438]Starnes, Jr., W.H. *J. Am. Chem. Soc.* ***1964***, *86*, 5603; Davies, D.I.; Waring, C. *Chem. Commun.* ***1965***, 263; Kochi, J.K.; Bacha, J.D.; Bethea III, T.W. *J. Am. Chem. Soc.* ***1967***, *89*, 6538; Cantello, B.C.C.; Mellor, J.M.; Scholes, G. *J. Chem. Soc. Perkin Trans. 2*, ***1974***, 348; Beckwith, A.L.J.; Cross, R.T.; Gream, G.E. *Aust. J. Chem.* ***1974***, *27*, 1673, 1693.

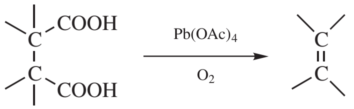
[439]Bacha, J.D.; Kochi, J.K. *J. Org. Chem.* ***1968***, *33*, 83; Kochi, J.K.; Bacha, J.D. *J. Org. Chem.* ***1968***, *33*, 2746; Torssell, K. *Ark. Kemi*, ***1970***, *31*, 401.

In another type of oxidative decarboxylation, arylacetic acids can be oxidized to aldehydes with one less carbon ($ArCH_2COOH \rightarrow ArCHO$) by tetrabutylammonium periodate.[440] Simple aliphatic carboxylic acids were converted to nitriles with one less carbon ($RCH_2COOH \rightarrow RC{\equiv}N$) by treatment with trifluoroacetic anhydride and $NaNO_2$ in F_3CCOOH.[441]

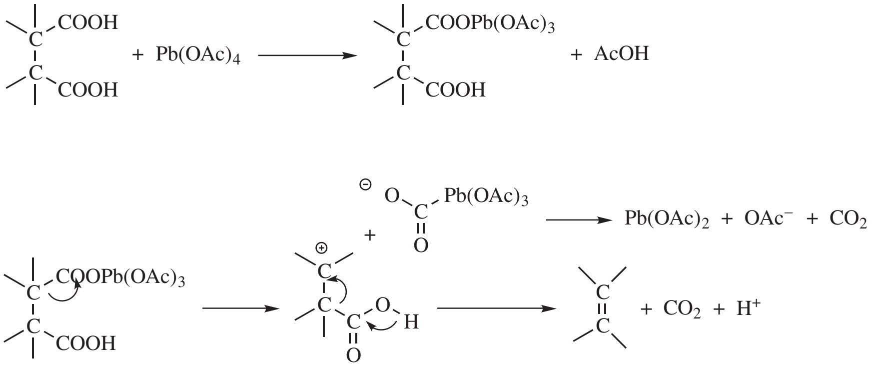
See also, **14-37**.

19-13 Bisdecarboxylation

Dicarboxy-elimination



Compounds containing carboxyl groups on adjacent carbons (succinic acid derivatives) can be bisdecarboxylated with lead tetraacetate in the presence of O_2.[433] The reaction is of wide scope. The elimination is stereoselective, but not stereospecific (both *meso*- and *dl*-2,3-diphenylsuccinic acid gave *trans*-stilbene);[442] a concerted mechanism is thus unlikely. The following mechanism is not inconsistent with the data:



though a free-radical mechanism seems to hold in some cases. Bis(decarboxylation) of succinic acid derivatives to give alkenes[443] has also been carried out by other methods, including treatment of the corresponding anhydrides with nickel, iron,

[440]Santaniello, E.; Ponti, F.; Manzocchi, A. *Tetrahedron Lett.* ***1980***, *21*, 2655. For other methods of accomplishing this and similar conversions, see Cohen, H.; Song, I.H.; Fager, J.H.; Deets, G.L. *J. Am. Chem. Soc.* ***1967***, *89*, 4968; Wasserman, H.H.; Lipshutz, B.H. *Tetrahedron Lett.* ***1975***, 4611; Kaberia, F.; Vickery, B. *J. Chem. Soc. Chem. Commun.* ***1978***, 459; Doleschall, G.; Tóth, G. *Tetrahedron* ***1980***, *36*, 1649.

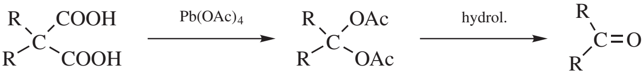
[441]Smushkevich, Yu.I.; Usorov, M.I.; Suvorov, N.N. *J. Org. Chem. USSR* ***1975***, *11*, 653.

[442]Corey, E.J.; Casanova, J. *J. Am. Chem. Soc.* ***1963***, *85*, 165.

[443]For a review, see De Lucchi, O.; Modena, G. *Tetrahedron* ***1984***, *40*, 2585, 2591–2608.

or rhodium complexes,[444] by decomposition of the corresponding bis(peroxyesters),[445] and electrolytically.[446]

Compounds containing geminal carboxyl groups (disubstituted malonic acid derivatives) can also be bisdecarboxylated with lead tetraacetate,[447] *gem*-diacetates (acylals) being produced, which are easily hydrolyzable to ketones:[448]



A related reaction involves α-substituted aryl nitriles having a sufficiently acidic α hydrogen, which can be converted to ketones by oxidation with air under phase transfer conditions.[449] The nitrile is added to NaOH in benzene or DMSO containing a catalytic amount of triethylbenzylammonium chloride (TEBA).[450] This reaction could not be applied to aliphatic nitriles, but an indirect method for achieving this conversion is given in **19-60**. α-Dialkylamino nitriles can be converted to ketones, $R_2C(NMe_2)CN \rightarrow R_2C{=}O$, by hydrolysis with $CuSO_4$ in aqueous methanol[451] or by autoxidation in the presence of *t*-BuOK.[452]

C. Reactions Involving Replacement of Hydrogen by Heteroatoms

19-14 Hydroxylation at an Aliphatic Carbon

Hydroxylation or **Hydroxy-de-hydrogenation**

$$R_3CH \xrightarrow[\text{silica gel}]{O_3} R_3COH$$

Compounds containing susceptible C—H bonds can be oxidized to alcohols.[453] Nearly always, the C—H bond involved is tertiary, so the product is a tertiary alcohol. This is partly because tertiary C—H bonds are more susceptible to free-radical attack than primary and secondary bonds and partly because the reagents involved

444Trost, B.M.; Chen, E.N. *Tetrahedron Lett.* ***1971***, 2603.

445Cain, E.N.; Vukov, R.; Masamune, S. *Chem. Commun.* ***1969***, 98.

446Plieninger, H.; Lehnert, W. *Chem. Ber.* ***1967***, *100*, 2427; Radlick, P.; Klem, R.; Spurlock, S.; Sims, J.J.; van Tamelen, E.E.; Whitesides, T. *Tetrahedron Lett.* ***1968***, 5117; Westberg, H.H.; Dauben Jr., H.J. *Tetrahedron Lett.* ***1968***, 5123. For additional references, see Fry, A.J. *Synthetic Organic Electrochemistry*, 2nd ed., Wiley, NY, ***1989***, pp. 253–254.

447For a similar reaction with ceric ammonium nitrate, see Salomon, R.G.; Roy, S.; Salomon, R.G. *Tetrahedron Lett.* ***1988***, *29*, 769.

448Tufariello, J.J.; Kissel, W.J. *Tetrahedron Lett.* ***1966***, 6145.

449For other methods of achieving this conversion, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, p. 1260.

450Masuyama, Y.; Ueno, Y.; Okawara, M. *Chem. Lett.* ***1977***, 1439; Donetti, A.; Boniardi, O.; Ezhaya, A. *Synthesis* ***1980***, 1009; Kulp, S.S.; McGee, M.J. *J. Org. Chem.* ***1983***, *48*, 4097.

451Büchi, G.; Liang, P.H.; Wüest, H. *Tetrahedron Lett.* ***1978***, 2763.

452Chuang, T.; Yang, C.; Chang, C.; Fang, J. *Synlett* ***1990***, 733.

453For reviews, see Chinn, L.J. *Selection of Oxidants in Synthesis*, Marcel Dekker, NY, ***1971***, pp. 7–11; Lee, D.G., in Augustine, R.L. *Oxidation*, Vol. 1, Marcel Dekker, NY, ***1969***, pp. 2–6. For a monograph on all types of alkane activation, see Hill, C.L. *Activation and Functionalization of Alkanes*, Wiley, NY, ***1989***.

would oxidize primary and secondary alcohols further. In the best method, the reagent is ozone and the substrate is absorbed on silica gel.[454] Yields as high as 99% have been obtained by this method. Other reagents are chromic acid,[455] potassium hydrogen persulfate ($KHSO_5$),[456] ruthenium tetroxide (RuO_4),[457] 2,6-dichloropyridine *N*-oxide with a ruthenium catalyst,[458] thallium acetate,[459] sodium chlorite ($NaClO_2$) with a metalloporphyrin catalyst,[460] and certain peroxybenzoic acids.[461] Alkanes and cycloalkanes have been oxidized at secondary positions, to a mixture of alcohols and trifluoroacetates, by 30% aq. H_2O_2 in trifluoroacetic acid.[462] This reagent does not oxidize the alcohols further and ketones are not found. As in the case of chlorination with *N*-haloamines and sulfuric acid (see **14-1**), the ω - 1 position is the most favored. Another reagent[463] that oxidizes secondary positions is iodosylbenzene, catalyzed by Fe^{III}–porphyrin catalysts.[464] Use of an optically active Fe^{III}–porphyrin gave enantioselective hydroxylation, with moderate ee.[465]

When chromic acid is the reagent, the mechanism is probably as follows: a Cr^{6+} species abstracts a hydrogen to give R_3C•, which is held in a solvent cage near the resulting Cr^{5+} species. The two species then combine to give R_3COCr^{4+}, which is hydrolyzed to the alcohol. This mechanism predicts retention of configuration; this is largely observed.[466] The oxidation by permanganate also involves predominant retention of configuration, and a similar mechanism has been proposed.[467]

Treatment of double-bond compounds with selenium dioxide introduces an OH group into the allylic position (see also, **19-17**).[468] This reaction also produces conjugated aldehydes in some cases.[469] Allylic rearrangements are common. There is

[454]Cohen, Z.; Keinan, E.; Mazur, Y.; Varkony, T.H. *J. Org. Chem.* ***1975***, *40*, 2141; *Org. Synth.* ***VI***, 43; Keinan, E.; Mazur, Y. *Synthesis* ***1976***, 523; McKillop, A.; Young, D.W. *Synthesis* ***1979***, 401, see pp. 418–419.

[455]For a review, see Cainelli, G.; Cardillo, G. *Chromium Oxidations in Organic Chemistry*, Springer, NY, ***1984***, pp. 8–23.

[456]De Poorter, B.; Ricci, M.; Meunier, B. *Tetrahedron Lett.* ***1985***, *26*, 4459.

[457]Tenaglia, A.; Terranova, E.; Waegell, B. *Tetrahedron Lett.* ***1989***, *30*, 5271; Bakke, J.M.; Braenden, J.E. *Acta Chem. Scand.* ***1991***, *45*, 418.

[458]Ohtake, H.; Higuchi, T.; Hirobe, M. *J. Am. Chem. Soc.* ***1992***, *114*, 10660.

[459]Lee, J.C.; Park, C.; Choi, Y. *Synth. Commun.* ***1997***, *27*, 4079.

[460]Collman, J.P.; Tanaka, H.; Hembre, R.T.; Brauman, J.I. *J. Am. Chem. Soc.* ***1990***, *112*, 3689.

[461]Schneider, H.; Müller, W. *Angew. Chem. Int. Ed.* ***1982***, *21*, 146; *J. Org. Chem.* ***1985***, *50*, 4609; Takaishi, N.; Fujikura, Y.; Inamoto, Y. *Synthesis* ***1983***, 293; Tori, M.; Sono, M.; Asakawa, Y. *Bull. Chem. Soc. Jpn.* ***1985***, *58*, 2669. See also, Querci, C.; Ricci, M. *Tetrahedron Lett.* ***1990***, *31*, 1779.

[462]Deno, N.C.; Jedziniak, E.J.; Messer, L.A.; Meyer, M.D.; Stroud, S.G.; Tomezsko, E.S. *Tetrahedron* ***1977***, *33*, 2503.

[463]For other procedures, see Sharma, S.N.; Sonawane, H.R.; Dev, S. *Tetrahedron* ***1985***, *41*, 2483; Nam, W.; Valentine, J.S. *New J. Chem.* ***1989***, *13*, 677.

[464]See Groves, J.T.; Nemo, T.E. *J. Am. Chem. Soc.* ***1983***, *105*, 6243.

[465]Groves, J.T.; Viski, P. *J. Org. Chem.* ***1990***, *55*, 3628.

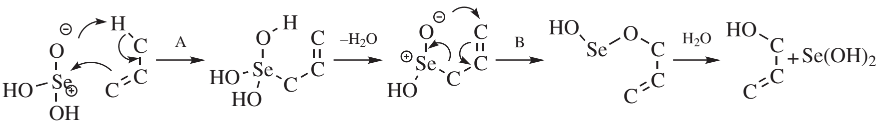
[466]Wiberg, K.B.; Eisenthal, R. *Tetrahedron* ***1964***, *20*, 1151.

[467]Wiberg, K.B.; Fox, A.S. *J. Am. Chem. Soc.* ***1963***, *85*, 3487; Brauman, J.I.; Pandell, A.J. *J. Am. Chem. Soc.* ***1970***, *92*, 329; Stewart, R.; Spitzer, U.A. *Can. J. Chem.* ***1978***, *56*, 1273.

[468]For reviews, see Rabjohn, N. *Org. React.* ***1976***, *24*, 261; Jerussi, R.A. *Sel. Org. Transform.* ***1970***, *1*, 301; Trachtenberg, E.N., in Augustine, R.L. *Oxidation*, Vol. 1, Marcel Dekker, NY, ***1969***, pp. 123–153.

[469]Singh, J.; Sharma, M.; Kad, G.L.; Chhabra, B.R. *J. Chem. Res. (S)* ***1997***, 264.

evidence that the mechanism does not involve free radicals, but includes two pericyclic steps (A and B):[470]



The step marked A is similar to the ene synthesis (**15-23**). The step marked B is a [2,3]-sigmatropic rearrangement (see **18-35**). The reaction can also be accomplished with *tert*-butyl hydroperoxide, if SeO_2 is present in catalytic amounts (the *Sharpless method*).[471] The SeO_2 is the actual reagent; the peroxide reoxidizes the $Se(OH)_2$.[472] This method makes work-up easier, but gives significant amounts of side products when the double bond is in a ring.[473] Alkynes generally give α,α'-dihydroxylation.[474]

Ketones and carboxylic esters can be α hydroxylated by treatment of their enolate forms (prepared by adding the ketone or ester to LDA) with a molybdenum peroxide reagent (MoO_5–pyridine–HMPA) in THF–hexane at −70°C.[475] The reaction of ketones with Ti(O*i*Pr)$_4$, diethyl tartrate and *tert*-butylhydroperoxide gave the α-hydroxy ketone with good enantioselectively, albeit in low yield.[476] The enolate forms of amides and esters[477] and the enamine derivatives of ketones[478] can similarly be converted to their α hydroxy derivatives by reaction with molecular oxygen. The MoO_5 method can also be applied to certain nitriles.[479] Ketones have also been α hydroxylated by treating the corresponding silyl enol ethers

[470]Arigoni, D.; Vasella, A.; Sharpless, K.B.; Jensen, H.P. *J. Am. Chem. Soc.* ***1973***, *95*, 7917; Woggon, W.; Ruther, F.; Egli, H. *J. Chem. Soc. Chem. Commun.* ***1980***, 706. For other mechanistic proposals, see Schaefer, J.P.; Horvath, B.; Klein, H.P. *J. Org. Chem.* ***1968***, *33*, 2647; Trachtenberg, E.N.; Nelson, C.H.; Carver, J.R. *J. Org. Chem.* ***1970***, *35*, 1653; Bhalerao, U.T.; Rapoport, H. *J. Am. Chem. Soc.* ***1971***, *93*, 4835; Stephenson, L.M.; Speth, D.R. *J. Org. Chem.* ***1979***, *44*, 4683.

[471]Umbreit, M.A.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1977***, *99*, 5526. See also, Uemura, S.; Fukuzawa, S.; Toshimitsu, A.; Okano, M. *Tetrahedron Lett.* ***1982***, *23*, 87; Singh, J.; Sabharwal, A.; Sayal, P.K.; Chhabra, B.R. *Chem. Ind. (London)* ***1989***, 533.

[472]For the use of the peroxide with O2 instead of SeO2, see Sabol, M.R.; Wiglesworth, C.; Watt, D.S. *Synth. Commun.* ***1988***, *18*, 1.

[473]Warpehoski, M.A.; Chabaud, B.; Sharpless, K.B. *J. Org. Chem.* ***1982***, *47*, 2897.

[474]Chabaud, B.; Sharpless, K.B. *J. Org. Chem.* ***1979***, *44*, 4202.

[475]Vedejs, E.; Telschow, J.E. *J. Org. Chem.* ***1976***, *41*, 740; Vedejs, E.; Larsen, S. *Org. Synth.* ***VII***, 277; Gamboni, R.; Tamm, C. *Tetrahedron Lett.* ***1986***, *27*, 3999; *Helv. Chim. Acta* ***1986***, *69*, 615. See also, Anderson, J.C.; Smith, S.C. *Synlett* ***1990***, 107; Hara, O.; Takizawa, J.-i.; Yamatake, T.; Makino, K.; Hamada, Y. *Tetrahedron Lett.* ***1999***, *40*, 7787.

[476]Paju, A.; Kanger, T.; Pehk, T.; Lopp, M. *Tetrahedron* ***2002***, *58*, 7321.

[477]Wasserman, H.H.; Lipshutz, B.H. *Tetrahedron Lett.* ***1975***, 1731. For another method, see Pohmakotr, M.; Winotai, C. *Synth. Commun.* ***1988***, *18*, 2141.

[478]Cuvigny, T.; Valette, G.; Larcheveque, M.; Normant, H. *J. Organomet. Chem.* ***1978***, *155*, 147.

[479]Rubottom, G.M.; Gruber, J.M. *J. Org. Chem.* ***1978***, *43*, 1599; Hassner, A.; Reuss, R.H.; Pinnick, H.W. *J. Org. Chem.* ***1975***, *40*, 3427; Andriamialisoa, R.Z.; Langlois, N.; Langlois, Y. *Tetrahedron Lett.* ***1985***, *26*, 3563; Rubottom, G.M.; Gruber, J.M.; Juve, Jr., H.D.; Charleson, D.A. *Org. Synth.* ***VII***, 282. See also, Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* ***1989***, *30*, 3323.

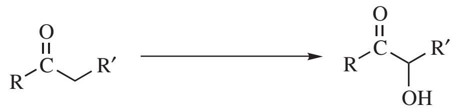
with *m*-chloroperoxybenzoic acid,[179] or with certain other oxidizing agents.[480] When the silyl enol ethers are treated with iodosobenzene in the presence of trimethylsilyl trifluoromethyl sulfonate, the product is the α-keto triflate.[481]

Tetrahydrofuran was converted to the hemiacetal 2-hydroxytetrahydrofuran (which was relatively stable under the conditions used) by electrolysis in water.[482]

OS **IV**, 23; **VI**, 43, 946; **VII**, 263, 277, 282.

19-15 Oxidation of Methylene to OH, O_2CR, or OR

Hydroxy (or alkoxy) -de-dihydro-bisubstitution



Methyl or methylene groups α to a carbonyl can be oxidized to give α-hydroxy ketones, aldehydes, or carboxylic acid derivatives. Ketones can be α hydroxylated in good yields, without conversion to the enolates, by treatment with the hypervalent iodine reagents[483] *o*-iodosobenzoic acid[484] or phenyliodoso acetate, $PhI(OAc)_2$, in methanolic NaOH.[485] The latter reagent has also been used on carboxylic esters.[486] Dioxygen (O_2) and a chiral phase-transfer catalyst gave enantioselective α-hydroxylation of ketones, if the α position was tertiary.[487] Dimethyl dioxirane is quite effective for hydroxylation of 1,3-dicarbonyl compounds,[488] and O_2 with a manganese catalyst also gives hydroxylation of such compounds.[489] Oxygen with a cerium catalyst α-hydroxylates β-keto esters.[490] Ceric ammonium nitrate has been used to hydroxylate C-2 of dibenzyl malonate.[491] Methyl ketones (RCOMe) react with ammonium peroxydisulfate, $(NH_4)_2S_2O_8$, and a catalytic amount of diphenyl diselenide in MeOH to give α-keto acetals, $RCOCH(OMe_2)$.[492]

[480]McCormick, J.P.; Tomasik, W.; Johnson, M.W. *Tetrahedron Lett.* ***1981***, *22*, 607; Moriarty, R.M.; Prakash, O.; Duncan, M.P. *Synthesis* ***1985***, 943; Iwata, C.; Takemoto, Y.; Nakamura, A.; Imanishi, T. *Tetrahedron Lett.* ***1985***, *26*, 3227; Davis, F.A.; Sheppard, A.C. *J. Org. Chem.* ***1987***, *52*, 954; Takai, T.; Yamada, T.; Rhode, O.; Mukaiyama, T. *Chem. Lett.* ***1991***, 281.

[481]Moriarty, R.M.; Epa, W.R.; Penmasta, R.; Awasthi, A.K. *Tetrahedron Lett.* ***1989***, *30*, 667.

[482]Wermeckes, B.; Beck, F.; Schulz, H. *Tetrahedron* ***1987***, *43*, 577.

[483]For a review, see Moriarty, R.M.; Prakash, O. *Acc. Chem. Res.* ***1986***, *19*, 244. Also see, Reddy, D.R.; Thornton, E.R. *J. Chem. Soc. Chem. Commun.* ***1992***, 172.

[484]Moriarty, R.M.; Hou, K. *Tetrahedron Lett.* ***1984***, *25*, 691; Moriarty, R.M.; Hou, K.; Prakash, O.; Arora, S.K. *Org. Synth.* ***VII***, 263.

[485]Moriarty, R.M.; Hu, H.; Gupta, S.C. *Tetrahedron Lett.* ***1981***, *22*, 1283. See Moriarty, R.M.; Berglund, B.A.; Penmasta, R. *Tetrahedron Lett.* ***1992***, *33*, 6065 for reactions with $PhI(O_2CCF_3)_2$.

[486]Moriarty, R.M.; Hu, H. *Tetrahedron Lett.* ***1981***, *22*, 2747.

[487]Masui, M.; Ando, A.; Shioiri, T. *Tetrahedron Lett.* ***1988***, *29*, 2835.

[488]Adam, W.; Smerz, A.K. *Tetrahedron* ***1996***, *52*, 5799. See Hull, L.A.; Budhai, L. *Tetrahedron Lett.* ***1993***, *34*, 5039 for a discussion of the thermal decomposition of dimethyl dioxirane. See Murray, R.W.; Singh, M.; Jeyaraman, R. *J. Am. Chem. Soc.* ***1992***, *114*, 1346 for the preparation of new dioxiranes.

[489]Christoffers, J. *J. Org. Chem.* ***1999***, *64*, 7668.

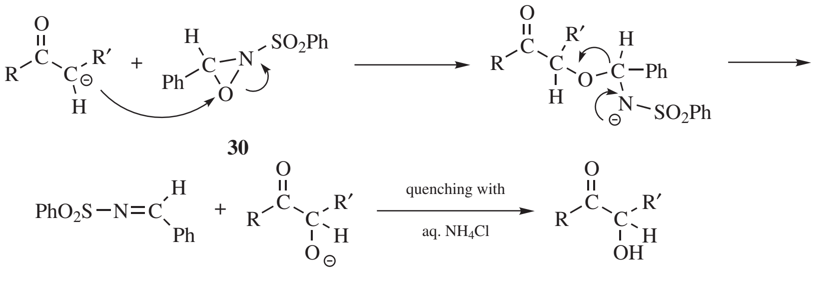
[490]Christoffers, J.; Werner, T. *Synlett* ***2002***, 119.

[491]Nair, V.; Nair, L.G.; Mathew, J. *Tetrahedron Lett.* ***1998***, *39*, 2801.

[492]Tiecco, M.; Testaferri, L.; Tingoli, M.; Bartoli, D. *J. Org. Chem.* ***1990***, *55*, 4523.

α-Acetoxylation of ketones with concurrent α-arylation occurs when ketones react with $Mn(OAc)_3$ in benzene.[493] α-Acetoxylation of ketones can occur under similar conditions without arylation.[494] α-Methyl ketones are converted to the α-acetoxy derivative under the same conditions.[495] Thallium (III) triflate converts acetophenone to α-formyloxy acetophenone.[496] α-Tosyloxy ketones are generated from acetophenone derivatives using PhI(OH)OTs.[497]

A different method for the conversion of ketones to α-hydroxy ketones consists of treating the enolate anion with a 2-sulfonyloxaziridine (e.g., **30**).[498] This is not a free-radical process; the following mechanism is likely:



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The method is also successful for carboxylic esters[351],[499] and *N,N*-disubstituted amides,[500] and can be made enantioselective by the use of a chiral oxaziridine.[501] Dimethyldioxirane also oxidizes ketones (through their enolate forms) to α-hydroxy ketones.[502] Titanium enolates can be oxidized with *tert*-butyl hydroperoxide [503] or with dimethyl dioxirane[504] and hydrolyzed with aqueous ammonium fluoride to give the α-hydroxy ketone. Ketones are converted to the α-oxamino derivative ($O{=}C{-}CH_2$- → O=C–CHONHPh) with excellent enantioselectivity using

[493]Tanyeli, C.; Özdemïrhan, D.; Sezen, B. *Tetrahedron* ***2002***, *58*, 9983.

[494]Tanyeli, C.; Tosun, A.; Turkut, E.; Sezen, B. *Tetrahedron* ***2003***, *59*, 1055; Demir, A.S.; Reis, Ö.; Igdir, A.C. *Tetrahedron* ***2004***, *60*, 3427.

[495]Tanyeli, C.; Iyigün,. *Tetrahedron* ***2003***, *59*, 7135.

[496]Lee, J.C.; Jin, Y.S.; Choi, J.-H. *Chem. Commun.* ***2001***, 956.

[497]Nabana, T.; Togo, H. *J. Org. Chem.* ***2002***, *67*, 4362.

[498]Davis, F.A.; Vishwakarma, L.C.; Billmers, J.M.; Finn, J. *J. Org. Chem.* ***1984***, *49*, 3241.

[499]For formation of α-benzyloxy lactones, see Brodsky, B.H.; DuBois, J. *Org. Lett.* ***2004***, *6*, 2619.

[500]Davis, F.A.; Vishwakarma, L.C. *Tetrahedron Lett.* ***1985***, *26*, 3539.

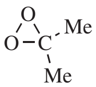
[501]Evans, D.A.; Morrissey, M.M.; Dorow, R.L. *J. Am. Chem. Soc.* ***1985***, *107*, 4346; Enders, D.; Bhushan, V. *Tetrahedron Lett.* ***1988***, *29*, 2437; Davis, F.A.; Sheppard, A.C.; Chen, B.; Haque, M.S. *J. Am. Chem. Soc.* ***1990***, *112*, 6679; Davis, F.A.; Weismiller, M.C. *J. Org. Chem.* ***1990***, *55*, 3715.

[502]Guertin, K.R.; Chan, T.H. *Tetrahedron Lett.* ***1991***, *32*, 715.

[503]Schulz, M.; Kluge, R.; Schüßler, M.; Hoffmann, F. *Tetrahedron* ***1995***, *51*, 3175.

[504]Adam, W.; Müller, M.; Prechtl, F. *J. Org. Chem.* ***1994***, *59*, 2358.

PhN=O and L-proline[505] or (S)-proline.[506] Aldehydes undergo a similar oxidation.[507] α-Lithio sulfones have been hydroxylated with Me_3SiOO*t*-Bu.[508]



Dimethyldioxirane

α-Hydroxyketones can be generated from silyl enol ethers with a catalytic amount of $MeReO_3$ and H_2O_2.[509] Silyl ketene ethers are converted to α-hydroxy esters with H_2O_2 and methyl trioxorhenium.[510] The α′-position of α,β-unsaturated ketones can be selectively oxidized.[511] *N*-Acyl amines are converted to the α-hydroxy derivative with PhIO and a manganese–salen catalyst.[512] Note that homoallylic-type oxidation occurs when an α,α-dimethyl oxime ether is treated with $PhI(OAc)_2$ and a palladium catalyst in acetic acid–acetic anhydride, converting one of the methyl groups to an acetoxymethyl.[513]

Simple alkanes can be converted to esters with dialkyloxiranes. Cyclic alkanes are oxidized to alcohols with dimethyl dioxirane.[514] Cyclohexane was converted to cyclohexyl trifluoroacetate with di(trifluoromethyl) dioxirane and trifluoroacetic anhydride[515] and also with $RuCl_3/MeCO_3H/CF_3CO_2H$.[516] Dimethyl dioxirane converts alkanes to alcohols in some cases.[517] Adamantane is converted to adamantyl alcohol with DDQ (p. 1710) and triflic acid.[518] The mechanism of oxygen insertion into alkanes has been examined.[519]

Benzylic methylene groups are more readily oxidized to benzylic alcohols when compared to simple alkanes. Typical reagents include manganese–salen and PhIO[520] or peroxides.[521] α-Hydroxy ethers are also generated by reaction of this regents with ethers.[522] *N*-Benzyl phthalimide reacts with NBS, NaOAc, and acetic

[505] Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Hibino, K.; Shoji, M. *J. Org. Chem.* ***2004***, *69*, 5966; Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem. Int. Ed.* ***2004***, *43*, 1112.

[506] Bøgevig, A.; Sundén, H.; Córdova, A. *Angew. Chem. Int. Ed.* ***2004***, *43*, 1109.

[507] Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* ***2003***, *44*, 8293.

[508] Chemla, F.; Julia, M.; Uguen, D. *Bull. Soc. Chim. Fr.* ***1993***, *130*, 547; ***1994***, *131*, 639.

[509] Stanković, S.; Espenson, J.H. *J. Org. Chem.* ***1998***, *63*, 4129.

[510] Stanković, S.; Espenson, J.H. *J. Org. Chem.* ***2000***, *65*, 5528.

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[512] Punniyamurthy, T.; Katsuki, T. *Tetrahedron* ***1999***, *55*, 9439.

[513] Desai, L.; Hull, K.L.; Sanford, M.S. *J. Am. Chem. Soc.* ***2004***, *126*, 9542.

[514] Curci, R.; D'Accolti, L.; Fusco, C. *Tetrahedron Lett.* ***2001***, *42*, 7087.

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[516] Murahashi, S.; Oda, Y.; Komiya, N.; Naota, T. *Tetrahedron Lett.* ***1994***, *35*, 7953; Komiya, N.; Noji, S.; Murahashi, S.-I. *Chem. Commun.* ***2001***, 65.

[517] Murray, R.W.; Gu, D. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 451.

[518] Tanemura, K.; Suzuki, T.; Nishida, Y.; Satsumabayashi, K.; Horaguchi, T. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 3230.

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[520] Hamada, T.; Irie, R.; Mihara, J.; Hamachi, K.; Katsuki, T. *Tetrahedron* ***1998***, *54*, 10017; Hamachi, K.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* ***1996***, *37*, 4979.

[521] Kawasaki, K.; Tsumura, S.; Katsuki, T. *Synlett* ***1995***, 1245.

[522] Miyafuji, A.; Katsuki, T. *Synlett* ***1997***, 836.

acid to give *N*-(α-acetoxybenzyl)phthalimide.[523] Methanesulfonic acid and CuO converts ketones to α-mesyloxy (—OMs) ketones[524] and PhI(OH)OTs converts ketones to α-tosyloxy (—OTs) ketones.[525] Aryl methyl carbinols ArCH(OH)Me react with polymer-bound hypervalent iodine complexes, (polymer)–I(OH)OTs, to give a homobenzylic tosylate, $ArCH(OH)CH_2OTs$.[526] Similar oxidation to an acetoxy benzyl derivative was accomplished with $PhI(OAc)_2$ in acetic acid with a palladium catalyst,[527] and with PhI(OH)OTs in aq. DMSO.[528] With minimal water, cerium (IV) triflate converts benzylic arenes to benzylic alcohols, although the major product is the ketone when >15% of water is present.[529]

Allylic hydroxylation[530] with selenium dioxide often gives aldehydes (**19-17**), but in the presence of acetic anhydride and oxygen, SeO_2 converts alkenes to homoallylic acetates as the major product, C=C—C—C → C=C—C—C—OAc.[531] Allylic benzyloxylation occurs when an alkene is treated with *t*-BuOOCOPh and a Cu—Na zeolite,[532] a copper catalyst,[533] or with a chiral copper catalyst to give modest enantioselectivity.[534] Allylic methylene groups can be converted to ester (—CH—OCOR) derivatives in a similar manner using copper triflate.[535] Cupric acetate has also been used,[536] as well as Cu_2O.[537] Acyl peroxides have been used as well.[538] α-Acetoxylation of allylic alkenes can proceed with allylic rearrangement.[539]

Hydroxylation can be accomplished using enzymatic systems. In the presence of *Bacillus megaterium* and oxygen, cyclohexane is converted to cyclohexanol.[540] Allylic oxidation to an allylic alcohol was accomplished with cultured cells of *Gossypium hirsutum*.[541] Benzylic arenes are converted to the corresponding α-hydroxy compound by treatment with the enzymes of *Bacillus megaterium*, with

[523]Cho, S.-D.; Kim, H.-J.; Ahn, C.; Falck, J.R.; Shin, D.-S. *Tetrahedron Lett.* ***1999***, *40*, 8215.

[524]Lee, J.C.; Choi, Y. *Tetrahedron Lett.* ***1998***, *39*, 3171.

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[527]Dick, A.R.; Hull, K.L.; Sanford, M.S. *J. Am. Chem. Soc.* ***2004***, *126*, 2300.

[528]Xie, Y.-Y.; Chen, Z.-C. *Synth. Commun.* ***2002***, *32*, 1875.

[529]Laali, K.K.; Herbert, M.; Cushnyr, B.; Bhatt, A.; Terrano, D. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 578.

[530]For a review, see Andrus, M.B.; Lashley, J.C. *Tetrahedron* ***2002***, *58*, 845.

[531]Koltun, E.S.; Kass, S.R. *Synthesis* ***2000***, 1366.

[532]Carloni, S.; Frullanti, B.; Maggi, R.; Mazzacani, A.; Bigi, F.; Sartori, G. *Tetrahedron Lett.* ***2000***, *41*, 8947.

[533]LeBras, J.; Muzart, J. *Tetrahedron Lett.* ***2002***, *43*, 431; LeBras, J.; Muzart, J. *Tetrahedron Asymmetry* ***2003***, *14*, 1911; Fache, F.; Piva, O. *Synlett* ***2002***, 2035.

[534]Lee, W.-S.; Kwong, H.-L.; Chan, H.-L.; Choi, W.-W.; Ng, L.-Y. *Tetrahedron Asymmetry* ***2001***, *12*, 1007.

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[536]Södergren, M.J.; Andersson, P.G. *Tetrahedron Lett.* ***1996***, *37*, 7577; Rispens, M.T.; Zondervan, C.; Feringa, B.L. *Tetrahedron Asymmetry*, ***1995***, *6*, 661.

[537]Levina, A.; Muzart, J. *Tetrahedron Asymmetry*, ***1995***, *6*, 147.

[538]Andrus, M.B.; Argade, A.B.; Chen, X.; Pamment, M.G. *Tetrahedron Lett.* ***1995***, *36*, 2945; Gokhale, A.S.; Minidis, A.B.E.; Pfaltz, A. *Tetrahedron Lett.* ***1995***, *36*, 1831.

[539]Chen, M.S.; White, M.C. *J. Am. Chem. Soc.* ***2004***, *126*, 1346.

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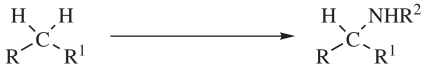
[541]Hamada, H.; Tanaka, T.; Furuya, T.; Takahata, H.; Nemoto, H. *Tetrahedron Lett.* ***2001***, *42*, 909.

modest enantioselectivity.[542] Cyclic amines react with *Pseudomonas oleovorans* GPol to give hydroxy amines; *N*-benzylpyrrolidine is converted to 3-hydroxy *N*-benzylpyrrolidine.[543] *Sphingomonas* sp. HXN-200 gives similar results.[544] In a similar manner, lactams are converted to the corresponding 3-hydroxy lactam with *sphingomonas* sp. HXN-200.[545] *N*-Benzyl piperidine is converted to the 4-hydroxy derivative under the same conditions. [546] The reaction of tetradecanoic acid with the α-oxidase from *Pisum sativum*, in the presence of molecular oxygen, gives 2(*R*)-hydroxytetradecanoic acid with high asymmetric induction.[547]

19-16 Oxidation of Methylene to Heteroatom Functional Groups Other Than Oxygen or Carbonyl

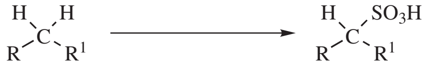
Amino (or amido) -de-dihydro-bisubstitution



α-Amination or amidation of a CH unit is possible in some cases. Cyclic alkanes are converted to the *N*-alkyl *N*-tosylamine with PhI=NTs and a copper complex.[548] Benzylic CH, such as in ethylbenzene, is oxidized with $PhI(OAc)_2$ in the presence of $TsNH_2$ and a fluorinated manganese porphyrin to give the corresponding *N*-tosylamine, PhCHMe(NHTs).[549] Alkenes with an allylic CH react with PhI=NTs and a ruthenium catalysts to give an allylic *N*-tosylamine.[550] When an α-keto ester reacts with DEAD (diethyl azodicarboxylate) and a chiral copper complex, an α- carbamate is formed, $RCH(NHCO_2Et)C(=O)CO_2Et$, with modest enantioselectivity.[551]

Similar reactions are possible, in some cases, to produce sulfur containing compounds.

Sulfo-de-dihydro-bisubstitution

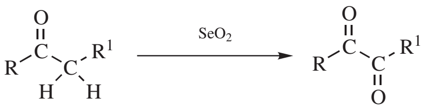


Cyclic alkanes are converted to the corresponding alkylsulfonic acid with SO_2/O_2 and a vanadium catalyst.[552]

[542]Adam, W.; Lukacs, Z.; Harmsen, D.; Saha-Möller, C.R.; Schreier, P. *J. Org. Chem.* ***2000***, *65*, 878.
[543]Li, Z.; Feiten, H.-J.; van Beilen, J.B.; Duetz, W.; Witholt, B. *Tetrahedron Asymmetry* ***1999***, *10*, 1323.
[544]Li, Z.; Feiten, H.-J.; Chang, D.; Duetz, W.A.; Beilen, J.B.; Witholt, B. *J. Org. Chem.* ***2001***, *66*, 8424.
[545]Chang, D.; Witholt, B.; Li, Z. *Org. Lett.* ***2000***, *2*, 3949.
[546]Chang, D.; Feiten, H.-J.; Engesser, K.-H.; van Beilen, J.; Witholt, B.; Li, Z. *Org. Lett.* ***2002***, *4*, 1859.
[547]Adam, W.; Boland, W.; Hartmann-Schreier, J.; Humpf, H.-U.; Lazarus, M.; Saffert, A.; Saha-Möller, C.R.; Schreier, P. *J. Am. Chem. Soc.* ***1998***, *120*, 11044.
[548]Díaz-Requejo, M.M.; Belderraín, T.R.; Nicasio, M.C.; Trofimenko, S.; Pérez, P.J. *J. Am. Chem. Soc.* ***2003***, *125*, 12078.
[549]Yu, X.-Q.; Huang, J.-S.; Zhou, X.-G.; Che, C.-M. *Org. Lett.* ***2000***, *2*, 2233.
[550]Au, S.-M.; Huang, J.-S.; Che, C.-M.; Yu, W.-Y. *J. Org. Chem.* ***2000***, *65*, 7858.
[551]Juhl, K.; Jørgensen, K.A. *J. Am. Chem. Soc.* ***2002***, *124*, 2420.
[552]Ishii, Y.; Matsunaka, K.; Sakaguchi, S. *J. Am. Chem. Soc.* ***200***, *122*, 7390.

19-17 Oxidation of Methylene to Carbonyl

Oxo-de-dihydro-bisubstitution



Methyl or methylene groups α to a carbonyl can be oxidized with selenium dioxide to give, respectively, α-keto aldehydes (see **19-18**) and α-diketones.[553] The reaction can also be carried out a to an aromatic ring or to a double bond, although in the latter case, hydroxylation (see **19-14**) is the more common result. Selenium dioxide, SeO_2, is the reagent most often used, but the reaction has also been carried out with N_2O_3 and other oxidizing agents,[554] including hypervalent iodine compounds.[555] Sodium nitrite/HCl oxidizes cyclic ketones to the diketone.[556] Substrates most easily oxidized contain two aryl groups on CH_2, and these substrates can be oxidized with many oxidizing agents (see **19-11**). The benzylic position of arenes have been oxidized to alkyl aryl ketones with several oxidizing agents, including CrO_3–acetic acid,[557] the Jones reagent,[558] CrO_3 on silica,[559] pyridinium chlorochromate,[560] DDQ,[561] CrO_2Cl_2 with ultrasound,[562] $KMnO_4$ supported on MnO_2,[563] $KMnO_4$ on alumina with microwave irradiation[564] or on Montmorillonite K10 with either ultrasound or microwave irradiation,[565] $KMnO_4/CuSO_4$ neat[566] or with ultrasound,[567] $NaBrO_3/CeO_2$,[568] manganese–salen/PhIO,[569] *tert*-butylhydroperoxide and a ruthenium catalyst,[570] $Ru(OH)_x$–Al_2O_3 and O_2,[571] hydrogen peroxide with a copper catalyst,[572] as well as with SeO_2. The combination of O_2 and

[553]For reviews of oxidation by SeO_2, see Krief, A.; Hevesi, L. *Organoselenium Chemistry I*, Springer, NY, ***1988***, pp. 115–180; Krongauz, E.S. *Russ. Chem. Rev.* ***1977***, *46*, 59; Rabjohn, N. *Org. React.* ***1976***, *24*, 261; Trachtenberg, E.N., in Augustine, R.L.; Trecker, D.J. *Oxidation*, Marcel Dekker, NY, pp. 119–187.

[554]For other methods, see Wasserman, H.H.; Ives, J.L. *J. Org. Chem.* ***1978***, *43*, 3238; ***1985***, *50*, 3573; Rao, D.V.; Stuber, F.A.; Ulrich, H. *J. Org. Chem.* ***1979***, *44*, 456.

[555]Lee, J.C.; Park, H.-J.; Park, J.Y. *Tetrahedron Lett.* ***2002***, *43*, 5661.

[556]Rüedi, G.; Oberli, M.A.; Nagel, M.; Weymuth, C.; Hansen, H.-J. *Synlett* ***2004***, 2315.

[557]For example, see Harms, W.M.; Eisenbraun, E.J. *Org. Prep. Proced. Int.* ***1972***, *4*, 67.

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[559]Borkar, S.D.; Khadilkar, B.M. *Synth. Commun.* ***1999***, *29*, 4295.

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[563]Wei, H.-X.; Jasoni, R.L.; Shao, H.; Hu, J.; Paré, P.W. *Tetrahedron* ***2004***, *60*, 11829.

[564]Oussaid, A.; Loupy, A. *J. Chem. Res. (S)* ***1997***, 342.

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[566]Shaabani, A. Lee, D.G. *Tetrahedron Lett.* ***2001***, *42*, 5833.

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[569]Komiya, N.; Noji, S.; Murahashi, S.-I. *Tetrahedron Lett.* ***1998***, *39*, 7921; Lee, N.H.; Lee, C.-S.; Jung, D.-S. *Tetrahedron Lett.* ***1998***, *39*, 1385.

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[571]Kamata, K.; Kasai, J.; Yamaguchi, K.; Mizuno, N. *Org. Lett.* ***2004***, *6*, 3577.

[572]Velusamy, S.; Punniyamurthy, T. *Tetrahedron Lett.* ***2003***, *44*, 8955.

mcpba oxidizes benzylic arenes to aryl ketones.[573] Note that benzyl methyl ether is oxidized to methyl benzoate with $KMnO_4$ in the presence of benzyltriethylammonium chloride.[574]

Alkenes of the form C=C—CH_2 (an allylic position) have been oxidized to α,β-unsaturated ketones[575] by sodium dichromate in HOAc—Ac_2O, by *t*-BuOOH and chromium compounds,[576] *t*-BuOOH and a palladium catalyst,[577] or a rhodium catalyst,[578] as well as electrolytically.[579] Oxygen, $MeSO_3H$ a palladium catalysts and a molybdobanadophosphate catalyst convert cyclic alkenes to saturated cyclic ketones.[580] Thallium(III) nitrate in aqueous acetic acid converts allylic alkenes to the corresponding saturated ketone, even in the presence of a primary alcohol elsewhere in the molecule.[581] The propargylic position of internal alkynes are oxidized to give propargylic ketones with an iron catalyst,[582] or with O_2/*t*-BuOOH in the presence of $CuCl_2$•H_2O.[583]

Cyclic amines are oxidized to lactams using a mixture of $RuCl_3$ and $NaIO_4$.[584] Lactams are also formed using $KMnO_4$ with benzyltriethylammonium chloride.[585] Tertiary amines are converted to amides[586] and cyclic tertiary amines can be converted to lactams by oxidation with Hg^{II}–EDTA complex in basic solution.[587] Lactams, which need not be *N*-substituted, can be converted to cyclic imides by oxidation with a hydroperoxide or peroxyacid and an Mn(II) or Mn(III) salt.[588] Lactams are oxidized to cyclic imides with oxygen and $Co(OAc)_2$ in the presence *N*-hydroxysuccinimide.[589]

Ethers in which at least one group is primary alkyl can be oxidized to the corresponding carboxylic esters in high yields with ruthenium tetroxide.[590] Molecular

[573]Ma, D.; Xia, C.; Tian, H. *Tetrahedron Lett.* ***1999***, *40*, 8915.

[574]Markgraf, J.H.; Choi, B.Y. *Synth. Commun.* ***1999***, *29*, 2405.

[575]For a review, see Muzart, J. *Bull. Soc. Chim. Fr.* ***1986***, 65. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1207–1210.

[576]Pearson, A.J.; Chen, Y.; Han, G.R.; Hsu, S.; Ray, T. *J. Chem. Soc. Perkin Trans. 1* ***1985***, 267; Muzart, J. *Tetrahedron Lett.* ***1987***, *28*, 2131; Chidambaram, N.; Chandrasekaran, S. *J. Org. Chem.* ***1987***, *52*, 5048.

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[579]Madurro, J.M.; Chiericato Jr., G.; De Giovani, W.F.; Romero, J.R. *Tetrahedron Lett.* ***1988***, *29*, 765.

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[581]Ferraz, H.M.C.; Longo, Jr., L.S.; Zukerman-Schpector, J. *J. Org. Chem.* ***2002***, *67*, 3518.

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[583]Li, P.; Fong, W.M.; Chao, L.C.F.; Fung, S.H.C.; Williams, I.D. *J. Org. Chem.* ***2001***, *66*, 4087.

[584]Sharma, N.K.; Ganesh, K.N. *Tetrahedron Lett.* ***2004***, *45*, 1403; Zhang, X.; Schmitt, A.C.; Jiang, W. *Tetrahedron Lett.* ***2001***, *42*, 5335.

[585]Markgraf, J.H.; Stickney, C.A. *J. Heterocyclic Chem.* ***2000***, *37*, 109.

[586]Markgraf, J.H.; Sangani, P.K.; Finkelstein, M. *Synth. Commun.* ***1995***, *27*, 1285.

[587]Wenkert, E.; Angell, E.C. *Synth. Commun.* ***1988***, *18*, 1331.

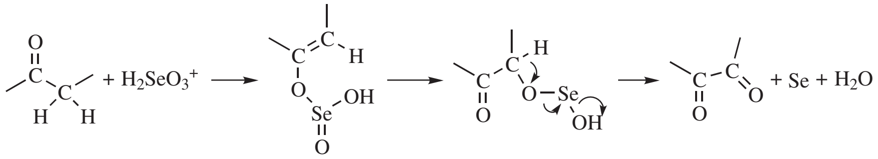
[588]Doumaux Jr., A.R.; McKeon, J.E.; Trecker, D.J. *J. Am. Chem. Soc.* ***1969***, *91*, 3992; Doumaux Jr., A.R.; Trecker, D.J. *J. Org. Chem.* ***1970***, *35*, 2121.

[589]Minisci, F.; Punta, C.; Recupero, F.; Fontana, F.; Pedulli, G.F. *J. Org. Chem.* ***2002***, *67*, 2671.

[590]Bakke, J.M.; Frøhaug, Az. *Acta Chem. Scand. B* ***1995***, *49*, 615; Lee, D.G.; van den Engh, M., in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B, Academic Press, NY, ***1973***, pp. 222–225; Smith III, A.B.; Scarborough, Jr., R.M. *Synth. Commun.* ***1980***, *10*, 205; Carlsen, P.H.J.; Katsuki, T.; Martin, V.S.; Sharpless, K.B. *J. Org. Chem.* ***1981***, *46*, 3936.

oxygen with a binuclear copperII complex[591] or $PdCl_2/CuCl_2/CO$[592] also converts ethers to esters. In a variation, benzyl *tert*-butyl ethers are oxidized to benzaldehyde derivatives with NO and *N*-hydroxysuccinimide.[593] Cyclic ethers are oxidized to lactones.[594] Cyclic ethers are oxidized to lactones with CrO_3/Me_3SiONO_2.[595] Lactones are also formed from cyclic ethers with $NaBrO_3$–$KHSO_4$ in water.[596]The reaction has also been accomplished with CrO_3 in sulfuric acid,[597] and with benzyltriethylammonium permanganate.[598]

Two mechanisms have been suggested for the reaction with SeO_2. One of these involves a selenate ester of the enol:[599]



In the other proposed mechanism,[600] the principal intermediate is α β-ketoseleninic acid

and a selenate ester is not involved.

It has proved possible to convert CH_2 to C=O groups, even if they are not near any functional groups, indirectly, by the remote oxidation method of Breslow[62] (see **19-2**). In a typical example, the keto ester **31** was irradiated to give the hydroxy lactone **32**, which was dehydrated to **33**. Ozonolysis of **33** gave the diketo ester

[591]Minakata, S.; Imai, E.; Ohshima, Y.; Inaki, K.; Ryu, I.; Komatsu, M.; Ohshiro, Y. *Chem. Lett.* ***1996***, 19.

[592]Miyamoto, M.; Minami, Y.; Ukaji, Y.; Kinoshita, H.; Inomata, K. *Chem. Lett.* ***1994***, 1149.

[593]Eikawa, M.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* ***1999***, *64*, 4676.

[594]For an example using titanium silicate/H_2O_2, see Sasidharan, M.; Suresh, S.; Sudalai, A. *Tetrahedron Lett.* ***1995***, *36*, 9071. For an example in which a bicyclic ether was converted to a monocyclic lactone, see Ferraz, H.M.C.; Longo Jr., L.S. *Org. Lett.* ***2003***, *5*, 1337.

[595]Shahi, S.P.; Gupta, A.; Pitre, S.V.; Reddy, M.V.R.; Kumareswaran, R.; Vankar, Y.D. *J. Org. Chem.* ***1999***, *64*, 4509.

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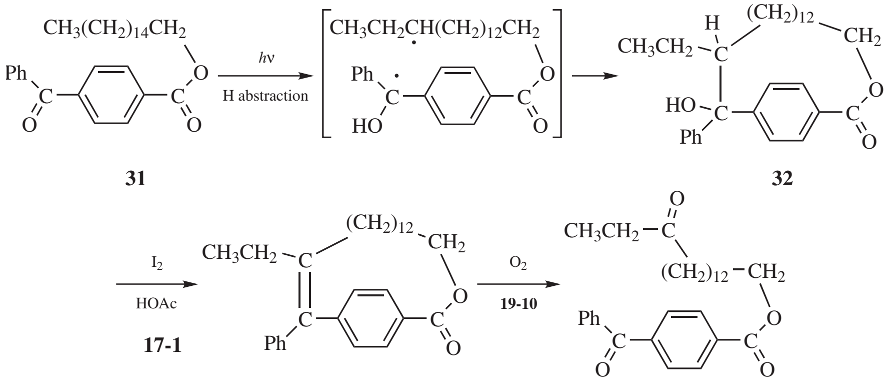
[597]Henbest, H.B.; Nicholls, B. *J. Chem. Soc.* ***1959***, 221, 227; Harrison, I.T.; Harrison, S. *Chem. Commun.* ***1966***, 752.

[598]Schmidt, H.; Schäfer, H.J. *Angew. Chem. Int. Ed.* ***1979***, *18*, 69.

[599]Corey, E.J.; Schaefer, J.P. *J. Am. Chem. Soc.* ***1960***, *82*, 918.

[600]Sharpless, K.B.; Gordon, K.M. *J. Am. Chem. Soc.* ***1976***, *98*, 300.



31 32 33 34

34, in which the C-14 CH_2 group of **31** has been oxidized to a C=O group.[601] The reaction was not completely regioselective: **34** comprised ~ 60% of the product, with the remainder consisting of other compounds in which the keto group was located at C-12, C-15, and other positions along the carbon chain. Greater regioselectivity was achieved when the aromatic portion was connected to the chain at two positions.[602] In the method so far described, the reaction takes place because one portion of a molecule (the benzophenone moiety) abstracts hydrogen from another portion of the same molecule, that is, the two portions are connected by a series of covalent bonds. However, the reaction can also be carried out where the two reacting centers are actually in different molecules, providing the two molecules are held together by hydrogen bonding. For example, one of the CH_2 groups of *n*-hexadecanol monosuccinate, $CH_3(CH_2)_{14}CH_2OCOCH_2CH_2COOH$, was oxidized to a C=O group by applying the above procedure to a mixture of it and benzophenone-4-carboxylic acid *p*-$PhCOC_6H_4COOH$ in CCl_4.[603]

Other remote oxidations[604] have also been reported. Among these are conversion of aryl ketones $ArCO(CH_2)_3R$ to 1,4-diketones $ArCO(CH_2)_2COR$ by photoirradiation in the presence of such oxidizing agents as $K_2Cr_2O_7$ or $KMnO_4$,[605] and conversion of alkyl ketones, $RCO(CH_2)_3R'$, to 1,3- and 1,4-diketones with $Na_2S_2O_8$ and $FeSO_4$.[606] 2-Octanol was oxidized to give 2-propyl-5-methyl γ-butyrolactone with lead tetraacetate in a CO atmosphere.[607]

[601]Breslow, R.; Rothbard, J.; Herman, F.; Rodriguez, M.L. *J. Am. Chem. Soc.* ***1978***, *100*, 1213.

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[603]Breslow, R.; Scholl, P.C. *J. Am. Chem. Soc.* ***1971***, *93*, 2331. See also, Breslow, R.; Heyer, D. *Tetrahedron Lett.* ***1983***, *24*, 5039.

[604]See also Beckwith, A.L.J.; Duong, T. *J. Chem. Soc. Chem. Commun.* ***1978***, 413.

[605]Mitani, M.; Tamada, M.; Uehara, S.; Koyama, K. *Tetrahedron Lett.* ***1984***, *25*, 2805. For an alternative photochemical procedure, see Negele, S.; Wieser, K.; Severin, T. *J. Org. Chem.* ***1998***, *63*, 1138.

[606]Nikishin, G.I.; Troyansky, E.I.; Lazareva, M.I. *Tetrahedron Lett.* ***1984***, *25*, 4987.

[607]Tsunoi, S.; Ryu, I.; Okuda, T.; Tanaka, M.; Komatsu, M.; Sonoda, N. *J. Am. Chem. Soc.* ***1998***, *120*, 8692. Also see, Tsunoi, S.; Ryu, I.; Sonoda, N. *J. Am. Chem. Soc.* ***1994***, *116*, 5473.

It is possible to perform the conversion $CH_2 \rightarrow C{=}O$ on an alkane, with no functional groups at all, although the most success has been achieved with substrates in which all CH_2 groups are equivalent, such as unsubstituted cycloalkanes. One method uses H_2O_2 and bis(picolinato)iron(II). Hydrogen peroxide and trifluoroacetic acid has also been used for oxidation of alkanes.[608] With this method, cyclohexane was converted with 72% efficiency to give 95% cyclohexanone and 5% cyclohexanol.[609] This was also accomplished with $BaRu(O)_2(OH)_3$.[610] The same type of conversion, with lower yields (20–30%), has been achieved with the *Gif system*.[611] There are several variations. One consists of pyridine–acetic acid, with H_2O_2 as oxidizing agent and tris(picolinato)iron(III) as catalyst.[612] Other Gif systems use O_2 as oxidizing agent and zinc as a reductant.[613] The selectivity of the Gif systems toward alkyl carbons is $CH_2 > CH \geq CH_3$, which is unusual, and shows that a simple free-radical mechanism (see p. 942) is not involved.[614] Another reagent that can oxidize the CH_2 of an alkane is methyl(trifluoromethyl)dioxirane, but this produces CH—OH more often than C=O (see **19-14**; **19-15**).[615] Simple unfunctionalized alkanes are oxidized to esters when treated with CBr_4/2 $AlBr_3$ and CO, but in very low yield.[616] Cyclic alkanes are oxidized to a mixture of the alcohol and the ketone with $PhI(OAc)_2$ and a manganese complex in an ionic liquid.[617] Oxidation of cyclic alkanes to cyclic ketones was accomplished using a ruthenium catalyst.[618]

OS **I**, 266; **II**, 509; **III**, 1, 420, 438; **IV**, 189, 229, 579; **VI**, 48; **IX**, 396. Also see, OS **IV**, 23.

[608]Camaioni, D.M.; Bays, J.T.; Shaw, W.J.; Linehan, J.C.; Birnbaum, J.C. *J. Org. Chem.* ***2001***, *66*, 789.

[609]Sheu, C.; Richert, S.A.; Cofré, P.; Ross Jr., B.; Sobkowiak, A.; Sawyer, D.T.; Kanofsky, J.R. *J. Am. Chem. Soc.* ***1990***, *112*, 1936. See also, Sheu, C.; Sobkowiak, A.; Jeon, S.; Sawyer, D.T. *J. Am. Chem. Soc.* ***1990***, *112*, 879; Tung, H.; Sawyer, D.T. *J. Am. Chem. Soc.* ***1990***, *112*, 8214.

[610]Lau, T.-C.; Mak, C.-K. *J. Chem. Soc. Chem. Commun.* ***1993***, 766.

[611]Named for Gif-sur-Yvette, France, where it was discovered. See Schuchardt, U.; Jannini, M.J.D.M.; Richens, D.T.; Guerreiro, M.C.; Spinacé, E.V. *Tetrahedron* ***2001***, *57*, 2685.

[612]About-Jaudet, E.; Barton, D.H.R.; Csuhai, E.; Ozbalik, N. *Tetrahedron Lett.* ***1990***, *31*, 1657. Also see, Minisci, F.; Fontana, F.; Araneo, S.; Recupero, F. *Tetrahedron Lett.* ***1994***, *35*, 3759; Barton, D.H.R.; Bévière, S.D.; Chavasiri, W.; Doller, D.; Hu, B. *Tetrahedron Lett.* ***1992***, *33*, 5473. For a review of the mechanism, see Barton, D.H.R. *Chem. Soc. Rev.* ***1996***, *25*, 237.

[613]See Barton, D.H.R.; Csuhai, E.; Ozbalik, N. *Tetrahedron* ***1990***, *46*, 3743, and references cited therein.

[614]Barton, D.H.R.; Csuhai, E.; Doller, D.; Ozbalik, N.; Senglet, N. *Tetrahedron Lett.* ***1990***, *31*, 3097. For mechanistic studies, see Barton, D.H.R.; Doller, D.; Geletii, Y.V. *Tetrahedron Lett.* ***1991***, *32*, 3911, and references cited therein; Knight, C.; Perkins, M.J. *J. Chem. Soc. Chem. Commun.* ***1991***, 925. Also see, Minisci, F.; Fontana, F. *Tetrahedron Lett.* ***1994***, *35*, 1427; Barton, D.H.R.; Hill, D.R. *Tetrahedron Lett.* ***1994***, *35*, 1431.

[615]Mello, R.; Fiorentino, M.; Fusco, C.; Curci, R. *J. Am. Chem. Soc.* ***1989***, *111*, 6749; D'Accolti, L.; Dinoi, A.; Fusco, C.; Russo, A.; Curci, R. *J. Org. Chem.* ***2003***, *68*, 7806.

[616]Akhrem, I.; Orlinkov, A.; Afanas'eva, L.; Petrovskii, P.; Vitt, S. *Tetrahedron Lett.* ***1999***, *40*, 5897.

[617]In bmim PF6, 1-butyl-3-methylimidazolium hexafluorophosphate: Li, Z.; Xiu, C.-G.; Xu, C.-Z. *Tetrahedron Lett.* ***2003***, *44*, 9229.

[618]Che, C.-M.; Cheng, K.-W.; Chan, M.C.W.; Lau, T.-C.; Mak, C.-K. *J. Org. Chem.* ***2000***, *65*, 7996.

19-18 Oxidation of Arylmethanes to Aldehydes

Oxo-de-dihydro-bisubstitution

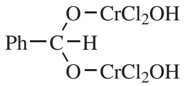
$$ArCH_3 \xrightarrow{CrO_2Cl_2} ArCHO$$

Methyl groups on an aromatic ring can be oxidized to the aldehyde stage by several oxidizing agents. The reaction is a special case of **19-17**. When the reagent is chromyl chloride (CrO_2Cl_2), the reaction is called the *Étard reaction*[619] and the yields are high.[620] Another oxidizing agent is a mixture of CrO_3 and Ac_2O. In this case, the reaction stops at the aldehyde stage because the initial product is $ArCH(OAc)_2$ (an acylal), which is resistant to further oxidation. Hydrolysis of the acylal gives the aldehyde.

Among other oxidizing agents[621] that have been used to accomplish the conversion of $ArCH_3$ to ArCHO are ceric ammonium nitrate,[622] ceric trifluoroacetate,[623] hypervalent iodoso compounds (see **19-3**),[624] urea–H_2O_2 with micrwoave irradiation,[625] and silver(II) oxide.[626] Oxidation of $ArCH_3$ to carboxylic acids is considered at **19-11**.

Conversion of $ArCH_3$ to ArCHO can also be achieved indirectly by bromination to give $ArCHBr_2$ (**14-1**), followed by hydrolysis (**10-2**).

The mechanism of the Étard reaction is not completely known.[627] An insoluble complex is formed on addition of the reagents, which is hydrolyzed to the aldehyde. The complex is probably a kind of acylal, but the identity of the structure is not fully settled, although many proposals have been made as to its structure and as to how it is hydrolyzed.



35

It is known that $ArCH_2Cl$ is not an intermediate (see **19-20**), since it reacts only very slowly with chromyl chloride. Magnetic susceptibility measurements[628]

[619]The name Étard reaction is often applied to any oxidation with chromyl chloride, for example, oxidation of glycols (**19-7**), alkenes (**19-10**), and so on.

[620]For a review, see Hartford, W.H.; Darrin, M. *Chem. Rev.* ***1958***, *58*, 1, see pp. 25–53.

[621]For a review of the use of oxidizing agents that are regenerated electrochemically, see Steckhan, E. *Top. Curr. Chem.* ***1987***, *142*, 1; 12–17.

[622]Trahanovsky, W.S.; Young, L.B. *J. Org. Chem.* ***1966***, *31*, 2033; Radhakrishna Murti, P.S.; Pati, S.C. *Chem. Ind. (London)* ***1967***, 702; Syper, L. *Tetrahedron Lett.* ***1967***, 4193. For oxidation with ceric ammonium nitrate and KBrO3, see Ganin, E.; Amer, I. *Synth. Commun.* ***1995***, *25*, 3149.

[623]Marrocco, M.; Brilmyer, G. *J. Org. Chem.* ***1983***, *48*, 1487. See also, Kreh, R.P.; Spotnitz, R.M.; Lundquist, J.T. *J. Org. Chem.* ***1989***, *54*, 1526.

[624]Nicolaou, K.C.; Baran, P.S.; Zhong, Y.-L. *J. Am. Chem. Soc.* ***2001***, *123*, 3183.

[625]Paul, S.; Nanda, P.; Gupta, R. *Synlett* ***2004***, 531.

[626]Syper, L. *Tetrahedron Lett.* ***1967***, 4193.

[627]For a review, see Nenitzescu, C.D. *Bull. Soc. Chim. Fr.* ***1968***, 1349.

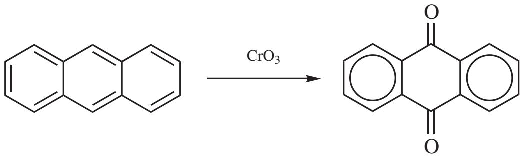
[628]Wheeler, O.H. *Can. J. Chem.* ***1960***, *38*, 2137. See also, Makhija, R.C.; Stairs, R.A. *Can. J. Chem.* ***1968***, *46*, 1255.

indicate that the complex from toluene is **35**, a structure first proposed by Étard. According to this proposal, the reaction stops after only two hydrogens have been replaced because of the insolubility of **35**. There is a disagreement on how **35** is formed, assuming that the complex has this structure. Both an ionic[629] and a free-radical[630] process have been proposed. An entirely different structure for the complex was proposed by Nenitzescu and co-workers.[631] On the basis of esr studies, they proposed that the complex is $PhCH_2OCrCl_2OCrOCl_2OH$, which is isomeric with **35**. However, this view has been challenged by Wiberg and Eisenthal,[336] who interpret the esr result as being in accord with **35**. Still another proposal is that the complex is composed of benzaldehyde coordinated with reduced chromyl chloride.[632]

OS **II**, 441; **III**, 641; **IV**, 31, 713.

19-19 Oxidation of Aromatic Hydrocarbons to Quinones

Arene-quinone transformation



Condensed aromatic systems (including naphthalenes) can be directly oxidized to quinones by various oxidizing agents.[258,633] Yields are generally not high, although good yields have been reported with ceric ammonium sulfate.[634] Benzene cannot be so oxidized by strong oxidizing agents, but can be electrolytically oxidized to benzoquinone.[635] Naphthalene derivatives, however, are oxidized to naphthoquinones with H_5IO_6 and CrO_3.[636] 1,4-Dimethoxy aromatic compounds are oxidized to para-quinones with an excess of CoF_3 in water–dioxane.[637]

OS **IV**, 698, 757. Also see, OS **II**, 554.

[629]Stairs, R.A. *Can. J. Chem.* ***1964***, *42*, 550.

[630]Wiberg, K.B.; Eisenthal, R. *Tetrahedron* ***1964***, *20*, 1151. See also, Gragerov, I.P.; Ponomarchuk, M.P. *J. Org. Chem. USSR* ***1969***, *6*, 1125.

[631]Necşoiu, I.; Przemetchi, V.; Ghenciulescu, A.; Rentea, C.N.; Nenitzescu, C.D. *Tetrahedron* ***1966***, *22*, 3037.

[632]Duffin, H.C.; Tucker, R.B. *Chem. Ind. (London)* ***1966***, 1262; *Tetrahedron* ***1968***, *24*, 6999.

[633]For reviews, see Naruta, Y.; Maruyama, K., in Patai, S.; Rappoport, Z. *The Chemistry of the Quinoid Compounds*, Vol. 2, pt. 1, Wiley, NY, ***1988***, pp. 242–247; Hudlický, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, pp. 94–96; Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Vol. 1, Academic Press, NY, ***1985***, pp. 182–185, 358–360; Thomson, R.H., in Patai, S. *The Chemistry of the Quinoid Compounds*, Vol. 1, pt. 1, Wiley, NY, ***1974***, pp. 132–134. See also, Sket, B.; Zupan, M. *Synth. Commun.* ***1990***, *20*, 933.

[634]Periasamy, M.; Bhatt, M.V. *Synthesis* ***1977***, 330; Balanikas, G.; Hussain, N.; Amin, S.; Hecht, S.S. *J. Org. Chem.* ***1988***, *53*, 1007.

[635]See, for example, Ito, S.; Katayama, R.; Kunai, A.; Sasaki, K. *Tetrahedron Lett.* ***1989***, *30*, 205.

[636]Yamazaki, S. *Tetrahedron Lett.* ***2001***, *42*, 3355.

[637]Tomatsu, A.; Takemura, S.; Hashimoto, K.; Nakata, M. *Synlett* ***1999***, 1474.

19-20 Oxidation of Primary Halides and Esters of Primary Alcohols to Aldehydes[638]

Oxo-de-hydro, halo-bisubstitution

$$RCH_2Cl \xrightarrow{Me_2SO} RCHO$$

Primary alkyl halides (chlorides, bromides, and iodides) can be oxidized to aldehydes easily and in good yields with dimethyl sulfoxide,[639] in what has been called the *Kornblum reaction*. In Kornblum's original work, the reaction of α-halo ketones with DMSO at elevated temperatures gave good yields of the corresponding glyoxal (an α-keto-aldehyde).[640] If the glyoxal could be removed from the reaction medium by distillation as it was formed, the reaction was very efficient. In many cases, it was difficult to isolate high boiling glyoxals from DMSO. Primary and secondary[641] alkyl iodides or tosylates[642] can be converted to aldehydes or ketones, although they are much less reactive than α-halo ketones. Epoxides[643] have been used to give α-hydroxy ketones or aldehydes.[644] The reaction with tosyl esters is an indirect way of oxidizing primary alcohols to aldehydes (**19-3**). Primary chlorides with DMSO, NaBr, and ZnO give the corresponding aldehyde when heated to 140°C.[645] Primary allylic bromides with a cyano group on the C=C unit are converted to conjugated α-cyano aldehydes with DMSO and $NaHCO_3$ at room temperature.[646]

[638]For reviews of the reactions in this section, see Tidwell, T.T. *Org. React.* ***1990***, *39*, 297; *Synthesis* ***1990***, 857; Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Vol. 2, Academic Press, NY, ***1988***, pp. 171–181, 402–406; Durst, T. *Adv. Org. Chem.* ***1969***, *6*, 285, see pp. 343–356; Epstein, W.W.; Sweat, F.W. *Chem. Rev.* ***1967***, *67*, 247; Moffatt, J.G., in Augustine, R.L.; Trecker, D.J. *Oxidation*, Vol. 2, Marcel Dekker, NY, ***1971***, pp. 1–64. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1222–1225.

[639]Nace, H.R.; Monagle, J.J. *J. Org. Chem.* ***1959***, *24*, 1792; Kornblum, N.; Jones, W.J.; Anderson, G.J. *J. Am. Chem. Soc.* ***1959***, *81*, 4113. This reaction is promoted by microwave irradiation; see Villemin, D.; Hammadi, M. *Synth. Commun.* ***1995***, *25*, 3141.

[640]Kornblum, N.; Powers, J.W.; Anderson, G.J.; Jones, W.J.; Larson, H.O.; Levand, O.; Weaver, W.M. *J. Am. Chem. Soc.* ***1957***, *79*, 6562.

[641]Baizer, M.M. *J. Org. Chem.*, ***1960***, *25*, 670.

[642]Kornblum, N.; Jones, W.J.; Anderson, G.J. *J. Am. Chem. Soc.* ***1959***, *81*, 4113.

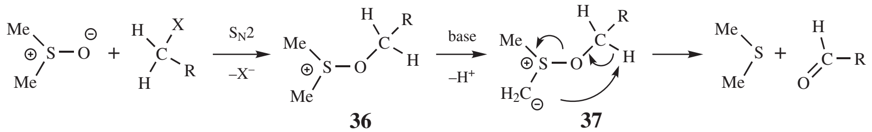
[643]Epoxides can be converted to α-halo ketones by treatment with bromodimethylsulfonium bromide: Olah, G.A.; Vankar, Y.D.; Arvanaghi, M. *Tetrahedron Lett.* ***1979***, 3653.

[644]Cohen, T.; Tsuji, T. *J. Org. Chem.* ***1961***, *26*, 1681; Tsuji, T. *Tetrahedron Lett.* ***1966***, 2413; Santosusso, T.M.; Swern, D. *Tetrahedron Lett.* ***1968***, 4261; *J. Org. Chem.* ***1975***, *40*, 2764.

[645]Guo, Z.; Sawyer, R.; Prakash, I. *Synth. Commun.* ***2001***, *31*, 667; Guo, Z.; Sawyer, R.; Prakash, I. *Synth. Commun.* ***2001***, *31*, 3395.

[646]Ravichandran, S. *Synth. Commun.* ***2001***, *31*, 2185.

The mechanism of these DMSO oxidations is probably as follows:[647]



36 37

although in some cases the base abstracts a proton directly from the carbon being oxidized, in which case the ylid **37** is not an intermediate. Alkoxysulfonium salts (**36**) have been isolated.[648] This mechanism predicts that secondary compounds should be oxidizable to ketones, and this is the case. In a related procedure for the oxidation of alcohols, the intermediate **36**[649] is formed without the use of DMSO by treating the substrate with a complex generated from chlorine or NCS and dimethyl sulfide.[650]

Another way to oxidize primary alkyl halides to aldehydes is by the use of hexamethylenetetramine followed by water. However, this reaction, called the *Sommelet reaction*,[651] is limited to benzylic halides. The reaction is seldom useful when the R in RCH_2Cl is alkyl. The first part of the reaction is conversion to the amine $ArCH_2NH_2$, which can be isolated. Reaction of the amine with excess hexamethylenetetramine gives the aldehyde. It is this last step that is the actual Sommelet reaction, although the entire process can be conducted without isolation of intermediates. Once the amine is formed, it is converted to an imine ($ArCH_2N{=}CH_2$) with formaldehyde liberated from the reagent. The key step then follows: transfer of hydrogen from another mole of the arylamine to the imine. This last imine is then hydrolyzed by water to the aldehyde. Alternatively, the benzylamine may transfer hydrogen directly to hexamethylenetetramine. Another method that converts secondary bromides to ketones heads the bromide with $NaIO_4$ in DMF.[652]

Another reagent that convert benzylic halides to aldehydes is pyridine followed by *p*-nitrosodimethylaniline and then water, called the *Kröhnke reaction*. Primary halides and tosylates have been oxidized to aldehydes by trimethylamine *N*-oxide,[653] and by pyridine *N*-oxide with microwave irradiation.[654]

[647]Pfitzner, K.E.; Moffatt, J.G. *J. Am. Chem. Soc.* ***1965***, *87*, 5661; Johnson, C.R.; Phillips, W.G. *J. Org. Chem.* ***1967***, *32*, 1926; Torssell, K. *Acta Chem. Scand.* ***1967***, *21*, 1.

[648]Torssell, K. *Tetrahedron Lett.* ***1966***, 4445; Johnson, C.R.; Phillips, W.G. *J. Org. Chem.* ***1967***, *32*, 1926; Khuddus, M.A.; Swern, D. *J. Am. Chem. Soc.* ***1973***, *95*, 8393.

[649]It has been suggested that in the DCC reaction, **36** is not involved, but the ylid **37** is formed directly from a precursor containing DCC and DMSO: Torssell, K. *Tetrahedron Lett.* ***1966***, 4445; Moffatt, J.G. *J. Org. Chem.* ***1971***, *36*, 1909.

[650]Vilsmaier, E.; Sprügel, W. *Liebigs Ann. Chem.* ***1971***, *747*, 151; Corey, E.J.; Kim, C.U. *J. Am. Chem. Soc.* ***1972***, *94*, 7586; *J. Org. Chem.* ***1973***, *38*, 1233; McCormick, J.P. *Tetrahedron Lett.* ***1974***, 1701; Katayama, S.; Fukuda, K.; Watanabe, T.; Yamauchi, M. *Synthesis* ***1988***, 178.

[651]For a review, see Angyal, S.J. *Org. React.* ***1954***, *8*, 197.

[652]Das, S.; Panigrahi, A.K.; Maikap, G.C. *Tetrahedron Lett.* ***2003***, *44*, 1375.

[653]Franzen, V.; Otto, S. *Chem. Ber.* ***1961***, *94*, 1360. For the use of other amine oxides, see Suzuki, S.; Onishi, T.; Fujita, Y.; Misawa, H.; Otera, J. *Bull. Chem. Soc. Jpn.* ***1986***, *59*, 3287.

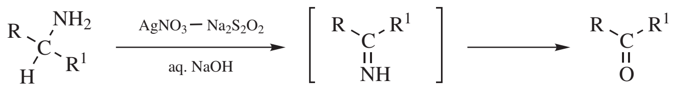
[654]Barbry, D.; Champagne, P. *Tetrahedron Lett.* ***1996***, *37*, 7725.

In a clearly related reaction, benzylic bromides are oxidized to aryl carboxylic acids by photolysis in acetone in the presence of mesoporous silica.[655]

OS **II**, 336: **III**, 811; **IV**, 690, 918, 932; **V**, 242, 668, 825, 852, 872. Also see, OS **V**, 689; **VI**, 218.

19-21 Oxidation of Amines or Nitro Compounds to Aldehydes, Ketones, or Dihalides

Oxo-de-hydro, amino-bisubstitution (overall transformation)



Primary aliphatic amines can be oxidized to aldehydes or ketones.[656] Other reagents used[657] have been *N*-bromoacetamide[658] (for benzylic amines), 3,5-di-*tert*-butyl-1,2-benzoquinone,[659] and aqueous NaOCl with phase-transfer catalysts.[660] Benzylic amine salts $PhCHRNR'_2\ H^+\ Cl^-$ (R,R′ = H or alkyl) give benzaldehydes or aryl ketones when heated in DMSO.[661] Several indirect methods for achieving the conversion $RR'CHNH_2 \rightarrow RR'C{=}O$ (R′ = alkyl, aryl, or H) have been reported.[662]

Primary, secondary, and tertiary aliphatic amines have been cleaved to give aldehydes, ketones, or carboxylic acids with aqueous bromine[663] and with neutral permanganate.[664] The other product of this reaction is the amine with one less alkyl group. In a different type of procedure, primary alkyl primary amines can be converted to *gem*-dihalides [$RCH_2NH_2 \rightarrow RCHX_2$ (X = Br or Cl)] by treatment with an alkyl nitrite and the anhydrous copper(I) halide.[665]

Primary and secondary aliphatic nitro compounds have been oxidized to aldehydes and ketones, respectively ($RR'CHNO_2 \rightarrow RR'C{=}O$) with sodium chlorite

[655]Itoh, A.; Kodama, T.; Inagaki, S.; Masaki, Y. *Org. Lett.* ***2000***, *2*, 2455.

[656]For a review, see Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Vol. 2, Academic Press, NY, ***1988***, pp. 200–220, 411–415.

[657]For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1225–1227; Hudlický, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, p. 240.

[658]Banerji, K.K. *Bull. Chem. Soc. Jpn.* ***1988***, *61*, 3717.

[659]Corey, E.J.; Achiwa, K. *J. Am. Chem. Soc.* ***1969***, *91*, 1429. For a study of the mechanism, see Klein, R.F.X.; Bargas, L.M.; Horak, V. *J. Org. Chem.* ***1988***, *53*, 5994.

[660]Lee, G.A.; Freedman, H.H. *Tetrahedron Lett.* ***1976***, 1641.

[661]Traynelis, V.J.; Ode, R.H. *J. Org. Chem.* ***1970***, *35*, 2207. For other methods, see Takabe, K.; Yamada, T. *Chem. Ind. (London)* ***1982***, 959; Azran, J.; Buchman, O.; Pri-Bar, I. *Bull. Soc. Chim. Belg.* ***1990***, *99*, 345.

[662]See, for example, Dinizo, S.E.; Watt, D.S. *J. Am. Chem. Soc.* ***1975***, *97*, 6900; Black, D.S.; Blackman, N.A. *Aust. J. Chem.* ***1975***, *28*, 2547; Scully, Jr., F.E.; Davis, R.C. *J. Org. Chem.* ***1978***, *43*, 1467; Doleschall, G. *Tetrahedron Lett.* ***1978***, 2131; Babler, J.H.; Invergo, B.J. *J. Org. Chem.* ***1981***, *46*, 1937.

[663]Deno, N.C.; Fruit, Jr., R.E. *J. Am. Chem. Soc.* ***1968***, *90*, 3502.

[664]Rawalay, S.S.; Shechter, H. *J. Org. Chem.* ***1967***, *32*, 3129. For another procedure, see Monković, I.; Wong, H.; Bachand, C. *Synthesis* ***1985***, 770.

[665]Doyle, M.P.; Siegfried, B. *J. Chem. Soc. Chem. Commun.* ***1976***, 433.

under phase transfer conditions,[666] tetrapropylammonium perruthenate (TPAP),[667] Oxone®,[668] as well as with other reagents.[669] Vinyl nitro compounds were converted to α-alkylated ketones, with good enantioselectivity, using R_2Zn, a chiral copper catalyst followed by hydrolysis with 20% aqueous sulfuric acid.[670]

19-22 Oxidation of Primary Alcohols to Carboxylic Acids or Carboxylic Esters

Oxo-de-dihydro-bisubstitution

$$RCH_2OH \xrightarrow{CrO_3} RCOOH$$

Primary alcohols can be oxidized to carboxylic acids by many strong oxidizing agents including chromic acid, permanganate,[671] and nitric acid.[672] Other reagents include H_5IO_6/CrO_3.[673] The reaction can be looked on as a combination of **19-3** and **19-23**. When acidic conditions are used, a considerable amount of carboxylic ester $RCOOCH_2R$ is often isolated, although this is probably not formed by a combination of the acid with unreacted alcohol, but by a combination of intermediate aldehyde with unreacted alcohol to give an acetal or hemiacetal, which is oxidized to the ester.[674] Aliphatic primary alcohols are converted to the carboxylic acid with 30% aq. H_2O_2, tetrabutylammonium hydrogen sulfate and a tungsten catalyst with microwave irradiation.[675] Oxone® in DMF also converts aliphatic aldehydes to the corresponding carboxylic acid.[676] Benzylic alcohols are oxidized to benzoic acid derivatives by treatment first with TEMPO[677] (p. 274), and then $NaClO_2$.[678] A combination of $NaClO_2$ and NaH_2PO_4 in aq. DMSO oxidizes aldehydes to acids even in the presence of a disulfide

[666]Ballini, R.; Petrini, M. *Tetrahedron Lett.* ***1989***, *30*, 5329.

[667]Tokunaga, Y.; Ihara, M.; Fukumoto, K. *J. Chem. Soc. Perkin Trans. 1* ***1997***, 207.

[668]Ceccherelli, P.; Curini, M., Marcotullio, M.C.; Epifano, F.; Rosati, O. *Synth. Commun.* ***1998***, *28*, 3057.

[669]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1227–1228.

[670]Luchaco-Cullis, C.A.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2002***, *124*, 8192.

[671]For a discussion of the mechanism of this oxidation, see Rankin, K.N.; Liu, Q.; Hendry, J.; Yee, H.; Noureldin, N.A.; Lee, D.G. *Tetrahedron Lett.* ***1998***, *39*, 1095.

[672]For reviews, see Hudlický, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, pp. 127–132; Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Vol. 2, Academic Press, NY, ***1988***, 148–165, 391–401. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1646–1650.

[673]Zhao, M.; Li, J.; Song, Z.; Desmond, R.; Tschaen, D.M.; Grabowski, E.J.J.; Reider, P.J. *Tetrahedron Lett.* ***1998***, *39*, 5323

[674]Craig, J.C.; Horning, E.C. *J. Org. Chem.* ***1960***, *25*, 2098. See also, Berthon, B.; Forestiere, A.; Leleu, G.; Sillion, B. *Tetrahedron Lett.* ***1981***, *22*, 4073; Nwaukwa, S.O.; Keehn, P.M. *Tetrahedron Lett.* ***1982***, *23*, 35.

[675]Bogdał, D.; Łukasiewicz, M. *Synlett* ***2000***, 143.

[676]Travis, B.R.; Sivakumar, M.; Hollist, G.O.; Borhan, B. *Org. Lett.* ***2003***, *5*, 1031.

[677]For other oxidations of this type utilizing TEMPO, see DeLuca, L.; Giacomelli, G.; Masala, S.; Porcheddu, A. *J. Org. Chem.* ***2003***, *68*, 4999. For a reaction using polymer-bound TEMPO, see Yasuda, K.; Ley, S.V. *J. Chem. Soc., Perkin Trans. 1* ***2002***, 1024.

[678]Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D.M.; Grabowski, E.J.J.; Reider, P.J. *J. Org. Chem.* ***1999***, *64*, 2564.

elsewhere in the molecule.[679] Similar oxidation to the acid occurred with $NaIO_4/RuCl_3$ in aqueous acetonitrile,[680] 30% aq. H_2O_2, and a cobalt–salen catalyst,[681] or oxygen on alumina with microwave irradiation.[682] Aliphatic alcohols are converted to a symmetrical ester ($RCH_2OH \rightarrow RCOOCH_2R$) by oxidation with PCC on aluminum without solvent.[683] Oxone in aqueous methanol also converts aryl aldehydes to the corresponding ester.[684] Allylic alcohols are converted to conjugated esters with MnO_2, NaCN in methanol–acetic acid.[685] Primary alcohols are oxidized to the methyl ester with trichloroisocyanuric acid in methanol.[686] This reagent also converts diols to lactones.

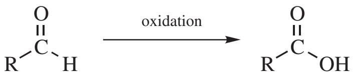
Primary alcohols RCH_2OH can be directly oxidized to acyl fluorides RCOF with cesium fluoroxysulfate.[687] Lactones can be prepared by oxidizing diols in which at least one OH is primary,[688] and addition of a chiral additive, such as sparteine, leads to lactones with high asymmetric induction.[689] 2-(3-Hydroxypropyl)aniline was oxidized to an acyl derivative that cyclized to give a lactam when heated with a rhodium catalyst.[690]

Primary alkyl ethers can be selectively cleaved to carboxylic acids by aq. Br_2 ($RCH_2OR' \rightarrow RCOOH$).[691] Secondary allylic alcohols are converted to ketones with 70% *tert*-butylhydroperoxide with a CrO_3 catalyst.[692]

OS **I**, 138, 168; **IV**, 499, 677; **V**, 580; **VII**, 406; **IX**, 462; **81**, 195. Also see, OS **III**, 745.

19-23 Oxidation of Aldehydes to Carboxylic Acids

Hydroxylation or **Hydroxy-de-hydrogenation**



[679]Fang, X.; Bandarage, U.P.; Wang, T.; Schroeder, J.D.; Garvey, D.S. *Synlett* ***2003***, 489.

[680]Prashad, M.; Lu, Y.; Kim, H.-Y.; Hu, B.; Repic, O.; Blacklock, T.J. *Synth. Commun.* ***1999***, *29*, 2937.

[681]Das, S.; Punniyamurthy, T. *Tetrahedron Lett.* ***2003***, *44*, 6033.

[682]Reddy, D.S.; Reddy, P.P.; Reddy, P.S.N. *Synth. Commun.* ***1999***, *29*, 2949.

[683]Bhar, S.; Chaudjuri, S.K. *Tetrahedron* ***2003***, *59*, 3493.

[684]Koo, B.-S.; Kim, E.-H.; Lee, K.-J. *Synth. Commun.* ***2002***, *32*, 2275.

[685]Foot, J.S.; Kanno, H.; Giblin, G.M.P.; Taylor, R.J.K. *Synlett* ***2002***, 1293.

[686]Hiegel, G.A.; Gilley, C.B. *Synth. Commun.* ***2003***, *33*, 2003.

[687]Stavber, S.; Planinsek, Z.; Zupan, M. *Tetrahedron Lett.* ***1989***, *30*, 6095.

[688]For examples of the preparation of lactones by oxidation of diols, see Jefford, C.W.; Wang, Y. *J. Chem. Soc. Chem. Commun.* ***1988***, 634; Jones, J.B.; Hirano, M.; Yakabe, S.; Morimoto, T. *Synth. Commun.* ***1998***, *28*, 123; Suzuki, T.; Morita, K.; Tsuchida, M.; Hiroi, K. *Org. Lett.* ***2002***, *4*, 2361; Hansen, T.M.; Florence, G.J.; Lugo-Mas, P.; Chen, J.; Abrams, J.N.; Forsynth, C.J. *Tetrahedron Lett.* ***2003***, *44*, 57; Suzuki, T.; Morita, K.; Matsuo, Y.; Hiroi, K. *Tetrahedron Lett.* ***2003***, *44,* 2003. For a list of reagents used to effect this conversion, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1650–1652.

[689]Yanagisawa, Y.; Kashiwagi, Y.; Kurashima, F.; Anzai, J.; Osa, T.; Bobbitt, J.M. *Chem. Lett.* ***1996***, 1043.

[690]Fujita, K.-i.; Takahashi, Y.; Owaki, M.; Yamamoto, K.; Yamaguchi, R. *Org. Lett.* ***2004***, *6*, 2785.

[691]Although these references refer to oxidation of alkyl ethers to ketones, oxidation to carboxylic acids is also possible. See Deno, N.C.; Potter, N.H. *J. Am. Chem. Soc.* ***1967***, *89*, 3550, 3555. See also, Miller, L.L.; Wolf, J.F.; Mayeda, E.A. *J. Am. Chem. Soc.* ***1971***, *93*, 3306; Saigo, K.; Morikawa, A.; Mukaiyama, T. *Chem. Lett.* ***1975***, 145; Olah, G.A.; Gupta, B.G.B.; Fung, A.P. *Synthesis* ***1980***, 897.

[692]Chandrasekhar, S.; Mohanty, P.K.; Ramachander, T. *Synlett* ***1999***, 1063.

Oxidation of aldehydes-to-carboxylic acids is quite common[693] and has been carried out with many oxidizing agents, the most popular of which is permanganate in acid, basic, or neutral solution.[694] Chromic acid,[695] bromine, and Oxone®,[696] are other reagents frequently employed. Bromate exchange resin in refluxing acetone oxidizes aryl aldehydes-to aryl-carboxylic acids.[697] Silver oxide is a fairly specific oxidizing agent for aldehydes and does not readily attack other groups. Benedict's and Fehling's solutions oxidize aldehydes,[698] and there is a test for aldehydes that depends on this reaction, but the method is seldom used for preparative purposes. In any case, it gives very poor results with aromatic aldehydes. α,β-Unsaturated aldehydes can be oxidized by sodium chlorite without disturbing the double bond.[699] Aldehydes are also oxidized to carboxylic acids by atmospheric oxygen, but the actual direct oxidation product in this case is the peroxy acid RCO_3H,[700] which with another molecule of aldehyde, disproportionates to give two molecules of acid (see **14-7**).[701] Aryl aldehydes are converted to the corresponding aryl carboxylic ester with hydrogen peroxide and a V_2O_5 catalyst[702] or a titanosilicate[703] in an alcohol solvent. Heating an α-bromoaldhyde with an alcohol and a triazolium carbene leads to the corresponding ester.[704] *N*-Bromophthalimide and mercuric

[693]For reviews, see Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Academic Press, NY, ***1988***, pp. 241–263, 423–428; Chinn, L.J. *Selection of Oxidants in Synthesis*, Marcel Dekker, NY, ***1971***, pp. 63–70; Lee, D.G., in Augustine, R.L. *Oxidataion*, Vol. 1, Marcel Dekker, NY, ***1969***, pp. 81–86.

[694]For lists of some of the oxidizing agents used, with references, see Hudlický, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, pp. 174–180; Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1653–1661; Srivastava, R.G.; Venkataramani, P.S. *Synth. Commun.* ***1988***, *18*, 2193. See also, Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Academic Press, NY, ***1988***.

[695]For a review, see Cainelli, G.; Cardillo, G. *Chromium Oxidations in Organic Chemistry*, Springer, NY, ***1984***, pp. 217–225.

[696]Webb, K.S.; Ruszkay, S.J. *Tetrahedron* ***1998***, *54*, 401.

[697]Chetri, A.B.; Kalita, B.; Das, P.J. *Synth. Commun.* ***2000***, *30*, 3317.

[698]For a review, see Nigh, W.G., in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B, Academic Press, NY, ***1973***, pp. 31–34.

[699]Bal, B.S.; Childers Jr., W.E.; Pinnick, H.W. *Tetrahedron* ***1981***, *37*, 2091; Dalcanale, E.; Montanari, F. *J. Org. Chem.* ***1986***, *51*, 567. See also Bayle, J.P.; Perez, F.; Courtieu, J. *Bull. Soc. Chim. Fr.* ***1990***, 565.

[700]For a review of the preparation of peroxy acids by this and other methods, see Swern, D., in Swern, D. *Organic Peroxides*, Vol. 1, Wiley, NY, ***1970***, pp. 313–516.

[701]For reviews of the autoxidation of aldehydes, see Vardanyan, I.A.; Nalbandyan, A.B. *Russ. Chem. Rev.* ***1985***, *54*, 532 (gas phase); Sajus, L.; Sérée de Roch, I., in Bamford, C.H., Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 16, Elsevier, NY, ***1980***, pp. 89–124 (liquid phase); Maslov, S.A.; Blyumberg, E.A. *Russ. Chem. Rev.* ***1976***, *45*, 155 (liquid phase). For a review of photochemical oxidation of aldehydes by O2, see Niclause, M.; Lemaire, J.; Letort, M. *Adv. Photochem.* ***1966***, *4*, 25. For a discussion of the mechanism of catalyzed atmospheric oxidation of aldehydes, see Larkin, D.R. *J. Org. Chem.* ***1990***, *55*, 1563.

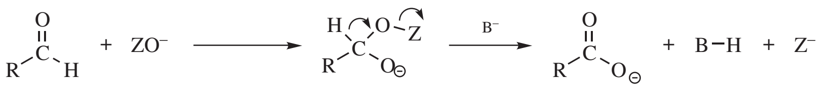
[702]Gopinath, R.; Patel, B.K. *Org. Lett.* ***2000***, *2*, 577.

[703]Chavan, S.P.; Dantale, S.W.; Govande, C.A.; Venkatraman, M.S.; Praveen, C. *Synlett* ***2002***, 267.

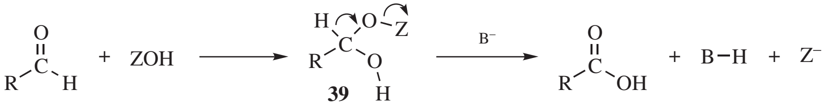
[704]Reynolds, N.T.; de Alaniz, J.R.; Rovis, T. *J. Am. Chem. Soc.* ***2004***, *126*, 9518.

acetate oxidizes aryl aldehydes to aryl carboxylic acids in chloroform at room temperature.[705] An aldehyde can be converted to the carboxylic acid by treatment with 30% hydrogen peroxide and methyl(trioctyl)ammonium hydrogen sulfate at 90°C.[706] Aryl aldehydes are similarly oxidized by a mixture of hydrogen peroxide and selenium dioxide (SeO_2).[707] Aldehydes (RCHO) can be directly converted to carboxylic esters (RCOOR′) by treatment with Br_2 in the presence of an alcohol.[708] Polymer-bound hypervalent iodine + TEMPO oxidizes aldehydes to acids.[709]

Mechanisms of aldehyde oxidation[710] are not firmly established, but there seem to be at least two main types: a free-radical mechanism and an ionic one. In the free-radical process, the aldehydic hydrogen is abstracted to leave an acyl radical, which obtains OH from the oxidizing agent. In the ionic process, the first step is addition of a species $^-$OZ to the carbonyl bond to give **38** in alkaline solution and **39** in acid or neutral solution. The aldehydic hydrogen of **38** or **39** is then lost as a proton to a base, while Z leaves with its electron pair.



38



39

For oxidation with acid dichromate the picture seems to be quite complex, with several processes of both types going on:[711]

[705]Anjum, A.; Srinivas, P. *Chem. Lett.* ***2001***, 900.

[706]Sato, K.; Hyodo, M.; Takagi, J.; Aoki, M.; Noyori, R. *Tetrahedron Lett.* ***2000***, *41*, 1439.

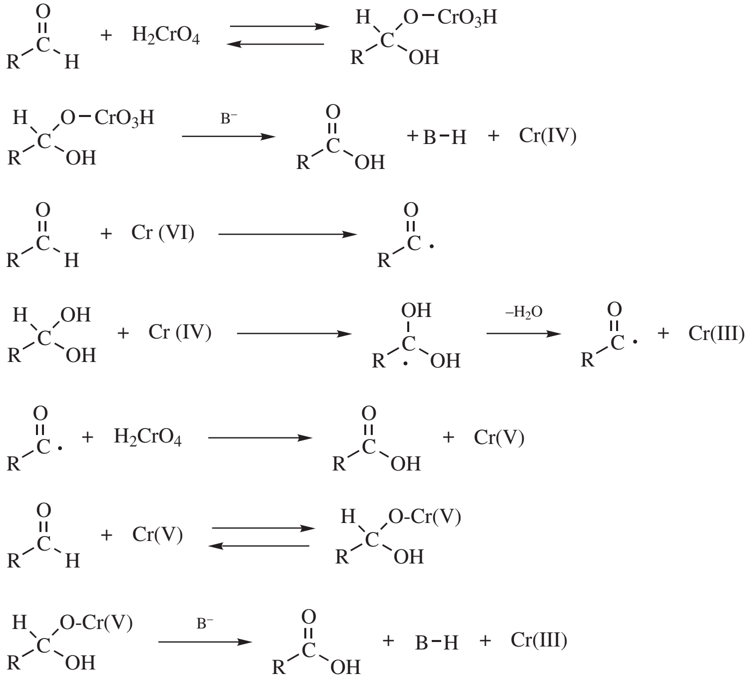
[707]Wójtowicz, H.; Brzą szcz, M.; Kloc, K.; M tochowski, J. *Tetrahedron* ***2001***, *57*, 9743.

[708]Williams, D.R.; Klingler, F.D.; Allen, E.E.; Lichtenthaler, F.W. *Tetrahedron Lett.* ***1988***, *29*, 5087; Al Neirabeyeh, M.; Pujol, M.D. *Tetrahedron Lett.* ***1990***, *31*, 2273. For other methods, see Sundararaman, P.; Walker, E.C.; Djerassi, C. *Tetrahedron Lett.* ***1978***, 1627; Grigg, R.; Mitchell, T.R.B.; Sutthivaiyakit, S. *Tetrahedron* ***1981***, *37*, 4313; Massoui, M.; Beaupère, D.; Nadjo, L.; Uzan, R. *J. Organomet. Chem.* ***1983***, *259*, 345; O'Connor, B.; Just, G. *Tetrahedron Lett.* ***1987***, *28*, 3235; McDonald, C.; Holcomb, H.; Kennedy, K.; Kirkpatrick, E.; Leathers, T.; Vanemon, P. *J. Org. Chem.* ***1989***, *54*, 1212. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1661–1669.

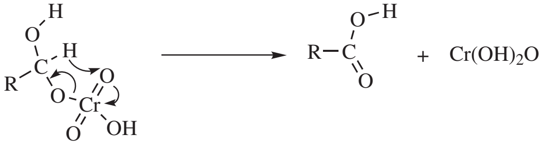
[709]Tashino, Y.; Togo, H. *Synlett* ***2004***, 2010.

[710]For a review, see Roček, J., in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 461–505.

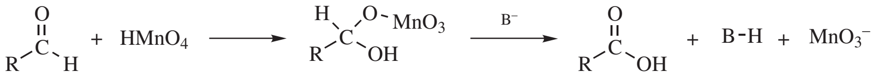
[711]Wiberg, K.B.; Szeimies, G. *J. Am. Chem. Soc.* ***1974***, *96*, 1889. See also, Roček, J.; Ng, C. *J. Am. Chem. Soc.* ***1974***, *96*, 1522, 2840; Sen Gupta, S.; Dey, S.; Sen Gupta, K.K. *Tetrahedron* ***1990***, *46*, 2431.



Steps 1 and 2 constitute an oxidation by the ionic pathway by Cr(VI), and steps 6 and 7 a similar oxidation by Cr(V), which is produced by an electron-transfer process. Either Cr(VI) (step 3) or Cr(IV) (step 4) [Cr(IV) is produced in step 2] may abstract a hydrogen and the resulting acyl radical is converted to carboxylic acid in step 5. Thus, chromium in three oxidation states is instrumental in oxidizing aldehydes. Still another possible process has been proposed in which the chromic acid ester decomposes as follows:[712]



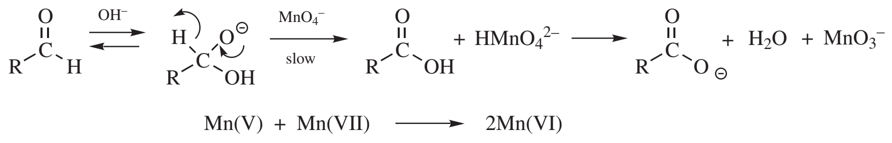
The mechanism with permanganate is less well known, but an ionic mechanism has been proposed[713] for neutral and acid permanganate, similar to steps 1 and 2 for dichromate:



[712]See Roček, J.; Ng, C. *J. Org. Chem.* ***1973***, *38*, 3348.

[713]See, for example, Freeman, F.; Lin, D.K.; Moore, G.R. *J. Org. Chem.* ***1982***, *47*, 56; Jain, A.L.; Banerji, K.K. *J. Chem. Res. (S)* ***1983***, 60.

For alkaline permanganate, the following mechanism has been proposed:[714]

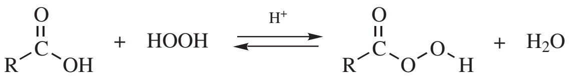


OS **I**, 166; **II**, 302, 315, 538; **III**, 745; **IV**, 302, 493, 499, 919, 972, 974.

The conversion of thioketones to sulfines ($R_2C{=}S{=}O$) is difficult to categorize into the sections available, and it placed after oxidation of ketones and aldehydes. The reaction of a thioketone with hydrogen peroxide and a catalytic amount of MTO (methyl trioxorhenium) gives the sulfine.[715]

19-24 Oxidation of Carboxylic Acids to Peroxy Acids

Peroxy-de-hydroxy-substitution

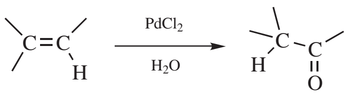


The oxidation of carboxylic acids with H_2O_2 and an acid catalyst is the best general method for the preparation of peroxy acids.[716] A mixture of $Me_2C(OMe)OOH$ and DCC has also been used.[717] The most common catalyst for aliphatic R is concentrated sulfuric acid. The reaction is an equilibrium and is driven to the right by removal of water or by the use of excess reagents. For aromatic R, the best catalyst is methanesulfonic acid, which is also used as the solvent.

D. Reactions in Which Oxygen is Added to the Substrate

19-25 Oxidation of Alkenes to Aldehydes and Ketones

1/Oxo-(1/→2/hydro)-*migro*-attachment



[714]Freeman, F.; Brant, J.B.; Hester, N.B.; Kamego, A.A.; Kasner, M.L.; McLaughlin, T.G.; Paul, E.W. *J. Org. Chem.* ***1970***, *35*, 982.

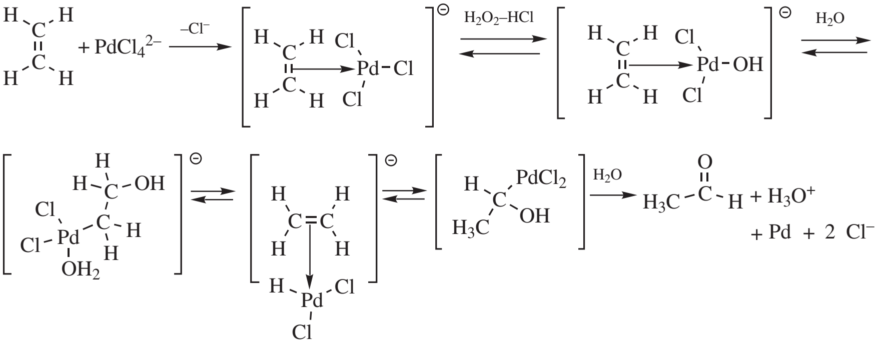
[715]Huang, R.; Espenson, J.H. *J. Org. Chem.* ***1999***, *64*, 6935.

[716]For a review of the preparation of peroxy acids, see Swern, D., in Swern, D. *Organic Peroxides*, Vol. 1, Wiley, NY, ***1970***, pp. 313–516.

[717]Dussault, P.; Sahli, A. *J. Org. Chem.* ***1992***, *57*, 1009.

Monosubstituted and 1,2-disubstituted alkenes can be oxidized to aldehydes and ketones by palladium chloride and similar salts of noble metals.[718] 1,1-Disubstituted alkenes generally give poor results. The reaction is used industrially to prepare acetaldehyde from ethylene (the *Wacker process*), but it is also suitable for laboratory preparations. The palladium chloride is reduced to palladium. Because the reagent is expensive, the reaction is usually carried out with a co-oxidant, most often $CuCl_2$, whose function is to reoxidize the Pd to Pd(II). The $CuCl_2$ is reduced to Cu(I), which itself is reoxidized to Cu(II) by air, so that atmospheric oxygen is the only oxidizing agent actually used up. Many other co-oxidants have been tried, among them O_3, Fe^{3+}, and PbO_2. Terminal alkenes are oxidized to methyl ketones with O_2 and a palladium catalyst with 20% pyridine in Z-propanol.[719] *tert*-Butylhydroperoxide in bromoperfluorooctane–benzene oxidizes styrene to acetophenone in a Wacker-type process.[720] The principal product is an aldehyde only from ethylene: With other alkenes Markovnikov's rule is followed, and ketones are formed predominantly.

The generally accepted mechanism involves π complexes of palladium.[721]



This mechanism accounts for the fact, established by deuterium labeling, that the four hydrogens of the acetaldehyde all come from the original ethylene and none from the solvent.

[718]For a monograph, see Henry, P.M. *Palladium Catalyzed Oxidation of Hydrocarbons*, D. Reidel Publishing Co., Dordrecht, ***1980***. For reviews, see Tsuji, J. *Organic Synthesis with Palladium Compounds*, Springer, NY, ***1980***, pp. 6–12; *Synthesis* ***1990***, 739; ***1984***, 369; *Adv. Org. Chem.* ***1969***, *6*, 109, see pp. 119–131; Heck, R.F. *Palladium Reagents in Organic Syntheses*, Academic Press, NY, ***1985***, pp. 59–80; Sheldon, R.A.; Kochi, J.K. *Metal-Catalyzed Oxidations of Organic Compounds*, Academic Press, NY, ***1981***, pp. 189–193, 299–303; Henry, P.M. *Adv. Organomet. Chem.* ***1975***, *13*, 363, see pp. 378–388; Jira, R.; Freiesleben, W. *Organomet. React.* ***1972***, *3*, 1, pp. 1–44; Khan, M.M.T.; Martell, A.E. *Homogeneous Catalysis by Metal Complexes*, Vol. 2, Academic Press, NY, ***1974***, pp. 77–91; Hüttel, R. *Synthesis* ***1970***, 225, see pp. 225–236; Aguiló, A. *Adv. Organomet. Chem.* ***1967***, *5*, 321; Bird, C.W. *Transition Metal Intermediates in Organic Synthesis*, Academic Press, NY, ***1967***, pp. 88–111.

[719]Nishimura, T.; Kakiuchi, N.; Onoue, T.; Ohe, K.; Uemura, S. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 1915.

[720]Betzemeier, B.; Lhermitte, F.; Knochel, P. *Tetrahedron Lett.* ***1998***, *39*, 6667.

[721]Henry, P.M. *J. Am. Chem. Soc.* ***1972***, *94*, 4437; Jira, R.; Sedlmeier, J.; Smidt, J. *Liebigs Ann. Chem.* ***1966***, *693*, 99; Hosokawa, T.; Maitlis, P.M. *J. Am. Chem. Soc.* ***1973***, *95*, 4924; Moiseev, I.I.; Levanda, O.G.; Vargaftik, M.N. *J. Am. Chem. Soc.* ***1974***, *96*, 1003; Bäckvall, J.; Åkermark, B.; Ljunggren, S.O. *J. Am. Chem. Soc.* ***1979***, *101*, 2411; Zaw, K.; Henry, P.M. *J. Org. Chem.* ***1990***, *55*, 1842.

Similar reactions have been carried out with other oxidizing agents. An example involving migration of an alkyl group instead of hydrogen is oxidation of $Me_2C{=}CMe_2$ with peroxytrifluoroacetic acid-boron trifluoride to give Me_3COMe (pinacolone).[722] This reaction consists of epoxidation (**15-50**) followed by pinacol rearrangement of the epoxide (**18-2**). A migration is also involved in the conversion of $ArCH{=}CHCH_3$ to $ArCH(CH_3)CHO$ by treatment with I_2-Ag_2O in aqueous dioxane.[723]

Other reagents used have been $Pb(OAc)_4$–F_3CCOOH[724] (e.g., $PhCH{=}CH_2 \rightarrow PhCH_2CHO$), H_2O_2 and a Pd catalyst,[725] H_2O–$PdCl_2$–polyethylene glycol,[726] CrO_3–H_2SO_4–Hg(II) salts,[727] and $Hg(OAc)_2$ followed by $PdCl_2$.[728] The reaction has also been accomplished electrochemically.[729] Terminal alkenes react with ceric ammonium nitrate in methanol to give α-methoxy ketones.[730]

Alkenes have also been converted to more highly oxidized products. Examples are (*1*) treatment with $KMnO_4$ in aqueous acetone containing acetic acid gives α-hydroxy ketones.[731] (*2*) 1,2-Disubstituted and trisubstituted alkenes give α-chloro ketones when oxidized with chromyl chloride in acetone: $RCH{=}CR'R^2 \rightarrow RCOCClR'R^2$.[732] (*3*) α-Iodo ketones can be prepared by treating alkenes with bis-(*sym*-collidine)iodine(I) tetrafluoroborate.[733] (*4*) potassium permanganate in acetic anhydride oxidizes large-ring cycloalkenes to 1,2-diketones.[734]

Enol ethers are oxidized to carboxylic esters ($RCH{=}CHOR' \rightarrow RCH_2COOR'$) with PCC[735] and enamines to α-amino ketones ($R^1CH{=}CR_2NR \rightarrow R^1COCR_2NR$) with *N*-sulfonyloxaziridines.[736] Enamines ($R^1R^4C{=}CR^2NR^3_2$, $R^4 \neq H$) do not give these products, but lose the amino group to give α-hydroxy ketones, $R^1R^4C(OH)$-COR^2.[736] Carboxylic acids can be prepared from terminal alkynes ($RC{\equiv}CH \rightarrow$

[722]Hart, H.; Lerner, L.R. *J. Org. Chem.* ***1967***, *32*, 2669.

[723]Kikuchi, H.; Kogure, K.; Toyoda, M. *Chem. Lett.* ***1984***, 341.

[724]Lethbridge, A.; Norman, R.O.C.; Thomas, C.B. *J. Chem. Soc. Perkin Trans. 1* ***1973***, 35.

[725]Roussel, M.; Mimoun, H. *J. Org. Chem.* ***1980***, *45*, 5387.

[726]Alper, H.; Januszkiewicz, K.; Smith, D.J.H. *Tetrahedron Lett.* ***1985***, *26*, 2263.

[727]Rogers, H.R.; McDermott, J.X.; Whitesides, G.M. *J. Org. Chem.* ***1975***, *40*, 3577.

[728]Rodeheaver, G.T.; Hunt, D.F. *Chem. Commun.* ***1971***, 818. See also, Hunt, D.F.; Rodeheaver, G.T. *Tetrahedron Lett.* ***1972***, 3595.

[729]See Tsuji, J.; Minato, M. *Tetrahedron Lett.* ***1987***, *28*, 3683.

[730]Nair, V.; Nair, L.G.; Panicker, S.B.; Sheeba, V.; Augustine, A. *Chem. Lett.* ***2000***, 584.

[731]Srinivasan, N.S.; Lee, D.G. *Synthesis* ***1979***, 520. See also, Baskaran, S.; Das, J.; Chandrasekaran, S. *J. Org. Chem.* ***1989***, *54*, 5182.

[732]Sharpless, K.B.; Teranishi, A.Y. *J. Org. Chem.* ***1973***, *38*, 185. See also, Cardillo, G.; Shimizu, M. *J. Org. Chem.* ***1978***, *42*, 4268; D'Ascoli, R.; D'Auria, M.; Nucciarelli, L.; Piancatelli, G.; Scettri, A. *Tetrahedron Lett.* ***1980***, *21*, 4521; Kageyama, T.; Tobito, Y.; Katoh, A.; Ueno, Y.; Okawara, M. *Chem. Lett.* ***1983***, 1481; Lee, J.G.; Ha, D.S. *Tetrahedron Lett.* ***1989***, *30*, 193.

[733]Evans, R.D.; Schauble, J.H. *Synthesis* ***1986***, 727.

[734]Jensen, H.P.; Sharpless, K.B. *J. Org. Chem.* ***1974***, *39*, 2314.

[735]Piancatelli, G.; Scettri, A.; D'Auria, M. *Tetrahedron Lett.* ***1977***, 3483. When $R^1CR^2C{=}CR^3OR^4$ are used, cleavage of the double bond takes place instead: Baskaran, S.; Islam, I.; Raghavan, M.; Chandrasekaran, S. *Chem. Lett.* ***1987***, 1175.

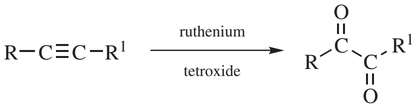
[736]Davis, F.A.; Sheppard, A.C. *Tetrahedron Lett.* ***1988***, *29*, 4365.

RCH_2COOH) by conversion of the alkyne to its phenylthio ether (RC≡CSPh) and treatment of this with $HgSO_4$ in HOAc–H_2SO_4.[737]

OS **VI**, 1028; **VII**, 137; **VIII**, 208.

19-26 The Oxidation of Alkynes to α-Diketones

Dioxo-biaddition



Internal alkynes have been oxidized[738] to α-diketones by several oxidizing agents,[739] including neutral $KMnO_4$,[740] bis(trifluoroacetoxy)iodobenzene,[741] $NaIO_4$–RuO_2,[742] I_2–DMSO,[743] $MeReO_3/H_2O_2$,[744] as well as by electrooxidation.[745] A ruthenium complex with a small amount of trifluoroacetic acid converts internal alkynes to the α-diketone.[746] Ozone generally oxidizes triple-bond compounds to carboxylic acids (**19-9**), but α-diketones are sometimes obtained instead. Selenium dioxide (SeO_2) with a small amount of H_2SO_4 oxidizes alkynes to α-diketones as well as arylacetylenes to α-keto acids (ArC≡CH → ArCOCOOH).[747]

19-27 Oxidation of Amines to Nitroso Compounds and Hydroxylamines and Related

***N*-Oxo-de-dihydro-bisubstitution**

$$ArNH_2 \xrightarrow{H_2SO_5} Ar{-}N{=}O$$

[737]Abrams. S. R. *Can. J. Chem.* ***1983***, *61*, 2423.

[738]For a review of this reaction, see Haines, A.H. *Methods for the Oxidation of Organic Compounds*,Vol. 1, Academic Press, NY, ***1985***, pp. 153–162, 332-338. For a review of oxidations of triple bonds in general, see Simándi, L.I., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 1, Wiley, NY, ***1983***, pp. 513–570.

[739]For a list of reagents, with references, see Hudlický, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, p. 92.

[740]Khan, N.A.; Newman, M.S. *J. Org. Chem.* ***1952***, *17*, 1063; Lee, D.G.; Lee, E.J.; Chandler, W.D. *J. Org. Chem.* ***1985***, *50*, 4306; Tatlock, J.H. *J. Org. Chem.* ***1995***, *60*, 6221.

[741]Vasil'eva, V.P.; Khalfina, I.L.; Karpitskaya, L.G.; Merkushev, E.B. *J. Org. Chem. USSR* ***1987***, *23*, 1967.

[742]Zibuck, R.; Seebach, D. *Helv. Chim. Acta* ***1988***, *71*, 237.

[743]Yusybov, M.S.; Filimonov, V.D. *Synthesis* ***1991***, 131.

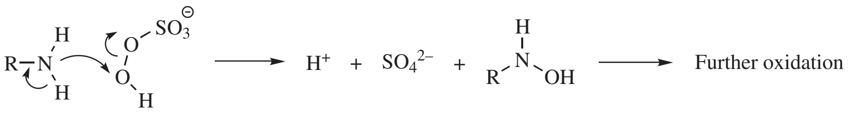
[744]Zhu, Z.; Espenson, J.H. *J. Org. Chem.* ***1995***, *60*, 7728.

[745]Torii, S.; Inokuchi, T.; Hirata, Y. *Synthesis* ***1987***, 377.

[746]Che, C.-M.; Yu, W.-Y.; Chan, P.-M.; Cheng, W.-C.; Peng, S.-M.; Lau, K.-C.; Li, W.-K. *J. Am. Chem. Soc.* ***2000***, *122*, 11380.

[747]Sonoda, N.; Yamamoto, Y.; Murai, S.; Tsutsumi, S. *Chem. Lett.* ***1972***, 229.

Primary aromatic amines can be oxidized[748] to nitroso compounds. Most often the conversion is accomplished by Caro's acid (H_2SO_5) or with H_2O_2 in HOAc.[749] Hydroxylamines, which are probably intermediates in most cases, can sometimes be isolated, but under the reaction conditions are generally oxidized to the nitroso compounds. Primary aliphatic amines can be oxidized in this manner, but the nitroso compound is stable only if there is no α hydrogen. If there is an α hydrogen, the compound tautomerizes to the oxime.[750] Among the reagents used for this oxidation are sodium perborate[751] H_2O_2 with a titanium complex,[752] HOF generated *in situ*,[753] and Na_2WO_4/H_2O_2.[754] The mechanism with H_2SO_5 has been postulated to be an example of category 5 (p. 1706).[755]



Secondary amines, R_2NH, are oxidized to hydroxylamines (R_2NHOH) which are resistant to further oxidation, by dimethyldioxirane[756] and by benzoyl peroxide and Na_2HPO_4.[757] Oxone® on silica also oxidizes secondary alcohols to the hydroxylamine.[758] Hydroxylamines are formed when secondary amines react with the enzyme cyclohexanone monooxygenase.[759] Carbamates, such as *N*-Boc amines, are converted tot he *N*-hydroxy compound with bis(trifluoromethyl)-dioxirane.[760] Note that secondary alcohols can be converted to nitrones with aq. H_2O_2 and a phosphotungstate polymer complex, presumably via an hydroxylamine (see **19-28**) formed *in situ*.[761] Dialkylamiens are oxidized to the *N*-nitroso compound with N_2O_2 on polyvinylpyrrolidinone.[762]

OS **III**, 334; **VIII**, 93; **80**, 207.

[748]For reviews on the oxidation of amines, see Rosenblatt, D.H.; Burrows, E.P., in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 2, Wiley, NY, ***1982***, pp. 1085–1149; Challis, B.C.; Butler, A.R., in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, pp. 320–338. For reviews confined to primary aromatic amines, see Hedayatullah, M. *Bull. Soc. Chim. Fr.* ***1972***, 2957; Surville, R. De; Jozefowicz, M.; Buvet, R. *Ann. Chim. (Paris)* ***1967***, *[14] 2*, 149.
[749]Holmes, R.R.; Bayer, R.P. *J. Am. Chem. Soc.* ***1960***, *82*, 3454.
[750]For example, see Kahr, K.; Berther, C. *Chem. Ber.* ***1960***, *93*, 132.
[751]Zajac Jr., W.W.; Darcy, M.G.; Subong, A.P.; Buzby, J.H. *Tetrahedron Lett.* ***1989***, *30*, 6495.
[752]Dewkar, G.K.; Nikalje, M.D.; Ali, I.S.; Paraskar, A.S.; Jagtap, H.S.; Sadalai, A. *Angew. Chem. Int. Ed.* ***2001***, *40*, 405.
[753]Dirk, S.M.; Mickelson, E.T.; Henderson, J.C.; Tour, J.M. *Org. Lett.* ***2002***, *2*, 3405.
[754]Corey, E.J.; Gross, A.W. *Org. Synth. 65*, 166.
[755]Gragerov, I.P.; Levit, A.F. *J. Gen Chem. USSR* ***1960***, *30*, 3690.
[756]Murray, R.W.; Singh, M. *Synth. Commun.* ***1989***, *19*, 3509. This reagent also oxidizes primary amines to hydroxylamines: Wittman, M.D.; Halcomb, R.L.; Danishefsky, S.J. *J. Org. Chem.* ***1990***, *55*, 1981.
[757]Biloski, A.J.; Ganem, B. *Synthesis* ***1983***, 537.
[758]Fields, J.D.; Kropp, P.J. *J. Org. Chem.* ***2000***, *65*, 5937.
[759]Colonna, S.; Pironti, V.; Carrea, G.; Pasta, P.; Zambianchi, F. *Tetahedron* ***2004***, *60*, 569.
[760]Detomaso, A.; Curci, R. *Tetrahedron Lett.* ***2001***, *42*, 755.
[761]Yamada, Y.M.A.; Tabata, H.; Takahashi, H.; Ikegami, S. *Synlett* ***2002***, 2031.
[762]Iranpoor, N.; Firouzabadi, H.; Pourali, A.R. *Synthesis* ***2003***, 1591.

19-28 Oxidation of Primary Amines, Oximes, Azides, Isocyanates, or Nitroso Compounds to Nitro Compounds

$$R_3CNH_2 \xrightarrow{KMnO_4} R_3CNO_2$$

$$R_2C{=}NOH \xrightarrow{F_3CCOOOH} R_2CHNO_2$$

Tertiary alkyl primary amines can be oxidized to nitro compounds in excellent yields with $KMnO_4$.[763] This type of nitro compound is not easily prepared in other ways. All classes of primary amine (including primary, secondary, and tertiary alkyl, as well as aryl) are oxidized to nitro compounds in high yields with dimethyldioxirane.[764] Other reagents that oxidize various types of primary amines to nitro compounds are dry ozone,[765] various peroxyacids,[766] $MeReO_3/H_2O_2$,[767] Oxone®,[768] *tert*-butyl hydroperoxide in the presence of certain molybdenum and vanadium compounds,[769] and sodium perborate.[770]

Dimethyldioxirane in wet acetone oxidizes isocyanates to nitro compounds ($RNCO \rightarrow RNO_2$).[771] Oximes can be oxidized to nitro compounds with peroxytrifluoroacetic acid, or Oxone®,[772] sodium perborate,[773] among other ways.[763] Secondary hydroxylamines are also oxidized to nitrones with MnO_2 in dichloromethane.[774] Primary and secondary alkyl azides have been converted to nitro compounds by treatment with Ph_3P followed by ozone.[775] Aromatic nitroso compounds are easily oxidized to nitro compounds by many oxidizing agents.[776]

OS **III**, 334; **V**, 367, 845; **VI**, 803; **81**, 204.

[763]Larson, H.O., in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, Vol. 1, Wiley, NY, ***1969***, pp. 306–310. See also, Barnes, M.W.; Patterson, J.M. *J. Org. Chem.* ***1976***, *41*, 733. For reviews of oxidations of nitrogen compounds, see Butler, R.N. *Chem. Rev.* ***1984***, *84*, 249; Boyer, J.H. *Chem. Rev.* ***1980***, *80*, 495.

[764]Murray, R.W.; Rajadhyaksha, S.N.; Mohan, L. *J. Org. Chem.* ***1989***, *54*, 5783. See also, Zabrowski, D.L.; Moorman, A.E.; Beck Jr., K.R. *Tetrahedron Lett.* ***1988***, *29*, 4501.

[765]Keinan, E.; Mazur, Y. *J. Org. Chem.* ***1977***, *42* 844; Bachman, G.B.; Strawn, K.G. *J. Org. Chem.* ***1968***, *33*, 313.

[766]Emmons, W.D. *J. Am. Chem. Soc.* ***1957***, *79*, 5528; Gilbert, K.E.; Borden, W.T. *J. Org. Chem.* ***1979***, *44*, 659.

[767]Murray, R.W.; Iyanar, K.; Chen, J.; Wearing, J.T. *Tetrahedron Lett.* ***1996***, *37*, 805; Cardona, F.; Soldaini, G.; Goti, A. *Synlett* ***2004***, 1553.

[768]Webb, K.S.; Seneviratne, V. *Tetrahedron Lett.* ***1995***, *36*, 2377.

[769]Howe, G.R.; Hiatt, R.R. *J. Org. Chem.* ***1970***, *35*, 4007. See also, Nielsen, A.T.; Atkins, R.L.; Norris, W.P.; Coon, C.L.; Sitzmann, M.E. *J. Org. Chem.* ***1980***, *45*, 2341.

[770]McKillop, A.; Tarbin, J.A. *Tetrahedron* ***1987***, *43*, 1753.

[771]Eaton, P.E.; Wicks, G.E. *J. Org. Chem.* ***1988***, *53*, 5353.

[772]Bose, D.S.; Vanajatha, G. *Synth. Commun.* ***1998***, *28*, 4531.

[773]Olah, G.A.; Ramaiah, P.; Lee, G.K.; Prakash, G.K.S. *Synlett* ***1992***, 337.

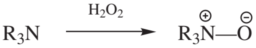
[774]Cicchi, S.; Marradi, M.; Goti, A.; Brandi, A. *Tetrahedron Lett.* ***2001***, *42*, 6503.

[775]Corey, E.J.; Samuelsson, B.; Luzzio, F.A. *J. Am. Chem. Soc.* ***1984***, *106*, 3682.

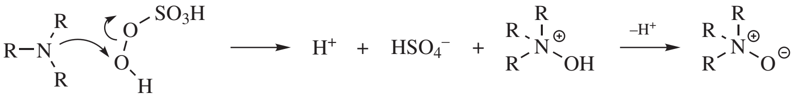
[776]See Boyer, J.H., in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, Vol. 1, Wiley, NY, ***1969***, pp. 264–265.

19-29 Oxidation of Tertiary Amines to Amine Oxides

N-Oxygen-attachment



Tertiary amines can be converted to amine oxides by oxidation. Hydrogen peroxide is often used, but peroxyacids are also important reagents for this purpose. Pyridine and its derivatives are oxidized by peroxyacids[777] rather than hydrogen peroxide. Note, however, that urea–H_2O_2 in formic acid does indeed oxidize pyridine.[778] In the attack by hydrogen peroxide there is first formed a trialkylammonium peroxide, a hydrogen-bonded complex represented as $R_3N{\bullet}H_2O_2$, which can be isolated.[779] The decomposition of this complex probably involves an attack by the OH moiety of the H_2O_2. Oxidation with Caro's acid has been shown to proceed in this manner:[780]



This mechanism is the same as that of **19-27**; the products differ only because tertiary amine oxides cannot be further oxidized. The mechanism with other peroxyacids is probably the same. A green procedure for oxidation of tertiary amines has been developed, using a Mg–Al complex with aq. hydrogen peroxide.[781]

An alternative oxidation using O_2 and a $RuCl_3$ catalyst converted pyridine to pyridine *N*-oxide.[782] Bromamine-T and $RuCl_3$ in aq. acetonitrile also oxidizes pyridine to the *N*-oxide.[783] Tertiary amines are oxidized to the *N*-oxide with O_2 and Fe_2O_3 in the presence of an aliphatic aldehyde.[784] Oxygen and a cobalt–Schiff base complex also oxidzes tertiary amines, including pyridine.[785]

It is noted that azo compounds can be oxidized to azoxy compounds by peroxyacids[786] or by hydroperoxides and molybdenum complexes.[787]

Analogous to the oxidation of tertiary amines, tertiary phosphines are oxidized to phosphine oxides, ($R_3P{=}O$). Triphenylphosphine is converted to triphenylphosphine

[777]For reviews, see Albini, A.; Pietra, S. *Heterocyclic N-Oxides*; CRC Press: Boca Raton, FL, ***1991***, pp. 31–41; Katritzky, A.R.; Lagowski, J.M. *Chemistry of the Heterocyclic N-Oxides*, Academic Press, NY, ***1971***, pp. 21–72, 539–542.

[778]Balicki, R.; Goliski, J. *Synth. Commun.* ***2000***, *30*, 1529.

[779]Oswald, A.A.; Guertin, D.L. *J. Org. Chem.* ***1963***, *28*, 651.

[780]Ogata, Y.; Tabushi, I. *Bull. Chem. Soc. Jpn.* ***1958***, *31*, 969.

[781]Choudary, B.M.; Bharathi, B.; Reddy, Ch.V.; Kantam, M.L.; Raghavan, K.V. *Chem. Commun.* ***2001***, 1736.

[782]Jain, S.L.; Sain, B. *Chem. Commun.* ***2002***, 1040.

[783]Sharma, V.B.; Jain, S.L.; Sain, B. *Tetrahedron Lett.* ***2004***, *45*, 4281.

[784]Wang, F.; Zhang, H.; Song, G.; Lu, X. *Synth. Commun.* ***1999***, *29*, 11.

[785]Jain, S.L.; Sain, B. *Angew. Chem. Int. Ed.* ***2003***, *42*, 1265.

[786]For reviews, see Yandovskii, V.N.; Gidaspov, B.V.; Tselinskii, I.V. *Russ. Chem. Rev.* ***1981***, *50*, 164; Newbold, B.T., in Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 1, Wiley, NY, ***1975***, pp. 557–563, 573–593.

[787]Johnson, N.A.; Gould, E.S. *J. Org. Chem.* ***1974***, *39*, 407. For a mechanistic discussion, see Mitsuhashi, T.; Simamura, O.; Tezuka, Y. *Chem. Commun.* ***1970***, 1300.

oxide with N_2O at 100°C, for example. Triphenylphosphine is also oxidized with PhIO on Montmorillonite K10.[788] *tert*-Butylhydroperoxide oxides $Ph_3{\rightarrow}BH_3$ to $Ph_3P{=}O$.[789]

OS **IV**, 612, 704, 828; **VI**, 342, 501; **VIII**, 87.

19-30 Oxidation of Thiols and Other Sulfur Compounds to Sulfonic Acids

Thiol-sulfonic acid oxidation

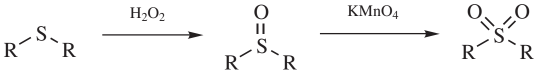
$$RSH \xrightarrow{HNO_3} RSO_3H$$

Thiols, sulfoxides, sulfones, disulfides,[790] and other sulfur compounds can be oxidized to sulfonic acids with many oxidizing agents, but for synthetic purposes the reaction is most important for thiols.[791] Among oxidizing agents used are boiling nitric acid, barium permanganate, and dimethyl dioxirane.[792] Autoxidation (oxidation by atmospheric oxygen) can be accomplished in basic solution.[793] Oxidation of thiols with chlorine and water gives sulfonyl chlorides directly.[794] Thiols can also be oxidized to disulfides (**19-34**).

OS **II**, 471; **III**, 226. Also see, OS **V**, 1070.

19-31 Oxidation of Thioethers to Sulfoxides and Sulfones

S-Oxygen-attachment



Thioethers can be oxidized to sulfoxides by 1 equivalent of 30% H_2O_2 or by many other oxidizing agents,[795] including H_2O_2–flavin catalyst,[796] H_2O_2 and a

[788]Mielniczak, G.; Łopusiń ski, A. *Synlett* ***2001***, 505.

[789]Uziel, J.; Darcel, C.; Moulin, D.; Bauduin, C.; Juge, S. *Tetrahedron Asymmetry* ***2001***, *12*, 1441.

[790]For a review of the oxidation of disulfides, see Savige, W.E.; Maclaren, J.A., in Kharasch, N.; Meyers, C.Y. *Organic Sulfur Compounds*, Vol. 2; pp. 367–402, Pergamon, NY, ***1966***.

[791]For a general review of the oxidation of thiols, see Capozzi, G.; Modena, G., in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, ***1974***, pp. 785–839. For a review specifically on the oxidation to sulfonic acids, see Gilbert, E.E. *Sulfonation and Related Reactions*, Wiley, NY, ***1965***, pp. 217–239.

[792]Gu, D.; Harpp, D.N. *Tetrahedron Lett.* ***1993***, *34*, 67.

[793]Wallace, T.J.; Schriesheim, A. *Tetrahedron* ***1965***, *21*, 2271.

[794]For a review, see Gilbert, E.E. *Sulfonation and Related Reactions*, Wiley, NY, ***1965***, pp. 202–214.

[795]For reviews, see Hudlický, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC ***1990***, pp. 252–263; Drabowicz, J.; Kiełbasinski, P.; Mikołajczyk, M., in Patai, S.; Rappoport, Z.; Stirling, C. *The Chemistry of Sulphones and Sulphoxides*, Wiley, NY, ***1988***, pp. 233–378, pp. 235–255; Madesclaire, M. *Tetrahedron* ***1986***, *42*, 5459; Block, E., in Patai, S. *The Chemistry of Functional Groups, Supplement E*, pt. 1, Wiley, NY, ***1980***, pp. 539–608. For reviews on methods of synthesis of sulfoxides, see Drabowicz, J.; Mikołajczyk, M. *Org. Prep. Proced. Int.* ***1982***, *14*, 45; Oae, S., in Oae, S. *The Organic Chemistry of Sulfur*, Plenum, NY, ***1977***, pp. 385–390. For a review with respect to enzymic oxidation, see Holland, H.L. *Chem. Rev.* ***1988***, *88*, 473.

[796]Lindén, A.A.; Krüger, L.; Bäckvall, J.-E. *J. Org. Chem.* ***2003***, *68*, 5890.

$Sc(OTf)_3$ catalyst,[797] $NaIO_4$,[798] dioxiranes,[799] $MeReO_3/H_2O_2$,[800] O_2 and a ceric ammonium nitrate catalyst,[801] trichloroisocyanuric acid,[802] $BnPh_3P$ HSO_5,[803] KO_2/Me_3SiCl,[804] $Fe(NO_3)_3/FeBr_3$/air,[805] singlet oxygen on MB–Bentonite composite,[806] MnO_2 with a H_2SO_4/SiO_2 catalyst,[807] hexamethylene triamine-Br_2 with $CHCl_3$—H_2O,[808] sodium perborate,[770] $H_5IO_6/FeCl_3$,[809] hypervalent iodine compounds,[810] and peroxyacids.[811] Sulfoxides can be further oxidized to sulfones by another equivalent of H_2O_2, $KMnO_4$, sodium perborate, or a number of other agents. If enough oxidizing agent is present, thioethers can be directly converted to sulfones without isolation of the sulfoxides.[812] Thioethers can be oxidized directly to the sulfone by treatment with excess NaOCl[813] tetramethylperruthenate (TPAP,)[814] H_2O_2 and an iron catalyst,[815] H_2O_2 and 10% Na_2WO_4,[816] H_2O_2/AcOH/ $MgSO_4$,[817] urea–H_2O_2,[818] peroxy monosulfate and a manganese catalyst,[819] or with $NaIO_4$/catalytic $RuCl_3$.[820]

These reactions give high yields, and many functional groups do not interfere.[821] As with tertiary amines (**19-29**), racemic thioethers can be kinetically resolved by

[797]Matteucci, M.; Bhalay, G.; Bradley, M. *Org.Lett.* ***2003***, *5*, 235.

[798]Leonard, N.J.; Johnson, C.R. *J. Org. Chem.* ***1962***, *27*, 282; Hiskey, R.G.; Harpold, M.A. *J. Org. Chem.* ***1967***, *32*, 3191. For oxidation using NaI4 on silica gel with microwave irradiation, see Varma, R.S.; Saini, R.K.; Meshram, H.M. *Tetrahedron Lett.* ***1997***, *38*, 6525.

[799]Colonna, S.; Gaggero, N. *Tetrahedron Lett.* ***1989***, *30*, 6233. For a discussion of the mechanism, see González-Núñez, M.E.; Mello, R.; Royo, J.; Ríos, J.V.; Asensio, G. *J. Am. Chem. Soc.* ***2002***, *124*, 9154.

[800]Yamazaki, S. *Bull. Chem. Soc. Jpn.* ***1996***, *69*, 2955. A combination of H2O2 and Na2WO2 gives oxidation to the sulfone, see Choi, S.; Yang, J.-D.; Ji, M.; Choi, H.; Kee, M.; Ahn, K.-H.; Byeon, S.-H.; Baik, W.; Koo, S. *J. Org. Chem.* ***2001***, *66*, 8192.

[801]Riley, D.P.; Smith, M.R.; Correa, P.E. *J. Am. Chem. Soc.* ***1988***, *110*, 177.

[802]Zhong, P.; Guo, M.-P.; Huang, N.-P. *Synth. Commun.* ***2002***, *32*, 175.

[803]Hajipour, A.R.; Mallakpour, S.E.; Adibi, H. *J. Org. Chem.* ***2002***, *67*, 8666.

[804]Chen, Y.-J.; Huang, Y.-P. *Tetrahedron Lett.* ***2000***, *41*, 5233.

[805]Martín, S.E.; Rossi, L.I. *Tetrahedron Lett.* ***2001***, *42*, 7147.

[806]Madhavan, D.; Pitchumani, K. *Tetrahedron* ***2001***, *57*, 8391.

[807]Firouzabadi, H.; Abbassi, M. *Synth. Commun.* ***1999***, *129*, 1485.

[808]Shaabani, A.; Teimouri, M.B.; Safaei, H.R. *Synth. Commun.* ***2000***, *30*, 265.

[809]Kim, S.S.; Nehru, K.; Kim, S.S.; Kim, D.W.; Jung, H.C. *Synthesis* ***2002***, 2484.

[810]Shukla, V.G.; Salgaonkar, P.D.; Akamanchi, K.G. *J. Org. Chem.* ***2003***, *68*, 5422.

[811]For lists of some of the many oxidizing agents used in this reaction, see Ref. 672 and Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***, p. 16.

[812]For a review, see Schank, K., in Patai, S.; Rappoport, Z.; Stirling, C. *The Chemistry of Sulphones and Sulphoxides*, Wiley, NY, ***1988***, pp. 165–231, 205–213.

[813]Khurana, J.M.; Panda, A.K.; Ragi, A.; Gogia, A. *Org. Prep. Proceed. Int.* ***1996***, *28*, 234.

[814]Guertin, K.R.; Kende, A.S. *Tetrahedron Lett.* ***1993***, *34*, 5369.

[815]Margues, A.; Marin, M.; Ruasse, M.-F. *J. Org. Chem.* ***2001***, *66*, 7588.

[816]Sato, K.; Hyodo, M.; Aoki, M.; Zheng, X.-Q.; Noyori, R. *Tetrahedron* ***2001***, *57*, 2469.

[817]Makosza, M.; Surowiec, M. *Org. Prep. Proceed. Int.* ***2003***, *35*, 412.

[818]Balicki, R. *Synth. Commun.* ***1999***, *29*, 2235.

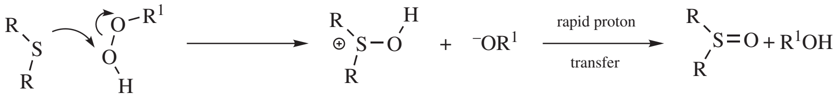
[819]Iranpoor, N.; Mohajer, D.; Rezaeifard, A.-R. *Tetrahedron Lett.* ***2004***, *45*, 3811.

[820]Su, W. *Tetrahedron Lett.* ***1994***, *35*, 4955.

[821]For a review of the oxidation of α-halo sulfides, see Venier, C.G.; Barager III, H.J. *Org. Prep. Proced. Int.* ***1974***, *6*, 77, pp. 85-86.

oxidation to sulfoxides with an optically active reagent, and this has often been done.[822] In addition, the use of chiral additives in conjunction with various oxidizing agents leads to chiral nonracemic sulfoxide with good-to-excellent enantioselectivity.[823] Asymmetric oxidation using bacterial monooxygenases is known,[824] and horseradish peroxidase gives modest enantioselectivity.[825] Chiral sulfur reagents are also known.[826] Selenides (R_2Se) can be oxidized to selenoxides and selenones.[827] It is possible to oxidize a thioether to a sulfoxide in the presence of an alcohol moiety using MnO_2/HCl.[828] Alkyl disulfides give oxidation of one sulfur to give a (RS—S(=O)R compound with good enantioselectivity when using aqueous hydrogen peroxide, a catalytic amount of a vanadium catalyst and a chiral Schiff base ligand.[829] *N*-Sulfonyloxaziridines can be used to oxidize sulfides to sulfoxides.[830]

When the oxidizing agent is a peroxide, the mechanism[831] of oxidation to the sulfoxide is similar to that of **19-29**.[832]



[822]For reviews, see Kagan, H.B.; Rebiere, F. *Synlett* ***1990***, 643; Drabowicz, J.; Kiebasinski, P.; Mikołajczyk, M. *Org. Prep. Proceed. Int.* ***1982***, *14*, 45, see p. 288.

[823]For example, see Donnoli, M.I.; Superchi, S.; Rosini, C. *J. Org. Chem.* ***1998***, *63*, 9392; Brunel, J.-M.; Kagan, H.B. *Synlett* ***1996***, 404; Brunel, J.-M.; Diter, P.; Deutsch, M.; Kagan, H.B. *J. Org. Chem.* ***1995***, *60*, 8086; Davis, F.A.; Reddy, R.T.; Han, W.; Carroll, P.J. *J. Am. Chem. Soc*, ***1992***, *114*, 1428; Palucki, M.; Hanson, P.; Jacobsen, E.N. *Tetrahedron Lett.* ***1992***, *33*, 7111; Sandrinelli, F.; Perrio, S.; Beslin, P. *Org. Lett.* ***1999***, *1*, 1177; Tokunaga, M.; Ota, M.; Haga, M.-a.; Wakatsuki, Y. *Tetrahedron Lett.* ***2001***, *42*, 3865; Massa, A.; Lattanzi, A.; Siniscalchi, F.R.; Scettri, A. *Tetrahedron Asymmetry* ***2001***, *12*, 2775; Sun, J.; Zhu, C.; Dai, Z.; Yang, M.; Pan, Y.; Hu, H. *J. Org. Chem.* ***2004***, *69*, 8500; Krief, A.; Lonez, F. *Tetrahedron Lett.* ***2002***, *43*, 6255; Massa, A.; Sinissalchi, F.R.; Bugatti, V.; Lattanzi, A.; Scettri, A. *Tetrahederon Asymmetry* ***2002***, *13*, 1277; Barbarini, A.; Maggi, R.; Muratori, M.; Sartori, G.; Sartorio, R. *Tetrahedron Asymmetry* ***2004***, *15*, 2467; Ohta, C.; Shimizu, H.; Kondo, A.; Katsuki, T. *Synlett* ***2002***, 161.

[824]Colonna, S.; Gaggero, N.; Pasta, P.; Ottolina, G. *Chem. Commun.* ***1996***, 2303; Pasta, P.; Carrea, G.; Holland, H.L.; Dallavalle, S. *Tetrahedron Asymmetry*, ***1995***, *6*, 933.

[825]Ozaki, S.-i.; Watanabe, S.; Hayasaka, S.; Konuma, M. *Chem. Commun.* ***2001***, 1654.

[826]Mikołajczyk, M.; Drabowicz, J.; Kiełbasiński, P. *Chiral Sulfur Reagents*, CRC Press, Boca Raton, FL, ***1997***.

[827]See Reich, H.J., in Trahanovsky, W.S. *Oxidations in Organic Chemistry*, pt. C, Academic Press, NY, ***1978***, pp. 7–13; Davis, F.A.; Stringer, O.D.; Billmers, J.M. *Tetrahedron Lett.* ***1983***, *24*, 1213; Kobayashi, M.; Ohkubo, H.; Shimizu, T. *Bull. Chem. Soc. Jpn.* ***1986***, *59*, 503.

[828]Gabbi, C.; Ghelfi, F.; Grandi, R. *Synth. Commun.* ***1997***, *27*, 2857.

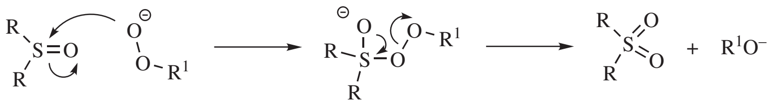
[829]Blum, S.A.; Bergman, R.G.; Ellman, J.A. *J. Org. Chem.* ***2003***, *68*, 150.

[830]For a review of *N*-sulfonyloxaziridines, see: Davis, F.A.; Sheppard, A.C. *Tetrahedron* ***1989***, *45*, 5703. For the use of trifluoromethyl substituted *N*-phosphinoyloxaziridines, see Jennings, W.B.; O'Shea, J.H.; Schweppe, A. *Tetrahedron Lett.* ***2001***, *42*, 101.

[831]For discussions of the mechanism with various other agents, see Rajasekaran, K.; Baskaran, T.; Gnanasekaran, C. *J. Chem. Soc. Perkin Trans. 2* ***1984***, 1183; Srinivasan, C.; Chellamani, A.; Rajagopal, S. *J. Org. Chem.* ***1985***, *50*, 1201; Agarwal, A.; Bhatt, P.; Banerji, K.K. *J. Phys. Org. Chem.* ***1990***, *3*, 174; Lee, D.G.; Chen, T. *J. Org. Chem.* ***1991***, *56*, 5346.

[832]Modena, G.; Todesco, P.E. *J. Chem. Soc.* ***1962***, 4920, and references cited therein.

The second oxidation, which is normally slower than the first[833] (which is why sulfoxides are so easily isolable), has the same mechanism in neutral or acid solution, but in basic solution it has been shown that the conjugate base of the peroxy compound ($R'OO^-$) also attacks the SO group as a nucleophile:[834]

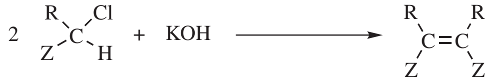


OS **V**, 791; **VI**, 403, 404, 482; **VII**, 453, 491; **VIII**, 464, 543; **IX**, 63; **80**, 190. Also see, OS **V**, 723; **VI**, 23.

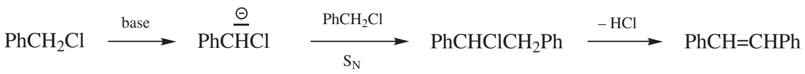
E. Oxidative Coupling

19-32 Coupling Involving Carbanions

De-hydro,chloro-coupling



Alkyl halides with an electron-withdrawing group on the halogen-bearing carbon can be dimerized to alkenes by treatment with bases. The Z group may be nitro, aryl, and so on. It is likely that in most cases the mechanism[835] involves nucleophilic substitution followed by elimination[836] (illustrated for benzyl chloride):



α,α-Dibromotoluenes ($ArCHBr_2$) give tolanes ArC≡CAr), by debromination of the intermediates ArCBr=CBrAr.[837] In a related reaction, diarylmethane dihalides

[833]There are some reagents that oxidize sulfoxides in preference to sulfides, for example, NaMnO4: see Henbest, H.B.; Khan, S.A. *Chem. Commun.* ***1968***, 1036.

[834]Curci, R.; Di Furia, F.; Modena, G. *J. Chem. Soc. Perkin Trans. 2* ***1978***, 603, and references cited therein. See also, Oae, S.; Takata, T. *Tetrahedron Lett.* ***1980***, *21*, 3213; Akasaka, T.; Ando, W. *J. Chem. Soc. Chem. Commun.* ***1983***, 1203.

[835]For discussion, see Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***, pp. 548–554.

[836]For example, see Hauser, C.R.; Brasen, W.R.; Skell, P.S.; Kantor, S.W.; Brodhag, A.E. *J. Am. Chem. Soc.* ***1956***, *78*, 1653; Hoeg, D.F.; Lusk, D.I. *J. Organomet. Chem.* ***1966***, *5*, 1; Reisdorf, D.; Normant, H. *Organomet. Chem. Synth.* ***1972***, *1*, 375; Hanna, S.B.; Wideman, L.G. *Chem. Ind. (London)* ***1968***, 486. In some cases, a radical anion chain mechanism can take place: Bethell, D.; Bird, R. *J. Chem. Soc. Perkin Trans. 2* ***1977***, 1856.

[837]Vernigor, E.M.; Shalaev, V.K.; Luk'yanets, E.A. *J. Org. Chem. USSR* ***1981***, *17*, 317.

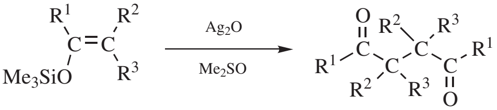
(Ar_2CX_2) have been dimerized to tetraaryl alkenes ($Ar_2C{=}CAr_2$) with copper,[838] and with iron(II) oxalate dihydrate.[839]

A somewhat different type of coupling is observed when salts of β-keto esters, arylacetonitriles ($ArCH_2CN$), and other compounds of the form ZCH_2Z' are treated with an oxidizing agent, such as iodine,[840] or Cu(II) salts.[841] Arylmethanesulfonyl chlorides ($ArCH_2SO_2Cl$) couple to give ArCH=CHAr when treated with Et_3N.[842]

OS **II**, 273; **IV**, 372, 869, 914; **VIII**, 298. Also see, OS **I**, 46; **IV**, 877.

19-33 Dimerization of Silyl Enol Ethers or of Lithium Enolates

3/*O*-De-trimethylsilyl-1/*C*-coupling



40

Silyl enol ethers can be dimerized to symmetrical 1,4-diketones by treatment with Ag_2O in DMSO or certain other polar aprotic solvents.[843] The reaction has been performed with R^2, R^3 = hydrogen or alkyl, although best yields are obtained when $R^2 = R^3 = H$. In certain cases, unsymmetrical 1,4-diketones have been prepared by using a mixture of two silyl enol ethers. Other reagents that have been used to achieve either symmetrical or cross-coupled products are iodosobenzene–BF_3–Et_2O,[844] ceric ammonium nitrate,[845] and lead tetraacetate.[846] If R^1 = OR (in which case the substrate is a ketene silyl acetal), dimerization with $TiCl_4$ leads to a dialkyl succinate (**40**, R^1 = OR).[847]

In a similar reaction, lithium enolates, RC(OLi)=CH_2, were dimerized to 1,4-diketones ($RCOCH_2CH_2COR$) with $CuCl_2$, $FeCl_3$, or copper(II) triflate, in a nonprotic solvent.[848]

[838]Buckles, R.E.; Matlack, G.M. *Org. Synth.* ***IV***, 914.

[839]Khurana, J.M.; Maikap, G.C.; Mehta, S. *Synthesis* ***1990***, 731.

[840]See, for example, Kaiser, E.M. *J. Am. Chem. Soc.* ***1967***, *89*, 3659; Belletire, J.L.; Spletzer, E.G.; Pinhas, A.R. *Tetrahedron Lett.* ***1984***, *25*, 5969; Mignani, S.; Lahousse, F.; Merényi, R.; Janousek, Z.; Viehe, H.G. *Tetrahedron Lett.* ***1985***, *26*, 4607; Aurell, M.J.; Gil, S.; Tortajada, A.; Mestres, R. *Synthesis* ***1990***, 317.

[841]Rathke, M.W.; Lindert, A. *J. Am. Chem. Soc.* ***1971***, *93*, 4605; Baudin, J.; Julia, M.; Rolando, C.; Verpeaux, J. *Bull. Soc. Chim. Fr.* ***1987***, 493.

[842]King, J.F.; Durst, T. *Tetrahedron Lett.* ***1963***, 585; King, J.F.; Harding, D.R.K. *Can. J. Chem.* ***1976***, *54*, 2652; Nakayama, J.; Tanuma, M.; Honda, Y.; Hoshino, M. *Tetrahedron Lett.* ***1984***, *25*, 4553.

[843]Ito, Y.; Konoike, T.; Saegusa, T. *J. Am. Chem. Soc.* ***1975***, *97*, 649.

[844]Moriarty, R.; Prakash, O.; Duncan, M.P. *J. Chem. Soc. Perkin Trans. 1* ***1987***, 559.

[845]Baciocchi, E.; Casu, A.; Ruzziconi, R. *Tetrahedron Lett.* ***1989***, *30*, 3707.

[846]Moriarty, R.M.; Penmasta, R.; Prakash, I. *Tetrahedron Lett.* ***1987***, *28*, 873.

[847]Inaba, S.; Ojima, I. *Tetrahedron Lett.* ***1977***, 2009. See also, Totten, G.E.; Wenke, G.; Rhodes, Y.E. *Synth. Commun.* ***1985***, *15*, 291, 301.

[848]Ito, Y.; Konoike, T.; Harada, T.; Saegusa, T. *J. Am. Chem. Soc.* ***1977***, *99*, 1487; Kobayashi, Y.; Taguchi, T.; Tokuno, E. *Tetrahedron Lett.* ***1977***, 3741; Frazier Jr., R.H.; Harlow, R.L. *J. Org. Chem.* ***1980***, *45*, 5408.

OS **VIII**, 467.

19-34 Oxidation of Thiols to Disulfides

***S*-De-hydrogen-coupling**

$$2\ \mathrm{RSH} \xrightarrow{H_2O_2} \mathrm{RSSR}$$

Thiols are easily oxidized to disulfides.[849] Hydrogen peroxide is the most common reagent,[850] but many oxidizing agents give the reaction, among them $KMnO_4$/$CuSO_4$,[851] Me_2SO—I_2,[852] Br_2 under phase-transfer conditions,[853] Br_2 on hydrated silica,[854] sodium perborate,[855] NaI/air,[856] *t*-BuOOH/VO(acac)$_2$,[857] SmI_2,[858] PPh_3 with a rhodium catalyst,[859] dibromohydantoin,[860] cetyltrimethylammonium dichromate,[861] and NO. It can also be done electrochemically.[862] Hydrogen peroxide 30% in hexafluoroisopropanol converts thiols to disulfides,[863] on Clayan with microwave irradiation,[864] and solventless reactions on MnO_2,[865] PCC (p. 1716)[866] or SO_2Cl_2[867] are also effective. However, strong oxidizing agents may give **19-26**. Even the oxygen in the air oxidizes thiols on standing, if a small amount of base is present. The reaction is reversible (see **19-75**), and the interconversion between cysteine and cystine is an important one in biochemistry.

[849]For a review, see Capozzi, G.; Modena, G., in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, ***1974***, pp. 785–839. For a list of reagents, with references, see Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***.

[850]It has been pointed out that, nevertheless, H2O2 is not a very good reagent for this reaction, since it gives sulfonic acids (**19-30**) as well as disulfides: Evans, B.J.; Doi, J.T.; Musker, W.K. *J. Org. Chem.* ***1990***, *55*, 2337.

[851]Noureldin, N.A.; Caldwell, M.; Hendry, J.; Lee, D.G. *Synthesis* ***1998***, 1587.

[852]Aida, T.; Akasaka, T.; Furukawa, N.; Oae, S. *Bull. Chem. Soc. Jpn.* ***1976***, *49*, 1441. See also, Fristad, W.E.; Peterson, J.R. *Synth. Commun.* ***1985***, *15*, 1.

[853]Drabowicz, J.; Mikołajczyk, M. *Synthesis* ***1980***, 32.

[854]Ali, M.H.; McDermott, M. *Tetrahedron Lett.* ***2002***, *43*, 6271.

[855]McKillop, A.; Koyunçu, D. *Tetrahedron Lett.* ***1990***, *31*, 5007.

[856]Iranpoor, N.; Zeynizadeh, B. *Synthesis* ***1999***, 49.

[857]Raghavan, S.; Rajender, A.; Joseph, S.C.; Rasheed, M.A. *Synth. Commun.* ***2001***, *31*, 1477.

[858]Zhan, Z.-P.; Lang, K.; Liu, F.; Hu, L.-m. *Synth. Commun.* ***2004***, *34*, 3203.

[859]Tanaka, K.; Ajiki, K. *Tetahedron Lett.* ***2004***, *45*, 25.

[860]Khazaei, A.; Zolfigol, M.A.; Rostami, A. *Synthesis* ***2004***, 2959.

[861]Patel, S.; Mishra, B.K. *Tetrahedron Lett.* ***2004***, *45*, 1371. See also Tajbakhsh, M.; Hosseinzadeh, R.; Shakoori, A. *Tetrahedron Lett.* ***2004***, *45*, 1889.

[862]See, for example, Leite, S.L.S.; Pardini, V.L.; Viertler, H. *Synth. Commun.* ***1990***, *20*, 393. For a review, see Shono, T. *Electroorganic Chemistry as a New Tool in Organic Synthesis*, Springer, NY, ***1984***, pp. 38–43.

[863]Kesavan, V.; Bonnet-Delpon, D.; Bégué, J.-P. *Synthesis* ***2000***, 223.

[864]Meshram, H.M.; Bandyopadhyay, A.; Reddy, G.S.; Yadav, J.S. *Synth. Commun.* ***2000***, *30*, 701.

[865]Firouzabadi, H.; Abbassi, M.; Karimi, B. *Synth. Commun.* ***1999***, *129*, 2527.

[866]Salehi, P.; Farrokhi, A.; Gholizadeh, M. *Synth. Commun.* ***2001***, *31*, 2777.

[867]Leino, R.; Lönnqvist, J.-E. *Tetrahedron Lett.* ***2004***, *45*, 8489.

The mechanism has been studied for several oxidizing agents and varies with the agent.[868] For oxygen it is[869]

$$RSH + B^- \rightleftharpoons RS^- + BH$$
$$RS^- + O_2 \longrightarrow RS\bullet + \bullet O_2^-$$
$$RS^- + \bullet O_2^- \longrightarrow RS\bullet + O_2^{2-}$$
$$2\ O_2^{2-} + 2\ BH \longrightarrow 2\ OH^- + 2\ B^- + O_2$$

With respect to the sulfur, this mechanism is similar to that of **14-16**, involving as it does loss of a proton, oxidation to a free radical, and radical coupling.

Unsymmetrical disulfides can be prepared[870] by treatment of a thiol RSH with diethyl azodicarboxylate EtOOCN=NCOOEt to give an adduct, to which another thiol R′SH is then added, producing the disulfide RSSR′.[871]

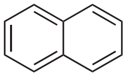
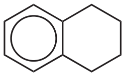
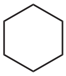
OS **III**, 86, 116.

REDUCTIONS

For the most part, reductions have been grouped into this chapter, with a few notable exceptions. Catalytic hydrogenation of alkenes and alkynes in **15-11** and **15-12**, hydrogenation of aromatic rings in **15-13** and reductive cleavage of cyclopropanes in **15-15** were placed in Chapter 15 to coincide with addition reactions, and protonolysis of alkyl boranes in **15-16** was placed there also for continuity. In general, reductions of functional groups encompass a variety of reaction types. The reactions in this section are classified into groups depending on the type of bond change involved. These groups are (*1*) attack at carbon (C—O and C=O), (*2*) attack at non-carbonyl multiple bonds to heteroatoms, (*3*) reactions in which a heteroatom is removed from the substrate, (*4*) reduction with cleavage, (*5*) reductive coupling, and (*6*) reactions in which an organic substrate is both oxidized and reduced. Most of the reagents in this section are metal hydrides, metals with an acid or a protic solvent, hydrogen gas with a catalyst, and so on. Other reducing agents are available, and will be introduced in the appropriate section. Note that plants can be used as reducing agents.[872]

[868]See Tarbell, D.S. in Kharasch, N. *Organic Sulfur Compounds*, Pergamon, Elmsford, NY, ***1961***, pp. 97–102.
[869]Wallace, T.J.; Schriesheim, A.; Bartok, W. *J. Org. Chem.* ***1963***, *28*, 1311.
[870]Mukaiyama, T.; Takahashi, K. *Tetrahedron Lett.* ***1968***, 5907.
[871]For other methods, see Boustany, K.S.; Sullivan, A.B. *Tetrahedron Lett.* ***1970***, 3547; Harpp, D.N.; Ash, D.K.; Back, T.G.; Gleason, J.G.; Orwig, B.A.; VanHorn, W.F.; Snyder, J.P. *Tetrahedron Lett.* ***1970***, 3551; Oae, S.; Fukushima, D.; Kim, Y.H. *J. Chem. Soc. Chem. Commun.* ***1977***, 407.
[872]Bruni, R.; Fantin, G.; Medici, A.; Pedrini, P.; Sacchetti, G. *Tetrahedron Lett.* **2002**, *43*, 3377.

TABLE 19.2. The Ease of Reduction of Various Functional Groups Toward Catalytic Hydrogenation.[876]

Reaction	Substrate[a]	Product	
19-39	RCOCl	RCHO	Easiest
19-45	RNO_2	RNH_2	
15-11	RC≡CR	RCH=CHR	
19-36	RCHO	RCH_2OH	
15-11	RCH=CHR	RCH_2CH_2R	
19-36	RCOR	RCHOHR	
19-56	$ArCH_2OR$	$ArCH_3$ + ROH	
19-43	RC≡N	RCH_2NH_2	
15-14			
19-38	RCOOR′	RCH_2OH + R′OH	
19-64	RCOHNR′	RCH_2NHR	
15-13			Most difficult
19-37	$RCOO^-$		Inert

[a]The groups are listed in approximate order of ease of reduction.

Selectivity[873]

It is often necessary to reduce one group in a molecule without affecting another reducible group. It is usually possible to find a reducing agent that will do this. The most common broad-spectrum reducing agents are the metal hydrides[874] and hydrogen (with a catalyst).[875] Many different metal-hydride systems and hydrogenation catalysts have been investigated in order to find conditions under which a given group will be reduced chemoselectively. Tables 19.2–19.4 list the reactivity of various functional groups toward catalytic hydrogenation, $LiAlH_4$, and BH_3, respectively.[876]

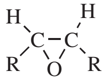
[873]For monographs on reductions in general, see Hudlický, M. *Reductions in Organic Chemistry*, Wiley, NY, ***1984***; Augustine, R.L. *Reduction*, Marcel Dekker, NY, ***1968***. For a review, see Candlin, J.P.; Rennie, R.A.C., in Bentley, K.W.; Kirby, G.W. *Elucidation of Chemical Structures by Physical and Chemical Methods* (Vol. 4 of Weissberger, A. *Techniques of Chemistry*), 2nd ed., pt. 2, Wiley, NY, ***1973***, pp. 77–135.

[874]For discussions of selectivity with metal hydride reducing agents, see Brown, H.C.; Krishnamurthy, S. *Tetrahedron* ***1979***, *35*, 567; Walker, E.R.H. *Chem. Soc. Rev.* ***1976***, *5*, 23; Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, ***1972***, pp. 209–251; Rerick, M.N., in Augustine, R.L. *Reduction*, Marcel Dekker, NY, ***1968***. For books, see, in Ref. 10, the works by Seyden-Penne, J.; Strouf, O. et al., and Hajós, A.

[875]For a discussion of catalyst selectivity for hydrogenations, see Rylander, P.N. *Aldrichimica Acta* ***1979***, *12*, 53. See also, Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, ***1985***.

[876]Table 19.2 is from House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, p. 9. Tables 19.3 and 19.4 are from Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, ***1972***, pp. 213 and 232, respectively.

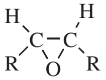
TABLE 19.3. The Ease of Reduction of Various Functional Groups with $LiAlH_4$ in Ether[876]

Reaction	Substrate[a]	Product	
19-36	RCHO	RCH_2OH	Easiest
19-36	RCOR	RCHOHR	
19-63	RCOCl	RCH_2OH	
19-38	Lactone	Diol	
19-35		RCH_2CHOHR	
19-38	RCOOR′	$RCH_2OH + R'OH$	
19-37	RCOOH	RCH_2OH	
19-37	$RCOO^-$	RCH_2OH	
19-64	$RCONR'_2$	$RCH_2NR'_2$	
19-43	RC≡N	RCH_2NH_2	
19-45	RNO_2	RNH_2	
19-80	$ArNO_2$	ArN=NAr	Most difficult
15-11	$RCH{=}CHR^-$		Inert

[a]However, $LiAlH_4$ is a very powerful reagent, and much less chemoselectivity is possible here than with most of the other metal hydrides.

Table 19.5 shows which groups can be reduced by catalytic hydrogenation and various metal hydrides.[877] Of course, the tables cannot be exact, because the nature of R and the reaction conditions obviously affect reactivity. Nevertheless, the tables do give a fairly good indication of which reagents reduce which

TABLE 19.4. The Ease of Reduction of Various Functional Groups With Borane[876]

Reaction	Substrate[a]	Product	
19-37	RCOOH	RCH_2OH	Easiest
15-16	RCH=CHR	$(RCH_2CHR)_3B$	
19-36	RCOR	RCHOHR	
19-43	RCN	RCH_2NH_2	
19-35		RCH_2CHOHR	
19-38	RCOOR′	$RCH_2OH + R'OH$	Most difficult
19-39,19-63	RCOCl		Inert

[a]It is evident that this reagent and $LiAlH_4$ (Table 19.3) complement each other.

[877]The first 10 columns are from Brown, H.C.; Krishnamurthy, S. *Tetrahedron* ***1979***, *35*, 567, p. 604. The column on (*i*-Bu)2AlH is from Yoon, N.M.; Gyoung, Y.S. *J. Org. Chem.* ***1985***, *50*, 2443; the one on NaAlEt2H2 from Stinson, S.R. *Chem. Eng. News, Nov. 3*, ***1980***, *58*, No. 44, 19; and the one on LiBEt3H from Brown, H.C.; Kim, S.C.; Krishnamurthy, S. *J. Org. Chem.* ***1980***, *45*, 1. For similar tables that show additional reducting agents, see Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, p. 129; Hajós, A. *Complex Hydrides*, Elsevier, NY, ***1979***, pp. 16–17. For tables showing which agents reduce a wide variety of functional groups, see Hudlický, M. *Reductions in Organic Chemistry*, Wiley, NY, ***1984***, pp. 177–200.

groups.[878] Lithium aluminium hydride is a very powerful and unselective reagent.[879] Consequently, other metal hydrides are generally used when chemoselectivity is required. As will be seen on p. 1794, a number of less reactive (and more selective) reagents have been prepared by replacing some of the hydrogens of $LiAlH_4$ with alkoxy groups (by treatment of $LiAlH_4$ with ROH).[880] Most of the metal hydrides are nucleophilic reagents and attack the carbon atom of a carbon-hetero single or multiple bond. Another useful reagent is LiAlHSeH.[881] However, BH_3[882,883] and AlH_3[884] are electrophiles (Lewis acids) and attack the heteroatom. This accounts for the different patterns of selectivity shown in the tables.

TABLE 19.5. Reactivity of Various Functional Groups With Some Metal Hydrides and Toward Catalytic Hydrogenation.[872]

Reaction[a]				A	B	C	D[374]	E[885]	F[886]	G	H	I	J[887]	K[888]	L	M	N
19-36	**RCHO**	⟶	**RCH_2OH**	+	+	+	+	+	+	+	+	+	+	+	+	+	+
19-36	**RCOR**	⟶	**RCHOHR**	+	+	+	+	+	+	+	+	+	+	+	+	+	+
19-39	**RCOCl**	↗	**RCHO**														
19-63		↘	**RCH_2OH**	+[889]	+	+	−	−	+	+	+	+	+	+	+	+	+
19-63	**lactone**	⟶	**diol**	−	+	+	+	+	+	±	+	+	+	+	+	+	+
19-35	**epoxide**	⟶	**alcohol**	−	+	+	+	±	±	±	+	+	+	+	+	+	+
19-38	**RCOOR′**	⟶	**RCH_2OH +R′OH**	−	+	+	±	−	±	±	+	+	+	+	+	+	+
19-37	**RCOOH**	⟶	**RCH_2OH**	−	−	+	+	−	±	−	+	+	+	−	+	+	−

(*Continued*)

[878]See also, the table in Hudlický, M. *J. Chem. Educ.* ***1977***, *54*, 100.

[879]For a review of LiAlH4, see Pizey, J.S. *Synthetic Reagents*, Vol. 1, Wiley, NY, ***1974***, pp. 101–194.

[880]For reviews of reductions by these reagents, see Málek, J. *J. Org. Chem.* ***1988***, *36*, 249; ***1985***, *34*, 1; Málek, J.; Č erny, M. *Synthesis* ***1972***, 217.

[881]Ishihara, H.; Koketsu, M.; Fukuta, Y.; Nada, F. *J. Am. Chem. Soc.* ***2001***, *123*, 8408.

[882]See Brown, H.C.; Heim, P.; Yoon, N.M. *J. Am. Chem. Soc.* ***1970***, *92*, 1637; Cragg, G.M.L. *Organoboranes in Organic Synthesis*, Marcel Dekker, NY, ***1973***, pp. 319–371. For reviews of reductions with BH3, see Wade, R.C. *J. Mol. Catal.* ***1983***, *18*, 273 (BH3 and a catalyst); Lane, C.F. *Chem. Rev.* ***1976***, *76*, 773; *Aldrichimica Acta* ***1977***, *10*, 41; Brown, H.C.; Krishnamurthy, S. *Aldrichimica Acta* ***1979***, *12*, 3. For reviews of reduction with borane derivatives, see Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, pp. 125–164; Pelter, A. *Chem. Ind. (London)* ***1976***, 888.

[883]Reacts with solvent, reduced in aprotic solvents.

[884]Reduced to aldehyde (**19-44**)

[885]Brown, H.C.; Bigley, D.B.; Arora, S.K.; Yoon, N.M. *J. Am. Chem. Soc.* ***1970***, *92*, 7161. For reductions with thexylborane, see Brown, H.C.; Heim, P.; Yoon, N.M. *J. Org. Chem.* ***1972***, *37*, 2942.

[886]Brown, H.C.; Krishnamurthy, S.; Yoon, N.M. *J. Org. Chem.* ***1976***, *41*, 1778.

[887]See Yoon, N.M.; Brown, H.C. *J. Am. Chem. Soc.* ***1968***, *90*, 2927.

[888]Brown, H.C.; Kim, S.C.; Krishnamurthy, S. *J. Org. Chem.* ***1980***, *45*, 1. For a review of the synthesis of alkyl-substituted borohydrides, see Brown, H.C.; Singaram, B.; Singaram, S. *J. Organomet. Chem.* ***1982***, *239*, 43.

[889]See Brown, H.C.; Heim, P.; Yoon, N.M. *J. Am. Chem. Soc.* ***1970***, *92*, 1637; Cragg, G.M.L. *Organoboranes in Organic Synthesis*, Marcel Dekker, NY, ***1973***, pp. 319–371. For reviews of reductions with BH3, see Wade, R.C. *J. Mol. Catal.*, ***1983***, *18*, 273 (BH3 and a catalyst); Lane, C.F. *Chem. Rev.* ***1976***, *76*, 773; *Aldrichimica Acta* ***1977***, *10*, 41; Brown, H.C.; Krishnamurthy, S. *Aldrichimica Acta* ***1979***, *12*, 3. For reviews of reduction with borane derivatives, see Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, pp. 125–164; Pelter, A. *Chem. Ind. (London)* ***1976***, 888.

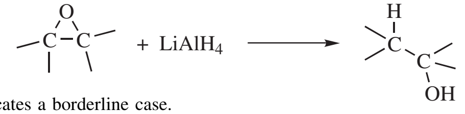
TABLE 19.5. (*Continued*)

Reaction[a]			A	B	C	D[374]	E[885]	F[886]	G	H	I	J[887]	K[888]	L	M	N
19-37	**$RCOO^-$**	⟶ **RCH_2OH**	−	−	+	−	−	−	−	+	+	+	−	−		−
19-64		⟶ **RCH_2NR_2'**														
	$RCNR_2'$	↗														
19-41		↘ **RCHO**	−	−	−	+	+	+	−	+	+	+	+	+	+	+
19-43	**RC≡N**	⟶ **RCH_2NH_2**	−	−	−	+	−	±	−	+	+	+	±	+[384]	+	+
19-45		⟶ **RCH_2NH_2'**														
	$RCONR_2'$	↗														
19-80		↘ **RCHO**	−	−	−	−	−	−	−	+	+	−	−	+[890]	+	+
15-11	**RCH=CHR**	⟶ **RCH_2CH_2R**	−	−	−	+	+	+	−	−	−	−	+	−	−	+

A = $NaBH_4$ in EtOH. B = $NaBH_4$ + LiCl in diglyme. C = $NaBH_4$ + $AlCl_3$ in diglyme. D = BH_3–THF. E = bis-3-methyl-2-butylborane (disiamylborane) in THF. F = 9-BBN. G = $LiAlH(O\textit{t}\text{-Bu})_3$ in THF. H = $LiAlH(OMe)_3$ in THF. I = $LiAlH_4$ in ether. J = AlH_3 in THF. K = $LiBEt_3H$. L = $(\textit{i}Bu)_2AlH$ [DIBALH). M = $NaAlEt_2H_2$. N = catalytic hydrogenation.

19-53 RX + $LiAlH_4$ ⟶ RH

19-57 R–OSO_2R' + $LiAlH_4$ ⟶ RH

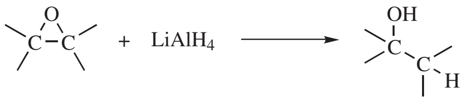
19-35 

±indicates a borderline case.

A. Attack at Carbon (C–O and C=O)

19-35 Reduction of Epoxides

(3)*OC-seco*-Hydro-de-alkoxylation



Reduction of epoxides is a special case of **19-56** and is easily carried out.[891] The most common reagent is $LiAlH_4$,[892] which reacts by the S_N2-type mechanism, giving inversion of configuration. An epoxide on a substituted cyclohexane ring cleaves in such a direction as to give an axial alcohol. As expected for an S_N2 mechanism, cleavage usually occurs so that a tertiary alcohol is formed if possible. If not, a secondary alcohol is preferred. However, for certain substrates, the epoxide ring can be opened the other way by reduction with $NaBH_4$–$ZrCl_4$,[893] Pd/C and

[890]Reduced to hydroxylamine (**19-46**).

[891]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1019–1027.

[892]See Healy, E.F.; Lewis, J.D.; Minniear, A.B. *Tetrahedron Lett.* ***1994***, *35*, 6647 for a discussion of the LiAlH4 reduction of unsaturated cyclic epoxides.

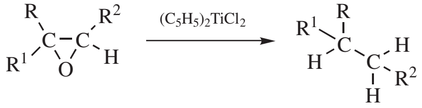
[893]Laxmi, Y.R.S.; Iyengar, D.S. *Synth. Commun.* ***1997***, *27*, 1731 (addition of L-proline to this reaction leads to moderate asymmetric induction).

$HCOONH_4$,[894] SiO_2–$Zn(BH_4)_2$,[895] or with BH_3 in THF.[896] The reaction has also been carried out with other reagents, for example, sodium amalgam in EtOH, Li in ethylenediamine,[897] Bu_3SnH–NaI,[898] and by catalytic hydrogenolysis.[899] Chemoselective and regioselective ring opening (e.g., of allylic epoxides and of epoxy ketones and esters) has been achieved with SmI_2,[900] HCOOH–NEt_3 and a palladium catalyst,[901] and sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al).[902] Highly hindered epoxides can be conveniently reduced, without rearrangement, with lithium triethylborohydride.[903]

Epoxy ketones are selectively reduced with lithium naphthalenide[904] or Cp_2TiCl in THF/MeOH[905] to the β-hydroxyketone. Other reduction methods can lead to the epoxy alcohol (see p.$$$). Reduction of epoxy amides with SmI_2 in methanol gave the α-hydroxyamide.[906]

Epi-sulfides can be reduced to give the alkene using Bu_3SnH in the presence of BEt_3.[907]

Epoxides can be reductively halogenated (the product is the alkyl bromide or iodide rather than the alcohol) with Me_3SiCl–NaX–$(Me_2SiH)_2O$ (1,1,3,3-tetramethyldisiloxane).[908]

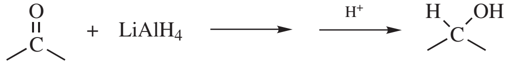


The usual product of epoxide reductions is the alcohol, but epoxides are reduced all the way to the alkane by titanocene dichloride[909] and by Et_3SiH–BH_3.[910]

[894]Dragovich, P.S.; Prins, T.J.; Zhou, R. *J. Org. Chem.* ***1995***, *60*, 4922. For reduction with a palladium catalyst in formic acid see Ley, S.V.; Mitchell, C.; Pears, D.; Ramarao, C.; Yu, J.Q.; Zhou, W. *Org. Lett.* ***2003***, *5*, 4665.
[895]Ranu, B.C.; Das, A.R. *J. Chem. Soc. Perkin Trans. 1* ***1992***, 1881.
[896]For a review of epoxide reduction with BH3, see Cragg, G.M.L. *Organoboranes in Organic Synthesis*, Marcel Dekker, NY, ***1973***, pp. 345–348. See also Yamamoto, Y.; Toi, H.; Sonoda, A.; Murahashi, S. *J. Chem. Soc. Chem. Commun.* ***1976***, 672.
[897]Brown, H.C.; Ikegami, S.; Kawakami, J.H. *J. Org. Chem.* ***1970***, *35*, 3243.
[898]Bonini, C.; Di Fabio, R. *Tetrahedron Lett.* ***1988***, *29*, 819.
[899]For a review, see Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, ***1967***, pp. 478–485. See Oshima, M.; Yamazaki, H.; Shimizu, I.; Nizar, M.; Tsuji, J. *J. Am. Chem. Soc.* ***1989***, *111*, 6280.
[900]Molander, G.A.; La Belle, B.E.; Hahn, G. *J. Org. Chem.* ***1986***, *51*, 5259; Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* ***1987***, *28*, 4437. See also, Miyashita, M.; Hoshino, M.; Suzuki, T.; Yoshikoshi, A. *Chem. Lett.* ***1988***, 507.
[901]Noguchi, Y.; Yamada, T.; Uchiro, H.; Kobayashi, S. *Tetrahedron Lett.* ***2000***, *41*, 7493, 7499.
[902]Gao, Y.; Sharpless, K.B. *J. Org. Chem.* ***1988***, *53*, 4081.
[903]Krishnamurthy, S.; Schubert, R.M.; Brown, H.C. *J. Am. Chem. Soc.* ***1973***, *95*, 8486.
[904]Jankowska, R.; Liu, H.-J.; Mhehe, G.L. *Chem. Commun.* ***1999***, 1581.
[905]Hardouin, C.; Chevallier, F.; Rousseau, B.; Doris, E. *J. Org. Chem.* ***2001***, *66*, 1046.
[906]Concellón, J.M.; Bardales, E. *Org. Lett.* ***2003***, *5*, 4783.
[907]Uenishi, J.; Kubo, Y. *Tetrahedron Lett.* ***1994***, *35*, 6697.
[908]Aizpurua, J.M.; Palomo, C. *Tetrahedron Lett.* ***1984***, *25*, 3123.
[909]van Tamelen, E.E.; Gladys, J.A. *J. Am. Chem. Soc.* ***1974***, *96*, 5290.
[910]Fry, J.L.; Mraz, T.J. *Tetrahedron Lett.* ***1979***, 849.

19-36 Reduction of Aldehydes and Ketones to Alcohols[911]

C,O-Dihydro-addition



Aldehydes can be reduced to primary alcohols, and ketones to secondary alcohols, by a number of reducing agents,[912] of which $LiAlH_4$ and other metallic hydrides are the most commonly used.[913] These reagents have two main advantages over many other reducing agents: They do not reduce carbon–carbon double or triple bonds (with the exception of propargylic alcohols),[914] and with $LiAlH_4$ all four hydrogens are usable for reduction. The reaction is broad and general. Lithium aluminum hydride easily reduces aliphatic, aromatic, alicyclic, and heterocyclic aldehydes, containing double or triple bonds and/or nonreducible groups, such as NR_3, OH, OR, and F. If the molecule contains a group reducible by $LiAlH_4$ (e.g., NO_2, CN, COOR), then it is also reduced. Since $LiAlH_4$ reacts readily with water and alcohols, these compounds must be excluded. Common solvents are ether and THF. The compound $NaBH_4$ has a similar scope, but is more selective and so may be used with NO_2, Cl, COOR, CN, and so on in the molecule. Another advantage of $NaBH_4$ is that it can be used in water or alcoholic solvents and so reduces compounds, such as sugars that are not soluble in ethers.[915] Other solvents can be used with some modification of the borohydride. For example, butyltriphenylphosphonium borohydride reduces aldehydes to alcohols in dichloromethane.[916] A polymer-bound phase-transfer material with $NaBH_4$ in wet THF has also been used.[917] Sodium borohydride on alumina, under microwave irradiation, is also an effective reagent.[918] Sodium borohydride has been used on silica gel.[919] The scope of these reagents with ketones is similar to that with aldehydes. Lithium aluminum hydride reduces even sterically hindered ketones.

[911]See Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY, ***2001***, pp. 306–368.

[912]For a review, see Hudlický, M. *Reductions in Organic Chemistry*, Ellis Horwood, Chichester, ***1984***, pp. 96–129. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1075–1113.

[913]For books on metal hydrides, see Abdel-Magid, A.F., Ed., *Reductions in Organic Synthesis*, American Chemical Society, Washington, DC, ***1996***; Seyden-Penne, J. *Reductions by the Alumino- and Borohydrides*, VCH, NY, ***1991***; Hajos, A. *Complex Hydrides*, Elsevier, NY, ***1979***. For reviews, see House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 49–71; Wheeler, O.H., in Patai, S. *The Chemistry of the Carbonyl Group*, pt. 1, Wiley, NY, **1966**, pp. 507–566.

[914]See Meta, C.T.; Koide, K. *Org. Lett.* ***2004***, *6*, 1785; Naka, T.; Koide, K. *Tetrahedron Lett.* ***2003***, *44*, 443.

[915]The compound NaBH4 reduces solid ketones in the absence of any solvent (by mixing the powders): Toda, F.; Kiyoshige, K.; Yagi, M. *Angew. Chem. Int. Ed.* ***1989***, *28*, 320.

[916]Hajipour, A.R.; Mallakpour, S.E. *Synth. Commun.* ***2001***, *31*, 1177.

[917]Tamami, B.; Mahdavi, H. *Tetrahedron* ***2003***, *59*, 821.

[918]Varma, R.S.; Saini, R.K. *Tetrahedron Lett.* ***1997***, *38*, 4337.

[919]Yakabe, S.; Hirano, M.; Morimoto, T. *Synth. Commun.* ***1999***, *29*, 295; Liu, W.-y.; Xu, Q.-h.; Ma, Y.-x. *Org. Prep. Proceed. Int.* ***2000***, *32*, 596.

The double bonds that are generally not affected by metallic hydrides may be isolated or conjugated, but double bonds that are conjugated with the C=O group may or may not be reduced, depending on the substrate, reagent, and reaction conditions.[920] Some reagents that reduce only the C=O bonds of α,β-unsaturated aldehydes and ketones are AlH_3,[921] $NaBH_4$, or $LiAlH_4$ in the presence of lanthanide salts,[922] cobalt complexes,[923] nickel compounds,[924] I_2,[925] $NaBH_3(OAc)$,[926] $Zn(BH_4)_2$[927] on Y-zeolite,[928] and Et_3SiH.,[929] Also, both $LiAlH_4$[930] and $NaBH_4$[931] predominantly reduce only the C=O bonds of C=C–C=O systems in most cases, although substantial amounts of fully saturated alcohols have been found in some cases[930] (**15-14**). For some reagents that reduce only the C=C bonds of conjugated aldehydes and ketones, see **15-11**. A mixture of $InCl_3$ and $NaBH_4$ reduced both the C=C and C=O units of conjugated ketones.[932]

When a functional group is selectively attacked in the presence of a different functional group, the reaction is said to be *chemoselective*.[933] A number of reagents have been found to reduce aldehydes much faster than ketones. Among these[934] are sodium triacetoxyborohydride[935] ($NaBH_4$–HCOOH),[936] zinc borohydride in THF,[937] bis-(isopropoxytitanium borohydride),[938] a complex of $LialH_4$ and *N*-methyl-2-pyrrolidinone (of particular interest since it is stable in air and to heating),[939] and Raney nickel.[940] On

[920]For a review of the reduction of α,β-unsaturated carbonyl compounds, see Keinan, E.; Greenspoon, N., in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 2, Wiley, NY, ***1989***, pp. 923–1022.

[921]Jorgenson, M.J. *Tetrahedron Lett.* ***1962***, 559; Dilling, W.L.; Plepys, R.A. *J. Org. Chem.* ***1970***, *35*, 2971.

[922]Gemal, A.L.; Luche, J. *J. Am. Chem. Soc.* ***1981***, *103*, 5454; Fukuzawa, S.; Fujinami, T.; Yamauchi, S.; Sakai, S. *J. Chem. Soc. Perkin Trans. 1* ***1986***, 1929. See also Chênevert, R.; Ampleman, G. *Chem. Lett.* ***1985***, 1489; Varma, R.S.; Kabalka, G.W. *Synth. Commun.* ***1985***, *15*, 985.

[923]Ohtsuka, Y.; Koyasu, K.; Ikeno, T.; Yamada, T. *Org. Lett.* ***2001***, *3*, 2543.

[924]Khurana, J.M.; Chauhan, S. *Synth. Commun.* ***2001***, *31*, 3485.

[925]Singh, J.; Kaur, I.; Kaur, J.; Bhalla, A.; Kad, G.L. *Synth. Commun.* ***2003***, *33*, 191.

[926]Nutaitis, C.F.; Bernardo, J.E. *J. Org. Chem.* ***1989***, *54*, 5629.

[927]For a review of the reactivity of this reagent, see Ranu, B. *Synlett* ***1993***, 885.

[928]Sreekumar, R.; Padmakumar, R.; Rugmini, P. *Tetrahedron Lett.* ***1998***, *39*, 5151.

[929]Ojima, I.; Kogure, T. *Organometallics* ***1982***, *1*, 1390.

[930]Johnson, M.R.; Rickborn, B. *J. Org. Chem.* ***1970***, *35*, 1041.

[931]Chaikin, S.W.; Brown, W.G. *J. Am. Chem. Soc.* ***1949***, *71*, 122.

[932]Ranu, B.C.; Samanta, S. *Tetrahedron* ***2003***, *59*, 7901.

[933]See Luibrand, R.T.; Taigounov, I.R.; Taigounov, A.A. *J. Org. Chem.* ***2001***, *66*, 7254.

[934]For some others (not all of them metal hydrides), see Hutchins, R.O.; Kandasamy, D. *J. Am. Chem. Soc.* ***1973***, *95*, 6131; Risbood, P.A.; Ruthven, D.M. *J. Org. Chem.* ***1979***, *44*, 3969; Babler, J.H.; Invergo, B.J. *Tetrahedron Lett.* ***1981***, *22*, 621; Fleet, G.W.J.; Harding, P.J.C. *Tetrahedron Lett.* ***1981***, *22*, 675; Yamaguchi, S.; Kabuto, K.; Yasuhara, F. *Chem. Lett.* ***1981***, 461; Kim, S.; Kang, H.J.; Yang, S. *Tetrahedron Lett.* ***1984***, *25*, 2985; Kamitori, Y.; Hojo, M.; Masuda, R.; Yamamoto, M. *Chem. Lett.* ***1985***, 253; Borbaruah, M.; Barua, N.C.; Sharma, R.P. *Tetrahedron Lett.* ***1987***, *28*, 5741.

[935]Gribble, G.W.; Ferguson, D.C. *J. Chem. Soc. Chem. Commun.* ***1975***, 535. See also, Nutaitis, C.F.; Gribble, G.W. *Tetrahedron Lett.* ***1983***, *24*, 4287.

[936]Blanton, J.R. *Synth. Commun.* ***1997***, *27*, 2093.

[937]Ranu, B.C.; Chakraborty, R. *Tetrahedron Lett.* ***1990***, *31*, 7663; See Ranu, B. *Synlett* ***1993***, 885.

[938]Ravikumar, K.S.; Chandrasekaran, S. *Tetrahedron* ***1996***, *52*, 9137.

[939]Fuller, J.C.; Stangeland, E.L.; Jackson, T.C.; Singaram, B. *Tetrahedron Lett.* ***1994***, *35*, 1515. See also, Mogali, S.; Darville, K.; Pratt, L.M. *J. Org. Chem.* ***2001***, *66*, 2368.

[940]Barrero, A.F.; Alvarez-Manzaneda, E.J.; Chahboun, R.; Meneses, R. *Synlett* ***2000***, 197.

the other hand, ketones can be chemoselectively reduced in the presence of aldehydes with $NaBH_4$ in aq. EtOH at $-15°C$ in the presence of cerium trichloride $CeCl_3$.[941] The reagent lithium *n*-dihydropyridylaluminum hydride reduces diaryl ketones much better than dialkyl or alkyl aryl ketones.[942] Most other hydrides reduce diaryl ketones more slowly than other types of ketones. Saturated ketones can be reduced in the presence of α,β-unsaturated ketones with $NaBH_4$-50% MeOH—CH_2Cl_2 at $-78°C$[943] and with zinc borohydride.[944]

In general, $NaBH_4$ reduces carbonyl compounds in this order: aldehydes > α,β-unsaturated aldehydes > ketones > α,β-unsaturated ketones, and a carbonyl group of one type can be selectively reduced in the presence of a carbonyl group of a less reactive type.[945] A number of reagents will preferentially reduce the less sterically hindered of two carbonyl compounds, but by the use of DIBALH in the presence of the Lewis acid methylaluminum bis(2,16-di-*tert*-butyl-4-methylphenoxide), it was possible selectively to reduce the *more hindered* of a mixture of two ketones.[946] It is obvious that reagents can often be found to reduce one kind of carbonyl function in the presence of another.[947] For a discussion of selectivity in reduction reactions, see p. 1787. A syn-selective reduction of β-hydroxy ketones was achieved using $(i\text{PrO})_2TiBH_4$.[948]

Quinones are reduced to hydroquinones by $LiAlH_4$, $SnCl_2$—HCl, or sodium hydrosulfite ($Na_2S_2O_4$), as well as by other reducing agents.

The reagent lithium tri-*sec*-butylborohydride LiBH(*sec*-Bu)$_3$ (L-Selectride) reduces cyclic and bicyclic ketones in a highly stereoselective manner,.[949] For example, 2-methylcyclohexanone gave *cis*-2-methylcyclohexanol with an isomeric purity >99%. Both L-Selectride and the potassium salt (K-Selectride) reduce carbonyls in cyclic and acyclic molecules with high diastereoselectivity.[950] The more usual reagents, for example, $LiAlH_4$, $NaBH_4$, reduce relatively unhindered cyclic ketones either with little or no stereoselectivity[951] or give predominant formation of the more stable isomer (axial attack).[952] Mixed reagents, such as

[941]See Gemal, A.L.; Luche, J. *Tetrahedron Lett.* ***1981***, *22*, 4077; Li, K.; Hamann, L.G.; Koreeda, M. *Tetrahedron Lett.* ***1992***, *33*, 6569.
[942]Lansbury, P.T.; Peterson, J.O. *J. Am. Chem. Soc.* ***1962***, *84*, 1756.
[943]Ward, D.E.; Rhee, C.K.; Zoghaib, W.M. *Tetrahedron Lett.* ***1988***, *29*, 517.
[944]Sarkar, D.C.; Das, A.R.; Ranu, B.C. *J. Org. Chem.* ***1990***, *55*, 5799.
[945]Ward, D.E.; Rhee, C.K. *Can. J. Chem.* ***1989***, *67*, 1206.
[946]Maruoka, K.; Araki, Y.; Yamamoto, H. *J. Am. Chem. Soc.* ***1988***, *110*, 2650.
[947]For lists of some of these chemoselective reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1089–1092, and references given in Ward, D.E.; Rhee, C.K. *Can. J. Chem.* ***1989***, *67*, 1206.
[948]Ravikumar, K.S.; Sinha, S.; Chandrasekaran, S. *J. Org. Chem.* ***1999***, *64*, 5841.
[949]Brown, H.C.; Krishnamurthy, S. *J. Am. Chem. Soc.* ***1972***, *94*, 7159; Krishnamurthy, S.; Brown, H.C. *J. Am. Chem. Soc.* ***1976***, *98*, 3383.
[950]K-Selectride: Lawson, E.C.; Zhang, H.-C.; Maryanoff, B.E. *Tetrahedron Lett.* ***1999***, *40*, 593.
[951]For reviews of the stereochemistry and mechanism, see Caro, B.; Boyer, B.; Lamaty, G.; Jaouen, G. *Bull. Soc. Chim. Fr.* ***1983***, II-281; Boone, J.R.; Ashby, E.C. *Top. Stereochem.* ***1979***, *11*, 53; Wigfield, D.C. *Tetrahedron* ***1979***, *35*, 449. For a review of stereoselective synthesis of amino alcohols by this method, see Tramontini, M. *Synthesis* ***1982***, 605.
[952]For a discussion of why this isomer is predominantly formed, see Mukherjee, D.; Wu, Y.; Fronczek, F.R.; Houk, K.N. *J. Am. Chem. Soc.* ***1988***, *110*, 3328.

$LiBH_3[N(C_3H_7)_2]$, gives high selectivity for axial attack.[953] Reduction of cyclohexanone derivatives with the very hindered $LiAlH(CEt_2CMe_3)_3$ gave primarily the cis-alcohol.[954] Cyclohexanones that have a large degree of steric hindrance near the carbonyl group usually give predominant formation of the less stable alcohol, even with $LiAlH_4$ and $NaBH_4$.

Other reagents reduce aldehydes and ketones to alcohols,[955] including:

1. *Hydrogen and a Catalyst.*[956] The most common catalysts are platinum and ruthenium, but homogeneous catalysts have also been used,[957] including copper on silica gel[958] and a ruthenium catalyst on mesoporous silica.[959] Before the discovery of the metal hydrides this was one of the most common ways of effecting this reduction, but it suffers from the fact that C=C, C≡C, C=N, and C≡N bonds are more susceptible to attack than C=O bonds.[960] For aromatic aldehydes and ketones, reduction to the hydrocarbon (**19-61**) is a side reaction, stemming from hydrogenolysis of the alcohol initially produced (**19-54**).
2. *Sodium in Ethanol.*[961] This is called the *Bouveault–Blanc procedure* and was more popular for the reduction of carboxylic esters (**19-38**) than of aldehydes or ketones before the discovery of $LiAlH_4$.

   For the reaction with sodium in ethanol the following mechanism[962] has been suggested:[963]

[953]Harrison, J.; Fuller, J.C.; Goralski, C.T.; Singaram, B. *Tetrahedron Lett.* ***1994***, *35*, 5201.

[954]Boireau, G.; Deberly, A.; Toneva, R. *Synlett* ***1993***, 585. In this study, reduction with LiAlH(O*t*-Bu)3 was shown to give primarily the trans-alcohol.

[955]This can also be done electrochemically. For a review, see Feoktistov, L.G.; Lund, H., in Baizer, M.M.; Lund, H. *Organic Electochemistry*, Marcel Dekker, NY, ***1983***, pp. 315–358, 315–326. See also, Coche, L.; Moutet, J. *J. Am. Chem. Soc.* ***1987***, *109*, 6887.

[956]For reviews, see Abdel-Magid, A.F., Ed., *Reductions in Organic Synthesis*, American Chemical Society Washington, DC, ***1996***, pp. 31–50; Parker, D., in Hartley, F.R. *The Chemistry of the Metal-Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 979–1047; Tanaka, K., in Červený, l. *Catalytic Hydrogenation*, Elsevier, NY, ***1986***, pp. 79–104; Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, ***1985***, pp. 66–77; Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY., ***1967***, pp. 238–290.

[957]For a review, see Heck, R.F. *Organotransition Metal Chemistry*, Academic Press, NY, ***1974***, pp. 65–70.

[958]Ravasio, N.; Psaro, R.; Zaccheria, F. *Tetrahedron Lett.* ***2002***, *43*, 3943.

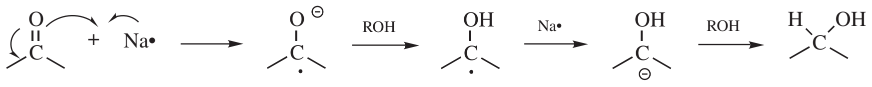
[959]Kesanli, B.; Lin, W. *Chem. Commun.* ***2004***, 2284.

[960]For catalysts that allow hydrogenation of only the C=O bond of α,β-unsaturated aldehydes, see Galvagno, S.; Poltarzewski, Z.; Donato, A.; Neri, G.; Pietropaolo, R. *J. Chem. Soc. Chem. Commun.* ***1986***, 1729; Farnetti, E.; Pesce, M.; Kaspar, J.; Spogliarich, R.; Graziani, M. *J. Chem. Soc. Chem. Commun.* ***1986***, 746; Narasimhan, C.S.; Deshpande, V.M.; Ramnarayan, K. *J. Chem. Soc. Chem. Commun.* ***1988***, 99.

[961]For a discussion, see House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 152–160.

[962]For reviews of the mechanisms of these reactions, see Pradhan, S.K. *Tetrahedron* ***1986***, *42*, 6351; Huffman, J.W. *Acc. Chem. Res.* ***1983***, *16*, 399. For discussions of the mechanism in the absence of protic solvents, see Huffman, J.W.; Liao, W.; Wallace, R.H. *Tetrahedron Lett.* ***1987***, *28*, 3315; Rautenstrauch, V. *Tetrahedron* ***1988***, *44*, 1613; Song, W.M.; Dewald, R.R. *J. Chem. Soc. Perkin Trans. 2* ***1989***, 269. For a review of the stereochemistry of these reactions in liquid NH3, see Rassat, A. *Pure Appl. Chem.* ***1977***, *49*, 1049.

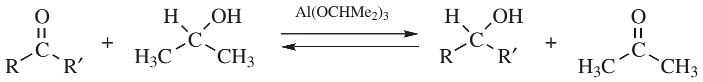
[963]House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, p. 151. See, however, Giordano, C.; Perdoncin, G.; Castaldi, G. *Angew. Chem. Int. Ed.* ***1985***, *24*, 499.



A ketyl

The ketyl intermediate can be isolated.[964]

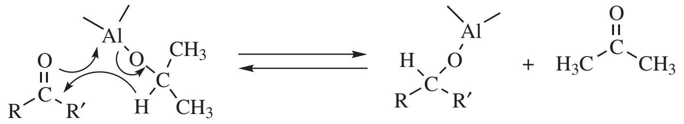
3. *Isopropyl Alcohol and Aluminum Isopropoxide*. This is called the *Meerwein–Ponndorf–Verley reduction*.[965] It is reversible, and the reverse reaction is known as the *Oppenauer oxidation* (see **19-3**):



The equilibrium is shifted by removal of the acetone by distillation. There is a report of the reduction of benzaldehyde to benzyl alcohol by heating with Z-propanol at 225°C for 1 day.[966] The reaction takes place under very mild conditions and is highly specific for aldehydes and ketones, so that C=C bonds (including those conjugated with the C=O bonds) and many other functional groups can be present without themselves being reduced.[967] This includes acetals, so that one of two carbonyl groups in a molecule can be specifically reduced if the other is first converted to an acetal. β-Keto esters, β-diketones, and other ketones and aldehydes with a relatively high enol content do not give this reaction. A SmI_3-assisted version of this reduction has been reported.[968] Zeolites have been used as a medium for this reduction.[969] This reduction can be done catalytically[970] and an aluminum-free, zirconium zeolite catalyst has been developed.[971] A combination of Z-propanol with BINOL and $AlMe_3$ leads to reduction of α-chloroketones to the chlorohydrin with good enantioselectivity.[972] Microwave irradiation of a ketone with Z-propanol, KOH, and activated alumina gives good yields of the alcohol.[973]

[964]For example, see Rautenstrauch, V.; Geoffroy, M. *J. Am. Chem. Soc.* ***1976***, *98*, 5035; ***1977***, *99*, 6280.
[965]For other catalysts, see Akamanchi, K.G.; Noorani, V.R. *Tetrahedron Lett.* ***1995***, *36*, 5085; Akamanchi, K.G.; Varalakshmy, N.R. *Tetrahedron Lett.* ***1995***, *36*, 3571; Maruoka, K.; Saito, S.; Concepcion, A.B.; Yamamoto, H. *J. Am. Chem. Soc.* ***1993***, *115*, 1183. For a microwave-induced version of this reaction, see Barbry, D.; Torchy, S. *Tetrahedron Lett.* ***1997***, *38*, 2959.
[966]Bagnell, L.; Strauss, C.R. *Chem. Commun.* ***1999***, 287.
[967]Diisobornyloxyaluminum isopropoxide gives higher yields under milder conditions than aluminum isopropoxide: Hutton, J. *Synth. Commun.* ***1979***, *9*, 483. For other substitutes for aluminum isopropoxide, see Namy, J.L.; Souppe, J.; Collin, J.; Kagan, H.B. *J. Org. Chem.* ***1984***, *49*, 2045; Okano, T.; Matsuoka, M.; Konishi, H.; Kiji, J. *Chem. Lett.* ***1987***, 181.
[968]Evans, D.A.; Nelson, S.G.; Gagné, M.R.; Muci, A.R. *J. Am. Chem. Soc.* ***1993***, *115*, 9800.
[969]Corma, A.; Domine, M.E.; Nemeth, L.; Valencia, S. *J. Am. Chem. Soc.* ***2002***, *124*, 3194.
[970]Campbell, E.J.; Zhou, H.; Nguyen, S.T. *Org. Lett.* ***2001***, *3*, 2391. See Albrecht, M.; Crabtree, R.H.; Mata, J.; Peris, E. *Chem. Commun.* ***2002***, 32.
[971]Zhu, Y.; Chuah, G.; Jaenicke, S. *Chem. Commun.* ***2003***, 2734.
[972]Campbell, E.J.; Zhou, H.; Nguyen, S.T. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1020.
[973]Kazemi, F.; Kiasat, A.R. *Synth. Commun.* ***2002***, *32*, 2255.

The Meerwein–Ponndorf–Verley reaction usually[974] involves a cyclic transition state:[975]



but in some cases 2 equivalents of aluminum alkoxide are involved: one attacking the carbon and the other the oxygen, a conclusion that stems from the finding that in these cases the reaction was 1.5 order in alkoxide.[976] Although, for simplicity, we have shown the alkoxide as a monomer, it actually exists as trimers and tetramers, and it is these that react.[977]

4. *Metal Reductions*. A single carbonyl group of an α-diketone can be reduced (to give an α-hydroxy ketone) by heating with zinc powder in aq. DMF[978] or zinc in methanol in the presence of benzyltriethylammonium chloride.[979] This has also been accomplished with aq. VCl_2[980] and with Zn—$ZnCl_2$—EtOH.[981] Aluminum and NaOH in aqueous methanol reduces ketones.[982] β-Hydroxy ketones are reduced with good anti-selectivity using an excess of SmI_2 in water,[983] and other ketones or aldehydes are reduced with SmI_2[984] in aq. THF,[985] in Z-propanol,[986] or methanol.[987] Other metals can be used, including $FeCl_3$/Zn in aq. DMF[988] or DME/MeOH.[989] 1,2-Diketones were reduced to the α-hydroxy ketone with TiI_4 in acetonitrile, followed by hydrolysis.[990] Ammonia and aq. $TiCl_3$ in methanol reduces ketones.[991]

[974]It has been that shown in some cases reduction with metal alkoxides, including aluminum isopropoxide, involves free-radical intermediates (SET mechanism): Screttas, C.G.; Cazianis, C.T. *Tetrahedron* ***1978***, *34*, 933; Nasipuri, D.; Gupta, M.D.; Banerjee, S. *Tetrahedron Lett.* ***1984***, *25*, 5551; Ashby, E.C.; Argyropoulos, J.N. *J. Org. Chem.* ***1986***, *51*, 3593; Yamataka, H.; Hanafusa, T. *Chem. Lett.* ***1987***, 643.

[975]See, for example, Shiner, Jr., V.J.; Whittaker, D. *J. Am. Chem. Soc.* ***1963***, *85*, 2337; Warnhoff, E.W.; Reynolds-Warnhoff, P.; Wong, M.Y.H. *J. Am. Chem. Soc.* ***1980***, *102*, 5956.

[976]Moulton, W.N.; Van Atta, R.E.; Ruch, R.R. *J. Org. Chem.* ***1961***, *26*, 290.

[977]Williams, E.D.; Krieger, K.A.; Day, A.R. *J. Am. Chem. Soc.* ***1953***, *75*, 2404; Shiner, Jr., V.J.; Whittaker, D. *J. Am. Chem. Soc.* ***1969***, *91*, 394.

[978]Kreiser, W. *Liebigs Ann. Chem.* ***1971***, *745*, 164.

[979]Kardile, G.B.; Desai, D.G.; Swami, S.S. *Synth. Commun.* ***1999***, *29*, 2129.

[980]Ho, T.; Olah, G.A. *Synthesis* ***1976***, 815.

[981]Toda, F.; Tanaka, K.; Tange, H. *J. Chem. Soc. Perkin Trans. 1* ***1989***, 1555.

[982]Bhar, S.; Guha, S. *Tetrahedron Lett.* ***2004***, *45*, 3775.

[983]Keck, G.E.; Wager, C.A.; Sell, T.; Wager, T.T. *J. Org. Chem.* ***1999***, *64*, 2172.

[984]See Prasad, E.; Flowers II, R.A. *J. Am. Chem. Soc.* ***2002***, *124*, 6895.

[985]Fukuzawa, S.-i.; Miura, M.; Matsuzawa, H. *Tetrahedron Lett.* ***2000***, *42*, 4167; Dahlén, A.; Hilmersson, G. *Tetrahedron Lett.* ***2002***, *43*, 7197.

[986]Fukuzawa, S.-i.; Nakano, N.; Saitoh, T. *Eur. J. Org. Chem.* ***2004***, 2863.

[987]Keck, G.E.; Wager, C.A. *Org. Lett.* ***2000***, *2*, 2307.

[988]Sadavarte, V.S.; Swami, S.S.; Desai, D.G. *Synth. Commun.* ***1998***, *28*, 1139.

[989]Chopade, P.R.; Davis, T.A.; Prasad, E.; Flowers II, R.A. *Org. Lett.* ***2004***, *6*, 2685.

[990]Hayakawa, R.; Sahara, T.; Shimizu, M. *Tetrahedron Lett.* ***2000***, *41*, 7939.

[991]Clerici, A.; Pastori, N.; Porta, O. *Eur. J. Org. Chem.* ***2001***, 2235.

5. *Boranes.* Borane (BH_3) and substituted boranes reduce aldehydes and ketones in a manner similar to their addition to C=C bonds (**15-16**).[992] That is, the boron adds to the oxygen and the hydrogen to the carbon:[993]

The borate is then hydrolyzed to the alcohol. Both 9-BBN[994] (p. 1077) and BH_3—Me_2S[995] reduce only the C=O group of conjugated aldehydes and ketones. A variety of alkylboranes can be used for reduction.[996] Borane reduction of a titanium complex of a 1,3-diketone gives the syn-diol.[997] Reduction occurs with $B_{10}H_{14}$ with $CeCl_3$,[998] Alane (AlH_3) derivatives can also be used, including diisobutylaluminum hydride.[999] Tributylborane in ionic solvents reduces aldehydes to alcohols.[1000]

6. *Tin Hydrides.* Tributyltin hydride reduces aldehydes to primary alcohols by simply heating in methanol.[1001] A mixture of Bu_3SnH and phenylboronic acid (p. 815) reduces aldehydes in dichloromethane.[1002] Reduction of ketones was achieved with Bu_2SnH_2 and a palladium catalyst.[1003] Using triaryltin hydrides with BF_3•OEt_2, where aryl is 2,6-diphenylbenzyl, selective reduction of aliphatic aldehydes in the presence of a conjugated aldehyde was achieved.[1004]

7. *Cannizzaro Reaction.* In the Cannizzaro reaction (**19-81**), aldehydes without an α hydrogen are reduced to alcohols.

8. *Silanes.* In the presence of bases, certain silanes can selectively reduce carbonyls. Epoxy-ketones are reduced to epoxy-alcohols, for example, with

[992]For a review, see Cragg, G.M.L. *Organoboranes in Organic Synthesis*, Marcel Dekker, NY, ***1973***, pp. 324–335. See Cha, J.S.; Moon, S.J.; Park, J.H. *J. Org. Chem.* ***2001***, *66*, 7514.

[993]Brown, H.C.; Subba Rao, B.C. *J. Am. Chem. Soc. 1960, 82*, 681; Brown, H.C.; Korytnyk, W. *J. Am. Chem. Soc.* ***1960***, *82*, 3866.

[994]Krishnamurthy, S.; Brown, H.C. *J. Org. Chem.* ***1975***, *40*, 1864; Lane, C.F. *Aldrichimica Acta* ***1976***, *9*, 31.

[995]Mincione, E. *J. Org. Chem.* ***1978***, *43*, 1829.

[996]Smith, K.; El-Hiti, G.A.; Hou, D.; De Boos, G.A. *J. Chem. Soc. Perkin Trans. 1* ***1999***, 2807.

[997]Bartoli, G.; Bosco, M.; Bellucci, M.C.; Daplozzo, R., Marcantoni, E.; Sambri, L. *Org. Lett.* ***2000***, *2*, 45.

[998]Bae, J.W.; Lee, S.H.; Jung, Y.J.; Yoon, C.-O.M.; Yoon, C.M. *Tetrahedron Lett.* ***2001***, *42*, 2137.

[999]Nakamura, S.; Kuroyanagi, M.; Watanabe, Y. Toru, T. *J. Chem. Soc. Perkin Trans. 1* ***2000***, 3143.

[1000]In bmim PF_6, 1-butyl-3-methylimidazoliium hexafluorophosphate and in emim PF_6, 1-ethyl-3-methylimidazolium hexafluorophosphate: Kabalka, G.W.; Malladi, R.R. *Chem. Commun.* ***2000***, 2191.

[1001]Kamiura, K.; Wada, M. *Tetrahedron Lett.* ***1999***, *40*, 9059; Fung, N.Y.M.; de Mayo, P.; Schauble, J.H.; Weedon, A.C. *J. Org. Chem.* ***1978***, *43*, 3977; Shibata, I.; Yoshida, T.; Baba, A.; Matsuda, H. *Chem. Lett.* ***1989***, 619; Adams, C.M.; Schemenaur, J.E. *Synth. Commun.* ***1990***, *20*, 2359. For a review, see Kuivila, H.G. *Synthesis* ***1970***, 499.

[1002]Yu, H.; Wang, B. *Synth. Commun.* ***2001***, *31*, 2719.

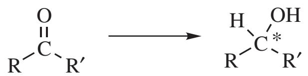
[1003]Kamiya, I.; Ogawa, A. *Tetrahedron Lett.* ***2002***, *43*, 1701.

[1004]Sasaki, K.; Komatsu, N.; Shivakawa, S.; Maruoka, K. *Synlett* ***2002***, 575.

$(MeO)_3SiH$ and LiOMe.[1005] Controlling temperature and solvent leads to different ratios of syn- and anti- products.[1006] Silanes reduce ketones in the presence of $BF_3•OEt_2$[1007] and transition-metal compounds catalyze this reduction.[1008] Ketones are reduced with Cl_3SiH in the presence of pyrrolidine carboxaldehyde[1009] or under photochemical conditions.[1010] Polymethylhydrosiloxane with tetrabutylammonium fluoride reduces α-amino ketones to give the syn-amino alcohol.[1011]

9. *Ammonium Formates*. Sodium formate and trialkylammonium formates can be used to reduce aldehydes and ketones to the corresponding alcohol. Decanal was reduced to decanol, for example, using sodium formate in *N*-methyl-2-pyrrolidinone as a solvent.[1012] A mixture of formic acid and ethyl magnesium bromide was used to reduce decanal to decanol in 70% yield.[1013]

Unsymmetrical ketones are prochiral (p. 193); that is, reduction creates a new stereogenic center:



Much effort has been put into finding optically active reducing agents that will produce one enantiomer of the alcohol enantioselectively, and considerable success has been achieved,.[1014] Each reagent tends to show a specificity for certain types of ketones.[1015] H.C. Brown and co-workers[1016] reduced various types of ketone with a number of reducing agents. These workers also determined the relative effectiveness of various reagents for reduction of eight other types of ketone, including heterocyclic, aralkyl, β-keto esters, β-keto acids,[1017] and so on.[1016] In most cases, good enantioselectivity can be obtained with the proper reagent.[1018] Substituents that are

[1005]Hojo, M.; Fujii, A.; Murakami, C.; Aihara, H.; Hosomi, A. *Tetrahedron Lett.* ***1995***, *36*, 571.
[1006]See Yamamoto, Y.; Matsuoka, K.; Nemoto, H. *J. Am. Chem. Soc.* ***1988***, *110*, 4475.
[1007]Smonou, I. *Tetrahedron Lett.* ***1994***, *35*, 2071.
[1008]Schmidt, T. *Tetrahedron Lett.* ***1994***, *35*, 3513.
[1009]Iwasaki, F.; Onomura, O.; Mishima, K.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* ***1999***, *40*, 7507.
[1010]Enholm, E.J.; Schulte II, J.P. *J. Org. Chem.* ***1999***, *64*, 2610.
[1011]Nadkarni, D.; Hallissey, J.; Mojica, C. *J. Org. Chem.* ***2003***, *68*, 594.
[1012]Babler, J.H.; Sarussi, S.J. *J. Org. Chem.* ***1981***, *46*, 3367.
[1013]Babler, J.H.; Invergo, B.J. *Tetrahedron Lett.* ***1981***, *22*, 621.
[1014]For reviews, see Singh, V.K. *Synthesis* ***1992***, 605; Midland, M.M. *Chem. Rev.* ***1989***, *89*, 1553; Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, ***1986***, pp. 105–130; in Morrison, J.D. *Asymmetric Synthesis*, Academic Press, NY, ***1983***, the articles by Midland, M.M. Vol. 2, pp. 45–69, and Grandbois, E.R.; Howard, S.I.; Morrison, J.D. Vol. 2, pp. 71–90; Haubenstock, H. *Top. Stereochem.* ***1983***, *14*, 231.
[1015]For a list of many of these reducing agents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1097–1111.
[1016]Brown, H.C.; Park, W.S.; Cho, B.T.; Ramachandran, P.V. *J. Org. Chem.* ***1987***, *52*, 5406.
[1017]Wang, Z.; La, B.; Fortunak, J.M.; Meng, X.-J.; Kabalka, G.W. *Tetrahedron Lett.* ***1998***, *39*, 5501.
[1018]See Brown, H.C.; Ramachandran, P.V.; Weissman, S.A.; Swaminathan, S. *J. Org. Chem.* ***1990***, *55*, 6328; Rama Rao, A.V.; Gurjar, M.K.; Sharma, P.A.; Kaiwar, V. *Tetrahedron Lett.* ***1990***, *31*, 2341; Midland, M.M.; Kazubski, A.; Woodling, R.E. *J. Org. Chem.* ***1991***, *56*, 1068.

remote to the carbonyl group can play a role in facial selectivity of the reduction.[1019] Successful asymmetric reductions have been achieved with biologically derived reducing agents,[1020] such as baker's yeast,[1021] enzymes from other organisms,[1022] or with biocatalysts.[1023] Immobilized bakers yeast has been used in an ionic liquid.[1024]

Asymmetric reduction with very high enantioselectivity has also been achieved with achiral reducing agents and optically active catalysts.[1025] Two approaches are represented by (*1*) homogeneous catalytic hydrogenation with the catalyst 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl-ruthenium acetate, BINAP—Ru(OAc)$_2$,[1026] which reduces

[1019]Kaselj, M.; Gonikberg, E.M.; le Noble, W.J. *J. Org. Chem.* ***1998***, *63*, 3218.

[1020]For a review, see Sih, C.J.; Chen, C. *Angew. Chem. Int. Ed.* ***1984***, *23*, 570.

[1021]See, for example, Fujisawa, T.; Hayashi, H.; Kishioka, Y. *Chem. Lett.* ***1987***, 129; Nakamura, K.; Kawai, Y.; Ohno, A. *Tetrahedron Lett.* ***1990***, *31*, 267; Spiliotis, V.; Papahatjis, D.; Ragoussis, N. *Tetrahedron Lett.* ***1990***, *31*, 1615; Ishihara, K.; Sakai, T.; Tsuboi, S.; Utaka, M. *Tetrahedron Lett.* ***1994***, *35*, 4569; Tsuboi, S.; Furutani, H.; Ansari, M.H.; Sakai, T.; Utaka, M.; Takeda, A. *J. Org. Chem.* ***1993***, *58*, 486; Hayakawa, R.; Nozawa, K.; Kimura, K.; Shimizu, M. *Tetrahedron* ***1999***, *55*, 7519; Kreutz, O.C.; Segura, R.C.M.; Rodrigues, J.A.R.; Moran, P.J.S. *Tetrahedron Asymmetry* ***2000***, *11*, 2107; Johns, M.K.; Smallridge, A.J.; Trewhella, M.A. *Tetrahedron Lett.* ***2001***, *42*, 4261; Attolini, M.; Bouguir, F.; Iacazio, F.; Peiffer, G.; Maffei, M. *Tetrahedron* ***2001***, *57*, 537; Wei, Z.-L.; Li, Z.-Y.; Lin, G.-Q. *Tetrahedron Asymmetry* ***2001***, *12*, 229. For reduction with designer yeast, see Chmur zyński, L *J. Heterocyclic Chem.* ***2000***, *37*, 71.

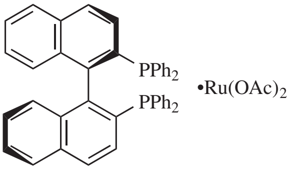
[1022]See Wei, Z.-L.; Li, Z.-Y.; Lin, G.-Q. *Tetrahedron* ***1998***, *54*, 13059; Guarna, A.; Occhiato, E.G.; Spinetti, L.M.; Vallecchi, M.E.; Scarpi, D. *Tetrahedron* ***1995***, *51*, 1775; Medson, C.; Smallridge, A.J.; Trewhella, M.A. *Tetrahedron Asymmetry*, ***1997***, *8*, 1049; Nakamura, K.; Inoue, Y.; Ohno, A. *Tetrahedron Lett.* ***1995***, *36*, 265; Casy, G.; Lee, T.V.; Lovell, H. *Tetrahedron Lett.* ***1992***, *33*, 817; Heiss, C.; Phillips, R.S. *J. Chem. Soc. Perkin Trans. 1* ***2000***, 2821; Gotor, V.; Rebolledo, F.; Liz, R. *Tetrahedron Asymmetry* ***2001***, *12*, 513; Hage, A.; Petra, D.G.I.; Field, J.A.; Schipper, D.; Wijnberg, J.B.P.A.; Kamer, P.C.J.; Reek, J.N.H.; van Leeuwen, P.W.N.M.; Wever, R.; Schoemaker, H.E. *Tetrahedron Asymmetry* ***2001***, *12*, 1025; Yasohara, Y.; Kizaki, N.; Hasegawa, J.; Wada, M.; Kataoka, M.; Shimizu, S. *Tetrahedron Asymmetry* ***2001***, *12*, 1713; Tsujigami, T.; Sugai, T.; Ohta, H. *Tetrahedron Asymmetry* ***2001***, *12*, 2543; Yadav, J.S.; Nanda, S.; Reddy, P.T.; Rao, A.B. *J. Org. Chem.* ***2002***, *67*, 3900; Stampfer, W.; Kosjek, B.; Faber, K.; Kroutil, W. *J. Org. Chem.* ***2003***, *68*, 402; Gröger, H.; Hummel, W.; Buchholz, S.; Drauz, K.; Nguyen, T.V.; Rollmann, C.; Hüsken, H.; Abokitse, K. *Org. Lett.* ***2003***, *5*, 173; Matsuda, T.; Nakajima, Y.; Harada, T.; Nakamura, K. *Tetrahedron Asymmetry* ***2002***, *13*, 971; Nakamura, K.; Yamanaka, R. *Tetrahedron Asymmetry* ***2002***, *13*, 2529, and references cited therein; Carballeira, J.D.; Álvarez, E.; Campillo, M.; Pardo, L.; Sinisterra, J.V. *Tetrahedron Asymmetry* ***2004***, *15*, 951; Shkmoda, K.; Kubota, N.; Hamada, H.; Kaji, M.; Hirata, T. *Tetrahedron Asymmetry* ***2004***, *15*, 1677; Salvi, N.A.; Chattopadhyay, S. *Tetrahedron Asymmetry* ***2004***, *15*, 3397. For enzymatic reduction of thio ketones, see Nielsen, J.K.; Madsen, J.Ø. *Tetrahedron Asymmetry* ***1994***, *5*, 403.

[1023]For a review, see Nakamura, K.; Yamanaka, R.; Matsuda, T.; Harada, T. *Tetrahedron Asymmetry* ***2003***, *14*, 2659.

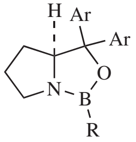
[1024]In bmim PF6, 1-butyl-3-methylimidazolium hexafluorophosphate: Howarth, J.; James, P.; Dai, J. *Tetrahedron Lett.* ***2001***, *42*, 7517.

[1025]See Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY, ***2001***, pp. 343–359.

[1026]For reviews of BINAP, see Noyori, R. *Science* ***1990***, *248*, 1194; Noyori, R.; Takaya, H. *Acc. Chem. Res.* ***1990***, *23*, 345. For the synthesis of BINAP, see Takaya, H.; Akutagawa, S.; Noyori, R. *Org. Synth. 67*, 20.



(*R*)(+)-BINAP



41

β-keto esters with high enantioselectivity.[1027] A variety of chiral additives and/or ligands have been used with catalytic hydrogenation reactions, and many functional groups can be tolerated.[1028] Asymmetric catalytic hydrogenation has been done in ionic liquids.[1029]

A second approach is reduction with BH_3—THF or catecholborane,[1030] using an oxazaborolidine **41** (R = H, Me, or *n*-Bu; Ar = Ph or β-naphthyl)[1031] or other chiral compounds[1032] as a catalyst. Both a polymer-bound oxazaborolidine[1033] and a

[1027]Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* ***1987***, *109*, 5856; Taber, D.F.; Silverberg, L.J. *Tetrahedron Lett.* ***1991***, *32*, 4227. See also, Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* ***1988***, *110*, 629.

[1028]Alonso, D.A.; Guijarro, D.; Pinho, P.; Temme, O.; Andersson, P.G. *J. Org. Chem.* ***1998***, *63*, 2749; Le Blond, C.; Wang, J.; Liu, J.; Andrews, A.T.; Sun, Y.-K. *J. Am. Chem. Soc.* ***1999***, *121*, 4920; ter Halle, R.; Colasson, B.; Schulz, E.; Spagnol, M.; Lemaire, M. *Tetrahedron Lett.* ***2000***, *41*, 643; ter Halle, R.; Schulz, E.; Spagnol, M.; Lemaire, M. *Synlett* ***2000***, 680; Ohkuma, T.; Ishii, D.; Takeno, H.; Noyori, R. *J. Am. Chem. Soc.* ***2000***, *122*, 6510; Burk, M.J.; Hems, W.; Herzberg, D.; Malan, C.; Zanotti-Gerosa, A. *Org. Lett.* ***2000***, *2*, 4173; Wu, J.; Chen, H.; Zhou, Z.-Y.; Yueng, C.H.; Chan, A.S.C. *Synlett* ***2001***, 1050; Madec, J.; Pfister, X.; Phansavath, P.; Ratovelomanana-Vidal, V.; Genêt, J.-P. *Tetrahedron* ***2001***, *57*, 2563; Ohkuma, T.; Hattori, T.; Ooka, H.; Inoue, T.; Noyori, R. *Org. Lett.* ***2004***, *6*, 2681; Xie, J.-H.; Wang, L.-X.; Fu, Y.; Zhu, S.-F.; Fan, B.-M.; Duan, H.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* ***2003***, *125*, 4404; Raja, R.; Thomas, J.M.; Jones, M.D.; Johnson, B.F.G.; Vaushan, D.E.W. *J. Am. Chem. Soc.* ***2003***, *125*, 14982; Lei, A.; Wu, S.; He, M.; Zhang, X. *J. Am. Chem. Soc.* ***2004***, *126*, 1626; Sun, Y.; Wan, X.; Guo, M.; Wang, D.; Dong, X.; Pan, Y.; Zhang, Z. *Tetrahedron Asymmetry* ***2004***, *15*, 2185. For a discussion of the mechanism, see Sandoval, C.A.; Ohkuma, T.; Muñiz, K.; Noyori, R. *J. Am. Chem. Soc.* ***2003***, *125*, 13490.

[1029]In bmim BF4, 1-butyl-3-methylimidazolium tetrafluoroborate: Ngo, H.L.; Hu, A.; Lin, W. *Chem. Commun.* ***2003***, 1912.

[1030]For an example using catecholborane and a chiral gallium complex, see Ford, A.; Woodward, S. *Angew. Chem. Int. Ed.* ***1999***, *38*, 335.

[1031]Corey, E.J.; Bakshi, R.K. *Tetrahedron Lett.* ***1990***, *31*, 611; Puigjaner, C.; Vidal-Ferran, A.; Moyano, A.; Pericàs, M.A.; Riera, A. *J. Org. Chem.* ***1999***, *64*, 7902; Yadav, J.S.; Reddy, P.T.; Hashim, S.R. *Synlett* ***2000***, 1049; Li, X.; Yeung, C.-h.; Chan, A.S.C.; Yang, T.-K. *Tetrahedron Asymmetry* ***1999***, *10*, 759; Cho, B.T.; Chun, Y.S. *J. Chem. Soc. Perkin Trans. 1* ***1999***, 2095; Santhi, V.; Rao, J.M. *Tetrahedron Asymmetry* ***2000***, *11*, 3553; Jones, S.; Atherton, J.C.C. *Tetrahedron Asymmetry* ***2000***, *11*, 4543; Cho, B.T.; Kim, D.J. *Tetrahedron Asymmetry* ***2001***, *12*, 2043; Jiang, B.; Feng, Y.; Hang, J.-F. *Tetrahedron Asymmetry* ***2001***, *12*, 2323; Gilmore, N.J.; Jones, S.; Muldowney, M.P. *Org. Lett.* ***2004***, *6*, 2805; Huertas, R.E.; Corella, J.A.; Soderquist, J.A. *Tetrahedron Lett.* ***2003***, *44*, 4435.

[1032]See Hong, Y.; Gao, Y.; Nie, X.; Zepp, C.M. *Tetrahedron Lett.* ***1994***, *35*, 6631; Quallich, G.J.; Woodall, T.M. *Tetrahedron Lett.* ***1993***, *34*, 4145; Brunel, J.M.; Legrand, O.; Buono, G. *Eur. J. Org. Chem.* ***2000***, 3313; Ford, A.; Woodward, S. *Synth. Commun.* ***1999***, *29*, 189; Calmes, M.; Escale, F. *Synth. Commun.* ***1999***, *29*, 1341; Kawanami, Y.; Murao, S.; Ohga, T.; Kobayashi, N. *Tetrahedron* ***2003***, *59*, 8411; Basaviah, D.; Reddy, G.J.; Chandrashekar, V. *Tetrahedron Asymmetry* ***2004***, *15*, 47; Zhang, Y.-X.; Du, D.-M.; Chen, X.; Lü, S.-F.; Hua, W.-T. *Tetrahedron Asymmetry* ***2004***, *15*, 177.

[1033]Price, M.D.; Sui, J.K.; Kurth, M.J.; Schore, N.E. *J. Org. Chem.* ***2002***, *67*, 8086.

dendritic chiral catalyst has been used in conjunction with borane,[1034] as well as other chiral additives can be used.[1035]

A third important method is the combination of $LiAlH_4$ or $NaBH_4$ with a chiral ligand, often in the presence of a transition-metal complex.[1036] Examples include $LiBH_4/NiCl_2$ and a chiral amino alcohol,[1037] $NaBH_4$ with chiral Lewis acid complexes,[1038] or $NaBH_4/Me_3SiCl$ and a chiral ligand.[1039] A mixture of $NaBH_4$ and Me_3SiCl with a catalytic amount of a chiral, polymer-bound sulfonamide leads to asymmetric reduction.[1040]

Enantioselective reduction is possible with the other methods mentioned above. Reduction with silanes and transition-metal catalysts, such as ruthenium compounds, is also very effective.[1041] This method gives high enantioselectivity with various types of ketone, especially α,β-unsaturated ketones. Chiral ruthenium catalysts have been used with triethylammonium formate for the enantioselective reduction.[1042] A ruthenium catalyst with a polymer-supported chiral ligand has been used with Bu_4NBr and HCO_2Na in water.[1043] Chiral additives mixed with surfactants have been used with sodium formate.[1044] Enantioselective reduction was observed with $PhSiH_3$ and copper compounds with a chiral ligand,[1045] with a mixture of ruthenium and silver catalysts,[1046] or with $Mn(dpm)_3$ and oxygen (dpm = diphenylmethylene).[1047] Asymmetric reduction was achieved using an

[1034]Bolm, C.; Derrien, N.; Seger, A. *Chem. Commun.* ***1999***, 2087.

[1035]Yanagi, T.; Kikuchi, K.; Takeuchi, H.; Ishikawa, T.; Nishimura, T.; Kamijo, T. *Chem. Lett.* ***1999***, 1203; Hu, J.-b.; Zhao, G.; Yang, G.-s.; Ding, Z.-d. *J. Org. Chem.* ***2001***, *66*, 303; Zhou, H.; Lü, S.; Xie, R.; Chan, A.S.C.; Yang, T.-K. *Tetrahedron Lett.* ***2001***, *42*, 1107; Basavaiah, D.; Reddy, G.J.; Chandrashekar, V. *Tetrahedron Asymmetry* ***2001***, *12*, 685.

[1036]For a review, see Daverio, P.; Zanda, M. *Tetrahedron Asymmetry* ***2001***, *12*, 2225.

[1037]Molvinger, K.; Lopez, M.; Court, J. *Tetrahedron Lett.* ***1999***, *40*, 8375.

[1038]Nozaki, K.; Kobori, K.; Uemura, T.; Tsutsumi, T.; Takaya, H.; Hiyama, T. *Bull. Chem. Soc. Jpn.* ***1999***, *72*, 1109.

[1039]Jiang, B.; Feng, Y.; Zheng, J. *Tetrahedron Lett.* ***2000***, *41*, 10281.

[1040]Zhao, G.; Hu, J.-b.; Qian, Z.-s.; Yin, X.-x. *Tetrahedron Asymmetry* ***2002***, *13*, 2095.

[1041]Hayashi, T.; Hayashi, C.; Uozumi, Y. *Tetrahedron Asymmetry,* ***1995***, *6*, 2503.

[1042]Koike, T.; Murata, K.; Ikariya, T. *Org. Lett.* ***2000***, *2*, 3833; Okano, K.; Murata, K.; Ikariya, T. *Tetrahedron Lett.* ***2000***, *41*, 9277; Cossy, J.; Eustache, F.; Dalko, P.I. *Tetrahedron Lett.* ***2001***, *42*, 5005; Rhyoo, H.Y.; Yoon, Y.-A.; Park, H.-J.; Chung, Y.K. *Tetrahedron Lett.* ***2000***, *42*, 5045; Chen, Y.-C.; Wu, T.-F.; Deng, J.-G.; Liu, H.; Jiang, Y.-Z.; Choi, M.C.K.; Chan, A.S.C. *Chem. Commun.* ***2001***, 1488; Liu, P.N.; Gu, P.M.; Wang, F.; Tu, Y.Q. *Org. Lett.* ***2004***, *6*, 169; Wu, X.; Li, X.; Hems, W.; King, F.; Xiao, J. *Org. Biomol. Chem.* ***2004***, *2*, 1818; Schlatter, A.; Kundu, M.K.; Woggon, W.-D. *Angew. Chem. Int. Ed.* ***2004***, *43*, 6731; Hannedouche, J.; Kenny, J.A.; Walsgrove, J.; Wills, M. *Synlett* ***2002***, 263.

[1043]Liu, P.N.; Deng, J.G.; Tu, Y.Q.; Wang, S.H. *Chem. Commun.* ***2004***, 2070.

[1044]Rhyoo, H.Y.; Park, H.-J.; Suh, W.H.; Chung, Y.K. *Tetrahedron Lett.* ***2002***, *43*, 269.

[1045]Sirol, S.; Courmarcel, J.; Mostefai, N.; Riant, O. *Org. Lett.* ***2001***, *3*, 4111; Lipshutz, B.H.; Lower, A.; Noson, K. *Org. Lett.* ***2002***, *4*, 4045; Lipshutz, B.H.; Noson, K.; Chrisman, W.; Lower, A. *J. Am. Chem. Soc.* ***2003***, *125*, 8779.

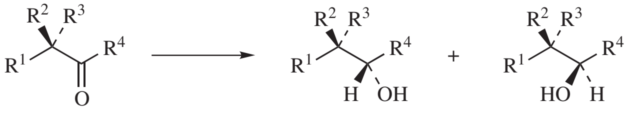
[1046]Gade, L.H.; César, V.; Bellemin-Laponnaz, S. *Angew. Chem. Int. Ed.* ***2004***, *43*, 1014.

[1047]Cecchetto, A.; Fontana, F.; Minisci, F.; Recupero, F. *Tetrahedron Lett.* ***2001***, *42*, 6651.

alkoxide or hydroxide base with a chiral rhodium,[1048] ruthenium,[1049] or iridium complex.[1050] A chiral samarium complex has been used in conjunction with Z-propanol.[1051] Chiral mercapto alcohols have also been used for asymmetric reduction.[1052]

Enantioselective reduction is not possible for aldehydes, since the products are primary alcohols in which the reduced carbon is not chiral, but deuterated aldehydes RCDO give a chiral product, and these have been reduced enantioselectively with B-(3-pinanyl)-9-borabicyclo[3.3.1]nonane (Alpine-Borane) with almost complete optical purity.[1053] Other chiral boranes can be used to reduce aldehydes or ketones.[1054]

In the above cases, an optically active reducing agent or catalyst interacts with a prochiral substrate. Asymmetric reduction of ketones has also been achieved with an achiral reducing agent, if the ketone is complexed to an optically active transition-metal Lewis acid.[1055]



There are other stereochemical aspects to the reduction of aldehydes and ketones. If there is a stereogenic center α to the carbonyl group,[1056] even an achiral reducing agent can give more of one diastereomer than of the other. Such

[1048]Murata, K.; Ikariya, T.; Noyori, R. *J. Org. Chem.* ***1999***, *64*, 2186.

[1049]With Yb(OTf)3 as a co-reagent, see Matsunaga, H.; Yoshioka, N.; Kunieda, T. *Tetrahedron Lett.* ***2001***, *42*, 8857. With microwave irradiation, see Lutsenko, S.; Moberg, C. *Tetrahedron Asymmetry* ***2001***, *12*, 2529.

[1050]Maillard, D.; Nguefack, C.; Pozzi, G.; Quici, S.; Valad, B.; Sinou, D. *Tetrahedron Asymmetry* ***2000***, *11*, 2881.

[1051]Ohno, K.; Kataoka, Y.; Mashima, K. *Org. Lett.* ***2004***, *6*, 4695.

[1052]Yang, T.-K.; Lee, D.-S. *Tetrahedron Asymmetry* ***1999***, *10*, 405.

[1053]Midland, M.M.; Greer, S.; Tramontano, A.; Zderic, S.A. *J. Am. Chem. Soc.* ***1979***, *101*, 2352. See also, Noyori, R.; Tomino, I.; Tanimoto, Y. *J. Am. Chem. Soc.* ***1979***, *101*, 3129; Brown, H.C.; Jadhav, P.K.; Mandal, A.K. *Tetrahedron* ***1981***, *37*, 3547; Midland, M.M.; Zderic, S.A. *J. Am. Chem. Soc.* ***1982***, *104*, 525.

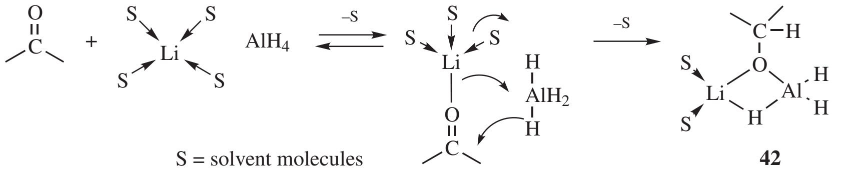
[1054]Wang, Z.; Zhao, C.; Pierce, M.E.; Fortunak, J.M. *Tetrahedron Asymmetry* ***1999***, *10*, 225; Ramachandran, P.V.; Pitre, S.; Brown, H.C. *J. Org. Chem.* ***2002***, *67*, 5315. For a discussion of the sources of stereoselectivity, see Rogic, M.M. *J. Org. Chem.* ***2000***, *65*, 6868; Xu, J.; Wei, T.; Zhang, Q. *J. Org. Chem.* ***2004***, *69*, 6860.

[1055]Dalton, D.M.; Gladysz, J.A. *J. Organomet. Chem.* ***1989***, *370*, C17.

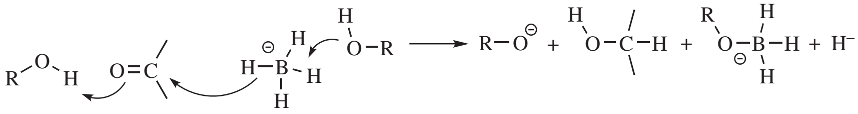
[1056]In theory, the chiral center can be anywhere in the molecule, but in practice, reasonable diastereoselectivity is most often achieved when it is in the α position. For examples of high diastereoselectivity when the chiral center is further away, especially in reduction of β-hydroxy ketones, see Narasaka, K.; Pai, F. *Tetrahedron* ***1984***, *40*, 2233; Hassine, B.B.; Gorsane, M.; Pecher, J.; Martin, R.H. *Bull. Soc. Chim. Belg.* ***1985***, *94*, 597; Bloch, R.; Gilbert, L.; Girard, C. *Tetrahedron Lett.* ***1988***, *53*, 1021; Evans, D.A.; Chapman, K.T.; Carreira, E.M. *J. Am. Chem. Soc.* ***1988***, *110*, 3560.

diastereoselective reductions have been carried out with considerable success.[1057] In most such cases Cram's rule (p. 168) is followed, but exceptions are known.[1058]

With most reagents there is an initial attack on the carbon of the carbonyl group by a hydride equivalent (H^-) although with BH_3[1059] the initial attack is on the oxygen. Detailed mechanisms are not known in most cases.[1060] With tetrahydroaluminate or borohydride compounds, the attacking species is the AlH_4^- (or BH_4^-) ion, which, in effect, transfers H^- to the carbon. The following mechanism has been proposed for $LiAlH_4$:[1061]



Evidence that the cation plays an essential role, at least in some cases, is that when the Li^+ was effectively removed from $LiAlH_4$ (by the addition of a crown ether), the reaction did not take place.[1062] The complex **42** must now be hydrolyzed to the alcohol. For $NaBH_4$, the Na^+ does not seem to participate in the transition state, but kinetic evidence shows that an OR group from the solvent does participate and remains attached to the boron:[1063]



Free H^- cannot be the attacking entity in most reductions with boron or aluminum hydrides because the reactions are frequently sensitive to the size of the MH_4^- [or MR_mH_n- or $M(OR)_mH_n^-$- etc.].

[1057]For reviews, see Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, ***1986***, pp. 131–148; Oishi, T.; Nakata, T. *Acc. Chem. Res.* ***1984***, *17*, 338.

[1058]One study showed that the Cram's rule product predominates with metal hydride reducing agents, but the other product with Bouveault-Blanc and dissolving metal reductions: Yamamoto, Y.; Matsuoka, K.; Nemoto, H. *J. Am. Chem. Soc.* ***1988***, *110*, 4475.

[1059]For a discussion of the mechanism with boranes, see Brown, H.C.; Wang, K.K.; Chandrasekharan, J. *J. Am. Chem. Soc.* ***1983***, *105*, 2340.

[1060]For reviews of the stereochemistry and mechanism, see Caro, B.; Boyer, B.; Lamaty, G.; Jaouen, G. *Bull. Soc. Chim. Fr.* ***1983***, II-281; Boone, J.R.; Ashby, E.C. *Top. Stereochem.* ***1979***, *11*, 53; Wigfield, D.C. *Tetrahedron* ***1979***, *35*, 449.

[1061]Ashby, E.C.; Boone, J.R. *J. Am. Chem. Soc.* ***1976***, *98*, 5524.

[1062]Pierre, J.; Handel, H. *Tetrahedron Lett.* ***1974***, 2317. See also Loupy, A.; Seyden-Penne, J.; Tchoubar, B. *Tetrahedron Lett.* ***1976***, 1677; Ashby, E.C.; Boone, J.R. *J. Am. Chem. Soc.* ***1976***, *98*, 5524.

[1063]Wigfield, D.C.; Gowland, F.W. *J. Org. Chem.* ***1977***, *42*, 1108; *Tetrahedron Lett.* ***1976***, 3373. See however Adams, C.; Gold, V.; Reuben, D.M.E. *J. Chem. Soc. Chem. Commun.* ***1977***, 182; *J. Chem. Soc. Perkin Trans. 2* ***1977***, 1466, 1472; Kayser, M.M.; Eliev, S.; Eisenstein, O. *Tetrahedron Lett.* ***1983***, *24*, 1015.

The question of whether the initial complex in the $LiAlH_4$ reduction (**42**, which can be written as $H{-}\overset{|}{\underset{|}{C}}{-}O\overset{\ominus}{A}lH_3$ = **43**) can reduce another carbonyl to give $H{-}\overset{|}{\underset{|}{C}}{-}O_2\overset{\ominus}{A}lH_4$ and so on has been controversial. It has been shown[1064] that this is probably not the case but that, more likely, **43** disproportionates to $(H{-}\overset{|}{\underset{|}{C}}{-}O)_4Al^{\ominus}$ and AlH_4^-, which is the only attacking species. Disproportionation has also been reported in the $NaBH_4$ reaction.[1065]

Aluminate, **43**, is essentially $LiAlH_4$ with one of the hydrogens replaced by an alkoxy group, that is, $LiAlH_3OR$. The fact that **43** and other alkoxy derivatives of $LiAlH_4$ are less reactive than $LiAlH_4$ itself has led to the use of such compounds as reducing agents that are less reactive and more selective than $LiAlH_4$.[1066] We have already met some of these, for example, $LiAlH(O{-}t{-}Bu)_3$ (reactions **19-39–19-41**; see also, Table 19.5). As an example of chemoselectivity in this reaction it may be mentioned that $LiAlH(O{-}t{-}Bu)_3$ has been used to reduce only the keto group in a molecule containing both keto and carboxylic ester groups.[1067] However, the use of such reagents is sometimes complicated by the disproportionation mentioned above, which may cause $LiAlH_4$ to be the active species, even if the reagent is an alkoxy derivative. Another highly selective reagent (reducing aldehydes and ketones, but not other functional groups), which does not disproportionate, is potassium triisopropoxyborohydride.[1068]

The mechanism of catalytic hydrogenation of aldehydes and ketones is probably similar to that of reaction **15-11**, although not much is known about it.[1069]

For other reduction reactions of aldehydes and ketones (see **19-61**, **19-76**, and **19-81**).

OS **I**, 90, 304, 554; **II**, 317, 545, 598; **III**, 286; **IV**, 15, 25, 216, 660; **V**, 175, 294, 595, 692; **VI**, 215, 769, 887; **VII**, 129, 215, 241, 402, 417; **VIII**, 302, 312, 326, 527; **IX**, 58, 362, 676.

19-37 Reduction of Carboxylic Acids to Alcohols

Dihydro-de-oxo-bisubstitution

$$RCOOH \xrightarrow{LiAlH_4} RCH_2OH$$

[1064]Haubenstock, H.; Eliel, E.L. *J. Am. Chem. Soc.* ***1962***, *84*, 2363; Malmvik, A.; Obenius, U.; Henriksson, U. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 1899, 1905.

[1065]Malmvik, A.; Obenius, U.; Henriksson, U. *J. Org. Chem.* ***1988***, *53*, 221.

[1066]For reviews of reductions with alkoxyaluminum hydrides, see Málek, J. *Org. React.* ***1988***, *36*, 249; ***1985***, *34*, 1; Málek, J.; Č erný, M. *Synthesis* ***1972***, 217.

[1067]Levine, S.G.; Eudy, N.H. *J. Org. Chem.* ***1970***, *35*, 549; Heusler, K.; Wieland, P.; Meystre, C. *Org. Synth. V*, 692.

[1068]Brown, C.A.; Krishnamurthy, S.; Kim, S.C. *J. Chem. Soc. Chem. Commun.* ***1973***, 391.

[1069]For a review of the mechanism of gas-phase hydrogenation, see Pavlenko, N.V. *Russ. Chem. Rev.* ***1989***, *58*, 453.

Carboxylic acids are easily reduced to primary alcohols by $LiAlH_4$.[1070] The reaction does not stop at the aldehyde stage (but see **19-40**). The conditions are particularly mild, the reduction proceeding quite well at room temperature. Other hydrides have also been used,[1071] but not $NaBH_4$ (see Table 19.5).[1072] Note, however, that complexion of the carboxylic acid with cyanuric chloride (2,4,6-trichlorotriazine) also smooth reduction to the alcohol.[1073] A combination of $NaBH_4$ and an arylboronic acid (p. 815) is also effective.[1074] Benzyltriethylammonium borohydride is dichloromethane also reduces carboxylic acids to the alcohol.[1075] Catalytic hydrogenation is also generally ineffective.[1076] Borane is particularly good for carboxyl groups (Table 19.4) and permits selective reduction of them in the presence of many other groups (although the reaction with double bonds takes place at about the same rate in ether solvents).[1077] Borane also reduces carboxylic acid salts.[1078] Aluminum hydride reduces COOH groups without affecting carbon–halogen bonds in the same molecule. The reduction has also been carried out with SmI_2 in basic media[1079] or aq. H_3PO_4,[1080] or simply with SmI_2 in water.[1081] A mixture of $NaBH_4$ and I_2 has been used to reduced amino acids to amino alcohols.[1082]

OS **III**, 60; **VII**, 221; 530; **VIII**, 26, 434, 528.

19-38 Reduction of Carboxylic Esters to Alcohols

Dihydro,hydroxy-de-oxo,alkoxy-tersubstitution

$$RCOOR' \xrightarrow{LiAlH_4} RCH_2OH + R'OH$$

[1070]For a review, see Gaylord, N.G. *Reduction with Complex Metal Hydrides*, Wiley, NY, ***1956***, pp. 322–373.

[1071]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1114–1116. Zinc borohydride has also been used; see Narashimhan, S.; Madhavan, S.; Prasad, K.G. *J. Org. Chem.* ***1995***, *60*, 5314.

[1072]NaBH4 in the presence of $Me2N{=}CHCl^+$ Cl^- reduces carboxylic acids to primary alcohols chemoselectively in the presence of halide, ester, and nitrile groups: Fujisawa, T.; Mori, T.; Sato, T. *Chem. Lett.* ***1983***, 835.

[1073]Falorni, M.; Porcheddu, A.; Taddei, M. *Tetrahedron Lett.* ***1999***, *40*, 4395.

[1074]Tale, R.H.; Patil, K.M.; Dapurkar, S.E. *Tetrahedron Lett.* ***2003***, *44*, 3427.

[1075]Narashimhan, S.; Swarnalakshmi, S.; Balakumar, R. *Synth. Commun.* ***2000***, *30*, 941.

[1076]See Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, ***1985***, pp. 78–79.

[1077]Brown, H.C.; Korytnyk, W. *J. Am. Chem. Soc.* ***1960***, *82*, 3866; Batrakov, S.G.; Bergel'son, L.D. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1965***, 348; Pelter, A.; Hutchings, M.G.; Levitt, T.E.; Smith, K. *Chem. Commun.* ***1970***, 347; Brown, H.C.; Stocky, T.P. *J. Am. Chem. Soc.* ***1977***, *99*, 8218; Chen, M.H.; Kiesten, E.I.S.; Magano, J.; Rodriguez, D.; Sexton, K.E.; Zhang, J.; Lee, H.T. *Org. Prep. Proceed. Int.* ***2002***, *34*, 665.

[1078]Yoon, N.M.; Cho, B.T. *Tetrahedron Lett.* ***1982***, *23*, 2475.

[1079]Kamochi, Y.; Kudo, T. *Bull. Chem. Soc. Jpn.* ***1992***, *65*, 3049.

[1080]Kamochi, Y.; Kudo, T. *Tetrahedron* ***1992***, *48*, 4301.

[1081]Kamochi, Y.; Kudo, T. *Chem. Lett.* ***1993***, 1495.

[1082]McKennon, M.J.; Meyers, A.I.; Drauz, K.; Schwarm, M. *J. Org. Chem.* ***1993***, *58*, 3568.

Lithium aluminum hydride reduces carboxylic esters to give 2 equivalents of alcohol.[1083] The reaction is of wide scope and has been used to reduce many esters. Where the interest is in obtaining R′OH, this is a method that is often a working equivalent of "hydrolyzing" esters. Lactones yield diols. Among the reagents that give the same products[1084] are DIBALH, lithium triethylborohydride, $LiAlH(Ot\text{-}Bu)_3$,[1085] and BH_3—SMe_2 in refluxing THF.[1086] Although $NaBH_4$ reduces phenolic esters, especially those containing electron-withdrawing groups,[1087] its reaction with other esters is usually so slow that it is not the reagent of choice (exceptions are known[1088]), and it is generally possible to reduce an aldehyde or ketone without reducing an ester function in the same molecule. Note that $NaBH_4$ in DMF—MeOH reduces aryl carboxylic esters to benzylic alcohols,[1089] and $NaBH_4$—LiCl with microwave irradiation also reduces esters to primary alcohols.[1090] However, $NaBH_4$ reduces esters in the presence of certain compounds (see Table 19.5).[1091] Carboxylic esters can also be reduced to alcohols by hydrogenation over copper chromite catalysts,[1092] although high pressures and temperatures are required. Ester functions generally survive low-pressure catalytic hydrogenations. Before the discovery of $LiAlH_4$, the most common way of carrying out the reaction was with sodium in ethanol, a method known as the *Bouveault–Blanc procedure*. This procedure is still sometimes used where selectivity is necessary (see also, **19-62**, **19-65**, and **19-59**).

Silanes, such as Ph_2SiH_2, with a catalytic amount of triphenylphosphine and a rhodium catalyst reduced esters to primary alcohols.[1093] Aliphatic silanes such as $EtMe_2SiH$, also reduced esters with a ruthenium catalyst.[1094]

OS **II**, 154, 325, 372, 468; **III**, 671; **IV**, 834; **VI**, 781; **VII**, 356; **VIII**, 155; **IX**, 251.

[1083]For a review, see Gaylord, N.G. *Reduction with Complex Metal Hydrides*, Wiley, NY, ***1956***, pp. 391–531.

[1084]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1116–1120.

[1085]Ayers, T.A. *Tetrahedron Lett.* ***1999***, *40*, 5467.

[1086]Brown, H.C.; Choi, Y.M. *Synthesis* ***1981***, 439; Brown, H.C.; Choi,Y.M.; Narasimhan, S. *J. Org. Chem.* ***1982***, *47*, 3153.

[1087]Takahashi, S.; Cohen, L.A. *J. Org. Chem.* ***1970***, *35*, 1505.

[1088]For example, see Brown, M.S.; Rapoport, H. *J. Org. Chem.* ***1963***, *28*, 3261; Bianco, A.; Passacantilli, P.; Righi, G. *Synth. Commun.* ***1988***, *18*, 1765; Boechat, N.; da Costa, J.C.S.; Mendonç a, J.de S.; de Oliveira, P.S.M.; DeSouza, M.V.N. *Tetrahedron Lett.* ***2004***, *45*, 6021.

[1089]Zanka, A.; Ohmori, H.; Okamoto, T. *Synlett* ***1999***, 1636.

[1090]Feng, J.-C.; Liu, B.; Dai, L.; Yang, X.-L.; Tu, S.-J. *Synth. Commun.* ***2001***, *31*, 1875.

[1091]See also Kikugawa, Y. *Chem. Lett.* ***1975***, 1029; Santaniello, E.; Ferraboschi, P.; Sozzani, P. *J. Org. Chem.* ***1981***, *46*, 4584; Brown, H.C.; Narasimhan, S.; Choi,Y.M. *J. Org. Chem.* ***1982***, *47*, 4702; Soai, K.; Oyamada, H.; Takase, M.; Ookawa, A. *Bull. Chem. Soc. Jpn.* ***1984***, *57*, 1948; Guida, W.C.; Entreken, E.E.; Guida, W.C. *J. Org. Chem.* ***1984***, *49*, 3024.

[1092]For a review, see Adkins, H. *Org. React.* ***1954***, *8*, 1.

[1093]Ohta, T.; Kamiya, M.; Kusui, K.; Michibata, T.; Nobutomo, M.; Furukawa, I. *Tetrahedron Lett.* ***1999***, *40*, 6963.

[1094]Matsubara, K.; Iura, T.; Maki, T.; Nagashima, H. *J. Org. Chem.* ***2002***, *67*, 4985.

19-39 Reduction of Acyl Halides

Hydro-de-halogenation or Dehalogenation

$$\text{RCOCl} \xrightarrow[-78^\circ\text{C}]{\text{LiAlH(O}t\text{-Bu)}_3} \text{RCHO}$$

Acyl halides can be reduced to aldehydes[1095] by treatment with lithium tri-*tert*-butoxyaluminum hydride in diglyme at −78°C.[1096] The R group may be alkyl or aryl and may contain many types of substituents, including NO_2, CN, and EtOOC groups. The reaction stops at the aldehyde stage because steric hindrance prevents further reduction under these conditions. Acyl halides can also be reduced to aldehydes by hydrogenolysis with palladium-on-barium sulfate as catalyst. This is called the *Rosenmund reduction*.[1097] A more convenient hydrogenolysis procedure involves palladium-on-charcoal as the catalyst, with ethyldiisopropylamine as acceptor of the liberated HCl and acetone as the solvent.[1098] The reduction of acyl halides to aldehydes has also been carried out[1099] with Bu_3SnH,[1100] with the $InCl_3$-catalyzed reaction with Bu_3SnH,[1101] with $NaBH_4$ in a mixture of DMF and THF,[1102] and with formic acid/NH_4OH.[1103] In some of these cases, the mechanisms are free-radical. There are several indirect methods for the conversion of acyl halides to aldehydes, most of them involving prior conversion of the halides to certain types of amides (see **19-41**). There is also a method in which the COOH group is replaced by a completely different CHO group (**16-87**).

OS **III**, 551, 627; **VI**, 529, 1007. Also see, OS **III**, 818; **VI**, 312.

[1095]For a review of the formation of aldehydes from acid derivatives, see Fuson, R.C., in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 211–232. For a review of the reduction of acyl halides, see Wheeler, O.H., in Patai, S. *The Chemistry of Acyl Halides*, Wiley, NY, ***1972***, pp. 231–251.

[1096]Cha, J.S.; Brown, H.C. *J. Org. Chem.* ***1993***, *58*, 4732, and references cited therein.

[1097]For a review, see Rylander, P.N. *Catalytic Hydrogenation Over Platinum Metals*, Academic Press, NY, ***1967***, pp. 398–404. For a discussion of the Pt catalyst, see Maier, W.F.; Chettle, S.J.; Rai, R.S.; Thomas, G. *J. Am. Chem. Soc.* ***1986***, *108*, 2608.

[1098]Peters, J.A.; van Bekkum, H. *Recl. Trav. Chim. Pays-Bas* ***1971***, *90*, 1323; ***1981***, *100*, 21. See also, Burgstahler, A.W.; Weigel, L.O.; Shaefer, C.G. *Synthesis* ***1976***, 767.

[1099]For some other methods, see Wagenknecht, J.H. *J. Org. Chem.* ***1972***, *37*, 1513; Smith, D.G.; Smith, D.J.H. *J. Chem. Soc. Chem. Commun.* ***1975***, 459; Leblanc, J.C.; Moise, C.; Tirouflet, J. *J. Organomet. Chem.* ***1985***, *292*, 225; Corriu, R.J.P.; Lanneau, G.F.; Perrot, M. *Tetrahedron Lett.* ***1988***, *29*, 1271. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1265–1266.

[1100]Kuivila, H.G. *J. Org. Chem.* ***1960***, *25*, 284; Walsh, Jr., E.J.; Stoneberg, R.L.; Yorke, M.; Kuivila, H.G. *J. Org. Chem.* ***1969***, *34*, 1156; Four, P.; Guibe, F. *J. Org. Chem.* ***1981***, *46*, 4439; Lusztyk, J.; Lusztyk, E.; Maillard, B.; Ingold, K.U. *J. Am. Chem. Soc.* ***1984***, *106*, 2923.

[1101]Inoue, K.; Yasuda, M.; Shibata, I.; Baba, A. *Tetrahedron Lett.* ***2000***, *41*, 113.

[1102]Babler, J.H. *Synth. Commun.* ***1982***, *12*, 839. For the use of NaBH4 and metal ions, see Entwistle, I.D.; Boehm, P.; Johnstone, R.A.W.; Telford, R.P. *J. Chem. Soc. Perkin Trans. 1* ***1980***, 27.

[1103]Shamsuddin, K.M.; Zubairi, Md.O.; Musharraf, M.A. *Tetrahedron Lett.* ***1998***, *39*, 8153.

19-40 Reduction of Carboxylic Acids, Esters, and Anhydrides to Aldehydes[1104]

Hydro-de-hydroxylation or Dehydroxylation (overall transformation)

$$RCOOH \longrightarrow RCHO$$
$$RCOOR' \longrightarrow RCHO$$

With most reducing agents, reduction of carboxylic acids generally gives the primary alcohol (**19-37**) and the isolation of aldehydes is not feasible. However, simple straight-chain carboxylic acids have been reduced to aldehydes[1105] by treatment with Li in $MeNH_2$ or NH_3 followed by hydrolysis of the resulting imine,[1106] with

$$RCOOH \xrightarrow[MeNH_2]{Li} RCH{=}N{-}Me \xrightarrow{H_2O} RCHO$$

with thexylchloro(or bromo)borane-Me_2S[1107] (see **15-16** for the thexyl group), $Me_2N{=}CHCl^+\ Cl^-$ in pyridine,[1108] and with diaminoaluminum hydrides.[1109] Benzoic acid derivatives were reduced to benzaldehyde derivatives with NaH_2PO_2 and a diacylperoxide and a palladium catalyst.[1110] Caproic and isovaleric acids have been reduced to aldehydes in 50% yields or better with DIBALH (i-Bu_2AlH) at -75 to $-70°C$.[1111] Carboxylic acids can be reduced directly on Claycop–H_2O_2 using microwave irradiation.[1112]

Carboxylic esters have been reduced to aldehydes with DIBALH at $-70°C$, with diaminoaluminum hydrides,[1113] with $LiAlH_4$–Et_2NH,[1114] and for phenolic esters with $LiAlH(O{-}t\text{-}Bu)_3$ at 0°C.[1115] Aldehydes have also been prepared by reducing ethyl thiol esters (RCOSEt) with Et_3SiH and a Pd—C catalyst.[1116] Pretreatment of

[1104]For a review, see Cha, J.S. *Org. Prep. Proced. Int.* ***1989***, *21*, 451.

[1105]For other reagents, see Lanneau, G.F.; Perrot, M. *Tetrahedron Lett.* ***1987***, *28*, 3941; Cha, J.S.; Kim, J.E.; Yoon, M.S.; Kim, Y.S. *Tetrahedron Lett.* ***1987***, *28*, 6231. See also, the lists, in Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1265–1268.

[1106]Bedenbaugh, A.O.; Bedenbaugh, J.H.; Bergin, W.A.; Adkins, J.D. *J. Am. Chem. Soc.* ***1970***, *92*, 5774.

[1107]Chloro - see Brown, H.C.; Cha, J.S.; Yoon, N.M.; Nazer, B. *J. Org. Chem.* ***1987***, *52*, 5400; Bromo, see Cha, J.S.; Kim, J.E.; Lee, K.W. *J. Org. Chem.* ***1987***, *52*, 5030.

[1108]Fujisawa, T.; Mori, T.; Tsuge, S.; Sato, T. *Tetrahedron Lett.* ***1983***, *24*, 1543.

[1109]Muraki, M.; Mukaiyama, T. *Chem. Lett.* ***1974***, 1447; ***1975***, 215; Cha, J.S.; Kim, J.M.; Jeoung, M.K.; Kwon, O.O.; Kim, E.J. *Org. Prep. Proceed. Int.* ***1995***, *27*, 95.

[1110]Gooßen, L.J.; Ghosh, K. *Chem. Commun.* ***2002***, 836.

[1111]Zakharkin, L.I.; Sorokina, L.P. *J. Gen. Chem. USSR* ***1967***, *37*, 525.

[1112]Varma, R.S.; Dahiya, R. *Tetrahedron Lett.* ***1998***, *39*, 1307.

[1113]Muraki, M.; Mukaiyama, T. *Chem. Lett.* ***1974***, 1447; ***1975***, 215; Cha, J.S.; Kim, J.M.; Jeoung, M.K.; Kwon, O.O.; Kim, E.J. *Org. Prep. Proceed. Int.* ***1995***, *27*, 95.

[1114]Cha, J.S.; Kwon, S.S. *J. Org. Chem.* ***1987***, *52*, 5486.

[1115]Zakharkin, L.I.; Khorlina, I.M. *Tetrahedron Lett.* ***1962***, 619, *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1963***, 288; ***1964***, 435; Zakharkin, L.I.; Gavrilenko, V.V.; Maslin, D.N.; Khorlina, I.M. *Tetrahedron Lett.* ***1963***, 2087; Zakharkin, L.I.; Gavrilenko, V.V.; Maslin, D.N. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1964***, 867; Weissman, P.M.; Brown, H.C. *J. Org. Chem.* ***1966***, *31*, 283.

[1116]Fukuyama, T.; Lin, S.; Li, L. *J. Am. Chem. Soc.* ***1990***, *112*, 7050.

the acid with Me_3SiCl followed by reduction with DIBALH also gives the aldehyde.[1117] Thioesters have been reduced to the aldehyde with lithium metal in THF at −78°C, followed by quenching with methanol.[1118]

Anhydrides, both aliphatic and aromatic, as well as mixed anhydrides of carboxylic and carbonic acids, have been reduced to aldehydes in moderate yields with disodium tetracarbonylferrate, $Na_2Fe(CO)_4$.[1119] Heating a carboxylic acid, presumably to form the anhydride, and then reaction with Na/EtOH leads to the aldehyde.[1120]

Acid chlorides are reduced to aldehydes with Bu_3SnH and a nickel catalyst.[1121]

Also see, **19-62** and **19-38**.

OS **VI**, 312; **VIII**, 241, 498.

19-41 Reduction of Amides to Aldehydes

Hydro-de-dialkylamino-substitution

$$RCONR_2' + LiAlH_4 \longrightarrow RCHO + NHR_2'$$

N,N-Disubstituted amides can be reduced to amines with $LiAlH_4$ (see **19-64**), but also to aldehydes.[1122] Keeping the amide in excess gives the aldehyde rather than the amine. Sometimes it is not possible to prevent further reduction and primary alcohols are obtained instead. Other reagents[1123] that give good yields of aldehydes are DIBALH,[1124] $LiAlH(O{-}t\text{-}Bu)_3$, diaminoaluminum hydrides,[1125] disiamylborane (see **15-16** for the disiamyl group), [1126] and $Cp_2Zr(H)Cl$.[1127]

Aldehydes have been prepared from carboxylic acids or acyl halides by first converting them to certain types of amides that are easily reducible. There are several examples:[1128]

[1117]Chandrasekhar, S.; Kumar, M.S.; Muralidhar, B. *Tetrahedron Lett.* ***1998***, *39*, 909.

[1118]Penn, J.H.; Owens, W.H. *Tetrahedron Lett.* ***1992***, *33*, 3737.

[1119]Watanabe, Y.; Yamashita, M.; Mitsudo, T.; Igami, M.; Takegami, Y. *Bull. Chem. Soc. Jpn.* ***1975***, *48*, 2490; Watanabe, Y.; Yamashita, M.; Mitsudo, T.; Igami, M.; Tomi, K.; Takegami, Y. *Tetrahedron Lett.* ***1975***, 1063.

[1120]Shi, Z.; Gu, H. *Synth. Commun.* ***1997***, *27*, 2701.

[1121]Malanga, C.; Mannucci, S.; Lardicci, L. *Tetrahedron Lett.* ***1997***, *38*, 8093.

[1122]For a review, see Fuson, R.C., in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 220–225.

[1123]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp.1269–1271.

[1124]Zakharkin, L.I.; Khorlina, I.M. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1959***, 2046.

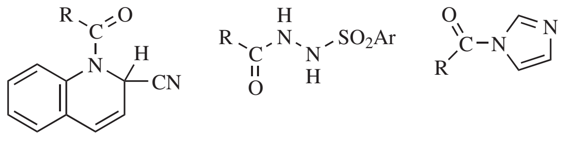
[1125]Muraki, M.; Mukaiyama, T. *Chem. Lett.* ***1975***, 875.

[1126]Godjoian, G.; Singaram, B. *Tetrahedron Lett.* ***1997***, *38*, 1717.

[1127]White, J.M.; Tunoori, A.R.; Georg, G.I. *J. Am. Chem. Soc.* ***2000***, *122*, 11995.

[1128]For other examples, see Doleschall, G. *Tetrahedron* ***1976***, *32*, 2549; Atta-ur-Rahman; Basha, A. *J. Chem. Soc. Chem. Commun.* ***1976***, 594; Izawa, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* ***1979***, *52*, 555; Craig, J.C.; Ekwurieb, N.N.; Fu, C.C.; Walker, K.A.M. *Synthesis* ***1981***, 303.

1. *Reissert Compounds.*[1129] Compounds such as **44** are prepared from the acyl halide by treatment with quinoline and cyanide ion. Treatment of **44** with sulfuric acid gives the corresponding aldehyde.



44 **45** **46**

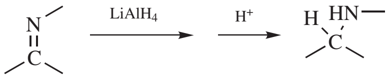
2. *Acyl Sulfonylhydrazides.* Compounds such as **45** are cleaved with base to give aldehydes. This is known as the *McFadyen–Stevens reduction* and is applicable only to aromatic aldehydes or aliphatic aldehydes with no a hydrogen.[1130] RCON=NH (see **19-67**) has been proposed as an intermediate in this reaction.[1131]
3. *Imidazoles.* Compounds **46**[1132] can be reduced to aldehydes with $LiAlH_4$.
4. *See Also the Sonn–Müller Method.* (**19-44**).

OS **VIII**, 68. See OS **IV**, 641, **VI**, 115 for the preparation of Reissert compounds.

B. Attack at Non-Carbonyl Multiple-Bonded Heteroatoms

19-42 Reduction of the Carbon–Nitrogen Double Bond

C,N-Dihydro-addition



Imines and Schiff bases,[1133] hydrazones,[1134] and other C=N compounds can be reduced with $LiAlH_4$, $NaBH_4$,[1135] Na—EtOH, hydrogen and a catalyst, as well as

[1129]For reviews of Reissert compounds, see Popp, F.D.; Uff, B.C. *Heterocycles* ***1985***, *23*, 731; Popp, F.D. *Bull. Soc. Chim. Belg.* ***1981***, *90*, 609; *Adv. Heterocycl. Chem.* ***1979***, *24*, 187; ***1968***, *9*, 1. See Bridge, A.W.; Hursthouse, M.B.; Lehmann, C.W.; Lythgoe, D.J.; Newton, C.G. *J. Chem. Soc. Perkin Trans. 1* ***1993***, 1839 for isoquinoline Reissert salts.

[1130]Babad, H.; Herbert, W.; Stiles, A.W. *Tetrahedron Lett.* ***1966***, 2927; Dudman, C.C.; Grice, P.; Reese, C.B. *Tetrahedron Lett.* ***1980***, *21*, 4645.

[1131]For discussions, see Cacchi, S.; Paolucci, G. *Gazz. Chem. Ital.* ***1974***, *104*, 221; Matin, S.B.; Craig, J.C.; Chan, R.P.K. *J. Org. Chem.* ***1974***, *39*, 2285.

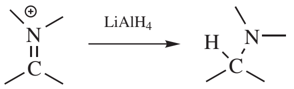
[1132]For a review, see Staab, H.A.; Rohr, W. *Newer Methods Prep. Org. Chem.* ***1968***, *5*, 61.

[1133]See Ranu, B.C.; Sarkar, A.; Majee, A. *J. Org. Chem.* ***1997***, *62*, 1841; Verdaguer, X.; Lange, U.E.W.; Buchwald, S.L. *Angew. Chem. Int. Ed.* ***1998***, *37*, 1103; Amin, Sk.R.; Crowe, W.E. *Tetrahedron Lett.* ***1997***, *38*, 7487; Vetter, A.H.; Berkessel, A. *Synthesis* ***1995***, 419.

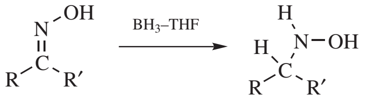
[1134]For an enantioselective reduction of hydrazone derivatives, see Burk, M.J.; Feaster, J.E. *J. Am. Chem. Soc.* ***1992***, *114*, 6266.

[1135]Bhattacharyya, S.; Neidigh, K.A.; Avery, M.A.; Williamson, J.S. *Synlett* ***1999***, 1781.

with other reducing agents.[1136] A mixture of Sm/I_2[1137] or In/NH_4Cl[1138] reduces imines. Reduction with Bu_2SnClH in HMPA has been shown to be chemoselective for imines.[1139] Iminium salts are also reduced by $LiAlH_4$, although here there is no "addition" to the nitrogen:[1140] Silanes[1141] with a triarylborane catalyst reduces *N*-sulfonyl imines[1142] as does TiI_4.[1143] Imines are reduced with Cl_3SiH and pyrrolidine carboxaldehyde,[1144] Samarium bromide in HMPA,[1145] Z-propanol with a ruthenium catalyst,[1146] and with triethylammonium formate with microwave irradiation.[1147] Oximes are reduced with hydrogen gas an a catalytic amount of 48% HBr.[1148]



Oximes are generally reduced to amines (**19-48**),[1149] but simple reduction to give hydroxylamines can be accomplished with borane[1150] or sodium cyanoborohydride.[1151] Oxime *O*-ethers are reduced with Bu_3SnH and BF_3•OEt_2.[1152] Diazo compounds (ArN=NAr) are reductively cleaved to aniline derivatives with Zn and ammonium formate in methanol.[1153]



[1136]For a review, see Harada, K., in Patai, S. *The Chemistry of the Carbon–Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 276–293. For a review with respect to catalytic hydrogenation, see Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, ***1967***, pp. 123–138.

[1137]Banik, B.K.; Zegrocka, O.; Banik, I.; Hackfeld, L.; Becker, F.F. *Tetrahedron Lett.* ***1999***, *40*, 6731.

[1138]Banik, B.K.; Hackfeld, L.; Becker, F.F. *Synth. Commun.* ***22001***, *31*, 1581.

[1139]Shibata, I.; Moriuchi-Kawakami, T.; Tanizawa, D.; Suwa, T.; Sugiyama, E.; Matsuda, H.; Baba, A. *J. Org. Chem.* ***1998***, *63*, 383.

[1140]For a review of nucleophilic addition to iminium salts, see Paukstelis, J.V.; Cook, A.G. in Cook, A.G. *Enamines*, 2nd ed., Marcel Dekker, NY, ***1988***, pp. 275–356.

[1141]For a discussion of noncovalent interactions in the reduction of imines, see Malkov, A.V.; Mariani, A.; MacDougall, K.N.; Koč ovský, P. *Org. Lett.* ***2004***, *6*, 2253.

[1142]Blackwell, J.M.; Sonmor, E.R.; Scoccitti, T.; Piers, W.E. *Org. Lett.* ***2000***, *2*, 3921.

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[1144]Iwasaki, F.; Onomura, O.; Mishima, K.; Kanematsu, T.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* ***2001***, *42*, 2525.

[1145]Knettle, B.W.; Flowers II, R.A. *Org. Lett.* ***2001***, *3*, 2321.

[1146]Samec, J.S.M.; Bäckvall, J.-E. *Chem. Eur. J.* ***2002***, *8*, 2955.

[1147]Moghaddam, F.M.; Khakshoor, O.; Ghaffarzadeh, M. *J. Chem. Res. (S)* ***2001***, 525.

[1148]Davies, I.W.; Taylor, M., Marcoux, J.-F.; Matty, L.; Wu, J.; Hughes, D.; Reider, P.J. *Tetrahedron Lett.* ***2000***, *41*, 8021.

[1149]For examples, see Bolm, C.; Felder, M. *Synlett* ***1994***, 655; Williams, D.R.; Osterhout, M.H.; Reddy, J.P. *Tetrahedron Lett.* ***1993***, *34*, 3271.

[1150]Feuer, H.; Vincent Jr., B.F.; Bartlett, R.S. *J. Org. Chem.* ***1965***, *30*, 2877; Kawase, M.; Kikugawa, Y. *J. Chem. Soc. Perkin Trans. 1* ***1979***, 643.

[1151]For reviews of $NaBH_3CN$, see Hutchins, R.O.; Natale, N.R. *Org. Prep. Proced. Int.* ***1979***, *11*, 201; Lane, C.F. *Synthesis* ***1975***, 135.

[1152]Ueda, M.; Miyabe, H.; Namba, M.; Nakabayashi, T.; Naito, T. *Tetrahedron Lett.* ***2002***, *43*, 4369.

[1153]Gowda, S.; Abiraj, K.; Gowda, D.C. *Tetrahedron Lett.* ***2002***, *43*, 1329.

Reduction of imines has been carried out enantioselectively.[1154] Catalytic hydrogenation with a chiral iridium[1155] or palladium[1156] catalyst has been used. Catalytic hydrogenation of iminium salts with a chiral ruthenium catalyst gives the amine.[1157] In a related reaction, enamines were reduced by hydrogenation over a chiral rhodium catalyst.[1158] An ammonium formate with a chiral ruthenium complex was used with imines.[1159] Hydrogenation of oximes with Pd/C and a nickel complex gives the imine, and in the presence of a lipase and ethyl acetate the final product was an acetamide, formed with high enantioselectivity.[1160] Conjugated *N*-sulfonyl imines are reduced to the conjugated sulfonamide with good enantioselectivity using a chiral rhodium catalyst in the presence of LiF and $PhSnMe_3$.[1161] Phosphinyl imines, $R_2C{=}N{-}P({=}O)Ar_2$, are reduced with high enantioselectivity using a chiral copper catalyst.[1162] Silanes, such as $PhSiH_3$, can be used for the reduction of imines, and in the presence of a chiral titanium catalyst the resulting amine was formed with excellent enantioselectivity.[1163]

Isocyanates have been catalytically hydrogenated to *N*-substituted formamides: RNCO → R–NH–CHO.[1164] Isothiocyanates were reduced to thioformamides with SmI_2 in HMPA/*t*-BuOH.[1165]

OS **III**, 328, 827; **VI**, 905; **VIII**, 110, 568. Also see, OS **IV**, 283.

19-43 The Reduction of Nitriles to Amines

***CC,NN*-Tetrahydro-biaddition**

$$R{-}C{\equiv}N + LiAlH_4 \longrightarrow R{-}CH_2{-}NH_2$$

Nitriles can be reduced to primary amines with many reducing agents,[1166] including $LiAlH_4$, and $H_3B{\bullet}SMe_2{\bullet}$.[1167] The reagent $NaBH_4$ does not generally

[1154]See Denmark, S.E.; Nakajima, N.; Nicaise, O. J.-C. *J. Am. Chem. Soc.* ***1994***, *116*, 8797; Fuller, J.C.; Belisle, C.M.; Goralski, C.T.; Singaram, B. *Tetrahedron Lett.* ***1994***, *35*, 5389; Willoughby, C.A.; Buchwald, S.L. *J. Org. Chem.* ***1993***, *58*, 7627; *J. Am. Chem. Soc.* ***1992***, *114*, 7562; Kawate, T.; Nakagawa, M.; Kakikawa, T.; Hino, T. *Tetrahedron Asymmetry* ***1992***, *3*, 227. For a review of asymmetric reductions involving the C=N unit, see Zhu, Q.-C.; Hutchins, R.O. *Org. Prep. Proceed. Int.* ***1994***, *26*, 193.

[1155]Kainz, S.; Brinkmann, A.; Leitner, W.; Pfaltz, A. *J. Am. Chem. Soc.* ***1999***, *121*, 6421; Xiao, D.; Zhang, X. *Angew. Chem. Int. Ed.* ***2001***, *40*, 3425; Trifonova, A.; Diesen, J.S.; Chapman, C.J.; Andersson, P.G. *Org. Lett.* ***2004***, *6*, 3825.

[1156]Abe, H.; Amii, H.; Uneyama, K. *Org. Lett.* ***2001***, *3*, 313.

[1157]Magee, M.P.; Norton, J.R. *J. Am. Chem. Soc.* ***2001***, *123*, 1778.

[1158]Tararov, V.I.; Kadyrov, R.; Riermeier, T.H.; Holz, J.; Börner, A. *Tetrahedron Lett.* ***2000***, *41*, 2351.

[1159]Mao, J.; Baker, D.C. *Org. Lett.* ***1999***, *1*, 841.

[1160]Choi, Y.K.; Kim, M.J.; Ahn, Y.; Kim, M.-J. *Org. Lett.* ***2001***, *3*, 4099.

[1161]Hayashi, T.; Ishigedani, M. *Tetrahedron* ***2001***, *57*, 2589.

[1162]Lipshutz, B.H.; Shimizu, H. *Angew. Chem. Int. Ed.* ***2004***, *43*, 2228.

[1163]Hansen, M.C.; Buchwald, S.L. *Org. Lett.* ***2000***, *2*, 713.

[1164]Howell, H.G. *Synth. Commun.* ***1983***, *13*, 635.

[1165]Park, H.S.; Lee, I.S.; Kim, Y.H. *Chem. Commun.* ***1996***, 1805.

[1166]For a review, see Rabinovitz, M., in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 307–340. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 875–878.

[1167]See Brown, H.C.; Choi, Y.M.; Narasimhan, S. *Synthesis* ***1981***, 605.

reduce nitriles except in alcoholic solvents with a catlayst, such as $CoCl_2$,[1168] $NiCl_2$,[1169] or Raney nickel.[1170] A mixture of $NaBH_4/NiCl_2$ in acetic anhydride reduces the nitrile to the amine, which is trapped as the acetamide.[1171] Lithium dimethylamino- borohydride ($LiBH_3NMe_2$) reduces aryl nitriles to the corresponding benzylamines.[1172]

The reduction of nitriles is of wide scope and has been applied to many nitriles. When catalytic hydrogenation is used, secondary amines, $(RCH_2)_2NH$, are often side products.[1173] These can be avoided by adding a compound, such as acetic anhydride, which removes the primary amine as soon as it is formed,[1174] or by the use of excess ammonia to drive the equilibria backward.[1175] Sponge nickel[1176] or nickel on silica gel[1177] have been used for the catalytic hydrogenation of aryl nitriles to amines.

Attempts to stop with the addition with only 1 equivalent of hydrogen, have failed that is, to convert the nitrile to an imine, except where the imine is subsequently hydrolyzed (**19-44**).

N-Alkylnitrilium ions are reduced to secondary amines by $NaBH_4$.[1178]

$$RCN \xrightarrow{R'_3O^+BF_4^-} R{-}C{\equiv}N^{\oplus}{-}R' \xrightarrow[\text{diglyme}]{NaBH_4} RCH_2{-}NH{-}R'$$

Since nitrilium salts can be prepared by treatment of nitriles with trialkyloxonium salts (see **16-8**), this is a method for the conversion of nitriles to secondary amines.

Note that the related compounds, the isonitriles ($R{-}^{\oplus}N{\equiv}C^{\ominus}$, also called isocyanides) have been reduced to *N*-methylamines with $LiAlH_4$, as well as with other reducing agents.

OS **III**, 229, 358, 720; **VI**, 223.

[1168]Satoh, T.; Suzuki, S. *Tetrahedron Lett.* ***1969***, 4555. For a discussion of the mechanism, see Heinzman, S.W.; Ganem, B. *J. Am. Chem. Soc.* ***1982***, *104*, 6801.

[1169]Khurana, J.M.; Kukreja, G. *Synth. Commun.* ***2002***, *32*, 1265.

[1170]Egli, R.A. *Helv. Chim. Acta* ***1970***, *53*, 47.

[1171]Caddick, S.; de K. Haynes, A.K.; Judd, D.B.; Williams, M.R.V. *Tetrahedron Lett.* ***2000***, *41*, 3513.

[1172]Thomas, S.; Collins, C.J.; Cuzens, J.R.; Spieciarich, D.; Goralski, C.T.; Singaram, B. *J. Org. Chem.* ***2001***, *66*, 1999.

[1173]For a method of making secondary amines the main products, see Galán, A.; de Mendoza, J.; Prados, P.; Rojo, J.; Echavarren, A.M. *J. Org. Chem.* ***1991***, *56*, 452.

[1174]For example, see Carothers, W.H.; Jones, G.A. *J. Am. Chem. Soc.* ***1925***, *47*, 3051; Gould, F.E.; Johnson, G.S.; Ferris, A.F. *J. Org. Chem.* ***1960***, *25*, 1658.

[1175]For example, see Freifelder, M. *J. Am. Chem. Soc.* ***1960***, *82*, 2386.

[1176]Tanaka, K.; Nagasawa, M.; Kasuga, Y.; Sakamura, H.; Takuma, Y.; Iwatani, K. *Tetrahedron Lett.* ***1999***, *40*, 5885.

[1177]Takamizawa, S.; Wakasa, N.; Fuchikami, T. *Synlett* ***2001***, 1623.

[1178]Borch, R.F. *Chem. Commun.* ***1968***, 442.

19-44 The Reduction of Nitriles to Aldehydes

Hydro,oxy-de-nitrilo-tersubstitution

$$R{-}C{\equiv}N \xrightarrow[\text{2. hydrolysis}]{\text{1. HCl, SnCl}_2} RCH{=}O$$

There are two principal methods for the reduction of nitriles to aldehydes.[1179] In one of these, known as the *Stephen reduction*, the nitrile is treated with HCl to form an iminium salt, **47**.

$$RCCl = \overset{\oplus}{N}H_2 \quad \overset{\ominus}{Cl}$$

47

Iminium salt **47** is reduced with anhydrous $SnCl_2$ to RCH=NH, which precipitates as a complex with $SnCl_4$ and is then hydrolyzed (**16-2**) to the aldehyde. The Stephen reduction is most successful when R is aromatic, but it can be done for aliphatic R up to about six carbons.[1180] It is also possible to prepare **47** in a different way, by treating ArCONHPh with PCl_5, which can then be converted to the aldehyde. This is known as the *Sonn–Müller method*. Aqueous formic acid in the presence of PtO_2, followed by treatment with aqueous acid, converts aryl nitriles to aryl aldehydes.[1181]

The other way of reducing nitriles to aldehydes involves using a metal hydride reducing agent to add 1 equivalent of hydrogen and hydrolysis, *in situ*, of the resulting imine (which is undoubtedly coordinated to the metal). This has been carried out with $LiAlH_4$, $LiAlH(OEt)_3$,[1182] $LiAlH(NR_2)_3$,[1183] and DIBALH.[1184] The metal hydride method is useful for aliphatic and aromatic nitriles.

OS **III**, 626, 818; **VI**, 631.

19-45 Reduction of Nitro Compounds to Amines

$$RNO_2 \xrightarrow[\text{HCl}]{\text{Zn}} RNH_2$$

Both aliphatic[1185] and aromatic nitro compounds can be reduced to amines, although the reaction has been applied much more often to aromatic nitro

[1179]For a review, see Rabinovitz, M., in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, p. 307. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1271–1272.

[1180]Zil'berman, E.N.; Pyryalova, P.S. *J. Gen. Chem. USSR* ***1963***, *33*, 3348.

[1181]Xi, F.; Kamal, F.; Schenerman, M.A. *Tetrahedron Lett.* ***2002***, *43*, 1395.

[1182]Brown, H.C.; Shoaf, C.J. *J. Am. Chem. Soc.* ***1964***, *86*, 1079. For a review of reductions with this and related reagents, see Málek, J. *Org. React.* ***1988***, *36*, 249, see pp. 287–289, 438–448.

[1183]Cha, J.S.; Lee, S.E.; Lee, H.S. *Org. Prep. Proceed. Int.* ***1992***, *24*, 331. Also see, Cha, J.S.; Jeoung, M.K.; Kim, J.M.; Kwon, O.O.; Lee, J.C. *Org. Prep. Proceed. Int.* ***1994***, *26*, 583.

[1184]Miller, A.E.G.; Biss, J.W.; Schwartzman, L.H. *J. Org. Chem.* ***1959***, *24*, 627; Marshall, J.A.; Andersen, N.H.; Schlicher, J.W. *J. Org. Chem.* ***1970***, *35*, 858.

[1185]For a review of selective reduction of aliphatic nitro compounds without disturbance of other functional groups, see Ioffe, S.L.; Tartakovskii, V.A.; Novikov, S.S. *Russ. Chem. Rev.* ***1966***, *35*, 19.

compounds, owing to their greater availability. Many reducing agents have been used to reduce aromatic nitro compounds, the most common being Zn, Sn, or Fe (or sometimes other metals) and acid, and catalytic hydrogenation.[1186] Indium metal in aqueous ethanol with ammonium chloride[1187] or with water in aq. THF[1188] also reduces aromatic nitro compounds to the corresponding aniline derivative. Indium metal in methanol, with acetic anhydride and acetic acid, converts aromatic nitro compounds to the acetanilide.[1189] Samarium and a catalytic amount of iodine also accomplishes this reduction,[1190] as does Sm with a bipyridinium dibromide in methanol.[1191] Samarium metal in methanol with ultrasound also reduces aryl nitro compounds.[1192] Sodium sulfide (NaHS) on alumina with microwave irradiation reduces aryl nitro compounds to aniline derivatives.[1193] A mild reduction uses Al(Hg) in aq. THF with ultrasound.[1194] An Al/$NiCl_2$ reagent was used to reduced the nitro group of a polymer-bound $CH_2OCH_2C_6H_4NO_2$ moiety.[1195] Some other reagents used[1196] were $Et_3SiH/RhCl(PPh_3)_3$,[1197] AlH_3—$AlCl_3$, Mn with $CrCl_2$,[1198] nanoparticulate iron in water at 210°C,[1199] formic acid and Pd—C[1200] for formic acid with Raney nickel in methanol,[1201] and sulfides, such as NaHS, $(NH_4)_2S$, or polysulfides. The reaction with sulfides or polysulfides is called the *Zinin reduction*.[1202] Amines are also the products when nitro compounds, both alkyl and aryl, are reduced with $HCOONH_4$—Pd—C.[1203] Many other functional groups (e.g., COOH, COOR, CN, amide) are not affected by this reagent (although ketones are reduced, see **19-33**). With optically active alkyl substrates this method gives

[1186]For reviews, see Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, ***1985***, pp. 104–116, *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, ***1967***, pp. 168–202. See Deshpande, R.M.; Mahajan, A.N.; Diwakar, M.M.; Ozarde, P.S.; Chaudhari, R.V. *J. Org. Chem.* ***2004***, *69*, 4835; Wu, G.; Huang, M.; Richards, M.; Poirer, M.; Wen, X.; Draper, R.W. *Synthesis* ***2003***, 1657.

[1187]Moody, C.J.; Pitts, M.R. *Synlett* ***1998***, 1028; Banik, B.K.; Suhendra, M.; Banik, I.; Becker, F.F. *Synth. Commun.* ***2000***, *30*, 3745.

[1188]Lee, J.G.; Choi, K.I.; Koh, H.Y.; Kim, Y.; Kang, Y.; Cho, Y.S. *Synthesis* ***2001***, 81.

[1189]Kim, B.H.; Han, R.; Piao, F.; Jun, Y.M.; Baik, W.; Lee, B.M. *Tetrahedron Lett.* ***2003***, *44*, 77.

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[1191]Yu, C.; Liu, B.; Hu, L. *J. Org. Chem.* ***2001***, *66*, 919.

[1192]Basu, M.K.; Becker, F.F.; Banik, B.K. *Tetrahedron Lett.* ***2000***, *41*, 5603.

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[1195]Kamal, A.; Reddy, K.L.; Devaiah, V.; Reddy, G.S.K. *Tetrahedron Lett.* ***2003***, *44*, 4741.

[1196]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 821–828.

[1197]Brinkman, H.R. *Synth. Commun.* ***1996***, *26*, 973.

[1198]Hari, A.; Miller, B.L. *Angew. Chem. Int. Ed.* ***1999***, *38*, 2777.

[1199]Wang, L.; Li, P.; Wu, Z.; Yan, J.; Wang, M.; Ding, Y. *Synthesis* ***2003***, 2001.

[1200]Entwistle, I.D.; Jackson, A.E.; Johnstone, R.A.W.; Telford, R.P. *J. Chem. Soc. Perkin Trans. 1* ***1977***, 443. See also, Terpko, M.O.; Heck, R.F. *J. Org. Chem.* ***1980***, *45*, 4992; Babler, J.H.; Sarussi, S.J. *Synth. Commun.* ***1981***, *11*, 925.

[1201]Gowda, D.C.; Gowda, A.S.P.; Baba, A.R.; Gowda, S. *Synth. Commun.* ***2000***, *30*, 2889.

[1202]For a review of the Zinin reduction, see Porter, H.K. *Org. React.* ***1973***, *20*, 455.

[1203]Ram, S.; Ehrenkaufer, R.E. *Tetrahedron Lett.* ***1984***, *25*, 3415.

retention of configuration.[1204] Ammonium formate in methanol reduces aromatic nitro compounds.[1205] Lithium aluminum hydride reduces aliphatic nitro compounds to amines, but with aromatic nitro compounds the products with this reagent are azo compounds (**19-80**). Most metal hydrides, including $NaBH_4$ and BH_3, do not reduce nitro groups at all, although both aliphatic and aromatic nitro compounds have been reduced to amines with $NaBH_4$ and various catalysts, such as $NiCl_2$ or $CoCl_2$[1206] phthalocyanine iron (II),[1207] and $ZrCl_4$.[1208] Borohydride exchange resin in the presence of $Ni(OAc)_2$, however, gives the amine.[1209] Treatment of aromatic nitro compounds with $NaBH_4$ alone has resulted in reduction of the *ring* to a cyclohexane ring with the nitro group still intact[1210] or in cleavage of the nitro group from the ring.[1211] With $(NH_4)_2S$ or other sulfides or polysulfides it is often possible to reduce just one of two or three nitro groups on an aromatic ring or on two different rings in one molecule.[1212] The nitro groups of *N*-nitro compounds can also be reduced to amino groups, for example, nitrourea $NH_2CONHNO_2$ gives semicarbazide $NH_2CONHNH_2$. Bakers yeast reduces aromatic nitro compounds to aniline derivatives.[1213] A combination of $NaH_2PO_2/FeSO_4$ with microwave irradiation reduces aromatic nitro compounds to aniline derivatives.[1214] Hydrazine on alumina, with $FeCl_3$ and microwave irradiation accomplishes this reduction.[1215] Hydrazine–formic acid with Raney nickel in methanol reduces aromatic nitro compounds.[1216] Heating aromatic nitro compounds with 57% HI reduces the nitro group to the amino group.[1217]

With some reducing agents, especially with aromatic nitro compounds, the reduction can be stopped at an intermediate stage, and hydroxylamines (**19-46**), hydrazobenzenes, azobenzenes (**19-80**), and azoxybenzenes (**19-79**) can be obtained in this manner. However, nitroso compounds, which are often postulated as intermediates, are too reactive to be isolated, if indeed they are intermediates. Reduction by metals in mineral acids cannot be stopped, but always produces the amine.

[1204]Barrett, A.G.M.; Spilling, C.D. *Tetrahedron Lett.* ***1988***, *29*, 5733.

[1205]Gowda, D.C.; Mahesh, B. *Synth. Commun.* ***2000***, *30*, 3639.

[1206]See, for example, Osby, J.O.; Ganem, B. *Tetrahedron Lett.* ***1985***, *26*, 6413; Petrini, M.; Ballini, R.; Rosini, G. *Synthesis* ***1987***, 713; He, Y.; Zhao, H.; Pan, X.; Wang, S. *Synth. Commun.* ***1989***, *19*, 3047. See also, references cited therein.

[1207]Wilkinson, H.S.; Tanoury, G.J.; Wald, S.A.; Senanayake, C.H. *Tetrahedron Lett.* ***2001***, *42*, 167.

[1208]Chary, K.P.; Ram, S.R.; Iyengar, D.S. *Synlett* ***2000***, 683.

[1209]Yoon, N.M.; Choi, J. *Synlett* ***1993***, 135.

[1210]Severin, T.; Schmitz, R. *Chem. Ber.* ***1962***, *95*, 1417; Severin, T.; Adam, M. *Chem. Ber.* ***1963***, *96*, 448.

[1211]Kaplan, L.A. *J. Am. Chem. Soc.* ***1964***, *86*, 740. See also, Swanwick, M.G.; Waters, W.A. *Chem. Commun.* ***1970***, 63.

[1212]This result has also been achieved by hydrogenation with certain catalysts [Lyle, R.E.; LaMattina, J.L. *Synthesis* ***1974***, 726; Knifton, J.F. *J. Org. Chem.* ***1976***, *41*, 1200; Ono, A.; Terasaki, S.; Tsuruoka, Y. *Chem. Ind. (London) 1983*, 477], and with hydrazine hydrate and Raney nickel: Ayyangar, N.R.; Kalkote, U.R.; Lugad, A.G.; Nikrad, P.V.; Sharma, V.K. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 3159.

[1213]Baik, W.; Han, J.L.; Lee, K.C.; Lee, N.H.; Kim, B.H.; Hahn, J.-T. *Tetrahedron Lett.* ***1994***, *35*, 3965.

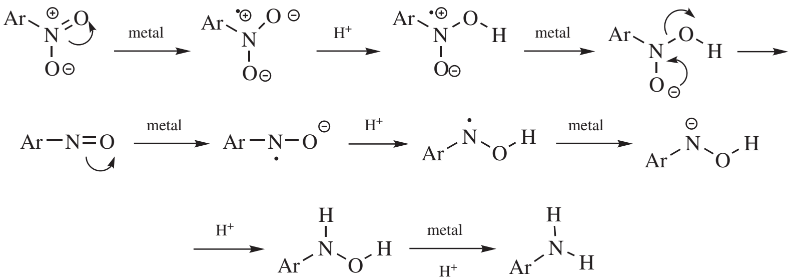
[1214]Meshram, H.M.; Ganesh, Y.S.S.; Sekhar, K.C.; Yadav, J.S. *Synlett* ***2000***, 993.

[1215]Vass, A.; Dudás, J.; Tóth, J.; Varma, R.S. *Tetrahedron Lett.* ***2001***, *42*, 5347.

[1216]Gowda, S.; Gowda, D.C. *Tetrahedron* ***2002***, *58*, 2211.

[1217]Kumar, J.S.D.; Ho, M.M.; Toyokuni, T. *Tetrahedron Lett.* ***2001***, *42*, 5601.

The mechanisms of these reductions have not been studied much, although it is usually presumed that, at least with some reducing agents, nitroso compounds and hydroxylamines are intermediates. Both of these types of compounds give amines when exposed to most of these reducing agents (**19-47**), and hydroxylamines can be isolated (**19-46**). With metals and acid the following path has been suggested:[1218]



Certain aromatic nitroso compounds (Ar—NO) can be obtained in good yields by irradiation of the corresponding nitro compounds in 0.1 *M* aq. KCN with uv light.[1219] The reaction has also been performed electrochemically.[1220] When nitro compounds are treated with most reducing agents, nitroso compounds are either not formed or react further under the reaction conditions and cannot be isolated.

Reductive alkylation of aromatic nitro compounds is possible. The reaction of nitrobenzene with allylic or benzyl halides in the presence of an excess of tin metal in methanol, leads to the *N,N*-diallyl or dibenzyl aniline.[1221] A similar reaction occurs with nitrobenzene, allyl bromide, and indium metal in aq. acetonitrile.[1222]

OS **I**, 52, 240, 455, 485; **II**, 130, 160, 175, 254, 447, 471, 501, 617; **III**, 56, 59, 63, 69, 73, 82, 86, 239, 242, 453; **IV**, 31, 357; **V**, 30, 346, 552, 567, 829, 1067, 1130; **81**, 188.

19-46 Reduction of Nitro Compounds to Hydroxylamines

$$ArNO_2 \xrightarrow[H_2O]{Zn} ArNHOH$$

When aromatic nitro compounds are reduced with zinc and water under neutral conditions,[1223] hydroxylamines are formed. Among other reagents used for this

[1218]House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, p. 211.

[1219]Petersen, W.C.; Letsinger, R.L. *Tetrahedron Lett.* ***1971***, 2197; Vink, J.A.J.; Cornelisse, J.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* ***1971***, *90*, 1333.

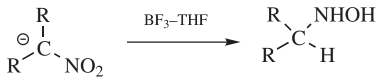
[1220]Lamoureux, C.; Moinet, C. *Bull. Soc. Chim. Fr.* ***1988***, 59.

[1221]Bieber, L.W.; da Costa, R.C.; da Silva, M.F. *Tetahedron Lett.* ***2000***, *41*, 4827.

[1222]Kang, K.H.; Choi, K.I.; Koh, H.Y.; Kim, Y.; Chung, B.Y.; Cho, Y.S. *Synth. Commun.* ***2001***, *31*, 2277.

[1223]For some other methods of accomplishing this conversion, see Rondestvedt Jr., C.S.; Johnson, T.A. *Synthesis* ***1977***, 850; Entwistle, I.D.; Gilkerson, T.; Johnstone, R.A.W.; Telford, R.P. *Tetrahedron* ***1978***, *34*, 213.

purpose have been SmI_2,[1224] N_2H_4—Rh—C,[1225] and $KBH_4/BiCl_3$.[1226] Borane in THF reduces aliphatic nitro enolate anions to hydroxylamines:[1227]



Nitro compounds have been reduced electrochemically, to hydroxylamines, as well as to other products.[1228]

OS **I**, 445; **III**, 668; **IV**, 148; **VI**, 803; **VIII**, 16.

19-47 Reduction of Nitroso Compounds and Hydroxylamines to Amines

N-Dihydro-de-oxo-bisubstitution

$$\mathrm{RNO} \xrightarrow[\mathrm{HCl}]{\mathrm{Zn}} \mathrm{RNH_2}$$

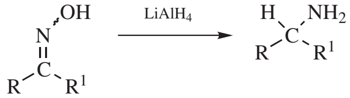
N-Hydro-de-hydroxylation or *N*-Dehydroxylation

$$\mathrm{RNHOH} \xrightarrow[\mathrm{HCl}]{\mathrm{Zn}} \mathrm{RNH_2}$$

Nitroso compounds and hydroxylamines can be reduced to amines by the same reagents that reduce nitro compounds (**19-45**). Reaction with CuCl, and then phenylboronic acid (p. 815), also reduces nitroso compounds to the amine.[1229] A hydroxylamine can be reduced to the amine with CS_2 in acetonitrile.[1230] Indium metal in EtOH/aq. NH_4Cl reduces hydroxylamines to the amine.[1231] *N*-Nitroso compounds are similarly reduced to hydrazinesm $R_2N—NO \rightarrow R_2N–NH_2$.[1232]

OS **I**, 511; **II**, 33, 202, 211, 418; **III**, 91; **IV**, 247. See also, OS **VIII**, 93.

19-48 Reduction of Oximes to Primary Amines or Aziridines



[1224]Kende, A.S.; Mendoza, J.S. *Tetrahedron Lett.* ***1991***, *32*, 1699.

[1225]Oxley, P.W.; Adger, B.M.; Sasse, M.J.; Forth, M.A. *Org. Synth.* ***67***, 187.

[1226]Ren, P.D-D.; Pan, X.-W.; Jin, Q.-H.; Yao, Z.-P. *Synth. Commun.* ***1997***, *27*, 3497.

[1227]Feuer, H.; Bartlett, R.S.; Vincent Jr., B.F.; Anderson, R.S. *J. Org. Chem.* ***1965***, *31*, 2880.

[1228]For reviews of the electroreduction of nitro compounds, see Fry, A.J. *Synthetic Organic Electrochemistry*, 2nd ed., Wiley, NY, ***1989***, pp. 188–198; Lund, H. in Baizer; Lund *Organic Electrochemistry*, Marcel Dekker, NY, ***1983***, pp. 285–313.

[1229]Yu, Y.; Srogl, J.; Liebeskind, L.S. *Org. Lett.* ***2004***, *6*, 2631.

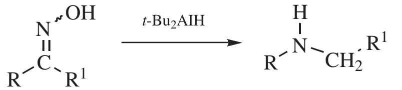
[1230]Schwartz, M.A..; Gu, J.; Hu, X. *Tetrahedron Lett.* ***1992***, *33*, 1687.

[1231]Cicchi, S.; Bonanni, M.; Cardona, F.; Revuelta, J.; Goti, A. *Org. Lett.* ***2003***, *5*, 1773.

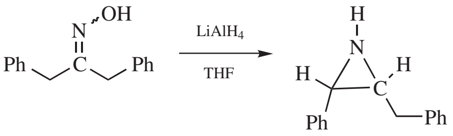
[1232]For examples of this reduction, accomplished with titanium reagents, see Entwistle, I.D.; Johnstone, R.A.W.; Wilby, A.H. *Tetrahedron* ***1982***, *38*, 419; Lunn, G.; Sansone, E.B.; Keefer, L.K. *J. Org. Chem.* ***1984***, *49*, 3470.

Both aldoximes and ketoximes can be reduced to primary amines with $LiAlH_4$. The reaction is slower than with ketones, so that, for example, PhCOCH=NOH gave 34% PhCHOHCH=NOH.[1233] Among other reducing agents that give this reduction[1234] are zinc and acetic acid, BH_3,[1235] $NaBH_3CN$—$TiCl_3$,[1236] polymethylhydrosiloxane (PMHS) with Pd-C,[1237] and sodium and an alcohol.[1238] Catalytic hydrogenation is also effective.[1239] The reduction has been performed enantioselectively with Baker's yeast[1240] and with Ph_2SiH_2 and an optically active rhodium complex catalyst.[1241] Reduction of oximes with indium metal in acetic anhydride/acetic acid–THF leads to the acetamide.[1242] Oxime *O*-ethers are reduced to the amine with modest enantioselectivity using a chiral oxazaboroline.[1243]

When the reducing agent is DIBALH, the product is a secondary amine, arising from a rearrangement:[1244]



With certain oximes (e.g., those of the type $ArCH_2CR$=NOH), treatment with $LiAlH_4$ gives aziridines,[1245] for example,



Hydrazones, arylhydrazones, and semicarbazones can also be reduced to amines with various reducing agents, including Zn—HCl and H_2 and Raney nickel.

[1233]Felkin, H. *C. R. Acad. Sci.* ***1950***, *230*, 304.
[1234]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 845–846.
[1235]Feuer, H.; Braunstein, D.M. *J. Org. Chem.* ***1969***, *34*, 1817.
[1236]Leeds, J.P.; Kirst, H.A. *Synth. Commun.* ***1988***, *18*, 777.
[1237]Chandrasekhar, S.; Reddy, M.V.; Chandraiah, L. *Synlett* ***2000***, 1351.
[1238]For example, see Sugden, J.K.; Patel, J.J.B. *Chem. Ind. (London)* ***1972***, 683.
[1239]For a review, see Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, ***1967***, pp. 139–159.
[1240]Gibbs, D.E.; Barnes, D. *Tetrahedron Lett.* ***1990***, *31*, 5555.
[1241]Brunner, H.; Becker, R.; Gauder, S. *Organometallics* ***1986***, *5*, 739; Takei, I.; Nishibayashi, Y.; Ishii, Y.; Mizobe, Y.; Uemura, S.; Hidai, M. *Chem. Commun.* ***2001***, 2360.
[1242]Harrison, J.R.; Moody, C.J.; Pitts, M.R. *Synlett* ***2000***, 1601.
[1243]Fontaine, E.; Namane, C.; Meneyrol, J.; Geslin, M.; Serva, L.; Russey, E.; Tissandié, S.; Maftouh, M.; Roger, P. *Tetrahedron Asymmetry* ***2001***, *12*, 2185.
[1244]Sasatani, S.; Miyazaki, T.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* ***1983***, *24*, 4711; Graham, S.H.; Williams, A.J.S. *Tetrahedron* ***1965***, *21*, 3263.
[1245]For a review, see Kotera, K.; Kitahonoki, K. *Org. Prep. Proced.* ***1969***, *1*, 305. For examples, see Tatchell, A.R. *J. Chem. Soc. Perkin Trans. 1* ***1974***, 1294; Ferrero, L.; Rouillard, M.; Decouzon, M.; Azzaro, M. *Tetrahedron Lett.* ***1974***, 131; Diab, Y.; Laurent, A.; Mison, P. *Tetrahedron Lett.* ***1974***, 1605.

Oximes have been reduced in a different way, to give imines ($RR'C{=}NOH \rightarrow RR'C{=}NH$), which are generally unstable but which can be trapped to give useful products. Among reagents used for this purpose have been $Bu_3P{-}SPh_2$[1246] and $Ru_3(CO)_{12}$.[1247] Oximes can also be reduced to hydroxylamines (**19-42**). Nitrones have been reduced to imines using $AlCl_3{\bullet}6\ H_2O/KI$ followed by $Na_2S_2O_3{-}H_2O$.[1248]

OS **II**, 318; **III**, 513; **V**, 32, 83, 373, 376.

19-49 Reduction of Aliphatic Nitro Compounds to Oximes or Nitriles

$$RCH_2NO_2 \xrightarrow[\text{HOAc}]{\text{Zn}} RCH{=}NOH$$

Nitro compounds that contain an α hydrogen can be reduced to oximes with zinc dust in acetic acid[1249] or with other reagents, among them $CS_2{-}NEt_3$,[1250] $CrCl_2$,[1251] and (for α-nitro sulfones) $NaNO_2$.[1252] α-Nitro alkenes have been converted to oximes

with sodium hypophosphite, indium with aq. $NH_4Cl/MeOH$,[1253] and with Pb—HOAc—DMF, as well as with certain other reagents.[1254]

$$RCH_2NO_2 \xrightarrow{NaBH_2S_3} RC{\equiv}N$$

Primary aliphatic nitro compounds can be reduced to aliphatic nitriles with sodium dihydro(trithio)borate[1087] or with *t*-BuN≡C/BuN=C=O.[1255] Secondary compounds give mostly ketones (e.g., nitrocyclohexane gave 45% cyclohexanone, 30% cyclohexanone oxime, and 19% *N*-cyclohexylhydroxylamine). Tertiary aliphatic nitro compounds do not react with this reagent (see also, **19-45**).

OS **IV**, 932.

[1246] Barton, D.H.R.; Motherwell, W.B.; Simon, E.S.; Zard, S.Z. *J. Chem. Soc. Chem. Commun.* ***1984***, 337.

[1247] Akazome, M.; Tsuji, Y.; Watanabe, Y. *Chem. Lett.* ***1990***, 635.

[1248] Boruah, M.; Konwar, D. *Synlett* ***2001***, 795.

[1249] Johnson, K.; Degering, E.F. *J. Am. Chem. Soc.* ***1939***, *61*, 3194.

[1250] Barton, D.H.R.; Fernandez, I.; Richard, C.S.; Zard, S.Z. *Tetrahedron* ***1987***, *43*, 551; Albanese, D.; Landini, D.; Penso, M. *Synthesis* ***1990***, 333.

[1251] Hanson, J.R. *Synthesis* ***1974***, 1, pp. 7-8.

[1252] Zeilstra, J.J.; Engberts, J.B.F.N. *Synthesis* ***1974***, 49.

[1253] Yadav, J.S.; Subba Reddy, B.V.; Srinivas, R.; Ramalingam, T. *Synlett* ***2000***, 1447.

[1254] See Kabalka, G.W.; Pace, E.D.; Wadgaonkar, P.P. *Synth. Commun.* ***1990***, *20*, 2453; Sera, A.; Yamauchi, H.; Yamada, H.; Itoh, K. *Synlett* ***1990***, 477.

[1255] El Kaim, L.; Gacon, A. *Tetrahedron Lett.* ***1997***, *38*, 3391.

19-50 Reduction of Azides to Primary Amines

N-Dihydro-de-diazo-bisubstitution

$$RN_3 \xrightarrow{LiAlH_4} RNH_2$$

Azides are easily reduced to primary amines by $LiAlH_4$, as well as by a number of other reducing agents,[1256] including $NaBH_4$, $NaBH_4/LiCl$,[1257] $NaBH_4/CoCl_2/H_2O$,[1258] $NaBH_4/ZrCl_4$,[1259] $BHCl_2$•SMe_2,[1260] H_2 and a catalyst, $Bu_3SnH/PhSiH_3$/AIBN,[1261] Mg or Ca in MeOH,[1262] $Sm/NiCl_2$,[1263] $Zn\text{-}FeCl_3$/EtOH,[1264] Zn/NH_4Cl/aq. EtOH,[1265] $FeCl_3$/NaI,[1266] $FeSO_4/NH_3$/MeOH,[1267] baker's yeast,[1268] Sm/I_2,[1269] Indium metal in EtOH,[1270] $LiMe_2NBH_3$,[1271] and tin complexes prepared from $SnCl_2$ or $Sn(SR)_2$.[1272] Reaction with PPh_3 leads to a phosphazide, $Ph_3P{=}N{-}N{=}N{-}R$, which loses nitrogen in what is called the *Staudinger reaction*[1273] a method to prepare phosphazo compounds, but in this case leads to reduction. Alkylation is possible, and the reaction of an alkyl azide with PMe_3, and then an excess of iodomethane leads to the *N*-methylated amine.[1274] This reaction, combined with RX → RN_3 (**10-43**), is an important way of converting alkyl halides RX to primary amines RNH_2; in some cases the two procedures have been combined into one laboratory step.[1275] Sulfonyl azides RSO_2N_3

[1256]For a review, see Scriven, E.F.V.; Turnbull, K. *Chem. Rev.* ***1988***, *88*, 297, see pp. 321–327. For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 815–820; Rolla, F. *J. Org. Chem.* ***1982***, *47*, 4327.

[1257]Ram, S.R.; Chary, K.P.; Iyengar, D.S. *Synth. Commun.* ***2000***, *30*, 4495.

[1258]Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Synthesis* ***2000***, 646.

[1259]Chary, K.P.; Ram, S.R.; Salahuddin, S.; Iyengar, D.S. *Synth. Commun.* ***2000***, *30*, 3559.

[1260]Salunkhe, A.M.; Ramachandran, P.V.; Brown, H.C. *Tetrahedron* ***2002***, *58*, 10059.

[1261]Hays, D.S.; Fu, G.C. *J. Org. Chem.* ***1998***, *63*, 2796.

[1262]Maiti, S.N.; Spevak, P.; Narender Reddy, A.V. *Synth. Commun.* ***1988***, *18*, 1201.

[1263]Wu, H.; Chen, R.; Zhang, Y. *Synth. Commun.* ***2002***, *32*, 189.

[1264]Pathak, D.; Laskar, D.D.; Prajapati, D.; Sandhu, J.S. *Chem. Lett.* ***2000***, 816.

[1265]Lin, W.; Zhang, X.; He, Z.; Jin, Y.; Gong, L.; Mi, A. *Synth. Commun.* ***2002***, *32*, 3279.

[1266]Kamal, A.; Ramana, K.V.; Ankati, H.B.; Ramana, A.V. *Tetrahedron Lett.* ***2002***, *43*, 6861.

[1267]Kamal, A.; Laxman, E.; Arifuddin, M. *Tetrahedron Lett.* ***2000***, *41*, 7743.

[1268]Kamal, A.; Damayanthi, Y.; Reddy, B.S.N.; Lakminarayana, B.; Reddy, B.S.P. *Chem. Commun.* ***1997***, 1015; Baruah, M.; Boruah, A.; Prajapati, D.; Sandhu, J.S. *Synlett* ***1996***, 1193.

[1269]Huang, Y.; Zhang, Y.; Wang, Y. *Tetrahedron Lett.* ***1997***, *38*, 1065.

[1270]Reddy, G.V.; Rao, G.V.; Iyengar, D.S. *Tetrahedron Lett.* ***1999***, *40*, 3937.

[1271]Alvarez, S.G.; Fisher, G.B.; Singaram, B. *Tetrahedron Lett.* ***1995***, *36*, 2567.

[1272]Bartra, M.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron* ***1990***, *46*, 587. See also, Bosch, I.; Costa, A.M.; Martín, M.; Urpí, F.; Vilarrasa, J. *Org. Lett.* ***2000***, *2*, 397.

[1273]First reported by Staudinger, H.; Meyer, J. *Helv. Chim. Acta* ***1919***, *2*, 635. For a review, see Golobov, Y.G.; Zhmurova, I.N.; Kasukhin, L.F. *Tetrahedron* ***1981***, *37*, 437. For a discussion of the mechanism, see Tian, W.Q.; Wang, Y.A. *J. Org. Chem.* ***2004***, *69*, 4299. For a modification that leads to β-lactams, see Krishnaswamy, D.; Bhawal, B.M.; Deshmukh, A.R.A.S. *Tetrahedron Lett.* ***2000***, *41*, 417; Wack, H.; Drury III, W.J.; Taggi, A.E.; Ferraris, D.; Lectka, T. *Org. Lett.* ***1999***, *1*, 1985.

[1274]Kato, H.; Ohmori, K.; Suzuki, K. *Synlett* ***2001***, 1003.

[1275]See, for example, Koziara, A.; Osowska-Pacewicka, K.; Zawadzki, S.; Zwierzak, A. *Synthesis* ***1985***, 202; ***1987***, 487. The reactions **10-48**, **10-43**, and **19-50** have also been accomplished in one laboratory step: Koziara, A. *J. Chem. Res. (S)* ***1989***, 296.

have been reduced to sulfonamides RSO_2NH_2 by irradiation in isopropyl alcohol[1276] and with NaH.[1277]

OS **V**, 586; **VII**, 433.

19-51 Reduction of Miscellaneous Nitrogen Compounds

Isocyanate–methylamine transformation $R{-}N{=}C{=}O \xrightarrow{LiAlH_4} R{-}NH{-}CH_3$

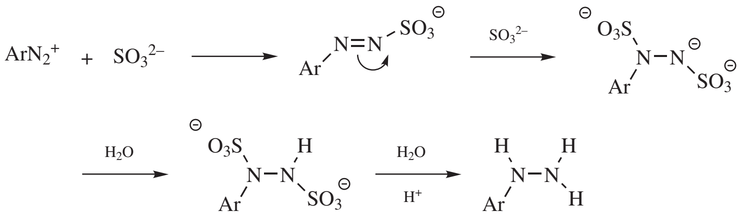
Isothiocyanate–methylamine transformation $R{-}N{=}C{=}S \xrightarrow{LiAlH_4} R{-}NH{-}CH_3$

***N,N*-Dihydro-addition** $Ar{-}N{=}N{-}Ar \xrightarrow[\text{catalyst}]{H_2} Ar{-}NH{-}NH{-}Ar$

Diazonium–arylhydrazone reduction $ArN_2^+\ Cl^- \xrightarrow{Na_2SO_3} ArNHNH_2$

***N*-Hydro-de-nitroso-substitution** $R_2N{-}NO \xrightarrow[Ni]{H_2} R_2NH$

Isocyanates and isothiocyanates are reduced to methylamines on treatment with $LiAlH_4$. $LiAlH_4$ does not usually reduce azo compounds[1278] (indeed these are the products from $LiAlH_4$ reduction of nitro compounds, **19-80**), but these can be reduced to hydrazo compounds by catalytic hydrogenation or with diimide[1279] (see **15-11**). Diazonium salts are reduced to hydrazines by sodium sulfite. This reaction probably has a nucleophilic mechanism.[1280]



The initial product is a salt of hydrazinesulfonic acid, which is converted to the hydrazine by acid treatment. Diazonium salts can also be reduced to arenes (**19-69**). *N*-Nitrosoamines can be denitrosated to secondary amines by a number of reducing agents, including H_2 and a catalyst,[1281] BF_3—THF—$NaHCO_3$,[1282] and $NaBH_4$—$TiCl_4$,[1283] as well as by hydrolysis.[1284]

[1276] Reagen, M.T.; Nickon, A. *J. Am. Chem. Soc.* ***1968***, *90*, 4096.

[1277] Lee, Y.; Closson, W.D. *Tetrahedron Lett.* ***1974***, 381.

[1278] For a review see Newbold, B.T., in Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 2, Wiley, NY, ***1975***, pp. 601, 604–614.

[1279] For example, see Ioffe, B.V.; Sergeeva, Z.I.; Dumpis,Yu.Ya. *J. Org. Chem. USSR* ***1969***, *5*, 1683.

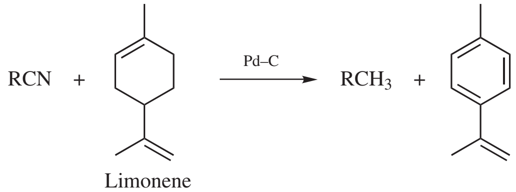
[1280] Huisgen, R.; Lux, R. *Chem. Ber.* ***1960***, *93*, 540.

[1281] Enders, D.; Hassel, T.; Pieter, R.; Renger, B.; Seebach, D. *Synthesis* ***1976***, 548.

[1282] Jeyaraman, R.; Ravindran, T. *Tetrahedron Lett.* ***1990***, *31*, 2787.

[1283] Kano, S.; Tanaka, Y.; Sugino, E.; Shibuya, S.; Hibino, S. *Synthesis* ***1980***, 741.

[1284] Fridman, A.L.; Mukhametshin, F.M.; Novikov, S.S. *Russ. Chem. Rev.* ***1971***, *40*, 34, pp. 41–42.



A cyano group can be reduced to a methyl group by treatment with a terpene, such as limonene (which acts as reducing agent) in the presence of palladium–charcoal.[1285] Hydrogen gas (H_2) is also effective,[1286] although higher temperatures are required. The group R may be alkyl or aryl. Cyano groups CN have also been reduced to CH_2OH, in the vapor phase, with 2-propanol and zirconium oxide.[1287]

Aryl nitro compounds are reduced to diaryl hydrazines with Al—KOH in methanol.[1288]

OS **I**, 442; **III**, 475. Also see, OS **V**, 43.

C. Reactions in Which a Heteroatom Is Removed from the Substrate

19-52 Reduction of Silanes to Methylene Compounds

***Si*-Hydrogen-uncoupling**

$$R\text{–}SiR'_3 \longrightarrow R\text{–}H$$

In certain cases, the C—Si bond of silanes can be converted to C—H. α-Silyl esters are reduced to esters with mercuric acetate and tetrabutylammonium fluoride, for example.[1289]

19-53 Reduction of Alkyl Halides

Hydro-de-halogenation or Dehalogenation

$$RX \longrightarrow RH$$

This type of reduction can be accomplished with many reducing agents.[1290] A powerful, but highly useful reagent is $LiAlH_4$,[1291] which reduces almost all types of

[1285]Kindler, K.; Lührs, K. *Chem. Ber.* ***1966***, *99*, 227; *Liebigs Ann. Chem.* ***1967***, *707*, 26.

[1286]See also Andrade, J.G.; Maier, W.F.; Zapf, L.; Schleyer, P.v.R. *Synthesis* ***1980***, 802; Brown, G.R.; Foubister, A.J. *Synthesis* ***1982***, 1036.

[1287]Takahashi, K.; Shibagaki, M.; Matsushita, H. *Chem. Lett.* ***1990***, 311.

[1288]Khurana, J.M.; Singh, *S. J. Chem. Soc., Perkin Trans. 1* ***1999***, 1893.

[1289]Poliskie, G.M.; Mader, M.M.; van Well, R. *Tetrahedron Lett.* ***1999***, *40*, 589.

[1290]For reviews, see Hudlický, M. *Reductions in Organic Chemistry*, Ellis Horwood, Chichester, ***1984***, pp. 62–67, 181; Pinder, A.R. *Synthesis* ***1980***, 425. For a list of reagents, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 29–39.

[1291]For a review of LiAlH4, see Pizey, J.S. *Synthetic reagents*, Vol. 1, Wiley, NY, ***1974***, pp. 101–294. For monographs on complex metal hydrides, see Seyden-Penne, J. *Reductions by the Alumino- and Borohydrides*, VCH, NY, ***1991***; Hajós, A. *Complex Hydrides*, Elsevier, NY, ***1979***.

alkyl halide, including vinylic, bridgehead, and cyclopropyl halides.[1292] Reduction with lithium aluminum deuteride serves to introduce deuterium into organic compounds. An even more powerful reducing agent, is lithium triethylborohydride ($LiEt_3BH$), which rapidly reduces primary, secondary, allylic, benzylic, and neopentyl halides, but not tertiary (these give elimination) or aryl halides.[1293] Another powerful reagent, which reduces primary, secondary, tertiary, allylic, vinylic, aryl, and neopentyl halides, is a complex formed from lithium trimethoxyaluminum hydride, $LiAlH(OMe)_3$, and CuI.[1294] A milder reducing agent is $NaBH_4$ in a dipolar aprotic solvent, such as Me_2SO, DMF, or sulfolane,[1295] which at room temperature or above reduces primary, secondary, and some tertiary[1296] halides in good yield without affecting other functional groups that would be reduced by $LiAlH_4$, for example, COOH, COOR, CN.[1297] A mixture of $NaBH_4$ and $InCl_3$ efficiently reduces secondary bromides.[1298] Borohydride exchange resin is also an effective reducing agent in the presence of metal catalysts, such as $Ni(OAc)_2$,[1299] and Bu_4NBH_4, is also effective.[1300]

Other reducing agents[1301] include zinc (with acid or base), $SnCl_2$, SmI_2—THF—HMPA,[1302] and Et_3SiH in the presence of $AlCl_3$.[1303] Diethyl phosphonate–Et_3N,[1304] phosphorus tris(dimethylamide) $(Me_2N)_3P$,[1305] and organotin hydrides R_nSnH_{4-n}[1306] (chiefly Bu_3SnH) usually used in conjunction with a radical

[1292]Jefford, C.W.; Kirkpatrick, D.; Delay, F. *J. Am. Chem. Soc.* ***1972***, *94*, 8905; Krishnamurthy, S.; Brown, H.C. *J. Org. Chem.* ***1982***, *47*, 276.

[1293]Krishnamurthy, S.; Brown, H.C. *J. Org. Chem.* ***1980***, *45*, 849; ***1983***, *48*, 3085.

[1294]Masamune, S.; Rossy, P.A.; Bates, G.S. *J. Am. Chem. Soc.* ***1973***, *95*, 6452; Masamune, S.; Bates, G.S.; Georghiou, P.E. *J. Am. Chem. Soc.* ***1974***, *96*, 3686.

[1295]Bell, H.M.; Vanderslice, C.W.; Spehar, A. *J. Org. Chem.* ***1969***, *34*, 3923; Hutchins, R.O.; Hoke, D.; Keogh, J.; Koharski, D. *Tetrahedron Lett.* ***1969***, 3495; Vol'pin, M.E.; Dvolaitzky, M.; Levitin, I. *Bull. Soc. Chim. Fr.* ***1970***, 1526; Hutchins, R.O.; Kandasamy, D.; Dux III, F.; Maryanoff, C.A.; Rotstein, D.; Goldsmith, B.; Burgoyne, W.; Cistone, F.; Dalessandro, J.; Puglis, J. *J. Org. Chem.* ***1978***, *43*, 2259.

[1296]Hutchins, R.O.; Bertsch, R.J.; Hoke, D. *J. Org. Chem.* ***1971***, *36*, 1568.

[1297]For the use of $NaBH_4$ under phase-transfer conditions, see Bergbreiter, D.E.; Blanton, J.R. *J. Org. Chem.* ***1987***, *52*, 472.

[1298]Inoue, K.; Sawada, A.; Shibata, I.; Baba, A. *J. Am. Chem. Soc.* ***2002***, *124*, 906.

[1299]Yoon, N.M.; Lee, H.J.; Ahn, J.H.; Choi, J. *J. Org. Chem.* ***1994***, *59*, 4687.

[1300]Narasimhan, S.; Swarnalakshmi, S.; Balakumar, R.; Velmathi, S. *Synth. Commun.* ***1999***, *29*, 685.

[1301]For some other reducing agents, not mentioned here, see Akiba, K.; Shimizu, A.; Ohnari, H.; Ohkata, K. *Tetrahedron Lett.* ***1985***, *26*, 3211; Kim, S.; Yi, K.Y. *Bull. Chem. Soc. Jpn.* ***1985***, *58*, 789; Cole, S.J.; Kirwan, J.N.; Roberts, B.P.; Willis, C.R. *J. Chem. Soc. Perkin Trans. 1* ***1991***, 103; Hudlický, M. *Reductions in Organic Chemistry*, Ellis Horwood, Chichester, ***1984***, pp. 62–67, 181, Pinder, A.R. *Synthesis* ***1980***, 425. For a list of reagents, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 29–39.

[1302]For discussions of mechansims related to SmI_2 reduction of halides. Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.* ***1987***, 1485; Shabangi, M.; Kuhlman, M.L.; Flowers II, R.A. *Org. Lett.* ***1999***, *1*, 2133. See also, Molander, G.A.; Hahn, G. *J. Org. Chem.* ***1986***, *51*, 1135. See Ogawa, A.; Ohya, S.; Hirao, T. *Chem. Lett.* ***1997***, 275 for reduction with SmI_2/hν.

[1303]Doyle, M.P.; McOsker, C.C.; West, C.T. *J. Org. Chem.* ***1976***, *41*, 1393; Parnes, Z.N.; Romanova, V.S.; Vol'pin, M.E. *J. Org. Chem. USSR* ***1988***, *24*, 254.

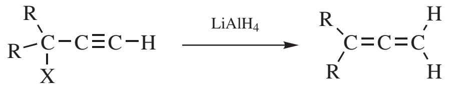
[1304]Hirao, T.; Kohno, S.; Ohshiro, Y.; Agawa, T. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 1881.

[1305]Downie, I.M.; Lee, J.B. *Tetrahedron Lett.* ***1968***, 4951.

[1306]Seyferth, D.; Yamazaki, H.; Alleston, D.L. *J. Org. Chem.* ***1963***, *28*, 703. For a novel trialkyltin hydride, see Gastaldi, S.; Stein, D. *Tetrahedron Lett.* ***2002***, *43*, 4309.

initiator, such as AIBN.[1307] Tributyltin hydride can be used in conjunction with transition-metal salts, such as $InCl_3$.[1308] The organotin hydride ($MeOCH_2$-$CH_2OCH_2CH_2CH_2)_3SnH$ reduces alkyl halides and is water soluble, unlike Bu_3SnH.[1309] In a related area, silylated cyclohexadienes have been used with AIBN as radical-chain reducing reagents, effective for tertiary halides.[1310] Other transition metal-based reducing agents include $NiCl_2$,[1311] $Ni(OAc)_2/Al(acac)_3$/NaH.[1312] Raney nickel in Z-propanol reduces primary iodides in the presence of a lactone moiety.[1313] Aluminum amalgam efficiently reduced an iodohydrin to the alcohol.[1314] A polymer-bound dialkyltin halide has been used in conjunction with $NaBH_4$ to reduce alkyl bromides.[1315]

Reduction, especially of bromides and iodides, can also be effected by catalytic hydrogenation,[1316] and electrochemically.[1317] Raney nickel by itself can reduce alkyl halides.[1318] A good reducing agent for the removal of all halogen atoms in a polyhalo compound (including vinylic, allylic, geminal, and even bridgehead halogens) is lithium[1319] or sodium[1320] and *t*-BuOH in THF. Propargylic halides can often be reduced with allylic rearrangement to give allenes.[1321]



The choice of a reducing agent usually depends on what other functional groups are present. Each reducing agent reduces certain groups and not others. This type of

[1307]For reviews of organotin hydrides, see Neumann, W.P. *Synthesis* ***1987***, 665; Kuivila, H.G. *Synthesis* ***1970***, 499, *Acc. Chem. Res.* ***1968***, *1*, 299. Tributyltin hydride also reduces vinyl halides in the prescence of a palladium catalyst. See Uenishi, J.; Kawahama, R.; Shiga, Y.; Yonemitsu, O.; Tsuji, J. *Tetrahedron Lett.* ***1996***, *37*, 6759.

[1308]Inoue, K.; Sawada, A.; Shibata, I.; Baba, A. *Tetrahedron Lett.* ***2001***, *42*, 4661; Hayashi, N.; Shibata, I.; Baba, A. *Org. Lett.* ***2004***, *6*, 4981.

[1309]Light, J.; Breslow, R. *Tetrahedron Lett.* ***1990***, *31*, 2957.

[1310]Studer, A.; Amrein, S.; Schleth, F.; Schulte, T.; Walton, J.C. *J. Am. Chem. Soc.* ***2003***, *125*, 5726.

[1311]Alonso, F.; Radivoy, G.; Yus, M. *Tetrahedron* ***1999***, *55*, 4441.

[1312]Massicot, F.; Schneider, R.; Fort, Y.; Illy-Cherry, S.; Tillement, O. *Tetrahedron* ***2000***, *56*, 4765.

[1313]Mebane, R.C.; Grimes, K.D.; Jenkins, S.R.; Deardorff, J.D.; Gross, B.H. *Synth. Commun.* ***2002***, *32*, 2049.

[1314]Wang, Y.-C.; Yan, T.-H. *Chem. Commun.* ***2000***, 545.

[1315]Enholm, E.J.; Schulte II, J.P. *Org. Lett.* ***1999***, *1*, 1275.

[1316]For a discussion, see Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, ***1985***. See also, Kantam, M.L.; Rahman, A.; Bandyopadhyay, T.; Haritha, Y. *Synth. Commun.* ***1999***, *29*, 691.

[1317]For reviews, see Fry, A.J. *Synthetic Organic Electrochemistry*, 2nd ed., Wiley, NY, ***1989***, pp. 136–151; Feoktistov, L.G., in Baizer, M.M.; Lund, H. *Organic Electrochemistry*, Marcel Dekker, NY, ***1983***, pp. 259–284.

[1318]For an example see Marquié, J.; Laporterie, A.; Dubac, J.; Roques, N. *Synlett* ***2001***, 493.

[1319]For example, see Gassman, P.G.; Pape, P.G. *J. Org. Chem.* ***1964***, *29*, 160; Fieser, L.F.; Sachs, D.H. *J. Org. Chem.* ***1964***, *29*, 1113; Berkowitz, D.B. *Synthesis* ***1990***, 649.

[1320]For example, see Gassman, P.G.; Aue, D.H.; Patton, D.S. *J. Am. Chem. Soc.* ***1968***, *90*, 7271; Gassman, P.G.; Marshall, J.L. *Org. Synth.* *V*, 424.

[1321]For examples, see Crandall, J.K.; Keyton, D.J.; Kohne, J. *J. Org. Chem.* ***1968***, *33*, 3655; Claesson, A.; Olsson, L. *J. Am. Chem. Soc.* ***1979***, *101*, 7302.

selectivity is called *chemoselectivity*. A chemoselective reagent is one that reacts with one functional group (e.g., halide), but not another (e.g., C=O). For example, there are several reagents that reduce only the halogen of α-halo ketones, leaving the carbonyl group intact.[1322] Among them are polymer-supported triphenylphosphine,[1323] decaborane with 10% Pd/C,[1324] Bi in aq. THF[1325] or In metal in water,[1326] and *i*-Bu_2AlH—$SnCl_2$.[1327] In a similar chemoselective reaction, the halogen in α-haloimines has been reduced with $SnCl_2$/MeOH without reducing the C=N bond.[1328]

Both $NaBH_3CN$—$SnCl_2$.[1329] and the *n*-butyllithium ate complex of B-*n*-butyl-9-BBN[1330] (see p. 1077) reduce tertiary alkyl, benzylic, and allylic halides, but do not react with primary or secondary alkyl or aryl halides. Another highly selective reagent, in this case for primary and secondary iodo and bromo groups, is sodium cyanoborohydride, $NaBH_3CN$, in HMPA.[1331] Most of the reducing agents mentioned reduce chlorides, bromides, and iodides, but organotin hydrides also reduce fluorides.[1332] See p. 1787 for a discussion of selectivity in reduction reactions.

Vinyl halides can be reduced to the corresponding alkene is some cases.[1333] As mentioned above, electrochemical reduction of aryl and vinyl halides is well known.[1334] When vinyl dibromides, such as $RCH{=}CBr_2$, are treated with $(MeO)_2P({=}O)H$ and triethylamine, for example, the product is the vinyl bromide RCH=HBr.[1335] Indium in ethanol accomplishes the same transformation.[1336] Similar reduction occurs when vinyl diiodides are treated with Zn–Cu in acetic acid.[1337]

[1322]For a review of reductive dehalogenation of polyhalo ketones, see Noyori, R.; Hayakawa, Y. *Org. React.* ***1983***, *29*, 163.

[1323]Dhuru, S.P.; Padiya, K.J.; Salunkhe, M.M. *J. Chem. Res. (S)* ***1998***, 56.

[1324]Lee, S.H.; Jung, Y.J.; Cho, Y.J.; Yoon, C.-O.M.; Hwang, H.-J.; Yoon, C.M. *Synth. Commun.* ***2001***, *31*, 2251.

[1325]Ren, P.-D.; Hin, Q.-H.; Yao, Z.-P. *Synth. Commun.* ***1997***, *27*, 2577.

[1326]Park, L.; Keum, G.; Kang, S.B.; Kim, K.S.; Kim, Y. *J. Chem. Soc. Perkin Trans. 1* ***2000***, 4462.

[1327]Oriyama, T.; Mukaiyama, T. *Chem. Lett.* ***1984***, 2069.

[1328]Aelterman, W.; Eeckhaut, A.; De Kimpe, N. *Synlett* ***2000***, 1283.

[1329]Kim, S.; Ko, J.S. *Synth. Commun.* ***1985***, *15*, 603.

[1330]Toi, H.; Yamamoto, Y.; Sonoda, A.; Murahashi, S. *Tetrahedron* ***1981***, *37*, 2261.

[1331]Hutchins, R.O.; Kandasamy, D.; Maryanoff, C.A.; Masilamani, D.; Maryanoff, B.E. *J. Org. Chem.* ***1977***, *42*, 82.

[1332]Fluorides can also be reduced by a solution of K and dicyclohexano-18-crown-6 in toluene or diglyme: Ohsawa, T.; Takagaki, T.; Haneda, A.; Oishi, T. *Tetrahedron Lett.* ***1981***, *22*, 2583. See also, Brandänge, S.; Dahlman, O.; Ölund, J. *Acta Chem. Scand. Ser. B* ***1983***, *37*, 141.

[1333]For a general discussion that includes reduction of vinyl halides with tin compounds, see Curran, D.P. *Synthesis* ***1988***, 417, 489.

[1334]Fry, A.; Mitnick, M.A.; Reed, R.G. *J. Org. Chem.* ***1970***, *35*, 1232; Bhuvaneswari, N.; Venkatachalam, C.S.; Balasubramanian, K.K. *Tetrahedron Lett.* ***1992***, *33*, 1499; Urove, G.A.; Peters, D.G.; Mubarak, M.S. *J. Org. Chem.* ***1992***, *57*, 786; Miller, L.L.; Rienkena, E. *J. Org. Chem.* ***1969***, *34*, 3359; Fry, A.J.; Mitnick, M.A. *J. Am. Chem. Soc.* ***1969***, *91*, 6207.

[1335]Abbas, S.; Hayes, C.J.; Worden, S. *Tetrahedron Lett.* ***2000***, *41*, 3215.

[1336]Ranu, B.C.; Samanta, S.; Guchhait, S.K. *J. Org. Chem.* ***2001***, *66*, 4102.

[1337]Kdota, I.; Ueno, H.; Ohno, A.; Yamamoto, Y. *Tetrhaedron Lett.* ***2003***, *44*, 8645.

With $LiAlH_4$ and most other metallic hydrides, the mechanism usually consists of simple nucleophilic substitution with attack by hydride ion that may or may not be completely free. The mechanism is S_N2 rather than S_N1, since primary halides react better than secondary or tertiary (tertiary generally give alkenes or do not react at all) and since Walden inversion has been demonstrated. However, rearrangements found in the reduction of bicyclic tosylates with $LiAlH_4$ indicate that the S_N1 mechanism can take place.[1338] There is evidence that $LiAlH_4$ and other metal hydrides can also reduce halides by an SET mechanism,[1339] especially those, such as vinylic,[1340] cyclopropyl,[1341] or bridgehead halides, that are resistant to nucleophilic substitution. Reduction of halides by $NaBH_4$ in 80% aqueous diglyme[1342] and by BH_3 in nitromethane[1343] takes place by an S_N1 mechanism. It is known that $NaBH_4$ in sulfolane reduces tertiary halides possessing a β-hydrogen by an elimination-addition mechanism.[1344]

The mechanism for reduction of alkyl halides is not always nucleophilic substitution. For example, reductions with organotin hydrides generally[1345] take place by free-radical mechanisms,[1346] as do those with $Fe(CO)_5$. Alkyl halides, including fluorides and polyhalides, can be reduced with magnesium and a secondary or tertiary alcohol (most often 2-propanol).[1347] This is actually an example of the occurrence in one step of the sequence:

$$RX \longrightarrow RMgX \longrightarrow H^+RH$$

More often the process is carried out in two separate steps (**12-36** and **12-22**).

OS **I**, 357, 358, 548; **II**, 320, 393; **V**, 424; **VI**, 142, 376, 731; **VIII**, 82. See also, OS **VIII**, 583.

[1338]Appleton, R.A.; Fairlie, J.C.; McCrindle, R. *Chem. Commun.* ***1967***, 690; Kraus, W.; Chassin, C. *Tetrahedron Lett.* ***1970***, 1443. See Omoto, M.; Kato, N.; Sogon, T.; Mori, A. *Tetrahedron Lett.* ***2001***, *42*, 939.

[1339]Singh, P.R.; Khurana, J.M.; Nigam, A. *Tetrahedron Lett.* ***1981***, *22*, 2901; Srivastava, S.; le Noble, W.J. *Tetrahedron Lett.* ***1984***, *25*, 4871; Ashby, E.C.; Pham, T.N. *J. Org. Chem.* ***1986***, *51*, 3598; Hatem, J.; Meslem, J.M.; Waegell, B. *Tetrahedron Lett.* ***1986***, *27*, 3723; Ashby, E.C.; Deshpande, A.K. *J. Org. Chem.* ***1994***, *59*, 3798; Ashby, E.C.; Welder, C.; Doctorovich, F. *Tetrahedron Lett.* ***1993***, *34*, 7235. See, however, Hirabe, T.; Takagi, M.; Muraoka, K.; Nojima, M.; Kusabayashi, S. *J. Org. Chem.* ***1985***, *50*, 1797; Park, S.; Chung, S.; Newcomb, M. *J. Org. Chem.* ***1987***, *52*, 3275.

[1340]Chung, S. *J. Org. Chem.* ***1980***, *45*, 3513.

[1341]McKinney, M.A.; Anderson, S.W.; Keyes, M.; Schmidt, R. *Tetrahedron Lett.* ***1982***, *23*, 3443; Hatem, J.; Waegell, B. *Tetrahedron* ***1990***, *46*, 2789.

[1342]Bell, H.M.; Brown, H.C. *J. Am. Chem. Soc.* ***1966***, *88*, 1473.

[1343]Matsumura, S.; Tokura, N. *Tetrahedron Lett.* ***1969***, 363.

[1344]Jacobus, J. *Chem. Commun.* ***1970***, 338; Hutchins, R.O.; Bertsch, R.J.; Hoke, D. *J. Org. Chem.* ***1971***, *36*, 1568.

[1345]For an exception, see Carey, F.A.; Tramper, H.S. *Tetrahedron Lett.* ***1969***, 1645.

[1346]Menapace, L.W.; Kuivila, H.G. *J. Am. Chem. Soc.* ***1964***, *86*, 3047; Tanner, D.D.; Singh, H.K. *J. Org. Chem.* ***1986***, *51*, 5182.

[1347]Bryce-Smith, D.; Wakefield, B.J.; Blues, E.T. *Proc. Chem. Soc.* ***1963***, 219.

19-54 Reduction of Alcohols[1348]

Hydro-de-hydroxylation or Dehydroxylation

$$ROH + H_2 \xrightarrow{\text{catalyst}} RH$$

The hydroxyl groups of most alcohols can seldom be cleaved by catalytic hydrogenation and alcohols are often used as solvents for hydrogenation of other compounds. However, benzyl-type alcohols undergo the reaction readily and have often been reduced.[1349] Diaryl and triarylcarbinols are similarly easy to reduce and this has been accomplished with $LiAlH_4$—$AlCl_3$,[1350] with $NaBH_4$ in F_3CCOOH,[1351] and with iodine, water, and red phosphorus (OS **I**, 224). Other reagents have been used,[1352] among them PPh_3/diethyl-azo-dicarboxylate and arylsulfonyl hydrazine,[1353] PPh_3 and electrolysis,[1354] Me_3SiCl—MeI—MeCN,[1355] Me_3SiCl—NaI,[1356] Et_3SiH—BF_3,[1357] SmI_2—THF—HMPA,[1358] and tin and HCl. The reduction of secondary alcohols was accomplished using Ph_2SiClH and $InCl_3$.[1359] 1,3-Diols are especially susceptible to hydrogenolysis. Tertiary alcohols can be reduced by catalytic hydrogenolysis when the catalyst is Raney nickel.[1360] Allylic alcohols (and ethers and acetates) can be reduced (often with accompanying allylic rearrangement) with Zn amalgam and HCl, as well as with certain other reagents.[1361] α-Acetylenic alcohols are converted to alkynes by reduction of their cobalt carbonyl complexes with $NaBH_4$ and CF_3COOH.[1362] Reagents that reduce the OH group

[1348]For a review, see Müller, P., in Patai, S. *The Chemistry of Functional Groups*, *Supplement E*, pt. 1, Wiley, NY, ***1980***, pp. 515–522.

[1349]For reviews, see Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, ***1985***, pp. 157–163, *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, ***1967***, pp. 449–468. For a review of the stereochemistry of hydrogenolysis, see Klabunovskii, E.I. *Russ. Chem. Rev.* ***1966***, *35*, 546.

[1350]Blackwell, J.; Hickinbottom, W.J. *J. Chem. Soc.* ***1961***, 1405; Avendaño, C.; de Diego, C.; Elguero, J. *Monatsh. Chem.* ***1990***, *121*, 649.

[1351]For a review, see Gribble, G.W.; Nutaitis, C.F. *Org. Prep. Proced. Int.* ***1985***, *17*, 317. Also see, Nutaitis, C.F.; Bernardo, J.E. *Synth. Commun.* ***1990***, *20*, 487.

[1352]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 44–46.

[1353]Myers, A.G.; Movassaghi, M.; Zheng, B. *J. Am. Chem. Soc.* ***1997***, *119*, 8572.

[1354]Maeda, H.; Maki, T.; Eguchi, K.; Koide, T.; Ohmori, H. *Tetrahedron Lett.* ***1994***, *35*, 4129.

[1355]Sakai, T.; Miyata, K.; Utaka, M.; Takeda, A. *Tetrahedron Lett.* ***1987***, *28*, 3817.

[1356]Cain, G.A.; Holler, E.R. *Chem. Commun.* ***2001***, 1168.

[1357]Orfanopoulos, M.; Smonou, I. *Synth. Commun.* ***1988***, *18*, 833; Smonou, I.; Orfanopoulos, M. *Tetrahedron Lett.* ***1988***, *29*, 5793. See Wustrow, D.J.; Smith III, W.J.; Wise, L.D. *Tetrahedron Lett.* ***1994***, *35*, 61 for reduction with $Et_3SiH/LiClO_4$.

[1358]Kusuda, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* ***1989***, *30*, 2945.

[1359]Yasuda, M.; Onishi, Y.; Ueba, M.; Miyai, T.; Baba, A. *J. Org. Chem.* ***2001***, *66*, 7741.

[1360]Krafft, M.E.; Crooks III, W.J. *J. Org. Chem.* ***1988***, *53*, 432. For another catalyst, see Parnes, Z.N.; Shaapuni, D.Kh.; Kalinkin, M.I.; Kursanov, D.N. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1974***, *23*, 1592.

[1361]For discussion, see Elphimoff-Felkin, I.; Sarda, P. *Org. Synth.* ***VI***, 769; *Tetrahedron* ***1977***, *33*, 511. For another reagent, see Lee, J.; Alper, H. *Tetrahedron Lett.* ***1990***, *31*, 4101.

[1362]Nicholas, K.M.; Siegel, J. *J. Am. Chem. Soc.* ***1985***, *107*, 4999.

of α-hydroxy ketones without affecting the C=O group include lithium diphenylphosphide, Ph_2PLi,[1363] red phosphorus–iodine,[1364] and Me_3SiI.[1365]

Alcohols can also be reduced indirectly by conversion to a sulfonate and reduction of that compound (**19-57**). The two reactions can be carried out without isolation of the sulfonate if the alcohol is treated with pyridine–SO_3 in THF, and $LiAlH_4$ then added.[1366] Another indirect reduction that can be done in one step involves treatment of the alcohol (primary, secondary, or benzylic) with NaI, Zn, and Me_3SiCl.[1367] In this case, the alcohol is first converted to the iodide, which is reduced. For other indirect reductions of OH, see **19-59**.

The mechanisms of most alcohol reductions are obscure.[1368] Hydrogenolysis of benzyl alcohols can give inversion or retention of configuration, depending on the catalyst.[1369] The mechanism of electroreduction of allylic alcohols in acidic aqueous media has been examined.[1370]

Note that tertiary benzylic alcohols are cleaved to give the aromatic compound [$ArC(OH)Ar'_2 \rightarrow$ Ar-H] by heating with cesium carbonate and $Pd(OAc)_2$.[1371]

OS **I**, 224; **IV**, 25, 218, 482; **V**, 339; **VI**, 769.

19-55 Reduction of Phenolic and Other Hydroxyaryl Compunds

Hydro-de-hydroxylation or Dehydroxylation, etc.

$$\text{ArOH} \xrightarrow{\text{Zn}} \text{ArH}$$

Oxygenated compounds, such as phenols, phenolic esters, and ethers, can be reduced.[1372] Phenols can be reduced by distillation over zinc dust or with HI and red phosphorus, but these methods are quite poor and are seldom feasible. Catalytic hydrogenation has also been used, but the corresponding cyclohexanol (see **15-13**) is a side product.[1373]

[1363]Leone-Bay, A. *J. Org. Chem.* ***1986***, *51*, 2378.

[1364]Ho, T.L.; Wong, C.M. *Synthesis* ***1975***, 161.

[1365]Ho, T.L. *Synth. Commun.* ***1979***, *9*, 665.

[1366]Corey, E.J.; Achiwa, K. *J. Org. Chem.* ***1969***, *34*, 3667.

[1367]Morita, T.; Okamoto, Y.; Sakurai, H. *Synthesis* ***1981***, 32.

[1368]For discussions of the mechanisms of the hydrogenolysis of benzyl alcohols, see Khan, A.M.; McQuillin, F.J.; Jardine, I. *Tetrahedron Lett.* ***1966***, 2649; *J. Chem. Soc. C* ***1967***, 136; Garbisch, Jr., E.W.; Schreader, L.; Frankel, J.J. *J. Am. Chem. Soc.* ***1967***, *89*, 4233; Mitsui, S.; Imaizumi, S.; Esashi, Y. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 2143.

[1369]Mitsui, S.; Kudo, Y.; Kobayashi, M. *Tetrahedron* ***1969***, *25*, 1921; Mitsui, S.; Imaizumi, S.; Esashi, Y. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 2143.

[1370]Shukun, H.; Yougun, S.; Jindong, Z.; Jian, S. *J. Org. Chem.* ***2001***, *66*, 4487.

[1371]Terao, Y.; Nomoto, M.; Satoh, T.; Miura, M.; Nomura, M. *J. Org. Chem.* ***2004***, *69*, 6942.

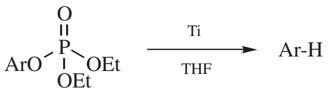
[1372]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 44–52ff.

[1373]Shuikin, N.I.; Erivanskaya, L.A. *Russ. Chem. Rev.* ***1960***, *29*, 309, see pp. 313–315. See also, Bagnell, L.J.; Jeffery, E.A. *Aust. J. Chem.* ***1981***, *34*, 697.

Much better results have been obtained by conversion of phenols to certain esters or ethers and reduction of the latter:

$$ArOSO_2CF_3 \xrightarrow[\text{Pd(OAc)}_2,\ \text{Ph}_3\text{P, DMF}]{\text{HCOOH, Et}_3\text{N}} ArH \qquad \text{Ref.}^{1374}$$

$$ArOTs + NaBH_4/NiCl_2 \longrightarrow ArH \qquad \text{Ref.}^{1375}$$



Ref.[1376]

OS **VI**, 150. See also, OS **VII**, 476.

19-56 Replacement of Alkoxyl by Hydrogen

Hydro-de-alkoxylation or Dealkoxylation

$$R{-}O{-}R' \longrightarrow R{-}H + R'{-}H$$

R, R′ = allyl, aryl, vinyl, benzylic

Simple ethers are not normally cleaved by reducing agents, although such cleavage has sometimes been reported[1377] (e.g., THF treated with $LiAlH_4{-}AlCl_3$[1378] or with a mixture of LiAlH(*O*—*t*-Bu)$_3$ and Et_3B[1379] gave 1-butanol; the latter reagent also cleaves methyl alkyl ethers).[1380] Certain types of ethers can be cleaved quite well by reducing agents.[1381] Among these are allyl aryl,[1382] vinyl aryl,[1383] benzylic ethers,[1349,1384] and anisole[1385] (for epoxides, see **19-35**). 7-Oxobicyclo[2.2.1]heptanes

[1374]Cacchi, S.; Ciattini. P.G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* ***1986***, *27*, 5541. See also, Peterson, G.A.; Kunng, F.; McCallum, J.S.; Wulff, W.D. *Tetrahedron Lett.* ***1987***, *28*, 1381; Chen, Q.; He, Y. *Synthesis* ***1988***, 896; Cabri, W.; De Bernardinis, S.; Francalanci, F.; Penco, S. *J. Org. Chem.* ***1990***, *55*, 350.

[1375]Wang, F.; Chiba, K.; Tada, M. *J. Chem. Soc. Perkin Trans. 1* ***1992***, 1897.

[1376]Welch, S.C.; Walters, M.E. *J. Org. Chem.* ***1978***, *43*, 4797. See also, Rossi, R.A.; Bunnett, J.F. *J. Org. Chem.* ***1973***, *38*, 2314.

[1377]Ranu, B.C.; Bhar, S. *Org. Prep. Proceed. Int.* ***1996***, *28*, 371.

[1378]Bailey, W.J.; Marktscheffel, F. *J. Org. Chem.* ***1960***, *25*, 1797.

[1379]Krishnamurthy, S.; Brown, H.C. *J. Org. Chem.* ***1979***, *44*, 3678.

[1380]For a review of ether reduction, see Müller, P., in Patai, S. *The Chemistry of Functional Groups, Supplement E*, pt. 1, Wiley, NY, ***1980***, pp. 522–528.

[1381]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1013–1019.

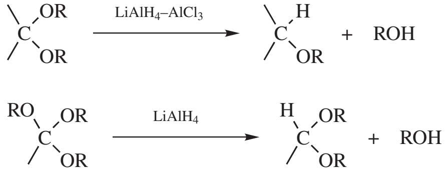
[1382]Tankguchi, T.; Ogasawara, K. *Angew. Chem. Int. Ed.* ***1998***, *37*, 1136; Rao, G.V.; Reddy, D.S.; Mohan, G.H.; Iyengar, D.S. *Synth. Commun.* ***2000***, *30*, 3565.

[1383]Tweedie, V.L.; Barron B.G. *J. Org. Chem.* ***1960***, *25*, 2023. See also, Hutchins, R.O.; Learn, K. *J. Org. Chem.* ***1982***, *47*, 4380.

[1384]Bouzide, A.; Sauvé, G. *Synlett* ***1997***, 1153; Thomas, R.M.; Mohan, G.H.; Iyengar, D.S. *Tetrahedron Lett.* ***1997***, *38*, 4721; Shi, L.; Xia, W.J.; Zhang, F.M.; Tu, Y.Q. *Synlett* ***2002***, 1505. See also Olivero, S.; Duñach, E. *Tetrahedron Lett.* ***1997***, *38*, 6193.

[1385]Majetich, G.; Zhang, Y.; Wheless, K. *Tetrahedron Lett.* ***1994***, *35*, 8727.

can be reductively cleaved with DIBAL and nickel catalysts.[1386] α-Methoxy ketones are demethoxylated (O=C—COMe → O=C—CH) with SmI_2.[1387]



Acetals and ketals are resistant to $LiAlH_4$ and similar hydrides, and carbonyl groups are often converted to acetals or ketals for protection (**16-5**). However, a combination of $LiAlH_4$ and $AlCl_3$[1388] does reduce acetals and ketals, removing one group, as shown above.[1389] The actual reducing agents in this case are primarily chloroaluminum hydride (AlH_2Cl) and dichloroaluminum hydride ($AlHCl_2$), which are formed from the reagents.[1390] This conversion can also be accomplished with DIBALH,[1391] as well as with other reagents.[1392] Ortho esters are easily reduced to acetals by $LiAlH_4$ alone, offering a route to aldehydes, which are easily prepared by hydrolysis of the acetals (**10-6**). Mixed ketals [R(OMe)OR′] can be demethoxylated (to give RHOR′) with $Bn_3SnCl/NaCHBH_3$ in the presence of AIBN.[1393]

OS **III**, 693; **IV**, 798; **V**, 303. Also see, OS **III**, 742; **VII**, 386.

19-57 Reduction of Tosylates and Similar Compounds

Hydro-de-sulfonyloxy-substitution

$$RCH_2OTs \; + \; LiAlH_4 \longrightarrow RCH_3$$

Tosylates and other sulfonates can be reduced[1394] with $LiAlH_4$,[1395] with $NaBH_4$ in a dipolar aprotic solvent,[1396] with $LiEt_3BH$, with *i*-Bu_2AlH (DIBALH),[1397] or with Bu_3SnH—NaI.[1398] The scope of the reaction seems to be similar to that of **19-53**.

[1386] Lautens, M.; Chiu, P.; Ma, S.; Rovis, T. *J. Am. Chem.Soc.* ***1995***, *117*, 532.

[1387] Mikami, K.; Yamaoka, M.; Yoshida, A. *Synlett* ***1998***, 607.

[1388] For a review of reductions by metal hydride–Lewis acid combinations, see Rerick, M.N., in Augustine, R.L. *Reduction*, Marcel Dekker, NY, ***1968***, pp. 1–94.

[1389] Eliel, E.L.; Badding, V.G.; Rerick, M.N. *J. Am. Chem. Soc.* ***1962***, *84*, 2371.

[1390] Ashby, E.C.; Prather, J. *J. Am. Chem. Soc.* ***1966***, *88*, 729; Diner, U.E.; Davis, H.A.; Brown, R.K. *Can. J. Chem.* ***1967***, *45*, 207.

[1391] See, for example, Zakharkin, L.I.; Khorlina, I.M. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1959***, 2156; Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* ***1983***, 1593.

[1392] For other reagents that accomplish this conversion, see Kotsuki, H.; Ushio, Y.; Yoshimura, N.; Ochi, M. *J. Org. Chem.* ***1987***, *52*, 2594; Hojo, M.; Ushioda, N.; Hosomi, A. *Tetrahedron Lett.* ***2004***, *45*, 4499; Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 931–942.

[1393] Srikrishna, A.; Viswajanani, R. *Synlett* ***1995***, 95.

[1394] For a list of substrate types and reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 46–52.

[1395] For examples, see Dimitriadis, E.; Massy-Westropp, R.A. *Aust. J. Chem.* ***1982***, *35*, 1895; Goodenough, K.M.; Moran, W.J.; Raubo, P.; Harrity, J.P.A. *J. Org. Chem.* ***2005***, *70*, 207.

[1396] Hutchins, R.O.; Hoke, D.; Keogh, J.; Koharski, D. *Tetrahedron Lett.* ***1969***, 3495.

[1397] Janssen, C.G.M.; Hendriks, A.H.M.; Godefroi, E.F. *Recl. Trav. Chim. Pays-Bas* ***1984***, *103*, 220.

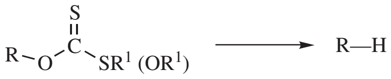
[1398] Ueno, Y.; Tanaka, C.; Okawara, M. *Chem. Lett.* ***1983***, 795.

When the reagent is $LiAlH_4$, alkyl tosylates are reduced more rapidly than iodides or bromides if the solvent is Et_2O, but the order is reversed in diglyme.[1399] The reactivity difference is great enough so that a tosylate function can be reduced in the presence of a halide and vice versa. Tertiary allylcyclopropyl tosylates have been reduced with BuZnCl and a palladium catalyst.[1400]

OS **VI**, 376, 762; **VIII**, 126. See also, OS **VII**, 66.

19-58 Hydrogenolysis of esters (Barton–McCombie Reaction)

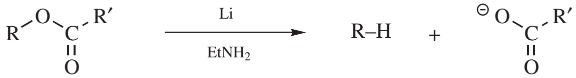
Hydro-de-thioacetoxylation



Alcohols can readily be converted to carbonate and thiocarbonate derivatives. Under radical conditions,[1401] using *azobis*-isobutyronitrile (AIBN, p. 935) and Bu_3SnH, the carbonate or thiocarbonate unit is reduced and replaced with hydrogen. The overall process is reduction of the ROH unit to RH. This is called the *Barton–McCombie reaction.*[1402] When R is cyclododecane (OCSOR), for example, this reduction yields the parent cyclododecane in 76% yield.[1403] When R = cyclododecane (OCSSMe), treatment with $Bu_3P{=}O$ and AIBN, gives the alkane in 94% yield.[1404] Both $PhSiH_3$/AIBN[1405] and $PhSiH_2$—BEt_3•O_2 can be used.[1406] This reaction can be catalytic in Bu_3SnH.[1407] Variations include reduction of ROCSNHPh derivatives using Ph_3SiH/BEt_3.[1408]

19-59 Reductive Cleavage of Carboxylic Esters

Hydro-de-acyloxylation or Deacyloxylation



[1399]Krishnamurthy, S. *J. Org. Chem.* ***1980***, *45*, 2550.

[1400]Ollivier, J.; Piras, P.P.; Stolle, A.; Aufranc, P.; de Meijere, A.; Salaün, J. *Tetrahedron Lett.* ***1992***, *33*, 3307.

[1401]Barton, D.H.R.; Jaszberenyi, J.Cs.; Tang, D. *Tetrahedron Lett.* ***1993***, *34*, 3381.

[1402]Barton, D.H.R.; McCombie, S.W. *J. Chem. Soc. Perkin Trans. 1* ***1975***, 1574; Robins, M.J.; Wilson, J.S.; Hansske, F. *J. Am. Chem. Soc.* ***1983***, *105*, 4059.

[1403]Jang, D.O.; Cho, D.H.; Kim, J. *Synth. Commun*, ***1998***, *28*, 3559. Also see Gimisis, T.; Ballestri, M.; Ferreri, C.; Chatgilialoglu, C.; Boukherroub, R.; Manuel, G. *Tetrahedron Lett.* ***1995***, *36*, 3897; Crimmins, M.T.; Dudek, C.M.; Cheung, A.W-H. *Tetrahedron Lett.* ***1992***, *33*, 181.

[1404]Jang, D.O.; Cho, D.H.; Barton, D.H.R. *Synlett* ***1998***, 39; Barton, D.H.R.; Parekh, S.I.; Tse, C.-L. *Tetrahedron Lett.* ***1993***, *34*, 2733.

[1405]Barton, D.H.R.; Jang, D.O.; Jaszberenyi, J.Cs. *Tetrahedron* ***1993***, *49*, 2793.

[1406]Barton, D.H.R.; Jang, D.O.; Jaszberenyi, J.Cs. *Tetrahedron* ***1993***, *49*, 7193.

[1407]Lopez, R.M.; Hays, D.S.; Fu, G.C. *J. Am. Chem. Soc.* ***1997***, *119*, 6949.

[1408]Oba, M.; Nishiyama, K. *Tetrahedron* ***1994***, *50*, 10193.

The alkyl group R of certain carboxylic esters can be reduced to RH[1409] by treatment with lithium in ethylamine.[1410] The reaction is successful when R is a tertiary or a sterically hindered secondary alkyl group. A free-radical mechanism is likely.[1411] Similar reduction, also by a free-radical mechanism, has been reported with sodium in HMPA—*t*-BuOH.[1412] In the latter case, tertiary R groups give high yields of RH, but primary and secondary R are converted to a mixture of RH and ROH. Both of these methods provide an indirect method of accomplishing **19-54** for tertiary R.[1413] The same thing can be done for primary and secondary R by treating alkyl chloroformates, ROCOCl, with tri-*n*-propylsilane in the presence of *tert*-butylperoxide[1414] and by treating thiono ethers ROC(=S)W (where W can be OAr or other groups) with Ph_2SiH_2[1415] or Ph_3SiH[1416] and a free-radical initiator. Allylic acetates can be reduced with $NaBH_4$ and a palladium complex,[1417] and with $SmI_2Pd(0)$.[1418] The last reagent converts propargylic acetates to allenes $R^1C{=}C{=}CR^2R^3OAc \rightarrow R^1CH{=}C{=}CR^2R^3$.[1418] For other carboxylic ester reductions, see **19-62**, **19-38**, and **19-65**.

Note that acid chlorides can be reduced (R—COCl → R—H) using $(Me_3Si)_3SiH$/AIBN.[1419]

OS **VII**, 139.

19-60 Reduction of Hydroperoxides and Peroxides

$$\text{R—O—O—H} \xrightarrow{\text{LiAlH}_4} \text{ROH}$$

Hydroperoxides can be reduced to alcohols with $LiAlH_4$ or Ph_3P[1420] or by catalytic hydrogenation. This functional group is very susceptible to catalytic

[1409]For a review of some of the reactions in this section and some others, see Hartwig, W. *Tetrahedron* ***1983***, *39*, 2609.

[1410]Barrett, A.G.M.; Godfrey, C.R.A.; Hollinshead, D.M.; Prokopiou, P.A.; Barton, D.H.R.; Boar, R.B.; Joukhadar, L.; McGhie, J.F.; Misra, S.C. *J. Chem. Soc. Perkin Trans. 1* ***1981***, 1501. See Garst, M.E.; Dolby, L.J.; Esfandiari, S.; Fedoruk, N.A.; Chamberlain, N.C.; Avey, A.A. *J. Org. Chem.* ***2000***, *65*, 7098.

[1411]Barrett, A.G.M.; Prokopiou, P.A.; Barton, D.H.R.; Boar, R.B.; McGhie, J.F. *J. Chem. Soc. Chem. Commun.* ***1979***, 1173.

[1412]Deshayes, H.; Pete, J. *Can. J. Chem.* ***1984***, *62*, 2063.

[1413]Also see Barton, D.H.R.; Crich, D. *J. Chem. Soc. Perkin Trans. 1* ***1986***, 1603.

[1414]Jackson, R.A.; Malek, F. *J. Chem. Soc. Perkin Trans. 1* ***1980***, 1207.

[1415]See Barton, D.H.R.; Jang, D.O.; Jaszberenyi, J.C. *Tetrahedron Lett.* ***1990***, *31*, 4681, and references cited therein. For similar methods, see Nozaki, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* ***1990***, *63*, 2578; Kirwan, J.N.; Roberts, B.P.; Willis, C.R. *Tetrahedron Lett.* ***1990***, *31*, 5093.

[1416]Oba, M.; Nishiyama, K. *Synthesis* ***1994***, 624.

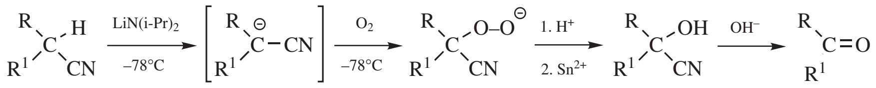
[1417]Hutchins, R.O.; Learn, K.; Fulton, R.P. *Tetrahedron Lett.* ***1980***, *21*, 27. See also Ipaktschi, J. *Chem. Ber.* ***1984***, *117*, 3320.

[1418]Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* ***1986***, *27*, 601, 5237. See also, Kusuda, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* ***1989***, *30*, 2945.

[1419]Ballestri, M.; Chatgilialoglu, C.; Cardi, N.; Sommazzi, A. *Tetrahedron Lett.* ***1992***, *33*, 1787.

[1420]For a review, see Rowley, A.G., in Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, ***1979***, pp. 318–320.

hydrogenation, as shown by the fact that a double bond may be present in the same molecule without being reduced.[1421]



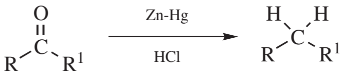
The reaction is an important step in a method for the oxidative decyanation of nitriles containing an α hydrogen.[1422] The nitrile is first converted to the α-hydroperoxy nitrile by treatment with base at −78°C followed by O_2. The hydroperoxy nitrile is then reduced to the cyanohydrin, which is cleaved (the reverse of **16-52**) to the corresponding ketone. The method is not successful for the preparation of aldehydes (R′ = H).

Peroxides are cleaved to 2 equivalents of alcohols by $LiAlH_4$, Mg/MeOH,[1423] or by catalytic hydrogenation. Peroxides can be reduced to ethers with $P(OEt)_3$.[1424] In a similar reaction, disulfides (RSSR′) can be converted to sulfides RSR′ by treatment with tris(diethylamino)phosphine, $(Et_2N)_3P$.[1425]

OS **VI**, 130.

19-61 Reduction of Carbonyl to Methylene in Aldehydes and Ketones

Dihydro-de-oxo-bisubstitution



There are various ways of reducing the C=O group of aldehydes and ketones to CH_2.[1426] The two oldest, but still very popular, methods are the *Clemmensen reduction*[1427] and the *Wolff–Kishner reduction*. The Clemmensen reduction consists of heating the aldehyde or ketone with zinc amalgam and aq. HCl.[1428] Ketones are reduced more often than aldehydes. In the Wolff–Kishner reduction,[1429] the aldehyde or ketone is heated with hydrazine hydrate and a base (usually NaOH

[1421]Rebeller, M.; Clément, G. *Bull. Soc. Chim. Fr.* ***1964***, 1302.

[1422]Freerksen, R.W.; Selikson, S.J.; Wroble, R.R.; Kyler, K.S.; Watt, D.S. *J. Org. Chem.* ***1983***, *48*, 4087. This paper also reports several other methods for achieving this conversion.

[1423]Dai, P.; Dussault, P.H.; Trullinger, T.K. *J. Org. Chem.* ***2004***, *69*, 2851.

[1424]Horner, L.; Jurgeleit, W. *Liebigs Ann. Chem.* ***1955***, *591*, 138. See also, Rowley, A.G., in Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, ***1979***, pp. 320–322.

[1425]Harpp, D.N.; Gleason, J.G. *J. Am. Chem. Soc.* ***1971***, *93*, 2437. For another method, see Comasseto, J.V.; Lang, E.S.; Ferreira, J.T.B.; Simonelli, F.; Correi, V.R. *J. Organomet. Chem.* ***1987***, *334*, 329.

[1426]For a review, see Reusch, W. in Augustine, R.L. *Reduction*, Marcel Dekker, NY, ***1968***, pp. 171–211.

[1427]Fragmentation reactions sometimes accompany Clemmenson reduction. See Bailey, K.E.; Davis, B.R. *Aust. J. Chem.* ***1995***, *48*, 1827. Also see Rosnati, V. *Tetrahedron Lett.* ***1992***, *33*, 4791.

[1428]For a review, see Vedejs, E. *Org. React.* ***1975***, *22*, 401. For a discussion of experimental conditions, see Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis*, Vol. 1, Wiley, NY, ***1967***, pp. 1287–1289.

[1429]For a review, see Todd, D. *Org. React.* ***1948***, *4*, 378.

or KOH). The *Huang–Minlon modification*[1430] of the Wolff–Kishner reaction, in which the reaction is carried out in refluxing diethylene glycol, has completely replaced the original procedure. A microwave-assisted Huang–Minlon procedure has been reported.[1431] The reaction can also be carried out under more moderate conditions (room temperature) in DMSO with potassium *tert*-butoxide as base.[1432] A new modification of the reduction treats a ketone with hydrazine in toluene with microwave irradiation, and subsequent reaction with KOH with microwave irradiation completes the Wolff–Kishner reduction.[1433] The Wolff–Kishner reaction can also be applied to the semicarbazones of aldehydes or ketones. The Clemmensen reduction is usually easier to perform, but it fails for acid-sensitive and high-molecular-weight substrates. For these cases, the Wolff–Kishner reduction is quite useful. For high-molecular-weight substrates, a modified Clemmensen reduction, using activated zinc and gaseous HCl in an organic solvent, such as ether or acetic anhydride, has proved successful.[1434] The Clemmensen and Wolff–Kishner reactions are complementary, since the former uses acidic and the latter basic conditions.

Both methods are fairly specific for aldehydes and ketones and can be carried out with many other functional groups present. However, certain types of aldehydes and ketones do not give normal reduction products. Under Clemmensen conditions,[1435] α-hydroxy ketones give either ketones (hydrogenolysis of the OH, **19-54**) or alkenes, and 1,3-diones usually undergo rearrangement (e.g., $MeCOCH_2$-COMe $\rightarrow$ $MeCOCHMe_2$).[1436] Neither method is suitable for α,β-unsaturated ketones. These give pyrazolines[1437] under Wolff–Kishner conditions, while under Clemmensen conditions both groups of these molecules may be reduced or if only one group is reduced, it is the C=C bond.[1438] Sterically hindered ketones are resistant to both the Clemmensen and Huang–Minlon procedures, but can be reduced by vigorous treatment with anhydrous hydrazine.[1439] In the Clemmensen reduction, pinacols (**19-76**) are often side products.

Other reagents have also been used to reduce the C=O of aldehydes and ketones to CH_2.[1440] Among these are Me_3SiCl followed by $Et_3SiH/TiCl_4$,[1441] $Ni(OAc)_2$ on borohydride exchange resin,[1442] Et_3SiH on pyridinium poly(hydrogen fluoride),

[1430]Huang-Minlon *J. Am. Chem. Soc.* ***1946***, *68*, 2487; ***1949***, *71*, 3301.

[1431]Jaisankar, P.; Pal, B.; Giri, V.S. *Synth. Commun.* ***2002***, *32*, 2569.

[1432]Cram, D.J.; Sahyun, M.R.V.; Knox, G.R. *J. Am. Chem. Soc.* ***1962***, *84*, 1734.

[1433]Gadhwal, S.; Baruah, M.; Sandhu, J.S. *Synlett* ***1999***, 1573.

[1434]Toda, M.; Hayashi, M.; Hirata, Y.; Yamamura, S. *Bull. Chem. Soc. Jpn.* ***1972***, *45*, 264.

[1435]For a review of Clemmensen reduction of diketones and unsaturated ketones, see Buchanan, J.G.S.; Woodgate, P.D. *Q. Rev. Chem. Soc.* ***1969***, *23*, 522.

[1436]Cusack, N.J.; Davis, B.R. *J. Org. Chem.* ***1965***, *30*, 2062; Wenkert, E.; Kariv, E. *Chem. Commun.* ***1965***, 570; Galton, S.A.; Kalafer, M.; Beringer, F.M. *J. Org. Chem.* ***1970***, *35*, 1.

[1437]Pyrazolines can be converted to cyclopropanes; see **17-34**.

[1438]See, however, Banerjee, A.K.; Alvárez, J.; Santana, M.; Carrasco, M.C. *Tetrahedron* ***1986***, *42*, 6615.

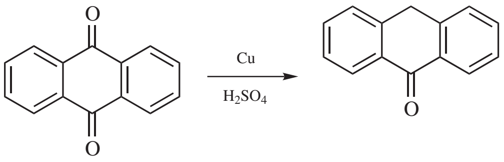
[1439]Barton, D.H.R.; Ives, D.A.J.; Thomas, B.R. *J. Chem. Soc.* ***1955***, 2056.

[1440]For a list, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 61–66.

[1441]Yato, M.; Homma, K.; Ishida, A. *Heterocycles* ***1995***, *41*, 17.

[1442]Bandgar, B.P.; Nikat, S.M.; Wadgaonkar, P.P. *Synth. Commun.* ***1995***, *25*, 863.

[PPHF],[1443] and, for aryl ketones (ArCOR and ArCOAr), $NaBH_4$—F_3CCOOH,[1444] $NaBH_4$—$AlCl_3$,[1445] $NaBH_3CN$ in THF—aq. HCl,[1446] Ni—Al in H_2O,[1447] HCOO-NH_4—Pd—C,[1448] H_3PO_2/AcOH and an I_2 catalyst,[1449] or trialkylsilanes in F_3CC-OOH.[1450] Silanes, such as Et_3SiH and a triarylborane catalyst, reduce aliphatic aldehydes to the alkane, —CHO → —CH_3.[1451] Chlorosilanes, such as Me_2SiClH, with an $InCl_3$ catalyst reduced ketones to the methylene compound.[1452] Polymethylhydroxysiloxane and a triarylborane catalyst deoxygenates ketones.[1453] Most of these reagents also reduce aryl aldehydes (ArCHO) to methylbenzenes ($ArCH_3$).[1454] Aliphatic aldehydes (RCHO) can be reduced to RCH_3 with titanocene dichloride, $(C_5H_5)_2TiCl_2$.[1455] One carbonyl group of 1,2-diketones can be selectively reduced by H_2S with an amine catalyst[1456] or by HI in refluxing acetic acid.[1457] One carbonyl group of quinones, such as **48**, can be reduced with copper and sulfuric acid or with tin and HCl.[1458] One carbonyl group of 1,3-diketones was selectively reduced by catalytic hydrogenolysis.[1459] Catalytic hydrogenation at 170°C with Pt/K10 removes oxygen from the molecule.[1460] Simply heating a ketone in supercritical Z-propanol reduces the ketone to the methylene compound.[1461]



48

[1443]Olah, G.A.; Wang, Q.; Prakash, G.K.S. *Synlett* ***1992***, 647.

[1444]Gribble, G.W.; Nutaitis, C.F. *Org. Prep. Proced. Int.* ***1985***, *17*, 317.

[1445]Ono, A.; Suzuki, N.; Kamimura, J. *Synthesis* ***1987***, 736.

[1446]Pashkovsky, F.S.; Lokot, I.P.; Lakhvich, F.A. *Synlett* ***2001***, 1391.

[1447]Ishimoto, K.; Mitoma, Y.; Negashima, S.; Tashiro, H.; Prakash, G.K.S.; Olah, G.A.; Tahshiro, M. *Chem. Commun.* ***2003***, 514.

[1448]Ram, S.; Spicer, L.D. *Tetrahedron Lett.* ***1988***, *29*, 3741.

[1449]Hicks, L.D.; Han, J.K.; Fry, A.J. *Tetrahedron Lett.* ***2000***, *41*, 7817; Gordon, P.E.; Fry, A.J. *Tetrahdron Lett.* ***2001***, *42*, 831.

[1450]Kursanov, D.N.; Parnes, Z.N.; Loim, N.M. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1966***, 1245; West, C.T.; Donnelly, S.J.; Kooistra, D.A.; Doyle, M.P. *J. Org. Chem.* ***1973***, *38*, 2675. See also, Fry, J.L.; Orfanopoulos, M.; Adlington, M.G.; Dittman, Jr., W.R.; Silverman, S.B. *J. Org. Chem.* ***1978***, *43*, 374; Olah, G.A.; Arvanaghi, M.; Ohannesian, L. *Synthesis* ***1986***, 770.

[1451]Gevorgyan, V.; Rubin, M.; Liu, J.-X.; Yamamoto, Y. *J. Org. Chem.* ***2001***, *66*, 1672.

[1452]Miyai, T.; Ueba, M.; Baba, A. *Synlett* ***1999***, 182.

[1453]Chandrasekar, S.; Reddy, Ch.R.; Babu, B.N. *J. Org. Chem.* ***2002***, *67*, 9080.

[1454]See, for example, Hall, S.S.; Bartels, A.P.; Engman, A.M. *J. Org. Chem.* ***1972***, *37*, 760; Kursanov, D.N.; Parnes, Z.N.; Loim, N.M.; Bakalova, G.V. *Doklad. Chem.* ***1968***, *179*, 328; Zahalka, H.A.; Alper, H. *Organometallics* ***1986***, *5*, 1909.

[1455]van Tamelen, E.E.; Gladys, J.A. *J. Am. Chem. Soc.* ***1974***, *96*, 5290.

[1456]Mayer, R.; Hiller, G.; Nitzschke, M.; Jentzsch, J. *Angew. Chem. Int. Ed.* ***1963***, *2*, 370.

[1457]Reusch, W.; LeMahieu, R. *J. Am. Chem. Soc.* ***1964***, *86*, 3068.

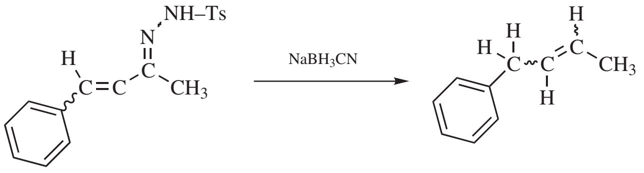
[1458]Meyer, K.H. *Org. Synth.* ***I***, 60; Macleod, L.C.; Allen, C.F.H. *Org. Synth.* ***II***, 62.

[1459]Cormier, R.A.; McCauley, M.D. *Synth. Commun.* ***1988***, *18*, 675.

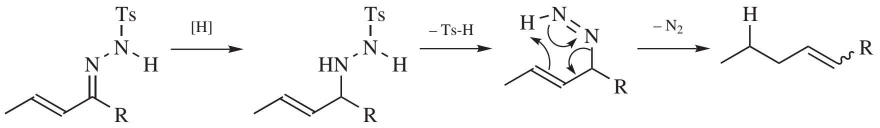
[1460]Török, B.; London, G. Bartók, M. *Synlett* ***2000***, 631.

[1461]Hatano, B.; Tagaya, H. *Tetraehedron Lett.* ***2003***, *44*, 6331.

An indirect method of accomplishing the reaction is reduction of tosylhydrazones ($R_2C{=}N{-}NHTs$) to R_2CH_2 with $NaBH_4$, BH_3, catecholborane, bis(benzyloxy)borane, or $NaBH_3CN$. The reduction of α,β-unsaturated tosylhydrazones with $NaBH_3CN$, with $NaBH_4$-HOAc, or with catecholborane proceeds with migration of the double bond to the position formerly occupied by the carbonyl carbon, even if this removes the double bond from conjugation with an aromatic ring,[1462] for example,



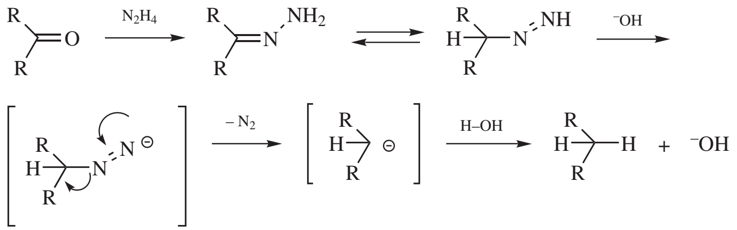
A cyclic mechanism is apparently involved:



Another indirect method is conversion of the aldehyde or ketone to a dithioacetal or ketal, and desulfurization of using Raney nickel or another reagent (**14-27**).

It is interesting to see that amines can be deaminated to give the corresponding methylene compounds with low-valent titanium ($TiCl_3$/Li/THF).[1463]

The first step in the mechanism[1464] of the Wolff–Kishner reaction consists of formation of the hydrazone (**16-14**). It is this species that undergoes reduction in the presence of base, most likely in the following manner:



[1462]Kabalka, G.W.; Yang, D.T.C.; Baker, Jr., J.D. *J. Org. Chem.* ***1976***, *41*, 574; Taylor, E.J.; Djerassi, C. *J. Am. Chem. Soc.* ***1976***, *98*, 2275; Hutchins, R.O.; Natale, N.R. *J. Org. Chem.* ***1978***, *43*, 2299; Greene, A.E. *Tetrahedron Lett.* ***1979***, 63.

[1463]Talukdar, S.; Banerji, A. *Synth. Commun*, ***1996***, *26*, 1051.

[1464]For a review of the mechanism, see Szmant, H.H. *Angew. Chem. Int. Ed.* ***1968***, *7*, 120. Also see, Taber, D.F.; Stachel, S.J. *Tetrahedron Lett.* ***1992***, *33*, 903.

Not much is known about the mechanism of the Clemmensen reduction. Several mechanisms have been proposed,[1465] including one going through a zinc–carbene intermediate.[1466] One thing reasonably certain is that the corresponding alcohol is not an intermediate, since alcohols prepared in other ways fail to give the reaction. Note that the alcohol is not an intermediate in the Wolff–Kishner reduction either.

OS **I**, 60; **II**, 62, 499; **III**, 410, 444, 513, 786; **IV**, 203, 510; **V**, 533, 747; **VI**, 62, 293, 919; **VII**, 393. Also see, OS **IV**, 218; **VII**, 18.

19-62 Reduction of Carboxylic Esters to Ethers

Dihydro-de-oxo-bisubstitution

$$RCOOR' \xrightarrow[\text{LiAlH}_4]{\text{BF}_3\text{–etherate}} RCH_2OR'$$

Carboxylic esters and lactones have been reduced to ethers, although 2 equivalents of alcohol are more commonly obtained (**19-38**). Reduction to ethers has been accomplished with a reagent prepared from BF_3–etherate and either $LiAlH_4$, $LiBH_4$, or $NaBH_4$,[1467] with trichlorosilane and uv light,[1468] and with catalytic hydrogenation. The reaction with the BF_3 reagent apparently succeeds with secondary R′, but not with primary R′, which give **19-38**. Lactones give cyclic ethers.[1469] Acyloxy groups are reduced by cleavage of the C—C=O bond, R(Ar)COO—C → C—H) with an excess of Ph_2SiH_2 and di-*tert*-butyl peroxide.[1470] Esters are reduced to ethers using Et_3SiH and $TiCl_4$.[1471] Lactones are converted to cyclic ethers by treatment with Cp_2TiCl_2 followed by Et_3SiH on Amberlyst 15.[1472]

Thiono esters RCSOR′ can be reduced to ethers RCH_2OR' with Raney nickel (**14-27**).[1473] Reaction of thio esters, such as C—OC(=O)Ph with Ph_2SiH_2 and Ph_3SnH with BEt_3, followed by AIBN (p. 935) leads to reduction of the C=S unit to give an ether.[1474] Since the thiono esters can be prepared from carboxylic

[1465]See, for example, Horner, L.; Schmitt, E. *Liebigs Ann. Chem.* ***1978***, 1617; Poutsma, M.L.; Wolthius, E. *J. Org. Chem.* ***1959***, *24*, 875; Nakabayashi, T. *J. Am. Chem. Soc.* ***1960***, *82*, 3900, 3906; Di Vona, M.L.; Rosnati, V. *J. Org. Chem.* ***1991***, *56*, 4269.

[1466]Burdon, J.; Price, R.C. *J. Chem. Soc. Chem. Commun.* ***1986***, 893.

[1467]Pettit, G.R.; Green, B.; Kasturi, T.R.; Ghatak, U.R. *Tetrahedron* ***1962***, *18*, 953; Ager, D.J.; Sutherland, I.O. *J. Chem. Soc. Chem. Commun.* ***1982***, 248. See also, Dias, J.R.; Pettit, G.R. *J. Org. Chem.* ***1971***, *36*, 3485.

[1468]Nagata, Y.; Dohmaru, T.; Tsurugi, J. *J. Org. Chem.* ***1973***, *38*, 795; Baldwin, S.W.; Haut, S.A. *J. Org. Chem.* ***1975***, *40*, 3885. See also, Kraus, G.A.; Frazier, K.A.; Roth, B.D.; Taschner, M.J.; Neuenschwander, K. *J. Org. Chem.* ***1981***, *46*, 2417.

[1469]See, for example, Pettit, G.R.; Kasturi, T.R.; Green, B.; Knight, J.C. *J. Org. Chem.* ***1961***, *26*, 4773; Edward, J.T.; Ferland, J.M. *Chem. Ind. (London)* ***1964***, 975.

[1470]Kim, J.-G.; Cho, D.H.; Jang, D.O. *Tetrahedron Lett.* ***2004***, *45*, 3031; Jiang, D.O.; Kim, J.; Cho, D.H.; Chung, C.-M. *Tetrahedron Lett.* ***2001***, *42*, 1073.

[1471]Yato, M.; Homma, K.; Ishida, A. *Tetrahedron* ***2001***, *57*, 5353.

[1472]Hansen, M.C.; Verdaguer, X.; Buchwald, S.L. *J. Org. Chem.* ***1998***, *63*, 2360.

[1473]Baxter, S.L.; Bradshaw, J.S. *J. Org. Chem.* ***1981***, *46*, 831.

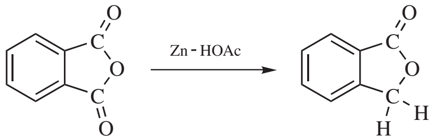
[1474]Jang, D.O.; Song, S.H. *Synlett* ***2000***, 811; Jang, D.O.; Song, S.H.; Cho, D.H. *Tetrahedron* ***1999***, *55*, 3479.

esters (**16-11**), this provides an indirect method for the conversion of carboxylic esters to ethers. Thiol esters (RCOSR′) have been reduced to thioethers (RCH_2SR').[1475]

See also, **19-65**, **19-59**.

19-63 Reduction of Cyclic Anhydrides to Lactones and Acid Derivatives to Alcohols

Dihydro-de-oxo-bisubstitution



Cyclic anhydrides can give lactones if reduced with Zn—HOAc, with hydrogen and platinum or $RuCl_2(Ph_3P)_3$,[1476] with $NaBH_4$,[1477] or even with $LiAlH_4$, although with the last-mentioned reagent diols are the more usual product. With a BINOL–AlHOEt complex, however, reduction to the lactone proceeds smoothly.[1478] With some reagents the reaction can be accomplished regioselectively, that is, only a specific one of the two C=O groups of an unsymmetrical anhydride is reduced.[1479] Open-chain anhydrides either are not reduced at all (e.g., with $NaBH_4$) or give 2 equivalents of alcohol. The $LiAlH_4$ usually reduces open-chain anhydrides to give 2 equivalents of alcohol. With cyclic anhydrides the reaction with $LiAlH_4$ can be controlled to give either diols or lactones.[1480] The $NaBH_4$ in THF, with dropwise addition of methanol, reduces open-chain anhydrides to 1 equivalent of primary alcohol and 1 equivalent of carboxylic acid.[1481]

Acyl halides are reduced[1482] to alcohols by $LiAlH_4$ or $NaBH_4$, as well as by other metal hydrides (Table 19.5), but not by borane.

In general, reduction of amides to alcohols is difficult. More commonly the amide is reduced to an amine. An exception uses LiH_2NBH_3 to give the alcohol.[1483] Reduction with sodium metal in propanol also gives the alcohol.[1484] Acyl

[1475]Eliel, E.L.; Daignault, R.A. *J. Org. Chem.* ***1964***, *29*, 1630; Bublitz, D.E. *J. Org. Chem.* ***1967***, *32*, 1630.

[1476]Lyons, J.E. *J. Chem. Soc. Chem. Commun.* ***1975***, 412; Morand, P.; Kayser, M.M. *J. Chem. Soc. Chem. Commun.* ***1976***, 314. See also Hara, Y.; Wada, K. *Chem. Lett.* ***1991***, 553.

[1477]Bailey, D.M.; Johnson, R.E. *J. Org. Chem.* ***1970***, *35*, 3574.

[1478]Matsuki, K.; Inoue, H.; Takeda, M. *Tetrahedron Lett.* ***1993***, *34*, 1167.

[1479]See, for example, Kayser, M.M.; Salvador, J.; Morand, P. *Can. J. Chem.* ***1983***, *61*, 439; Ikariya, T.; Osakada, K.; Ishii, Y.; Osawa, S.; Saburi, M.; Yoshikawa, S. *Bull. Chem. Soc. Jpn.* ***1984***, *57*, 897; Soucy, C.; Favreau, D.; Kayser, M.M. *J. Org. Chem.* ***1987***, *52*, 129.

[1480]Bloomfield, J.J.; Lee, S.L. *J. Org. Chem.* ***1967***, *32*, 3919.

[1481]Soai, K.; Yokoyama, S.; Mochida, K. *Synthesis* ***1987***, 647.

[1482]For a review of the reduction of acyl halides, see Wheeler, O.H., in Patai, S. *The Chemistry of Acyl Halides*, Wiley, NY, ***1972***, pp. 231–251. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1263–1264.

[1483]Myers, A.G.; Yang, B.H.; Kopecky, D.J. *Tetrahedron Lett.* ***1996***, *37*, 3623.

[1484]Moody, H.M.; Kaptein, B.; Broxterman, Q.B.; Boesten, W.H.J.; Kamphuis, J. *Tetrahedron Lett.* ***1994***, *35*, 1777.

imidazoles are also reduced to the corresponding alcohol with $NaBH_4$ in aq. HCl.[1485]

There are no *Organic Syntheses* references, but see OS **II**, 526, for a related reaction. See OS **VI**, 482 for reduction to alcohols and OS **IV**, 271 for reduction of acyl halides.

19-64 Reduction of Amides to Amines

Dihydro-deoxo-bisubstitution

$$RCONH_2 \xrightarrow{LiAlH_4} RCH_2NH_2$$

Amides can be reduced[1486] to amines with $LiAlH_4$ or by catalytic hydrogenation, but high temperatures and pressures are usually required for the latter. Even with $LiAlH_4$, the reaction is more difficult than the reduction of most other functional groups, and other groups often can be reduced without disturbing an amide function. Although $NaBH_4$ by itself does not reduce amides, it does so in the presence of certain other reagents[1487] including iodine.[1488] Lithium borohydride reduces acetamides.[1489] Substituted amides can be reduced with these powerful reagents; secondary amides to secondary amine and tertiary amides to tertiary amines. Borane[1490] and sodium in 1-propanol[1491] are good reducing agents for all three types of amides. Another reagent that reduces disubstituted amides to amines is trichlorosilane.[1492] Other silanes, such as Et_3SiH in the presence of a rhenium catalyst, reduce amides to amines.[1493] Sodium (dimethylamino)borohydride reduces unsubstituted and disubstituted, but not monosubstituted amides.[1494] Electrolytic reduction of carbamates to give an amine are possible.[1495]

[1485]Sharma, R.; Voynov, G.H.; Ovaska, T.V.; Marquez, V.E. *Synlett* ***1995***, 839.

[1486]For a review, see Challis, B.C.; Challis, J.A., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 795–801. For a review of the reduction of amides, lactams, and imides with metallic hydrides, see Gaylord, N.G. *Reduction with Complex Metal Hydrides*, Wiley, NY, ***1956***, p. 544. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 869–872.

[1487]See, for example, Satoh, T.; Suzuki, S.; Suzuki, Y.; Miyaji, Y.; Imai, Z. *Tetrahedron Lett.* ***1969***, 4555; Rahman, A.; Basha, A.; Waheed, N.; Ahmed, S. *Tetrahedron Lett.* ***1976***, 219; Kuehne, M.E.; Shannon, P.J. *J. Org. Chem.* ***1977***, *42*, 2082; Wann, S.R.; Thorsen, P.T.; Kreevoy, M.M. *J. Org. Chem.* ***1981***, *46*, 2579; Mandal, S.B.; Giri, V.S.; Pakrashi, S.C. *Synthesis* ***1987***, 1128; Akabori, S.; Takanohashi, Y. *Chem. Lett.* ***1990***, 251.

[1488]Prasad, A.S.B.; Kanth, J.V.B.; Periasamy, M. *Tetrahedron* ***1992***, *48*, 4623.

[1489]Tanaka, H.; Ogasawara, K. *Tetrahedron Lett.* ***2002***, *43*, 4417.

[1490]Brown, H.C.; Narasimhan, S.; Choi, Y.M. *Synthesis* ***1981***, 441, 996; Krishnamurthy, S. *Tetrahedron Lett.* ***1982***, *23*, 3315; Bonnat, M.; Hercourt, A.; Le Corre, M. *Synth. Commun.* ***1991***, *21*, 1579.

[1491]Bhandari, K.; Sharma, V.L.; Chatterjee, S.K. *Chem. Ind. (London)* ***1990***, 547.

[1492]Nagata, Y.; Dohmaru, T.; Tsurugi, J. *Chem. Lett.* ***1972***, 989. See also, Benkeser, R.A.; Li, G.S.; Mozdzen, E.C. *J. Organomet. Chem.* ***1979***, *178*, 21.

[1493]Igarashi, M.; Fuchikami, T. *Tetrahedron Lett.* ***2001***, *42*, 1945.

[1494]Hutchins, R.O.; Learn, K.; El-Telbany, F.; Stercho, Y.P. *J. Org. Chem.* ***1984***, *49*, 2438.

[1495]Franco, D.; Duñach, E. *Tetrahedron Lett.* ***2000***, *41*, 7333.

With some RCONR, $LiAlH_4$ causes cleavage, and the aldehyde (**10-41**) or alcohol is obtained. Lithium triethylborohydride produces the alcohol with most *N,N*-disubstituted amides, but not with unsubstituted or *N*-substituted amides.[1496] Lactams are reduced to cyclic amines in high yields with $LiAlH_4$, although cleavage sometimes occurs here too. A mixture of $LiBHEt_3/Et_3SiH$ is also effective.[1497] Lactams are also reduced to cyclic amines with 9-BBN[1498] (p. 1077) or $LiBH_3NMe_2$.[1499] Imides are generally reduced on both sides,[1500] although it is sometimes possible to stop with just one. Both cyclic and acyclic imides have been reduced in this manner, although with acyclic imides cleavage is often obtained, for example,[1501]

$$PhN(COMe)_2 \longrightarrow PhNHEt$$

Acyl sulfonamides have been reduced ($RCONHSO_2Ph \rightarrow RCH_2NHSO_2Ph$) with BH_3—SMe_2[1502] and with SmI_2/DMPU.[1503]

OS **IV**, 339, 354, 564; **VI**, 382; **VII**, 41.

19-65 Reduction of Carboxylic Acids and Esters to Alkanes

Trihydro-de-alkoxy,oxo-tersubstitution, and so on.

$$RCOOR' \xrightarrow{(C_5H_5)_2TiCl_2} RCH_3 + R'OH$$

The reagent titanocene dichloride reduces carboxylic esters in a different manner from that of **19-59**, **19-62**, or **19-38**. The products are the alkane RCH_3 and the alcohol R′OH.[909] The mechanism probably involves an alkene intermediate. Aromatic acids can be reduced to methylbenzenes by a procedure involving refluxing first with trichlorosilane in MeCN, then with tripropylamine added, and finally with KOH and MeOH (after removal of the MeCN).[1504] The following sequence has been suggested:[1504]

$$ArCOOH \xrightarrow{SiHCl_3} (ArCO)_2O \xrightarrow[R_3N]{SiHCl_3} ArCH_2SiCl_3 \xrightarrow[MeOH]{KOH} ArCH_3$$

Esters of aromatic acids are not reduced by this procedure, so an aromatic COOH group can be reduced in the presence of a COOR′ group.[1505] However, it is also

[1496]Brown, H.C.; Kim, S.C. *Synthesis* ***1977***, 635.

[1497]Pedregal, C.; Ezquerra, J.; Escribano, A.; Carreño, M.C.; García Ruano, J.L.G. *Tetrahedron Lett.* ***1994***, *35*, 2053.

[1498]Colllins, C.J.; Lanz, M.; Singaram, B. *Tetrahedron Lett.* ***1999***, *40*, 3673.

[1499]Flaniken, J.M.; Collins, C.J.; Lanz, M.; Singaram, B. *Org. Lett.* ***1999***, *1*, 799.

[1500]For a reduction with borane•THF, see Akula, M.R.; Kabalka, G.W. *Org. Prep. Proceed. Int.* ***1999***, *31*, 214.

[1501]Witkop, B.; Patrick, J.B. *J. Am. Chem. Soc.* ***1952***, *74*, 3861.

[1502]Belletire, J.L.; Fry, D.F. *Synth. Commun.* ***1988***, *18*, 29.

[1503]Vedejs, E.; Lin, S. *J. Org. Chem.* ***1994***, *59*, 1602.

[1504]Benkeser, R.A.; Foley, K.M.; Gaul, J.M.; Li, G.S. *J. Am. Chem. Soc.* ***1970***, *92*, 3232.

[1505]Benkeser, R.A.; Ehler, D.F. *J. Org. Chem.* ***1973***, *38*, 3660.

possible to reduce aromatic ester groups, by a variation of the trichlorosilane procedure.[1506] Both *o*- and *p*-hydroxybenzoic acids and their esters have been reduced to cresols $HOC_6H_4CH_3$ with sodium bis(2-methoxyethoxy)aluminum hydride, $NaAlH_2(OC_2H_4OMe)_2$ (Red-Al).[1507] Heating a 2-pyridylbenzyl ester with ammonium formate and a rutheniumc atlyst leads to reduction of the CH_2COO unit to the the alkane.[1508]

Carboxylic acids can also be converted to alkanes, indirectly,[1509] by reduction of the corresponding tosylhydrazides $RCONHNH_2$ with $LiAlH_4$ or borane.[1510]

OS **VI**, 747.

19-66 Hydrogenolysis of Nitriles

Hydro-de-cyanation

$$R{-}CN \longrightarrow R{-}H$$

This transformation is not common, but given the proliferation of nitriles in organic chemistry, it is potentially quite useful. In the presence of mercuric compounds, tertiary nitriles can be reduced to the hydrocarbon with sodium cyanoborohydride.[1511] *gem*-Dinitriles can be reduced to the corresponding mononitrile with SmI_2.[1512]

19-67 Reduction of the C—N Bond

Hydro-de-amination or Deamination

$$RNH_2 \longrightarrow RH$$

Benzylic amines are particularly susceptible to hydrogenolysis by catalytic hydrogenation[1513] or dissolving metal reduction.[1514] Note that the Wolff–Kishner reduction in **19-61** involved formation of a hydrazone and deprotonation by base led to loss of nitrogen and reduction. Ceric ammonium nitrate in aqueous acetonitrile has also been shown to reductively cleave the *N*-benzyl group.[1515] Primary amines have been reduced to RH with hydroxylamine-*O*-sulfonic acid and

[1506]Benkeser, R.A.; Mozdzen, E.C.; Muth, C.L. *J. Org. Chem.* ***1979***, *44*, 2185.

[1507]Černý, M.; Málek, J. *Collect. Czech. Chem. Commun.* ***1970***, *35*, 2030.

[1508]Chatani, N.; Tatamidani, H.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* ***2001***, *123*, 4849.

[1509]For another indirect method, which can also be applied to acid derivatives, see Degani, I.; Fochi, R. *J. Chem. Soc. Perkin Trans. 1* ***1978***, 1133. For a direct method, see Le Deit, H.; Cron S.; Le Corre, M. *Tetrahedron Lett.* ***1991***, *32*, 2759.

[1510]Attanasi, O.; Caglioti, L.; Gasparrini, F.; Misiti, D. *Tetrahedron* ***1975***, *31*, 341, and references cited therein.

[1511]Sassaman, M.B. *Tetrahedron* ***1996***, *52*, 10835.

[1512]Kang, H.-Y.; Hong, W.S.; Cho, Y.S.; Koh, H.Y. *Tetrahedron Lett.* ***1995***, *36*, 7661.

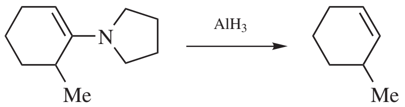
[1513]Hartung, W.H.; Simonoff, R. *Org. React.* ***1953***, *7*, 263.

[1514]du Vigneaud, V.; Behrens, O.K. *J. Biol. Chem.* ***1937***, *117*, 27.

[1515]Bull, S.D.; Davies, S.G.; Fenton, G.; Mulvaney, A.W.; Prasad, R.S.; Smith, A.D. *J. Chem. Soc. Perkin Trans. 1* ***2000***, 3765.

aq. NaOH to give the hydrocarbon, nitrogen gas, and the sulfate anion.[1516] It is postulated that R—N=N—H is an intermediate that decomposes to the carbocation. The reaction has also been accomplished with difluoroamine HNF_2;[1517] the same intermediates are postulated in this case. Treatment of aniline with 20 equivalents of NO gave benzene.[1518] An indirect means of achieving the same result is the conversion of the primary amine to the sulfonamide, $RNHSO_2R'$ (**16-102**), and treatment of this with NH_2OSO_2OH[1519] or NaOH, and then NH_2Cl.[1520] Tosylaziridines derived from terminal alkenes are reduced to the corresponding primary tosylamine with polymethylhydrosiloxane/Pd—C.[1521]

Other indirect methods involve reduction of *N,N*-ditosylates (p. 497) with $NaBH_4$ in HMPA[1522] and modifications of the Katritzky pyrylium–pyridinium method.[1523] Allylic and benzylic amines[1349] can be reduced by catalytic hydrogenolysis. Aziridines can be reductively opened with SmI_2[1524] or with Bu_3SnH and AIBN.[1525] The C—N bond of enamines is reductively cleaved to give an alkene with alane (AlH_3).[1526]



and with 9-BBN (p. 1077) or borane methyl sulfide (BMS).[1527] Since enamines can be prepared from ketones (**16-13**), this is a way of converting ketones to alkenes. In the latter case, BMS gives retention of configuration [an (*E*) isomer gives the (*E*) product], while 9-BBN gives the other isomer.[1527] Diazo ketones are reduced to methyl ketones by HI: $RCOCHN_2 + HI \rightarrow RCOCH_3$.[1528]

Quaternary ammonium salts can be cleaved with $LiAlH_4$, $R_4N^+ + LiAlH_4 \rightarrow R_3N + R^-$, as can quaternary phosphonium salts R_4P^+. Other reducing agents have also been used, for example, lithium triethylborohydride (which preferentially cleaves methyl groups)[1529] and sodium in liquid ammonia. When quaternary salts

[1516] Doldouras, G.A.; Kollonitsch, J. *J. Am. Chem. Soc.* ***1978***, *100*, 341.
[1517] Bumgardner, C.L.; Martin, K.J.; Freeman, J.P. *J. Am. Chem. Soc.* ***1963***, *85*, 97.
[1518] Itoh, T.; Matsuya, Y.; Nagata, K.; Ohsawa, A. *Tetrahedron Lett.* ***1996***, *37*, 4165.
[1519] Nickon, A.; Hill, R.H. *J. Am. Chem. Soc.* ***1964***, *86*, 1152.
[1520] Guziec Jr., F.S.; Wei, D. *J. Org. Chem.* ***1992***, *57*, 3772.
[1521] Chandrasekhar, S.; Ahmed, M. *Tetahedron Lett.* ***1999***, *40*, 9325.
[1522] Hutchins, R.O.; Cistone, F.; Goldsmith, B.; Heuman, P. *J. Org. Chem.* ***1975***, *40*, 2018.
[1523] See Katritzky, A.R.; Bravo-Borja, S.; El-Mowafy, A.M.; Lopez-Rodriguez, G. *J. Chem. Soc. Perkin Trans. 1* ***1984***, 1671.
[1524] Molander, G.A.; Stengel, P.J. *Tetrahedron*, ***1997***, *53*, 8887.
[1525] Schwan, A.L.; Refvik, M.D. *Tetrahedron Lett.* ***1993***, *34*, 4901.
[1526] Coulter, J.M.; Lewis, J.W.; Lynch, P.P. *Tetrahedron* ***1968***, *24*, 4489.
[1527] Singaram, B.; Goralski, C.T.; Rangaishenvi, M.V.; Brown, H.C. *J. Am. Chem. Soc.* ***1989***, *111*, 384.
[1528] For example, see Pojer, P.M.; Ritchie, E.; Taylor, W.C. *Aust. J. Chem.* ***1968***, *21*, 1375.
[1529] Cooke Jr., M.P.; Parlman, R.M. *J. Org. Chem.* ***1975***, *40*, 531.

are reduced with sodium amalgam in water, the reaction is known as the *Emde reduction*. However, this reagent is not applicable to the cleavage of ammonium salts with four *saturated* alkyl groups. Of course, aziridines[899] can be reduced in the same way as epoxides (**19-35**).

Nitro compounds, RNO_2, can be reduced to RH[1530] by sodium methylmercaptide, CH_3SNa, in an aprotic solvent[1531] or by Bu_3SnH.[1532] Both reactions have free-radical mechanisms.[1533] Tertiary nitro compounds can be reduced to RH by NaHTe.[1534] Hydrogenolysis with a Pt catalyst in the gas phase has been reported to reduce nitro compounds, as well as primary and secondary amines.[1535] The nitro group of aromatic nitro compounds has been removed with sodium borohydride.[1536] This reaction involves an addition–elimination mechanism. Reduction of the C—N bond on aromatic amines with Li metal in THF generates the aryl compounds.[1537] Sodium nitrite, sodium bisulfite in EtOH/water/acetic acid does a similar reduction.[1538] Conversion of the aniline derivative to the methanesulfonamide and subsequent treatment with NaH and NH_2Cl gives the same result.[1539] The Bu_3SnH reagent also reduces isocyanides, RNC (prepared from RNH_2 by formylation followed by **17-31**), to RH,[1540] a reaction that can also be accomplished with Li or Na in liquid NH_3,[1541] or with K and a crown ether in toluene.[1542] α-Nitro ketones can be reduced to ketones with $Na_2S_2O_4$—Et_3SiH in HMPA—H_2O.[1543]

OS **III**, 148; **IV**, 508; **VIII**, 152.

[1530]For a method of reducing allylic nitro groups, see Ono, N.; Hamamoto, I.; Kamimura, A.; Kaji, A. *J. Org. Chem.* ***1986***, *51*, 3734.

[1531]Kornblum, N.; Carlson, S.C.; Smith, R.G. *J. Am. Chem. Soc.* ***1979***, *101*, 647; Kornblum, N.; Widmer, J.; Carlson, S.C. *J. Am. Chem. Soc.* ***1979***, *101*, 658.

[1532]For reviews, see Ono, N., in Feuer, H.; Nielsen, A.T. *Nitro Compounds; Recent Advances in Synthesis and Chemistry*, VCH, NY, ***1990***, pp. 1–135, 1–45; Rosini, G.; Ballini, R. *Synthesis* ***1988***, 833, see pp. 835–837; Ono, N.; Kaji, A. *Synthesis* ***1986***, 693. For discussions of the mechanism, see Korth, H.; Sustmann, R.; Dupuis, J.; Geise, B. *Chem. Ber.* ***1987***, *120*, 1197; Kamimura, A.; Ono, N. *Bull. Chem. Soc. Jpn.* ***1988***, *61*, 3629.

[1533]For a discussion of the mechanism with Bu_3SnH, see Tanner, D.D.; Harrison, D.J.; Chen, J.; Kharrat, A.; Wayner, D.D.M.; Griller, D.; McPhee, D.J. *J. Org. Chem.* ***1990***, *55*, 3321. If an α substituent is present, it may be reduced instead of the NO_2. For a mechanistic discussion, see Bowman, W.R.; Crosby, D.; Westlake, P.J. *J. Chem. Soc. Perkin Trans. 2* ***1991***, 73.

[1534]Suzuki, H.; Takaoka, K.; Osuka, A. *Bull. Chem. Soc. Jpn.* ***1985***, *58*, 1067.

[1535]Guttieri, M.J.; Maier, W.F. *J. Org. Chem.* ***1984***, *49*, 2875.

[1536]Severin, T.; Schmitz, R.; Temme, H. *Chem. Ber.* ***1963***, *96*, 2499; Kniel, P. *Helv. Chim. Acta* ***1968***, *51*, 371. For another method, see Ono, N.; Tamura, R.; Kaji, A. *J. Am. Chem. Soc.* ***1983***, *105*, 4017.

[1537]Azzena, U.; Dessanti, F.; Melloni, G.; Pisano, L. *Tetrahedron Lett.* ***1999***, *40*, 8291.

[1538]Geoffroy, O.J.; Morinelli, T.A.; Meier, G.B. *Tetrahedron Lett.* ***2001***, *42*, 5367.

[1539]Wang, Y.; Guziec, Jr., F.S. *J. Org. Chem.* ***2001***, *66*, 8293.

[1540]Barton, D.H.R.; Bringmann, G.; Motherwell, W.B. *Synthesis* ***1980***, 68.

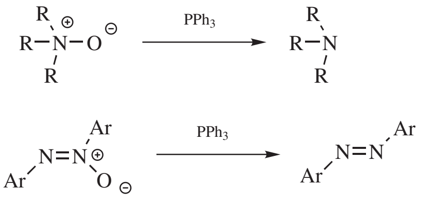
[1541]See Niznik, G.E.; Walborsky, H.M. *J. Org. Chem.* ***1978***, *43*, 2396; Yadav, J.S.; Reddy, P.S.; Joshi, B.V. *Tetrahedron Lett.* ***1988***, *44*, 7243.

[1542]Ohsawa, T.; Mitsuda, N.; Nezu, J.; Oishi, T. *Tetrahedron Lett.* ***1989***, *30*, 845.

[1543]Kamimura, A.; Kurata, K.; Ono, N. *Tetrahedron Lett.* ***1989***, *30*, 4819.

19-68 Reduction of Amine Oxides and Azoxy Compounds

N-Oxygen-detachment



Amine oxides[1544] and azoxy compounds (both alkyl and aryl)[1545] can be reduced practically quantitatively with triphenylphosphine.[1546] Other reducing agents, for example, $LiAlH_4$, $NaBH_4/LiCl$,[1547] H_2—Ni, PCl_3, $TiCl_3$,[1548] Ga/H_2O,[1549] In/$TiCl_4$,[1550] $LiAlH_4/TiCl_4$, or $SbCl_2$ have also been used. Indium metal with aqueous ammonium chloride in methanol gives good yields of pyridine from pyridine *N*-oxide.[1551] Similar results are obtained using ammonium formate and Raney nickel[1552] or zinc.[1553] Indium (III) chloride has been used for the reduction of quinoline *N*-oxide to quinoline.[1554] Polymethylhydrosiloxane with Pd—C is also an effective reducing agent for amino oxides.[1555] Nitrile oxides[1556] ($R{-}C{\equiv}N^+{-}O^-$) can be reduced to nitriles with trialkylphosphines,[1557] and isocyanates (RNCO) to isocyanides (RNC) with Cl_3SiH—Et_3N.[1558]

Analogous to amino *N*-oxides, phosphine oxides ($R_3P{=}O$) are reduced to phosphines (R_3P). Treatment of a phosphine oxide with MeOTf followed by reduced

[1544]For reviews of the reduction of heterocyclic amine oxides, see Albini, A.; Pietra, S. *Heterocyclic N-Oxides*, CRC Press, Boca Raton, FL, ***1991***, pp. 120–134; Katritzky, A.R.; Lagowski, J.M. *Chemistry of the Heterocyclic N-Oxides*, Academic Press, NY, ***1971***, pp. 166–231.

[1545]For a review, see Newbold, B.T., in Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 2, Wiley, NY, ***1975***, pp. 602–603, 614–624.

[1546]For a review, see Rowley, A.G., in Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, ***1979***, pp. 295–350.

[1547]Ram, S.R.; Chary, K.P.; Iyengar, D.S. *Synth. Commun.* ***2000***, *30, 3*511.

[1548]Kuz'min, S.V.; Mizhiritskii, M.D.; Kogan, L.M. *J. Org. Chem. USSR* ***1989***, *25*, 596.

[1549]Han, J.H.; Choi, K.I.; Kim, J.H.; Yoo, B.W. *Synth. Commun.* ***2004***, *34*, 3197.

[1550]Yoo, B.W.; Choi, K.H.; Choi, K.I.; Kim, J.H. *Synth. Commun.* ***2003***, *33*, 4185.

[1551]Yadav, J.S.; Reddy, B.V.S.; Reddy, M.M. *Tetrahedron Lett.* ***200***, *41*, 2663.

[1552]Balicki, R.; Maciejewski, G. *Synth. Commun.* ***2002***, *32*, 1681.

[1553]Balicki, R.; Cybulski, M.; Maciejewski, G. *Synth. Commun.* ***2003***, *33*, 4137.

[1554]Ilias, Md.; Barman, D.C.; Prajapati, D.; Sandhu, J.S. *Tetrahedron Lett.* ***2002***, *43*, 1877.

[1555]Chandrasekhar, S.; Reddy, Ch.R.; Rao, R.J.; Rao, J.M. *Synlett* ***2002***, 349.

[1556]For reviews of the chemistry of nitrile oxides, see Torssell, K.B.G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*, VCH, NY, ***1988***, pp. 55–74; Grundmann, C. *Fortschr. Chem. Forsch.* ***1966***, *7*, 62.

[1557]Grundmann, C.; Frommeld, H.D. *J. Org. Chem.* ***1965***, *30*, 2077.

[1558]Baldwin, J.E.; Derome, A.E.; Riordan, P.D. *Tetrahedron* ***1983***, *39*, 2989.

with $LiAlH_4$ gives the phosphine.[1559] Chiral phosphine oxides are reduced to the phosphine with excellent enantioselectivity using PPh_3 and Cl_3SiH.[1560]

OS **IV**, 166. See also, OS **VIII**, 57.

19-69 Replacement of the Diazonium Group by Hydrogen

Dediazoniation or **Hydro-de-diazoniation**

$$ArN_2^+ + H_3PO_2 \longrightarrow ArH$$

Reduction of the diazonium group (*dediazoniation*) provides an indirect method for the removal of an amino group from an aromatic ring.[1561] The best and most common way of accomplishing this is by use of hypophosphorous acid H_3PO_2, although many other reducing agents[1562] have been used, among them ethanol, HMPA,[1563] thiophenol,[1564] and sodium stannite. Ethanol was the earliest reagent used, and it frequently gives good yields, but often ethers (ArOEt) are side products. When H_3PO_2 is used, 5–15 equivalents of this reagent are required per equivalent of substrate. Diazonium salts can be reduced in nonaqueous media by several methods, including treatment with Bu_3SnH or Et_3SiH in ethers or MeCN[1565] and by isolation as the BF_4^- salt and reduction of this with $NaBH_4$ in DMF.[1566] Aromatic amines can be deaminated ($ArNH_2 \longrightarrow ArH$) in one laboratory step by treatment with an alkyl nitrite in DMF[1567] or boiling THF.[1568] The corresponding diazonium salt is an intermediate.

Not many investigations of the mechanism have been carried out. It is generally assumed that the reaction of diazonium salts with ethanol to produce ethers takes place by an ionic (S_N1) mechanism while the reduction to ArH proceeds by a free-radical process.[1569] The reduction with H_3PO_2 is also believed to have a free-radical mechanism.[1570] In the reduction with $NaBH_4$, an aryldiazene intermediate

[1559]Imamoto, T.; Kikuchi, S.-i.; Miura, T.; Wada, Y. *Org. Lett.* ***2001***, *3*, 87.

[1560]Wu, H.-C.; Yu, J.-Q.; Spencer, J.B. *Org. Lett.* ***2004***, *6*, 4675.

[1561]For a review, see Zollinger, H., in Patai, S.; Rappoport, Z. *The Chemistry of Functinal Groups, Supplement C* pt. 1, Wiley, NY, ***1983***, pp. 603–669.

[1562]For lists of some of these, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 39–41; Tröndlin, F.; Rüchardt, C. *Chem. Ber.* ***1977***, *110*, 2494.

[1563]Shono, T.; Matsumura, Y.; Tsubata, K. *Chem. Lett.* ***1979***, 1051.

[1564]For a list of some of these, with references, see Korzeniowski, S.H.; Blum, L.; Gokel, G.W. *J. Org. Chem.* ***1977***, *42*, 1469.

[1565]Nakayama, J.; Yoshida, M.; Simamura, O. *Tetrahedron* ***1970***, *26*, 4609.

[1566]Hendrickson, J.B. *J. Am. Chem. Soc.* ***1961***, *83*, 1251. See also, Threadgill, M.D.; Gledhill, A.P. *J. Chem. Soc. Perkin Trans. 1* ***1986***, 873.

[1567]Doyle, M.P.; Dellaria, Jr., J.F.; Siegfried, B.; Bishop, S.W. *J. Org. Chem.* ***1977***, *42*, 3494.

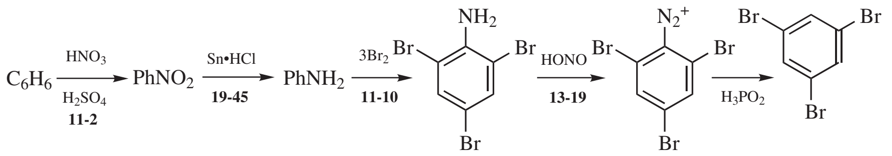
[1568]Cadogan, J.I.G.; Molina, G.A. *J. Chem. Soc. Perkin Trans. 1* ***1973***, 541.

[1569]For examples, see DeTar, D.F.; Kosuge, T. *J. Am. Chem. Soc.* ***1958***, *80*, 6072; Lewis, E.S.; Chambers, D.J. *J. Am. Chem. Soc.* ***1971***, *93*, 3267; Broxton, T.J.; Bunnett, J.F.; Paik, C.H. *J. Org. Chem.* ***1977***, *42*, 643.

[1570]See, for example, Kornblum, N.; Cooper, G.D.; Taylor, J.E. *J. Am. Chem. Soc.* ***1950***, *72*, 3013; Beckwith, A.L.J. *Aust. J. Chem.* ***1972***, *25*, 1887; Levit, A.F.; Kiprianova, L.A.; Gragerov, I.P. *J. Org. Chem. USSR* ***1975***, *11*, 2395.

(ArN=NH) has been demonstrated,[1571] arising from nucleophilic attack by BH_4^- on the β nitrogen. Such diazenes can be obtained as moderately stable (half-life of several hours) species in solution.[1572] It is not entirely clear how the aryldiazene decomposes, but there are indications that either the aryl radical AR• or the corresponding anion Ar^- may be involved.[1573]

An important use of the dediazoniation reaction is to remove an amino group after it has been used to direct one or more other groups to ortho and para positions. For example, the compound 1,3,5-tribromobenzene cannot be prepared by direct bromination of benzene because the bromo group is ortho–para-directing; however, this compound is easily prepared by the following sequence:



Many other compounds that would otherwise be difficult to prepare are easily synthesized with the aid of the dediazoniation reaction.

Unwanted dediazoniation can be suppressed by using hexasulfonated calix[6]arenes (see p. 122).[1574]

OS **I**, 133, 415; **II**, 353, 592; **III**, 295; **IV**, 947; **VI**, 334.

19-70 Desulfurization

Hydro-de-thio-substitution, and so on

$$\text{RSH} \longrightarrow \text{RH}$$

$$\text{RSR}' \longrightarrow \text{RH} + \text{R}'\text{H}$$

$$\text{RS(O)}_n\text{R}' \longrightarrow \text{RH} + \text{R}'\text{H}$$

Thiols and thioethers,[1575] both alkyl and aryl, can be desulfurized by hydrogenolysis with Raney nickel.[1576] The hydrogen is usually not applied externally, since

[1571]König, E.; Musso, H.; Záhorszky, U.I. *Angew. Chem. Int. Ed.* ***1972***, *11*, 45; McKenna, C.E.; Traylor, T.G. *J. Am. Chem. Soc.* ***1971***, *93*, 2313.

[1572]Huang, P.C.; Kosower, E.M. *J. Am. Chem. Soc.* ***1968***, *90*, 2354, 2362, 2367; Smith III, M.R.; Hillhouse, G.L. *J. Am. Chem. Soc.* ***1988***, *110*, 4066.

[1573]Rieker, A.; Niederer, P.; Leibfritz, D. *Tetrahedron Lett.* ***1969***, 4287; Kosower, E.M.; Huang, P.C.; Tsuji, T. *J. Am. Chem. Soc.* ***1969***, *91*, 2325; König, E.; Musso, H.; Záhorszky, U.I. König, E.; Musso, H.; Záhorszky, U.I. *Angew. Chem. Int. Ed.* ***1972***, *11*, 45; McKenna, C.E.; Traylor, T.G. *J. Am. Chem. Soc.* ***1971***, *93*, 2313.; Broxton, T.J.; McLeish, M.J. *Aust. J. Chem.* ***1983***, *36*, 1031.

[1574]Shinkai, S.; Mori, S.; Araki, K.; Manabe, O. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 3679.

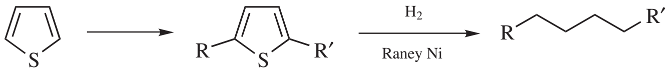
[1575]For a review of the reduction of thioethers, see Block, E., in Patai, S. *The Chemistry of Functional Groups*, *Supplement E*, pt. 1, Wiley, NY, ***1980***, pp. 585–600.

[1576]For reviews, see Belen'kii, L.I., in Belen'kii, L.I. *Chemistry of Organosulfur Compounds*, Ellis Horwood, Chichester, ***1990***, pp. 193–228; Pettit, G.R.; van Tamelen, E.E. *Org. React.* ***1962***, *12*, 356; Hauptmann, H.; Walter, W.F. *Chem. Rev.* ***1962***, *62*, 347.

Raney nickel already contains enough hydrogen for the reaction. Other sulfur compounds can be similarly desulfurized, including disulfides, thiono esters,[1577] thioamides, sulfoxides, and thioacetals.[1578] Reduction of thioacetals is an indirect way of accomplishing reduction of a carbonyl to a methylene group (see **19-61**), and it can also give the alkene if a hydrogen is present.[1579] In most of the examples given, R can also be aryl. Other reagents[1580] have also been used.[1581]

Lithium aluminum hydride reduces most sulfur compounds with cleavage of the C—S bond, including thiols.[1582] Thioesters can be reduced with Ni_2B (from $NiBr_2/NaBH_4$).[1583] β-Ketosulfones are reduced with $TiCl_4$—Zn,[1584] $TiCl_4$—Sm,[1585] or Bu_3SnCl—$NaCNBH_3$/AIBN.[1586]

An important special case of RSR reduction is desulfurization of thiophene derivatives. This proceeds with concomitant reduction of the double bonds. Many compounds have been made by alkylation of thiophene to **49**, followed by reduction to give **50**.



49 **50**

Thiophenes can also be desulfurized to alkenes ($RCH_2CH{=}CHCH_2R'$ from **49**) with a nickel boride catalyst prepared from nickel(II) chloride and $NaBH_4$ in methanol.[1587] It is possible to reduce just one SR group of a dithioacetal by treatment with borane–pyridine in trifluoroacetic acid or in CH_2Cl_2 in the presence of $AlCl_3$.[1588] Phenyl selenides RSePh can be reduced to RH with Ph_3SnH[1589] and with nickel boride.[1590] Cleavage of the C—Se bond can also be achieved with SmI_2.[1591]

[1577]See Baxter, S.L.; Bradshaw, J.S. *J. Org. Chem.* ***1981***, *46*, 831.

[1578]For desulfurization of the mixed acetal PhCHC(OBu)SPh to $PhCH_2OBu$ see Nakata, D.; Kusaka, C.; Tani, S.; Kunishima, M. *Tetrahedron Lett.* ***2001***, *42*, 415.

[1579]Fishman, J.; Torigoe, M.; Guzik, H. *J. Org. Chem.* ***1963***, *28*, 1443.

[1580]For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 53–60. For a review with respect to transition-metal reagents, see Luh, T.; Ni, Z. *Synthesis* ***1990***, 89. For some very efficient nickel-containing reagents, see Becker, S.; Fort, Y.; Vanderesse, R.; Caubère, P. *J. Org. Chem.* ***1989***, *54*, 4848.

[1581]For example, diphosphorus tetraiodide by Suzuki, H.; Tani, H.; Takeuchi, S. *Bull. Chem. Soc. Jpn.* ***1985***, *58*, 2421; Shigemasa, Y.; Ogawa, M.; Sashiwa, H.; Saimoto, H. *Tetrahedron Lett.* ***1989***, *30*, 1277; $NiBr_2$-Ph_3P-$LiAlH_4$ by Ho, K.M.; Lam, C.H.; Luh, T. *J. Org. Chem.* ***1989***, *54*, 4474.

[1582]Smith, M.B.; Wolinsky, J. *J. Chem. Soc. Perkin Trans. 2* ***1998***, 1431.

[1583]Back, T.G.; Baron D.L.; Yang, K. *J. Org. Chem.* ***1993***, *58*, 2407.

[1584]Guo, H.; Ye, S.; Wang, J.; Zhang, Y. *J. Chem. Res. (S)* ***1997***, 114.

[1585]Wang, J.; Zhang, Y. *Synth. Commun.* ***1996***, *26*, 1931.

[1586]Giovannini, R.; Petrini, M. *Synlett* ***1995***, 973.

[1587]Schut, J.; Engberts, J.B.F.N.; Wynberg, H. *Synth. Commun.* ***1972***, *2*, 415.

[1588]Kikugawa, Y. *J. Chem. Soc. Perkin Trans. 1* ***1984***, 609.

[1589]Clive, D.L.J.; Chittattu, G.; Wong, C.K. *J. Chem. Soc. Chem. Commun.* ***1978***, 41.

[1590]Back, T.G. *J. Chem. Soc. Chem. Commun.* ***1984***, 1417.

[1591]Ogawa, A.; Ohya, S.; Doi, M.; Sumino, Y.; Sonoda, N.; Hirao, T. *Tetrahedron Lett.* ***1998***, *39*, 6341.

The exact mechanism of the Raney nickel reactions are still in doubt, although they are probably of the free-radical type.[1592] It has been shown that reduction of thiophene proceeds through butadiene and butene, not through 1-butanethiol or other sulfur compounds, that is, the sulfur is removed before the double bonds are reduced. This was demonstrated by isolation of the alkenes and the failure to isolate any potential sulfur-containing intermediates.[1593]

Sulfonamides are reduced to the corresponding amine by heating with Me_3SiCl and NaI.[1594]

OS **IV**, 638; **V**, 419; **VI**, 109, 581, 601. See also, OS **VII**, 124, 476.

19-71 Reduction of Sulfonyl Halides and Sulfonic Acids to Thiols or Disulfides

$$RSO_2Cl \xrightarrow{LiAlH_4} RSH$$

Thiols can be prepared by the reduction of sulfonyl halides[1595] with $LiAlH_4$. Usually, the reaction is carried out on aromatic sulfonyl chlorides. Zinc and acetic acid, and HI, also give the reduction. Another reagent for this reduction is Me_2SiCl_2 and Zn with dimethyl acetamide.[1596] Sulfonic acids have been reduced to thiols with a mixture of triphenylphosphine and either I_2 or a diaryl disulfide.[1597] For the reduction of sulfonyl chlorides to sulfinic acids, see **16-104**.

Disulfides RSSR can also be produced.[1598] Other sulfonic acid derivatives can be converted to disulfides. Esters, such as PhSAc, are converted to disulfides PhS—SPh with Clayan and microwave irradiation.[1599] Thiobenzoate derivatives PhSBz are similarly converted to PhS—SPh with SmI_2.[1600] In a similar manner, RS—SO_3Na is converted to RS—SR when heated with samarium metal in water.[1601]

OS **I**, 504; **IV**, 695; **V**, 843.

[1592]For a review, see Bonner, W.A.; Grimm, R.A., in Kharasch, N.; Meyers, C.Y. *The Chemistry of Organic Sulfur Compounds*, Vol. 2, Pergamon, NY, ***1966***, pp. 35–71, 410–413. For a review of the mechanism of desulfurization on molybdenum surfaces, see Friend, C.M.; Roberts, J.T. *Acc. Chem. Res.* ***1988***, *21*, 394.

[1593]Owens, P.J.; Ahmberg, C.H. *Can. J. Chem.* ***1962***, *40*, 941.

[1594]Sabitha, G.; Reddy, B.V.S.; Abraham, S.; Yadav, J.S. *Tetrahedron Lett.* ***1999***, *40*, 1569.

[1595]For a review, see Wardell, J.L., in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, ***1974***, pp. 216–220.

[1596]Uchiro, H.; Kobayashi, S. *Tetrahedron Lett.* ***1999***, *40*, 3179.

[1597]Oae, S.; Togo, H. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 3802; ***1984***, *57*, 232.

[1598]For example, see Alper, H. *Angew. Chem. Int. Ed.* ***1969***, *8*, 677; Chan, T.H.; Montillier, J.P.; Van Horn, W.F.; Harpp, D.N. *J. Am. Chem. Soc.* ***1970***, *92*, 7224. See also, Olah, G.A.; Narang, S.C.; Field, L.D.; Karpeles, R. *J. Org. Chem.* ***1981***, *46*, 2408; Oae, S.; Togo, H. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 3813; Suzuki, H.; Tani, H.; Osuka, A. *Chem. Lett.* ***1984***, 139; Babu, J.R.; Bhatt, M.V. *Tetrahedron Lett.* ***1986***, *27*, 1073; Narayana, C.; Padmanabhan, S.; Kabalka, G.W. *Synlett* ***1991***, 125.

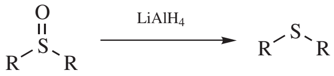
[1599]Meshram, H.M.; Bandyopadhyay, A.; Reddy, G.S.; Yadav, J.S. *Synth. Commun.* ***1999***, *29*, 2705.

[1600]Yoo, B.W.; Baek, H.S.; Keum, S.R.; Yoon, C.M.; Nam. G.S.; Kim, S.H.; Kim, J.H. *Synth. Commun.* ***2000***, *30*, 4317.

[1601]Wang, L.; Li, P.; Zhou, L. *Tetrahedron Lett.* ***2002***, *43*, 8141.

19-72 Reduction of Sulfoxides and Sulfones

S-Oxygen-detachment



Sulfoxides can be reduced to sulfides by many reagents,[1602] among them Ph_3P,[1603] $LiAlH_4$, HI, Bu_3SnH,[1604] $MeSiCl_3$—NaI,[1605] H_2—Pd—C,[1606] $NaBH_4$—$NiCl_2$,[1607] $NaBH_4/I_2$,[1608] catecholborane,[1609] TiI_4,[1610] $TiCl_4$/In,[1611] Cp_2TiCl_2/In,[1612] Sm/methanolic NH_4Cl with ultrasound,[1613] $(EtO)_2PCl/NEt_3$,[1614] and $SiO_2/SOCl_2$. Sulfones, however, are usually stable to reducing agents, although they have been reduced to sulfides with DIBALH, $(i\text{Bu})_2AlH$.[1615] A less general reagent is $LiAlH_4$, which reduces some sulfones to sulfides, but not others.[1616] Heating sulfoxides with 2,6-dihydroxypyridine gives the corresponding sulfide.[1617] Both sulfoxides and sulfones can be reduced by heating with sulfur (which is oxidized to SO_2), although the reaction with sulfoxides proceeds at a lower temperature. It has been shown by using substrate labeled with ^{35}S that sulfoxides simply give up the oxygen to the sulfur, but that the reaction with sulfones is more complex, since $\sim$ 75% of the original radioactivity of the sulfone is lost.[1618] This indicates that most of the sulfur in the sulfide product comes in this case from the *reagent*. There is no direct general

[1602]For reviews, see Kukushkin, V.Yu. *Russ. Chem. Rev.* ***1990***, *59*, 844; Madesclaire, M. *Tetrahedron* ***1988***, *44*, 6537; Drabowicz, J.; Togo, H.; Mikołajczyk, M.; Oae, S. *Org. Prep. Proced. Int.* ***1984***, *16*, 171; Drabowicz, J.; Numata, T.; Oae, S. *Org. Prep. Proced. Int.* ***1977***, *9*, 63. For a list of reagents, with references, see Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***.

[1603]For a review, see Rowley, A.G., in Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, ***1979***, pp. 301–304.

[1604]Kozuka, S.; Furumai; S.; Akasaka, T.; Oae, S. *Chem. Ind. (London)* ***1974***, 496.

[1605]Olah, G.A.; Husain, A.; Singh, B.P.; Mehrotra, A.K. *J. Org. Chem.* ***1983***, *48*, 3667. See also, Schmidt, A.H. Russ *Chem. Ber.* ***1981***, *114*, 822.

[1606]Ogura, K.; Yamashita, M.; Tsuchihashi, G. *Synthesis* ***1975***, 385.

[1607]Khurana, J.M.; Ray, A.; Singh, S. *Tetrahedron Lett.* ***1998***, *39*, 3829.

[1608]Karimi, B.; Zareyee, D. *Synthesis* ***2003***, 335.

[1609]Harrison, D.J.; Tam, N.C.; Vogels, C.M.; Langler, R.F.; Baker, R.T.; Decken, A.; Westcott, S.A. *Tetrahedron Lett.* ***2004***, *45*, 8493.

[1610]Shimizu, M.; Shibuya, K.; Hayakawa, R. *Synlett* ***2000***, 1437.

[1611]Yoo, B.W.; Choi, K.H.; Kim, D.Y.; Choi, K.I.; Kim, J.H. *Synth. Commun.* **2003**, 33, 53.

[1612]Yoo, B.W.; Choi, K.H.; Lee, S.J.; Yoon, C.M.; Kim, S.H.; Kim, J.H. *Synth. Commun.* ***2002***, *32*, 63.

[1613]Yadav, J.S.; Subba Reddy, B.V.; Srinivas, C.; Srihari, P. *Synlett* ***2001***, 854.

[1614]Jie, Z.; Rammoorty, V.; Fischer, B. *J. Org. Chem.* ***2002***, *67*, 711.

[1615]Gardner, J.N.; Kaiser, S.; Krubiner, A.; Lucas, H. *Can. J. Chem.* ***1973***, *51*, 1419.

[1616]Bordwell, F.G.; McKellin, W.H. *J. Am. Chem. Soc.* ***1951***, *73*, 2251; Whitney, T.A.; Cram, D.J. *J. Org. Chem.* ***1970***, *35*, 3964; Weber, W.P.; Stromquist, P.; Ito, T.I. *Tetrahedron Lett.* ***1974***, 2595.

[1617]Miller, S.J.; Collier, T.R.; Wu, W. *Tetrahedron Lett.* ***2000***, *41*, 3781.

[1618]Kiso, S.; Oae, S. *Bull. Chem. Soc. Jpn.* ***1967***, *40*, 1722. See also, Oae, S.; Nakai, M.; Tsuchida, Y.; Furukawa, N. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 445.

method for the reduction of sulfones to sulfoxides, but an indirect method has been reported.[1619] Selenoxides can be reduced to selenides with a number of reagents.[1620]

OS IX, 446

D. Reduction With Cleavage

19-73 de-Alkylation of Amines and Amides

$$R'_2N{-}R \longrightarrow R'_2N{-}H$$

Certain amines can be dealkylated, usually under reductive conditions. *N*-Allyl amines, $R_2N{-}CH_2CH{=}CH_2$ are converted to the corresponding amine, $R_2N{-}H$, with Dibal/$NiCl_2$dppp,[1621] and with Pd(dba)$_2$dppb.[1622] A mixture of $TiCl_3$ and Li converts *N*-benzylamines to the amine ($R_2NCH_2Ph \rightarrow R_2NH$).[1623] In the case of *N,N*-dimethyl amines, $RuCl_3$ and H_2O_2 demethylate the amine ($ArNMe_2 \rightarrow ArNHMe$).[1624] Tribenzylamines are dealkylated to give the dibenzylamine with ceric ammonium nitrate in aqueous acetonitrile.[1625] *N*-Benzyl indoles are cleaved to indoles with O_2, DMSO/KO*t*-Bu[1626] or with tetrabutylammonium fluoride.[1627]

The process is not limited to amines. Amides can also be dealkylated. *N*-Benzyl amides are debenzylated in the presence of NBS and AIBN.[1628]

N-Alkyl sulfonamides are dealkylated with PhI(OAc)$_2$ and I_2 with ultrasound to give a primary sulfonamide.[1629] Similar results are obtained with H_5IO_6 and a chromium catalyst.[1630] *tert*-Butyl sulfonamides are cleaved to the primary sulfonamide with BCl_3.[1631]

[1619]Still, I.W.J.; Ablenas, F.J. *J. Org. Chem.* ***1983***, *48*, 1617.

[1620]See, for example, Sakaki, K.; Oae, S. *Chem. Lett.* ***1977***, 1003; Still, I.W.J.; Hasan, S.K.; Turnbull, K. *Can. J. Chem.* ***1978***, *56*, 1423; Denis, J.N.; Krief, A. *J. Chem. Soc. Chem. Commun.* ***1980***, 544.

[1621]Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* ***1998***, *39*, 4679.

[1622]Lemaire-Audoire, S.; Savignac, M.; Dupuis, C.; Genêt, J.-P. *Bull. Soc. Chim. Fr.* ***1995***, *132*, 1157; Lemaire-Audoire, S.; Savignac, M.; Genêt, J.-P.; Bernard, J.-M. *Tetrahedron Lett.* ***1995***, *36*, 1267.

[1623]Talukdar, S.; Banerji, A. *Synth. Commun.* ***1995***, *25*, 813.

[1624]Murahashi, S.-I.; Naota, T.; Miyaguchi, N.; Nakato, T. *Tetrahedron Lett.* ***1992***, *33*, 6991.

[1625]Bull, S.D.; Davies, S.G.; Mulvaney, A.W.; Prasad, R.S.; Smith, A.D.; Fenton, G. *Chem. Commun.* ***2000***, 337.

[1626]Haddach, A.A.; Kelleman, A.; Deaton-Rewoliwski, M.V. *Tetrahedron Lett.* ***2002***, *43*, 399.

[1627]Routier, S.; Saugé, L.; Ayerbe, N,; Couderet, G.; Mérour, J.-Y. *Tetrahedron Lett.* ***2002***, *43*, 589. For a related debenzylation see Meng, G.; He, Y.-P.; Chen, F.-E. *Synth. Commun.* ***2003***, *33*, 2593.

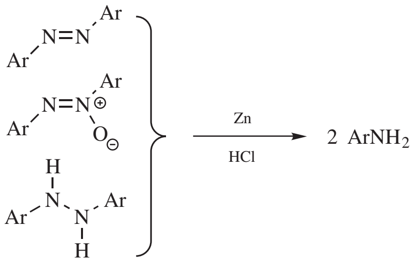
[1628]Baker, S.R.; Parsons, A.F.; Wilson, M. *Tetrahedron Lett.* ***1998***, *39*, 331.

[1629]Katohgi, M.; Yokoyama, M.; Togo, H. *Synlett* ***2000***, 1055; Katohgi, M.; Togo, H. *Tetrahedron* ***2001***, *57*, 7481.

[1630]Xu, L.; Zhang, S.; Trudell, M.L. *Synlett* ***2004***, 1901.

[1631]Wan, Y.; Wu, X.; Kannan, M.A.; Alterman, M. *Tetrahedron Lett.* ***2003***, *44*, 4523.

19-74 Reduction of Azo, Azoxy, and Hydrazo Compounds to Amines

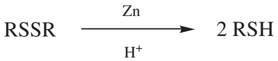


Azo, azoxy, and hydrazo compounds can all be reduced to amines.[1632] Metals (notably zinc) and acids, and $Na_2S_2O_4$, are frequently used as reducing agents, and Bu_3SnH with a copper catalyst has been used.[1633] Borane reduces azo compounds to amines, although it does not reduce nitro compounds.[1634] $LiAlH_4$ does not reduce hydrazo compounds or azo compounds, although with the latter, hydrazo compounds are sometimes isolated. With azoxy compounds, $LiAlH_4$ gives only azo compounds (**19-68**). Noted that azo compounds are reduced to the hydrazine by reaction with hydrazine hydrate in ethanol.[1635]

OS **I**, 49; **II**, 35, 39; **III**, 360; **X**, 327. Also see, OS **II**, 290.

19-75 Reduction of Disulfides to Thiols

S-Hydrogen-uncoupling



Disulfides can be reduced to thiols by mild reducing agents,[1636] such as zinc and dilute acid, In and NH_4Cl/EtOH,[1637] or Ph_3P and H_2O.[1638] The reaction can also be accomplished simply by heating with alkali.[1639] Among other reagents used have been $LiAlH_4$, $NaBH_4/ZrCl_4$,[1640] Mg/MeOH,[1641] KBH(*O*—*i*Pr)$_3$,[1642] and hydrazine or substituted hydrazines.[1643]

[1632]For a review, see Newbold, B.T., in Patai, S. *The Chemistry of Hydrazo, Azo, and azoxy Groups*, pt. 2, Wiley, NY, ***1975***, pp. 629–637.

[1633]Tan, Z.; Qu, Z.; Chen, B.; Wang, J. *Tetrahedron* ***2000***, *56*, 7457.

[1634]Brown, H.C.; Subba Rao, B.C. *J. Am. Chem. Soc.* ***1960***, *82*, 681.

[1635]Zhang, C.-R.; Wang, Y.-L. *Synth. Commun.* ***2003***, *33*, 4205.

[1636]For a review, see Wardell, J.L., in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, ***1974***, pp. 220–229.

[1637]Reddy, G.V.S.; Rao, G.V.; Iyengar, D.S. *Synth. Commun.* ***2000***, *30*, 859.

[1638]Overman, L.E.; Smoot, J.; Overman, J.D. *Synthesis* ***1974***, 59.

[1639]For discussions, see Danehy, J.P.; Hunter, W.E. *J. Org. Chem.* ***1967***, *32*, 2047.

[1640]Chary, K.P.; Rajaram, S.; Iyengar, D.S. *Synth. Commun.* ***2000***, *30*, 3905.

[1641]Sridhar, M.; Vadivel, S.K.; Bhalerao, U.T. *Synth. Commun.* ***1997***, *27*, 1347.

[1642]Brown, H.C.; Nazer, B.; Cha, J.S. *Synthesis* ***1984***, 498.

[1643]Maiti, S.N.; Spevak, P.; Singh, M.P.; Micetich, R.G.; Narender Reddy, A.V. *Synth. Commun.* ***1988***, *18*, 575.

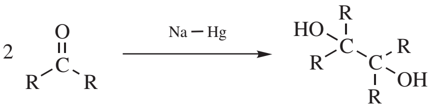
Aryl diselenides are similarly cleaved to selenols (ArSeH) with Cp_2TiH followed by $Ph_2I^+X^-$.[1644]

OS **II**, 580. Also see, OS **IV**, 295.

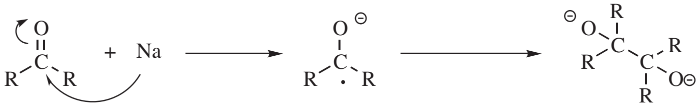
E. Reductive Coupling

19-76 Bimolecular Reduction of Aldehydes and Ketones to 1,2-Diols and Imines to 1,2-Diamines

2/*O*-Hydrogen-coupling and 2/*N*-Hydrogen-coupling



1,2-Diols (pinacols) can be synthesized by reduction of aldehydes and ketones with active metals, such as sodium, magnesium, or aluminum.[1645] Aromatic ketones give better yields than aliphatic ones. The use of a Mg—MgI_2 mixture has been called the *Gomberg–Bachmann pinacol synthesis*.[1646] As with a number of other reactions involving sodium, there is a direct electron transfer here, converting the ketone or aldehyde to a ketyl, which dimerizes.



Other reagents have been used,[1647] including Sm,[1648] Yb,[1649] Yb-Me_3SiCl,[1650] $InCl_3$ catalyst with Mg,[1651] Al/$TiCl_3$,[1652] $VOCl_3$ catalyst with Me_3SiCl,[1653]

[1644]Huang, X.; Wu, L.-L.; Xu, X.-H. *Synth. Commun.* ***2001***, *31*, 1871.

[1645]For efficient methods, see Schreibmann, A.A.P. *Tetrahedron Lett.* ***1970***, 4271; Fürstner, A.; Csuk, R.; Rohrer, C.; Weidmann, H. *J. Chem. Soc. Perkin Trans. 1* ***1988***, 1729. For an ultrasound promoted reaction with aluminum, see Bian, Y.-J.; Liu, S.-M.; Li, J.-T.; Li, T.-S. *Synth. Commun.* ***2002***, *32*, 1169.

[1646]For an ultrasound promoted reaction, see Li, J.-T.; Bian, Y.-J.; Zang, H.-J.; Li, T.-s. *Synth. Commun.* ***2002***, *32*, 547.

[1647]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp.1111–1114.

[1648]Ghatak, A.; Becker, F.F.; Banik, B.K. *Tetrahedron Lett.* ***2000***, *41*, 3793; Talukdar, S.; Fang, J.-M. *J. Org. Chem.* ***2001***, *66*, 330; Yu, M.; Zhang, Y. *Org. Prep. Proceed. Int.* ***2001***, *33*, 187; Hélion, F.; Lannou, M.-I.; Namy, J.-L. *Tetrahedron Lett.* ***2003***, *44*, 5507.

[1649]Hou, Z.; Takamine, K.; Fujiwara, Y.; Taniguchi, K. *Chem. Lett.* ***1987***, 2061.

[1650]Ogawa, A.; Takeuchi, H.; Hirao, T. *Tetrahedron Lett.* ***1999***, *40*, 7113.

[1651]Mori, K.; Ohtaka, S.; Uemura, S. *Bull. Chem. Soc. Jpn.* ***2001***, *74*, 1497.

[1652]Li, J.-T.; Lin, Z.-P.; Qi, N.; Li, T.-S. *Synth. Commun.* ***2004***, *34*, 4339.

[1653]Hirao, T.; Hatano, B.; Imamoto, Y.; Ogawa, A. *J. Org. Chem.* ***1999***, *64*, 7665.

activated Mn,[1654] In with ultrasound,[1655] Zn,[1656] and a reagent prepared from $TiCl_4$[1657] and Mg amalgam[1658] (a low-valent titanium reagent;[1659] see **19-76**). A mixture of $TiCl_4$[1660] or $TiCl_2$[1661] and Zn can also be used. Unsymmetrical coupling between two different aldehydes has been achieved by the use of a vanadium complex,[1662] while $TiCl_3$ in aqueous solution has been used to couple two different ketones.[1663] Two aldehydes have also been coupled using magnesium in water.[1664] Coupling leads to a mixture of syn- and anti-diols. "Syn-selective" reagents are Cp_2TiCl_2/Mn,[1665] $TiCl_4/Bu_4I$,[1666] TiI_4,[1667] $TiBr_2$+Cu,[1668] and $NbCl_3$.[1669] With SmI_2,[1670] coupling in the presence of a primary alkyl iodide leads to acyl addition using an excess of HMPA, but pinacol coupling with an excess of LiBr.[1671] "Anti-selective" coupling reactions are also known: Ti–salen,[1672] Mg with a $NiCl_2$ catalyst,[1673] Sm/$SmCl_3$,[1674] and $TiCl_4(thf)_2$ with a chiral Schiff base.[1675] Aryl

[1654]Rieke, R.D.; Kim, S.-H. *J. Org. Chem.* ***1998***, *63*, 5235. For a reaction using Mn, Me_3SiCl and a cerium catalyst, see Groth, U.; Jeske, M. *Synlett* ***2001***, 129.

[1655]Lim, H.J.; Keum, G.; Kang, S.B.; Chung, B.Y.; Kim, Y. *Tetrahedron Lett.* ***1998***, *39*, 4367.

[1656]Hekmatshoar, R.; Yavari, I.; Beheshtiha, Y.S.; Heravi, M.M. *Monat. Chem.* ***2001***, *132*, 689.

[1657]For a discussion of pinacol versus reduction with this reagent, and mechanistic considerations, see Clerici, A.; Pastori, N.; Porta, O. *Tetrahaedron Lett.* ***2004***, *45*, 1825.

[1658]Corey, E.J.; Danheiser, R.L.; Chandrasekaran, S. *J. Org. Chem.* ***1976***, *41*, 260; Pons, J.; Zahra, J.; Santelli, M. *Tetrahedron Lett.* ***1981***, *22*, 3965. For some other titanium-containing reagents, see Clerici, A.; Porta, O. *J. Org. Chem.* ***1985***, *50*, 76; Handa, Y.; Inanaga, J. *Tetrahedron Lett.* ***1987***, *28*, 5717. For a review of such coupling with Ti and V halides, see Lai, Y. *Org. Prep. Proced. Int.* ***1980***, *12*, 363.

[1659]For a discussion of the mechanism, see Hashimoto, Y.; Mizuno, U.; Matsuoka, H.; Miyahara, T.; Takakura, M.; Yoshimoto, M.; Oshima, K.; Utimoto, K.; Matsubara, S. *J. Am. Chem Soc.* ***2001***, *123*, 1503.

[1660]Li, T.; Cui, W.; Liu, J.; Zhao, J.; Wang, Z. *Chem. Commun.* ***2000***, 139.

[1661]Kagayama, A.; Igarashi, K.; Mukaiyama, T. *Can. J. Chem.* ***2000***, *78*, 657.

[1662]Freudenberger, J.H.; Konradi, A.W.; Pedersen, S.F. *J. Am. Chem. Soc.* ***1989***, *111*, 8014.

[1663]Clerici, A.; Porta, O. *J. Org. Chem.* ***1982***, *47*, 2852; *Tetrahedron* ***1983***, *39*, 1239. For some other unsymmetrical couplings, see Hou, Z.; Takamine, K.; Aoki, O.; Shiraishi, H.; Fujiwara, Y.; Taniguchi, H. *J. Chem. Soc. Chem. Commun.* ***1988***, 668; Delair, P.; Luche, J. *J. Chem. Soc. Chem. Commun.* ***1989***, 398; Takahara, P.M.; Freudenberger, J.H.; Konradi, A.W.; Pedersen, S.F. *Tetrahedron Lett.* ***1989***, *30*, 7177.

[1664]Zhang, W.-C.; Li, C.-J. *J. Chem. Soc. Perkin Trans. 1* ***1998***, 3131.

[1665]Gansäuer, A.; Bauer, D. *Eur. J. Org. Chem.* ***1998***, 2673. Also see, Barden, M.C.; Schwartz, J. *J. Am. Chem. Soc.* ***1996***, *118*, 5484; Gansäuer, A. *Chem. Commun.* ***1997***, 457; Gansäuer, A. *Synlett* ***1997***, 363; Clerici, A.; Clerici, L.; Porta, O. *Tetrahedron Lett.* ***1996***, *37*, 3035.

[1666]Tsuritani, T.; Ito, S.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2000**, 65, 5066.

[1667]Hayakawa, R.; Shimizu, M. *Chem. Lett.* ***2000***, 724. For a syn-selective coupling with conjugated aldehydes, see Shimizu, M.; Goto, H.; Hayakawa, R. *Org. Lett.* ***2002***, *4*, 4097.

[1668]Mukaiyama, T.; Yoshimura, N.; Igarashi, K.; Kagayama, A. *Tetrahedron* ***2001***, *57*, 2499.

[1669]Szymoniak, J.; Besançon, J.; Moïse, C. *Tetrahedron* ***1994***, *50*, 2841.

[1670]Namy, J.L.; Souppe, J.; Kagan, H.B. *Tetrahedron Lett.* ***1983***, *24*, 765; Nomura, R.; Matsuno, T.; Endo, T. *J. Am. Chem. Soc*, ***1996***, *118*, 11666; Honda, T.; Katoh, M. *Chem. Commun.* ***1997***, 369; Shiue, J.-S.; Lin, C.-C.; Fang, J.-M. *Tetrahedron Lett.* ***1993***, *34*, 335. Also see Yamashita, M.; Okuyama, K.; Kawasaki, I.; Ohta, S. *Tetrahedron Lett.* ***1996***, *37*, 7755.

[1671]Miller, R.S.; Sealy, J.M.; Shabangi, M.; Kuhlman, M.L.; Fuchs, J.R.; Flowers II, R.A. *J. Am. Chem. Soc.* ***2000***, *122*, 7718.

[1672]Chatterjee, A.; Bennur, T.H.; Joshi, N.N. *J. Org. Chem.* ***2003***, *68*, 5668.

[1673]Shi, L.; Fan, C.-A.; Tu, Y.-Q.; Wang, M.; Zhang, F.-M. *Tetrahedron* ***2004***, *60*, 2851.

[1674]Matsukawa, S.; Hinakubo, Y. *Org. Lett.* ***2003***, *5*, 1221.

[1675]Li, Y.-G.; Tian, Q.-S.; Zhao, J.; Feng, Y.; Li, M.-J.; You, T.-P. *Tetrahedron Asymmetry* ***2004***, *15*, 1707.

aldehydes are coupled to give the bis-trimethylsilyl ether using Mn, Me_3SiCl, and Cp_2TiCl_2.[1676]

A crossed-pinacol coupling was reported using Et_2Zn and with a BINOL catalyst gave good enantioselectivity.[1677] A combination of Mg and Me_3SiCl was also used to a crossed-pinacol.[1678]

Intramolecular pinacol coupling reactions are known, giving cyclic 1,2-diols.[1679] Dialdehydes have been cyclized by reaction with $TiCl_3$ to give cyclic 1,2-diols in good yield.[1680] A radical-induced coupling of an α,ω-dialdehyde led to *cis*-1,2-cyclopentanediol when treated with Bu_3SnH and AIBN.[1681] or induced photochemically.[1682]

Chiral additives with pinacol couplings lead to formation of a diol with moderate to good enantioselectivity.[1683] Chiral metal complexes in conjunction with a metal leads to diol formation with good enantioselectivity.[1684]

A variation of the pinacol coupling treats acyl nitriles with indium metal and ultrasound to give a 1,2-diketone.[1685] Another variation couples acetals to give 1,2-diols.[1686]

The dimerization of ketones to 1,2-diols can also be accomplished photochemically; indeed, this is one of the most common photochemical reactions.[1687] The substrate, which is usually a diaryl or aryl alkyl ketone (though a few aromatic aldehydes and dialkyl ketones have been dimerized), is irradiated with UV light in the presence of a hydrogen donor, such as isopropyl alcohol, toluene, or an amine.[1688]

[1676]Dunlap, M.S.; Nicholas, K.M. *Synth. Commun.* ***1999***, *29*, 1097.

[1677]Kumagai, N.; Matsunaga, S.; Kinoshita, T.; Harada, S.; Okada, S.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* ***2003***, *125*, 2169.

[1678]Maekawa, H.; Yamamoto, Y.; Shimada, H.; Yonemura, K.; Nishiguchi, I. *Tetraheron Lett.* ***2004***, *45*, 3869.

[1679]**With a Ti catalyst + Zn**: Yamamoto, Y.; Hattori, R.; Itoh, K. *Chem. Commun.* ***1999***, 825; Yamamoto, Y.; Hattori, R.; Miwa, T.; Nakagai, Y.-I.; Kubota, T.; Yamamoto, C.; Okamoto, Y.; Itoh, K. *J. Org. Chem.* ***2001***, *66*, 3865. **With SmI_2/*t*-BuOH**: Handa, S.; Kachala, M.S.; Lowe, S.R. *Tetrahedron Lett.* ***2004***, *45*, 253.

[1680]McMurry, J.E.; Rico, J.G. *Tetrahedron Lett.* ***1989***, *30*, 1169. For the stereochemistry of this coupling, see McMurry, J.E.; Siemers, N.O. *Tetrahedron Lett.* ***1993***, *34*, 7891. For other cyclization reactions of dialdehydes and ketoaldehydes, see Molander, G.A.; Kenny, C. *J. Am. Chem. Soc.* ***1989***, *111*, 8236; Raw, A.S.; Pedersen, S.F. *J. Org. Chem.* ***1991***, *56*, 830; Chiara, J.L.; Cabri, W.; Hanessian, S. *Tetrahedron Lett.* ***1991***, *32*, 1125.

[1681]Hays, D.S.; Fu, G.C. *J. Org. Chem.* ***1998***, *63*, 6375.

[1682]Hays, D.S.; Fu. G.C. *J. Am. Chem. Soc.* ***1995***, *117*, 7283.

[1683]Enders, D.; Ullrich, E.C. *Tetrahedron Asymmetry* ***2000***, *11*, 3861.

[1684]See Bensari, A.; Renaud, J.-L.; Riant, O. *Org. Lett.* ***2001***, *3*, 3863; Takenaka, N.; Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* ***2004***, *126*, 13198.

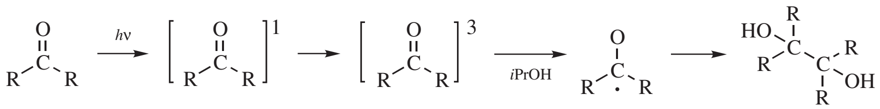
[1685]Baek, H.S. et al. *Tetrahedron Lett.* ***2000***, *41*, 8097.

[1686]Studer, A.; Curran, D.P. *Synlett* ***1996***, 255.

[1687]For reviews, see Schönberg, A. *Preparative Organic Photochemistry*, Springer, NY, ***1968***, pp. 203–217; Neckers, D.C. *Mechanistic Organic Photochemistry*, Reinhold, NY, ***1967***, pp. 163–177; Calvert, J.G.; Pitts Jr., J.N. *Photochemistry*, Wiley, NY, ***1966***, pp. 532–536; Turro, N.J. *Modern Molecular Photochemistry*, W.A. Benjamin, NY, ***1978***, pp. 363–385; Kan, R.O. *Organic Photochemistry*, McGraw-Hill, NY, ***1966***, pp. 222–229.

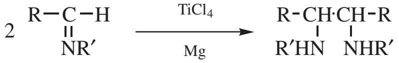
[1688]For a review of amines as hydrogen donors in this reaction, see Cohen, S.G.; Parola, A.; Parsons, Jr., G.H. *Chem. Rev.* ***1973***, *73*, 141.

In the case of benzophenone, irradiated in the presence of 2-propanol, the ketone molecule initially undergoes $n \rightarrow \pi^*$ excitation, and the singlet species thus formed crosses to the T_1 state with a very high efficiency.



Singlet Triplet **51**

The T_1 species abstracts hydrogen from the alcohol (p. 347), and then dimerizes. The *i*PrO• radical, which is formed by this process, donates H• to another molecule of ground-state benzophenone, producing acetone and another molecule of **51**. This mechanism[1689] predicts that the quantum yield for the disappearance of benzophenone should be 2, since each quantum of light results in the conversion of 2 equivalents of benzophenone to **51**. Under favorable experimental conditions, the observed quantum yield does approach 2. Benzophenone abstracts hydrogen with very high efficiency. Other aromatic ketones are dimerized with lower quantum yields, and some (e.g., *p*-aminobenzophenone, *o*-methylacetophenone) cannot be dimerized at all in 2-propanol (although *p*-aminobenzophenone, e.g., can be dimerized in cyclohexane[1690]). The reaction has also been carried out electrochemically.[1691]



A coupling reaction similar to pinacol coupling has been used with imines, which dimerize to give 1,2-diamines. A number of reagents have been used, including treatment with $TiCl_4$—Mg,[1692] In/aq. EtOH,[1693] Zn/aq. NaOH,[1694] Cp_2VCl_2/Zn/

[1689]For some of the evidence for this mechanism, see Pitts, Jr., J.N.; Letsinger, R.L.; Taylor, R.; Patterson, S.; Recktenwald, G.; Martin, R.B. *J. Am. Chem. Soc.* ***1959***, *81*, 1068; Moore, W.M.; Hammond, G.S.; Foss, R.P. *J. Am. Chem. Soc.* ***1961***, *83*, 2789; Huyser, E.S.; Neckers, D.C. *J. Am. Chem. Soc.* ***1963***, *85*, 3641.

[1690]Porter, G.; Suppan, P. *Proc. Chem. Soc.* ***1964***, 191.

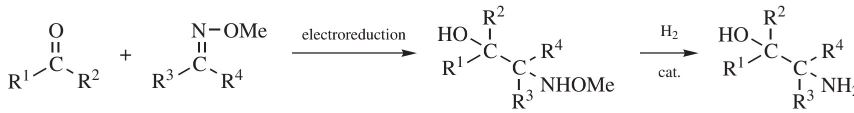
[1691]Elinson, M.N.; Feducovich, S.K.; Dorofeev, A.S.; Vereshchagin, A.N.; Nikishin, G.I. *Tetrahedron* ***2000***, *56*, 9999. For reviews, see Fry, A.J. *Synthetic Organic Electrochemistry*, 2nd ed., Wiley, NY, ***1989***, pp. 174–180; Shono, T. *Electroorganic Chemistry as a New Tool in Organic Synthesis*, Springer, NY, ***1984***, pp. 137–140; Baizer, M.M.; Petrovich, J.P. *Prog. Phys. Org. Chem.* ***1970***, *7*, 189. For a review of electrolytic reductive coupling, see Baizer, M.M. in Baizer, M.M.; Lund, H. *Organic Electrochemistry*, Marcel Dekker, NY, ***1983***, pp. 639–689.

[1692]Betschart, C.; Schmidt, B.; Seebach, D. *Helv. Chim. Acta* ***1988***, *71*, 1999; Mangeney, P.; Tejero, T.; Alexakis, A.; Grosjean, F.; Normant, J. *Synthesis* ***1988***, 255; Alexakis, A.; Aujard, I.; Mangeney, P. *Synlett* ***1998***, 873, 875.

[1693]Kalyanam, N.; Rao, G.V. *Tetrahedron Lett.* ***1993***, *34*, 1647.

[1694]Dutta, M.P.; Baruah, B.; Boruah, A.; Prajapati, D.; Sandu, J.S. *Synlett* ***1998***, 857.

$PhMe_2SiCl$,[1695] Et_2AlCl,[1696] SmI_2,[1697] and (for silylated imines) $NbCl_4(thf)_2$.[1698] When electroreduction was used, it was even possible to obtain cross-products, by coupling a ketone to an *O*-methyl oxime:[1699] *O*-Methyl oxime ethers are coupled to give 1,2-diamines using Zn and $TiCl_4$.[1700] Aldehydes are converted to 1,2-diamines by treatment with TMS_2NH, NaH, and Li metal in 5 *M* $LiClO_4$ in ether, with sonication.[1701] Hemiaminals are coupled to give 1,2-diamines with TiI_4/Zn.[1702] Amides are converted to 1,2-diamines with Cp_2TiF_2 and $PhMeSiH_2$.[1703] Samarium(II) iodide was used to couple iminium salts, giving the 1,2-diamine.[1704] Ketones can be treated with Yb, and then an imine to give amino alcohols.[1705]

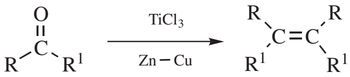


The *N*-methoxyamino alcohol could then be reduced to the amino alcohol.[1699] A photochemical coupling has also been reported.[1706] A variation of this reaction treats an imine with Yb in THF/HMPA and then an aldehyde to give a 1,2-bis(imine).[1707]

OS **I**, 459; **II**, 71; **X**, 312; **81**, 26.

19-77 Bimolecular Reduction of Aldehydes or Ketones to Alkenes

De-oxygen-coupling



Aldehydes and ketones, both aromatic and aliphatic (including cyclic ketones), can be converted in high yields to dimeric alkenes by treatment low valent titanium,[1708] initially generated with $TiCl_3$ and a zinc–copper couple.[1709] This is called

[1695]Hatano, B.; Ogawa, A.; Hirao, T. *J. Org. Chem.* ***1998***, *63*, 9421.

[1696]This reaction proceeds with *N*-ethylation. See Shimizu, M.;Niwa, Y. *Tetrahedron Lett.* ***2001***, *42*, 2829.

[1697]Enholm, E.J.; Forbes, D.C.; Holub, D.P. *Synth. Commun.* ***1990***, *20*, 981; Imamoto, T.; Nishimura, S. *Chem. Lett.* ***1990***, 1141; Zhong, Y.-W.; Izumi, K.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* ***2004***, *6*, 4747.

[1698]Roskamp, E.J.; Pedersen, S.F. *J. Am. Chem. Soc.* ***1987***, *109*, 3152.

[1699]Shono, T.; Kise, N.; Fujimoto, T. *Tetrahedron Lett.* ***1991***, *32*, 525.

[1700]Kise, N.; Ueda, N. *Tetrahedron Lett.* ***2001***, *42*, 2365.

[1701]Mojtahedi, M.M.; Saidi, M.R.; Shirzi, J.S.; Bolourtchian, M. *Synth. Commun.* ***2001***, *31*, 3587.

[1702]Yoshimura, N.; Mukaiyama, T. *Chem. Lett.* ***2001***, 1334.

[1703]Selvakumar, K.; Harrod, J.F. *Angew. Chem. Int. Ed.* ***2001***, *40*, 2129.

[1704]Kim, M.; Knettle, B.W.; Dahlén, A.; Hilmersson, G.; Flowers III, R.A. *Tetrahedron* ***2003***, *59*, 10397.

[1705]Su, W.; Yang, B. *Synth. Commun.* ***2003***, *33*, 2613.

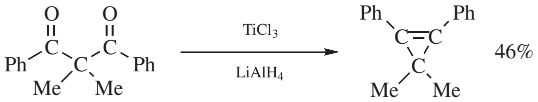
[1706]Campos, P.J.; Arranz, J.; Rodríguez, M.A. *Tetrahedron* ***2000***, *56*, 7285; Ortega, M.; Rodríguez, M.A.; Campos, P.J. *Tetrahedron* ***2004***, *60*, 6475.

[1707]Jin, W.; Makioka, Y.; Kitamura, T.; Fujiwara, Y. *J. Org. Chem.* ***2001***, *66*, 514.

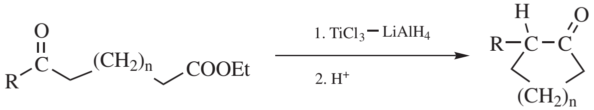
[1708]For a highly active reagent see Rele, S.; Chattopadhyay, S.; Nayak, S.K. *Tetrahedron Lett.* ***2001***, *42*, 9093.

[1709]McMurry, J.E.; Fleming, M.P.; Kees, K.L.; Krepski, L.R. *J. Org. Chem.* ***1978***, *43*, 3255. For an optimized procedure, see McMurry, J.E.; Lectka, T.; Rico, J.G. *J. Org. Chem.* ***1989***, *54*, 3748.

the *McMurry reaction*.[1710] The reagent produced in this way is called a *low-valent titanium reagent*, and the reaction has also been accomplished[1711] with low-valent titanium reagents prepared in other ways, for example, from Mg and a $TiCl_3$–THF complex,[1712] from $TiCl_4$ and Zn or Mg,[1713] from $TiCl_3$ and $LiAlH_4$,[1714] from $TiCl_3$ and lamellar potassium graphite,[1715] from $TiCl_3$ and K or Li,[1716] as well as with $ZnMe_3SiCl$[1717] and with certain compounds prepared from WCl_6 and either lithium, lithium iodide, $LiAlH_4$, or an alkyllithium[1718] (see **17-18**). The reaction has been used to convert dialdehydes and diketones to cycloalkenes.[1719] Rings of 3–16 and 22 members have been closed in this way, for example,[1720]



The same reaction on a keto ester gives a cycloalkanone.[1721]



[1710]For reviews, see McMurry, J.E. *Chem. Rev.* ***1989***, *89*, 1513; *Acc. Chem. Res.* ***1983***, *16*, 405; Lenoir, D. *Synthesis* ***1989***, 883; Betschart, C.; Seebach, D. *Chimia* ***1989***, *43*, 39; Lai, Y. *Org. Prep. Proceed. Int.* ***1980***, *12*, 363. For related reviews, see Kahn, B.E.; Rieke, R.D. *Chem. Rev.* ***1988***, *88*, 733; Pons, J.; Santelli, M. *Tetrahedron* ***1988***, *44*, 4295. For the stereochemistry associated with this reaction, see Andersson, P.G. *Tetrahedron Lett.* ***1994***, *35*, 2609.

[1711]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 305–308.

[1712]Tyrlik, S.; Wolochowicz, I. *Bull. Soc. Chim. Fr.* ***1973***, 2147.

[1713]Mukaiyama, T.; Sato, T.; Hanna, J. *Chem. Lett.* ***1973***, 1041; Lenoir, D. *Synthesis* ***1977***, 553; Lenoir, D.; Burghard, H. *J. Chem. Res. (S)* ***1980***, 396; Carroll, A.R.; Taylor, W.C. *Aust. J. Chem.* ***1990***, *43*, 1439.

[1714]McMurry, J.E.; Fleming, M.P. *J. Am. Chem. Soc.* ***1974***, *96*, 4708; Dams, R.; Malinowski, M.; Geise, H.J. *Bull. Soc. Chim. Belg.* ***1982***, *91*, 149, 311; Bottino, F.A.; Finocchiaro, P.; Libertini, E.; Reale, A.; Recca, A. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 77. This reagent has been reported to give capricious results; see McMurry, J.E.; Fleming, M.P. *J. Org. Chem.* ***1976***, *41*, 896.

[1715]Fürstner, A.; Weidmann, H. *Synthesis* ***1987***, 1071.

[1716]McMurry, J.E.; Fleming, M.P. *J. Org. Chem.* ***1976***, *41*, 896; Richardson, W.H. *Synth. Commun.* ***1981***, *11*, 895; Rele, S.; Talukdar, S.; Banerji, A.; Chattopadhyay, S. *J. Org. Chem.* ***2001***, *66*, 2990.

[1717]Banerjee, A.K.; Sulbaran de Carrasco, M.C.; Frydrych-Houge, C.S.V.; Motherwell, W.B. *J. Chem. Soc. Chem. Commun.* ***1986***, 1803.

[1718]Sharpless, K.B.; Umbreit, M.A.; Nieh, M.T.; Flood, T.C. *J. Am. Chem. Soc.* ***1972***, *94*, 6538; Fujiwara, Y.; Ishikawa, R.; Akiyama, F.; Teranishi, S. *J. Org. Chem.* ***1978***, *43*, 2477; Dams, R.; Malinowski, M.; Geise, H.J. *Bull. Soc. Chim. Belg.* ***1982***, *19*, 149, 311. See also, Petit, M.; Mortreux, A.; Petit, F. *J. Chem. Soc. Chem. Commun.* ***1984***, 341; Chisholm, M.H.; Klang, J.A. *J. Am. Chem. Soc.* ***1989***, *111*, 2324.

[1719]Baumstark, A.L.; Bechara, E.J.H.; Semigran, M.J. *Tetrahedron Lett.* ***1976***, 3265; McMurry, J.E.; Fleming, M.P.; Kees, K.L.; Krepski, L.R. *J. Org. Chem.* ***1978***, *43*, 3255.

[1720]Baumstark, A.L.; McCloskey, C.J.; Witt, K.E. *J. Org. Chem.* ***1978***, *43*, 3609.

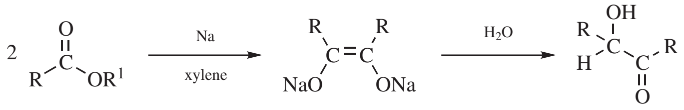
[1721]McMurry, J.E.; Miller, D.D. *J. Am. Chem. Soc.* ***1983***, *105*, 1660.

Indoles have been prepared form ortho-acyl amides with Ti(powder) and Me_3SiCl[1722] or with $TiCl_3$—C_8K.[1723] Benzofurans have been prepared by a closely related reaction.[1724]

Unsymmetrical alkenes can be prepared from a mixture of two ketones in a cross-coupling reaction, if one is in excess.[1725] An aldehyde and a ketone were cross-coupled using $Yb(OTf)_3$, for example.[1726] The mechanism consists of initial coupling of two radical species to give a 1,2-dioxygen compound (a titanium pinacolate), which is then deoxygenated.[1727]

OS **VII**, 1.

19-78 Acyloin Ester Condensation



52

When carboxylic esters are heated with sodium in refluxing ether or benzene, a bimolecular reduction takes place, and the product is an α-hydroxy ketone (called an acyloin).[1728] The reaction, called the *acyloin ester condensation*,[1729] is quite successful when R is alkyl. Acyloins with long chains have been prepared in this way, for example, R = $C_{17}H_{35}$, but for high-molecular-weight esters, toluene or xylene is used as the solvent. Modifications to this procedure have been reported, including an ultrasound-promoted acyloin condensation in ether,[1730] which imporvied the yields of four-, five-, and six-membered rings, and Olah's procedure, which was also done in ether.[1731]

The acyloin condensation has been used with great success, in boiling xylene, to prepare cyclic acyloins from diesters.[1732] The yields are 50–60% for the preparation

[1722]Fürstner, A.; Hupperts, A. *J. Am. Chem. Soc.* ***1995***, *117*, 4468.

[1723]Fürstner, A.; Hupperts, A.; Ptock, A.; Janssen, E. *J. Org. Chem.* ***1994***, *59*, 5215.

[1724]Fürstner, A.; Jumbam, D.N. *Tetrahedron* ***1992***, *48*, 5991.

[1725]McMurry, J.E.; Fleming, M.P.; Kees, K.L.; Krepski, L.R. *J. Org. Chem.* ***1978***, *43*, 3255; Nishida, S.; Kataoka, F. *J. Org. Chem.* ***1978***, *43*, 1612; Coe, P.L.; Scriven, C.E. *J. Chem. Soc. Perkin Trans. 1* ***1986***, 475; Chisholm, M.H.; Klang, J.A. *J. Am. Chem. Soc.* ***1989***, *111*, 2324.

[1726]Curini, M.; Epifano, F.; Maltese, F., Marcotullio, M.C. *Eur. J. Org. Chem.* ***2003***, 1631.

[1727]McMurry, J.E.; Fleming, M.P.; Kees, K.L.; Krepski, L.R. *J. Org. Chem.* ***1978***, *43*, 3255; Dams, R.; Malinowski, M.; Westdorp, I.; Geise, H.Y. *J. Org. Chem.* ***1982***, *47*, 248. See Villiers, C.; Ephritikhine, M. *Angew. Chem,. Int. Ed.* ***1997***, *36*, 2380; Stahl, M.; Pindur, U.; Frenking, G. *Angew. Chem. Int. Ed.* ***1997***, *36*, 2234.

[1728]For a review, see Bloomfield, J.J.; Owsley, D.C.; Nelke, J.M. *Org. React.* ***1976***, *23*, 259. For a list of reactions, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1313–1315.

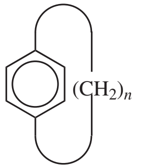
[1729]For reaction with tethered diesters, see Daynard, T.S.; Eby, P.S.; Hutchinson, J.H. *Can. J. Chem.* ***1993***, *71*, 1022.

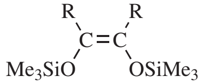
[1730]Fadel, A.; Canet, J,-L.; Salaün, J. *Synlett* ***1990***, 89.

[1731]Olah, G.A.; Wu, A. *Synthesis* ***1991***, 1177.

[1732]For a review of cyclizations by means of the acyloin condensation, see Finley, K.T. *Chem. Rev.* ***1964***, *64*, 573.

of 6- and 7-membered rings, 30–40% for 8- and 19-membered, and 60–95% for rings of 10–20 members. Even larger rings have been closed in this manner. This is one of the best ways of closing rings of 10 members or more. The reaction has been used to close 4-membered rings,[1733] although this is generally not successful. The presence of double or triple bonds does not interfere.[1734] Even a benzene ring can be present, and many paracyclophane derivatives (**53**) with $n = 9$ or more have been synthesized in this manner.[1735]

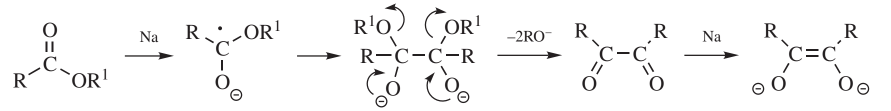




53 **54**

Yields in the acyloin condensation can be improved by running the reaction in the presence of chlorotrimethylsilane Me_3SiCl, in which case the dianion **52** is converted to the bis silyl enol ether **54**, which can be isolated and subsequently hydrolyzed to the acyloin with aqueous acid.[1736] This is now the standard way to conduct the acyloin condensation. Among other things, this method inhibits the Dieckmann condensation[1737] (**16-85**), which otherwise competes with the acyloin condensation when a five-, six-, or seven-membered ring can be closed (note that the ring formed by a Dieckmann condensation is always one carbon atom smaller than that formed by an acyloin condensation of the same substrate). The Me_3SiCl method is especially good for the closing of four-membered rings.[1738]

The mechanism is not known with certainty, but it is usually presumed that the diketone RCOCOR is an intermediate,[1739] since small amounts of it are usually isolated as side products, and when it is resistant to reduction (e.g., *t*-Bu—COCO—*t*-Bu), it is the major product. A possible sequence (analogous to that of **19-76**) is



[1733]Cope, A.C.; Herrick, E.C. *J. Am. Chem. Soc.* ***1950***, *72*, 983; Bloomfield, J.J.; Irelan, J.R.S. *J. Org. Chem.* ***1966***, *31*, 2017.

[1734]Cram, D.J.; Gaston, L.K. *J. Am. Chem. Soc.* ***1960***, *82*, 6386.

[1735]For a review, see Cram, D.J. *Rec. Chem. Prog.*, ***1959***, *20*, 71.

[1736]Schräpler, U.; Rühlmann, K. *Chem. Ber.* ***1964***, *97*, 1383. For a review of the Me_3SiCl method, see Rühlmann, K. *Synthesis* ***1971***, 236.

[1737]Bloomfield, J.J. *Tetrahedron Lett.* ***1968***, 591.

[1738]Gream, G.E.; Worthley, S. *Tetrahedron Lett.* ***1968***, 3319; Wynberg, H.; Reiffers, S.; Strating, J. *Recl. Trav. Chim. Pays-Bas* ***1970***, *89*, 982; Bloomfield, J.J.; Martin, R.A.; Nelke, J.M. *J. Chem. Soc. Chem. Commun.* ***1972***, 96.

[1739]Another mechanism, involving addition of the ketyl to another molecule of ester (rather than a dimerization of two ketyl radicals), in which a diketone is not an intermediate, has been proposed: Bloomfield, J.J.; Owsley, D.C.; Ainsworth, C.; Robertson, R.E. *J. Org. Chem.* ***1975***, *40*, 393.

A large surface area for the sodium is usually required for good results in this coupling, consistent with a surface reaction. In order to account for the ready formation of large rings, which means that the two ends of the chain must approach each other even although this is conformationally unfavorable for long chains, it may be postulated that the two ends become attached to nearby sites on the surface[1740] of the sodium. Although high dilution techniques are not always necessary, effective stirring (high speed stirrer at 2000–2500 rpm) is usually required to generate "sodium sand". Highly pure sodium gives poorer results, and a small percentage of potassium is important. Up to 50% potassium (1:1 Na/K)[1741] has been used in acyloin condensations.

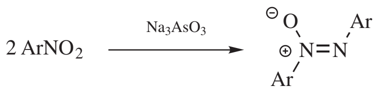
In a related reaction, aromatic carboxylic acids were condensed to α-diketones (2ArCOOH → ArCOCOAr) on treatment with excess Li in dry THF in the presence of ultrasound.[1742]

The acyloin condensation was used in an ingenious manner to prepare the first reported catenane (see p. 131).[1743] This synthesis of a catenane produced only a small yield and relied on chance for threading the molecules before ring closure.

OS **II**, 114; **IV**, 840; **VI**, 167.

19-79 Reduction of Nitro to Azoxy Compounds

Nitro-azoxy reductive transformation



Azoxy compounds can be obtained from nitro compounds with certain reducing agents, notably sodium arsenite, sodium ethoxide, NaTeH,[1744] $NaBH_4$–PhTe-TePh,[1745] and glucose. The most probable mechanism with most reagents is that one molecule of nitro compound is reduced to a nitroso compound and another to a hydroxylamine (**19-46**), and these combine (**12-51**). The combination step is rapid compared to the reduction process.[1746] Nitroso compounds can be reduced to azoxy compounds with triethyl phosphite or triphenylphosphine[1747] or with an alkaline aqueous solution of an alcohol.[1748]

OS **II**, 57.

[1740]For the preparation of high-surface sodium, see Makosza, M.; Grela, K. *Synlett* ***1997***, 267.

[1741]Vogel, I.A. *A Textbook of Practical Organic Chemistry*, 3rd ed, Wiley, NY, ***1966***, p. 856.

[1742]Karaman, R.; Fry, J.L. *Tetrahedron Lett.* ***1989***, *30*, 6267.

[1743]For reviews of the synthesis of catenanes, see Sauvage, J. *Acc. Chem. Res.* ***1990***, *23*, 319; *Nouv. J. Chim.* ***1985***, *9*, 299; Dietrich-Buchecker, C.O.; Sauvage, J. *Chem. Rev.* ***1987***, *87*, 795.

[1744]Osuka, A.; Shimizu, H.; Suzuki, H. *Chem. Lett.* ***1983***, 1373.

[1745]Ohe, K.; Uemura, S.; Sugita, N.; Masuda, H.; Taga, T. *J. Org. Chem.* ***1989***, *54*, 4169.

[1746]Ogata, Y.; Mibae, J. *J. Org. Chem.* ***1962***, *27*, 2048.

[1747]Bunyan, P.J.; Cadogan, J.I.G. *J. Chem. Soc.* ***1963***, 42.

[1748]See, for example, Hutton, J.; Waters, W.A. *J. Chem. Soc. B* ***1968***, 191. See also, Porta, F.; Pizzotti, M.; Cenini, S. *J. Organomet. Chem.* ***1981***, *222*, 279.

19-80 Reduction of Nitro to Azo Compounds

N-De-bisoxygen-coupling

$$2\,ArNO_2 \xrightarrow{LiAlH_4} Ar{-}N{=}N{-}Ar$$

Nitro compounds can be reduced to azo compounds with various reducing agents, of which $LiAlH_4$ and zinc and alkali are the most common. A combination of triethylammonium formate and lead in methanol is also effective.[1749] With many of these reagents, slight differences in conditions can lead either to the azo or azoxy (**19-79**) compound. By analogy to **19-79**, this reaction may be looked on as a combination of ArN=O and $ArNH_2$ (**13-24**). However, when the reducing agent was $NaBH_4$,[1750] it was shown that azoxy compounds were intermediates. Nitroso compounds can be reduced to azo compounds with $LiAlH_4$. Dicarborane, with a catalytic amount of acetic acid, reduces aromatic nitro compounds to the amine.[1751]

Nitro compounds can be further reduced to hydrazo compounds with zinc and sodium hydroxide, with hydrazine hydrate and Raney nickel,[1752] or with $LiAlH_4$ mixed with a metal chloride such as $TiCl_4$ or VCl_3.[1753] The reduction has also been accomplished electrochemically.

OS **III**, 103.

F. Reactions in Which an Organic Substrate is Both Oxidized and Reduced

Some reactions that belong in this category have been considered in earlier chapters. Among these are the Tollens' condensation (**16-43**), the benzil–benzilic acid rearrangement (**18-6**), and the Wallach rearrangement (**18-43**).

19-81 The Cannizzaro Reaction

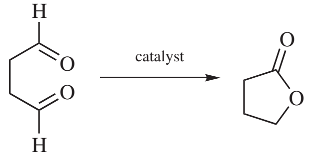
Cannizzaro Aldehyde Disproportionation

$$2\,ArCHO \xrightarrow{NaOH} ArCH_2OH + ArCOO^-$$

Aromatic aldehydes, and aliphatic ones with no a hydrogen, give the *Cannizzaro reaction* when treated with NaOH or other strong bases.[1754] In this reaction, one molecule of aldehyde oxidizes another to the acid and is itself reduced to the primary alcohol. Aldehydes with an α-hydrogen do not give the reaction, because when these compounds are treated with base the aldol reaction (**16-34**) is much faster.[1755] Normally, the best yield of acid or alcohol is 50% each, but this can

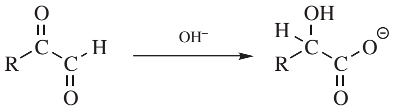
[1749]Srinavasa, G.R.; Abiraj, K.; Gowda, D.C. *Tetrahedron Lett.* ***2003***, *44*, 5835.
[1750]Hutchins, R.O.; Lamson, D.W.; Rufa, L.; Milewski, C.; Maryanoff, B. *J. Org. Chem.* ***1971***, *36*, 803.
[1751]Bae, J.W.; Cho, Y.J.; Lee, S.H.; Yoon, C.M. *Tetrahedron Lett.* ***2000***, *41*, 175.
[1752]Furst, A.; Moore, R.E. *J. Am. Chem. Soc.* ***1957***, *79*, 5492.
[1753]Olah, G.A. *J. Am. Chem. Soc.* ***1959***, *81*, 3165.
[1754]For a review, see Geissman, T.A. *Org. React.* ***1944***, *2*, 94.
[1755]An exception is cyclopropanecarboxaldehyde: van der Maeden, F.P.B.; Steinberg, H.; de Boer, T.J. *Recl. Trav. Chim. Pays-Bas* ***1972***, *91*, 221.

be altered in certain cases. Solvent-free reactions are known.[1756] On the other hand, high yields of alcohol can be obtained from almost any aldehyde by running the reaction in the presence of formaldehyde.[1757] In this case, the formaldehyde reduces the aldehyde to alcohol and is itself oxidized to formic acid. In such a case, where the oxidant aldehyde differs from the reductant aldehyde, the reaction is called the *crossed-Cannizzaro reaction*.[1758] The Tollens' condensation (**16-43**) includes a crossed-Cannizzaro reaction as its last step. A Cannizzaro reaction run on 1,4-dialdehydes (note that α hydrogens are present here) with a rhodium catalyst gives ring closure, for example,[1759]



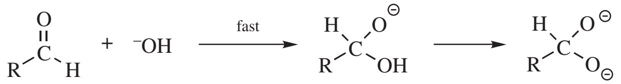
The product is the lactone derived from the hydroxy acid that would result from a normal Cannizzaro reaction. Chiral additives have been used, but with bis(oxazolidine) derivatives the reaction proceeded with poor enantioselectivity.[1760]

α-Keto aldehydes give internal Cannizzaro reactions:



This product is also obtained on alkaline hydrolysis of compounds of the formula $RCOCHX_2$. Similar reactions have been performed on α-keto acetals[1761] and γ-keto aldehydes.

The mechanism[1762] of the Cannizzaro reaction[1763] involves a hydride shift (an example of mechanism type 2, p. 1706). First ^{-}OH adds to the C=O to give **55**, which may lose a proton in the basic solution to give the diion **56**.



55 **56**

[1756]Yoshizawa, K.; Toyota, S.; Toda, F. *Tetrahedron Lett.* ***2001***, *42*, 7983.

[1757]For an example using microwave irradiation, see Thakuria, J.A.; Baruah, M.; Sandhu, J.S. *Chem. Lett.* ***1999***, 995.

[1758]For a microwave assisted crossed Cannizzaro reaction, see Varma, R.S.; Naicker, K.P.; Liesen, P.J. *Tetrahedron Lett.* ***1998***, *39*, 8437. See Reddy, B.V.S.; Srinivas, R.; Yadav, J.S.; Ramalingam, T. *Synth. Commun.* ***2002***, *32*, 219.

[1759]Bergens, S.H.; Fairlie, D.P.; Bosnich, B. *Organometallics* ***1990***, *9*, 566.

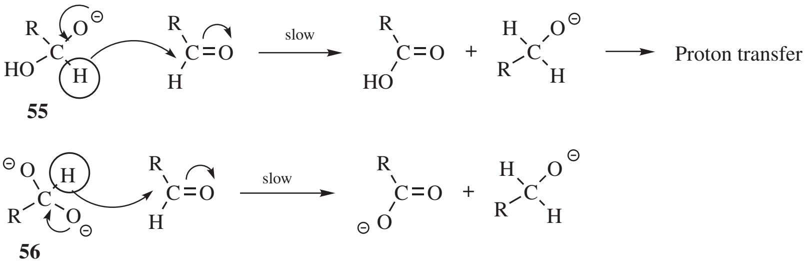
[1760]Russell, A.E.; Miller, S.P.; Morken, J.P. *J. Org. Chem.* ***2000***, *65*, 8381.

[1761]Thompson, J.E. *J. Org. Chem.* ***1967***, *32*, 3947.

[1762]For evidence that an SET pathway may intervene, see Ashby, E.C.; Coleman III, D.T.; Gamasa, M.P. *J. Org. Chem.* ***1987***, *52*, 4079; Fuentes, A.; Marinas, J.M.; Sinisterra, J.V. *Tetrahedron Lett.* ***1987***, *28*, 2947.

[1763]See for example, Swain, C.G.; Powell, A.L.; Sheppard, W.A.; Morgan, C.R. *J. Am. Chem. Soc.* ***1979***, *101*, 3576; Watt, C.I.F. *Adv. Phys. Org. Chem.* ***1988***, *24*, 57, 81–86.

The strong electron-donating character of O^- greatly facilitates the ability of the aldehydic hydrogen to leave with its electron pair. Of course, this effect is even stronger in **56**. Hydride is transferred to another molecule of aldehyde. The hydride can come from **55** or **56**:



If the hydride ion comes from **55**, the final step is a rapid proton transfer. In the other case, the acid salt is formed directly, and the alkoxide ion acquires a proton from the solvent. Evidence for this mechanism is (*1*) The reaction can be first order in base and second order in substrate (thus going through **55**) or, at higher base concentrations, second order in each (going through **56**); and (*2*) when the reaction was run in D_2O, the recovered alcohol contained no α deuterium,[1764] indicating that the hydrogen comes from another equivalent of aldehyde and not from the medium.[1765]

OS **I**, 276; **II**, 590; **III**, 538; **IV**, 110.

19-82 The Tishchenko Reaction

Tishchenko aldehyde-ester disproportionation

$$2\,ArCHO \xrightarrow{Al(OEt)_3} ROOCH_2R$$

When aldehydes, with or without a hydrogen, are treated with aluminum ethoxide, one molecule is oxidized and another reduced, as in **19-81**, but here they are found as the ester. The process is called the *Tishchenko reaction*. Crossed-Tishchenko reactions are also possible. With more strongly basic alkoxides, such as magnesium or sodium alkoxides, aldehydes with an a hydrogen give the aldol reaction. Treatment of a dialdehyde, such as phthalic dicarboxaldehyde (phthalaldehyde) with CaO, leads to a lactone.[1766] Like **19-81**, this reaction has a mechanism that

[1764]Fredenhagen, H.; Bonhoeffer, K.F. *Z. Phys. Chem. Abt. A* ***1938***, *181*, 379; Hauser, C.R.; Hamrick, Jr., P.J.; Stewart, A.T. *J. Org. Chem.* ***1956***, *21*, 260.

[1765]When the reaction was run at 100°C, in MeOH–H_2O, isotopic exchange was observed (the product from PhCDO had lost some of its deuterium): Swain, C.G.; Powell, A.L.; Lynch, T.J.; Alpha, S.R.; Dunlap, R.P. *J. Am. Chem. Soc.* ***1979***, *101*, 3584. Side reactions were postulated to account for the loss of deuterium. See, however, Chung, S. *J. Chem. Soc. Chem. Commun.* ***1982***, 480.

[1766]Seki, T.; Hattori, H. *Chem. Commun.* ***2001***, 2510.

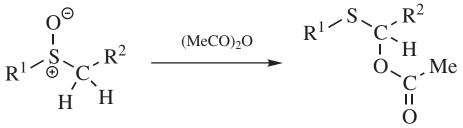
involves hydride transfer.[1767] The Tishchenko reaction can also be catalyzed[1768] by ruthenium complexes,[1769] by Cp_2ZrH_2[1770] or BuTi(*Oi*Pr)$_4$Li,[1771] and, for aromatic aldehydes, by disodium tetracarbonylferrate, $Na_2Fe(CO)_4$.[1772] Both CaO (noted above) and SrO have been used as catalysts.[1773] A bisphenylenedioxy bis-(aluminum) catalyst has been used to convert aliphatic aldehydes to the corresponding ester.[1774] The bis Al(*Oi*Pr)$_2$ derivative of catechol has also been used as a catalyst.[1775]

A Tishchenko–aldol-transfer reaction was reported using β-hydroxy ketones and an aldehydes with an $AlMe_3$ catalyst, giving a mono acyl diol.[1776]

OS **I**, 104.

19-83 The Pummerer Rearrangement[1777]

Pummerer methyl sulfoxide rearrangement



When sulfoxides bearing an a hydrogen are treated with acetic anhydride, the product is an α-acetoxy sulfide. This is one example of *the Pummerer rearrangement*, in which the sulfur is reduced while an adjacent carbon is oxidized.[1778] The product is readily hydrolyzed (**10-6**) to the aldehyde R_2CHO.[1779] Besides acetic anhydride, other anhydrides and acyl halides give similar products. Inorganic acids, such as HCl, also give the reaction, and $RSOCH_2R'$ can be converted to RSCHClR′ in this way. Sulfoxides can also be converted to α-halo sulfides[1780] by other

[1767]See, for example, Zakharkin, L.I.; Sorokina, L.P. *J. Gen. Chem. USSR* ***1967***, *37*, 525; Saegusa, T.; Ueshima, T.; Kitagawa, S. *Bull. Chem. Soc. Jpn.* ***1969***, *42*, 248; Ogata, Y.; Kishi, I. *Tetrahedron* ***1969***, *25*, 929.

[1768]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1653–1655.

[1769]Ito, T.; Horino, H.; Koshiro,Y.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* ***1982***, *55*, 504.

[1770]DeMico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* ***1997***, *62*, 6974.

[1771]Mahrwald, R.; Costisella, B. *Synthesis* ***1996***, 1087.

[1772]Yamashita, A.; Watanabe, Y.; Mitsudo, T.; Takegami, Y. *Bull. Chem. Soc. Jpn.* ***1976***, *49*, 3597.

[1773]Seki, T.; Akutsu, K.; Hattori, H. *Chem. Commun.* ***2001***, 1000.

[1774]Ooi, T.; Miura, T.; Takaya, K.; Maruoka, K. *Tetrahedron Lett.* ***1999***, *40*, 7695.

[1775]Simpura, I.; Nevalainen, V. *Tetrahedron* ***2001***, *57*, 9867.

[1776]Mascarenhas, C.M.; Duffey, M.O.; Liu, S.-Y.; Morken, J.P. *Org. Lett.* ***1999***, *1*, 1427; Simpura, I.; Nevalainen, V. *Tetrahedron Lett.* ***2001***, *42*, 3905; Cavazzini, M.; Pozzi, G.; Quici, S.; Maillard, D.; Sinou, D. *Chem. Commun.* ***2001***, 1220.

[1777]For a review of the Pummerer reaction for the synthesis of heterocyclic compounds, see Bur, S.K.; Padwa, A. *Chem. Rev.* ***2004***, *104*, 2401.

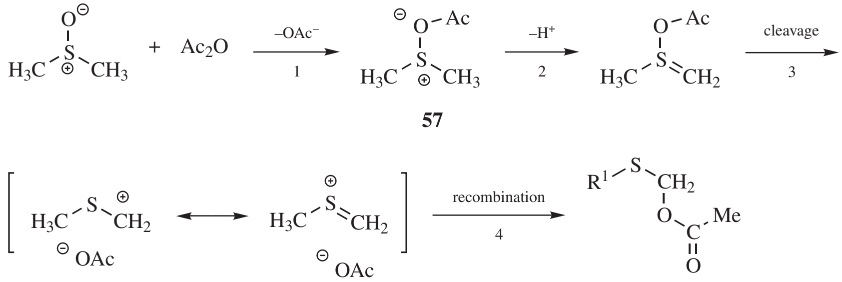
[1778]For reviews, see De Lucchi, O.; Miotti, U.; Modena, G. *Org. React.* ***1991***, *40*, 157; Warren, S. *Chem. Ind. (London)* ***1980***, 824; Oae, S.; Numata, T. *Isot. Org. Chem.* ***1980***, *5*, 45; Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***, pp. 154–162.

[1779]See, for example, Sugihara, H.; Tanikaga, R.; Kaji, A. *Synthesis* ***1978***, 881.

[1780]For a review of α-chloro sulfides, see Dilworth, B.M.; McKervey, M.A. *Tetrahedron* ***1986***, *42*, 3731.

reagents, including sulfuryl chloride, NBS, and NCS. Enantioselective Pummerer rearrangements are known.[1781] Uncatalyzed thermal rearrangements are also known.[1782]

The following four-step mechanism has been proposed for the reaction between acetic anhydride and DMSO:[1783]



57

For DMSO and acetic anhydride, step 4 is intermolecular, as shown by ^{18}O isotopic labeling studies.[1784] With other substrates, however, step 4 can be inter- or intramolecular, depending on the structure of the sulfoxide.[1785] Depending on the substrate and reagent, any of the first three steps can be rate determining. In the case of Me_2SO treated with $(F_3CCO)_2O$, the intermediate corresponding to **57**[1786] could be isolated at low temperature, and on warming gave the expected product.[1787] There is much other evidence for this mechanism.[1788]

A sila-Pummerer rearrangement has been reported.[1789]

19-84 The Willgerodt Reaction

Willgerodt carbonyl transformation

$$ArCOCH_3 \xrightarrow{(NH_4)_2S_x} ArCH_2CONH_2 + ArCH_2COO^- NH_4^+$$

[1781]Kita, Y.; Shibata, N.; Kawano, N.; Tohjo, T.; Fujimori, C.; Matsumoto, K. *Tetrahedron Lett.* ***1995***, *36*, 115; Kita, Y.; Shibata, N.; Fukui, S.; Fujita, S. *Tetrahedron Lett.* ***1994***, *35*, 9733; Kita, Y.; Shibata, N.; Kawano, N.; Fukui, S.; Fujimori, C. *Tetrahedron Lett.* ***1994***, *35*, 3575; Kita, Y.; Shibata, N.; Yoshida, N. *Tetrahedron Lett.* ***1993***, *34*, 4063.

[1782]Wladislaw, B.; Marzorati, L.; Biaggio, F.C. *J. Org. Chem.* ***1993***, *58*, 6132.

[1783]See, for example, Numata, T.; Itoh, O.; Yoshimura, T.; Oae, S. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 257; Kita, Y.; Shibata, N.; Yoshida, N.; Fukui, S.; Fujimori, C. *Tetrahedron Lett.* ***1994***, *35*, 2569.

[1784]Oae, S.; Kitao, T.; Kawamura, S.; Kitaoka, Y. *Tetrahedron* ***1963***, *19*, 817.

[1785]See, for example, Itoh, O.; Numata, T.; Yoshimura, T.; Oae, S. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 266; Oae, S.; Itoh, O.; Numata, T.; Yoshimura, T. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 270.

[1786]For a review of sulfur-containing cations, see Marino, J.P. *Top. Sulfur Chem.* ***1976***, *1*, 1.

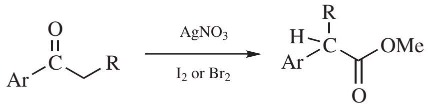
[1787]Sharma, A.K.; Swern, D. *Tetrahedron Lett.* ***1974***, 1503.

[1788]See Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***, pp. 154–156; Oae, S.; Numata, T. *Isot. Org. Chem.* ***1980***, *5*, 45, 48; Wolfe, S.; Kazmaier, P.M. *Can. J. Chem.* ***1979***, *57*, 2388, 2397; Russell, G.A.; Mikol, G.J. *Mech. Mol. Migr.* ***1968***, *1*, 157.

[1789]Kirpichenko, S.V.; Suslova, E.N.; Albanov, A.I.; Shainyan, B.A. *Tetrahedron Lett.* ***1999***, *40*, 185.

In the *Willgerodt reaction*, a straight- or branched-chain aryl alkyl ketone is converted to the amide and/or the ammonium salt of the acid by heating with ammonium polysulfide.[1790] The carbonyl group of the product is always at the end of the chain. Thus $ArCOCH_2CH_3$ gives the amide and the salt of $ArCH_2CH_2COOH$, and $ArCOCH_2CH_2CH_3$ gives derivatives of $ArCH_2CH_2CH_2COOH$. However, yields sharply decrease with increasing length of chain. The reaction has also been carried out on vinylic and ethynyl aromatic compounds and on aliphatic ketones, but yields are usually lower in these cases. Unlike the Pummerer rearrangement (**19-83**), which involves transposition of an oxygen from S to C, the Willgerodt reaction involves oxygen migration *and* oxidation of the organic species. The use of sulfur and a dry primary or secondary amine (or ammonia), as the reagent is called the *Kindler modification* of the Willgerodt reaction.[1791] The product in this case is $Ar(CH_2)_nCSNR_2$,[1792] which can be hydrolyzed to the acid. Particularly good results are obtained with morpholine as the amine. For volatile amines, the HCl salts can be used instead, with NaOAc in DMF at 100°C.[1793] Dimethylamine has also been used in the form of dimethylammonium dimethylcarbamate, $Me_2NCOO^- Me_2NH_2^+$.[1794] The Kindler modification has also been applied to aliphatic ketones.[1795] Thioamides have been prepared from ketones in a base-catalyzed reaction.[1796]

Alkyl aryl ketones can be converted to arylacetic acid derivatives in an entirely different manner. The reaction consists of treatment of the substrate with silver nitrate and I_2 or Br_2,[1797] or with thallium nitrate, MeOH, and trimethyl orthoformate adsorbed on Montmorillonite K10, an acidic clay.[1798]



The mechanism of the Willgerodt reaction is not completely known, but some conceivable mechanisms can be excluded. Thus, one might suppose that the alkyl group becomes completely detached from the ring, and then attacks it with its other

[1790]For a review, see Brown, E.V. *Synthesis* ***1975***, 358.

[1791]For a review, see Mayer, R., in Oae, S. *The Organic Chemistry of Sulfur*, Plenum, NY, ***1977***, pp. 58–63. For a study of the optimum conditions for this reaction, see Lundstedt, T.; Carlson, R.; Shabana, R. *Acta Chem. Scand. Ser. B* ***1987***, *41*, 157, and other papers in this series. See also, Carlson, R.; Lundstedt, T. *Acta Chem. Scand. Ser. B* ***1987***, *41*, 164; Kanyonyo, M.R.; Gozzo, A.; Lambert, D.M.; Lesieur, D.; Poupaert, J.H. *Bull. Soc. Chim. Belg.* ***1997***, *106*, 39.

[1792]The reaction between ketones, sulfur, and ammonia can also lead to heterocyclic compounds. For a review, see Asinger, F.; Offermanns, H. *Angew. Chem. Int. Ed.* ***1967***, *6*, 907.

[1793]Amupitan, J.O. *Synthesis* ***1983***, 730.

[1794]Schroth, W.; Andersch, J. *Synthesis* ***1989***, 202.

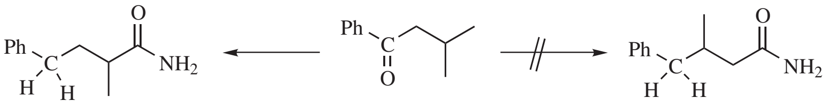
[1795]See Dutron-Woitrin, F.; Merényi, R.; Viehe, H.G. *Synthesis* ***1985***, 77.

[1796]For a review, see Poupaert, J.H.; Bouinidane, K.; Renard, M.; Lambert, D.; Isa, M. *Org. Prep. Proceed. Int.* ***2001***, *33*, 335.

[1797]Higgins, S.D.; Thomas, C.B. *J. Chem. Soc. Perkin Trans. 1* ***1982***, 235. See also, Higgins, S.D.; Thomas, C.B. *J. Chem. Soc. Perkin Trans. 1* ***1983***, 1483.

[1798]Taylor, E.C.; Conley, R.A.; Katz, A.H.; McKillop, A. *J. Org. Chem.* ***1984***, *49*, 3840.

end. However, this possibility is ruled out by experiments such as the following: When isobutyl phenyl ketone (**58**) is subjected to the Willgerodt reaction, the product is **59**, not **60**, which would arise if the end carbon of the ketone became bonded to the ring in the product:[1799]



59 **58** **60**

This also excludes a cyclic-intermediate mechanism similar to that of the Claisen rearrangement (**18-33**). Another important fact is that the reaction is successful for singly branched side chains, such as **58**, but not for doubly branched side chains, as in $PhCOCMe_3$.[1799] Still another piece of evidence is that compounds oxygenated along the chain give the same products; thus $PhCOCH_2CH_3$, $PhCH_2COMe$, and $PhCH_2CH_2CHO$ all give $PhCH_2CH_2CONH_2$.[1800] All these facts point to a mechanism consisting of consecutive oxidations and reductions along the chain, although just what form these take is not certain. Initial reduction to the hydrocarbon can be ruled out, since alkylbenzenes do not give the reaction. In certain cases, imines[1801] or enamines[1802] have been isolated from primary and secondary amines, respectively, and these have been shown to give the normal products, leading to the suggestion that they may be reaction intermediates.

[1799]King, J.A.; McMillan, F.H. *J. Am. Chem. Soc.* ***1946***, *68*, 632.

[1800]For an example of this type of behavior, see Asinger, F.; Saus, A.; Mayer, A. *Monatsh. Chem.* ***1967***, *98*, 825.

[1801]Asinger, F.; Halcour, K. *Monatsh. Chem.* ***1964***, *95*, 24. See also, Nakova, E.P.; Tolkachev, O.N.; Evstigneeva, R.P. *J. Org. Chem. USSR* ***1975***, *11*, 2660.

[1802]Mayer, R., in Janssen, M.J. *Organosulfur Chemistry*, Wiley, NY, ***1967***, pp. 229–232.

APPENDIX A

The Literature of Organic Chemistry

All discoveries in the laboratory must be published somewhere if the information is to be made generally available. A new experimental result that is not published might as well not have been obtained, insofar as it benefits the entire chemical world. The total body of chemical knowledge (called *the literature*) is located on the combined shelves of all the chemical libraries in the world. Anyone who wishes to learn whether the answer to any chemical question is known, and, if so, what the answer is, has only to turn to the contents of these shelves. Indeed, the very expressions "is known," "has been done," and so on, really mean "has been published." To the uninitiated, the contents of the shelves may appear formidably large, but fortunately the process of extracting information from the literature of organic chemistry is usually not difficult. In this appendix, we will examine the literature of organic chemistry.[1] It is quite clear that The Literature can be divided into two broad categories: primary sources and secondary sources. A *primary source* publishes the original results of laboratory investigations. Books, indexes, and other publications that cover material that has previously been published in primary sources are called *secondary sources*. It is because of the excellence of the secondary sources in organic chemistry (especially *Chemical Abstracts*™, SciFinder®, and Beilstein) that literature searching is comparatively not difficult. The two chief kinds of primary source are journals and patents. There are several types of secondary source.

[1]For books on the chemical literature, see Wolman, Y. *Chemical Information*, 2nd ed., Wiley, NY, ***1988***; Maizell, R.E. *How to Find Chemical Information,* 2nd ed., Wiley, NY, ***1987***; Mellon, M.G. *Chemical Publications,* 5th ed., McGraw-Hill, NY, ***1982***; Skolnik, H. *The Literature Matrix of Chemistry*, Wiley, NY, ***1982***; Antony, A. *Guide to Basic Information Sources in Chemistry,* Jeffrey Norton Publishers, NY, ***1979***; Bottle, R.T. *Use of the Chemical Literature,* Butterworth, London, ***1979***; Woodburn, H.M. *Using the Chemical Literature,* Marcel Dekker, NY, ***1974***. For a three-part article on the literature of organic chemistry, see Hancock, J.E.H. *J. Chem. Educ.* ***1968***, *45*, 193–199, 260–266, 336–339.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Sixth Edition, by Michael B. Smith and Jerry March
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PRIMARY SOURCES

Journals

For well over 100 years, nearly all new work in organic chemistry (except for that disclosed in patents) has been published in journals. There are thousands of journals that publish chemical papers, in many countries and in many languages. Some print papers covering all fields of science; some are restricted to chemistry; some to organic chemistry; and some are still more specialized. Fortunately for the sanity of organic chemists, the vast majority of important papers in "pure" organic chemistry (as opposed to "applied") are published in relatively few journals, perhaps 50 or fewer. The concept of "pure" organic chemistry is not as useful because organic chemistry is now important in many areas. Literature that is important to an organic chemist is found in journals and patents that focus on bioorganic, organometallic, materials science, separation science, medicinal chemistry, pharmaceutical sciences, and medicine to name a few. The reader is therefore cautioned that the journals listed in this section have organic chemistry as their primary focus, but are by no means the only sources of information concerning organic chemistry. The literature is vast and many journals are published weekly, and some semimonthly.

In addition to ordinary papers, there are two other types of publications in which original work is reported: *notes* and *communic*ation*s*. A note is a brief paper, often without a summary (nearly all papers are published with summaries or abstracts prepared by the author). Otherwise, a note is similar to a paper.[2] Communications (also called *letters*) are also brief and usually without summaries (though some journals now publish summaries along with their communications, a welcome trend). However, communications differ from notes and papers in three respects:

1. They are brief, not because the work is of small scope, but because they are condensed. Usually, they include only the most important experimental details or none at all.
2. They are often of immediate significance. Journals that publish communications make every effort to have them appear as soon as possible after they are received. Some papers and notes are of great importance, and some are of lesser importance, but all communications are supposed to be of high importance. With modern computer technology, communications can often be published in a matter of weeks, and the on-line version (e.g., the American Chemical Society ASAP papers) can be found before the print version appears.
3. Communications are preliminary reports, and the material in them may be republished as papers at a later date, in contrast to the material in papers and notes, which cannot be republished.

[2]In some journals, notes are called "short communications," an unfortunate practice, because they are not communications as that term is defined in the text.

Although papers (we use the term in its general sense, to cover notes and communications also) are published in many languages, the English-speaking chemist is in a fairly fortunate position. At present well over half of the important papers in organic chemistry are published in English. Not only are American, British, and British Commonwealth journals published almost entirely in English, but so are many others around the world. There are predominantly English-language journals published in Japan, Italy, Czechoslovakia, Sweden, The Netherlands, Israel, and other countries. In a reorganization, six prominent European journals (*Chemische Berichte, Liebigs Annalen der Chemie*, *Bulletin de la Société Chimique de France, Bulletin des Sociétés Chimique Belges, Recueil des Travaux Chimiques des Pays-Bas, and Gazzetta Chimica Italiana*) have been discontinued. In their place is the *European Journal of Organic Chemistry, published in English.* Most of the articles published in other languages have summaries printed in English also. For many years, the second most important language (in terms of the number of organic chemical papers published) was Russian, and most of these papers are available in English translation, although in most cases, 6 months to 1 year later. With the political changes in Russia, however, many of these Journals have been modified or discontinued. Important papers have been published in German and French for >200 years, and these are generally not available in translation, so that the organic chemist should have at least a reading knowledge of these languages. In recent years, however, fewer papers in French or German have appeared without an English translation, such as in the journal *Angewandte Chemie*, which in 1962 became available in English under the title *Angewandte Chemie International Edition in English*. Of course, a reading knowledge of French and German (especially German) is critical for the older literature. Before ~1920, more than one-half of the important chemical papers were in these languages. It must be realized that the original literature is never obsolete. With the rise of China in the scientific community, journals are published in Chinese, and there are journals published in Japanese. Work by Chinese and Japanese scientists regularly appears in English-language journals, however. Secondary sources become superseded or outdated, but nineteenth century journals are found in most chemical libraries and are still consulted. Table A.1 presents a list of the more important current journals that publish original papers[3] and communications in organic chemistry. Some of them also publish review articles, book reviews, and other material. Changes in journal title have not been infrequent; footnotes to the table indicate some of the more important, but some of the other journals listed have also undergone title changes. In 1999, the *Journal of Organic Chemistry* stopped publishing communications, and these are now published in a new journal, *Organic Letters*.

The primary literature has grown so much in recent years that attempts have been made to reduce the volume. One such attempt is the *Journal of Chemical Research*, begun in 1977. The main section of this journal, called the "Synopses," publishes synopses, which are essentially long abstracts, with references. The full texts of most of the papers are published only in microfiche and miniprint versions.

[3]In Table A.1, notes are counted as papers.

TABLE A.1. A List of the More Important *Current* Journals That Currently Publish Original Papers in Organic Chemistry[a]

No.	Name	Papers or Communications	Issues per Year
1	**Angew**andte **Chem**ie (1887)[4]	C[5]	12
2	**Angew**andte **Chem**ie **Int**ernational **Edition** (1962)[6]	C[7]	48
3	**Aust**ralian **J**ournal of **Chem**istry (1948)	P	12
4	**Bioorg**anic **Chem**istry (1971)	P[5]	4
5	**Bioorg**anic & **Med**icinal **Chem**istry **Lett**ers (1991)	C	12
6	**Bull**etin of the **Chem**ical **Soc**iety of **Japan** (1926)	P	12
7	**Can**adian **J**ournal of **Chem**istry (1929)	P,C	12
8	**Carbohydr**ate **Res**earch (1965)	P,C	22
9	**Chem**istry, a **Eur**opean **Journal** (1995)	P	24
10	**Chem**istry, an **Asian J**ournal (2006)	New	New
11	**Chem**istry and **Ind**ustry **(London)** (1923)	C	24
12	**Chem**istry **Lett**ers (1972)	C	12
13	**Chimia** (1947)	C[5]	12
14	**Collect**ion of **Czech**oslovak **Chem**ical **Commun**ications (1929)	P	12
15	**Dokl**ady **Chem**istry (1922)[4]	C	12
17	**Eur**opean **J**ournal of **Org**anic **Chem**istry (1998)	P	12
18	**Helv**etica **Chim**ica **Acta** (1918)	P	8
19	**Heteroat**om **Chem**istry (1990)	P	6
20	**Heterocycles** (1973)	C[5]	12
21	**Ind**ian **J**ournal of **Chem**istry (Section **B**)	P	12
22	**Int**ernational **J**ournal of chemical **Kinet**ics (1969)	P	12
23	**Isr**ael **J**ournal of **Chem**istry (1963)	P[8]	4
23	**J**ournal of the **Am**erican **Chem**ical **Soc**iety (1879)	P,C	52
25	**J**ournal of **Carbohydr**ate **Chem**istry (1981)	P,C	6
26	**J**ournal of **Chem**ical **Res**earch, **Synop**ses (1977)	P	12
27	**Chem**ical **Commun**ications (1965)	C	24
28	**J**ournal of **Comb**inatorial **Chem**istry (2000)	P,C	6
29	**J**ournal of **Comput**ational **Chem**istry (1979)	P	16
30	**J**ournal of **Fluorine Chem**istry (1971)	P,C	12

[4]These journals are available in English translation.
[5]These journals also publish review articles regularly.
[6]These journals are available in English translation.
[7]These journals also publish review articles regularly.
[8]Each issue of this journal is devoted to a specific topic.

TABLE A.1 (*Continued*)

No.	Name	Papers or Communications	Issues per Year
31	**J**ournal of **Heterocycl**ic **Chem**istry (1964)	P,C	12
32	**J**ournal of the **Indian** Chemical **Soc**iety (1924)	P	12
33	**J**ournal of **Lipid Res**earch (1959)	P	12
34	**J**ournal of **Med**icinal **Chem**istry (1958)	P,C	12
35	**J**ournal of **Mol**ecular **Struct**ure (1967)	P,C	16
36	**J**ournal of **Organomet**allic **Chem**istry (1963)	P,C	48
37	**J**ournal of **Org**anic **Chem**istry (1936)	P,C	26
38	**J**ournal of **Photochem**istry and **Photobiol**ogy, **A**: Chemistry (1972)	P	12
39	**J**ournal of **Phys**ical **Org**anic **Chem**istry (1988)	P	12
40	Journal of Polymer Science Part A (1962)	P	24
41	**J**ournal für **Prakt**ische **Chem**ie (1834)	P	6
42	**Macromolecules** (1968)	P,C	26
43	**Liebigs Ann**alen der **Chem**ie (1832)	P	12
44	**Mendeleev Commun**ications (1991)	C	8
45	**Monatsh**efte für **Chem**ie (1870)	P	12
46	**New J**ournal of **Chem**istry (1977)[9]	P	11
47	**Organometallics** (1982)	P,C	12
48	**Org**anic and **Biomol**ecular **Chem**istry (2003)	P	24
49	**Org**anic **Lett**ers (1999)	C	12
50	**Org**anic **Mass Spectrom**etry (1968)	PC	12
51	**Org**anic **Prep**arations and **Proced**ures **Int**ernational (1969)	P[5]	6
52	**Org**anic **Process Res**earch & **Dev**elopment (1997)	P	6
53	**Photochem**istry and **Photobiol**ogy (1962)	P[5]	12
54	**Pol**ish **J**ournal of **Chem**istry (1921)[9]	PC	12
55	**Pure** and **Appl**ied **Chem**istry (1960)	[10]	12
56	**Res**earch on Chemical **Intermed**iates (1973)[11]	P[5]	6
57	**Russ**ian **J**ournal of **Org**anic **Chem**istry (1984)	P,C	12
58	**Sulf**ur **Lett**ers (1982)	C	6
59	**Synlett** (1989)	C[5]	12
60	**Synth**etic **Commun**ications (1971)	C	22
61	**Synthesis** (1969)	P[5]	12
62	**Tetrahedron** (1958)	P[5]	52
63	**Tetrahedron: Asymmetry** (1990)	PC	12
64	**Tetrahedron Lett**ers (1959)	C	52

[a]These Journals are listed in alphabetical order of *Chemical Abstracts*™ abbreviations, Which Are Indicated in Boldface. Also given are the year of founding, number of issues per year as of 1998, and whether the journal primarily publishes papers (P), communications (C), or both.

[9]Before 1978 this journal was called ***Roczniki Chemii***.
[10]*Pure Appl. Chem.* publishes IUPAC reports and lectures given at IUPAC meetings.
[11]Before 1989 this journal was called ***Rev**iews of **Chem**ical **Intermed**iates*.

For some years, the American Chemical Society journals, including *J. Am. Chem. Soc.* and *J. Org. Chem.*, have provided supplementary material for some of their papers. This material is available on-line, and for older literature from the Microforms and Back Issues Office at the ACS Washington, DC, office, either on microfiche or as a photocopy. Many other journals now offer supplementary material, generally experimental procedures, supporting spectral data and crystallographic data. These practices have not yet succeeded in substantially reducing the total volume of the world's primary chemical literature.

Patents

In many countries, including the United States, it is possible to patent a new compound or a new method for making a known compound (either laboratory or industrial procedures), as long as the compounds are useful. It comes as a surprise to many to learn that a substantial proportion of the patents granted (perhaps 20–30%) have been chemical patents. Chemical patents are part of the chemical literature, and both U.S. and foreign patents are regularly abstracted by *Chemical Abstracts*™. In addition to learning about the contents of patents from this source, chemists may consult the *Official Gazette* of the U.S. Patent Office, which, published weekly and available in many libraries, lists titles of all patents issued that week. Bound volumes of all U.S. patents are kept in a number of large libraries, including the New York Public Library, which also has an extensive collection of foreign patents. Photocopies of any U.S. patent and most foreign patents can be obtained at low cost from the U.S. Patent and Trademark Office, Washington, DC, 20231. Many patents can now be obtained on-line as well. In addition, *Chemical Abstracts*™ lists, in the introduction to the first issue of each volume, instructions for obtaining patents from 26 countries. Patents are also available via SciFinder®.

Although patents are often very useful to the laboratory chemist, and no literature search is complete that neglects relevant patents, as a rule they are not as reliable as papers. There are two reasons for this:

1. It is in the interest of the inventor to claim as much as possible. Therefore, they may, for example, actually have carried out a reaction with ethanol and with 1-propanol, but will claim all primary alcohols, and perhaps even secondary and tertiary alcohols, glycols, and phenols. An investigator repeating the reaction on an alcohol that the inventor did not use may find that the reaction gives no yield at all. In general, it is safest to duplicate the actual examples given, of which most chemical patents contain one or more.
2. Although legally a patent gives an inventor a monopoly, any alleged infringements must be protected in court, and this may cost a good deal of money. Therefore some patents are written so that certain essential details are concealed or entirely omitted. This practice is not exactly cricket, because a patent is supposed to be a full disclosure, but patent attorneys are generally

skilled in the art of writing patents, and procedures given are not always sufficient to duplicate the results.

Fortunately, the above statements do not apply to all chemical patents: many make full disclosures and claim only what was actually done. It must also be pointed out that it is not always possible to duplicate the work reported in every paper in a journal due to the use of proprietary catalysts, equipment, or procedures. Note, however, that some work is not published or patented, but rather maintained within the company as a trade secret. Such work is not, of course, available to the public.

SECONDARY SOURCES

Journal articles and patents contain virtually all of the original work in organic chemistry. However, if therewere no indexes, abstracts, review articles, and other secondary sources, the literature would be unusable, because it is so vast that no one could hope to find anything in particular. Fortunately, the secondary sources are excellent. There are various kinds and the categories tend to merge. Our classification is somewhat arbitrary.

Listings of Titles

The profusion of original papers is so great that publications that merely list the titles of current papers find much use. Such lists are primarily methods of alerting the chemist to useful papers published in journals that they do not normally read. This approach, using print versions containing lists or journals and articles, is not used much nowadays. Most journals are available on-line, and many have the original papers, with supplemental material, as HTML and pdf[12] documents. The pdf document can be downloaded to the searcher's desktop, usually for a fee, and is most convenient. *Chemical Abstracts*™ was originally available on-line as *CAS ONLINE*. CAS ONLINE was discontinued when STN® (a service that CAS operates in cooperation with the German organization FIZ Karlsruhe, see below) was introduced in 1984. All of the *Chemical Abstracts*™ literature can be accessed using CAS databases online. Many libraries and companies pay the appropriate fees, so accessing the journals is usually quite easy via those organizations. Search engines allow one to quickly scan an enormous amount of literature from office or home. in addition, most browsers have on-line searching capabilities via various search engines, and simply typing in an author, a topic, a chemical, or a few key words can lead to important articles or information. Some of the important on-line technology will be discussed below. However, some of the available resources[13] include Specialty Citation Indexes, Science Citation Index Expanded™, Web of Science®,

[12]Adobe Acrobat© files.
[13]See http://scientific.thomson.com/products/categories/citation/

Science Citation Index®, ISI ProceedingsSM, Reaction Citation Index™, and the Derwent Innovations IndexSM. Science Citation Index® is available on STN®, where it is called SciSearch. We will begin with the older print-versions for chemical searches.

A print-version "title" publication covering the whole of chemistry is *Current Contents Physical, Chemical & Earth Sciences*,[14] which began in 1967 and appears weekly, contains the contents pages of all issues of ~800 journals in chemistry, physics, earth sciences, mathematics, and allied sciences. Each issue contains an index of important words taken from the titles of the papers listed in that issue, and an author index, which, however, lists only the first-named author of each paper. The author's address is also given, so that one may write for reprints. An on-line service is available called Current Contents Connect® is a multidisciplinary Web resource providing access to complete bibliographic information from >8000 of the world's leading scholarly journals and >2000 books.[15]

CAS databases on-line described below allows one to search a variety of databases, including journal titles.

Abstracts

Listings of titles are valuable, as far as they go, but they do not tell what is in the paper, beyond the implications carried by the titles. Most current journals contain a graphic abstract as well as a title and a brief print description of the research. The graphical abstract is extremely useful for scanning the literature presented in a journal, and both the print and graphical abstracts are available on-line for most journals.

From the earliest days of organic chemistry, abstracts of papers have been widely available, often as sections of journals whose principal interests lay elsewhere.[16] At the present time there are only two publications entirely devoted to abstracts covering the whole field of chemistry. One of these, *Referativnyi Zhurnal, Khimiya*, which began in 1953, is published in Russian and is chiefly of interest to Russian-speaking chemists. The other is *Chemical Abstracts*™ (CA). This publication, which appears weekly, prints abstracts in English of virtually every paper containing original work in pure or applied chemistry published anywhere in the world.[17] More than 9500 currently published journals are covered, in many languages. In addition, *CA* publishes abstracts of every patent of chemical interest from 50 national and international patent offices. *Chemical Abstracts*™ lists and indexes, but does not abstract review articles and books. The abstracts currently appear in 80 sections, of which sections 21–34 are devoted to organic chemistry, under such

[14]Title pages of organic chemistry journals are also carried by *Current Contents Life Sciences*, which is a similar publication covering biochemistry and medicine.

[15]http://scientific.thomson.com/products/ccc/

[16]For example, *Chem. Ind. (London)* publishes abstracts of papers that appear in other journals. In the past, journals, such as *J. Am. Chem. Soc., J. Chem Soc.,* and *Berchti* also did so.

[17]For a guide to the use of *CA*, see Schulz, H. *From CA to CAS ONLINE*; VCH: NY, ***1988***.

headings as Alicyclic Compounds, Alkaloids, Physical Organic Chemistry, Heterocyclic Compounds (One Heteroatom), and so on. Each abstract of a paper begins with a heading that gives (*1*) the abstract number;[18] (*2*) the title of the paper; (*3*) the authors' names as fully as given in the paper; (*4*) the authors' address; (*5*) the abbreviated name of the journal (see Table A.1);[19] (*6*) the year, volume, issue, and page numbers; and (*7*) the language of the paper. In earlier years, *CA* gave the language only if it differed from the language of the journal title. Abstracts of patents begin with the abstract number, title, inventor and company (if any), patent number, patent class number, date patent issued, country of priority, patent application number, date patent applied for, and number of pages in the patent. The body of the abstract is a concise summary of the information in the paper. For many common journals the author's summary (if there is one) is used in *CA* as it appears in the original paper, with perhaps some editing and additional information. Each issue of *CA* contains an author index, a patent index, and an index of keywords taken from the titles and the texts or contexts of the abstracts. The patent index lists all patents in order of number. The same compound or method is often patented in several countries. *Chemical Abstracts* will abstract only the first patent, but it does list the patent numbers of the duplicated patents in the patent index along with all previous patent numbers that correspond to it. Before 1981, there were separate Patent Number Indexes and Patent Concordances (the latter began in 1963).

At the end of each section of *CA*, there is a list of cross-references to related papers in other sections.

Chemical Abstracts™ is, of course, highly used for "current awareness"; it allows one to read, in one place, abstracts of virtually all new work in chemistry, though its large size puts a limit on the extent of this type of usefulness.[20] *Chemical Abstracts*™ is even more useful as a repository of chemical information, a place for finding out what was done in the past. This value stems from the excellent indexes, which enable the chemist in most cases to ascertain quickly where information is located. From the time of its founding in 1907 until 1961, *CA* published annual indexes. Since 1962 there are two volumes published each year, and a separate index is issued for each volume. For each volume there is an index of subjects, authors, formulas, and patent numbers. Beginning in 1972, the subject index has been issued in two parts, a chemical substance index and a general subject index, which includes all entries that are not the names of single chemical substances. However, the indexes to each volume become essentially superseded as collective indexes are issued. The first collective indexes are 10-year (decennial) indexes, but the volume of information has made 5-year indexes necessary since 1956. Collective indexes published to date are shown in Table A.2. Thus a user of the indexes at the time of this writing would consult the collective indexes through 1995 and the semiannual indexes thereafter. The 14th collective index (covering

[18]Beginning in 1967. See p. 1880.

[19]These abbreviations are changed from time to time. Therefore the reader may notice inconsistencies.

[20]It is possible to subscribe to *CA Selects,* which provides copies of all abstracts within various narrow fields, such as organofluorine chemistry, organic reaction mechanisms, and organic stereochemistry.

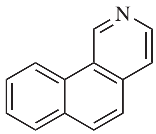
TABLE A.2. *CA* Collective Indexes Published

Collective Index	Subject and General Subject	Chemical Substance	Author	Formula	Patent
1	1907–1916		1907–1916		
2	1917–1926		1917–1926		1907–1936
3	1927–1936		1927–1936	1920–1946	
4	1937–1946		1937–1946		1937–1946
5	1947–1956		1947–1956	1947–1956	1947–1956
6	1957–1961		1957–1961	1957–1961	1957–1961
7	1962–1966		1962–1966	1962–1966	1962–1966
8	1967–1971		1967–1971	1967–1971	1967–1971
9	1972–1976	1972–1976	1972–1976	1972–1976	1972–1976
10	1977–1981	1977–1981	1977–1981	1977–1981	1977–1981
11	1982–1986	1982–1986	1982–1986	1982–1986	1982–1986
12	1987–1991	1987–1991	1987–1991	1987–1991	1987–1991
13	1992–1996	1992–1996	1992–1996	1992–1996	1992–1996
14	1997–2001	1997–2001	1997–2001	1997–2001	1997–2001
15	2002–2006	2002–2006	2002–2006	2002–2006	2002–2006

1997–2001) appeared in 2002. The 15th Collective index will be issued only in CD ROM, as well as any subsequent collective, presumably.

Beginning with the eighth collective index period, *CA* has published an *Index Guide*. This publication gives structural formulas and/or alternate names for thousands of compounds, as well as many other cross-references. It is designed to help the user efficiently and rapidly to find *CA* references to subjects of interest in the general subject, formula, and chemical substance indexes. Each collective index contains its own *Index Guide*. A new *Index Guide* is issued every 18 months. The *Index Guide* is necessary because the *CA* general subject index is a "controlled index," meaning it restricts its entries only to certain terms. For example, anyone who looks for the term "refraction" in the general subject index will not find it. The *Index Guide* includes this term, and directs the reader to "Electromagnetic wave, refraction of," "Sound and ultrasound, refraction of," and other terms, all of which will be found in the general subject index. Similarly, the chemical substance index usually lists a compound only under one name, the approved *CA* name. Trivial and other names will be found in the *Index Guide*. For example, the term "methyl carbonate" is not in the chemical substance index, but the *Index Guide* does have this term, and tells us to look for it in the chemical substance index under the headings "carbonic acid, esters, dimethyl ester" (for Me_2CO_3) and "carbonic acid, esters, monomethyl ester" (for $MeHCO_3$). Furthermore, the *Index Guide* gives terms related to the chosen term, helping users to broaden a search. For example, one who looks for "Atomic orbital" in the *Index Guide* will find the terms "Energy Level," "Molecular orbital," "Atomic integral," and "Exchange, quantum mechanical, integrals for," all of which are controlled index terms.

Along with each index (annual, semiannual, or collective) appears an index of ring systems. This valuable index enables the user to ascertain immediately if any ring system appears in the corresponding subject or chemical substance index and under what names. For example, someone wishing to determine whether any compounds containing this ring system



Benz(*h*)isoquinoline

are reported in the 1982–1986 collective index (even if they did not know the name) would locate, under the heading "3-ring systems," the listing **6**, **6**, **6** (since the compound has three rings of six members each), under which they would find the sublisting C_5N—C_6—C_6 (since one ring contains five carbons and a nitrogen while the others are all-carbon), under which is listed the name benz(*h*)isoquinoline, as well as the names of 30 other systems C_5N—C_6—C_6. A search of the chemical substance index under these names will give all references to these ring systems that appeared in *CA* from 1982 to 1986.

Before 1967, *CA* used a two-column page, with each column separately numbered. A row of letters from *a* to *h* appeared down the center of the page. These letters are for the guidance of the user. Thus an entry 7337*b* refers to the *b* section of column 7337. In early years, superscript numbers (e.g., 4327^5), were used in a similar manner. In very early years, these numbers were not printed on the page at all, though they are given in the decennial indexes, so that the user must mentally divide the page into nine parts. Beginning with 1967, abstracts are individually numbered and column numbers are discarded. Therefore, beginning with 1967, index entries give abstract number rather than column number. The abstract numbers are followed by a letter that serves as a check character to prevent miscopying errors in computer handling. To use the *CA* general subject, chemical substance, and formula indexes intelligently requires practice, and the student should become familiar with representative volumes of these indexes and with the introductory sections to them, as well as with the *Index Guides*.

In the *CA* formula indexes, formulas are listed in order of (*1*) number of carbon atoms; (*2*) number of hydrogen atoms; (*3*) other elements in alphabetic order. Thus, all C_3 compounds are listed before any C_4 compound; all C_5H_7 compounds before any C_5H_8 compound; $C_7H_{11}Br$ before $C_7H_{11}N$; $C_9H_6N_4S$ before C_9H_6O, and so on. Deuterium and tritium are represented by D and T and treated alphabetically, for example, C_2H_5DO after C_2H_5Cl and before C_2H_5F or C_2H_6.

Since 1965, *CA* has assigned a Registry Number to each unique chemical substance; CAS Registry Number®. This is a number of the form [*766-51-8*] that remains invariant, no matter what names are used in the literature. More than

10 million numbers have already been assigned and thousands are added each week. At one time, all numbers published with the *CA* preferred names appeared in a multivolume "Registry Handbook," but this work was discontinued. The CAS Registry contains >27 million organic and inorganic substances and >57 million sequences.[21] For a discussion of online searching see pp. 1901–1905.

There were a number of earlier abstracting publications now defunct. The most important are *Chemisches Zentralblatt* and *British Abstracts*. These publications are still valuable because they began before *CA* and can therefore supply abstracts for papers that appeared before 1907. Furthermore, even for papers published after 1907, *Zentralblatt* and *British Abstracts* are often more detailed. *Zentralblatt* was published, under various names, from 1830 to 1969.[22] *British Abstracts* was a separate publication from 1926 to 1953, but earlier abstracts from this source are available in the *Journal of the Chemical Society* from 1871 to 1925.

Beilstein

This publication is so important to organic chemistry that it deserves a section by itself. Beilstein's *Handbuch der Organischen Chemie*, usually referred to as *Beilstein*, lists all the known organic compounds reported in the literature during its period of coverage. We will first describe the print version, particularly important for older literature. This discussion will be followed by a description of the on-line version of Beilstein – Crossfire Beilstein. For each compound are given: all names; the molecular formula; the structural formula; all methods of preparation (briefly, e.g., "by refluxing 1-butanol with NaBr and sulfuric acid"); physical constants, such as melting point and refractive index; other physical properties; chemical properties including reactions; occurrence in nature (i.e., which species it was isolated from); biological properties, if any; derivatives with melting points; analytical data, and any other information that has been reported in the literature.[23] Equally important, for every piece of information, a reference is given to the original literature. Furthermore, the data in *Beilstein* have been critically evaluated. That is, all information is carefully researched and documented, and duplicate and erroneous results are eliminated. Some compounds are discussed in two or three lines and others require several pages. The value of such a work should be obvious.

The first three editions of *Beilstein* are obsolete. The fourth edition (*vierte Auflage*) covers the literature from its beginnings through 1909. This edition, called *das Hauptwerk*, consists of 27 volumes. The compounds are arranged in order of a

[21]This total is updated daily. See http://www.cas.org/cgi-bin/regreport.pl.

[22]An "obituary" of *Zentralblatt* by Weiske, which gives its history and statistical data about its abstracts and indexes, was published in the April 1973 issue of *Chem. Ber.* (pp. I–XVI).

[23]For a discussion of how data are processed for inclusion in *Beilstein*, see Luckenbach, R.; Ecker, R.; Sunkel, J. *Angew. Chem. Int. Ed.* ***1981***, *20*, 841.

system too elaborate to discuss fully here.[24] The compounds are divided into three divisions that are further subdivided into "systems":

Division	Volumes	System Numbers
I. Acyclic Compounds	1–4	1–499
II. Carbocyclic Compounds	5–16	450–2359
III. Heterocyclic Compounds	17–27	2360–4720

Das Hauptwerk is still the basis of *Beilstein* and has not been superseded. The later literature is covered by supplements that have been arranged to parallel *das Hauptwerk*. The same system is used, so that the compounds are treated in the same order. The first supplement (*erstes Ergänzungswerk*) covers 1910–1919; the second supplement (*zweites Ergänzungwerk*) covers 1920–1929; the third supplement (*drittes Ergänzungswerk*) covers 1930–1949; the fourth supplement (*viertes Ergänzungswerk*) covers 1950–1959, and the fifth supplement covers 1960-1979. Like *das Hauptwerk*, each supplement contains 27 volumes,[25] except that supplements 3 and 4 are combined for Vols. 17–27, so that for these volumes the combined third and fourth supplement covers the years 1930–1959. Each supplement has been divided into volumes in the same way as *das Hauptwerk*, and, for example, compounds found in Vol. 3, system number 199 of *das Hauptwerk* will also be found in Vol. 3, system number 199 of each supplement. To make cross-referencing even easier, each supplement gives, for each compound, the page numbers at which the same compound can be found in the earlier books. Thus, on page 554 of Vol. 6 of the fourth supplement, under the listing phenetole are found the symbols (H 140; E I 80; E II 142; E III 545) indicating that earlier information on phenetole is given on page 140 of Vol. 6 of *das Hauptwerk*, on page 80 of the first, page 142 of the second, and page 545 of the third supplement. Furthermore, each page of the supplements contains, at the top center, the corresponding page numbers of *das Hauptwerk*. Since the same systematic order is followed in all six series, location of a compound in any one series gives its location in the other five. If a compound is found, for example, in Vol. 5 of *das Hauptwerk*, one has but to note the page number and scan Vol. 5 of each supplement until that number appears in the top center of the page (the same number often covers several pages). Of course, many compounds are found in only one, two, three, four, or five of the series, since no work may have been published on that compound during a

[24]For descriptions of the *Beilstein* system and directions for using it, see Sunkel, J.; Hoffmann, E.; Luckenbach, R. *J. Chem. Educ.* ***1981***, *58*, 982; Luckenbach, R. *CHEMTECH* ***1979***, 612. The Beilstein Institute has also published two English-language guides to the system. One, available free, is *How to Use Beilstein*; Beilstein Institute: Frankfurt/Main, ***1979***. The other is by Weissbach, O. *A Manual for the Use of Beilstein's Handbuch der Organischen Chemie*, Springer, NY, ***1976***. An older work, which many students will find easier to follow, is by Huntress, E.H. *A Brief Introduction to the Use of Beilstein's Handbuch der Organischen Chemie,* 2nd ed., Wiley, NY, ***1938***.

[25]In some cases, to keep the system parallel and to avoid books that are too big or too small, volumes are issued in two or more parts, and, in other cases, two volumes are bound as one.

particular period covered. From *das Hauptwerk* to the fourth supplement, *Beilstein* is in German, though it is not difficult to read since most of the words are the names of compounds (a *Beilstein* German–English Dictionary, available free from the publisher, is in many libraries). For the fifth supplement (covering 1960–1979), which is in English, publication of Division III began before the earlier divisions. At the time of this writing, Vols. 17–22 (totaling 70 separate parts exclusive of index volumes) of this supplement have been published, as well as a combined index for Volumes 17–19. This index covers only the fifth supplement. The subject portion of this index, which lists compound names only, gives these names in English.

Volumes 28 and 29 of *Beilstein* are subject and formula indexes, respectively. The most recent complete edition of these volumes is part of the second supplement and covers only *das Hauptwerk* and the first two supplements (though complete indexes covering *das Hauptwerk* and the first four supplements have been announced to appear in the next few years). For Vol. 1, there is a cumulative subject and a cumulative formula index, which combine *das Hauptwerk* and the first four supplements.[26] Similar index volumes, covering all four supplements, have been issued for the other volumes, 2–27. Some of these are combined (e.g., 2–3, 12–14, and 23–25). For English-speaking chemists (and probably for many German-speaking chemists) the formula indexes are more convenient. Of course (except for the fifth supplement indexes), one must still know some German, because most formula listings contain the names of many isomers. If a compound is found only in *das Hauptwerk*, the index listing is merely the volume and page numbers (e.g., **1**, 501). Roman numbers are used to indicate the supplements, for example, **26**, 15, I 5, II 7. Thus the subject and formula indexes lead at once to locations in *das Hauptwerk* and the first four supplements. The *Beilstein* formula indexes are constructed the same way as the *CA* indexes (p. 1880).

There is also a fourth division of *Beilstein* (systems 4721–4877) that covers natural products of uncertain structure: rubbers, sugars, and so on. These are treated in Vols. 30 and 31, which do not go beyond 1935, and which are covered in the collective indexes. These volumes will not be updated. All such compounds are now included in the regular *Beilstein* volumes.

Like *CA*, *Beilstein* is available on-line, with the useful search engine *CrossFire Beilstein*. The *Beilstein* database is one of the best databases for organic chemistry, particularly synthetic organic chemistry. It contains information on ~9.4 million organic substances that have been fully characterized, as well as 9.8 million reactions. Information available includes:[27]

- Structure and reaction diagrams
- Identification information (name, formula, registry numbers, etc.)

[26]Most page number entries in the combined indexes contain a letter, for example, $CHBr_2Cl$ 67f, II 33a, III 87d, IV, 81. These letters tell where on the page to find the compound and are useful because the names given in the index are not necessarily those used in the earlier series. The letter "a" means the compound is the first on its page, "b" is the second, and so on. No letters are given for the fourth supplement.

[27]http://gethelp.library.upenn.edu/guides/tutorials/scitech/beilstein/BCWhat.html

- Isolation and purification information
- Derivatives
- Physical properties, including
- Structure and energy parameters
- State of matter and change of state information
- Transport phenomena
- Optical properties
- Spectra (UV, VIS, MS, NMR, IR, ESR, X-ray, etc.)
- Electrical and magnetic properties
- Electrochemistry
- Behavior of liquid/solid, liquid/liquid, and liquid/vapor systems
- Solution behavior
- Energy data
- Optical data
- Boundary surface phenomena
- Adsorption
- Association
- Pharmacological and ecological data

Not all compounds contain all different types of data. Some data, often those quantities that can be described by a number, word, or short phrase, are given explicitly in the record for the compound. Others simply have a literature reference. The factual data, of which there are 260 million, are only experimental data, scientifically measured.

Coverage of the Literature and Search Capabilities

Beilstein references the chemical literature published in ~175 prestigious organic chemistry journals[28] from 1771 to date. It is updated quarterly. The database may be searched using structures and/or text (property information, chemical name, molecular formula)." Figure A. 1 shows the on-line page after a structure has been drawn using the drawing tools provided with the program, used by Crossfire to begin a session. Figure A. 2 shows an on-line page that displays data obtained after a structure search. The variety of tools available for searching is much more extensive than the ones shown in Figs. A.1 and A.2. One can use the structure editor to draw a specific structure, and it is possible to draw two or more structures, label them as reactant and/or product and search for a chemical reactions or transformation. A variety of data can be accessed for a compound or a reaction, and the output includes the chemical structures, references to the primary literature, physical, and spectral properties where available.

[28]See http://www.mdl.com/products/pdfs/BSJournals.pdf.

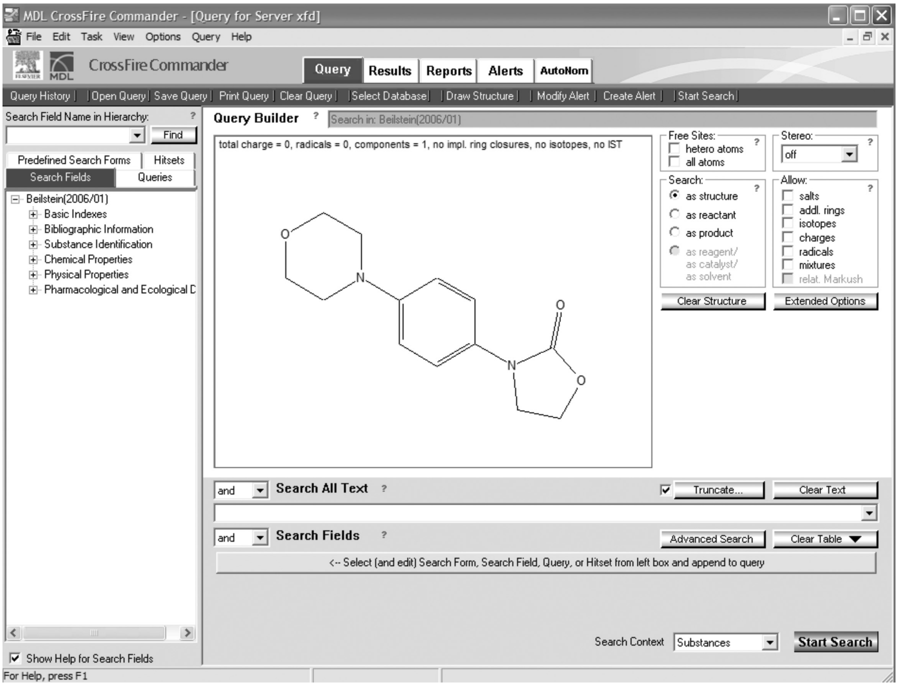


Fig. A.1. Structure Search for CrossFire Beilstein[29] Beilstein Data: Copyright (c) 1988–2006, Beilstein Institut zur Foerderung der Chemischen Wissenschaften licensed to Beilstein GmbH and MDL Information Systems GmbH. All rights reserved.

Tables of Information

In addition to *Beilstein*, there are many other reference works in organic chemistry that are essentially compilations of data. These books are very useful and often save the research worker a great deal of time. In this section we discuss some of the more important of such works.

1. The sixth edition of *Heilbron's Dictionary of Organic Compounds*, J. Buckingham, Ed., 9 vols., Chapman and Hall, London, ***1996***, contains brief listings of >150,000 organic compounds, giving names, structural formulas, physical properties, and derivatives, with references. For many entries additional data concerning occurrence, biological activity, and toxicity hazard information are also given. The arrangement is alphabetical. The dictionary contains indexes of names, formulas, heteroatoms, and *CA* Registry Numbers. Annual supplements, with cumulative indexes, have appeared since 1983. A similar work, devoted to organometallic compounds, is the 2nd edition of the *Dictionary of Organometallic Compounds*, 6 vols. in its 5th supplement,

[29]See http://www.mdl.com/products/knowledge/crossfire_commander/.

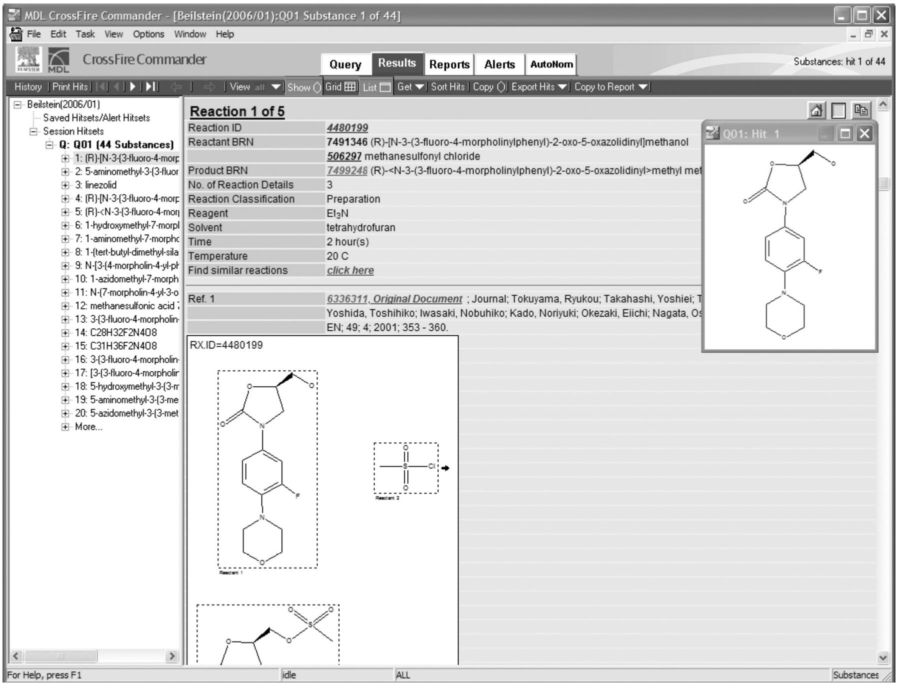


Fig. A.2. Preparation Data from CrossFire Beilstein.[30] Beilstein Data: Copyright (c) 1988–2006, Beilstein Institut zur Foerderung der Chemischen Wissenschaften licensed to Beilstein GmbH and MDL Information Systems GmbH. All rights reserved.

published by Chapman and Hall in ***1989***. Another, *Dictionary of Steroids*, 2 vols., 1991, is also published by Chapman and Hall.

2. A multivolume compendium of physical data is Landolt-Börnstein's *Zahlenwerte und Funktionen aus Physik, Chemie, Astronomie, Geophysik, und Technik*, 6th ed., Springer, Berlin, **1950**–. There is also a "New Series," for which the volumes are given the English title *Numerical Data and Functional Relationships in Science and Technology*, as well as the German title. This compendium, which is not yet complete, lists a great deal of data, some of which are of interest to organic chemists (e.g., indexes of refraction, heats of combustion, optical rotations, and spectral data). Literature references are given for all data.
3. *The Handbook of Chemistry and Physics*, CRC Press, Boca Raton, FL (called the "rubber handbook"), which is revised annually (87th ed., ***2006–2007***), is a valuable repository of data quickly found. For organic chemists the most important table is "Physical Constants of Organic Compounds,"

[30]See http://www.mdl.com/products/knowledge/crossfire_beilstein/index.jsp. Also see, http://chemistry.library.wisc.edu/beilstein/quickguide6.htm

which lists names, formulas, color, solubilities, and physical properties of thousands of compounds. However, there are many other useful tables. A similar work is *Lange's Handbook of Chemistry*, 16th ed., McGraw-Hill, New York, ***2004***. Another such handbook, but restricted to data of interest to organic chemists, is *Dean's Handbook of Organic Chemistry*, 2nd ed., McGraw-Hill, New York, ***2003***. This book also contains a long table of "Physical Constants of Organic Compounds," and has much other information including tables of thermodynamic properties, spectral peaks, pK_a values, bond distances, and dipole moments.

4. A list of most of the known natural compounds (e.g., terpenes, alkaloids, carbohydrates), to which structures have been assigned, along with structural formulas, melting points, optical rotations, and references, is provided in Devon and Scott, *Handbook of Naturally Occurring Compounds*, 3 vols., Academic Press, New York, ***1972***.
5. Dreisbach, *Physical Properties of Chemical Compounds*, Advances in Chemistry Series Nos. 15, 22, 29, American Chemical Society, Washington, DC, ***1955–1961*** lists many physical properties of >1000 organic compounds.
6. Physical properties of thousands of organometallic compounds, with references, are collected in five large compendia: the *Dictionary of Organometallic Compounds*, mentioned under item 1, above; Dub, *Organometallic Compounds*, 2nd ed., 3 vols. with supplements and index, Springer, New York, ***1966–1975***; Hagihara, Kumada, and Okawara, *Handbook of Organometallic Compounds*, W. A. Benjamin, New York, 1968; and Kaufman, *Handbook of Organometallic Compounds*, Van Nostrand, Princeton, NJ, 1961; *Comprehensive Organometallic Chemistry II,* 14 Vols, Pergamon, 1995.
7. The *Merck Index*, 13th ed., Merck and Company, Rahway, NJ, ***2001*** is a good source of information about chemicals of medicinal importance. Many drugs are given three types of name: chemical *name* (which is the name an organic chemist would give it; of course, there may well be more than one); *generic name*, which must be placed on all containers of the drug; and *trade names,* which are different for each company that markets the drug. For example, the generic name for 1-(4-chlorobenzhydryl)-4-methylpiperazine is chlorcyclazine. Among the trade names for this drug, which is an antihistamine, are Trihistan, Perazyl, and Alergicide. The *Merck Index* is especially valuable because it gives all known names of all three types for each compound and the names are cross-indexed. Also given, for each compound, are the structural formula, *CA* preferred name and Registry Number, physical properties, medicinal and other uses, toxicity indications, and references to methods of synthesis. There are indexes of formulas and Registry Numbers, and miscellaneous tables. The 10th edition of the *Merck Index* (1983) also includes a lengthy list of organic name reactions, with references. Although the 11th edition omitted this list, it was restored in the 12th and subsequent editions.

Note that the Merck Index Online™ is also available.

8. There are two publications that list properties of azeotropic mixtures. Timmermans, *The Physicochemical Constants of Binary Systems in Concentrated Solutions*, 4 vols., Interscience, New York, ***1959–1960***, is by far the more comprehensive. The other is *Azeotropic Data*, 2 vols., Advances in Chemistry Series Nos. 6 and 35, American chemical Society, Washington, DC, ***1952***, ***1962***.
9. Thousands of dipole moments, with references, are collected in McClellan, *Tables of Experimental Dipole Moments*, Vol. 1, W.H. Freeman, San Francisco, CA, ***1963***; Vol. 2, Rahara Enterprises, El Cerrita, CA, ***1974***.
10. *Tables of Interatomic Distances and Configurations in Molecules and Ions*, London chemical Society Special publication No. 11, 1958, and its supplement, Special publication No. 18, ***1965***, include bond distances and angles for hundreds of compounds, along with references.
11. The *Ring Systems Handbook*, published in ***1988*** by the Chemical Abstracts Service, provides the names and formulas of ring and cage systems that have been published in *CA*. The ring systems are listed under a system essentially the same as that used for the *CA* index of ring systems (p. $$$). Each entry gives the *CA* index name and Registry Number for that ring system. In many cases, a *CA* reference is also given. There is a separate Formula Index (for the parent ring systems) and a Ring Name Index. Cumulative supplements are issued twice a year. The *Ring Systems Handbook* supersedes earlier publications called *The Parent Compound Handbook* and *The Ring Index*.
12. The Sadtler Research Laboratories publish large collections of IR, UV, NMR and other spectra, in loose-leaf form. Indexes are available.
13. Infrared, UV, NMR, Raman, and mass spectral data, as well as melting-point, boiling-point, solubility, density, and other data for >30,000 organic compounds are collected in the *CRC Handbook of Data on Organic Compounds*, 2nd ed., 9 vols., CRC Press, Boca Raton, FL, ***1988***, edited by Weast and Grasselli. It differs from the Sadtler collection in that the data are given in tabular form (lists of peaks) rather than reproduction of the actual spectra, but this book has the advantage that all the spectral and physical data for a given compound appear at one place. References are given to the Sadtler and other collections of spectra. Volumes 7–9 contain indexes of spectral peaks for IR, UV, ^{1}H NMR, ^{13}C NMR, mass, and Raman spectra, as well as indexes of other names, molecular formulas, molecular weights, and physical constants. Annual updates began appearing in ***1990*** (the first one is called Vol. 10).
14. The *Aldrich Library of Infrared Spectra*, 3rd ed., Aldrich chemical Company, Milwaukee, WI, ***1981***, by Pouchert contains >12,000 IR spectra so arranged that the user can readily see the change that takes place in a given spectrum when a slight change is made in the structure of a molecule. The same company also publishes the *Aldrich Library of FT–IR Spectra* and the *Aldrich Library of NMR Spectra*, both also by Pouchert. A similar volume, which has IR and Raman spectra of ~1000 compounds, is *Raman/Infrared Atlas of Organic Compounds*, 2nd ed., VCH, New York, ***1989***, by Schrader.

15. An extensive list of visible and UV peaks is given in *Organic Electronic Spectral Data*, Wiley, New York. Twenty-six volumes have appeared so far, covering the literature through ***1984***.

16. A collection of 500 ^{13}C NMR spectra is found in Johnson and Jankowski, *Carbon-13 NMR Spectra*, Wiley, New York, ***1972***.

Reviews

A review article is an intensive survey of a rather narrow field; for example, the titles of some recent reviews are "Desulfonation Reactions: Recent Developments,"[31] "Pyrrolizidine and Indolizidine Syntheses Involving 1,3-Dipolar Cycloaddition,"[32] and "From Corrin Chemistry to Asymmetry Catalysis—A Personal Account."[33] A good review article is of enormous value, because it is a thorough survey of all the work done in the field under discussion. Review articles are printed in review journals and in certain books. The most important review journals in organic chemistry (though most are not exclusively devoted to organic chemistry) are shown in Table A.3. Some of the journals listed in Table A.1, for

TABLE A.3. Review Journals, With Year of Founding and Issues per Year as of 1998

Journal	Issues
Accounts of **Chem**ical **Res**earch (1968)	12
Aldrichimica **Acta** (1968)	4
Angewandte **Chem**ie (1888) and its English Translation:	12
Angewandte **Chem**ie, **Int**ernational **Ed**ition (1962)	12
Chemical **Rev**iews (1924)	8
Chemical **Soc**iety **Rev**iews (1947)[34]	4
Heterocycles (1973)	12
Natural **Prod**uct **Rep**orts (1984)	6
Organic **Prep**arations and **Proc**edures **Int**ernational (1969)	6
Soviet **Sci**entific **Rev**iews, **Sect**ion **B,** Chemistry Reviews (1979) Irreg.	
Sulfur Reports (1980)	6
Synlett (1989)	12
Synthesis (1969)	12
Tetrahedron (1958)	52
Topics in **Curr**ent **Chem**istry (1949)[35]	Irreg.
Uspekhi **Khim**ii (1932)	12
and its English translation: **Russ**ian chemical **Rev**iews (1960)	12

[31]Nájera, C.; Yus, M. *Tetrahedron* ***1999***, *55*, 10547.

[32]Broggini, G.; Zecchi, G. *Synthesis* ***1999***, 905.

[33]Pfaltz, A. *Synlett* ***1999***, 835.

[34]Successor to *Quarterly Reviews* (abbreviated as *Q. Rev., Chem. Soc.*).

[35]Formerly called ***Fortschr**itte der **Chem**ischen **Forsch**ung*.

example, *Synlett, Tetrahedron, Synthesis, Organic Preparations and Procedures International,* and *J. Organomet. Chem.* also publish occasional review articles.

There are several open-ended serial publications that are similar in content to the review journals, but are published irregularly (seldom more often than once a year) and are hardbound. Some of these publish reviews in all fields of chemistry; some cover only organic chemistry; some specialize further. The coverage is indicated by the titles. Table A.4 shows some of the more important such publications, with *CA* abbreviations.

There are several publications that provide listings of review articles in organic chemistry. The most important is the *J. Org. Chem.*, which began to list review articles in 1978 (the first list is at *J. Org. Chem.*, *43*, 3085), suspended the listings in 1985, and resumed them in 1990 (at *J. Org. Chem.*, *55*, 398). These lists, which appear about four times a year, give the titles and reference sources of virtually

TABLE A.4. Irregularly Published Serial Publications

Advances in **Carbo**cation **Chem**istry
Advances in **Carbohydr**ate **Chem**istry and **Biochem**istry
Advances in **Catal**ysis
Advances in **Cycloadd**ition
Advances in **Free Radical Chem**istry
Advances in **Heterocycl**ic **Chem**istry
Advances in **Met**al-**Org**anic **Chem**istry
Advances in **Mol**ecular **Model**ing
Advances in **Organomet**allic **Chem**istry
Advances in **Oxygenated Processes**
Advances in **Photochem**istry
Advances in physical **Org**anic **Chem**istry
Advances in **Protein Chem**istry
Advances in **Theor**etically **Interesting Mol**ecules
Fluorine Chemistry **Rev**iews
Fortshritte der **Chem**ie **Org**anischer **Naturst**offe
Isotopes in **Org**anic **Chem**istry
Molecular **Struct**ure and **Energ**etics
Organic **Photochem**istry
Organometallic **React**ions
Organic **React**ions
Organic **Synth**esis: **Theory** and **Appl**ications
Progress in **Heterocycl**ic **Chem**istry
Progress in **Macrocyclic Chem**istry
Progress in physical **Org**anic **Chem**istry
Reactive **Int**ermediates (Plenum)
Reactive **Int**ermediates (Wiley)
Survey of **Prog**ress in **Chem**istry
Topics in physical **Organomet**allic **Chem**istry
Topics in **Stereochem**istry

all review articles in the field of organic chemistry that have appeared in the preceding 3 months, including those in the review journals and serials mentioned above, as well as those in monographs and treatises. There is also a listing of new monographs on a single subject. Each list includes a subject index.

Another publication is the *Index of Reviews in Organic Chemistry*, complied by Lewis, Chemical Society, London, a classified listing of review articles. The first volume, published in 1971, lists reviews from ~1960 (in some cases much earlier) to ≈ 1970 in alphabetical order of topic. Thus four reviews are listed under "Knoevenagel condensation," five under "Inclusion compounds," and one under "Vinyl ketones." There is no index. A second volume (1977) covers the literature to 1976. Annual or biannual supplements appeared from 1979 until the publication was terminated in 1985. Classified lists of review articles on organometallic chemistry are found in articles by Smith and Walton[36] and by Bruce.[37] A similar list for heterocyclic chemistry is found in articles by Katritzky and others.[38] See also the discussion of the *Index of Scientific Reviews*, p. 1908.

Annual Reviews

The review articles discussed in the previous section are each devoted to a narrow topic covering the work done in that area over a period of years. An annual review is a publication that covers a broad area, but limits the period covered, usually to 1 or 2 years.

1. The oldest annual review publication still publishing is *Annual Reports on the Progress of Chemistry*, published by the Royal Society of Chemistry (formerly the chemical Society), which began in 1905 and which covers the whole field of chemistry. Since 1967 it has been divided into sections. Organic chemistry is found in Section B.
2. Because the number of papers in chemistry has become so large, the Royal Society of Chemistry publishes annual-review-type volumes of smaller scope, called *Specialist Periodical Reports*. Among those of interest to organic chemists are "Carbohydrate Chemistry" (Vol. 22 covers 1988); "Photochemistry" (Vol. 21 covers 1988–1989); and "General and Synthetic Methods," (Vol. 12 covers 1987).
3. *Organic Reaction Mechanisms*, published by Wiley, New York, is an annual survey that covers the latest developments in the field of mechanisms. The first volume, covering 1965, appeared in 1966.
4. There are two annual reviews devoted to progress in organic synthesis. Theilheimer, *Synthetic Methods of Organic Chemistry*, S. Karger Verlag,

[36]Smith, J.D.; Walton, D.R.M. *Adv. Organomet. Chem.* ***1975***, *13,* 453.
[37]Bruce, M.IK. *Adv. Organomet. Chem.* ***1972***, *10,* 273, ***1973***, *11,* 447, ***1974***, *12,* 380.
[38]Belen'kii, L.I. *Adv. Heterocyclic Chem.* ***1988***, *44,* 269; Katritzky, A.R.; Jones, P.M. *Adv. Heterocyclic Chem.* ***1979***, *25,* 303; Katritzky, A.R.; Weeds, S.M. *Adv. Heterocyclic Chem.* ***1966***, *7,* 225.

Basel, is an annual compilation, beginning in 1946, of new methods for the synthesis of organic compounds, arranged according to a system based on bond closing and bond breaking reactions. Equations, brief procedures, yields, and literature references are given. Volume 44 was issued in 1990. Volumes 3 and 4 are available only in German, but all the rest are in English. There is an index to each volume. Cumulative indexes appear in every fifth volume. Beginning with Vol. 8, each volume includes a short summary of trends in synthetic organic chemistry. A more recent series is *Annual Reports in Organic Synthesis*, Academic Press, New York, which has covered the literature of each year since 1970. Equations are listed with yields and references according to a fairly simple system.

5. The *Journal Of Organometallic Chemistry* several times a year publishes annual surveys arranged according to metallic element. For example, Vol. 404, published in February 1991, contains annual surveys for 1989 of organic compounds containing Sb, Bi, and Fe, and the use of transition metals in organic synthesis, and surveys for 1988 covering B, Ru, and Os.

Awareness Services

Besides the annual reviews and the title and abstract services previously mentioned, there exist a number of publications designed to keep readers aware of new developments in organic chemistry or in specific areas of it.

1. *Chemtracts: Organic Chemistry* is a bimonthly periodical, begun in 1988, that prints abstracts of certain recently published papers (those that the editors consider most important), with commentaries on these papers by distinguished organic chemists. Important current research in bioorganic, organometallic, synthesis, physical-organic and theoretical chemistry, and pharmaceutical–medicinal chemistry is covered in each issue, giving readers updates on the newest trends and developments in organic chemistry by summarizing and commenting on current and past research..
2. The Institute for Scientific Information (ISI), besides publishing *Current Contents* (p. 1877) and the *Science Citation Index* (p. 1877), also publishes *Index Chemicus* (formerly called *Current Abstracts of Chemistry and Index Chemicus*). This publication, begun in 1960 and appearing weekly, is devoted to printing structural formulas of all new compounds appearing in >100 journals, along with equations to show how they were synthesized and an author's summary of the work. Each issue contains five indexes: author, journal, biological activity, labeled compounds, and intermediates that were not isolated. These indexes are cumulated annually.
3. Theilheimer and the *Annual Reports on Organic Synthesis*, mentioned in the previous section, list new synthetic methods once a year. There are several publications that do this monthly. Among these are *Current Chemical Reactions* (begun in 1979 and published by ISI), *Journal of Synthetic*

Methods (begun in 1975 and published by Derwent publications), and *Methods in Organic Synthesis*, begun in 1984 and published by the Royal Society of Chemistry. *Methods in Organic Synthesis* also lists books and review articles pertaining to organic synthesis.

4. *Natural Product Updates*, a monthly publication begun in 1987 and published by the Royal Society of Chemistry, lists recent results in the chemistry of natural products, along with structural formulas. It covers new compounds, struc ture determinations, new properties and total syntheses, among other topics.

General Treatises

There are a number of large-scale multivolume treatises that cover the whole field of organic chemistry or large areas of it.

1. *Rodd's Chemistry of Carbon Compounds*, edited by Coffey, Elsevier, Amsterdam, The Netherlands, is a treatise consisting of five main volumes, each of which contains several parts. publication began in 1964 and is not yet complete. The organization is not greatly different from most textbooks, but the coverage is much broader and deeper. Supplements to many of the volumes have appeared. An earlier edition, called *Chemistry of Carbon Compounds*, edited by Rodd, was published in 10 parts from 1951 to 1962.
2. Houben–Weyl's, *Methoden der Organischen Chemie*, Georg Thieme Verlag, Stuttgart, is a major treatise in German devoted to laboratory methods. The fourth edition, which was begun in 1952 and consists of 20 volumes, most of them in several parts, is edited by E. Muller. The series includes supplementary volumes. The first four volumes contain general laboratory methods, analytical methods, physical methods, and general chemical methods. The later volumes are devoted to the synthesis of specific types of compounds, for example, hydrocarbons, oxygen compounds, and nitrogen compounds. Beginning in 1990 parts of the series have appeared in English.
3. *Comprehensive Organic Chemistry*, Pergamon, Elmsford, NY, ***1979***, is a six-volume treatise on the synthesis and reactions of organic compounds. The first three volumes cover the various functional groups, Vol. 4, heterocyclic compounds, and Vol. 5, biological compounds, such as proteins, carbohydrates, and lipids. Probably the most useful volume is Vol. 6, which contains formula, subject, and author indexes, as well as indexes of reactions and reagents. The last two of these not only refer to pages within the treatise, but directly give references to review articles and original papers. For example, on p. 1129, under "Chromic acid-sulphuric acid (Jones reagent), oxidation, alcohols," are listed 13 references to original papers. Several similar treatises, including the nine-volume *Comprehensive Organometallic Chemistry* (1982), the eight volume *Comprehensive Heterocyclic Chemistry* (1984), and the six volume *Comprehensive Medicinal Chemistry* (1989) are also published by Pergamon. The indexes to these works also include references.

4. A major treatise devoted to experimental methods of chemistry is *Techniques of Chemistry*, edited first by Weissberger and then by Saunders, Wiley, New York. This publication, which began in 1970, so far consists of 21 volumes, most of them in several parts, covering such topics as electrochemical and spectral methods, kinetic methods, photochromism, and organic solvents. *Techniques of Chemistry* is a successor to an earlier series, called *Techniques of Organic Chemistry*, which appeared in 14 volumes, some of them in more than one edition, from 1945 to 1969.
5. *Comprehensive Chemical Kinetics*, edited by Bamford and Tipper, 1969–, Elsevier, Amsterdam, The Netherlands, is a multivolume treatise covering the area of reaction kinetics. Six of these volumes (not all published at the time of writing) deal with the kinetics and mechanisms of organic reactions in a thorough and comprehensive manner.
6. Three multivolume treatises that cover specific areas are Elderfield, *Heterocyclic Compounds*, Wiley, New York, 1950-; Manske and Holmes, *The Alkaloids*, Academic Press, New York, 1950-; and Simonson, Owen, Barton, and Ross, *The Terpenes*, Cambridge University Press, London, 1947–1957.
7. *Encyclopedia of Reagents for Organic Synthesis*, edited by Paquette, Wiley, New York, was published in 1995. It is an eight volume, alphabetic listing of reagents used in organic chemistry with descriptions of the preparation, use and chemistry, with references. Each reagent was researched by organic chemists active in research, who contributed to the total publication.

   This work is available on-line as **eEROS.** The *Encyclopedia of Reagents for Organic Synthesis*, e-EROS, provides updated information on ~3800 reagents with a database of close to 50,000 reactions. Each reagent entry includes properties such as physical data, solubility, form supplied in, purification, and preparative methods; examples of use in reactions; and literature references. Search options include: name, CAS number, structure and reaction.
8. *Comprehensive Organic Synthesis*, edited by Trost and Fleming, Pergamon, was published in 1991. It is a nine volume compilation.
9. *Comprehensive Organic Functional Group Transformations*, edited by Katritzky, Meth-Cohn, and Rees, Pergamon, was published in 1995. It is a seven volume compilation.

Monographs and Treatises on Specific Areas

Organic chemistry is blessed with a large number of books devoted to a thorough coverage of a specific area. Many of these are essentially very long review articles, differing from ordinary review articles only in size and scope. Some of the books are by a single author, and others have chapters by different authors but all are carefully planned to cover a specific area. Many of these books have been referred to in footnotes in appropriate places in this book. There have been several series of monographs, one of which is worth special mention: *The Chemistry of Functional Groups*, under the general editorship of Patai, published by

Wiley, New York. Each volume deals with the preparation, reactions, and physical and chemical properties of compounds containing a given functional group. Volumes covering >20 functional groups have appeared so far, including books on alkenes, cyano compounds, amines, carboxylic acids and esters, and quinones.

Textbooks

There are many excellent textbooks in the field of organic chemistry. We restrict ourselves to listing only a few of those published, mostly since 1985. Some of these are first-year texts and some are advanced (advanced texts generally give references; first-year texts do not, though they may give general bibliographies, suggestions for further reading, etc.); some cover the whole field, and others cover reactions, structure, and/or mechanism only. All the books listed here are not only good textbooks and the advanced books are valuable reference books for graduate students and practicing chemists.

Bruckner, *Advanced Organic Chemistry: Reaction Mechanisms*, Academic Press, NY ***2001***.

Bruice, *Organic Chemistry*, 4th ed., Prentice-Hall, NJ, ***2004***.

Carey, *Organic Chemistry*, 6th ed., McGraw-Hill, NY, ***2006***.

Carey and Sundberg, *Advanced Organic Chemistry: Structure and Mechanisms (Part A)*, 4th ed., Springer, ***2004.***

Carey and Sundberg, *Advanced Organic Chemistry: Structure and Mechanisms (Part B)*, 4th ed., Springer, ***2001.***

Carruthers and Coldham, *Some Modern Methods of Organic Synthesis*, 4th ed., Cambridge University Press, Cambridge, ***2004***.

Ege, *Organic Chemistry: Structure and Reactivity*, 5th ed., D.C. Houghton Mifflin, Boston, ***2003***.

Fox and Whitesell, *Organic Chemistry*, 3rd ed, Jones and Bartlett, Sudbury, MA, ***2004.***

Grossman, *The Art of Writing Reasonable Organic Reaction Mechanisms*, 2nd ed, Springer, ***2005.***

House, *Modern Synthetic Reactions*, 2nd ed., W. A. Benjamin, New York, ***1972***.

Ingold, *Structure and Mechanism in Organic Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, ***1969***.

Isaacs, *Physical Organic Chemistry*, Wiley, NY, ***1987***.

Jones, *Organic Chemistry*, 3rd ed. W.W. Norton, NY, ***2004***.

Loudon, *Organic Chemistry*, 4th ed., Oxford University Press, Cambridge, ***2001***.

Lowry and Richardson, *Mechanism and Theory in Organic Chemistry*, 3rd ed., Harper and Row, New York, ***1987***.

McMurry, *Organic Chemistry*, 6th ed., Brooks/Cole, Monterey CA, ***2003***.

Maskill, *The Physical Basis of Organic Chemistry*, Oxford University Press, Oxford, ***1985***.

Morrison, Boyd and Boyd, *Organic Chemistry*, 6th ed., Benjamin Cummings, CA, ***1992***.

Mundy, Ellerd, and Favaloro, Jr., *Name Reactions and Reagents in Organic Synthesis*, 2nd ed, Wiley, Hoboken, ND, ***2005.***

Ritchie, *Physical Organic Chemistry*, 2nd ed., Marcel Dekker, NY, ***1989***.

Solomons and Fryhle, *Organic Chemistry*, 8th ed., Wiley, NY, ***2003***.

Smith, *Organic Synthesis*, 2nd edition McGraw-Hill, NY, ***2000***.

Streitwieser, Heathcock, and Kosower, *Introductory Organic Chemistry*, 4th ed., Prentice-Hall, Saddle River, NJ, ***1998***.

Sykes, *A Guidebook to Mechanism in Organic Chemistry*, 6th ed., Longmans Scientific and Technical, Essex, ***1986***.

Vollhardt and Schore, *Organic Chemistry*, 4th ed., W.H. Freeman, New York, ***2002***.

Wade, *Organic Chemistry*, 4th ed., Prentice-Hall, Upper Saddle River, NJ, ***1999***.

Other Books

In this section, we mention several books that do not fit conveniently into the previous categories. All but the last have to do with laboratory synthesis.

1. *Organic Syntheses*, published by Wiley, New York is a collection of procedures for the preparation of specific compounds. The thin annual volumes have appeared each year since 1921. For the first 59 volumes, the procedures for each 10- (or 9-) year period are collected in cumulative volumes. Beginning with Vol. 60, the cumulative volumes cover five-year periods. The cumulative volumes published so far are

Annual Volumes	Collective Volumes
1–9	**I**
10–19	**II**
20–29	**III**
30–39	**IV**
40–49	**V**
50–59	**VI**
60–64	**VII**
65–69	**VIII**
70–74	**IX**
75–80	**X**

The advantage of the procedures in *Organic Syntheses*, compared with those found in original journals, is that these procedures are *tested*. Each preparation is

carried out first by its author, and then by a member of the *Organic Syntheses* editorial board, and only if the yield is essentially duplicated is the procedure published. While it is possible to repeat most procedures given in journals, this is not always the case. All *Organic Syntheses* preparations are noted in *Beilstein* and in *CA*. In order to locate a given reaction in *Organic Syntheses*, the reader may use the OS references given in the present volume (through OS **69**); the indexes in *Organic Syntheses* itself; Shriner and Shriner, *Organic Syntheses* Collective Volumes I, II, III, IV, V *Cumulative Indices*, Wiley, New York, 1976, or Sugasawa and Nakai; Reaction Index of *Organic Syntheses*, Wiley, New York, 1967 (through OS **45**). Another book classifies virtually all the reactions in *Organic Syntheses* (collective vols. I–VII and annual vols. 65–68) into 11 categories: annulation, rearrangement, oxidation, reduction, addition, elimination, substitution, C—C bond formation, cleavage, protection–deprotection, and miscellaneous. This is *Organic Syntheses*: *Reaction Guide*, by Liotta and Volmer, published by Wiley, New York, in 1991. Some of the categories are subdivided further, and some reactions are listed in more than one category. What is given under each entry are the equation and the volume and page reference to *Organic Syntheses*.

2. Volume 1 of *Reagents for Organic Synthesis*, by Fieser and Fieser, Wiley, New York, 1967, is a 1457–page volume that discusses, in separate sections, some 1120 reagents and catalysts. It tells how each reagent is used in organic synthesis (with references) and, for each, tells which companies sell it, or how to prepare it, or both. The listing is alphabetical. Eighteen additional volumes have so far been published, which continue the format of Vol. 1 and add more recent material. A cumulative index for Vols. 1–12, by Smith and Fieser, was published in 1990. A complete cumulative index for Vol. 1–22 was published in 2005, by M.B. Smith. The series included Vol. 1–18 with Mary Fieser. After the death of Mary Fieser, the series was resumed by T. -L. Ho, and now includes Vol. 19–22.

3. *Comprehensive Organic Transformations*, 2nd ed. by Larock, Wiley-VCH, New York, ***1999***, has been frequently referred to in footnotes in Part 2 of this book. This compendium is devoted to listings of methods for the conversion of one functional group into another, and covers the literature through 1987. It is divided into nine sections covering the preparation of alkanes and arenes, alkenes, alkynes, halides, amines, ethers, alcohols and phenols, aldehydes and ketones, and nitriles, carboxylic acids and derivatives. Within each section are given many methods for synthesizing the given type of compound, arranged in a logical system. A schematic equation is given for each method, and then a list of references (without author names, to save space) for locating examples of the use of that method. When different reagents are used for the same functional group transformation, the particular reagent is shown for each reference. There is a 164-page index of group transformations. The 2nd edition has only recently been published and is *not* referenced in this edition, and a CD ROM version is now available.

4. *Survey of Organic Synthesis*, by Buehler and Pearson, Wiley, New York, 2 vols., ***1970***, ***1977***, discusses hundreds of reactions used to prepare the principal types of organic compounds. The arrangement is by chapters, each covering a functional group, (e.g., ketones, acyl halides, amines). Each reaction is thoroughly discussed and brief synthetic procedures are given. There are many references.
5. A similar publication is Sandler and Karo, *Organic Functional Group Preparations*, 2nd ed., 3 vols., Academic Press, New York, ***1983–1989***. This publication covers more functional groups than Buehler and Pearson.
6. *Compendium of Organic Synthetic Methods*, Wiley, New York, contains equations describing the preparation of thousands of monofunctional and difunctional compounds with references. Eleven volumes have been published so far (vol. 1–2, edited by Harrison and Harrison; Vol. 3, edited by Hegedus and Wade; Vol. 4–5, edited by Wade; Vol. 6–11 edited by Smith). Volume 12 will appear in 2007.
7. *The Vocabulary of Organic Chemistry*, by Orchin, Kaplan, Macomber, Wilson, and Zimmer, Wiley, New York, ***1980***, presents definitions of >1000 terms used in many branches of organic chemistry, including stereochemistry, thermodynamics, wave mechanics, natural products, and fossil fuels. There are also lists of classes of organic compounds, types of mechanism, and name reactions (with mechanisms). The arrangement is topical rather than alphabetical, but there is a good index. *Compendium of Chemical Terminology*, by Gold, Loening, McNaught, and Sehmi (the "Gold book"), published by Blackwell Scientific publications, Oxford, in 1987, is an official IUPAC list of definitions of terms in several areas of chemistry, including organic.

LITERATURE SEARCHING

Until recently searching the chemical literature meant looking only at printed materials (some of which might be on microfilm or microfiche). Now, however, much of the literature can be searched online, including some of the most important. Whether the search is online or uses only the printed material, there are two basic types of search, (*1*) searches for information about one or more specific compounds or classes of compounds, and (*2*) other types of searches. First, we will discuss searches using only printed materials, and then on-line searching.[39]

Literature Searching Using Printed Materials

Searching for Specific Compounds. Organic chemists often need to know if a compound has ever been prepared and if so, how, and/or they may be seeking a melting point, an ir spectrum, or some other property. Someone who wants all

[39]For a monograph that covers both online searching and searching using printed materials, see Wiggins, G. *Chemical Information Sources*, McGraw-Hill: NY, ***1991***.

the information that has ever been published on any compound begins by consulting the formula indexes in *Beilstein* (p. 1883). At this time there are two ways to do this. (*1*) The formula index to the second supplement (Vol. 29, see p. $$$) will quickly show whether the compound is mentioned in the literature through 1929. If it is there, the searcher turns to the pages indicated, where all methods used to prepare the compound are given, as well as all physical properties, with references. Use of the page heading method described on p. 1882 will then show the locations, if any, in the third and later supplements. (*2*) If one has an idea which volume of *Beilstein* the compound is in (and the tables of contents at the front of the volumes may help), one may search the cumulative index for that volume. If not sure, one may consult several indexes. One of these two procedures will locate all compounds mentioned in the literature through 1959. If the compound is heterocyclic, it may be in the fifth supplement. If it is in Vols. 17–19 (or in a later volume whose index has been published), the corresponding indexes may be consulted. If not, the page heading method will find it, if it was reported before 1960.[40] There is a way by which all of the above can be avoided. A computer program, called SANDRA (available from the *Beilstein* publisher), allows the user to find the *Beilstein* location by using a mouse to draw the structural formula of the compound sought. At this point, the investigator will know (*1*) all information published through 1959 or 1979,[34] or (*2*) that the compound is not mentioned in the literature through 1959 or 1979.[41] In some cases, scrutiny of *Beilstein* will be sufficient, perhaps if only a boiling point or a refractive index is required. In other cases, especially where specific laboratory directions are needed, the investigator will have to turn to the original papers.

To carry the search past 1959 (or 1979), the chemist next turns to the collective formula indexes of *Chemical Abstracts*™*:* 1957–1961; 1962–1966; 1967–1971; 1972–1976; 1977–1981; 1982–1986; 1987–1991; 1992–1996; 1997–2002, and such later collective indexes as have appeared; and the semiannual indexes thereafter. If a given formula index contains only a few references to the compound in question, the pages or abstract numbers will be given directly in the formula index. However, if there are many references, the reader will be directed to see the chemical substance index or (before 1972) the subject index for the same period; and here the number of page or abstract numbers may be very large indeed. Fortunately, numerous subheadings are given, and these often help the user to narrow the search to the more promising entries. Nevertheless, one will undoubtedly turn to many abstracts that do not prove to be helpful. In many cases, the information in the abstracts will be sufficient. If not, the original references must be consulted. In some cases (the index entry is marked by an asterisk or a double asterisk), the

[40]Compounds newly reported in the fifth supplement that are in a volume whose index has not yet been published will not be found by this procedure. To find them in *Beilstein* it is necessary to know something about the system (see Ref. 25), but they may also be found by consulting *CA* indexes beginning with the sixth collective index, or by using *Beilstein* on-line.

[41]For those heterocyclic compounds that would naturally belong to a volume for which the fifth supplement has been published.

compound is not mentioned in the abstract, though it is in the original paper or patent. Incidentally, all entries in the *CA* indexes that refer to patents are prefixed by the letter P. Since 1967, the prefixes B and R have also been used, to signify books and reviews, respectively.

By the procedure outlined above, all information regarding a specific compound that has been published up to about 1 year before the search can be found by a procedure that is always straightforward and that in many cases is rapid (if the compound has been reported only a few times). Equally important, if the compound has not been reported, the investigator will know that, too. It should be pointed out that for common compounds, such as benzene, ether, acetone, trivial mentions in the literature are not indexed (so they will not be found by this procedure), only significant ones. Thus, if acetone is converted to another compound, an index entry will be found, but not if it is used as a solvent or an eluant in a common procedure.

The best way to learn if a compound is mentioned in the literature after the period covered by the latest semiannual formula index of *CA* is to use the online services. However, if one lacks access to these, one may consult the keyword index at the end of each issue of *CA*. In these cases, of course, it is necessary to know what name might be used for the compound. The name is not necessary for *Index Chemicus*; one consults the formula indexes. However, these methods are far from complete. *Index Chemicus* lists primarily new compounds, those that would not have been found in the earlier search. The keyword indexes in *CA* are more complete, being based on internal subject matter, as well as title, but they are by no means exhaustive. Furthermore, all three of these publications lag some distance behind the original journals. To locate all references to a compound after the period covered by the latest semiannual formula index of *CA*, it is necessary to use *CAS* on-line.

The complete procedure described above may not be necessary in all cases. Often all the information one needs about a compound will be found in one of the handbooks (p. 1887), in the *Dictionary of Organic Compounds* (p. 1885), or in one of the other compendia listed in this chapter, most of which give references to the original literature.

Other Searches.[42] There is no definite procedure for making other literature searches using only printed materials. Any chemist who wishes to learn all that is known about the mechanism of the reaction between aldehydes and HCN, or which compounds of the general formula Ar_3CR have been prepared, or which are the best catalysts for Friedel–Crafts acylation of naphthalene derivatives with anhydrides, or where the group $-C(NH_2){=}N-$ absorbs in the IR, is dependent on their ingenuity and knowledge of the literature. If a specific piece of information is needed, it may be possible to find it in one of the compendia mentioned previously. If the topic is more general, the best procedure is often to begin by consulting one or more monographs, treatises, or textbooks that will give general

[42]This discussion is necessarily short. For much more extensive discussions, consult the books in Refs. 1 and 17.

background information and often provide references to review articles and original papers. In many cases, this is sufficient, but when a complete search is required, it is necessary to consult the *CA* subject and/or chemical substance indexes, where the ingenuity of the investigator is most required, for now it must be decided which words to look under. If one is interested in the mechanism of the reaction between aldehydes and HCN, one might look under "aldehydes," or "hydrogen cyanide," or even under "acetaldehyde" or "benzaldehyde," and so on, but then the search is likely to prove long. A better choice in this case would be "cyanohydrin," since these are the normal products and references there would be fewer. It would be a waste of time to look under "mechanism." In any case, many of the abstracts would not prove helpful. Literature searching of this kind is necessarily a wasteful process. Of course, the searcher would not consult the *CA* annual indexes, but only the collective indexes as far as they go and the semiannual indexes thereafter. If it is necessary to search before 1907 (and even before 1920, since *CA* was not very complete from 1907 to ~1920), recourse may be made to *Chemisches Zentralblatt* and the abstracts in the *Journal of the Chemical Society*.

Literature Searching Online[39]

Most of the *Chemical Abstracts*™ literature can be accessed using CAS databases on-line. The CAS registry[43] is the largest and most current database of chemical substance information in the world containing >26 million organic and inorganic substances and 56 million sequences. CAS is a team of scientists who provide digital information environment for scientific research and discovery and provides pathways to published research in the world's journal and patent literature back to the beginning of the twentieth century. Since 1907, CAS has indexed and summarized chemistry-related articles from >40,000 scientific journals, in addition to patents, conference proceedings and other documents pertinent to chemistry, life sciences and many other fields. In total, abstracts for >24 million documents are accessible online through CAS. Through the printed CA, CA on CD, STN, the CAS files distributed through licensed vendors, the SciFinder® and SciFinder Scholar™ desktop research tools, and the STN® Easy or STN® on the Web services, data produced by CAS is accessible to virtually any scientific researcher worldwide in industry, governmental research institutions, and academia.

Substance identification is a special strength of CAS. It is widely known as the CAS Registry, the largest substance identification system in existence. When a chemical substance, newly encountered in the literature, is processed by CAS, its molecular structure diagram, systematic chemical name, molecular formula, and other identifying information are added to the Registry and it is assigned a unique CAS Registry Number®. Registry now contains records for >26 million organic and inorganic substances and >56 million sequences.

The CAS REGISTRY contains >27 million organic and inorganic substances and >57 million sequences. A current count of substance records like this is

[43]http://www.cas.org/about.html

updated daily on the CAS web site.[44] An important piece of information that assists in such a search is the CAS Registry Number®. Each substance in REGISTRY is identified by a unique numeric identifier called a CAS Registry Number®.[45] "The CAS Registry Number® is a unique number assigned to a chemical by the Chemical Abstracts Service.[46] A fairly large collection of CAS numbers, with links to safety data for many chemicals, can be found at the listing of chemicals by CAS number at the Safety Home Page of the Physical and Theoretical Chemistry Laboratory at Oxford University."[47] The CAS Registry Number® is a unique numeric identifier that designates only one substance, has no chemical significance, and is a link to finding information about a specific chemical substance. A CAS Registry Number® includes up to nine digits that are separated into three groups by hyphens. The first part of the number, starting from the left, has up to six digits; the second part has two digits. The final part consists of a single check digit.[48]

CAS is located in Columbus, Ohio and is a division of the American Chemical Society. CAS can be contacted at Chemical Abstracts Service, 2540 Olentangy River Road, P.O. Box 3012, Columbus, Ohio 43210 (E-mail: help@cas.org).

Online searching means using a computer terminal to search a *database*. Although databases in chemistry are available from several organizations, STN® International (The Scientific & Technical Information Network) is important because it is comprehensive and available in many countries. STN® has dozens of databases, including many that cover chemistry and chemical engineering. To access these databases a chemistry department, a library, or an individual subscribes to STN® (for a nominal fee), and receives code numbers that will permit access to the system. Then all one needs is a computer and a modem. STN® charges for each use, depending on which databases are used, for how long, and what kind of information is requested. One of the nice features of STN® is that the same command language is used for all databases, so when one has mastered the language for one database, one can use it for all the others. In this section, we will discuss literature searching using *CAS* databases online, which is one of the databases available from STN. One thing that must be remembered is that *CAS databases online* is complete only from 1967 to the present,[49] so that searches for earlier abstracts must use the printed volumes. However, for the period since 1967, not only is online searching a great deal faster than searching the printed *CA*, but, as we will see, one can do kinds of searches online that are simply not possible using only the printed volumes. Furthermore, the on-line files are updated every two weeks, so that one will find all the abstracts on-line well past the appearance of the latest semiannual indexes, often even before the library has received the latest

[44] http://www.cas.org/cgi-bin/regreport.pl
[45] http://www.cas.org/EO/regsys.html
[46] http://www.cas.org/
[47] http://ptcl.chem.ox.ac.uk/MSDS/glossary/casnumber.html
[48] http://www.cas.org/EO/checkdig.html
[49] There is also a file called CAOLD that has some papers earlier than 1967.

weekly printed issue of *CA*. The *CAS databases online* is extremely flexible; one can search in a great many ways. It is beyond the scope of this book to discuss the system in detail (*CA* conducts workshops on its use), but even with the few commands we will give here, a user can often find all that he or she is looking for. The *CAS databases online* has two major files, *the CA File* and *the Registry File*.[50] T

SciFinder®: A Search Tool for Exploring CAS Databases[51]

Tutorials are available to help use SciFinder®,[52] which is a searching tool and not the CAS database. SciFinder® can search a research topic[53] or a compound can be searched by structure.[54] Another search engine is available, different from SciFinder®, known as STN Express® with Discover!,[55] and this searching tool can also be used to search CAS databases.[56] The Analysis Edition of STN Express® with Discover! allows one to search, analyze, visualize, and discover sci-tech information by the ability to create a table for substance analysis that identifies the common substructure for an answer set of structurally related substances,; Group related author–inventor names and company names for better analysis and visualization results; Analyze and tabulate data from single- or multi-file search results, and create a data table and 3D chart; Save an answer set from databases such as CAplusSM, PCTFULL, and USPATFULL with the Save for STN® AnaVist Wizard, and then import and open it in STN® AnaVistTM; Create an interactive spreadsheet from all or only hit CAS Registry Number®s and their corresponding CAS Roles through the CAS Registry Number®; Upload lengthy genetic sequences automatically for searching in DGENE and PCTGEN via the Upload Query Wizard. STN Express® was developed in collaboration with Hampden Data Services. Note that the CAplus database makes it possible to see not only what a paper has cited, but also what papers it been cited by.

To illustrate how STN® is used, an on-line tutorial is available.[57] A few on-line windows from a SciFinder® search are provided to illustrate how searches can be done. This presentation is by no means complete or intended as an alternative to the actual tutorial. Indeed, one could *not* use SciFinder® properly after simply reading this discussion. The intent is to illustrate some features that are available and to present an overview of the use of this important tool.

[50]There is also a file, LCA, which is used for learning the system. It includes only a small fraction of the papers in the CA File, and is not updated. There is no charge for using the LCA File, except for a small hourly fee.

[51]http://www.cas.org/. For a tutorial, see http://www.cas.org/SCIFINDER/citation.html.

[52]http://www.cas.org/SCIFINDER/SCHOLAR/interact/

[53]http://www.cas.org/SCIFINDER/SCHOLAR/page2a.html

[54]http://www.cas.org/SCIFINDER/SCHOLAR/scholstruc.html

[55]http://www.cas.org/ONLINE/STN/discover.html

[56]http://www.cas.org/stn.html

[57]http://www.cas.org/ONLINE/STN/expressmac.pdf

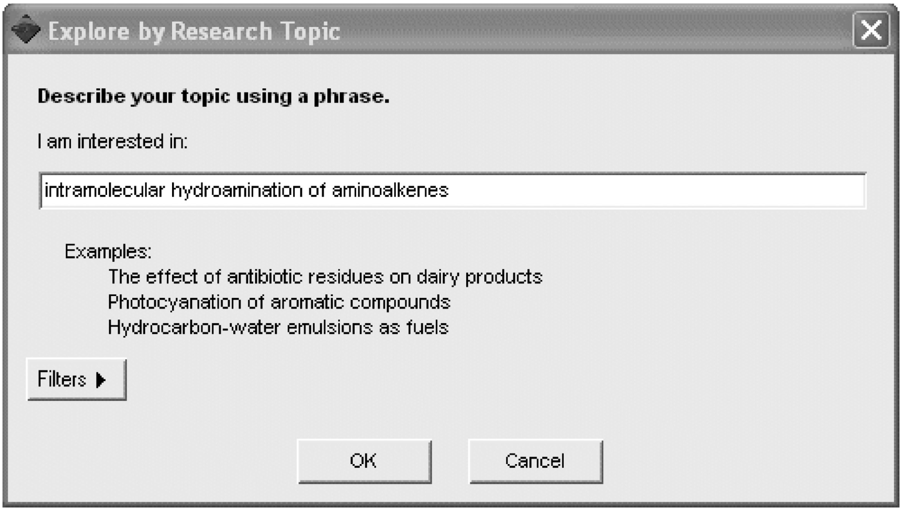


Fig. A.3. Explore by research topic.

Using SciFinder®, a search can be done in one of several different ways. In one example, a search is done by research topic:[58] The example shown in Fig. A.3 shows a search for intramolecular hydroamination of aminoalkenes. To begin, click Explore by research topic and enter the appropriate information.

It is possible to use filters (see Fig. A.3) in order to refine the search by year, document type (journal, patent, review, etc.), author, or company. A window is returned containing references categorized by their relationship to the search phrase, as shown in Fig. A.4. One then simply checks those reference lists that appear closest to the area of interest.

After clicking on ‘‘get references,’’ a screen is returned (Fig. A.5) that has the original references as shown in the window. One is given the option of refining this list further, and for each reference, most browsers allow viewing of the abstract or the full references as an HTML or a pdf file. Two icons appear beside each reference in the list: a microscope, which can be clicked on to see the abstract, and an document icon that can be clicked on to see the full-text, original article on the publisher's web-site. This feature is an alternative to document delivery in the traditional sense.

Other examples of typical searches allowed by SciFinder® include search by authors name, as with Professor K. Barry Sharpless shown in Fig. A.6. Search by structure is also possible, such as the one shown in Fig. A.7, and the program provides drawing tools. SciFinder® then searches to finds matches based on structure or reaction.

It is also possible to using the drawing tools to search by reaction and reaction type. SciFinder® returns reaction information, such as that shown in Fig. A. 8. In

[58]http://www.cas.org/SCIFINDER/topic.html

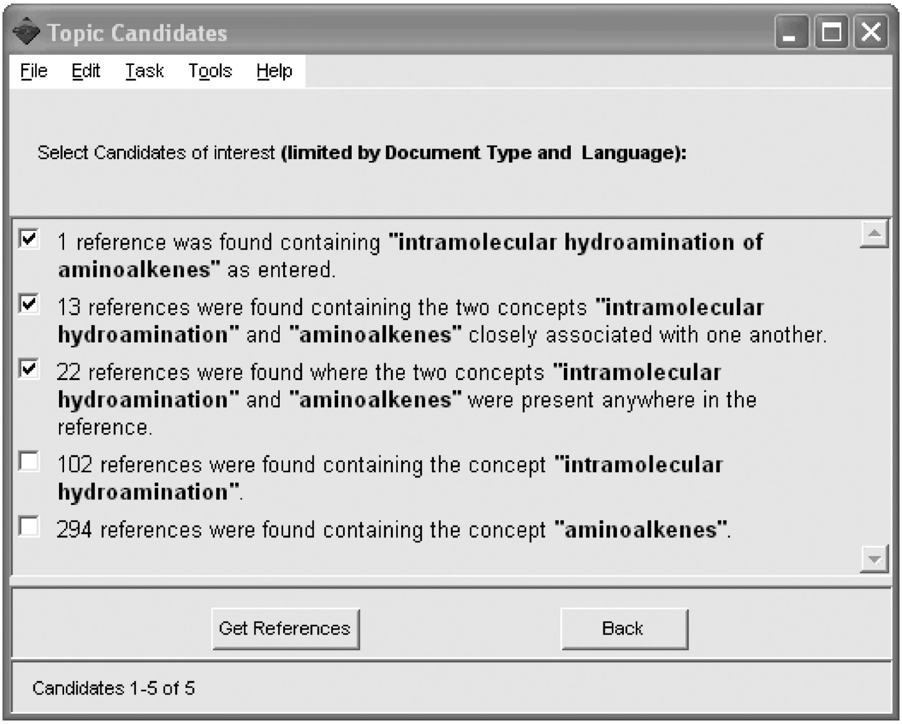


Fig. A.4. Selection of candidates of interest for search by research topic.

all cases, journal articles and/or patents are returned that provide direct access to the literature of interest.

Science Citation Index

As seen in the SciFinder® search tutorials, it is possible to track papers that have cited a particular article or author. A publication that can greatly facilitate literature searching is *Science Citation Index (SCI)*, begun in 1961. This publication, which is quite different from any other mentioned in this chapter, gives a list of all papers in a given year that have cited a given paper, patent, or book. Its utility lies in the fact that it enables the user to search *forward* from a given paper or patent, rather than backward, as is usually the case. For example, suppose a chemist is familiar with a paper by Jencks and Gilchrist (*J. Am. Chem. Soc.,* ***1968***, *90*, 2622) entitled "Nonlinear Structure–Reactivity Correlations. The Reactivity of Nucleophilic Reagents toward Esters." The chemist is easily able to begin a search for earlier papers by using references supplied in this paper, and can then go further backward with the aid of references in those papers, and so on. But for obvious reasons, the paper itself supplies no way to locate *later* papers.

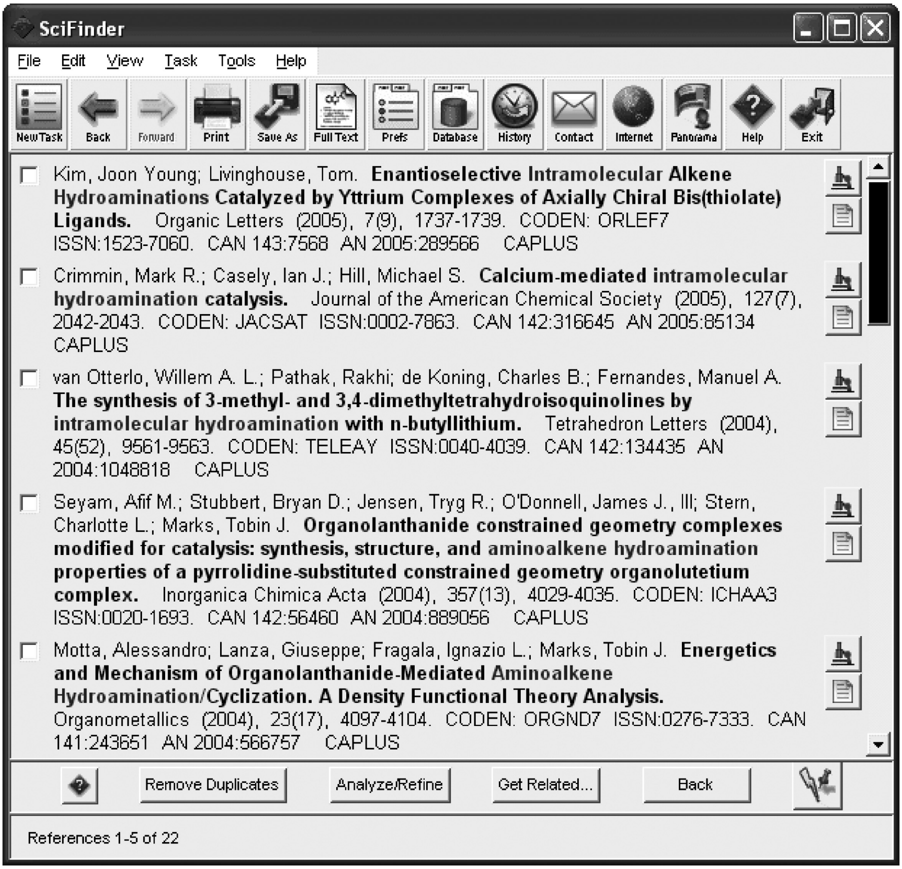


Fig. A.5. Original literature references returned for search by research topic.

The *SCI* is designed to make up for this gap. The citation index of *SCI* lists all papers, patents, or books cited in a given year or 2-month period (by first author only) and then gives a list of papers that have done the citing. The index is published bimonthly and cumulated annually. For example, column 43,901 of the 1989 citation index shows that the Jencks paper mentioned above was cited as a footnote in 16 papers published in 1989. It is reasonable to assume that most of the papers that cited the Jencks paper were on closely related subjects. For each of the 16 papers are listed the first author, journal abbreviation, volume and page numbers, and year. In a similar manner, if one consulted *SCI* for all the years from 1968 on, one would have a complete list of papers that cited that paper. One could obviously broaden the search by then consulting *SCI* (from 1989 on) for papers that cited these 16 papers, and so on. Papers, patents, or books listed, for example, in the 1989 *SCI* may go back many years (e.g., papers published by Einstein in 1905 and 1906 are included). The only

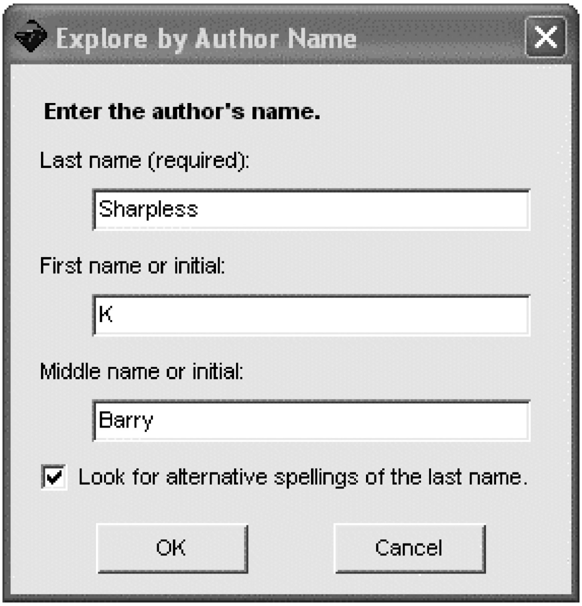


Fig. A.6. Screen shot for beginning a search by author.

requirement is that a paper published in 1989 (or late 1988) has mentioned the earlier paper in a footnote. The arrangement of cited papers or books is alphabetical by cited first author and then by cited year. Cited patents are listed in a separate table, in order of patent number, though the inventor and country are also given.

The *SCI* covers ∼3200 journals in the physical and biological sciences, as well as in medicine, agriculture, and technology. In addition to the citation index, each bimonthly and annual *SCI* also includes three other indexes. One of these, called *Source Index*, is similar to the *CA* author index. It lists the titles, journal abbreviations, volume, issue, page numbers, and year of all papers published by a given author during that 2-month period or year. All authors are listed; not just first authors. The second, called the *Corporate Index*, lists all publications that have been published from a given institution during that period, by first author. Thus, the corporate index for 1989 lists 63 papers by 45 different first authors emanating from the Department of Chemistry of Rutgers University, New Brunswick, NJ. The main section of the corporate index (the Geographic Section) lists institutions by country or (for the U.S.) by state. There is also an Organization Section, which lists the names of institutions alphabetically, and for each gives the location, so it can be found in the geographic section. The third index included in *SCI* is the *Permuterm*[59] *Subject Index*. This index alphabetically lists every significant word in the titles of

[59]Registered trade name.

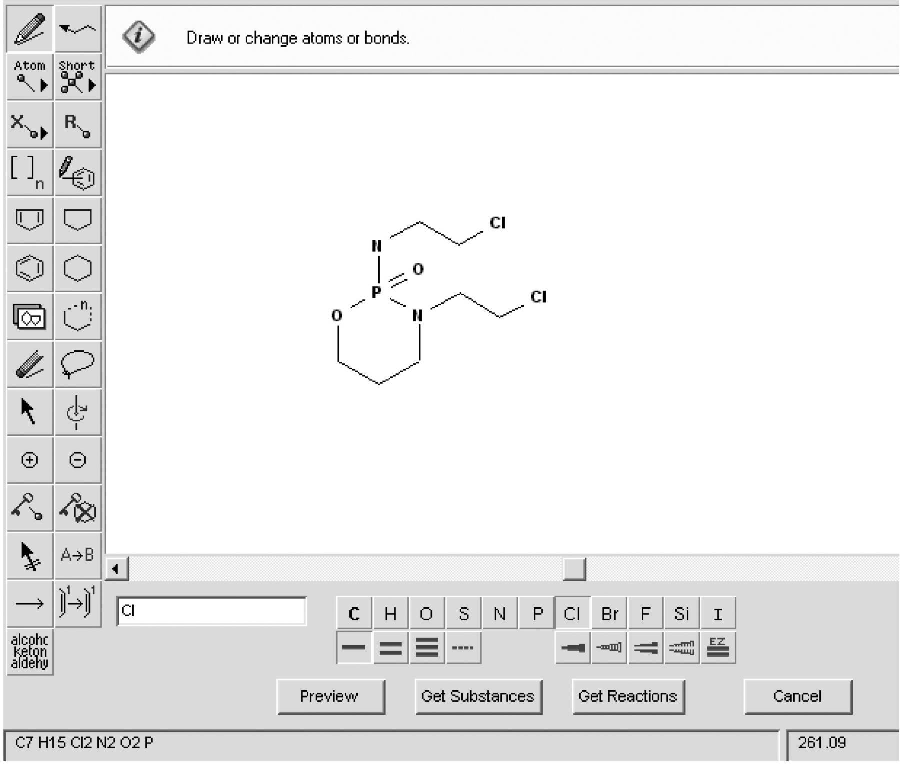


Fig. A.7. Screen shot for beginning a search by structure, using the drawing tools.

all papers published in that year or bimonthly period, paired with all other significant words in the same title. Thus, for example, a title with seven significant words appears at 42 separate places in the index. Each of the seven words appears six times as the main word, each time paired with a different word as the coword. The user is then led to the *Source Index*, where the full reference is given. The *SCI* is also available on-line (though not through STN) and on CD ROM disks. A version of *SCI* that is restricted to chemistry, but also includes searchable abstracts, is available only in the CD ROM format.

The publishers of *SCI* also produce another publication, called *Index to Scientific Reviews*, that appears semiannually. This publication, which began in 1974, is very similar to *SCI*, but confines itself to listing citations to review articles. The citations come from ~2500 journals in the same general areas as are covered by *SCI*. The review articles cited appeared in ~215 review journals and books, as well as in those journals that publish occasional review articles. Like *SCI*, the *Index to Scientific Reviews* contains citation, source, corporate, and Permuterm indexes. It also contains a "Research Front Specialty Index," which classifies reviews by subject.

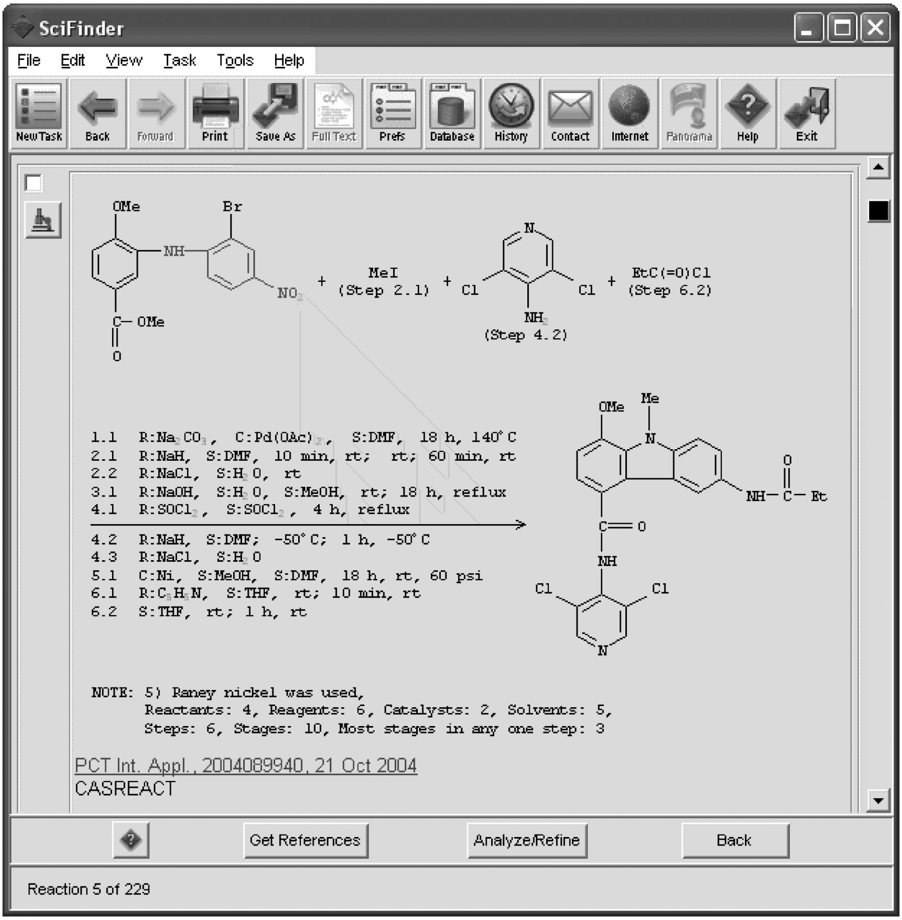


Fig. A.8. Screen shot of results for a search by reaction, using the drawing tools.

How to Locate Journal Articles

Having obtained a reference from various sources or searches, one often needs to consult the original journal (the location of patents is discussed on p. $$$). The first step is to ascertain the full name of the journal, since it is the abbreviation that is generally given. Of course, everyone should be familiar with the abbreviations of the very important journals, such as *J. Org. Chem.*, *Angew. Chem. Int. Ed.*, and so on, but references are often found to journals whose titles are not at all familiar (e.g., *K. Skogs Lantbruksakad. Tidskr.* or *Nauchn. Tr. Mosk. Lesotekh. Inst.*). In such cases, one consults the *Chemical Abstracts Service Source Index (CASSI)*, with the most recent abbreviations in bold print. *CASSI* is available in a 1907–2004 cumulative, containing information 80,000 serial and nonserial publications. *CASSI* also lists journals covered by *Chemisches Zentralblatt* and its predecessors

from 1830 to 1969, and journals cited in *Beilstein* before 1907. The journals are listed in alphabetical order of the *abbreviations*, not of the titles. Journal title changes have not been infrequent, and *CASSI* also contains all former names, with cross-references to the current names. Quarterly supplements, cumulated annually, to *CASSI* have appeared since 1990 listing new journals and recent changes in journal titles. It should be pointed out that, while many publications use the *CA* abbreviations, not all do. The student will find that usage will vary from country to country, and even from journal to journal within a country. Furthermore, the *CA* abbreviations have changed from time to time. Articles can be accessed directly from SciFinder® using the CAS ChemPort feature.[60]

Once the complete title is known, the journal can easily be obtained if it is in the library customarily used by the chemist. If not, one must use another library, and the next step is to find out which libraries carry the journal. *CASSI* answers this question too, since it carries a list of some 360 libraries in the United States and other countries, and *for each journal it tells which of these libraries carries it*, and furthermore, if the holdings are incomplete, which volumes of that journal are carried by each library. It may be possible to visit the closest library personally. If not, a copy of the article can usually be obtained through interlibrary loan. *CASSI* also includes lists of journal publishers, sales agents, and document depositories. Photocopies of most documents cited in *CA* can be obtained from *Chemical Abstracts*™ Document Delivery Service, Customer Services, 2540 Olentangy River Road, Columbus OH, 43210, U.S. Orders for documents can be placed by mail, telephone, Telex, fax, or on-line through STN® or other services.

These latter comments are largely out of date given the on-line status of most journals. As mentioned above, pdf files of an article can be downloaded, or they can be read directly via the HTML file using any current browser. The reader is encouraged to contact the library person in your establishment that is responsible for chemical literature and to learn which on-line services are available through your local library.

[60]See http://www.cas.org/chemport/index.html

APPENDIX B

Classification of Reactions by Type of Compounds Synthesized

ACETALS

acetals + RM **10-64**
aldehydes + alcohols **16-05**
by transetherification **10-13**
from dihalides **10-8**
from hydroxy-ethers **14-06**
ortho esters + RM **10-64**
reductive cleavage of ortho esters **19-56**

ACYLALS (DIESTERS)

aldehydes + anhydrides **16-06**

ACYLOINS – see hydroxy ketones

ALCOHOLS

addition of other organometallics to carbonyls **16-25**
aldehydes + allylic silanes **16-51**
alkenes + alcohols **15-33**
alkenes + aldehydes or ketones **16-54**
alkenes-oxymercuration **15-03**
amides + organometallic compounds **16-82**
amines + KOH **10-23**
anhydrides + organometallic compounds **16-82**
arylation of ketones **11-12**
boranes + CO–oxidation **18-23**
boranes + CO–reduction **18-24**
by the Cannizzaro reaction **19-81**
by Wittig rearrangement **18-21**
cleavage of ethers **10-49**
condensation of aldehydes **19-81**
conjugate reduction **15-14**
carboxylic esters + organometallics **16-82**
epoxides + organometallics **10-65**
epoxides + silanes **10-55**
from boranes **10-01**
from boronates **18-23**
Grignard addition to aldehydes or ketones **16-24**
hydration of alkenes **15-03**
hydrolysis of acetals and ketals **10-06**
hydrolysis of alkyl halides **10-01**
hydrolysis of inorganic esters **10-04**
hydrolysis of sulfonate esters **10-04**
hydrolysis of vinyl ethers **10-06**
hydroxylation at aliphatic carbon **19-14**
hydroxymethylation of arenes **11-12**
organolithium addition to aldehydes or ketones **16-24**
oxidation of boranes **12-27**
oxidation of boranes **15-16**
oxidation of methylene **19-15**

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Sixth Edition, by Michael B. Smith and Jerry March
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oxidation of silanes **10-16**
radical addition to carbonyl compounds **16-56**
rearrangement of ethers **18-22**
rearrangement of peroxides **18-20**
reduction of acyl halides **19-63**
reduction of aldehydes or ketones **19-36**
reduction of carbonyls with Grignard reagents **16-24**
reduction of carboxylic acids **19-37**
reduction of carboxylic esters **19-38**
reduction of carboxylic esters **19-65**
reduction of epoxides **19-35**
reduction peroxides **19-60**
ring expansion of amines **18-03**
silanes + aldehydes or ketones **16-26**

ALCOHOLS, ALLYLIC
addition of allylic organometallics to carbonyls **16-25**
alkenes + formaldehyde **16-54**
allylic silanes + aldehydes or ketones **16-26**
deprotonation of epoxides **17-03**
rearrangement of alkene-sulfoxides **18-35**

ALDEHYDES
alkenes + aldehydes **15-33**
alkyl halides + organoiron compounds **10-76**
alkylation of aldehydes **10-68**
alkylation of imines **10-68**
alkylation reactions **10-67**
and keto-enol tautomerism **12-03**
aromatic compounds + chloroform **11-18**
aromatic compounds + formaldehyde **11-18**
aromatic compounds + formamides **11-18**
aromatic compounds + halo-ethers **11-18**
arylation of aldehydes **13-14**
boranes + MeO(ArS)CH_2Li **18-24**
by decarboxylation **12-40**
by Michael addition **15-24**
by rearrangement of aldehydes **18-04**
by the Wacker process **19-25**
carbonylation of aromatic compounds **11-18**
carbonylation of hydrocarbons **12-33**
formylation of aromatic compounds **11-18**
from aryl imines **11-18**
from dihydrooxazines **10-72**
from dithioaldehydes **16-11**
hydroformylation **15-37**
hydrolysis of acetals **10-06**
hydrolysis of C=N compounds **16-02**
hydrolysis of *gem*-dihalides **10-02**
hydrolysis of nitro compounds **16-03**
hydrolysis of vinyl ethers **10-06**
oxidation of alcohols **19-03**
oxidation of aryl methyl groups **19-18**
oxidation of nitro compounds **19-21**
oxidation of primary alkyl halides **19-20**
oxidative cleavage of diols **19-07**
oxidative cleavage of epoxides **19-07**
ozonolysis of alkenes **19-09**
reduction anhydrides **19-40**
reduction nitriles **19-44**
reduction of acyl halides **19-39**
reduction of acyl halides **19-40**
reduction of amides **19-41**
reduction of carboxylic acids **19-40**
reduction of carboxylic esters **19-40**

ALKANES
addition of alkanes to alkenes **15-18**
alcohols + RM **10-63**
alkenes + diimide **15-12**
alkenes + metals **15-12**
alkenes + organometallics **15-21**
alkyl halides + metals **10-56**
alkyl halides + metals **10-56**
alkyl halides + organocuprates **10-58**
alkyl halides + RM (Li, Na, K) **10-57**

alkyl halides + RM (other metals) **10-59**
alkyl halides + silanes **10-55**
Barton–McCombie reaction **19-58**
by decarboxylation **12-40**
by [3+2]-cycloaddition **15-59**
cleavage of alkanes **12-47**
cleavage of ketones **12-46**
coupling of boranes **14-26**
coupling of carboxylate salts **14-29**
coupling of Grignard reagents **14-24**
coupling of organocuprates **14-25**
coupling of two alkanes **14-15**
decarbonylation of aldehydes **14-32**
decyanation **12-48**
from alcohols **19-58**
from alkylborates **10-59**
from boranes **10-59**
hydrogen exchange **12-01**
hydrogenation of alkenes **15-11**
hydrogenation of alkynes **15-11**
hydrogenation of aromatic compounds **15-13**
inorganic esters + RM **10-61**
insertion by carbenes **12-21**
pyrolysis of peroxides **17-37**
radical addition to alkenes **15-29**
radical coupling of alkanes **14-14**
radical cyclization of alkenes **15-30**
reduction dithioketals **10-71**
reduction of acyl halides **19-59**
reduction of alkyl halides **19-53**
reduction of carbonyls to methylene **19-61**
reduction of nitro compounds **19-67**
reduction of silanes **19-52**
reduction of sulfonate esters **19-57**
reduction of sulfur compounds **19-70**
reduction of thioethers **14-27**
reduction of thiols **14-27**
reduction of thiols **19-70**
reduction of xanthate esters **19-58**
reductive cleavage of cyclopropanes **15-15**
reductive cleavage of ethers **19-56**
replacement of metals in RM by hydrogen **12-24**
σ-bond rearrangements **18-38**
sulfonate esters + metals **10-56**
sulfonate esters + organocuprates **10-58**
sulfonyl compounds + organometallics **10-61**
via transmetallation **12-22**

ALKENE-ALCOHOLS

rearrangement of alkene-ethers **18-35**

ALKENE-ALDEHYDES

Claisen rearrangement **18-33**
Cope rearrangement **18-32**
rearrangement of allyl vinyl ethers **18-33**

ALKENE-ALKYNES

addition of alkynes to alkynes **15-20**

ALKENE-AMINES

rearrangement of alkene-ammonium salts **18-35**

ALKENE-CARBOXYLIC ACIDS

Claisen rearrangement **18-33**
rearrangement of alkene-esters **18-33**

ALKENE-KETONES

Claisen rearrangement **18-33**
rearrangement of allyl vinyl ethers **18-33**

ALKENE-THIOETHERS

rearrangement of alkene sulfonium salts **18-35**

ALKENES

1,3-elimination of diols **17-25**
1,3-elimination of halo-amines **17-25**
1,3-elimination of halohydrins **17-25**
addition of alkanes to alkynes **15-18**
addition of alkenes to alkenes **15-20**

aldehydes or ketones + active H compounds **16-38**
alkene metathesis **18-37**
alkenes + arylboronic acids **13-10**
alkenes + aryldiazonium compounds **13-10**
alkenes + carbenes **15-64**
alkenes + carbocations **12-20**
alkynes + aryl halides + RM (M = metal) **15-22**
alkynes + metals or metal hydrides **15-12**
allylic halides + metals **10-56**
allylic silanes + esters **10-60**
base induced elimination of halo-sulfones **17-20**
base induced elimination of sulfonyl hydrazones **17-11**
base-induced elimination of ammonium salts **17-08**
base-induced elimination of halides **17-13**
base-induced elimination of sulfonate esters **17-06**
base-induced elimination of sulfonyl halides **17-14**
bis-decarboxylation of dicarboxylic acids **19-13**
by decarboxylation **12-40**
by McMurry coupling **19-77**
by Peterson alkenylation **16-41**
by the Diels–Alder reaction **15-60**
by the ene reaction **15-23**
by the Heck reaction **13-10**
by the heteroatom Diels–Alder reaction **15-61**
by the Horner–Wadsworth–Emmons reaction **16-44**
by the Knoevenagel reaction **16-38**
by the Ramberg–Bäcklund reaction **17-20**
by the Sakurai reaction **15-26**
by the Wittig reaction **16-44**
by [2+2]-cycloaddition **15-63**
by [3+2]-cycloaddition **15-59**
cleavage of ethers **17-02**
cleavage of vinyl ethers **17-02**
conjugated addition of allylsilanes **15-26**
deacyloxylation **19-59**
decarbonylation of acyl halides **17-17**
decarboxylation of hydroxy-carboxylic acids **17-26**
dehydration of alcohols **17-01**
dehydrogenation **19-02**
deoxygenation of 1,2-diols **17-18**
diazoalkanes + aldehydes **15-64**
dimerization of alkyl halides **19-32**
elimination of 1,2-dihalides **17-22**
elimination of boranes **17-15**
elimination of halo-ethers **17-24**
enamines + boranes **15-16**
esters + organometallics **10-60**
extrusion from oxathiolanes **17-38**
extrusion of CO from cyclic ketones **17-35**
fro episulfones **16-48**
from bis(xanthates) **17-18**
from boranes **10-59**
from carbenes **12-21**
from dienes **18-37**
from epoxides or thiiranes **17-03**
from imines **16-44**
hydroboration of alkynes **18-25**
hydrogenation of alkynes **15-11**
hydrogenation of aromatic compounds **15-13**
isomerization of double bonds **15-01**
ketones or aldehydes + bis-Grignards **16-24**
migration of boranes **12-02**
migration of double bonds **12-02**
nitrosation of aziridines **17-21**
organometallics + ketones **16-25**
organometallics + tosylhydrazones **16-38**
other cycloaddition reactions **15-66**
oxidative decarboxylation of carboxylic acids **19-12**

Petasis alkenylation **16-45**
protonolysis of vinyl boranes **18-25**
protonolysis of vinyl boranes **18-26**
pyrolysis of amine oxides (Cope) **17-09**
pyrolysis of ammonium salts (Hofmann) **17-07**
pyrolysis of β-lactones **17-26**
pyrolysis of esters **17-04**
pyrolysis of hydroxy-alkenes **17-32**
pyrolysis of sulfones **17-12**
pyrolysis of sulfoxides **17-12**
pyrolysis of thionocarbonates **17-19**
pyrolysis of xanthates (Chugaev) **17-05**
reduction of alcohols **19-54**
reduction of amines **19-67**
reduction of carboxylic esters **19-65**
reduction of enamines **19-67**
reduction of nitriles **19-66**
reduction of thiiranes **19-35**
reduction of thiophene derivatives **19-70**
reduction of vinyl halides **19-53**
reduction of vinyl imines **19-61**
reductive coupling of aldehydes or ketones **19-77**
reductive coupling of epoxides **19-35**
sigmatropic carbon migration **18-30**
sigmatropic H migration **18-29**
silyl-organometallics + aldehydes or ketones **16-41**
Tebbe alkenylation **16-45**
vinyl boranes + halogen/base **18-25**
vinyl halides + arylboronic acids **13-10**
vinyl-cyclopropane rearrangement **18-31**
vinyl-X + alkyl(aryl)boronic acids **12-15**
Wagner–Meerwein rearrangement of alcohols **18-01**
Wagner–Meerwein rearrangement of halides **18-01**

ALKYNE-ALCOHOLS
addition of alkynes to carbonyls **16-25**

ALKYNES
alkyl halides + alkyne anions **10-74**
alkyl halides + propargylic RM **10-57**
alkynes + aryliodonium salts **13-13**
alkynes + boranes **18-26**
aryl halides + alkyne-M (M = a metal) **13-13**
aryl halides + alkynes **10-74**
base-induced elimination of dihalo compounds **17-16**
base-induced elimination of halides **17-13**
by Sonogashira coupling **13-13**
dimerization of dihalides **19-32**
elimination of alkenes **17-16**
hypervalent iodine + alkyne-M (M = a metal) **12-26**
metathesis of **18-37**
pyrolysis of bis(ammonium salts) **17-07**
pyrolysis of thiirene dioxides **17-20**
pyrolysis of ylids **17-10**

ALLENES
base-induced rearrangement of halocyclopropanes **18-03**
by Claisen rearrangement **18-33**
by the Wittig reaction **16-44**
Cope rearrangement of di-yens **18-32**
elimination of dihalides **17-22**
propargylic esters + organocuprates **10-60**
reduction of alkynes **19-53**

ALLOPHANATES
carbamates + isocyanates **16-08**

AMIDE-ESTERS
aziridines + amides **10-14**

AMIDES
acyl halides + ammonia or amines **16-72**
addition of organometallics to isocyanates **16-33**

alcohols + cyanogen halides **16-09**
aldehydes + ammonia + oxidant **14-11**
alkanes + nitriles **14-12**
alkenes + amides **15-09**
alkenes + nitriles **16-91**
alkyl halides + amides **10-41**
alkylation of amides **19-73**
amides + aldehydes **10-41**
amides + amines **16-76**
amines + CO + alkenes **15-36**
amines + CO **12-53**
amines + haloformates **10-53**
amines + organoiron compounds **10-77**
amines + vinyl esters **16-75**
anhydrides + ammonia or amines **16-73**
aromatic compounds + amides **11-22**
aromatic compounds + hydroxamic acids **11-06**
aromatic compounds + isocyanates **11-21**
aryl halides + amides **10-41**
aryl halides + amides **13-05**
aryl halides, DMF and $POCl_3$ **11-21**
by Beckmann rearrangement **18-17**
by Michael addition **15-24**
by the Willgerodt reaction **19-84**
carboxylic acids + amino-boranes **16-74**
carboxylic acids and ammonia or amines **16-74**
carboxylic esters + ammonia or amines **16-75**
cleavage of ketones **12-46**
condensation of methyl ketones **19-84**
from alcohols **10-41**
hydrolysis of isonitriles **16-97**
hydrolysis of nitriles **16-04**
imines + borane + CO **12-33**
insertion of acyl nitrenes **12-13**
insertion of diazo amides **12-21**
ketenes + amines **15-08**
ketones + HN_3 **18-16**
N-alkylation **10-41**
N-arylation **10-41**
nitriles + alcohols **16-91**
nitriles + amines **16-21**
oxidation of methylene in amines **19-17**
oxidation of methylene in lactams **19-17**
oximes + halogenating or oxidizing agents **18-17**
pyrolysis of imino esters **18-42**
rearrangement of oximes **18-17**
reduction of imides **19-64**
transamidation **16-70**

AMIDINES
ketenimines + amines **15-08**
nitriles + ammonia or amines **16-21**

AMINE OXIDES
oxidation of amines **19-29**

AMINES
addition of organometallics to C=N compounds **16-31**
addition of silanes to C=N **16-31**
alkenes + amines or ammonia **15-08**
alkyl halides + amines **10-31**
alkylation of amines **10-31**
alkylation of formamidines **10-71**
alkylation of nitroso amines **10-71**
amides + organometallic compounds **16-82**
amination of active methylene compounds **12-12**
amination of alkanes **10-39**
amination of alkanes **12-12**
amination of methylene **19-16**
amines + aryl halides **13-05**
amines + diaryliodonium compounds **11-06**
amines + diazo compounds **10-34**
aminomethylation of aromatic compound **11-22**
aromatic compounds + amide bases **13-18**

aromatic compounds + aryl azides **11-06**
aromatic compounds + halo-amines **11-06**
aromatic compounds + hydrazoic acid **11-06**
aryl halides + alkyl organometallics **13-05**
aryl halides + hydroxylamine-*O*-sulfonic acid **18-15**
azides + haloboranes **12-32**
aziridines + RM **10-66**
boranes + ammonia + NaOCl **12-32**
boranes + chloramine **12-32**
by the Stevens rearrangement **18-21**
by transamination **10-33**
Curtius rearrangement **18-14**
cyclization of halo-amines **18-40**
dealkylation of amines **19-73**
displacement of cyano **10-62**
diynes + amines **15-08**
enamines + boranes **15-16**
from alcohols **10-31**
from alcohols **10-32**
from amides **18-13**
from amines **10-33**
from amino-nitriles **10-62**
from boranes **10-31**
from cyanohydrins **10-32**
from ethers **10-32**
from halo-amines **10-31**
Hofmann rearrangement **18-13**
hydrolysis of isocyanates **18-13**
hydrolysis of isocyanates **18-15**
hydrolysis of isocyanates **18-16**
hydroxylamines + alkyl organometallics **12-32**
insertion of nitrenes **12-13**
Lossen rearrangement **18-15**
Michael addition with *N* nucleophiles **15-31**
phenols + amines or ammonia **13-06**
radical addition to C=N compounds **16-56**
rearrangement of ammonium salts **13-31**
rearrangement of ammonium salts **18-21**
rearrangement of aryl hydroxylamines **13-32**
reduction nitroso compounds **19-47**
reduction of amine oxides **19-68**
reduction of amines **19-64**
reduction of azides **19-50**
reduction of azo compounds **19-74**
reduction of azoxy compounds **19-74**
reduction of C=N compounds **19-42**
reduction of hydrazines **19-74**
reduction of hydroxylamines **19-47**
reduction of isocyanates **19-51**
reduction of isothiocyanates **19-51**
reduction of lactams **19-64**
reduction of nitriles **19-43**
reduction of nitro compounds **19-45**
reduction of nitroso-amines **19-51**
reduction oximes **19-48**
reductive alkylation of aldehydes or ketones **16-17**
Schmidt reaction **18-16**

AMINO-ACIDS
lactones + ammonia or amines **16-75**

AMINO-ALCOHOLS : see hydroxy-amines

AMINO-ALDEHYDES
aldehydes + C=N compounds **16-31**

AMINO-ESTERS
diazoesters + amines **15-64**

AMINO-ETHERS
aziridines + alcohols **10-14**

AMINO-KETONES
base-induced rearrangement of sulfonyl oximes **18-12**
ketones + HCHO + amines **16-19**
Mannich reaction **16-19**

AMINO-NITRILES
from cyanohydrins **10-32**
HCN or cyanide + C=N compounds **16-53**

AMINO-THIOETHERS
alkenes + sulfonamides **15-55**
alkenes + sulfonium salts + amines **15-55**

AMINO-THIOLS
episulfides + amines or ammonia **10-35**

AMMONIUM SALTS
alkyl halides + amines **10-31**

ANHYDRIDES
acyl halides + carboxylic acids **16-66**
aldehydes + acyl peroxides **14-09**
carboxylic acids + vinyl esters **16-67**
dehydration of carboxylic acids **16-67**
dehydration of dicarboxylic acids **16-67**

ANHYDRIDES, ORGANIC–INORGANIC
anhydrides + mineral acids **16-68**

ARENES
α-halo ketones + organocuprates **10-58**
alkyl halides + ArM (Li, Na, K) **10-57**
alkyl halides + aryl-M (M = a metal) **13-17**
alkyl halides + arylboronic acids **13-09**
alkyl halides + organocuprates **10-58**
alkyl halides + aryl organometallics **10-57**
aromatic compounds + active H compounds **13-17**
aromatic compounds + acylperoxides **14-17**
aromatic compounds + alcohols **11-11**
aromatic compounds + alkenes **11-11**
aromatic compounds + alkyl halides **11-11**
aromatic compounds + carboxylic acids **14-19**
aromatic compounds + ketones **11-12**
aryl halides + active methylene compounds **13-14**
aryl halides + alkenes **13-10**
aryl halides + alkenes **15-21**
aryl halides + alkynes **15-21**
aryl halides + organocuprates **10-58**
aryl halides + RM (other metals) **10-59**
aryl halides + vinylboronic acids **13-09**
aryl halides + trifluoroborates **13-09**
aryldiazonium salts + alkenes **13-25**
aryldiazonium salts + alkenes **13-26**
aryldiazonium salts + alkyl organometallics **13-25**
by decarboxylation **12-40**
by radical cyclization **15-30**
coupling of aromatic compounds **11-15**
cyclodehydration of carbonyl compounds **11-13**
Friedel–Crafts alkylation **11-11**
from alkylborates **10-59**
from boranes **10-59**
hydrogen exchange **11-01**
rearrangement of *N*-alkyl aryl amines **11-32**
replacement of aryl nitro **13-29**

AROMATIC COMPOUNDS
aromatic compounds + carbenes **15-64**
aromatization of six-membered rings **19-01**
cleavage of arenes **11-33**
cleavage of aryl alkyl ethers **11-37**
cyclization of ene-diynes **18-27**
cyclotrimerization of alkynes **15-65**
deamination of aromatic compounds **19-69**
decarbonylation of aryl aldehydes **11-34**
decarboxylation of aryl carboxylic acids **11-35**

dehalogenation of aryl halides **11-39**
dehydrogenation of cyclic alkanes **19-01**
desulfonylation of aryl sulfonic acids **11-38**
from aromatic compounds **18-28**
protonation of aryl organometallics **11-41**
pyrolysis of bicyclic dienones **17-28**
reduction aryl diazonium salts **19-69**
reduction of phenols **19-55**
reduction of quinones **19-01**

AZIDES
aldehydes + metal azides **16-78**
alkenes + hydrazoic acid **15-10**
alkenes + metal azides **15-53**
amides + sulfonyl azides **12-11**
from acyl halides **10-43**
from alkyl halides **10-43**
hydrazines + HONO or nitrosyl compounds **12-49**

AZIDO-ALCOHOLS
from epoxides **10-43**

AZIDO-AMINES
from aziridines **10-38**

AZIRIDINES
alkenes + alkyl azides **15-54**
alkenes + halogen + haloamines **15-54**
C=N compounds + sulfur ylids **16-47**
extrusion of nitrogen from triazolines **17-34**
form halo-amines **10-31**
from allene amides **15-09**
from azido-alcohols **10-43**
from epoxides **10-36**
from halo-azides **15-45**
from hydroxy-amines **10-32**
from imines **16-32**
from triazolines **15-58**
imines + diazo compounds **16-32**

AZIRINES
alkynes + amino-nitrenes **15-54**

AZO COMPOUNDS
aryl amines + nitroso compounds **13-24**
aryl diazonium salts + aromatic compounds **11-04**
from aryldiazonium salts **13-28**
oxidation of hydrazines **19-05**
rearrangement of aryl triazenes **11-30**
rearrangement of azoxy compounds **18-43**
reduction of azoxy compounds **19-68**
reduction of nitro compounds **19-80**

AZOXY COMPOUNDS
from alkyl halides **10-45**
nitroso compounds + hydroxylamines **12-51**
reduction of nitro compounds **19-79**

BIARYLS
aromatic compounds + aryl halides ($h\nu$) **14-18**
aromatic compounds + aryl organometallics **11-16**
aromatic compounds + aryl organometallics **14-17**
aromatic compounds + arylboronates **11-16**
aryl halides + alkyl or aryl organometallics **13-09**
aryl halides + aryl organometallics **13-11**
aryl halides + arylboronic acids **13-09**
aryl halides + arylboronic acids **13-12**
aryl halides + trifluoroborates **13-12**
aryldiazonium salts + aromatic compounds **13-27**
arylsulfonic acid + arylboronic acids **13-05**
by benzidine rearrangement **18-36**
by Suzuki–Miyaura coupling **13-12**
coupling 2 aryldiazonium salts **13-28**

coupling aryl halides **13-11**
coupling of aromatic compounds **11-15**
coupling of aryl sulfonates **13-12**
Ullmann coupling **13-11**

BISAMIDES
aldehydes + amides **16-18**

BISULFITES
metal bisulfite + carbonyl compounds **16-12**

BORANES
alkenes + borane or alkyl boranes **15-16**
boranes
thermal migration of boron in boranes **18-11**

BORATES (TRIFLUORO)
boranes + KHF_2 **12-28**

BORATES
alcohols + boranes **12-28**
borates
oxidation of boranes **12-27**

BORONIC ACIDS
alkyl borates + alkyl organometallics **12-28**

BUNTE SALTS
from alkyl halides **10-28**

CARBAMATES
alkyl halides + amines **10-17**
amines + alkyl halides + CO_2 **12-53**
amines + CO_2 **12-53**
from aziridines **12-53**
haloformates + amines **16-72**
isocyanates + alcohols **16-08**

CARBONATES
alcohols + phosphine **16-10**

CARBOXYLIC ACIDS
acyl halides + diazo compounds **18-08**
acyl peroxides + alkyl organometallics **12-26**
alkylation of carboxylic acids **10-70**
aromatic compounds + carbon dioxide **11-20**
aromatic compounds + carbon monoxide **11-20**
aromatic compounds + phosgene **11-19**
aryl nitro compounds + cyanide **13-30**
Barbier–Wieland procedure **19-10**
boranes + ether-acids **18-24**
by decarboxylation **12-40**
by Michael addition **15-24**
carboxylation of alkenes **15-35**
cleavage of diketones **12-43**
cleavage of keto-esters **12-43**
cleavage of ketones **12-45**
cleavage of methyl ketones **12-44**
deacyloxylation **19-59**
esters + metal halides **10-51**
from lactones **10-51**
from RM + arenes **10-57**
hydrolysis of acyl halides **16-57**
hydrolysis of amides **16-60**
hydrolysis of anhydrides **16-58**
hydrolysis of carboxylic esters **16-59**
hydrolysis of diazo ketones **18-08**
hydrolysis of nitriles **16-04**
hydrolysis of ortho esters **10-6**
hydrolysis of trihalide **10-03**
ketones + peroxy acids **18-19**
organometallics + CO_2 **16-30**
oxidation of aldehydes **19-23**
oxidation of aromatic rings **19-10**
oxidation of aromatic side chains **19-11**
oxidation of organoiron compounds **10-77**
oxidation of primary alcohols **19-22**
oxidative cleavage of alkenes **19-10**
oxidative cleavage of alkynes **19-10**
ozonolysis of alkenes **19-09**

phosphoranes + CO_2 **16-44**
pyrolysis of esters **17-04**
rearrangement of ketones **18-19**
via the haloform reaction **12-44**

CARBOXYLIC ESTERS
acyl halides + alcohols **16-61**
acyl halides + ethers **16-61**
alcohols + CO + alkenes **15-36**
alcohols + ketenes **15-05**
alcohols + organoiron compounds **10-77**
alcoholysis of acyl oxazolidinones **16-65**
alcoholysis of amides **16-65**
alcoholysis of nitriles **16-09**
alcoholysis of trihalides **10-03**
aldehydes + acyl halides **16-07**
alkenes + acyl peroxides **14-09**
alkenes + carboxylic acids **15-06**
alkenes + carboxylic esters **15-33**
alkyl halides + carboxylate anions **10-17**
alkylation of oxazolidines **10-72**
allylic carbonates + malonates **10-60**
allylic esters + malonates **10-60**
anhydrides + alcohols **16-62**
aryl halides + alcohols + CO **13-15**
aryl halides + alcohols + metal carbonyls **13-15**
Baeyer–Villiger rearrangement **18-19**
by Favorskii rearrangement **18-07**
by Michael addition **15-24**
by the Tishchenko reaction **19-82**
carbonylation of alkyl halides and alcohols **10-77**
carboxylic acids + diazo compounds **10-19**
cleavage of keto-esters **12-43**
condensation of aldehydes **19-82**
condensation of ketones **19-84**
esterification of carboxylic acids **16-63**
esters + ethers **10-18**
ethers + anhydrides **10-18**
from acyl peroxides **14-09**
from alkyl halo sulfites **10-17**
from coupling of activated esters **10-61**
from onium salts **10-17**
from tosyl amides **10-17**
hydrolysis of ortho esters **10-06**
insertion of diazo esters **12-21**
ketones + acyl halides **16-07**
ketones + peroxides **18-19**
oxidation of methylene in ethers **19-17**
oxidation of primary alcohols **19-22**
oxidation of vinyl ethers **19-25**
oxidative decarboxylation **19-12**
oxygenation of organometallics **12-29**
rearrangement of halo ketones **18-07**
ring contraction of diazo ketones **18-08**
transesterification **16-64**
via Mitsunobu coupling **10-17**

CONJUGATED ALDEHYDES
by aldol condensation **16-34**

CONJUGATED AMIDES
isocyanates + vinyl-M (metal) **15-22**

CONJUGATED CARBOXYLIC ACIDS
aldehydes + anhydrides **16-39**
by the Knoevenagel reaction **16-38**
CO_2 + vinyl-M (metal) **15-22**

CONJUGATED DIACIDS
by the Knoevenagel reaction **16-38**

CONJUGATED DIKETONES
by the Knoevenagel reaction **16-38**

CONJUGATED ESTERS
by the Knoevenagel reaction **16-38**
Claisen condensation **16-36**

CONJUGATED KETO-ESTERS
by the Knoevenagel reaction **16-38**

CONJUGATED KETONES
alkenes + acyl halides **12-16**
by aldol condensation **16-34**
by the Pauson–Khand reaction **15-36**
carbonylation of vinyl-M (M = metal) **12-33**
coupling of dienones **15-20**
oxidation of methylene **19-17**

CONJUGATED NITRILES
by the Knoevenagel reaction **16-38**

COUMARINS
from phenols **11-11**

CUMULENES
elimination of propargylic halides **17-22**

CYANAMIDES
amines + cyanogen halides **10-54**

CYANATES, ARYL
phenols + cyanogen halides **10-08**

CYANIDES, ACYL
acyl halides + metal cyanides **16-88**

CYANO IMINES
nitroso compounds + nitriles **16-42**

CYANOAMINES
see amino-nitriles

CYANOHYDRINS
aldehydes or ketones + HCN **16-52**
aldehydes or ketones + R_3SiCN **16-52**

CYCLOBUTANES
by [2+2]-cycloaddition **15-63**
extrusion of SO_2 **17-36**

CYCLOBUTENES
ring closure of dienes **18-27**

CYCLOPROPANES
alkenes + carbenes **15-64**
alkenes + diazo esters **15-58**
by the Simmons–Smith reaction **15-64**
conjugated carbonyls + sulfur ylids **16-49**
extrusion of nitrogen from pyrazolines **17-34**
extrusion off CO from cyclobutanones **17-35**
from pyrazoles **17-34**
from pyrazolines **15-58**
rearrangement of dienes **18-39**

DIACETATES
oxidation of dicarboxylic acids **19-13**

DIALDEHYDES
alkylation reactions **10-67**

DIAMINES
aziridines + amines or ammonia **10-38**
diamination of alkenes **15-53**
from azido-amines **10-38**
reductive coupling of imines **19-76**

DIAZO COMPOUNDS
acyl halides + diazomethane **16-89**
base-induced elimination of *N*-nitroso compounds **17-33**
oxidation of hydrazones **19-06**

DIAZONIUM COMPOUNDS
active methylene compounds + sulfonyl azides **12-10**
aldehydes + sulfonyl azides **12-10**
aromatic compounds + HONO **11-05**
aryl amines + HONO **13-19**

DICARBOXYLIC ACIDS
by Michael addition **15-24**
from aryl isothiocyanates **11-21**
oxidative cleavage of cyclic alkenes **19-10**
oxidative cleavage of ketones **19-08**

DIENES
addition of alkenes to dienes **15-20**
addition of alkynes to alkynes **15-20**
allylic halides + metals **10-56**
by the Diels–Alder reaction **15-60**
by the Wittig reaction **16-44**
cleavage of cyclobutanes **15-63**
Cope rearrangement **18-32**
coupling of alkynes and allenes **15-20**
coupling vinyl boranes **14-26**
cycloaddition of dienes **15-66**
dehydration of alkyne-alcohols **17-01**
dienes + acyl metal compounds **12-16**
from aromatic compounds **18-27**
hydrogenation of aromatic compounds **15-13**
hydrogenation of diynes **15-11**
metathesis of alkenes **18-37**
other cycloaddition reactions **15-66**
pyrolysis of bicyclic alkene-ketones **17-28**
pyrolysis of sulfoxides **17-20**
rearrangement of dienes **18-32**
ring closure of trienes **18-27**
ring opening of cyclic alkenes **18-27**
sigmatropic carbon migration **18-30**
sigmatropic H migration **18-29**
Stille coupling **12-15**
vinyl halides + metals **10-56**
vinyl halides + RM (other metals) **10-59**
vinyl-X + vinyl-M **12-15**

DIESTERS
active methylene compounds + alkyl halides **10-67**
alkenes + acyloxy salts **15-56**
alkylation reactions **10-67**
dimerization of acetals **10-64**

DIHALIDES (GEMINAL)
alkenes + halogenating agents **16-23**
ketones + halogenating agents **16-23**

DIHALIDES
alkynes + HX **15-02**
dihalogenation of alkenes **15-39**
from alkyl halides + trihalides **10-57**

DIKETONES
acyl halides + active H compounds **16-84**
acylation of enamines **10-69**
alkylation reactions **10-67**
by Michael addition **15-24**
conjugate addition of acyl halides **15-32**
conjugate addition of RM with metal carbonyls **15-32**
conjugated ketones + metals **10-56**
coupling acyl halides **16-83**
dimerization of silyl enol ethers **19-33**
esters + ketones **16-86**
from dithioketals **16-86**
hydrolysis of furans **10-6**
ketones + diazo-ketones **12-21**
oxidation of alkynes **19-26**
oxidation of methylene **19-17**
oxidative cleavage of cyclic alkenes **19-10**

DINITRILES
alkylation reactions **10-67**

DIOLS
alkenes + formaldehyde **16-53**
alkenes + halogens + metal carboxylates **15-48**
by the Tollens reaction **16-43**
dihydroxylation of alkenes **15-48**
from halo-esters **15-48**
hydride shifts of epoxides **18-41**
hydrolysis of epoxides **10-7**
hydrolysis of epoxides **15-48**
ketones + formaldehyde **16-43**
oxidation of aromatic compounds **15-49**
pinacol coupling **19-76**

reduction of lactones **19-38**
reductive coupling of aldehydes or ketones **19-76**

DISULFIDES
aryl halides + sulfides **13-04**
from alkyl halides **10-27**
oxidation of thiols **19-34**
reduction of sulfonyl halides **19-71**

DITHIOACETALS
aldehydes + thiols **16-11**
from dihalides **10-26**

DITHIOCARBAMATES
amines + carbon disulfide **16-22**

DITHIOKETALS
alkylation of dithioketals **10-71**
from dithioketals **10-13**
from dithiols **10-13**
ketones + CS_2 **16-42**
ketones + thiols **16-11**
vinyl sulfides + thiols **15-07**

DITHIOLS
alkenes + sulfur reagents **15-51**

DIYNES
metal coupling of alkynes **14-16**

ENAMIDES
amines + vinyl halides **12-32**

ENAMINES
alkylation of enamines **10-71**
alkynes + amines **15-08**
from hydroxy-amines **16-13**

ENOL ETHERS : see vinyl ethers

ENOLS
and keto–enol tautomerism **12-03**

EPISULFIDES : see thiiranes

EPOXIDES
aldehydes or ketones + halo-organometallics **16-24**
diazonium compounds + aldehydes or ketones **16-46**
epoxidation of alkenes **15-50**
from halohydrins **10-9**
sulfur ylids + aldehydes or ketones **16-46**

EPOXY-ALCOHOLS
allylic alcohols + peroxides **15-50**

EPOXY-AMIDES
epoxidation of conjugated esters **15-50**

EPOXY-CARBOXYLIC ACIDS
epoxidation of conjugated acids **15-50**

EPOXY-ESTERS
diazo esters + aldehydes **15-64**
epoxidation of conjugated esters **15-50**
halo esters + aldehydes or ketones **16-40**

EPOXY-KETONES
epoxidation of conjugated ketones **15-50**

EPOXY-NITRILES
epoxidation of conjugated nitriles **15-50**

ESTER-AMIDES
isonitriles + carboxylic acids + aldehydes **16-98**
isonitriles + carboxylic acids + ketones **16-98**

ESTER-SULFIDES
by the Pummerer rearrangement **19-83**
rearrangement of sulfoxides **19-83**

ESTERS : see carboxylic esters

ESTERS, INORGANIC
from alcohols **10-22**
from sulfonyl halides **10-22**
phosphites + alkyl halides **16-44**

ETHER-AMINES
rearrangement of halo-amines **18-18**

ETHER-ESTERS
conjugated esters + alcohols **15-05**

ETHER-KETONES
acetals + vinyl ethers **10-64**
oxidation of methylene **19-15**

ETHERS
acyl peroxides + alkyl organometallics **12-26**
alcohols + diazo compounds **10-11**
alcohols + onium salts **10-15**
alcohols + sulfonate esters **10-10**
aldehydes + alcohols **16-07**
alkenes + alcohols **15-05**
alkenes-alkoxymercuration **15-05**
alkylation of ethers **10-71**
aryl halides + alkoxides **13-03**
cleavage of oxonium salts **10-49**
dehydration of alcohols **10-12**
from alcohols (Williamson ether synthesis) **10-08**
from alcohols + phenols **10-12**
from alkyl halides (Williamson ether synthesis) **10-08**
from carboxylic esters **10-10**
from dihalides **10-10**
from halo-ethers **10-08**
from halohydrins **10-09**
from lactones and organometallics **16-30**
from trichloroimidates **10-10**
ketones + alcohols **16-07**
Michael addition with *O* nucleophiles **15-31**
oxidative cyclization of alcohols **14-06**
phenols + diazo compounds **10-11**
rearrangement of aryl sulfones **13-33**
reduction of esters **19-62**
reduction of lactones **19-62**
reductive cleavage of acetals or ketals **19-56**
transetherification **10-13**

ETHERS, SILYL
Brook rearrangement **18-44**
cleavage of ethers **10-49**
rearrangement of hydroxy-silanes **18-44**

FORMAMIDES
amines + trihalides **10-40**

GLYCIDIC ESTERS : see epoxy-esters

HALIDES, ACYL
acyl halides + HF **16-80**
aldehydes + halogens **14-04**
anhydrides + HF **16-80**
carboxyl acids + halogenating agents **16-79**
oxidation of primary alcohols **19-22**

HALIDES, ALKYL
alcohols + HX **10-48**
alcohols + inorganic acid halides **10-48**
aldehydes + halo-boranes **16-23**
alkenes + alkyl halides **15-46**
alkenes + halogens **14-01**
alkenes + HX **15-02**
carboxylate salts + halogens **14-30**
cleavage of amines **10-53**
cleavage of ethers **10-49**
cleavage of oxonium salts **10-49**
from amines **10-53**
from esters **10-51**
from inorganic esters **10-47**
from silyl ethers **10-48**

from sulfonate esters **10-47**
halide exchange with alkyl halides **10-46**
halo-decarboxylation of acids **16-71**
halogens + alkyl organometallics **12-31**
halogens + boranes **12-31**
halomethylation of arenes **11-14**

HALIDES, ALLYLIC
alkanes + halo-succinimides **14-03**
alkenes + halogens **14-03**

HALIDES, ARYL
aromatic compounds + halo-succinimides **11-10**
aromatic compounds + halogen **11-10**
aryl ammonium salts + halide ion **11-32**
aryl halides + metal halides **13-07**
aryldiazonium salts + metal halides **14-20**
aryldiazonium salts + metal iodides **13-22**
from aryl amines **14-20**
from phenols **13-22**
heating aryldiazonium tetrafluoroborates **13-23**
phenols + phosphonium halides **13-07**
rearrangement of *N*-halo amides **11-31**
sulfonyl halides + transition-metal halides **11-38**

HALIDES, SULFONYL
alkanes + SO_2 + halogens **14-10**
aromatic compounds + sulfonyl halides **11-08**
aryldiazonium salts + SO_2 **14-22**
sulfonic acids + halogenating **16-103**

HALIDES, VINYL
base-induced elimination of halides **17-13**
elimination of dihalides **17-22**
from alkynes **12-31**
halide exchange with vinyl halides **10-46**
halogens + vinyl boranes **12-31**
halogens + vinyl-M (M = a metal) **12-31**

HALO-ALCOHOLS
cleavage of cyclic ethers **10-49**
from aldehydes or ketones **16-24**

HALO-ALDEHYDES
aldehydes + halogen **12-04**
aldehydes + halogenating agent **12-04**
alkenes + formamides **15-47**

HALO-ALKYNES
from alkynes **12-31**

HALO-AMIDES
amides + hypohalites **12-53**
from aziridines **10-50**

HALO-AMINES
alkenes + *N*-halo-amines **15-43**
amines + hypohalites **12-52**

HALO-AZIDES
alkenes + X—N_3 **15-45**

HALO-CARBOXYLIC ACIDS
carboxylic acid + halogen **12-05**
carboxylic acid + halogenating agents **12-05**
from amino acids **10-52**

HALO-ESTERS
from epoxides **10-50**

HALO-ETHERS
from alkene-alcohols **15-51**

HALO-KETONES
alkenes + acyl halides **15-47**

from diazoketones **10-52**
ketone + halogen **12-04**
ketone + halogenating agents **12-04**

HALO-LACTAMS
halolactamization **15-41**

HALO-LACTONES
halolactonization **15-41**

HALO-NITRO COMPOUNDS
alkenes + NOX **15-44**

HALO-NITROSO COMPOUNDS
alkenes + NOX **15-44**

HALO-SILANES
from silanes **10-16**
silanes + halogens **14-02**

HALO-SULFONES
sulfones + halogenation agents **12-06**

HALO-SULFOXIDES
sulfoxides + halogenating agents **12-06**

HALOHYDRINS
alkenes + alcohols + halogens **15-40**
alkenes + hypohalous acids **15-40**
from epoxides **10-50**

HETEROCYCLES
acylation of amines **16-77**
aromatization of six-membered rings **19-01**
by the heteroatom Diels–Alder reaction **15-61**
by the Paterno–Büchi reaction **15-63**
by [3+2]-cycloaddition **15-58**
condensation of aldehydes **16-92**
cyclization of amino-ketones or aldehydes **16-13**
cyclization of halo-amines **18-40**
dehydrogenation reactions **19-02**
dinitriles + ammonia or amines **16-21**
rearrangement of acyl aziridines **18-31**
thermal rearrangement of azides **18-14**
furans–from diketones **16-05**
indoles:Fischer indole synthesis **18-34**
oxetanes–alkenes + aldehydes or ketones **16-95**
oxetanes–alkenes + ketones **15-63**
pyrans–from diketones **16-05**
pyrazoles–hydrazines + di-ketones **16-14**
pyrazolines–alkenes + diazoalkanes **15-58**
pyrazolines–hydrazines + keto-esters **16-14**
pyridine derivatives–by the heteroatom Diels–Alder reaction **15-61**
pyrrazolidines–alkenes + azomethine imines **15-58**
pyrrolidines–cleavage of aziridines **15-58**
pyrrolines–rearrangement of cyclopropyl imines **18-31**
quinolines (dihydro)–cyclodehydration of imines **11-13**
quinolines (dihydro)–from amines **11-13**
quinolines (tetrahydro)–cyclodehydration of amides **11-13**
quinolines (tetrahydro)–from amines **11-13**

HYDRATES
from ketones or aldehydes **16-01**

HYDRAZIDES
carboxylic esters + hydrazine **16-75**

HYDRAZINES
reduction of azo compounds **19-51**
reduction of diazo compounds **19-51**

HYDRAZONES
active methylene compounds + aryldiazonium **12-07**
exchange of hydrazine + hydrazones **16-14**
from azo compounds **12-07**
from ketones **12-07**
hydrazines + aldehydes or ketones **16-14**

HYDROXAMIC ACIDS
carboxylic esters + hydroxylamine **16-75**

HYDROXY-ALDEHYDES
by aldol condensation **16-34**
dihydrooxazines + epoxides **10-72**
imines + ketones **16-34**
Mukaiyama aldol **16-35**
oxidation of epoxides **19-20**
silyl enol ethers + aldehydes **16-35**

HYDROXY-AMIDES
aldehydes + amides **16-18**
alkenes + amides **15-52**
alkenes + sulfonyl amines **15-52**

HYDROXY-AMINES
alkenes + amines **15-52**
epoxides + amines or ammonia **10-35**
from isonitriles **10-40**
from nitro-alcohols **10-35**
oxetanes + amines or ammonia **10-37**
reductive coupling of C=N with C=O **19-76**
water induced rearrangement of halo-amines **18-10**

HYDROXY-AZIRIDINES
from amino-epoxides **10-36**

HYDROXY-CARBOXYLIC ACIDS
by the Cannizzaro reaction **19-81**
rearrangement of 1,2-diketones **18-06**

HYDROXY-ESTERS
Baylis–Hillman reaction **16-27**
Claisen condensation **16-36**
epoxides + carboxylate anions **10-14**
from epoxides and RCOOH **10-18**
Reformatsky reaction **16-28**
transesterification of lactones **16-64**

HYDROXY-ETHERS
epoxides + alcohols **10-14**

HYDROXY-KETONES
acyloin condensation **19-78**
aldehydes + cyanide **16-55**
aldehydes and cyanide **15-32**
Baylis–Hillman reaction **16-27**
by aldol condensation **16-34**
by rearrangement of hydroxy ketones **18-04**
by the Tollens reaction **16-43**
coupling of carboxylic esters **19-78**
hydrolysis of diazo ketones **10-05**
ketones + formaldehyde **16-43**
Mukaiyama aldol **16-35**
oxidation epoxides **19-20**
oxidation of methylene **19-15**
photolysis of epoxy-ketones **10-07**
rearrangement of silyloxy epoxides **18-02**
reduction of epoxy ketones **19-35**
silyl enol ethers + ketones **16-35**

HYDROXY-NITRILES: see cyanohydrins

HYDROXY-NITRO COMPOUNDS
from epoxides **10-35**
the Henry reaction **16-37**

HYDROXY-PHOSPHONATES
phosphonate esters + carbonyl compounds **16-44**

HYDROXY-PHOSPHORAMIDES
phosphoramides + carbonyl compounds **16-44**

HYDROXY-THIOCYANATES
epoxides + thiocyanate **10-14**

HYDROXY-THIOETHERS
Claisen condensation **16-36**
alkenes + disulfides + carboxylic acids **15-51**
from epoxides **10-26**

HYDROXYLAMINES
addition of organometallics to oximes **16-31**
oxidation of amines **19-27**
rearrangement of amine oxides **18-21**
reduction of nitro compounds **19-46**

IMIDES
acylation of amines **16-77**
alkyl halides + imides **10-41**
anhydrides + ammonia or amines **16-73**
from alcohols **10-41**
from aryl isothiocyanates **11-21**
isocyanates + phosphine oxides **16-93**

IMIDINES
dinitriles + ammonia or amines **16-21**

IMINES
active methylene compound + nitroso compound **12-08**
addition of organometallics to nitriles **16-33**
aldehydes + amines or ammonia **16-13**
alkynes + amines **15-08**
ketones + amines or ammonia **16-13**
oxidation of primary amines **19-21**
rearrangement of cyclopropyl **18-31**
reductive alkylation of aldehydes or ketones **16-17**
thermal rearrangement of alkyl azides **18-14**

IMINO ESTERS
halo-imines + aroxides **18-42**

ISOCYANATES
amides + hypohalites **18-13**
amines + CO **12-53**
base induced rearrangement of hydroxamic acids **18-15**
carboxylic acids + HN_3 **18-16**
Curtius rearrangement **18-14**
from acyl halides **10-44**
from alkyl halides **10-44**
from nitrile oxides **18-44**
Hofmann rearrangement **18-13**
phosgene + amines **16-72**
the Schmidt reaction **18-16**
thermal rearrangement of acyl azides **18-14**

ISONITRILES (ISOCYANIDES)
alkyl halides + cyanide **10-75**
amines + trihalides **10-40**
dehydration of formamides **17-31**
from oxetanes **10-40**

ISOTHIOCYANATES
from acyl halides **10-44**
from alkyl halides **10-44**

ISOTHIOURONIUM SALTS
from alkyl halides **10-25**

KETALS
ketones + alcohols **16-05**
reductive cleavage of ortho esters **19-56**

KETENES
base-induced elimination of acyl halides **17-14**

dehydration of carboxylic acids **17-01**
elimination of halo acyl halides **17-23**

KETENIMINES
by the Wittig reaction **16-44**
dehydration of amides **17-01**

KETO-ALDEHYDES
ketals + formamides **12-16**

KETO-ALKYNES
elimination of epoxy-hydrazones **17-27**

KETO-AMIDES
alkenes + acyloxy salts + nitriles **15-56**
amino acids + anhydrides **12-42**

KETO-CARBOXYLIC ACIDS
active H compounds + CO_2 or CS_2 **16-42**
carboxylic acids + esters **16-87**

KETO-ESTERS
acyl halides + active H compounds **16-84**
aldehydes + diazoketones **12-18**
alkylation reactions **10-67**
Claisen condensation **16-85**
halo-esters + esters **16-28**
halo-esters + nitriles **16-28**

KETO-NITRILES
acyl halides + active H compounds **16-84**
by the Thorpe reaction **16-50**
condensation of nitriles **16-50**
esters + nitriles **16-86**

KETO-SULFONES
acyl halides + active H compounds **16-84**

KETO-SULFONIC ACIDS
ketone + sulfur trioxide **12-14**

KETONES
1,3-elimination of diols **17-25**
1,3-elimination of halo-amines **17-25**
1,3-elimination of halohydrins **17-25**
acyl halides + organometallic compounds **16-81**
addition of organometallics to nitriles **16-33**
aldehydes + boranes **12-18**
aldehydes + transition-metal complexes **12-18**
alkenes + aldehydes **15-34**
alkenes + alkenes + CO **15-36**
alkenes + ketones **15-33**
alkyl halides + organoiron compounds **10-76**
alkylation of enamines **10-69**
alkylation of hydrazones **10-68**
alkylation of ketones **10-68**
alkylation reactions **10-67**
amines + HONO **12-50**
and keto–enol tautomerism **12-03**
aromatic compounds + acyl halides **11-17**
aromatic compounds + aldehydes **14-19**
aromatic compounds + anhydrides **11-17**
aromatic compounds + carboxylic acids **11-17**
aromatic compounds + nitriles **11-24**
arylation of ketones **13-14**
by decarboxylation **12-40**
by Michael addition **15-24**
by Pinacol rearrangement **18-02**
by rearrangement of ketones **18-04**
by the Wacker process **19-25**
carbonyl transposition **12-14**
carbonylation of metal alkyls **13-15**
carboxylic acids + organolithium reagents **16-29**
cleavage of alkoxides **12-41**

cleavage of diketones **12-43**
conjugate addition of organometallics **15-25**
conjugated addition of boranes **15-27**
cyanoboranes + anhydrides **18-23**
decarboxylative alkylation **14-31**
decarboxylative coupling of 2 acids **16-90**
diazo ketones + boranes **10-73**
Friedel–Crafts acylation **11-17**
from cyanohydrins **10-68**
from dihydrooxazines **10-72**
from dithioketals **16-11**
from keto-sulfoxides **10-67**
halo ketones + boranes **10-73**
homologation of ketones **18-09**
hydration of alkynes **15-04**
hydration of allenes **15-04**
hydrolysis of C=N compounds **16-02**
hydrolysis of dithioketals **10-71**
hydrolysis of *gem*-dihalides **10-2**
hydrolysis of imines **16-33**
hydrolysis of ketals **10-6**
hydrolysis of nitro compounds **16-03**
hydrolysis of vinyl ethers **10-6**
hydrolysis of vinyl halides **10-1**
imines + RM **10-69**
insertion of diazo ketones **12-21**
ketenes + alkenes **15-63**
keto esters + alkyl halides **10-67**
ketones + diazomethane **18-09**
oxidation alkenes **19-25**
oxidation of alcohols **19-03**
oxidation of dicarboxylic acids **19-13**
oxidation of methylene **19-17**
oxidation of nitro compounds **19-21**
oxidation of primary amines **19-21**
oxidation of vinyl boranes **18-26**
oxidative cleavage of alkenes **19-10**
oxidative cleavage of diols **19-07**
oxidative cleavage of enamines **19-10**
ozonolysis of alkenes **19-09**
pyrolysis of hydroxy-alkenes **17-32**
radical addition to conjugated ketones **15-28**
rearrangement of diols **18-02**
rearrangement of epoxides **18-02**
rearrangement of peroxides **18-20**
reductive coupling of keto-esters **19-77**
ring expansion of amino-alcohols **18-03**
ring expansion of halohydrins **18-03**
silyl enol ethers + alkyl halides **10-68**
transesterification of vinyl esters **16-64**
transition metal carbonyls + RM (M = metal) **12-33**
Weinreb amides + organometallic compounds **16-82**

LACTAMS
alkyl halides from amides **10-41**
and Michael addition **15-31**
by Beckmann rearrangement **18-17**
cyclic ketones + HN_3 **18-16**
cyclic ketones + silyl azides **18-16**
from amino carboxylic acids **16-74**
from halo-amides **10-41**
lactams + amines **16-76**
lactones + ammonia or amines **16-75**
N-arylation **10-41**
N-vinylation **10-41**
oxidation of methylene in amines **19-17**
rearrangement of oximes **18-17**
reduction of imides **19-64**
Schmidt reaction **18-16**

LACTAMS, β
diazoketones + C=N compounds **16-96**
enamines + ketenimines **16-96**
ketones + C=N compounds **16-96**

rearrangement of hydroxy-halo-amines **18-18**

LACTONES
alkenes + carboxylic acids **15-57**
and Michael addition **15-31**
Bayer–Villiger rearrangement **18-19**
condensation of dialdehydes **19-81**
cyclization of allene carboxylic acids **15-06**
from halo-carboxylic acids **10-17**
from hydroxy-carboxylic acids **16-63**
oxidation of methylene in ethers **19-17**
photolysis of halo-amides **18-40**
rearrangement of cyclic ketones **18-19**
rearrangement of lactones **18-44**
reduction of anhydrides **19-63**

LACTONES, β
ketones + aldehydes or ketones **16-95**

NITRATES : see inorganic esters

NITRILES
aldehydes + hydroxylamines **16-16**
alkenes + HCN **15-38**
alkyl halides + cyanide **10-75**
aromatic compounds + trihalo nitriles **11-25**
aryl halides + metal cyanides **13-08**
aryl triflates + metal cyanides **11-25**
base-induced elimination of hydrazones **17-29**
by decarboxylation **12-40**
by Michael addition **15-24**
carboxylic acids + cyanogen halides **16-94**
cyanation α to active hydrogen compounds **12-19**
cyanation α to nitrogen **12-19**
cyanoborates + metal cyanide **12-34**
dehydration of amides **17-30**
dehydration of oximes **17-29**
dehydrogenation of amines **19-05**
metal cyanides + aryl organometallics **13-08**
metal cyanides + alkyl organometallics **12-34**
rearrangement of isonitriles **18-21**
reduction of nitro compounds **19-49**

NITRITES : see inorganic esters

NITRO COMPOUNDS
alkanes + alkyl nitrates **12-09**
alkanes + nitronium salts **12-09**
alkenes + nitric acid **12-09**
aryldiazonium salts + metal nitrites **14-21**
by Michael addition **15-24**
conjugated carboxylic acids + HNO_3 **14-13**
from alcohols **10-42**
from alkyl halides **10-42**
nitration of aromatic rings **11-02**
oxidation of amines **19-28**
oxidation of isocyanates **19-28**
oxidation of oximes **19-28**
rearrangement of nitro-amines **11-28**

NITRO-ALCOHOLS: see hydroxy-nitro compounds

NITRONES
from oximes **10-24**
oxidation of oximes **19-06**

NITROSO COMPOUNDS
Barton rearrangement **18-40**
nitrosation of aromatic rings **11-03**
oxidation of amines **19-27**
rearrangement of nitroso-amines **11-29**

NITROSO-AMINES
amines + HONO **12-50**

ORGANOMETALLICS
alkanes + metals **12-23**

alkanes + alkyl organometallics **12-22**
alkenes + metal hydrides **15-17**
alkyl halides + metals **12-38**
alkyl halides + alkyl organometallics **12-39**
alkynes + metal hydrides **15-17**
aryl halides + metals **11-40**
aryl halides + R-M (M = a metal) **11-40**
formation of enolate anions **12-23**
isonitriles + organolithium reagents **16-99**
metal halides + RM (M = metals) **12-36**
metalation of aromatic compounds **13-17**
metals + RM (M = metals) **12-35**
thioethers + organometallics **14-28**
transmetallation of RM + R′M′ (M = metals) **12-37**

ORTHO ESTERS
by transetherification **10-13**
carboxylic acids + alcohols **16-05**
from trihalides **10-8**

OSAZONES
hydrazines + hydroxy aldehydes or ketones **16-14**

OXIMES
alcohols + NOCl **18-40**
aldehydes or ketones + hydroxylamine **16-15**
alkenes + NOX **15-44**
aryldiazonium salts + oximes **14-23**
Barton rearrangement **18-40**
carbonyl compounds + nitrous acid **12-08**
O-alkylation of oximes **10-24**
reduction of nitro compounds **19-49**

OXONIUM SALTS
alkyl halides + ethers **10-20**

PEROXIDES
acid halides + alkyl hydroperoxides **10-21**
alkenes + oxygen **14-07**
alkenes + oxygen **15-62**
alkenes + peroxides **14-08**
alkyl halides + hydroperoxide anion **10-21**
alkyl halides + hydroperoxide anion **10-21**
acid halides + hydrogen peroxide **10-21**
anhydrides + hydrogen peroxide **10-21**
dienes + oxygen **15-62**
oxidation of carboxylic acids **19-24**
oxygen + alkyl organometallics **12-25**
oxygen + organoboranes **12-25**
photooxidation of dienes **15-62**

PHENOLS
aromatic compounds + acyl peroxides **11-26**
aromatic compounds + peroxides **14-05**
aryl halides + hydroxide **13-01**
aryl sulfonic acids + hydroxide **13-02**
aryldiazonium salts + water **13-20**
by Wallach rearrangement **18-43**
Claisen rearrangement **18-33**
Fries rearrangement **11-27**
oxidation of aromatic compounds **11-26**
oxidation of aryl borates **13-01**
oxidation of arylboronic acids **13-01**
rearrangement of allyl aryl ethers **18-33**
rearrangement of aryl esters **11-27**
rearrangement of aryl hydroxylamines **13-32**
rearrangement of dienones **18-05**

PHOSPHINES
alkenes + phosphines **15-08**
phosphines + aryl halides **13-05**
reduction of phosphine oxides **19-68**

PHOSPHONATE ESTERS : see inorganic esters

PHOSPHONIUM SALTS
alkyl halides + amines **10-31**
phosphines + ammonium salts **10-31**

PHOSPHORANES
and the Wittig reaction **16-43**

QUINONES
and dyotropic rearrangement **18-44**
oxidation of aromatic compounds **19-04**
oxidation of aromatic compounds **19-19**
oxidation of phenols **19-04**

SELENIDES
aryl halides + selenide **13-04**
from alkyl halides **10-26**

SELENOCARBONATES
from isocyanates **16-08**

SELENOETHER-ALDEHYDES
aldehyde + diselenide **12-14**

SELENOETHER-KETONES
ketone + diselenide **12-14**

SELENOXIDES
alkylation of selenoxides **10-71**

SILANES
addition of silanes to alkene **15-19**
and dyotropic rearrangement **18-44**
aryl halides + silanes **13-16**
from metalated aryls **10-55**

SULFINIC ACIDS
RM (M = a metal) + sulfonating agents **12-30**

SULFONAMIDES
addition or arylboronates to C=N **16-31**
dealkylation of sulfonamides **19-73**
reduction of acyl sulfonamides **19-64**
reduction of sulfonyl azides **19-50**
sulfonyl halides + ammonia or amines **16-102**

SULFONATE ESTERS
alkenes + sulfonic acids **15-06**
sulfonamides + alcohols **16-101**
sulfonyl halides + alcohols **16-101**

SULFONES
alkenes + sulfonyl halides **15-42**
alkyl halides + sulfinic acid salts **10-29**
alkyl halides + sulfonyl halides **10-29**
alkylation of sulfones **10-67**
alkylation of sulfones **10-71**
and Michael addition **15-31**
aromatic compounds + sulfonic acids **11-09**
aromatic compounds + sulfonyl halides **11-09**
aryl halides + sulfonate **13-04**
oxidation of sulfoxides **19-31**
oxidation of thioethers **19-31**
sulfones + organometallics **10-61**
sulfonyl halides + arylboronic acids **16-105**
sulfonyl halides + organometallics **16-105**

SULFONIC ACIDS
aryl halides + sulfonates **13-04**
hydrolysis of sulfonyl halides **16-100**
oxidation of sulfur compounds **19-30**
oxidation of thiols **19-30**
rearrangement of aryl sulfones **13-33**
reduction of sulfonyl halides **16-104**
sulfonation of aromatic compounds **11-07**

sulfonation of aromatic compounds **11-36**
sulfonation of methylene **19-16**

SULFONIUM SALTS
alkyl halides + thioethers **10-26**

SULFONYL IMINES
sulfonamides + aldehydes **16-18**

SULFOXIDES
alkylation of sulfoxides **10-67**
aromatic compounds + sulfonyl halides **11-09**
oxidation of thioethers **19-31**

TELLURIDES
from alkyl halides **10-26**

THIIRANES (EPISULFIDES)
diazo compounds + sulfur **16-48**
alkenes + sulfur reagents **15-50**
from epoxides **10-26**
from halo-ketones **10-9**
thioketones + sulfur ylids **16-48**

THIOAMIDES
amides + sulfur reagents **16-11**
amides + sulfur reagents **16-70**
from nitriles **16-04**

THIOCARBAMATES
from isocyanates **16-08**
hydrolysis of thiocyanates **16-04**

THIOCARBOXYLIC ACIDS
acyl halides + sulfur reagents **16-69**

THIOCYANATES
aryl halides + thiocyanate **13-04**
aryldiazonium salts + thiocyanate **13-21**
from alkyl halides **10-30**
from amines **10-30**

THIOESTERS
acyl halides + thiols **16-69**
esters + sulfur reagents **16-11**

THIOETHER-ALDEHYDES
aldehyde + disulfides **12-14**

THIOETHER-KETONES
enol ethers + disulfides **12-14**
ketone + disulfides **12-14**

THIOETHERS (SULFIDES)
alkenes + thiols **15-07**
aromatic compounds + sulfones **11-23**
aryl halides + alkyl sulfides **13-04**
aryldiazonium salts + sulfide **13-21**
aryldiazonium salts + thiols **13-21**
from alcohols **10-26**
from alkyl halides **10-26**
from ammonium salts **10-26**
from dihalides **10-26**
Michael addition with *S* nucleophiles **15-31**
rearrangement of sulfonium salts **18-21**
reduction of sulfones **19-72**
reduction of sulfoxides **19-72**
sulfur + alkyl organometallics **12-30**
thiols + arylboronic acids **13-04**
thiophenols + aromatic compounds **13-04**

THIOKETONES
ketones + sulfur reagents **16-11**

THIOLACTAMS
lactam + sulfur reagents **16-11**
lactones + sulfur reagents **16-11**

THIOLS
alkyl halides + hydrogen sulfide or HS^- **10-25**
aryl halides + sulfide **13-04**

aryldiazonium salts + hydrogen sulfide **13-21**
from alcohols **10-25**
hydrolysis of Bunte salts **10-28**
reduction of disulfides **19-75**
reduction of sulfonyl halides **19-71**
sulfur + alkyl organometallics **12-30**

THIOUREAS
amines + CS_2 **16-22**
isothiocyanates + amines **16-20**

TRIAZOLES
alkenes + alkyl halides **15-58**

TRIAZOLINES
alkenes + alkyl azides **15-58**

TRIENES
aromatic compounds + carbenes **15-64**
cycloaddition of dienes **15-66**
ring opening of cyclic dienes **18-27**

TRIHALIDES
acyl halides + halogenating agents **16-23**
cleavage of methyl ketones **12-44**

TRIOXANES
from aldehydes **16-92**

UREAS
amines + CO_2 **16-22**
isocyanates + amines **16-20**

VINYL ETHERS (including silyl enol ethers)

alcohol + enol ester **10-13**
alcohol + enol ether **10-13**
by the Wittig reaction **16-44**
cleavage of acetals or ketones **17-02**
form esters **16-45**
from aldehydes **12-17**
from ketones **12-17**
from phenols **10-8**
peroxides + vinyl-M (M = a metal) **12-26**
Petasis alkenylation **16-45**
Tebbe alkenylation **16-45**

VINYL PHOSPHINES
alkynes + phosphines **15-08**

VINYL SILANES
addition of silanes to alkynes **15-19**

VINYL SULFIDES
alkynes + thiols **15-07**
ketones + thiols **16-11**

VINYL SULFONES
alkynes + sulfonyl halides **15-42**
from sulfinic acid salts **10-29**

XANTHATES
carbon disulfide + alcohols **16-10**

AUTHOR INDEX

Entries in this index refer to chapter number (**boldface**) and reference number.

Aalbersberg, W.G.L., **17**-0227
Aalten, H.L., **11**-0615
Aamouche, A., **04**-0114
Aaron, H.S., **01**-0087, **03**-0037
Aarts, G.H.M., **15**-0012
Abarbri, M., **10**-1419, **12**-0272, **12**-0297
Abatjoglou, A.G., **05**-0130
Abazi, S., **15**-1247
Abbadi, A., **16**-0431
Abbas S., **19**-1335
Abbassi, M., **19**-0807, **19**-0865
Abbiati, G., **15**-2423
Abbott, D.E., **10**-1187
Abbott, S.J., **04**-0031
Abbotto, A., **05**-0115, **05**-0194
Abboud J.M., **08**-0235
Abboud, J.L.M., **08**-0228
Abboud, J.M., **02**-0371, **03**-0015, **10**-0443, **10**-0448
Abboud, K.A., **10**-1462
Abdel-Magid, A.F., **16**-0362, **16**-1024, **19**-0913, **19**-0956
Abdel-Malik, M.M., **10**-0290, **11**-0594
Abdesaken, F., **01**-0011
Abdi, S.H.R., **15**-1830
Abdourazak, A.H., **02**-0360
Abduljaber, M.H., **10**-0196
Abdulla, N.I., **18**-0400
Abdulla, R.F., **10**-1599
Abe, H., **10**-1565, **11**-0328, **12**-0503, **13**-0135, **13**-0146, **19**-1156
Abe, M., **15**-1217, **16**-2092
Abe, S., **10**-1417, **11**-0285, **19**-0526
Abe, T., **10**-0448, **15**-0168
Abe, Y., **10**-0375, **15**-1359
Abel, E.W., **12**-0276
Abel, T., **16**-0563
Ãbele, E., **10**-0767
Abele, E., **13**-0570
Abele, R., **13**-0570
Abell, A.D., **10**-1518, **16**-1340
Abell, C., **16**-1793
Abell, P.I., **15**-0050, **15**-0054, **15**-0058
Abella, C.A.M., **11**-0438
Abelman, M.M., **17**-0170
Aben, R.W., **16**-2081
Abenhaïm, D., **16**-0493
Abenhaïm, D., **16**-0683
Abeywickrema, A.N., **13**-0706, **13**-0713
Abeywickreyma, A.N., **05**-0310
Abidi, S., **10**-1191
Abidi, S.L., **17**-0323
Abiko, A., **15**-2297, **16**-0985, **16**-1142, **16**-1315
Abiko, S., **18**-0453
Abiko, T., **18**-0727
Abiraj, K., **19**-1153, **19**-1749
Abis, L., **18**-0193
Ablenas, F.J., **19**-1619
Abokitse, K., **19**-1022
About-Jaudet, E., **19**-0612
Abraham, L., **18**-0405, **18**-0666, **18**-0702
Abraham, M.H., **03**-0002, **08**-0101, **03**-0015, **04**-0333, **08**-0132, **08**-0133, **10**-0429, **10**-0432, **10**-0443, **10**-0448, **10**-1320, **12**-0002, **12**-0020, **12**-0021, **12**-0023, **12**-0024, **12**-0038, **12**-0040, **12**-0424, **12**-0431, **12**-0482, **12**-0504, **12**-0551
Abraham, N.A., **11**-0391
Abraham, R.J., **04**-0283, **04**-0284, **04**-0314, **04**-0332, **04**-0345, **04**-0384, **15**-0016
Abraham, S., **10**-0958, **19**-1594
Abraham, W., **02**-0158
Abraham, W.D., **15**-1109, **18**-0235
Abrahams, S.C., **01**-0082
Abrahamson, E.W., **18**-0476
Abrahamsson, P., **16**-0979
Abraitys, V.Y., **15**-2236
Abram, T.S., **05**-0067
Abramenkov, A.V., **04**-0437
Abramov, A.I., **16**-1480
Abramovitch, A., **18**-0449
Abramovitch, R.A., **05**-0396, **05**-0406, **05**-0411, **07**-0105, **07**-0116, **11**-0068, **13**-0580, **13**-0739, **14**-0286, **14**-0331, **18**-0283, **18**-0715
Abrams, J.N., **19**-0688
Abrams, S.R., **12**-0067, **19**-0737
Abrouki, Y., **15**-1029, **15**-1328
Abrunhosa, I., **10**-1454
Abt, A., **19**-1764
Abu-Hasanayn, F., **05**-0193, **12**-0420
Abu-Omar, M.M., **15**-1754
Abu-Raqabah, A., **05**-0284
Aburatani, R., **04**-0175
Aburel, P.S., **15**-0996, **16**-0899
Acemoglu, M., **15**-1969
Acevedo, O., **13**-0002
Acharya, J., **10**-0835
Achiwa, K., **15**-0607, **15**-1932, **18**-0551, **19**-0659, **19**-1366
Achmatowicz Jr., O., **16**-1481, **16**-1482
Achmatowicz, O., **15**-0984
Acke, M., **16**-0182
Ackerman, J.H., **04**-0508
Ackerman, J.J.H., **10**-1742
Ackerman, L., **15**-0367, **18**-0772

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Ackermann, L., **15**-0331, **15**-0357, **15**-0367, **15**-0776, **15**-0835
Acott, B., **18**-0271
Acton, N., **04**-0440
Adachi, K., **12**-0170
Adachi, M., **10**-0850, **11**-0390, **11**-0524, **11**-0530
Adachi, S., **15**-1014
Adam, G., **10**-1023
Adam, J., **14**-0182
Adam, M., **19**-1210
Adam, W., **05**-0257, **07**-0045, **07**-0048, **07**-0054, **11**-0563, **12**-0435, **14**-0229, **15**-0991, **15**-1741, **15**-1743, **15**-1766, **15**-1768, **15**-1769, **15**-1791, **15**-1807, **15**-1812, **15**-1826, **15**-1828, **15**-1832, **15**-1841, **15**-1845, **15**-1849, **15**-2153, **15**-2157, **15**-2159, **15**-2161, **16**-1649, **16**-2088, **16**-2089, **17**-0415, **17**-0502, **18**-0070, **18**-0361, **18**-0463, **18**-0487, **18**-0495, **18**-0853, **19**-0010, **19**-0205, **19**-0211, **19**-0237, **19**-0262, **19**-0488, **19**-0504, **19**-0540, **19**-0542, **19**-0547
Adams, A.D., **19**-0065
Adams, C., **19**-1063
Adams, C.M., **18**-0903, **18**-0757, **19**-1001
Adams, D.B., **04**-0035
Adams, D.G., **05**-0171
Adams, D.J., **09**-0109
Adams, D.R., **16**-1462
Adams, H., **03**-0069, **04**-0372, **16**-0803
Adams, H.J., **16**-1383
Adams, J., **03**-0018, **12**-0348, **12**-0368, **15**-2292, **16**-1378
Adams, J.P., **10**-1672, **12**-0260
Adams, J.S., **05**-0298
Adams, J.T., **16**-2014
Adams, N.D., **16**-0557
Adams, R., **04**-0001, **04**-0013, **04**-0055, **04**-0056, **16**-1881, **18**-0623
Adams, R.D., **04**-0519
Adams, R.M., **04**-0098
Adams, W.R., **14**-0227, **15**-2151
Adamsky, F., **18**-0559
Adapa, S.R., **10**-1849, **14**-0205, **15**-1020, **16**-0087, **18**-0357
Adcock, J.L., **14**-0130
Adcock, W., **01**-0042, **04**-0340, **05**-0092, **09**-0060
Adcock, J.L., **10**-0323
Addadi, L., **04**-0102, **04**-0188, **04**-0188
Addess, K.J., **10**-1150
Addy, J.K., **10**-0495
Adelaere, B., **16**-0209
Adema, E.H., **11**-0377
Ader, J.C., **10**-1006
Adewuyi, Y.G., **07**-0085
Adger, B.M., **19**-1225
Adibi, H., **16**-0083, **19**-0152, **19**-0803
Adickes, H.W., **10**-1733, **10**-1735, **10**-1736, **18**-0347
Adimurthy, S., **11**-0296
Adinolfi, M., **15**-1685
Adjabeny, G., **13**-0491
Adkins, H., **19**-1092
Adkins, J.D., **19**-1106
Adkins, S., **15**-1776
Adler, A., **15**-1017
Adler, E., **19**-0269, **19**-0314
Adlhart, C., **18**-0833
Adlington, M.G., **19**-1450
Adlington, R.M., **17**-0268, **18**-0159, **18**-0175
Adolfsson, H., **15**-1707, **15**-1753, **16**-0788, **16**-0792, **16**-0806, **18**-0773
Adrian Jr., J.C., **16**-0867, **16**-0886
Adrian, F.J., **05**-0219, **05**-0283
Adrio, J., **12**-0262, **15**-1418
Adude, R.N., **11**-0211
Aebisher, D., **15**-0149
Aechtner, T., **15**-2400
Aelterman, W., **19**-1328
Aerssens, M.H.P.J., **15**-0502
Aeungmaitrepirom, W., **03**-0136
Afanas'ev, I.B., **09**-0016, **09**-0061, **15**-0064
Afanas'eva, L., **10**-1835, **19**-0616
Affanasiev, V.V., **12**-0524
Affandi, H., **10**-1027
Afonso, C.A.M., **09**-0116, **10**-1151, **10**-1213, **15**-1703, **15**-1703, **16**-0779
Agababyan, A.G., **16**-0392, **16**-0393
Agadzhanyan, Ts.E., **18**-0888
Agam, G., **03**-0194
Agami, C., **10**-1493, **16**-1072, **16**-1403
Aganov, A.V., **06**-0056
Agapiou, K., **16**-0720
Agarrabetia, A.R., **18**-0570
Agarwal, A., **19**-0831
Agarwal, S., **19**-0080, **19**-0249
Agata, I., **10**-1426
Agawa, T., **19**-1304
Agbaria, K., **03**-0124
Agdeppa Jr., D.A., **18**-0126
Ager, D., **12**-0311, **16**-1233
Ager, D.J., **10**-1693, **13**-0238, **14**-0413, **16**-1232, **16**-1243, **19**-1467
Aggarwal, V., **16**-0473
Aggarwal, V.K., **04**-0372, **12**-0323, **15**-0851, **15**-0974, **15**-0986, **15**-2301, **16**-0743, **16**-0774, **16**-0777, **16**-0803, **16**-0947, **16**-0949, **16**-1230, **16**-1326, **16**-1371, **16**-1383, **16**-1386, **18**-0250, **18**-0800
Aggen, D.H., **16**-0174
Aghapoor, G., **17**-0466
Aghapoor, K., **19**-0101
Aghapour, G., **10**-1106, **18**-0660
Aghmiz, A., **10**-1454
AgirBas H., **05**-0323
Agmon, N., **08**-0141
Agnihotri, R.K., **15**-0549
Agranat, A., **02**-0186
Agranat, I., **02**-0360, **04**-0187, **11**-0447, **11**-0607
Agrios, K.A., **18**-0297
Aguero, A., **16**-1366, **16**-1367, **19**-0718
Aguirre, G., **16**-1438
Aguirre, S., **11**-0327, **15**-2398
Agwada, V.C., **16**-0372
Agwaramgbo, E.L.O., **16**-1234
Ahamed, M., **19**-0120
Ahern, M.F., **13**-0691
Ahiko, T.-a., **16**-0698
Ahlberg, P., **03**-0057, **06**-0059, **08**-0209, **17**-0050, **17**-0056, **17**-0147, **17**-0216, **18**-0009
Ahlbrecht, H., **10**-1492, **10**-1662, **10**-1716, **10**-1729
Ahmad, A., **17**-0457
Ahmad, M., **10**-0527, **16**-0344
Ahmad, S., **12**-0316, **16**-1614, **16**-1725, **18**-0700
Ahmad, T., **12**-0468
Ahmadi, N., **10**-0928
Åhman, J., **05**-0081, **10**-1635, **13**-0188, **13**-0587, **18**-0545, **18**-0419
Ahmar, M., **15**-1445
Ahmberg, C.H., **14**-0409, **19**-1593
Ahmed, E.A.A., **10**-0341, **18**-0408
Ahmed, G., **15**-1773, **15**-1782, **15**-1958
Ahmed, M., **15**-0333, **15**-0342, **16**-0306, **16**-0355, **18**-0793, **19**-1521
Ahmed, M.S.M., **13**-0629
Ahmed, Md.M., **10**-1549
Ahmed, S., **19**-1487

Ahn, C., **10**-0703, **13**-0637, **19**-0523
Ahn, H., **16**-0596
Ahn, J.H., **10**-1166, **16**-0548, **19**-1299
Ahn, K.-H., **15**-1834, **19**-0800
Ahn, K.H., **13**-0506, **15**-0934, **15**-0995, **15**-1312, **16**-1975
Ahn, T.W., **15**-0933
Ahn, Y., **16**-1955, **19**-1160
Ahn, Y.M., **18**-0777
Ahola, C.J., **04**-0494
Ahond, A., **16**-0402
Ahonen, M., **16**-0562
Ahramjian, L., **16**-1216
Ahrendt, K.A., **15**-2051
Ahrens, A.F., **10**-0345
Ahuja, J., **15**-1694
Aida, T., **10**-0805, **10**-1098, **15**-0906, **15**-1837, **19**-0852
Aihara, H., **15**-0876, **19**-1005
Aihara, J-i., **02**-0027, **02**-0313
Aihara, J., **02**-0006, **02**-0345
Aihara, M., **10**-1040
Aikawa, K., **04**-0061, **16**-0571
Aikawa, T., **11**-0332, **16**-0545
Aikawa, Y., **15**-1055
Ainslie, R.D., **12**-0554
Ainsworth, C., **16**-2038, **19**-1739
Aires-de-Sousa, J., **15**-1891
Aït Haddou Mouloud, H., **10**-1308
Aït-Mohand, S., **16**-0572
Aitken, E.J., **08**-0234
Aitken, R.A., **17**-0264, **17**-0265, **17**-0266
Aizawa, T., **16**-0434, **17**-0487
Aizenshtat, Z., **13**-0481
Aizman, A., **10**-0032
Aizpurua, J.M., **10**-1141, **16**-0372, **16**-0810, **19**-0908
Ajami, D., **02**-0340, **19**-0101, **19**-0102, **19**-0147, **19**-0153, **19**-0154
Ajamian, A., **15**-0809, **15**-0835
Ajiki, K., **19**-0859
Ajithkumar, E.S., **07**-0062
Ajjou, A.N., **19**-0157
Akaba, R., **19**-0367
Akabori, S., **07**-0058, **10**-0490, **13**-0218, **19**-1487
Akada, T., **11**-0540
Akamanchi, K.G., **10**-1067, **17**-0430, **19**-0155, **19**-0810, **19**-0965
Akao, H., **04**-0106
Akasaka, M., **18**-0685
Akasaka, T., **15**-1892, **19**-0834, **19**-0852, **19**-1604
Akashi, K., **15**-1661, **19**-0079
Akashi, M., **15**-2428
Akazome, M., **15**-0340, **16**-0268, **19**-1247
Akehi, M., **10**-0641
Akelah, A., **16**-1817
Åkermark, B., **10**-1504, **13**-0393, **14**-0252, **14**-0252, **15**-0328, **15**-0329, **19**-0721, **13**-0396
Akhbari, M., **13**-0092
Akhlaghinia, B., **10**-0708, **10**-1807
Akhmatdinov, R.T., **05**-0053, **10**-0528
Akhmedov, N.G., **16**-1993
Akhmetova, N.E., **17**-0308
Akhrem, A.A., **10**-0494, **15**-0533, **18**-0194, **18**-0556
Akhrem, I., **10**-1835, **14**-0139, **19**-0616
Akhtar, M., **14**-0207, **18**-0872
Akhtar, M.I., **15**-0124
Akiba, D., **16**-1384
Akiba, K., **16**-0645, **19**-1301
Akiba, M., **15**-1586
Akila, S., **11**-0473
Akimoto, H., **12**-0695
Akine, S., **03**-0135
Akins, B.G., **11**-0120
Akita, M., **10**-0688
Akita, Y., **13**-0128
Akiyama, F., **19**-1718
Akiyama, K., **05**-0317
Akiyama, M., **19**-1391
Akiyama, R., **10**-1586, **13**-0487, **15**-0420, **15**-1705, **16**-0871
Akiyama, S., **02**-0301, **02**-0326, **02**-0328, **19**-0066
Akiyama, T., **11**-0649, **15**-2377, **16**-0409, **16**-0644, **16**-0871, **16**-0873, **16**-1103
Akiyama, Y., **16**-1854
Akiyoshi, K., **10**-1634
Akkerman, O.S., **12**-0566, **12**-0583, **12**-0585, **12**-0604, **12**-0613
Akritopoulou, I., **16**-1356
Aksel'rod, Zh.I., **11**-0068
Aksenov, V.S., **10**-0315
Aksnes, G., **16**-1338, **17**-0119
Akula, M.R., **13**-0714, **19**-1500
Akutagawa, S., **14**-0246, **19**-1026, **19**-1027
Akutsu, K., **19**-1773
Al Jihad, I., **08**-0197
Al Neirabeyeh, M., **19**-0708
Al-Aseer, M.A., **16**-0538
Al-Awadi, N.A., **17**-0133
Al-Borno, A., **12**-0650
Al-Duri, B., **15**-1950
Al-Haq, N., **19**-0118
Al-Ka'bi, J., **11**-0608
Al-Mallah, K.Y., **18**-0400
Al-Sader, B.H., **15**-1945, **18**-0589
Al-Shalchi, W., **16**-1559
Al-Talib, M., **05**-0060, **11**-0455
Al-Tel, T.H., **15**-2436
Alabugin, I.V., **05**-0029
Aladro, F.J., **14**-0177, **15**-1710
Alajarin, M., **16**-0434, **17**-0425
Alam, M.M., **15**-1020, **18**-0357
Alam, N., **13**-0058, **13**-0127, **13**-0343
Alamdari, R.F., **10**-1127
Alami, M., **10**-1410, **10**-1413, **13**-0325, **13**-0559
Alarcon, S.H., **02**-0423
Alarid-Sargent, M., **16**-2100
Alauddin, M.M., **15**-2002
Alauze, V., **10**-0960, **16**-0747
Albanese, D., **10**-0951, **13**-0324, **19**-1250
Albaneze-Walker, J., **13**-0541, **13**-0606
Albano, C., **10**-0178
Albanov, A.I., **19**-1789
Albeck, M., **17**-0055
Albéniz, A.C., **13**-0366
Albert, K., **19**-0191
Albert, M., **15**-1042
Albert, S., **15**-0234
Alberti, A., **10**-1209, **15**-0705
Albery, W.J., **06**-0022, **06**-0024, **06**-0026, **08**-0139, **10**-0352
Albini, A., **07**-0025, **13**-0072, **19**-0777, **19**-1544
Albizati, K.F., **19**-0132
Albonico, S.M., **15**-1585
Alborz, M., **16**-1571
Albrech, H., **08**-0067
Albrecht, M., **19**-0970
Albrecht, P., **11**-0344
Albright, J.D., **10**-1663, **19**-0160, **19**-0163, **19**-0166
Albright, T.A., **01**-0001, **12**-0278
Alcaide, B., **16**-0729
Alcaidi, B., **16**-1041
Alcais, P., **15**-0036
Alcaraz, L., **16**-1381, **17**-0211
Alcazar-Roman, L.M., **13**-0173
Alcock, N.W., **04**-0061
Alcock, W.G., **19**-0361
Alconcel, L.S., **08**-0216
Alcorn, P.G.E., **11**-0073
Alcudia, F., **04**-0357, **04**-0362
Alden, L., **16**-1894
Alder, K., **15**-0961, **15**-2050

Alder, R., **04**-0236
Alder, R.W., **04**-0237, **04**-0238, **04**-0239, **04**-0240, **04**-0241, **04**-0244, **04**-0248, **04**-0249, **08**-0086, **08**-0181, **08**-0186, **13**-0116, **18**-0523, **18**-0524
Aldersey-Williams, H., **02**-0355
Alderson, T., **15**-0796
Alderweireldt, F.C., **04**-0017
Aldous, G., **05**-0092
Aldred, S.E., **10**-0750
Aldridge, C.L., **15**-1498
Alekseeva, L.A., **16**-0448
Aleksiuk, O., **03**-0124, **11**-0345
Alemany, L.B., **14**-0002
Alemdaroğlu, N.H., **15**-1495
Aleskerov, M.A., **10**-1476, **17**-0003
Aleskovskii, V.B., **14**-0228, **15**-2156
Alessi, D.M., **04**-0175
Alewood, P.F., **12**-0232
Alexakis, A., **04**-0111, **10**-1295, **10**-1339, **10**-1437, **10**-1471, **10**-1520, **10**-1525, **10**-1531, **10**-1538, **10**-1543, **10**-1550, **15**-0947, **15**-0949, **15**-0952, **15**-0955, **15**-0994, **15**-1004, **15**-1062, **15**-1066, **15**-1092, **15**-1133, **15**-1136, **15**-1137, **17**-0217, **17**-0218, **19**-1692
Alexander, C.W., **10**-1273, **15**-1084
Alexander, D.W., **18**-0852
Alexander, R., **04**-0372, **17**-0072
Alexander, V.M., **11**-0303
Alexanian, V., **16**-1665
Alfassi, Z.B., **05**-0202
Algarín, W., **17**-0428
Ali, H., **07**-0101
Ali, I.S., **19**-0752
Ali, M., **10**-0557
Ali, M.B., **15**-2096
Ali, M.H., **13**-0179, **19**-0074, **19**-0074, **19**-0854
Ali, M.M., **11**-0473
Ali, S.I., **15**-1635
Ali, T., **15**-2131
Aliyan, H., **10**-0670, **16**-0173, **16**-1671
Alkabets, R., **15**-0498
Alker, D., **14**-0133, **14**-0134
Alkorta, I., **02**-0348, **08**-0012
Allaire, F.S., **13**-0708
Allan, G.R., **04**-0199
Allavena, C., **15**-1199
Allegretti, M., **13**-0504, **15**-1924, **16**-1865
Allemann, C., **16**-1029
Allen Jr., D.S., **19**-0399
Allen, A.D., **02**-0238, **05**-0055, **10**-0083, **10**-0209, **10**-0294, **15**-0024, **15**-0079, **16**-1572
Allen, C.F.H., **19**-1458
Allen, D., **15**-0421
Allen, D.J., **12**-0630
Allen, E.E., **19**-0708
Allen, F.H., **01**-0052, **01**-0063, **01**-0070, **02**-0031, **03**-0017, **03**-0070, **04**-0097, **04**-0464
Allen, J.C., **15**-1357
Allen, J.G., **15**-0606
Allen, J.V., **15**-1813
Allen, L.C., **01**-0026, **03**-0001, **04**-0033, **04**-0247, **04**-0298, **05**-0002, **05**-0076
Allen, L.E., **14**-0456, **14**-0457
Allen, N.T., **16**-0659
Allen, R.G., **15**-0055
Allen, R.H., **11**-0600, **11**-0601
Allen, W.D., **02**-0062
Allenmark, S., **18**-0672
Allenmark, S.G., **04**-0173
Allerhand, A., **03**-0052, **03**-0058, **16**-0988
Alleston, D.L., **19**-1306
Allin, S.M., **18**-0610
Allinger, J., **12**-0028
Allinger, N.L., **01**-0053, **01**-0087, **04**-0261, **04**-0263, **04**-0279, **04**-0296, **04**-0331, **04**-0350, **04**-0387, **04**-0399, **04**-0400, **04**-0406, **12**-0668, **15**-0437, **18**-0872
Allmendinger, H., **04**-0175
Allred, A.L., **03**-0067
Allred, E.L., **04**-0445, **10**-0106, **10**-010, **10**-0177
Allukian, M., **18**-0125
Allwein, S.P., **18**-0816
Almeer, S., **11**-0136
Almeida, L.M.P.M., **07**-0121
Almeida, W.P., **16**-0776
Almendros, P., **16**-1041
Almond Jr., H.R., **16**-1303
Almond, M.R., **18**-0272
Almond, S.W., **18**-0613
Almy, J., **12**-0031, **12**-0064
Alnajjar, M.S., **12**-0631
Alonso, D.A., **15**-1901, **19**-1028
Alonso, E., **16**-0949, **18**-0800
Alonso, F., **15**-0506, **15**-0507, **15**-0928, **16**-0839, **19**-1311
Alonso, I., **15**-2063
Alonso, R.A., **07**-0096, **11**-0647, **13**-0062, **13**-0589
Alonso-Cires, L., **15**-1873, **15**-1880
Alpatova, N.M., **15**-0540, **19**-0010
Alper, H., **03**-0083, **10**-0453, **10**-1193, **10**-1855, **10**-1859, **10**-1860, **10**-1861, **12**-0541, **12**-0747, **12**-0748, **12**-0750, **13**-0292, **13**-0368, **13**-0557, **13**-0599, **13**-0600, **13**-0602, **15**-0341, **15**-0524, **15**-0579, **15**-0961, **15**-1383, **15**-1385, **15**-1398, **15**-1401, **15**-1460, **15**-1463, **15**-1466, **15**-1478, **15**-1487, **16**-0187, **16**-1289, **16**-2123, **17**-0223, **18**-0143, **19**-0336, **19**-0726, **19**-1361, **19**-1454, **19**-1598
Alpha, S.R., **19**-1765
Alphonse, P., **15**-2407, **19**-0181
Alsters, P.L., **15**-1741
Alston, P.V., **15**-2005, **15**-2044
Alt, G.H., **10**-1674, **10**-1682
Altamura, A., **19**-0301
Alterman, M., **13**-0174, **13**-0602, **19**-1631
Altland, H.W., **13**-0099, **13**-0100, **13**-0263, **13**-0284
Altman, L.J., **10**-1737, **14**-0028
Altmann, J.A., **02**-0036
Altona, C., **04**-0354, **04**-0365
Altuddaş, R., **19**-0392
Alumbaugh, R.L., **10**-0497
Alunni, S., **11**-0470, **17**-0101
Aluotto, P.F., **08**-0050
Alvarado, L., **15**-1523
Alvarado, S.I., **13**-0263, **13**-0660
Álvarez, E., **19**-1022
Alvarez, C., **16**-2063, **19**-0089
Alvarez, E., **17**-0155
Alvarez, F.J., **06**-0087
Alvarez, F.S., **10**-0693
Alvarez, M.T., **10**-1005
Alvarez, P., **15**-0194
Alvarez, R., **13**-0518
Alvarez, R.M., **11**-0471, **16**-2057
Alvarez, S.G., **10**-1005, **19**-1271
Alvárez, J., **19**-1438
Alvarez-Builla, J., **11**-0356, **12**-0271, **13**-0544
Alvarez-Manzaneda, E.J., **15**-0578, **16**-1618, **17**-0155, **19**-0316, **19**-0355, **19**-0940
Alvarez-Manzaneda, R., **17**-0155
Alvarez-Toledano, C., **19**-0261
Alvernhe, G., **12**-0508, **15**-0115, **15**-1545, **16**-0954
Alves, E.F., **16**-0687
Alves, L.M., **16**-0276

Alzérreca, A., **02**-0220
Amabilino, D.B., **03**-0184, **03**-0191
Amano, S., **10**-1818
Amantini, D., **10**-0672, **10**-1152
Amaratunga, S., **12**-0541
Amaratunga, W., **12**-0534
Amardeil, R., **13**-0541
Amaresh, R.R., **11**-0474
Amariglio, A., **04**-0136
Amariglio, H., **04**-0136
Amatore, C., **12**-0277, **13**-0054, **13**-0058, **13**-0089, **13**-0127, **13**-0343, **13**-0462
Ambenge, R.O., **15**-1583
Amberg, W., **15**-1691, **15**-1693, **15**-1704
Ambidge, I.C., **10**-0209
Ambroise, L., **15**-1301
Ambrosetti, R., **15**-0022
Ambroz, H.B., **05**-0068, **13**-0026, **13**-0027
Amedio Jr., J.C., **12**-0654
Amedio Jr., J.C., **19**-0168
Amedjkouh, M., **08**-0195, **17**-0216
Amemiya, R., **10**-1777
Amemiya, T., **15**-1362
Amengual, R., **15**-1125
Amer, I., **10**-1855, **15**-1478, **19**-0622
Amer, M.I., **11**-0528
Ameriks, M.K., **10**-1856
Amey, A., **16**-0475
Amice, P., **12**-0155
Amick, D.R., **11**-0519
Amiel, Y., **02**-0291, **14**-0303, **15**-0050, **15**-1600
Amii, H., **15**-2, **19**-1156
Amin, H.B., **09**-0028
Amin, M., **17**-0062, **17**-0064
Amin, N.V., **15**-0473
Amin, S., **19**-0634
Amin, Sk.R., **19**-1133
Amishiro, N., **15**-1178
Amiya, T., **16**-1604
Amorati, R., **01**-0110
Amos, D.T., **15**-2125
Amos, R.D., **04**-0168, **04**-0287
Amosova, S.V., **10**-0775
Amouroux, R., **10**-1125, **10**-1134, **16**-0516, **16**-1933
Ampleman, G., **11**-0052, **19**-0922
Amrani, Y., **15**-0598
Amrein, S., **19**-1310
Amrollah-Madjdabadi, A.A., **10**-0095
Amstutz, D., **05**-0191
Amstutz, E.D., **17**-0397
Amstutz, R., **05**-0191, **05**-0192
Amupitan, J.O., **19**-1793
Amurrio, I., **16**-1429
Amyes, T.L., **05**-0011, **05**-0019, **05**-0094, **08**-0063, **10**-0058, **10**-0083, **10**-0084, **10**-0527, **10**-0533, **6**-1936, **18**-0304
An, G.-i., **18**-0327, **19**-0309
An, M., **15**-0479
An, T.D., **17**-0026
Anand, M., **18**-0025
Anand, N.K., **16**-0552
Anand, R.C., **16**-1688
Anand, R.V., **10**-0959, **15**-1794, **16**-0233
Ananikov, V.P., **15**-0306
Anantakrishnan, S.V., **15**-0027
Anastasia, L., **12**-0296, **13**-0552
Anastasiou, D., **15**-1493
Anastassiou, A.G., **02**-0253, **02**-0256, **02**-0257, **02**-0258, **02**-0274, **12**-0235, **15**-2282
Anatol, J., **16**-2061
Anbar, M., **07**-0066
Anbazhagan, M., **17**-0150
Andappan, M.M.S., **07**-0117, **13**-0375
Andell, O.S., **15**-1504
Anders, E., **05**-0183
Anders, K., **14**-0064
Andersch, J., **19**-1794
Andersen, K., **13**-0077
Andersen, K.K., **04**-0029, **04**-0047, **04**-0048, **04**-0213, **16**-2141
Andersen, M.W., **15**-0984
Andersen, N.G., **04**-0161
Andersen, N.H., **05**-0121, **10**-0724, **19**-1184
Andersen, P., **05**-0283
Andersen, T.P., **16**-1807
Andersh, B., **11**-0235
Anderson III, F.E., **14**-0163
Anderson Jr., A.G., **10**-1135, **16**-1888
Anderson, A.G., **11**-0337
Anderson, A.M., **18**-0146
Anderson, B.R., **04**-0475
Anderson, C.E., **18**-0689
Anderson, D.J., **15**-1894
Anderson, E.D., **05**-0342
Anderson, E.W., **04**-0323, **10**-0131
Anderson, G.J., **19**-0639, **19**-0640, **19**-0642
Anderson, G.K., **10**-1841, **15**-1375
Anderson, H.J., **11**-0068
Anderson, J.E., **04**-0348
Anderson, J.C., **11**-0556, **12**-0354, **18**-0419, **18**-0687, **19**-0475
Anderson, J.E., **04**-0264, **04**-0324, **04**-0368, **04**-0375
Anderson, J.M., **14**-0339
Anderson, K.R., **01**-0011
Anderson, K.R., **07**-0080
Anderson, K.W., **11**-0421, **13**-0177, **13**-0229
Anderson, L.L., **15**-0352
Anderson, M.R., **18**-0520
Anderson, O.P., **16**-2099
Anderson, P.E., **09**-0100
Anderson, P.H., **10**-0269, **18**-0098
Anderson, R., **10**-0481, **12**-0390, **16**-1242
Anderson, R.J., **10**-1557, **15**-1080, **15**-1940, **16**-1980
Anderson, R.S., **19**-1227
Anderson, S.R., **16**-1629
Anderson, S.W., **10**-0431, **10**-0432, **10**-0436, **19**-1341
Anderson, T.J., **15**-0280
Anderson, W.K., **16**-0335, **18**-0693
Andersson, C., **12**-0305, **13**-0361
Andersson, C.-M., **15**-0276
Andersson, K., **02**-0397
Andersson, P.G., **15**-0230, **15**-1696, **15**-1895, **15**-1901, **15**-2119, **16**-0858, **17**-0219, **19**-0536, **19**-1028, **19**-1155, **19**-1710
Andisik, D., **10**-1022, **15**-0398
Ando, A., **16**-1032, **19**-0487
Ando, H., **10**-1014, **11**-0476
Ando, J.-i., **13**-0449, **14**-0323
Ando, K., **12**-0092, **15**-1042, **16**-0706, **16**-1319, **16**-1332, **16**-1590
Ando, M., **10**-0676, **13**-0415, **15**-0993, **17**-0343, **18**-0340, **18**-0359
Ando, T., **06**-0067, **07**-0083, **07**-0098, **10**-0063, **10**-0163, **10**-0170, **10**-0171, **10**-0202, **10**-0971, **10**-1789, **15**-1896, **16**-2045, **18**-0332, **18**-0754, **19**-0106
Ando, W., **10**-0785, **14**-0234, **15**-2158, **15**-2313, **16**-1754, **18**-0215, **18**-0218, **19**-0834
Ando, Y., **15**-0823
Andrade, C.K.Z., **16**-0276, **16**-0652, **16**-0622, **16**-0871
Andrade, J.G., **16**-2042, **19**-1286

Andrea, T., **16**-0968
Andreades, S., **16**-0456
Andreae, M.R.M., **18**-0358
Andreas Hirsch, A., **02**-0354
Andred'Avignon, D., **15**-0239
Andree, R., **02**-0277
Andreev, A.A., **10**-1784
Andreev, S.A., **12**-0711
Andreev, S.M., **16**-1816
Andrejević, V., **14**-0212, **19**-0274
Andres, J., **10**-0232
Andres, P.C., **16**-0610
Andrés, J., **15**-2057
Andrés, J.M., **16**-0831, **16**-0837, **16**-1962
Andresen, B.M., **15**-0497
Andréu, P., **17**-0176, **17**-0314
Andrews Jr., T.G., **02**-0163
Andrews, A.E., **16**-1352
Andrews, A.T., **13**-0480, **19**-1028
Andrews, B.K., **05**-0298
Andrews, C.W., **10**-0537
Andrews, G.C., **10**-1726, **18**-0737
Andrews, G.D., **15**-0098, **18**-0589
Andrews, L., **05**-0204, **05**-0276, **05**-0340, **14**-0167, **19**-0361
Andrews, L.J., **11**-0271, **17**-0139
Andrews, M.A., **17**-0333
Andrews, P.C., **16**-0883
Andrey, O., **15**-0994, **15**-1004
Andriamialisoa, R.Z., **19**-0479
Andrianov, K.A., **15**-0705
Andrieux, J., **10**-1023
Andringa, H., **15**-0532
Andrioletti, B., **13**-0470
Andrisano, R., **10**-0264
Andrist, A.H., **15**-0135, **15**-2111, **18**-0498
Andriukhova, N.V., **13**-0377, **13**-0391
Andrukiewicz, R., **15**-1242
Andrus, A., **10**-1816
Andrus, M.B., **13**-0353, **15**-1729, **16**-0743, **19**-0530, **19**-0538
Andrus, W.A., **10**-0547
Andrussow, K., **08**-0018
Andryukhova, N.L., **10**-1306
Andrzejewski, D., **17**-0253, **17**-0262
Aneja, R., **12**-0654
Anelli, P.L., **03**-0204, **03**-0205, **05**-0253, **16**-1705, **19**-0109
Anet, F.A.L., **01**-0087, **03**-0106, **04**-0207, **04**-0264, **04**-0320, **04**-0323, **04**-0329, **04**-0335, **04**-0387, **04**-0394, **04**-0467, **10**-0156, **18**-0642
Anet, R., **04**-0264, **04**-0467
Ang, K.P., **08**-0049
Angel, L.A., **10**-0016
Angelaud, R., **16**-1383
Angeletti, E., **10**-1583
Angelici, R.J., **15**-1843
Angelini, G., **10**-0009, **10**-0259, **17**-0095
Angelis, Y., **15**-1767
Angelis, Y.S., **19**-0234
Angell, E.C., **19**-0587
Angell, R.M., **16**-0759
Angelo, B., **16**-2038
Angeloni, A.S., **10**-0264
Angeloni, L., **16**-0392
Angelov, Kh.M., **15**-0060
Angibeaud, P., **15**-0467
Angiolini, L., **16**-0392
Angioloni, S., **04**-0314
Angle, S.R., **18**-0247
Angus Jr., R.O., **04**-0488
Angus, J.C., **17**-0041
Angyal, S.J., **04**-0261, **04**-0263, **04**-0350, **04**-0363, **04**-0387, **19**-0328, **19**-0651
Anh, N.T., **01**-0048, **04**-0137, **16**-1022
Anilkumar, G., **12**-0252
Anilkumar, R., **18**-0333
Anjaneyulu, S., **10**-0865, **10**-1549, **16**-0749, **16**-0930, **18**-0301, **18**-0662
Anjum, A., **19**-0705
Ankala, S.V., **13**-0111
Ankati, H.B., **19**-1266
Anker, D., **15**-0115
Anker, W., **02**-0282
Anlauf, U., **16**-1786
Annaka, K., **13**-0541
Annby, U., **15**-0276
Annese, C., **19**-0235
Anniyappan, M., **15**-2119
Annoura, H., **11**-0521
Annunziata, R., **04**-0029, **05**-0138, **11**-0607, **15**-1697, **16**-1118
Anosike, P., **15**-2040
Ansari, I.A., **19**-0194
Ansari, M.H., **19**-1021
Ansell, H.V., **11**-0049, **11**-0072
Ansell, M.F., **15**-0271, **16**-1874
Anselme, J., **06**-0015, **16**-2094, **18**-0238, **18**-0739
Anselmi, C., **10**-1418, **15**-0125
Ansersh, B., **10**-1390
Ansmann, A., **15**-2179
Anson, M.S., **13**-0411, **13**-0412
Antebi, S., **13**-0599
Anteunis, M., **10**-0078, **16**-0182, **16**-1469
Anthony, J.E., **02**-0323, **15**-2394, **18**-0490
Antilla, J.C., **13**-0201, **13**-0207, **13**-0212
Anton, D.R., **17**-0301
Antonioletti, R., **15**-1558, **15**-1818
Antoniotti, S., **18**-0151
Antonova, N.D., **16**-1480
Antony, A., appendixA-0001
Antoulinakis, E.G., **12**-0359
Antras, F., **15**-1445
Antunes, A.M.M., **15**-1907
Antúnez, S., **04**-0327
Anunziata, J.D., **13**-0013
Anuradha, K., **15**-1340
Anuradha, M.V., **16**-1769
Anvia, F., **08**-0092, **08**-0161
Anwer, M.K., **11**-0645
Anzai, J., **19**-0689
Aoi, K., **10**-1446
Aoki, K., **10**-1230, **15**-1685, **15**-2198
Aoki, M., **19**-0706, **19**-0816
Aoki, O., **19**-1663
Aoki, S., **10**-1358, **10**-1372, **12**-0656, **13**-0595
Aoki, T., **11**-0390, **16**-0687
Aoki, Y., **15**-2337
Aono, M., **15**-1932
Aonuma, S., **05**-0117, **05**-0201
Aouad, E., **12**-0371
Aoyagi, K., **15**-1313
Aoyagi, T., **16**-1708
Aoyagi, Y., **16**-0818
Aoyama, H., **16**-1307
Aoyama, M., **15**-1187
Aoyama, N., **16**-0619, **16**-0753
Aoyama, T., **12**-0512, **16**-0947, **18**-0216, **18**-0231
Aoyama, Y., **03**-0149
Aparicio, D., **16**-0304
Aped, P., **04**-0366
Apeloig, Y., **02**-0080, **02**-0395, **05**-0263, **10**-0177, **10**-0178, **10**-0247, **10**-0255, **13**-0031, **15**-1790, **15**-2116
Apfel, R.E., **07**-0068, **07**-0067
Apler, H., **10**-1551
Apodaca, R., **16**-0354
Aponte, G.S., **18**-0070
Apparu, M., **15**-0187, **17**-0206
Appel, R., **01**-0009, **10**-1099, **17**-0459, **17**-0484
Appelbaum, A., **14**-0263

Appella, D.H., **15**-0425, **15**-0592
Appelman, E.H., **15**-1570
Appendino, G., **16**-0984
Appl, M., **18**-0285
Applegate, L.E., **10**-0262
Applegath, F., **12**-0736
Appleman, J.O., **16**-2071
Applequist, D.E., **02**-0059, **04**-0050, **05**-0102, **10**-1234, **12**-0013, **14**-0047, **5**-0142
Applequist, J., **04**-0050, **04**-0127, **04**-0146, **15**-0597
Appleton, R.A., **19**-1338
Appukkuttan, P., **07**-0119, **07**-0121, **13**-0547
Aprahamian, N.S., **11**-0305
Aprile, C., **15**-0224
ApSimon, J., **04**-0136
ApSimon, J.W., **04**-0136
Aquino, L.B., **11**-0437, **11**-0438
Arabindoo, B., **19**-0085
Arad, D., **02**-0080, **02**-0395, **10**-0177, **10**-0178, **13**-0031
Arad-Yellin, R., **04**-0164, **04**-0165, **09**-0012
Arai, H., **16**-1011
Arai, K., **16**-1840
Arai, M., **10**-1372, **13**-0407, **14**-0192, **18**-0127, **18**-0316
Arai, S., **12**-0068, **15**-1791, **15**-1807, **15**-1807, **16**-1008, **16**-1221, **16**-1225, **16**-1229, **16**-1314, **16**-1392
Arai, T., **15**-0156, **15**-1808
Araki, H., **12**-0289, **13**-0509
Araki, K., **03**-0126, **10**-0309, **10**-1347, **19**-1574
Araki, M., **15**-2010, **16**-1937
Araki, S., **10**-0221, **10**-1512, **10**-1549, **15**-1400, **16**-0600, **16**-0606, **16**-0645, **16**-0678, **16**-0816, **16**-0874, **16**-0878, **16**-1393
Araki, T., **18**-0357
Araki, Y., **05**-0250, **19**-0946
Arbabian, M., **11**-0292
Aramendia, M.A., **13**-0525, **13**-0576
Aramini, A., **16**-1865
Araneo, S., **19**-0612
Arapakos, P.G., **12**-0691
Arase, A., **12**-0546, **15**-1183, **15**-1192
Arata, K., **02**-0383, **08**-0015
Araújo, M.A., **16**-0582
Arbuzov, B.A., **18**-0096
Arbuzov, P.V., **14**-0158
Arbuzov, Yu.A., **15**-2151, **16**-1480
Arcadi, A., **11**-0654, **13**-0480, **13**-0504, **15**-0245, **15**-0848, **15**-2423, **16**-0163, **16**-0279
Arcand, H.R., **18**-0685
Arcari, A.R., **16**-0154
Arcari, J.T., **16**-1352
Arce de Sanabia, J., **11**-0563
Arcelli, A., **10**-0900, **10**-0916
Archelas, A., **10**-0582
Archer, C.M., **16**-0510
Archer, D.A., **17**-0244
Archer, S., **18**-0874
Arcoria, A., **16**-2143
Ardakani, A., **15**-1782
Ardoin, N., **13**-0077
Arduengo III, A.J., **05**-0382, **12**-0365
Arena, C.G., **10**-1453, **15**-1136
Arend, M., **16**-0406
Arends, I.W.C.E., **15**-1739, **15**-1750, **15**-1753, **18**-0355, **19**-0181, **19**-0183, **19**-0225, **18**-0350
Arens, J.F., **10**-1536, **15**-0216, **15**-0217
Arentsen, K., **13**-0480
Arenz, T., **16**-1195
Aretakis, A.J., **15**-0101
Argabright, P.A., **10**-1033, **13**-0667, **17**-0286
Argade, A.B., **19**-0538
Argade, N.P., **15**-0161
Argile, A., **05**-0378, **09**-0021, **15**-0016
Argyropoulos, J.N., **10**-1602, **16**-0974, **19**-0974
Arhart, R., **14**-0158
Arias, L.A., **15**-1776
Arifuddin, M., **16**-0084, **16**-0088, **16**-0089, **16**-0337, **19**-1267
Ariga, M., **15**-1939
Arigoni, D., **04**-0021, **15**-0781, **17**-0504, **19**-0470
Arii, T., **15**-2374
Arikan, N., **16**-0334
Arimatsu, S., **17**-0175
Arime, T., **16**-0823
Arimoto, K., **15**-0587, **15**-1019, **18**-0357
Arimura, T., **15**-0176
Arinich, A.K., **11**-0582
Arisawa, M., **10**-0831, **10**-1777, **14**-0175, **15**-0780, **18**-0331
Arison, B.H., **15**-1945
Ariza, X., **16**-1759
Arjona, O., **15**-0302, **18**-0781
Arkle, S.R., **16**-2126
Arlt, R.E., **10**-0223
Armani, E., **12**-0118
Armantrout, J.R., **02**-0290
Armesto, D., **18**-0570, **18**-0858
Armet, O., **05**-0256
Armit, J.W., **02**-0098
Armor, J.N., **16**-0319
Armspach, D., **03**-0179
Armstrong III, J.D., **13**-0504, **15**-0615, **18**-0679
Armstrong, A., **10**-0630, **15**-1770, **15**-1782
Armstrong, D., **15**-0360
Armstrong, D.A., **01**-0101
Armstrong, D.R., **13**-0654
Armstrong, D.W., **10**-0465
Armstrong, K.B., **04**-0375
Armstrong, R., **14**-0103
Arnason, I., **04**-0371
Arnauld, T., **13**-0584
Arnauld, T., **18**-0793
Arnaut, L.G., **07**-0044
Arndt, D., **19**-0010
Arnestad, B., **11**-0145
Arnett, E.M., **02**-0371, **04**-0500, **04**-0502, **04**-0504, **05**-0002, **05**-0072, **05**-0072, **05**-0075, **05**-0075, **05**-0130, **05**-0200, **06**-0087, **08**-0018, **08**-0020, **08**-0029, **08**-0031, **08**-0033, **08**-0111, **08**-0118, **08**-0192, **08**-0219, **08**-0220, **08**-0223, **08**-0231, **10**-0051, **10**-0177, **10**-0178, **10**-0184, **12**-0661, **15**-2365, **16**-0998, **16**-1295, **18**-0493
Arnett, J.F., **05**-0135
Arnold, A.P., **03**-0209, **03**-0210
Arnold, B.R., **02**-0218, **15**-1221
Arnold, C., **10**-1786
Arnold, D.R., **05**-0264, **14**-0089, **15**-2236, **16**-2083, **16**-2085, **17**-0507, **17**-0509
Arnold, J., **15**-0352
Arnold, J.N., **16**-0071, **16**-0174
Arnold, J.R.P., **18**-0370
Arnold, L.A., **10**-1374, **15**-1136, **16**-0787
Arnold, R.T., **12**-0177, **15**-0969, **16**-1480, **17**-0117, **17**-0491, **17**-0493, **18**-0553
Arnold, S., **15**-0004, **15**-0033
Arnold, Z., **11**-0469
Arnoldi, A., **14**-0344
Arnould, D., **10**-1713
Arnould, J.C., **13**-0709
Aroella, T., **08**-0105
Aroney, M., **04**-0280
Aronica, L.A., **16**-1925, **17**-0375
Aronoff, M.S., **12**-0605, **15**-0631

Aronovitch, H., **10**-0078
Arora, A., **10**-1568
Arora, S., **12**-0445
Arora, S.K., **19**-0484, **19**-0885
Arotsky, J., **11**-0307
Arouisse, A., **16**-1926
Arques, A., **16**-0329, **16**-0434
Arrad, O., **10**-0699
Arranz, J., **19**-1706
Arrayás, R.G., **10**-1454, **15**-2148
Arrhenius, G.M.L., **16**-0030
Arrieta, A., **15**-1944, **15**-2055, **16**-0832, **16**-1664
Arrowood, B.N., **15**-0925
Arrowsmith, C.H., **08**-0105
Arrowsmith, R.J., **04**-0240
Arroyo, N., **16**-0687
Arsenijević, L., **16**-1942
Arsenijević, V., **16**-1942
Arseniyadis, S., **10**-1610, **19**-0320
Arsenyan, P., **13**-0570
Arshinova, R.P., **04**-0387
Arslancan, E., **16**-0656
Arsmtrong, A., **15**-1773
Artamanova, N.N., **13**-0107
Artamkina, G.A., **10**-1310, **12**-0626, **12**-0632, **13**-0008, **13**-0267
Artaud, I., **10**-1620
Arterburn, J.B., **15**-0584, **19**-0129
Arthur Jr., P., **15**-1503
Artigas, L., **18**-0487
Artok, L., **13**-0480
Arukwe, J., **02**-0431
Arulananda, S., **12**-0355
Arumugam, N., **05**-0378, **11**-0541
Aruna, S., **17**-0386
Arunan, E., **03**-0072
Arvanaghi, M., **10**-0139, **10**-0200, **11**-0263, **11**-0458, **11**-0460, **12**-0156, **16**-0111, **16**-1940, **16**-2043, **19**-0643, **19**-1450
Arvela, R.K., **13**-0260, **13**-0271, **13**-0277
Arvidsson, P.I., **08**-0209, **16**-0490
Arya, P., **13**-0599
Arzoumanian, H., **15**-0691
Asai, S., **10**-1198
Asaka, N., **15**-1939
Asakawa, K., **16**-0754, **16**-1121
Asakawa, Y., **19**-0461
Asami, K., **15**-1247
Asami, M., **04**-0136, **16**-0978, **17**-0216
Asano, F., **19**-0109
Asano, K., **12**-0722
Asano, R., **10**-0712
Asano, S., **12**-0731
Asano, T., **09**-0087, **10**-0476, **11**-0172, **15**-2027, **17**-0067, **18**-0222
Asano, Y., **15**-1107
Asanuma, Y., **16**-0437
Asao, N., **10**-1544, **15**-0745, **15**-0787, **15**-0940, **15**-1085
Asao, T., **02**-0200, **05**-0045, **05**-0046
Asaumi, T., **15**-2443
Aschberger, J., **10**-1008
Asencio, G., **11**-0015
Asensio, A., **05**-0240
Asensio, G., **15**-0370, **15**-1199, **15**-1546, **15**-1547, **15**-1873, **15**-1880, **19**-0515, **19**-0799
Asfandiarov, N.L., **04**-0039
Asfari, Z., **03**-0136, **03**-0139, **03**-0140
Asghari, J., **10**-1131, **11**-0238, **16**-0078
Ash, D.K., **19**-0871
Ashby, E.C., **04**-0138, **05**-0156, **05**-0158, **05**-0162, **05**-0167, **05**-0168, **05**-0169, **05**-0170, **05**-0244, **05**-0361, **10**-0089, **10**-0090, **10**-0091, **10**-0095, **10**-0098, **10**-0101, **10**-0618, **10**-0772, **10**-1319, **10**-1602, **12**-0554, **12**-0587, **12**-0591, **12**-0611, **12**-0627, **12**-0631, **15**-0571, **15**-0948, **15**-1146, **16**-0005, **16**-0523, **16**-0523, **16**-0524, **16**-0525, **16**-0526, **16**-0527, **16**-0530, **16**-0676, **16**-0963, **16**-0974, **16**-2025, **17**-0177, **19**-0951, **19**-0974, **19**-1060, **19**-1061, **19**-1062, **19**-1339, **19**-1390, **19**-1762
Ashby, M.T., **15**-0598
Ashe III, A.H., **05**-0047
Ashe III, A.J., **10**-0192, **10**-0195
Ashe III, A.J., **10**-0197
Ashford, S.W., **19**-0333
Ashley, K.R., **19**-0323
Ashmawy, M.I.A., **15**-1851
Ashtiani, A.M., **16**-0160
Ashton, P.R., **02**-0312, **03**-0184, **03**-0185, **03**-0186, **03**-0191, **03**-0200
Asinger, F., **12**-0480, **12**-0554, **19**-1792, **19**-1800, **19**-1801
Asirvatham, E., **16**-1148
Askani, R., **15**-2255, **18**-0494
Askitoğlu, E., **16**-1858
Aslam, M., **10**-1705, **17**-0349
Aslapovskaya, T.I., **11**-0583
Asleson, G.L., **13**-0463
Aso, H., **10**-1280
Aso, N., **16**-2156
Aspari, P., **07**-0032
Aspinall, H.C., **10**-0600, **16**-0624, **16**-0871, **16**-1439
Assadourian, L., **08**-0014
Asscher, M., **15**-1536, **15**-1598, **15**-1598, **15**-1642
Assenheim, H.M., **05**-0208
Assfeld, X., **15**-2059
Astaf’ev, I.V., **12**-0061
Astin, K.B., **10**-0217
Astruc, D., **13**-0077, **13**-0556
Asveld, E.W.H., **14**-0242
Atanas’ev, V.V., **15**-0372
Atanesyan, K.A., **15**-1650
Atavin, A.S., **10**-0661, **15**-0250
Ateeq, H.S., **15**-2438
Ates, A., **10**-0549, **15**-0316, **16**-1239
Atherton, J.C.C., **19**-1031
Atherton, J.H., **11**-0158, **11**-0161
Atherton, J.I., **17**-0264
Atherton, M., **16**-0454
Atherton, M.J., **11**-0314
Atienza, C., **15**-2392
Atkins, K.E., **10**-0902
Atkins, R.L., **19**-0769
Atkins, T.J., **18**-0840, **18**-0843
Atkinson, J.G., **12**-0055, **15**-0465, **15**-0466
Atkinson, R., **19**-0385, **19**-0386
Atkinson, R.C., **15**-0073
Atkinson, R.F., **17**-0240
Atkinson, R.S., **15**-1892
Atkinson, V.A., **04**-0332
Atobe, M., **11**-0328
Atsumi, K., **16**-1729
Atta-ur-Rahman, **10**-1081, **19**-1128
Attanasi, O., **17**-0425, **19**-1510
Attea, M., **10**-0171
Attenni, B., **15**-0899
Attiná, M., **13**-0752, **11**-0098
Attolini, M., **19**-1021
Atwood, **04**-0164
Atwood, J.L., **03**-0059, **03**-0101, **03**-0105, **03**-0119, **03**-0141, **03**-0155, **03**-0157, **03**-0162, **03**-0164, **03**-0166, **03**-0167, **03**-0174, **03**-0175, **03**-0177, **03**-0210
Au, S.-M., **19**-0550
Au-Yeung, T.T.-L., **15**-1125, **15**-1133
Aubé, J., **18**-0296, **18**-0297, **18**-0298

Aubert, C., **15**-0834, **15**-2386, **15**-2400, **15**-2442
Aubert, D., **16**-1384
Aubrecht, K.B., **08**-0201, **12**-0268
Aubrey, D.W., **17**-0230
Aubry, J.-M., **14**-0233
Aubry, J.M., **14**-0231
Auclair, K., **14**-0082
Audeh, C.A., **04**-0512
Audhuy, M., **07**-0114
Audic, N., **18**-0771
Audrain, H., **15**-2146
Aue, D.H., **08**-0191, **08**-0219, **08**-0224, **12**-0237, **19**-1320
Auerbach, R.A., **16**-2011
Aufdermarsh Jr., C.A., **10**-0049
Aufranc, P., **19**-1400
Augé, J., **15**-1028, **15**-1161, **15**-2033, **15**-2143, **16**-0555, **16**-0595, **16**-0777, **16**-1917
Augstine, A., **15**-1532
August, R., **17**-0133
Augustijn, G.J.P., **11**-0638
Augustín, J., **16**-1755
Augustine, A., **15**-1599
Augustine, A., **15**-1624
Augustine, A., **19**-0730
Augustine, R.L., **10**-1609, **12**-0240, **12**-0418, **14**-0227, **14**-0249, **15**-0401, **15**-0458, **15**-0461, **15**-0533, **15**-0572, **15**-1726, **15**-1742, **15**-2151, **16**-0972, **16**-0994, **18**-0352, **19**-0011, **19**-0015, **19**-0047, **19**-0070, **19**-0311, **19**-0345, **19**-0453, **19**-0468, **19**-0553, **19**-0638, **19**-0693, **19**-0873, **19**-0874, **19**-1388, **19**-1426
Aujard, I., **19**-1692
Aulmich, G., **05**-0234
Ault, A., **04**-0250
Ault, B.S., **03**-0047, **05**-0402
Aumiller, J.C., **10**-1235
Aurell, M.J., **15**-1119, **15**-1999, **15**-2099, **19**-0840
Aurich, H.G., **05**-0254, **05**-0255
Aurrekoetxea, N., **16**-0810
Ausloos, P., **07**-0049
Austad, T., **10**-0487
Austel, V., **18**-0493
Austin, E., **11**-0647, **16**-1021
Autrey, T., **05**-0401
Auvray, P., **06**-0016
Avakian, S., **13**-0042
Avalos, M., **04**-0004, **04**-0300, **04**-0303, **15**-2004, **15**-2097
Avasthi, K., **18**-0429
Avedissian, H., **10**-1298, **10**-1301
Avellan, A.-V., **11**-0193
Avendaño, C., **10**-0990, **15**-2144, **19**-1350
Aver'yanov, V.A., **14**-0116, **14**-0118
Averko-Antonovich, I.G., **10**-1053
Avery, M.A., **16**-0357, **19**-1135
Avey, A.A., **19**-1410
Avila, D.V., **15**-1212
Avila, W.B., **13**-0640
Avila-Zárraga, J.G., **10**-0720
Avilov, D.V., **16**-0656
Avison, A.W.D., **16**-1721
Aviyente, V., **18**-0683, **18**-0707
Avnir, D., **04**-0080
Avramovitch, B., **10**-0242, **10**-0265
Awachat, M.M., **16**-0243
Awachie, P.I., **16**-0372
Awasthi, A.K., **10**-0046, **15**-1716, **19**-0406, **19**-0481
Awasthi, S., **13**-0434
Awasthy, A., **19**-0249
Awazu, K., **15**-0158
Axe, F.U., **04**-0302
Axelrod, E.H., **10**-1102, **10**-1263
Axelrod, J., **14**-0202
Axelsson, A.-K., **15**-2039
Axelsson, O., **13**-0495, **13**-0675
Axenrod, T., **16**-1768
Axiotis, G., **16**-0811
Axiotis, G.P., **16**-0954
Ay, M., **12**-0507
Ayad, K.N., **11**-0589
Ayala, L., **10**-1433
Ayala, P.Y., **01**-0100
Aycard, J., **18**-0225
Aycock, B.F., **15**-0054
Aydin, R., **02**-0277, **18**-0642
Ayerbe, N., **19**-1627
Ayers, J.T., **16**-1629
Ayers, P.W., **08**-0148
Ayers, T.A., **15**-1492, **19**-1085
Ayhan, P., **16**-0986
Aylett, B.J., **04**-0025, **12**-0001
Ayling, A., **16**-0928
Aylward, F., **15**-0484
Aylward, J.B., **19**-0010, **19**-0311
Ayres, D.C., **19**-0408
Ayres, R.L., **15**-1514
Ayrey, G., **13**-0018, **17**-0059
Ayrey, P.M., **16**-1327
Ayuba, S., **10**-1044, 10-, **15**-1548
Ayyangar, N.R., **04**-0192, **13**-0723, **15**-0650, **19**-1212
Azadbar, M.R., **19**-0087
Azadi, R., **10**-0708
Azar, J.C., **14**-0120
Azar, J.K., **18**-0611
Azarm, M., **16**-0063
Azevedo, N.R., **16**-0622, **16**-0652
Azizi, N., **10**-1569, **15**-1293
Aznar, F., **15**-1875, **15**-2289, **15**-2418
Azovskaya, V.A., **15**-0118
Azrak, R.G., **03**-0051
Azran, J., **19**-0661
Azuma, N., **05**-0277
Azzaro, M., **19**-1245
Azzaro, M.E., **06**-0074
Azzena, U., **11**-0376, **19**-1537

Ba, T., **16**-0378
Baader, W.J., **15**-2161
Baag, Md.M., **15**-0161
Baarda, D.G., **17**-0503
Baardman, F., **15**-2197
Baarrero, A.F., **15**-0578
Baarschers, W.H., **16**-2173
Baas, J.M.A., **11**-0051
Baati, R., **17**-0316
Baba, A., **10**-0788, **10**-1014, **10**-1093, **10**-1515, **10**-1627, **12**-0317, **15**-0622, **15**-1061, **6**-0376, **16**-0377, **16**-0382, **16**-0458, **16**-0609, **16**-0617, **16**-0620, **16**-0638, **16**-0822, **16**-0871, **16**-1904, **19**-1101, **19**-1139, **19**-1298, **19**-1308, **19**-1359, **19**-1452
Baba, A.R., **19**-1201
Baba, H., **02**-0026
Baba, K., **18**-0144, **18**-0153
Baba, S., **10**-1378
Baba, T., **18**-0429
Baba, Y., **15**-0876
Babad, H., **15**-1585, **19**-1130
Babanyan, Sh.O., **12**-0065
Babayan, E.V., **15**-1650
Babayan, V.I., **18**-0054
Babiak, K.A., **12**-0571
Babiano, R., **04**-0004, **04**-0300, **04**-0303, **15**-2004, **15**-2097
Babich, E.D., **18**-0761
Babichev, S.S., **15**-2088
Babinski, D., **12**-0296
Babitskii, B.D., **15**-2287
Babić, D., **02**-0106
Babler, J.H., **10**-1048, **19**-0662, **19**-0934, **19**-1012, **19**-1013, **19**-1102, **19**-1200
Babot, O., **12**-0316
Baboul, A.G., **14**-0036
Babrizi, G., **13**-0609
Babston, R.E., **18**-0677

Babu, A., **12**-0355
Babu, B.N., **19**-1453
Babu, G., **15**-2142
Babu, J.R., **19**-1598
Babu, K.G., **10**-1177
Babu, R.S., **10**-0942
Babu, S.A., **12**-0369, **16**-0233
Babudri, F., **10**-1325, **16**-1924, **16**-1929
Baburao, K., **16**-1869
Bacaloglu, R., **13**-0019, **16**-0016
Bacci, J.P., **15**-0393
Bach, P., **15**-2140
Bach, R.D., **04**-0414, **04**-0415, **14**-0036, **01**-0100, **04**-0306, **10**-0228, **12**-0209, **15**-0280, **15**-1731, **15**-1776, **15**-2218, **17**-0253, **17**-0254, **17**-0262
Bach, T., **10**-1527, **15**-1368, **16**-0724, **16**-1090, **16**-1118, **16**-2083, **16**-2088
Bacha, J.D., **19**-0435, **19**-0438, **19**-0439
Bachand, C., **19**-0664
Bachhuber, H., **15**-0488
Bachman, G.B., **14**-0427, **19**-0765
Bachman, G.L., **04**-0151
Bachman, R.E., **18**-0172
Bachmann, C., **18**-0225
Bachmann, S., **12**-0124, **19**-0191
Bachmann, W.E., **18**-0036
Bachrach, S.M., **02**-0091, **04**-0355, **10**-0022, **15**-2200, **18**-0541
Baciocchi, E., **11**-0010, **11**-0101, **11**-0107, **11**-0228, **11**-0279, **15**-1647, **17**-0031, **17**-0033, **17**-0051, **17**-0052, **17**-0101, **17**-0110, **17**-0300, **17**-0367, **19**-0845
Baciocchi, W., **17**-0387
Back, R.A., **14**-0052, **15**-0482, **15**-0485
Back, T.G., **04**-0512, **12**-0244, **14**-0407, **15**-0240, **16**-1651, **17**-0290, **19**-0048, **19**-0871, **19**-1583, **19**-1590
Backeberg, O.G., **14**-0010
Backer, H.J., **17**-0497
Backnejad, H., **19**-0086
Bäckvall, J., **15**-0327, **15**-1878, **19**-0721
Bäckvall, J.-E., **10**-0226, **10**-1293, **10**-1300, **10**-1437, **10**-1438, **11**-0335, **15**-0230, **15**-0289, **15**-0832, **15**-1504, **15**-1663, **15**-1664, **15**-1670, **15**-1707, **15**-1716, **15**-1760, **15**-1858, **15**-1867, **16**-1132, **19**-0221, **19**-0796, **19**-1146
Bacon, J., **05**-0023
Bacon, R.G.R., **13**-0218, **13**-0256
Badaev, F.Z., **12**-0609
Badanyan, Sh.O., **15**-1650, **19**-0387
Badaringarayana, V., **13**-0228
Baddar, F.G., **12**-0088
Badding, V.G., **19**-1389
Bade, T.R., **14**-0209, **16**-1218
Bader, J., **04**-0151
Bader, R.F.W., **02**-0153, **04**-0278, **04**-0405, **04**-0420, **10**-0622, **12**-0648, **16**-1731, **17**-0236
Badet, B., **10**-0400, **10**-0825
Badger, G.M., **02**-0093
Badger, R.C., **12**-0209
Badiger, V.V., **10**-0261, **16**-1403
Badine, D.M., **16**-1416
Badlani, R.N., **09**-0100
Badone, D., **12**-0261, **13**-0471
Badri, M., **10**-0460
Bae, C., **05**-0093
Bae, D., **10**-0618
Bae, J.W., **16**-0351, **16**-0352, **19**-0998, **19**-1751
Bae, Y.H., **12**-0122, **12**-0129
Baechler, R.D., **04**-0034, **04**-0247
Baeckström, P., **10**-1377
Baek, D.Y., **13**-0599
Baek, H.S., **19**-1600, **19**-1685
Baele, J., **10**-0873
Baenziger, N., **17**-0328
Baer, D.R., **18**-0160
Baer, H.H., **15**-1004, **16**-0397, **16**-1149
Baer, S., **10**-0359
Baerends, E.J., **15**-1494
Baes, M., **04**-0068, **04**-0186
Baeza, J., **16**-1649
Baeza, J., **17**-0415
Bafus, D.A., **05**-0152
Bagal, L.I., **14**-0358, **18**-0293
Baganz, H., **10**-0639
Baggott, J.E., **02**-0355
Baghel, S.S., **11**-0653
Bagheri, V., **12**-0348, **19**-0135
Bagherzadeh, M., **11**-0134
Bagherzadeh, M., **12**-0705
Baghurst, D.R., **10**-0471
Baghurst, D.R., **07**-0105
Bagley, M.C., **15**-2426, **16**-0138
Bagnell, L., **15**-1146, **19**-0966
Bagnell, L.J., **19**-1373
Bagno, A., **05**-0070, **08**-0009, **08**-0129, **14**-0367, **16**-1576
Bagnol, L., **14**-0038, **15**-0273
Bagrovskaya, N.A., **11**-0632
Bagutskii, V., **18**-0087
Bahl, M.K., **08**-0234
Bahmanyar, S., **16**-1063
Bahn, C.A., **10**-0256
Bahr, M.L., **10**-1006
Bahrmann, H., **10**-1837, **10**-1838, **15**-1375
Bahule, B.B., **15**-1535
Bahzad, D., **11**-0231, **11**-0276
Bai, C., **10**-1453, **15**-0428, **16**-1433
Bai, D., **16**-1794
Bai, K., **16**-0872
Bai, L., **07**-0118, **13**-0414, **16**-1919
Bai, Y., **19**-0037
Baigrie, L.M., **16**-1059
Baik, I., **04**-0175
Baik, T.-G., **13**-0295, **13**-0340, **15**-0236, **15**-2175, **16**-0722
Baik, W., **16**-0872, **19**-0800, **19**-1189, **19**-1213
Baiker, A., **10**-0900, **19**-0120
Bailen, M.A., **16**-1784
Bailey, D.M., **19**-1477
Bailey, D.S., **17**-0026, **17**-0027, **17**-0096, **17**-0097
Bailey, G.C., **18**-0756, **18**-0763, **18**-0828
Bailey, K.E., **19**-1427
Bailey, M., **15**-1529
Bailey, N.A., **02**-0259, **02**-0265
Bailey, P.L., **15**-1791
Bailey, P.S., **19**-0345, **19**-0354, **19**-0358, **19**-0361, **19**-0377
Bailey, T.R., **13**-0376
Bailey, W.F., **04**-0321, **10**-1239, **12**-0617, **12**-0626, **12**-0627, **15**-0877, **15**-0878, **15**-0879, **15**-0883, **15**-0884, **15**-1226, **15**-1245, **18**-0406
Bailey, W.J., **16**-0194, **17**-0127, **17**-0142, **17**-0231, **18**-0550, **19**-1378
Baillargeon, M.M., **15**-0167
Baillargeon, V.P., **10**-1822
Baille, C., **13**-0498, **13**-0496
Baine, P., **08**-0024
Baines, K.M., **01**-0009
Bains, S., **15**-2040, **16**-0130, **16**-1876
Baiocchi, F., **12**-0736
Bair, K.W., **10**-1712, **17**-0253
Baird Jr., W.C., **11**-0297, **13**-0622, **15**-1536
Baird, C.P., **16**-1384

Baird, C.W., **14**-0444
Baird, J.C., **05**-0208
Baird, J.D., **13**-0504
Baird, M.C., **12**-0006, **14**-0443, **15**-0515
Baird, M.S., **04**-0464, **16**-1959, **18**-0086, **18**-0173
Baird, N.C., **02**-0187, **08**-0231
Baishya, G., **10**-0822, **15**-1327
Baizer, M.M., **10**-1337, **14**-0130, **14**-0415, **19**-0641, **19**-0955, **19**-1228, **19**-1317, **19**-1691
Baj, S., **15**-0150
Bajwa, G.S., **18**-0724
Bak, D.A., **13**-0253, **15**-2178, **15**-2186
Bak, R.R., **11**-0146, **15**-0624
Bakac, A., **19**-0074
Bakalova, G.V., **19**-1454
Bakalova, S.M., **15**-2046
Bakendale, I.R., **16**-1428
Baker III, T.N., **15**-1618
Baker Jr., J.D., **19**-1462
Baker, A.D., **01**-0013, **01**-0016, **01**-0013
Baker, B.E., **13**-0378, **13**-0421, **13**-0421
Baker, C., **01**-0013
Baker, D.C., **19**-1159
Baker, E.B., **05**-0015
Baker, G., **13**-0157
Baker, G.R., **16**-2009
Baker, J.W., **02**-0378
Baker, J.M., **14**-0072
Baker, J.R., **16**-1621
Baker, J.W., **02**-0367, **02**-0368, **02**-0369, **10**-0313
Baker, K.V., **12**-0580
Baker, K.V., **12**-0597
Baker, N.J., **11**-0028
Baker, R., **10**-0060, **10**-1251, **15**-2429, **18**-0761
Baker, R.T., **15**-0696, **19**-1609
Baker, S.R., **15**-1254, **19**-1628
Bakinovskii, L.V., **15**-1652
Bakke, J.M., **03**-0059, **11**-0145, **13**-0681, **19**-0457, **19**-0590
Bakker, C.N.M., **11**-0312
Baklouti, A., **10**-0920
Bakó, P., **15**-1001, **16**-1212
Bakos, J., **15**-0598, **15**-1491
Bakoss, H.J., **11**-0598
Bakshi, R.K., **16**-0997, **18**-0433, **19**-1031
Bakthadoss, M., **11**-0333
Bakulev, V.A., **16**-1447
Bakunin, V.N., **12**-0034, **12**-0037
Bal'yan, Kh.V., **18**-0713
Bal, B.S., **19**-0699
Bal, G., **13**-0178
Balaban, A.T., **02**-0093, **02**-0094, **02**-0097, **02**-0118, **02**-0288, **11**-0408, **12**-0302, **15**-1648, **15**-2073, **18**-0646, **18**-0648, **18**-0756
Balachandran, K.S., **19**-0010
Balagopal, L., **15**-1624
Balakrishna, M.S., **16**-1309
Balakrishnan, P., **12**-0251
Balakumar, R., **19**-1075, **19**-1300
Balalaie, S., **16**-0129, **16**-1174
Balamraju, Y., **16**-1021
Balan, D., **16**-0788, **16**-0792, **16**-0806, **18**-0773
Balanarsaiah, E., **10**-1570
Balandin, A.A., **01**-0095, **15**-0450
Balanikas, G., **19**-0634
Balas, L., **13**-0077
Balasubramanian, A., **02**-0377
Balasubramanian, K., **11**-0473, **19**-0100
Balasubramanian, K.K., **11**-0659, **18**-0565, **19**-1334
Balasubramanian, N., **15**-1932
Balasubramaniyan, V., **15**-0654
Balavoine, G.G.A., **18**-0401
Balcells, D., **04**-0049
Balch, A.L., **02**-0364, **05**-0222
Balchunis, R.J., **12**-0241, **16**-1586
Balci, M., **02**-0247, **15**-2153
Balcom, B.J., **16**-1659
Balderman, D., **10**-1021
Baldisera, L., **07**-0101
Baldridge, K.K., **02**-0082, **02**-0359, **03**-0200, **11**-0079
Baldwin, A.R., **16**-1881
Baldwin, F.P., **16**-1762
Baldwin, J.E., **05**-0385, **06**-0015, **06**-0015, **06**-0017, **06**-0019, **12**-0408, **14**-0457, **15**-1349, **15**-2049, **15**-2111, **15**-2183, **15**-2210, **15**-2217, **15**-2218, **16**-0210, **16**-1203, **16**-1276, **16**-1687, **17**-0482, **18**-0079, **18**-0159, **18**-0169, **18**-0175, **18**-0204, **18**-0387, **18**-0396, **18**-0473, **18**-0480, **18**-0498, **18**-0539, **18**-0544, **18**-0548, **18**-0560, **18**-0567, **18**-0569, **18**-0582, **18**-0589, **18**-0629, **18**-0629, **18**-0727, **18**-0733, **18**-0734, **19**-0063, **19**-1558
Baldwin, J.J., **04**-0206
Baldwin, M.A., **17**-0248
Baldwin, S.W., **14**-0147, **15**-2235, **18**-0239, **19**-0062
Baldwin, S.W., **19**-1468
Baleizão, C., **16**-1440
Balenkova, E.S., **15**-1918, **15**-1920
Balestra, M., **18**-0735
Balicki, R., **19**-0236, **19**-0778, **19**-0818, **19**-1552, **19**-1553
Baliga, B.T., **15**-0024
Balint, A.E., **12**-0457
Balkenhol, F., **16**-1823
Balkovec, J.M., **04**-0206
Balkus Jr., K.J., **15**-0433
Ball Jr., A.L., **12**-0013
Ball, D.L., **19**-0255
Ball, R.E., **15**-1776
Ball, R.G., **13**-0689, **15**-0008
Ball, Z.T., **10**-1471, **15**-0477, **15**-0741, **15**-0905
Balla-Achs, M., **03**-0164
Ballantine, J.A., **10**-0916, **15**-0268
Ballard, D.H., **15**-0263
Ballard, R.E., **01**-0013
Ballard, S.A., **12**-0465
Ballatore, A., **10**-1227
Ballester, M., **05**-0238, **05**-0256, **16**-1215
Ballester, P., **13**-0021
Ballestero, C., **18**-0487
Ballesteros, A., **10**-0669
Ballestri, M., **10**-1209, **14**-0081, **15**-0067, **19**-1403, **19**-1419
Ballini, R., **10**-0845, **10**-1002, **12**-0083, **12**-0686, **15**-1005, **15**-1033, **16**-0108, **16**-0113, **16**-0233, **16**-0255, **16**-0327, **16**-0808, **16**-1149, **16**-1156, **16**-1666, **19**-0666, **19**-1206, **19**-1532
Ballistreri, F.P., **16**-2143
Ballod, A.P., **12**-0203
Balls, D.M., **15**-2185, **15**-2196
Bally, T., **02**-0208, **05**-0407
Balme, G., **10**-0547
Balog, M., **02**-0428
Balquist, J.M., **18**-0170
Balsells, J., **15**-2337, **16**-0646
Baltork, I.M., **16**-0096, **19**-0152
Baltzly, R., **10**-0914
Balu, N., **16**-0775
Balzani, V., **03**-0184, **07**-0011
Bałczewski, P., **15**-1205
Bambridge, K., **16**-0851
Bamfield, P., **13**-0467
Bamford, C.H., **05**-0359, **06**-0008, **06**-0046, **06**-0049, **06**-0052, **06**-0052, **06**-0053, **06**-0054, **07**-0044, **08**-0096,

Bamford, C.H., (*Continued*) **08**-0102, **08**-0135, **10**-0213, **11**-0001, **11**-0108, **11**-0203, **11**-0214, **11**-0271, **11**-0543, **11**-0609, **11**-0612, **11**-0626, **11**-0631, **11**-0660, **12**-0002, **12**-0024, **12**-0038, **12**-0057, **12**-0424, **12**-0504, **12**-0551, **12**-0638, **13**-0003, **13**-0658, **14**-0062, **14**-0214, **15**-0001, **15**-0050, **15**-0451, **15**-1932, **15**-1980, **15**-2166, **16**-0014, **16**-1510, **16**-1516, **16**-1549, **16**-1560, **16**-1588, **17**-0003, **17**-0007, **17**-0037, **17**-0039, **17**-0057, **17**-0122, **17**-0176, **18**-0471, **18**-0526, **18**-0569, **18**-0594, **18**-0739, **19**-0002, **19**-0701
Bamford, W.R., **17**-0279
Bamkole, T., **17**-0144
Bamoniri, A., **10**-0642
Bampfield, H.A., **15**-2187, **18**-0559
Ban, H., **15**-1427
Ban, Y., **13**-0678
Banait, N., **10**-0329, **15**-0218
Banait, N.S., **17**-0049
Banciu, M., **02**-0093, **02**-0288, **18**-0646, **18**-0648
Banco-Urgoiti, J., **15**-1438
Bandarage, U.K., **19**-0175
Bandarage, U.P., **19**-0679
Bandgar, B.P., **10**-0774, **10**-1107, **11**-0221, **11**-0430, **13**-0347, **16**-0050, **16**-0178, **16**-1159, **16**-1602, **16**-1616, **16**-1681, **16**-1684, **16**-2179, **17**-0438, **19**-1442
Bandin, E., **15**-2174
Bandini, M., **10**-1469, **16**-1434
Bando, T., **18**-0738
Bandyapadhyay, A., **17**-0366, **17**-0399, **19**-0864, **19**-1599
Bandyopadhyay, A.K., **10**-1537
Bandyopadhyay, T., **19**-1316
Baneres, J.-L., **18**-0156
Banerjee, A.K., **19**-1438, **19**-1717
Banerjee, B., **11**-0247, **16**-0177
Banerjee, J., **15**-1141, **16**-1527
Banerjee, M., **16**-0715
Banerjee, S., **17**-0212, **18**-0668, **19**-0974
Banerjee, S.K., **10**-0603
Banerji, A., **19**-1463, **19**-1623, **19**-1716
Banerji, K.K., **19**-0658, **19**-0713, **19**-0831
Banert, K., **10**-0317
Banfi, L., **12**-0230
Banfi, S., **05**-0253, **15**-1814
Bang, K., **16**-0599
Bang, K.S., **13**-0077
Bang, L., **12**-0454
Bangert, K.F., **02**-0178
Banik, B.K., **07**-0105, **07**-0116, **11**-0143, **15**-1287, **16**-0072, **16**-0283, **16**-0607, **16**-2097, **19**-0119, **19**-0224, **19**-1137, **19**-1138, **19**-1187, **19**-1190, **19**-1192, **19**-1648
Banik, I., **16**-0283, **19**-1137, **19**-1187
Banik, N.K., **16**-0231
Banitt, E.H., **17**-0415
Banjoko, O., **13**-0017, **16**-2143
Bank, J., **10**-0968
Bank, S., **10**-0089, **10**-0122, **10**-0916, **12**-0063
Bankovskii, Yu.A., **03**-0049
Banks, J.-T., **18**-0089
Banks, J.T., **05**-0310, **14**-0067, **14**-0074
Banks, M.L.A., **14**-0378
Banks, R.B., **10**-1296, **14**-0378
Banks, R.L., **18**-0756, **18**-0763, **18**-0765, **18**-0828
Bankston, D., **19**-0415
Bannard, R.A.B., **18**-0250
Bannerman, C.G.F., **15**-2322, **18**-0469, **18**-0470
Bannet, D.M., **17**-0343
Bannister, T.D., **04**-0124
Bannister, W.J., **12**-0464
Bannwarth, W., **16**-1821
Banoli, L., **18**-0697
Bansal, G., **17**-0368
Bansal, P., **10**-1071
Bansal, R.K., **16**-1213
Banthorpe, D.V., **03**-0080, **11**-0029, **11**-0572, **11**-0575, **17**-0085, **17**-0089, **17**-0111, **17**-0114, **17**-0248, **18**-0096, **18**-0099, **18**-0279, **18**-0290, **18**-0739, **18**-0742, **18**-0743, **18**-0744, **18**-0745
Bañuls, M.J., **15**-1119
Banwell, M., **16**-1787
Banwell, M.G., **04**-0464, **15**-2277
Banwell, T., **11**-0058
Banziu, M., **18**-0648
Bao, F., **15**-0740
Bao, J., **15**-0604
Bao, L.Q., **12**-0174
Bao, W., **16**-0653, **16**-0872, **16**-1008, **16**-1910
Baquer, S.M., **16**-0131
Barager III, H.J., **12**-0180, **19**-0821
Barahate, N.B., **10**-0660
Barak, G., **10**-0610
Baram, S.G., **09**-0020
Baran Jr., J.R., **12**-0585
Baran, J., **15**-1963
Baran, P.S., **17**-0297, **17**-0298, **19**-0624
Baranne-Lafont, J., **19**-0279
Baránski, A., **13**-0677
Barany, G., **16**-1816
Barar, D.G., **17**-0178
Barash, L., **15**-2063
Baratta, W., **17**-0267
Barba, G.R., **17**-0293
Barbachyn, M.R., **04**-0047, **15**-1712
Barbara, C., **18**-0687
Barbarini, A., **19**-0823
Barbas III, C.F., **15**-0994, **15**-1004, **16**-0415, **16**-0877, **16**-0917, **16**-1035, **16**-1036, **16**-1037, **16**-1068, **16**-1268
Barber, J., **10**-1179
Barber, J.J., **12**-0605
Barber, M., **04**-0502
Barberis, M., **15**-2304
Barbero, M., **10**-1866
Barbier, G., **15**-0016
Barbier, J., **15**-0424
Barbier, P., **16**-0478
Barbieri, G., **15**-1724
Barbillat, J., **14**-0233
Barboni, L., **10**-1002, **15**-1033, **16**-0233, **16**-0808
Barborak, J.C., **04**-0441, **18**-0009
Barbosa, A.G.H., **11**-0119
Barbosa, M.C.N., **14**-0338, **14**-0342, **14**-0343
Barbot, F., **12**-0660, **15**-0041
Barbour, J.B., **05**-0033
Barbour, L.J., **03**-0088, **03**-0169
Barbry, D., **16**-0366, **16**-0368, **18**-0382, **19**-0654, **19**-0965
Barbu, E., **10**-0999
Barchín, B.M., **12**-0271
Barcina, J.O., **10**-0791, **10**-1362, **10**-1400, **11**-0471
Barckholtz, C., **02**-0024
Barckholtz, T.A., **02**-0024
Barclay, L.R.C., **04**-0502, **11**-0361, **16**-1563, **18**-0078
Barco, A., **15**-2179
Barcóczy, J., **02**-0431
Barczynski, P., **02**-0095
Bard, A.J., **05**-0318, **12**-0658, **14**-0416
Bard, R.R., **13**-0596, **13**-0597
Bardales, E., **10**-1167, **17**-0214, **17**-0398, **19**-0906

Barden, M.C., **15**-1958
Barden, M.C., **19**-1665
Bardenm, T.C., **14**-0457
Barder, T.E., **13**-0533
Baret, P., **04**-0243
Baretta, A., **18**-0197
Bärfacker, L., **15**-0341
Bargar, T., **13**-0596
Bargas, L.M., **19**-0659
Barger, T.M., **17**-0463
Bargiggia, F., **15**-0151
Bargiotti, A., **17**-0343
Bargon, J., **05**-0218, **05**-0222, **14**-0327
Bargon, R.M., **15**-1845, **15**-1849
Barhate, N.B., **11**-0255
Barhdadi, R., **10**-1811
Barid Jr., T.A., **04**-0454
Barilli, P., **14**-0341
Bark, T., **15**-1264
Barker, G.K., **15**-2431
Barker, J.M., **18**-0288
Barker, P.J., **05**-0296
Barkhash, V.A., **10**-0119, **10**-0393
Barkin, J.L., **16**-0867, **16**-0886
Barkley, R.M., **10**-0491
Barlet, R., **15**-2277
Barlin, G.B., **08**-0160
Barlow, M.G., **18**-0493
Barlow, S.E., **05**-0106, **10**-0344
Barltrop, J.A., **07**-0001, **11**-0658, **16**-2074, **16**-2084
Barluenga, J., **10**-0669, **12**-0125, **12**-0409, **12**-0430, **14**-0141, **15**-0357, **15**-0370, **15**-1546, **15**-1547, **15**-1873, **15**-1875, **15**-1880, **15**-2289, **15**-2415, **15**-2418, **16**-0500, **16**-1413
Barma, D.K., **16**-1369, **17**-0316
Barman, D.C., **19**-0306, **19**-1554
Barnard, C.F.J., **13**-0440
Barnard, P.W.C., **10**-0517
Barnatt, A., **17**-0230
Barnea, E., **16**-0968
Barner, L., **16**-0213
Barner, R., **18**-0705
Barnes, C.E., **11**-0101
Barnes, C.L., **15**-0675, **15**-2434
Barnes, C.S., **19**-0051
Barnes, D., **19**-1240
Barnes, D.M., **15**-1004, **15**-2064
Barnes, D.S., **03**-0083
Barnes, M.W., **19**-0763
Barneto, J.L., **04**-0300, **04**-0303
Barnett, B., **15**-2431
Barnett, G.H., **08**-0180
Barnett, J.W., **11**-0097, **16**-1600
Barnette, W.E., **12**-0133
Barney, C.L., **16**-0361
Barnhart, R.W., **15**-1361, **15**-1366
Barnhart, T.M., **10**-1333
Barnhurst, L.A., **10**-0813
Barnier, J.P., **18**-0553
Barnum, C., **12**-0251
Baron D.L., **19**-1583
Baron W., **10**-0917
Barón, M., **16**-2064
Barone, G., **15**-1685
Baroni, A.C.M., **15**-0313, **15**-1551
Baroni, M., **13**-0471
Barot, B.C., **16**-0989
Barr, D., **13**-0654
Barr, D.P., **05**-0293
Barra, M., **15**-0164
Barrau, J., **01**-0009
Barrault, J., **10**-0778
Barreiro, E., **10**-1434, **16**-0580, **16**-0580
Barrelle, M., **15**-0187
Barren, J.P., **11**-0653
Barrero, A.F., **15**-1233, **16**-1618, **19**-0316, **19**-0355, **19**-0940
Barrett, A.G.M., **10**-0717, **10**-0994, **11**-0137, **11**-0410, **11**-0423, **16**-0759, **16**-1149, **16**-1189, **16**-1243, **16**-1312, **16**-1777, **16**-1835, **16**-2111, **17**-0268, **17**-0336, **18**-0793, **19**-0115, **19**-1204, **19**-1410, **19**-1411
Barrett, G.C., **04**-0268
Barrett, I.C., **13**-0004, **16**-0305
Barrett, J.H., **15**-2116
Barriault, L., **18**-0599
Barrientos-Astigarraga, R.E., **16**-0582
Barrio, J.R., **10**-1055
Barrish, J.C., **15**-0655
Barron B.G., **19**-1383
Barron L.D., **04**-0016, **04**-0154
Barron, L.D., **04**-0005
Barros, D., **15**-1782
Barrow, M.J., **02**-0163
Barry, B.J., **12**-0072
Barry, G.W., **08**-0118
Barry, J., **16**-1689, **17**-0307
Barsanti, P.A., **10**-1155
Barstow, J.F., **18**-0676
Bart, S.C., **15**-0629
Barta, N.S., **18**-0608
Bartell, L.S., **02**-0035, **01**-0056, **01**-0061, **01**-0074, **06**-0074
Bartels, A.P., **19**-1454
Bartels, B., **10**-1463
Bartels, H.M., **15**-0101, **15**-0112
Barter, R.M., **19**-0253
Barth, G., **04**-0021
Barth, J., **10**-1176
Barth, W.E., **02**-0358
Barthuber, A., **16**-1422
Bartik, K., **07**-0076
Bartkus, E.A., **13**-0758
Bartlett, P.A., **04**-0136, **04**-0138, **10**-1522, **15**-0003, **15**-0782, **15**-1584, **16**-0005, **16**-0112, **18**-0594, **18**-0654, **18**-0676
Bartlett, P.D., **04**-0511, **09**-0007, **10**-0042, **10**-0049, **10**-0119, **10**-0122, **10**-0134, **14**-0232, **15**-0026, **15**-0028, **15**-1732, **15**-2091, **15**-2112, **15**-2159, **15**-2161, **15**-2182, **15**-2207, **15**-2209, **15**-2221, **15**-2222, **15**-2251, **16**-0514
Bartlett, R.J., **03**-0042
Bartlett, R.S., **19**-1150, **19**-1227
Bartlett, W.R., **18**-0676
Bartley, J.P., **10**-1054
Bartley, W.J., **04**-0465
Bartmess, J., **08**-0147
Bartmess, J.E., **02**-0234, **08**-0223, **08**-0231, **08**-0235, **08**-0236, **08**-0238
Bartnicka, H., **08**-0229
Bartok, W., **19**-0869
Bartók, M., **10**-0376, **17**-0172, **18**-0124, **19**-1460
Bartoletti, I., **10**-1849
Bartoli, D., **19**-0492
Bartoli, G., **10**-0545, **10**-0931, **10**-1064, **10**-1123, **11**-0457, **13**-0078, **15**-0875, **15**-1018, **15**-1105, **15**-1167, **15**-1170, **15**-1289, **16**-0487, **16**-0521, **16**-0615, **16**-1618, **17**-0160, **19**-0997
Barton, D.H.R., **04**-0512, **05**-0309, **09**-0015, **10**-0558, **10**-0757, **10**-0887, **10**-1089, **12**-0247, **12**-0339, **12**-0520, **12**-0655, **12**-0729, **13**-0224, **13**-0580, **13**-0581, **13**-0584, **14**-0133, **14**-0134, **14**-0207, **14**-0225, **14**-0286, **14**-0331, **14**-0332, **14**-0387, **14**-0420, **14**-0434, **15**-0124, **15**-1199, **15**-1519, **16**-2058, **17**-0124, **17**-0136, **17**-0144, **17**-0336, **17**-0525, **18**-0868, **18**-0869, **18**-0870, **18**-0872, **19**-0010, **19**-0051, **19**-0058, **19**-0058,

Barton, D.H.R., (*Continued*) **19**-0267, **19**-0436, **19**-0437, **19**-0612, **19**-0613, **19**-0614, **19**-1246, **19**-1250, **19**-1401, **19**-1402, **19**-1404, **19**-1405, **19**-1406, **19**-1410, **19**-1411, **19**-1413, **19**-1415, **19**-1439, **19**-1540
Barton, J.K., **10**-0209
Barton, S., **18**-0182
Barton, T.J., **08**-0078, **18**-0534, **18**-0636
Bartoń, H.J., **16**-1871
Bartra, M., **19**-1272
Bartroli, J., **16**-1018
Bartsch, M., **15**-1865
Bartsch, R.A., **03**-0107, **03**-0174, **09**-0118, **10**-0470, **13**-0691, **16**-0815, **17**-0007, **17**-0015, **17**-0021, **17**-0022, **17**-0029, **17**-0029, **17**-0031, **17**-0088, **17**-0091, **17**-0092, **17**-0093, **17**-0094, **17**-0101
Bartuska, V.J., **10**-1119
Barua, N.C., **10**-0946, **10**-1004, **10**-1108, **16**-0117, **19**-0934
Baruah, A., **10**-1004
Baruah, B., **16**-1902, **17**-0384, **19**-1694
Baruah, J.N., **17**-0198
Baruah, M., **10**-1394, **15**-1018, **16**-0395, **19**-1268, **19**-1433, **19**-1757
Baruah, R.N., **17**-0198
Baruchello, R., **16**-1260
Barun, O., **18**-0248
Barvian, N.C., **13**-0784
Barzana, E., **12**-0213
Barzilay, C.M., **15**-0842
Basak, A., **10**-0720
Basak, A.K., **09**-0115, **13**-0159, **16**-1174
Basavaiah, D., **11**-0333
Basavaiah, D., **15**-0644, **16**-0771, **16**-0807, **18**-0435, **18**-0444, **18**-0448, **19**-1035, **16**-0766, **19**-1032
Basch, H., **01**-0016, **10**-0023, **10**-0024, **10**-0319, **10**-0321
Baseer, M.A., **11**-0258
Basetti, M., **15**-0194
Basha, A., **12**-0511, **16**-1835, **19**-1128, **19**-1487
Bashe, R.W., **10**-1350
Bashore, C., **05**-0392
Baskaran, S., **10**-0959, **12**-0732, **15**-0192, **15**-0193, **15**-1936, **16**-1013, **19**-0731, **19**-0735
Baskaran, T., **19**-0831
Baskin, J.M., **13**-0148
Bass, K.C., **14**-0031
Bass, L.S., **15**-1712
Basselier, J., **11**-0226
Bassendale, A.R., **18**-0898
Basset, J.-M., **05**-0383, **19**-0042
Basset, J.M., **18**-0756, **18**-0821
Bassetti, M., **15**-0280
Bassi, P., **15**-0087
Bassindale, A., **04**-0001
Bassindale, A.R., **01**-0045, **15**-0293, **16**-1234, **16**-1237
Bässler, T., **10**-0248, **10**-0250
Basso, E.A., **04**-0353
Bast, P., **05**-0148
Bastiaan, E.W., **02**-0062
Bastiansen, O., **02**-0030, **02**-0240, **03**-0050, **04**-0261, **04**-0317, **04**-0350
Bastide, J., **15**-1964, **15**-1992
Bastien, I.J., **05**-0015
Bastin, S., **16**-0687
Bastos, C., **04**-0146, **15**-0597
Basu, A., **05**-0187, **10**-0631, **10**-1279
Basu, B., **13**-0196, **13**-0489, **15**-0618
Basu, M.K., **16**-0072, **16**-0127, **16**-0231, **16**-0607, **16**-1522, **19**-1192
Basu, P.K., **15**-1277
Basu, S., **15**-1535
Basu, S.N., **19**-0247, **19**-0249
Batal, D.J., **15**-1804
Bateman, L.C., **10**-0036, **10**-0039, **10**-0330
Bates, C.G., **12**-0295, **13**-0201
Bates, D.M., **07**-0082
Bates, G.S., **16**-1651, **18**-0563, **19**-1294
Bates, R.B., **05**-0099, **13**-0128, **15**-0548, **18**-0727
Bates, T.F., **05**-0151
Batey R.A., **10**-1423, **10**-0629, **10**-1213, **10**-1423, **13**-0215, **13**-0533, **16**-0740, **16**-0741, **16**-0742, **16**-1803
Batlaw, R., **12**-0611, **15**-0515
Batlle, A., **13**-0064
Batog, A.E., **15**-1735
Batr, R., **19**-0065
Batra, H., **10**-0848, **15**-1605
Batrak, T.A., **15**-1735
Batrakov, S.G., **19**-1077
Bats, J.-P., **10**-0952
Batsanov, A., **15**-1271
Batsanov, A.S., **15**-1940
Batsanov, S.S., **01**-0022
Batt, L., **05**-0297, **06**-0049
Battioni, J., **15**-1170
Battioni, P., **12**-0224, **15**-1892
Battiste, M.A., **02**-0160, **08**-0071, **10**-0146, **10**-0148, **10**-0149, **10**-0152, **15**-0134, **15**-0138, **16**-1235
Battle, G.M., **16**-2107
Batts, B.D., **10**-0516, **11**-0110
Baud, C., **15**-1901
Bauder, A., **02**-0183, **02**-0402, **19**-0386
Baudin, J., **19**-0841
Baudjouk, P., **11**-0648
Baudoux, D., **10**-1681
Baudouy, R., **10**-1349
Baudry, D., **18**-0208
Baudry, M., **15**-0888
Bauduin, C., **19**-0789
Bauer, A., **13**-0442
Bauer, D., **19**-1665
Bauer, D.P., **19**-0173
Bauer, L., **15**-0080, **18**-0286
Bauer, M., **10**-0616, **16**-2066
Bauer, P., **16**-0478, **16**-0514, **18**-0035
Bauer, T., **04**-0135
Bauer, W., **05**-0154, **05**-0175, **05**-0176, **05**-0184, **12**-0407, **12**-0550
Baugh, S.P.D., **10**-0732
Baughman, E.H., **08**-0118
Bauld, N.L., **02**-0210, **14**-0417, **15**-2013, **15**-2014, **15**-20, **18**-0588, **19**-0377
Baum, A.A., **18**-0852
Baum, E.W., **10**-1469
Baum, J.S., **02**-0196, **12**-0218
Baum, K., **12**-0212, **12**-0728
Baum, M.W., **06**-0066
Baum, S., **18**-0646
Baumann, H., **02**-0291, **02**-0298
Baumann, M.E., **18**-0132
Baumann, W., **15**-0608
Baume, E., **13**-0461
Baumgarten, H.E., **18**-0257, **18**-0262, **18**-0271
Baumgarten, R.J., **10**-0384, **10**-0385, **10**-0724, **17**-0246
Baumgartner, M.T., **13**-0343
Bäuml, E., **15**-1927
Baumstark, A.L., **10**-1505, **19**-0234, **19**-1719, **19**-1720
Baumstark, R., **05**-0010
Baus, U., **04**-0143
Bausch, C.C., **16**-1501
Bausch, M.J., **05**-0246
Bauslaugh, P.G., **15**-2238
Bautista, F.M., **15**-0454
Bautista, R.G., **04**-0320
Bavry, R.H., **15**-1598
Baxendale, I.R., **15**-0147, **16**-0341

Baxter III, H.N., **14**-0118, **14**-0163
Baxter, A.G.W., **18**-0173
Baxter, I., **03**-0186
Baxter, S.L., **14**-0399, **19**-1473, **19**-1577
Bay, E., **13**-0253, **18**-0852, **18**-0855
Bayer, E., **10**-0860, **10**-1081, **16**-1816
Bayer, R.P., **19**-0749
Bayeroju, I.A., **13**-0017
Bayle, J.P., **19**-0699
Bayless, J., **17**-0269
Bayless, J.H., **10**-0203, **17**-0280
Baylis, A.B., **16**-0771
Baylon, C., **10**-1208
Baylouny, R.A., **17**-0142, **18**-0550
Bayne, D.W., **13**-0782
Bayne, W.F., **17**-0031
Bayón, J.C., **15**-1492
Bayón, P., **16**-0899
Bayquen, A.V., **10**-1027
Bays, J.T., **19**-0608
Bazan, G.C., **18**-0768
Bazán-Tejeda, B., **16**-1113
Bazanova, G.V., **11**-0125
Bazaral, C., **13**-0606
Bazarova, I.M., **10**-1578, **12**-0194
Baze, M.E., **04**-0478, **15**-2208
Bazgir, A., **19**-0565
Bazhenov, D.V., **15**-0280
Bazikian, C.M., **16**-1593
Bazureau, J.P., **15**-1949
Beadle, B.M., **10**-0112
Beadle, J.R., **13**-0691, **13**-0737
Beagley, B., **04**-0289
Beak, P., **02**-0406, **02**-0415, **02**-0416, **05**-0124, **10**-0049, **10**-0050, **10**-1272, **10**-1273, **10**-1279, **10**-1281, **10**-1720, **10**-1723, **10**-1730, **12**-0303, **12**-0405, **12**-0409, **12**-0509, **12**-0510, **12**-0511, **12**-0630, **13**-0644, **15**-1116, **15**-1733, **15**-1978, **16**-0004, **16**-0845, **16**-1485
Beal, M.F., **05**-0212
Beale, J.H., **10**-0372
Beale, W.J., **12**-0072
Beam, C.F., **16**-1057
Bean, F.R., **12**-0448
Beard, C., **11**-0589
Beard, R.D., **12**-0398
Beard, W.Q., **13**-0760, **13**-0761
Bearpark, M.J., **15**-2244
Beasley, G.H., **18**-0630
Beatle, J.C., **18**-0611
Beaton, J.M., **18**-0870
Beatty, H.R., **13**-0249
Beauchamp, J.L., **05**-0073, **05**-0075, **05**-0083, **08**-0219, **10**-0184, **18**-0836
Beauchamp, P.S., **11**-0327, **15**-2398
Beauchamp, T., **05**-0253
Beauchemin, A., **15**-2340, **15**-2342
Beaudegnies, R., **15**-2147
Beaudoin, S., **16**-1316, **16**-1326
Beaulieu, C., **16**-2180
Beaupère, D., **19**-0708
Bebb, R.L., **10**-1285, **12**-0388
Bebbington, D., **15**-1244
Bebout, D.C., **05**-0077
Becattini, B., **15**-1235
Bechara, E.J.H., **19**-1719
Becht, J.-M., **13**-0290, **13**-0639, **15**-1022
Beck Jr., K.R., **19**-0764
Beck, A.K., **16**-2012
Beck, B., **13**-0270
Beck, B.R., **04**-0445
Beck, E.J., **17**-0359
Beck, F., **19**-0482
Beck, J.P., **15**-2032
Beck, J.R., **13**-0083
Beck, K., **18**-0772
Beck, S.M., **11**-0565
Becker, A., **10**-0060
Becker, A.R., **12**-0716
Becker, D., **15**-2219, **15**-2241, **15**-2249
Becker, D.A., **05**-0212
Becker, E.I., **02**-0165
Becker, E.I., **17**-0423
Becker, F.F., **11**-0143, **16**-0072, **16**-0231, **16**-2097, **19**-0224, **19**-1137, **19**-1138, **19**-1187, **19**-1190, **19**-1192, **19**-1648
Becker, H., **02**-0397, **11**-0637, **16**-1918, **19**-0021, **19**-0314
Becker, H.-C., **04**-0054
Becker, H.-D., **04**-0054, **07**-0035
Becker, H.G.O., **13**-0719
Becker, I.F., **19**-0119
Becker, J., **16**-1256
Becker, J.Y., **02**-0184
Becker, K.B., **04**-0493, **04**-0494, **14**-0433, **15**-0034, **16**-1334, **17**-0403
Becker, L.W., **10**-0317
Becker, N., **01**-0042, **15**-1735
Becker, P.N., **15**-1879
Becker, R., **19**-1241
Becker, R.H., **18**-0387
Becker, S., **10**-1243, **14**-0401, **19**-1580
Becker, W.E., **05**-0164
Becker, Y., **17**-0328
Beckers, J., **13**-0481
Beckhaus, H., **04**-0294, **05**-0246, **05**-0273, **09**-0077
Beckhaus, H.-D., **01**-0107, **04**-0386, **05**-0267
Beckhaus, K., **04**-0406
Beckler, J.D., **12**-0575
Beckley, R.S., **18**-0842
Beckman, E.J., **09**-0098
Beckman, J.A., **17**-0015
Beckmann, O., **18**-0361, **18**-0363
Beckmann, W., **03**-0194
Beckwith, A.L., **14**-0021
Beckwith, A.L.J., **01**-0107, **05**-0267, **05**-0310, **11**-0648, **13**-0706, **13**-0713, **14**-0070, **14**-0084, **14**-0097, **14**-0262, **15**-0052, **15**-0103, **15**-0104, **15**-1224, **15**-1257, **16**-0009, **16**-0126, **16**-1745, **16**-1767, **16**-1783, **16**-1824, **16**-2053, **18**-0054, **18**-0060, **18**-0078, **18**-0271, **18**-0293, **18**-0315, **18**-0868, **19**-0438, **19**-0604, **19**-1570
Beckwith, R.E.J., **12**-0359, **12**-0360
Bedekar, A.V., **11**-0239, **11**-0249, **11**-0255, **11**-0296, **15**-1294, **15**-1651, **15**-1898, **15**-1901
Bedenbaugh, A.O., **10**-0135, **19**-1106
Bedenbaugh, J.H., **19**-1106
Bedford, A.F., **01**-0097
Bedford, C.D., **12**-0709
Bedford, R.B., **10**-1296, **13**-0339, **13**-0473, **13**-0498
Bedi, G., **12**-0224, **15**-1892
Bednar, R.A., **08**-0104
Bedworth, P.V., **16**-0500
Beebe Jr., T.P., **15**-0457
Beech, W.F., **14**-0362
Beels, C.M.D., **17**-0343
Beer, P.D., **07**-0061
Beggs, J.J., **18**-0011
Begley, M.J., **16**-0851
Bégué, J., **10**-0295, **10**-0485, **18**-0208, **19**-0064
Bégué, J.-P., **10**-0672, **10**-0929, **15**-1753, **15**-1770, **16**-0863, **16**-0901, **19**-0863
Beguin, C., **15**-0115
Behar, V., **05**-0322

Behbahani, F.K., **10**-0655, **10**-0668
Behenna, D.C., **10**-1631
Beheshtiha, Y.S., **19**-1656
Behforouz, M., **16**-0301
Behling, J.R., **12**-0571
Behnam, S.E., **12**-0092
Behnam, S.M., **12**-0092
Behnke, M., **15**-1176
Beholz, L.G., **18**-0608
Behr, L.C., **18**-0885
Behrens, C.H., **10**-0494, **10**-0496, **10**-0678
Behrens, O.K., **19**-1514
Behrens, S., **02**-0111
Behrman, E.J., **10**-0372, **11**-0538, **11**-0540, **15**-1776
Bei, X., **13**-0177, **19**-0218
Beilen, J.B., **19**-0544
Beiner, J.M., **16**-1398
Beirich, C., **16**-0565
Bejan, E., **18**-0401
Bejan, E.V., **14**-0216
Bekárek, V., **10**-0448
Bekker, R.A., **02**-0400
Belanger, D.B., **18**-0814
Bélanger, J.M.R., **15**-2022
Belarmino, A.T.N., **10**-0529
Belderraín, T.R., **12**-0366, **15**-2293, **15**-2299, **19**-0548
Belelie, J.L., **10**-1461, **10**-1473
Belen'kii, G.G., **15**-0072
Belen'kii, L.I., **04**-0451, **04**-0456, **11**-0321, **11**-0404, **14**-0398, **19**-1576, appendixA-0038
Beletskaya, I.P., **05**-0099, **05**-0100, **05**-0129, **05**-0130, **08**-0013, **08**-0014, **10**-0053, **10**-0242, **10**-0341, **10**-0478, **10**-0488, **10**-0489, **10**-0490, **10**-0769, **10**-1267, **10**-1306, **10**-1310, **10**-1400, **10**-1483, **10**-1782, **10**-1846, **10**-1851, **11**-0287, **11**-0297, **12**-0002, **12**-0034, **12**-0037, **12**-0043, **12**-0045, **12**-0276, **12**-0506, **12**-0524, **12**-0526, **12**-0626, **12**-0632, **12**-0670, **13**-0008, **13**-0052, **13**-0152, **13**-0267, **13**-0534, **13**-0577, **13**-0601, **13**-0602, **13**-0619, **14**-0376, **14**-0384, **15**-0306, **15**-0372, **15**-0373, **15**-0382, **15**-0759, **15**-0928, **15**-1199, **16**-0523, **16**-0675, **18**-0408, **19**-0433
Belevskii, V.N., **05**-0211
Belew, J.S., **19**-0345
Belfield, A.J., **15**-0851
Belfield, K.D., **18**-0560
Belfoure, V., **11**-0371
Belikov, V.M., **04**-0136, **04**-0169, **04**-0209
Belin, B., **10**-0891
Belinka Jr., B.A., **12**-0512
Belisle, C.M., **19**-1154
Belkin, Yu.V., **02**-0089, **16**-1402
Bell, A., **15**-2189, **16**-0290
Bell, F., **11**-0074
Bell, H.C., **14**-0330
Bell, H.M., **19**-1295, **19**-1342
Bell, J.A., **12**-0381
Bell, K., **10**-0534
Bell, M., **16**-0757
Bell, M.L., **02**-0289
Bell, N.A., **05**-0156, **05**-0244
Bell, R.P., **06**-0059, **06**-0064, **08**-0001, **08**-0002, **08**-0021, **08**-0042, **08**-0135, **08**-0136, **08**-0160, **12**-0084, **12**-0095, **12**-0149, **15**-0005, **16**-0036, **16**-0037, **16**-0044
Bell, T.W., **10**-1150, **10**-1306
Bellarmine, M., **14**-0237
Bellassoued, M., **10**-1643, **16**-0836, **16**-1078, **16**-1244, **16**-1999
Bellatti, M., **14**-0344
Bellemin-Laponnaz, S., **19**-1046
Bellenie, B.R., **16**-1384
Beller, M., **10**-1297, **11**-0512, **13**-0162, **13**-0274, **13**-0288, **13**-0399, **13**-0483, **13**-0611, **14**-0280, **15**-0314, **15**-0314, **15**-0320, **15**-0331, **15**-0333, **15**-0342, **15**-0343, **15**-0348, **15**-0351, **15**-1381, **15**-1481, **15**-1691, **15**-1764, **16**-0306, **16**-0344, **19**-0238
Bellesia, F., **12**-0152, **12**-0114, **12**-01, **12**-0119, **12**-0123, **15**-1527, **15**-1602
Belletire, J.L., **04**-0206, **19**-0840, **19**-1502
Belley, M., **15**-0296
Bellina, F., **10**-1418, **13**-0473, **13**-0536
Bellini, F., **11**-0391
Bellmann, P., **16**-1413
Belloli, R., **02**-0138, **04**-0025, **05**-0396
Bellosta, V., **05**-0299, **10**-0925, **10**-0960, **15**-0318, **16**-1475, **16**-1961
Bellucci, G., **15**-0012, **15**-0014, **15**-0022, **15**-0036, **15**-1522, **15**-1524, **15**-1531
Bellucci, M.C., **10**-1064, **15**-1018, **17**-0160, **19**-0997
Bellus, D., **11**-0560, **15**-1642, **16**-1393
Belluš, D., **11**-0557, **11**-0560, **15**-2178
Belmonte, F.G., **15**-0550
Belokon', Y., **16**-1426
Belokon, Y.N., **16**-1436, **16**-1438, **16**-1444
Belokurova, A.P., **11**-0637
Belotti, D., **15**-0318
Belotti, D., **16**-1492, **19**-0014
Belotti, S., **19**-0265
Belskaia, N., **15**-1940
Belsner, K., **10**-1168
Belson, D.J., **11**-0150
Belter, R.K., **15**-0858
Beltrame, P., **10**-0242, **15**-1932, **15**-1980, **15**-2166, **17**-0077
Belyaev, E.Yu., **11**-0583, **11**-0584
Belyaev, V.A., **14**-0220
Bemis, A.G., **14**-0225
Ben Rayana, E., **17**-0209
Ben Salem, R., **16**-1481, **16**-1482
Ben-Daniel, R., **15**-1756, **19**-0181
Ben-David, Y., **10**-1822, **13**-0607
Ben-Efraim, D.A., **02**-0291, **04**-0213, **10**-1765, **17**-0148, **17**-0311, **18**-0824, **18**-0825
Ben-Mergui, N., **02**-0065
Ben-Shoshan, B., **15**-0144
Ben-Shushan, G., **14**-0134
Ben-Zion, M., **10**-0025
Benach, E., **16**-0073
Benaglia, M., **16**-0861
Benaim, J., **10**-1684
Benati, L., **15**-1912, **18**-0300
Benbrook, D.M., **19**-0338
Benchegroun, M., **16**-0391
Bencini, E., **13**-0613
Bendale, P.M., **16**-0076, **16**-0128
Bender, C., **03**-0098
Bender, D.D., **13**-0361
Bender, D.R., **13**-0237
Bender, M.L., **03**-0174, **06**-0037, **06**-0071, **08**-0135, **10**-0357, **16**-0021, **16**-0022, **16**-0024, **16**-0031, **16**-0033, **16**-1511, **16**-1520, **16**-1558, **16**-1570, **16**-1584, **16**-1596, **16**-1763
Bender, R., **12**-0742
Benderly, A., **16**-0996, **16**-1835
Bendikov, M., **05**-0263

Benedetti, E., **08**-0024
Benedetti, F., **06**-0012
Benedict, D.A., **10**-0589
Benedikt, G.M., **11**-0607
Benet-Buchholz, J., **02**-0055, **04**-0339
Benezra, C., **10**-1142
Benfey, O.T., **10**-0035
Bengtson, A., **10**-0754
Benhaim, C., **10**-1437, **15**-1137
Beni, Y.A., **16**-0074, **19**-0263
Benicewicz, B.C., **15**-0299, **16**-1674
Benjamin, B.M., **10**-0395, **18**-0016, **18**-0040, **18**-0056, **18**-0100, **18**-0179
Benjamin, S.B., **16**-1701
Benjaminov, B.S., **18**-0040
Benkeser, R.A., **12**-0410, **12**-0411, **12**-0576, **12**-0660, **15**-0468, **15**-0549, **15**-0550, **19**-1492, **19**-1504, **19**-1505, **19**-1506
Benkovic, P.A., **16**-0401
Benkovic, S.J., **16**-0401
Benn, F.R., **15**-0970
Benn, R., **05**-0163
Bennabi, S., **15**-1065
Bennani, Y.L., **15**-1693, **15**-1704
Benner, C.W., **18**-0621
Benner, J.P., **16**-1486
Benner, S.A., **04**-0252
Bennet, A.J., **15**-0012, **16**-1595, **16**-1596
Bennett, M.A., **04**-0480
Bennett, C.E., **15**-0768
Bennett, G.B., **16**-1894, **18**-0654
Bennett, G.D., **16**-0591
Bennett, J.M., **11**-0106, **11**-0271
Bennett, J.N., **15**-1980, **15**-2080
Bennett, M., **15**-0523
Bennett, M.A., **02**-0043, **03**-0083, **16**-0132
Bennett, M.J., **10**-0148
Bennett, R.G., **07**-0028
Bennett, R.P., **11**-0178, **12**-0741
Bennett, S.G., **14**-0372
Bennett, S.M., **15**-0911
Bennett, W.D., **13**-0581
Benning, W.F., **16**-0310
Bennouna, L., **03**-0136
Bennur, T.H., **19**-1672
Beno, B.R., **15**-2004, **15**-2088
Benoit, R.L., **08**-0191, **08**-0219
Bensari, A., **11**-0428, **19**-1684
Benson, C.L., **15**-1412
Benson, G.A., **11**-0567
Benson, H., **15**-0126
Benson, R.E., **02**-0255
Benson, S.W., **01**-0089, **01**-0090, **15**-0059
Benson, W.R., **18**-0516
Bent, H.A., **01**-0005, **01**-0050, **03**-0098
Bentley, J., **15**-1244
Bentley, K.W., **04**-0102, **04**-0136, **04**-0268, **08**-0160, **15**-0401, **17**-0243, **17**-0243, **19**-0012, **19**-0310, **19**-0873
Bentley, M.D., **03**-0082, **10**-0170
Bentley, P.A., **15**-1813
Bentley, T.W., **10**-0082, **10**-0133, **10**-0282, **10**-0325, **10**-0326, **10**-0379, **10**-0399, **10**-0404, **10**-0421, **10**-0430, **10**-0433, **10**-0434, **10**-0435, **10**-0437, **10**-0438, **10**-0439, **16**-0015, **16**-1509, **16**-1511, **16**-1512, **16**-1601
Benton, F.L., **19**-0351
Bentor, Y., **11**-0607
Bentrude, W.G., **05**-0249, **14**-0049, **18**-0061
Bentrup, KL.H., **16**-2016
Bentz, E., **10**-1404
Benzaïd, A., **16**-1573
Benzon, M.S., **18**-0623
Beockman Jr., R.K., **15**-1349
Beránek, L., **17**-0176
Bercaw, J.E., **15**-0336, **15**-0747, **15**-2405
Bérces, A., **04**-0272
Bérces, T., **07**-0044
Berchtold, G.A., **15**-2190
Bercot, E.A., **16**-1985, **16**-1986
Berdahl, D.R., **15**-2283
Berdnikov, V.M., **14**-0319
Berecoechea, J., **16**-2061
Berecz, E., **03**-0164
Berenschot, D.R., **19**-0203
Berestova, S.S., **15**-1199
Berezin, G.H., **04**-0422
Berezovskii, G.A., **11**-0637
Berezovskii, V.M., **11**-0068
Berg, U., **04**-0274, **04**-0332, **04**-0505, **09**-0065, **09**-0068, **10**-0854
Bergbreiter, D.E., **10**-1334, **10**-1686, **10**-1742, **12**-0015, **13**-0399, **15**-0651, **15**-1641, **16**-1896, **19**-1297
Bergel'son, L.D., **19**-1077, **16**-1255
Bergens, S.H., **12**-0079, **15**-1361, **19**-1759
Berger, D., **15**-1462
Berger, J.G., **05**-0389, **12**-0349
Berger, K.R., **12**-0303
Berger, M., **19**-0349
Berger, R., **02**-0235, **16**-0916
Berger, S., **15**-1143, **16**-1299
Bergeron R., **10**-0992, **16**-2164
Bergeron, R.J., **03**-0174
Bergeron, R., **03**-0174
Bergin, W.A., **19**-1106
Berglund, B.A., **19**-0485
Berglund-Larsson, U., **11**-0006
Bergman, A., **04**-0469
Bergman, R., **15**-2026
Bergman, R.G., **05**-0288, **10**-0250, **10**-0254, **10**-0255, **10**-0257, **15**-0352, **15**-0367, **15**-0927, **15**-1321, **15**-1879, **15**-2405, **16**-0947, **17**-0461, **18**-0039, **18**-0100, **18**-0168, **18**-0170, **18**-0487, **18**-0650, **19**-0829
Bergmann, D., **01**-0028
Bergmann, E.D., **02**-0093, **02**-0174, **02**-0204, **10**-1146, **14**-0448, **14**-0449, **14**-0451, **15**-0992
Bergon, M., **16**-1570
Bergson, G., **12**-0063, **12**-0064
Bergstad, K., **15**-1663
Bergstrom, R.G., **10**-0520, **13**-0034
Beringer, F.M., **19**-1436
Berk, S.C., **12**-0599, **15**-0773, **16**-1897
Berkessel, A., **15**-2298, **16**-0647, **18**-0358, **19**-1133
Berkheimer, H.E., **05**-0071, **08**-0121
Berkoff, C.E., **12**-0693
Berkovitch-Yellin, Z., **04**-0102, **04**-0188
Berkowitz, D.B., **19**-1319
Berkowitz, W.F., **10**-1391, **18**-0260
Berks, A.H., **05**-0126
Berlan, J., **07**-0105, **07**-0114, **15**-1039, **15**-1066, **15**-1170, **15**-2022, **16**-0122
Berlin, A.J., **04**-0323
Berlin, K.D., **19**-0338
Berliner, E., **09**-0037, **11**-0073, **13**-0070, **15**-0080, **15**-0084, **15**-0087
Berman, A.M., **13**-0214
Berman, J.D., **14**-0454
Bermejo, F., **10**-1554
Bermudez, A., **18**-0369
Bernabé, M., **10**-1530
Bernabé, P., **12**-0273, **16**-1734
Bernad, P.L., **17**-0398
Bernadou, F., **10**-1765, **17**-0148

Bernard, D., **10**-1245
Bernard, H.W., **05**-0342
Bernard, J.-M., **19**-1622
Bernard, M., **16**-1269
Bernardelli, P., **10**-1513
Bernardi, A., **16**-1051
Bernardi, C.R., **13**-0451
Bernardi, F., **02**-0089, **04**-0047, **04**-0291, **05**-0119, **05**-0120, **05**-0121, **10**-0771, **15**-0021, **15**-2105, **15**-2211, **15**-2336, **16**-1402, **18**-0847
Bernardi, L., **10**-1495, **16**-0926
Bernardi, R., **14**-0153, **14**-0347
Bernardinelli, G., **04**-0467, **15**-0994, **15**-1887, **15**-2050
Bernardo, J.E., **19**-0926, **19**-1351
Bernasconi, C.F., **05**-0122, **05**-0208, **06**-0006, **06**-0022, **06**-0030, **06**-0037, **06**-0038, **06**-0041, **06**-0052, **06**-0053, **06**-0056, **06**-0058, **06**-0059, **08**-0103, **08**-0107, **09**-0016, **10**-0240, **13**-0003, **13**-0013, **13**-0014, **15**-0024, **15**-0041, **15**-0195, **15**-0198, **15**-0325
Bernasconi, S., **15**-1758
Bernatchez, M., **16**-1935
Bernath, P.F., **05**-0399
Bernath, T., **14**-0271
Bernáth, G., **16**-0034
Berndt, A., **15**-0094, **17**-0055
Berneis, H.L., **17**-0109
Berner, D., **10**-0391, **18**-0126
Bernett, W.A., **04**-0416
Bernhardt, J.C., **10**-1377, **14**-0382, **14**-0384
Bernheim, M., **12**-0509
Bernheim, R.A., **05**-0342
Bernier, C., **16**-0977
Berninger, R.W., **11**-0616
Bernini, R., **13**-0149, **18**-0356
Bernocchi, E., **15**-0848
Bernsmann, H., **15**-0604
Bernstein, E.R., **03**-0072, **04**-0267
Bernstein, H.I., **18**-0013
Bernstein, M.D., **16**-0361
Bernstein, M.P., **05**-0188, **08**-0205
Bernstein, R.B., **06**-0013, **17**-0041
Bernstein, S., **19**-0049
Bernstein, W.J., **04**-0068, **04**-0155
Beronius, P., **10**-0088
Berova, N., **04**-0117
Berrier, A.L., **10**-0139, **10**-0191, **17**-0451
Berrier, C., **11**-0536
Berrigan, P.J., **10**-0488
Berry, J.F., **15**-1840
Berry, R.S., **02**-0036, **13**-0047
Bersohn, R., **05**-0208
Berson, J.A., **04**-0213, **09**-0090, **15**-2096, **15**-2111, **17**-0422, **18**-0038, **18**-0039, **18**-0040, **18**-0100, **18**-0104, **18**-0168, **18**-0170, **18**-0551, **18**-0558, **18**-0559, **18**-0561, **18**-0562, **18**-0589, **18**-0599, **18**-0628, **18**-0629, **18**-0630
Berteau, P., **17**-0176
Bertelli, D.J., **02**-0156, **02**-0163, **02**-0173, **02**-0174
Berthe, B., **15**-0323
Berthelette, C., **16**-1240
Berthelot, J., **11**-0226
Berthelot, M., **01**-0051, **08**-0090, **08**-0091, **08**-0092, **08**-0093, **08**-0094, **08**-0095
Berther, C., **19**-0750
Berthet, J.-C., **16**-0968
Berthier, G., **02**-0013
Berthiol, F., **13**-0401, **13**-0445, **13**-0539
Berthon, B., **19**-0674
Berti, F., **17**-0152
Berti, G., **10**-0580, **10**-0623, **15**-0036, **15**-0125, **15**-1726, **15**-1737, **16**-1212, **16**-1375
Bertie, J.E., **02**-0214
Bertilsson, S.K., **17**-0219
Bertin, J., **14**-0159
Bertini, F., **12**-0585, **14**-0155, **16**-0499, **16**-0500
Bertolini, G., **12**-0230, **16**-1077
Bertounesque, E., **16**-0811
Bertoux, F., **15**-1381, **15**-2085
Bertram, A.K., **12**-0353
Bertran, J., **12**-0087
Bertrand, G., **16**-1736
Bertrand, J.A., **18**-0122
Bertrand, M., **15**-2187, **15**-2212, **15**-2284
Bertrand, M.-J., **16**-0578
Bertrand, M.P., **17**-0138
Bertrand, N., **16**-1847
Bertrand, R., **15**-0251
Bertrand, S., **15**-1049
Bertrand, W.S., **14**-0436
Bertsch, H., **17**-0149
Bertsch, R.J., **19**-1296, **19**-1344
Bertus, P., **12**-0293, **12**-0329, **16**-0856, **16**-1115, **16**-1411
Bertz, S.H., **10**-1319, **10**-1334, **10**-1355, **10**-1357, **10**-1365, **10**-1366, **12**-0560, **12**-0570, **14**-0377, **15**-1066, **15**-1169, **15**-1174, **16**-0848
Berwin, H.J., **11**-0107
Besace,Y., **15**-1066
Besançon, J., **19**-1669
Besemer, A.C., **19**-0195
Besev, M., **15**-1261
Beslin, P., **12**-0242, **19**-0823
Bespalova, N.B., **18**-0761
Bessard, Y., **10**-1847
Besseau, F., **08**-0091, **08**-0093, **08**-0094
Bessho, K., **16**-1525, **17**-0377
Bessho, Y., **15**-0596
Bessieres, B., **16**-0502
Besson, L., **15**-1612
Besson, T., **11**-0382
Best, D.C., **10**-0161, **10**-0170
Bestetti, G., **15**-1758
Bestian, H., **16**-2111
Bestmann, H.J., **04**-0068, **10**-0870, **10**-0998, **16**-1255, **16**-1263, **16**-1265, **16**-1287, **16**-1336, **16**-1343, **16**-1344, **16**-1408, **17**-0489
Bestre, R.D., **14**-0260
Beswick, P.J., **15**-0993
Betancor, C., **17**-0154
Betancort, J.M., **15**-0994, **16**-1268
Betchaku, A., **16**-1521
Bethea III, T.W., **19**-0438
Bethell, D., **12**-0374, **05**-0002, **05**-0070, **05**-0219, **05**-0327, **05**-0330, **06**-0064, **10**-0119, **10**-0638, **12**-0345, **12**-0385, **13**-0216, **15**-1782, **15**-2261, **19**-0836
Bethmont, V., **10**-0605
Bethune, D.S., **02**-0356
Betkouski, M., **07**-0057
Betschart, C., **19**-1692, **19**-1710
Bettadaiah, B.K., **10**-0851
Betteridge, D., **01**-0013, **01**-0016
Bettigeri, S.V., **13**-0347, **16**-2179
Bettinger, H.F., **02**-0262, **05**-0385
Betts, J., **14**-0214
Betts, M.J., **16**-2111
Betz, J., **05**-0175
Betz, W., **18**-0643
Betzemeier, B., **10**-1407, **15**-1749, **19**-0182, **19**-0185, **19**-0720
Beuchet, P., **10**-1688, **16**-0874
Beug, M., **11**-0010
Beugelmans, R., **13**-0343, **13**-0589

Beumel Jr., O.F., **10**-1768, **16**-1185
Beutler, M., **15**-1486
Beutner, G.L., **16**-1110
Bevan, C.W.L., **16**-1513
Beveridge, D.L., **02**-0016
Beverwijk, C.D.M., **03**-0083
Bévière, S.D., **19**-0612
Bevington, J.C., **16**-2062
Bevins, C.L., **12**-0059
Bewersdorf, M., **12**-0623
Bewick, A., **15**-1851, **15**-1917
Beyer, K., **03**-0176
Beylerian, N.M., **19**-0255
Beynek, H., **16**-1345
Bez, G., **10**-0946, **15**-1773, **16**-0117
Bezbarua, M., **10**-0946
Bezbarua, M.S., **16**-0117
Bezbozhnaya, T.V., **10**-0202, **10**-0278, **10**-0425
Bezman, S.A., **15**-2202
Bezrodnyi, V.P., **16**-2146
Bhacca, N.S., **18**-0859
Bhaduri, A.P., **10**-0861, **11**-0225
Bhagwat, M.M., **15**-0512
Bhagwat, V.V., **18**-0309
Bhalay, G., **19**-0797
Bhalerao, U.T., **10**-0459, **18**-0295, **19**-0470, **19**-1641
Bhalla, A., **19**-0925
Bhamare, N.K., **16**-0335
Bhanange, B.M., **14**-0407
Bhanamathi, N., **10**-0958
Bhandari, A., **15**-0509
Bhandari, K., **19**-0429, **19**-1491
Bhanu, S., **10**-1769
Bhanumathi, N., **10**-0925, **10**-0579
Bhar, S., **10**-1587, **15**-1059, **19**-0683, **19**-0982, **19**-1377
Bharadwaj, A.R., **15**-1339, **15**-1368, **16**-0724
Bharadwaj, P.K., **03**-0118
Bharathi, B., **10**-0943, **19**-0781
Bharathi, P., **13**-0664, **16**-1973
Bhardwaj, N., **13**-0272
Bhat, K.S., **16**-0493
Bhat, N.G., **10**-1752, **12**-0492, **12**-0494, **15**-1186, **18**-0435, **18**-0444, **18**-0453, **18**-0456
Bhat, S.V., **16**-0775
Bhatia, B., **14**-0100
Bhatia, K.A., **18**-0140
Bhatnagar, A.K., **19**-0063
Bhatnagar, S.P., **16**-1462
Bhatt, A., **19**-0529
Bhatt, A.K., **11**-0239
Bhatt, M.V., **10**-1114, **17**-0321, **18**-0644, **19**-0634, **19**-1598
Bhatt, P., **19**-0831
Bhattacharjee, M., **14**-0440
Bhattacharjya, G., **16**-1767
Bhattacharya, A.K., **16**-1309
Bhattacharya, S., **13**-0540, **13**-0726
Bhattacharya, S.N., **12**-0476
Bhattacharyya, A., **10**-0633
Bhattacharyya, S., **13**-0365, **16**-0347, **16**-0357, **16**-0357, **16**-0363, **16**-1746, **19**-1135
Bhatti, A.M., **12**-0688
Bhatti, Z.A., **16**-1515
Bhaumik, A., **15**-0224
Bhawal, B.M., **10**-1027, **19**-1273
Bhinderwala, N.S., **10**-1273
Bhor, S., **15**-1764
Bhuiyan, Md.M.H., **13**-0196, **13**-0489, **15**-0618
Bhupathy, M., **14**-0410, **18**-0235
Bhusare, S.R., **11**-0258
Bhushan, V., **04**-0194, **15**-1656, **15**-1674, **15**-1694, **19**-0501
Bhuvaneswari, N., **11**-0659
Bhuvaneswari, N., **19**-1334
Biaggio, F.C., **19**-1782
Biale, G., **17**-0070, **17**-0072, **17**-0077
Biali, D.A., **02**-0396
Biali, S.E., **02**-0394, **02**-0396, **02**-0397, **03**-0124, **03**-0125, **03**-0130, **04**-0326, **04**-0344, **04**-0504, **04**-0506, **11**-0345
Bian, Y.-J., **19**-1645, **19**-1646
Bianchi, D., **04**-0196
Bianchi, G., **15**-1932, **15**-1932, **15**-1943, **15**-2423
Bianchi, M., **10**-1837, **15**-1375, **15**-1477
Bianchi, R., **02**-0268
Bianchi, T.A., **10**-0589, **16**-2171
Bianchini, C., **15**-0279, **15**-2406
Bianchini, J., **15**-0108
Bianchini, R., **15**-0012, **15**-0012, **15**-0014, **15**-0022, **15**-1524, **15**-1531
Bianco, A., **19**-1088
Białeck-Florjańczyk, E., **15**-0984
Bible Jr., R.H., **15**-0139
Bible, R., **02**-0364
Bickart, P., **18**-0737
Bickel, A.F., **14**-0226
Bickelhaupt, F., **02**-0061, **02**-0062, **02**-0063, **10**-0317, **12**-0566, **12**-0582, **12**-0583, **12**-0584, **12**-0585, **12**-0604, **12**-0613, **15**-2282, **18**-0649
Bickley, J.F., **15**-1316, **15**-1813, **18**-0155
Bida, G., **19**-0255
Bidd, I., **10**-1050
Bieber, J.B., **18**-0411
Bieber, L.W., **10**-0828, **16**-0826, **19**-1221
Bieber, W., **10**-0808
Bieberbach, A., **02**-0257
Biechler, S.S., **16**-1591
Biedermann, P.U., **02**-0186, **02**-0360
Biehl, E.R., **13**-0080, **13**-0574
Bielawski, C.W., **18**-0794
Biella, S., **19**-0117
Biellmann, J.F., **10**-1264, **10**-1706, **10**-1727, **12**-0074, **12**-0388, **15**-0407, **15**-0465, **15**-0466, **17**-0278, **17**-0382, **18**-0727
Bielmann, R., **10**-0175
Bielski, B.H.J., **05**-0210
Bielski, R., **17**-0336
Biemann, K., **16**-2052
Bieniarz, C., **13**-0130
Bieniek, M., **18**-0781
Bienz, S., **04**-0137, **12**-0669
Bierbaum, V.M., **02**-0024, **05**-0106, **10**-0267, **10**-0344, **10**-0368, **17**-0183
Bieri, J.H., **04**-0460
Bierling, B., **19**-0056
Biermann, D., **15**-2073, **15**-0909
Bieron J.F., **17**-0458, **11**-0586
Biethan, U., **18**-0640
Biffi, C., **05**-0253, **19**-0109
Biffin, M.E.C., **10**-1005, **15**-0397, **15**-1624
Bigam, G., **02**-0250
Bigdeli, M.A., **16**-0059
Bigeleisen, J., **06**-0059
Bigg, D.C.H., **16**-1736
Biggs, J., **10**-0495
Bigi, F., **11**-0409, **11**-0497, **15**-1770, **16**-1151, **19**-0532
Bigler, P., **18**-0190
Bigley, D.B., **12**-0643, **12**-0644, **12**-0650, **16**-2074, **19**-0885
Bihan, D., **16**-1383
Bijoy, P., **11**-0365
Bijvoet, J.M., **04**-0097
Bilevitch, K.A., **05**-0313, **12**-0616
Bilgrien, C., **19**-0109
Biller, W.T., **16**-0414
Billet, J., **16**-0527
Billet, M., **16**-0379
Billingham, N.C., **14**-0453
Billington, D.C., **10**-1251
Billion, A., **12**-0339

Billmers, J.M., **19**-0498, **19**-0827
Billups, W.E., **02**-0080, **02**-035, **02**-0081, **02**-0196, **04**-0466, **04**-0491, **06**-0041, **14**-0154, **14**-0157, **18**-0172, **18**-0367, **18**-0589
Bilodeau, M.T., **16**-1015
Biloski, A.J., **19**-0757
Bindu, K.H., **16**-1611, **16**-1906
Binev, I.G., **09**-0023
Bingel, W.A., **01**-0079
Binger, P., **12**-0445, **15**-1975, **15**-2201, **15**-2284
Bingham, R., **12**-0325
Bingham, R.C., **02**-0018, **05**-0281, **10**-0057, **10**-0279, **10**-0280, **10**-0326, **14**-0101, **18**-0113
Bingham, T.E., **18**-0281
Binkley, R.W., **18**-0641
Binnesmans, K., **11**-0121
Binsch, G., **04**-0369, **04**-0381, **06**-0056, **15**-2212
Binshtok, E.V., **16**-1301
Binzet, S., **04**-0514, **10**-0276
Biolatto, B., **10**-1426, **12**-0470, **13**-0354, **13**-0533
Biordi, J., **10**-0599
Bir, G., **15**-2064
Biran, C., **12**-0320
Birch, A.J., **12**-0691, **15**-0406, **15**-0423, **15**-0466, **15**-0533, **15**-0538, **15**-0541
Birchal, J.M., **11**-0593
Birckbichler, P.J., **19**-0338
Bird, C.W., **15**-1381
Bird, C.N., **17**-0127, **17**-0231
Bird, C.W., **02**-0095, **02**-0139, **02**-0147, **02**-0150, **12**-0074, **14**-0443, **15**-1393, **17**-0015, **19**-0718
Bird, P.H., **15**-2202
Bird, R., **10**-1636, **10**-1713, **19**-0836
Bird, S.J., **16**-1621
Biresaw, G., **15**-2341
Birikaki, L., **16**-1423
Birladeanu, L., **18**-0590
Birlirakis, N., **19**-0320
Birmingham, J.M., **12**-0562
Birnbaum, G., **01**-0037
Birnbaum, J.C., **19**-0608
Birney, D.M., **17**-0422
Birr, C., **16**-1816
Birum, G.H., **16**-1302
Bisaha, J., **10**-1640, **15**-2063, **16**-1144
Bisai, A., **10**-0961, **16**-1453, **19**-0167
Bisaro, F., **10**-1499
Bisarya, S.C., **11**-0233
Bischof, P., **02**-0180
Bishop III, K.C., **18**-0837
Bishop, C.A., **17**-0066
Bishop, C.E., **17**-0524, **19**-0379
Bishop, R., **03**-0155
Bishop, R.J., **01**-0087
Bishop, S.W., **19**-1567
Biskup, M., **02**-0259, **02**-0264, **02**-0265, **02**-0266, **02**-0277
Biss, J.W., **19**-1184
Bissell, E.R., **15**-1521
Bissett, J.S., **16**-0624, **16**-0871
Bissinger, H.J., **04**-0471
Biswas, G., **10**-0842
Bisztray, K., **07**-0118, **07**-0119
Bitsi, G., **12**-0731
Bittl, R., **07**-0018
Bittler, K., **15**-1378
Bittner, S., **19**-0596
Björkling, F., **10**-1377
Bjorklund, C., **12**-0692
Björkman, E.E., **15**-1867
Bjørsvik, H.-R., **14**-0138, **19**-0331, **19**-0336
Black, C.J., **12**-0174
Black, D.J., **18**-0362
Black, D.S., **15**-1932, **18**-0688, **19**-0662
Black, K.A., **18**-0605
Black, K.W., **18**-0121
Black, P.J., **15**-0904
Black, S.J., **11**-0136
Black, T.H., **10**-0478, **17**-0496, **18**-0895
Blackburn, L., **16**-1278
Blackburn, B.K., **15**-1691
Blackburn, E.V., **14**-0045, **18**-0512
Blackburn, G.M., **16**-1847, **16**-1849, **18**-0727
Blackburn, L., **16**-1292
Blackburn, P., **16**-1383
Blackburne, I.D., **01**-0087
Blacker, A.J., **10**-1463, **15**-1782
Blackert, J.F., **14**-0058
Blacklock, T., **13**-0487
Blacklock, T.J., **11**-0254, **16**-1825, **18**-0574, **18**-0630, **19**-0680
Blackman, N.A., **19**-0662
Blackman, S.W., **10**-0914
Blackmond, D.G., **13**-0178, **13**-0399, **13**-0419, **15**-0434
Blackstock, S.C., **03**-0095
Blackstock, S.C., **05**-0321
Blackwell, J., **19**-1350
Blackwell, J.M., **12**-0319, **19**-1142
Blackwell, L.F., **17**-0063, **17**-0065
Blackwood, R.K., **10**-0486
Bladé-Font, A., **16**-1304, **16**-1792
Blades, K., **15**-1680
Blagoev, B., **10**-1689, **12**-0401
Blagoveschenskii, V.S., **04**-0372
Bláha, K., **10**-1674
Blain, D.A., **02**-0353
Blair, L.K., **08**-0077, **08**-0224, **08**-0231, **08**-0233, **08**-0234
Blake, A.J., **15**-0311, **15**-1271
Blake, J.F., **10**-0020, **15**-2098
Blake, M.R., **11**-0116
Blake, P., **15**-0106
Blake, P.G., **15**-0290
Blakey, S.B., **13**-0512
Blakskjær, P., **15**-1338
Blanc, J., **10**-0326
Blanch, R., **04**-0476
Blanch, R.J., **03**-0209, **03**-0210
Blanchard, E.J., **16**-1762
Blanchard, E.P., **15**-2205, **15**-2333, **15**-2336
Blanchard, M., **16**-2052
Blanchette, P.E., **15**-1731
Blanchfield, J.T., **16**-1637
Blanchot-Courtois, V., **10**-1540
Blanco, B., **13**-0481
Blanco, L., **12**-0155
Blanco, O.M., **18**-0782
Blanco-Urgoiti, J., **15**-1430, **15**-1441
Blancou, H., **12**-0599
Bland, W.J., **15**-1641
Blandamer, M.J., **02**-0406, **06**-0057, **09**-0092, **10**-0033, **10**-0034, **10**-0078, **15**-2029
Blander, M., **03**-0007
Blank, J., **15**-1368, **16**-0724
Blankert, J.F., **10**-1252
Blankinship, M.J., **16**-0057
Blanksby, S.J., **01**-0088
Blanton, J.R., **19**-0936, **19**-1297
Blanzat, J., **04**-0242
Blaschke, G., **04**-0173, **04**-0174, **04**-0513
Blaser, D., **11**-0464
Blaser, H.-U., **16**-1177
Bläser, D., **02**-0081, **03**-0065, **04**-0467, **15**-0430
Blaskó, A., **13**-0019, **16**-0016
Blass, B.E., **10**-0981
Blavins, J.J., **15**-1954
Blay, G., **16**-0073, **16**-1528
Blazejewski, J., **13**-0581
Blazek, J.M., **18**-0146
Blažević, N., **10**-0891

Blechert, S., **15**-1250, **18**-0691, **18**-0755, **18**-0774, **18**-0781, **18**-0784, **18**-0789, **18**-0792, **18**-0800, **18**-0804
Bleeke, J.R., **15**-0523
Blettner, C.G., **13**-0485
Blindheim, U., **15**-0793
Bliznets, I.V., **16**-0673
Bloch, R., **02**-0181, **19**-1056
Block Jr., P., **16**-0320
Block, E., **02**-0089, **05**-0119, **10**-0111, **10**-1666, **10**-1705, **12**-0402, **13**-0768, **14**-0397, **16**-1375, **16**-1402, **17**-0337, **17**-0349, **18**-0700, **19**-0795, **19**-0811, **19**-0849, **19**-1575, **19**-1602, **19**-1778, **19**-1788
Blodgett, J.K., **18**-0272
Blokzijl, W., **02**-0406, **15**-2029, **15**-2029
Blom, C.E., **02**-0402
Blom, H.P., **15**-0696
Blomberg, C., **05**-0162, **12**-0583, **12**-0603, **12**-0604, **16**-0478, **16**-0523, **16**-0532
Blomgren, P.A., **13**-0530, **13**-0555
Blomquist, A.T., **04**-0078, **04**-0472, **16**-1465, **18**-0050
Bloodworth, A.J., **15**-0263, **15**-2153
Bloom, S.H., **17**-0276
Bloomfield, J.J., **16**-1412, **16**-2022, **19**-1480, **19**-1728, **19**-1733, **19**-1737, **19**-1738, **19**-1739
Blotny, G., **16**-2169
Blough, B.E., **15**-0552
Blouin, M., **10**-0620
Blount, J.F., **10**-1451
Blucher, W.G., **11**-0139
Blues, E.T., **19**-1347
Bluet, G., **16**-1112, **16**-1113
Bluhm, A.L., **19**-0350
Bluhm, H.J., **19**-0025
Blukis, V., **01**-0081
Blum, J., **10**-1017, **11**-0360, **11**-0634, **13**-0322, **14**-0448, **14**-0449, **14**-0451, **16**-0891, **18**-0143
Blum, L., **19**-1564
Blum, S.A., **19**-0829
Blume, E., **16**-1198
Blume, R.C., **16**-1649
Blunt, J.W., **15**-0562
Bly, R.K., **10**-0135
Bly, R.S., **10**-0134, **10**-0135, **10**-0137, **18**-0085
Blyumberg, E.A., **15**-1798, **19**-0701
Boar, R.B., **19**-1410, **19**-1411
Boaz, N.W., **10**-0229, **10**-0233, **10**-1364, **10**-1453, **15**-1066, **15**-1170, **15**-1173
Bobbitt, J.M., **19**-0196, **19**-0344, **19**-0689
Bobrowski, K., **07**-0033, **07**-0034
Bobylev, V.A., **10**-0493
Bocarsly, A.B., **19**-0109
Bocharov, B.V., **17**-0486
Boche, G., **02**-0257, **05**-0136, **05**-0136, **05**-0143, **05**-0148, **05**-0270, **12**-0030, **12**-0509, **12**-0509, **16**-1189, **18**-0505, **18**-0506
Bocher, S., **10**-0256
Bochkov, A.F., **08**-0157
Bocian, W., **16**-0584
Bock, C.W., **02**-0028
Bock, H., **01**-0013, **11**-0181, **16**-0263, **19**-0271
Bock, M.G., **16**-0232, **17**-0147
Bock, P.L., **12**-0013
Bockman, T.M., **15**-0515, **15**-1497
Bockrath, B., **05**-0109
Bockstiegel, B., **10**-1661
Bodansky, M., **16**-1795
Bodanszky, A., **16**-1797
Bodanszky, M., **16**-1797
Bode, J.W., **15**-1939, **16**-0760
Bode, K., **16**-0188
Boden, D.J., **13**-0379
Boden, E.P., **16**-1665
Boden, H., **10**-1794
Bodepudi, V.R., **15**-0119
Bodewitz, H.W.H.J., **12**-0604
Bodkin, J.A., **15**-1863
Bodmann, K., **16**-1308
Bodot, H., **18**-0225
Bodrikov, I.V., **15**-0021, **16**-0198
Bodwell, G.J., **02**-0067, **02**-0068, **02**-0281
Bodyston, A.J., **02**-0290
Boebel, T.A., **15**-2303
Boechat, N., **19**-1088
Boeckman Jr., R.K., **10**-1636, **15**-0133, **15**-0136, **15**-0266, **15**-1350, **16**-1071, **18**-0579, **18**-0657, **18**-0665
Boeder, H., **16**-1816
Boehm, P., **19**-1102
Boehshar, M., **12**-0441
Boekelheide, V., **02**-0276, **02**-0295, **02**-0298, **02**-0333, **06**-0074, **10**-1697, **10**-1702, **17**-0182
Boele, J., **08**-0084
Boele, M.D.K., **13**-0369
Boelens, H., **17**-0275
Boelens, M., **10**-0873
Boelhouwer, C., **10**-1218, **18**-0827
Boer, F.P., **05**-0063, **05**-0075, **11**-0454
Boerner, D., **10**-0232
Boero, M., **18**-0316
Boersma, J., **16**-0833
Boersma, M.A.M., **18**-0566
Boerth, D.W., **08**-0068, **08**-0070, **08**-0074
Boerwinkle, F., **15**-0020
Boese, R., **02**-0055, **02**-0081, **03**-0065, **04**-0339, **04**-0467, **15**-0430, **18**-0087
Boese, W.T., **19**-0061
Boesten, W.H.J., **16**-1734, **19**-1484
Boeters, C., **17**-0266
Boettcher, R.J., **18**-0853
Boev, V.I., **12**-0354
Boezio, A.a., **10**-0705
Bogatkov, S.V., **16**-0031
Bogatskii, A.V., **10**-0470
Bogavac, M., **16**-1942
Bogdal, D., **10**-0590
Bogdanov, G.N., **18**-0187
Bogdanov, V.S., **15**-0049
Bogdanović, B., **04**-0146, **12**-0578, **15**-0597, **15**-0709
Bogdał, D., **19**-0675
Bogen, S., **15**-1224
Boger, D.L., **15**-0145, **15**-1118, **15**-1352, **15**-2102, **15**-2122, **15**-2139
Bøgevig, A., **16**-0384, **19**-0506
Boggio, C., **15**-0318
Boggs, J.E., **04**-0261, **04**-0350
Boggs, J.K., **10**-0543
Boggs, R.A., **07**-0049
Bogseth, R.C., **10**-0527
Boguslavskaya, L.S., **04**-0131, **10**-0759, **14**-0135, **14**-0293, **15**-1542, **15**-1544, **15**-1556, **16**-0449
Bohé, L., **15**-1780
Bohlmann, F., **07**-0008, **14**-0320
Böhm, H.P., **12**-0583
Böhm, M., **14**-0244
Böhm, S., **11**-0087
Böhm, V.P.W., **10**-1303, **13**-0538
Bohme, D.K., **08**-0051, **08**-0077, **08**-0223, **08**-0237, **10**-0336, **10**-0345, **10**-0346
Böhme, H., **16**-0101
Böhme, M., **10**-1333

Böhmer, V., **03**-0120, **03**-0123, **03**-0124, **03**-0139
Bohn, A.A., **02**-0051
Bohne, C., **02**-0387
Boiadjiev, S.E., **04**-0058
Boireau, G., **16**-0493, **16**-0683, **19**-0954
Bois-Choussy, M., **13**-0343
Boiteau, J.-G., **15**-1125, **15**-1131
Boitiaux, J.P., **15**-0424
Boivin, J., **12**-0339, **16**-1504, **16**-1505
Bojanowska, I., **08**-0229
Bojarski, J.T., **16**-1871
Bokova, A.I., **11**-0607
Bolan, J.L., **16**-0301
Boland, W., **16**-1370, **19**-0547
Boldeskul, I.E., **16**-1403
Boldi, A.M., **18**-0905
Boldt, P., **10**-1605, **10**-1606, **15**-0101, **15**-0112, **15**-1927
Boleslawski, M.P., **16**-0500
Bolesov, I.G., **15**-2260, **16**-1959, **18**-0616
Bolestova, G.I., **10**-1382, **15**-0514, **15**-0717, **16**-0743
Bolhofer, W.A., **10**-0983
Bolitt, V., **10**-1780, **15**-0252
Böll, W.A., **02**-0259, **02**-0264, **02**-0265, **02**-0266, **17**-0507, **17**-0509
Bollinger, F.W., **12**-0216
Bollinger, J.M., **04**-0500, **04**-0502, **04**-0504, **10**-0117, **15**-2365, **18**-0493, **18**-0361, **18**-0363, **19**-0184, **19**-0191, **19**-1034, **19**-1149
Bolm, C., **19**-0190
Bolon, D.A., **10**-0134
Bolourtchian, M., **15**-0472, **19**-0147, **19**-0242, **19**-1701
Bols, M., **15**-2140, **16**-1873
Bolster, J.M., **04**-0478
Bolton, G.L., **10**-1710, **10**-1726, **15**-0879
Bolton, J.R., **05**-0208
Bolton, P.D., **08**-0160, **08**-0238, **08**-0239
Bolton, R., **13**-0736, **14**-0031, **14**-0325, **15**-0001
Bolze, C., **12**-0736
Bolze, R., **15**-0094
Bomben, K.D., **08**-0234
Bombicz, P., **16**-1212
Bombrun, A., **10**-0883
Bombrun, A., **10**-1293
Bommer, P., **04**-0203
Bon, E., **16**-1736
Bonadies, F., **15**-1818
Bonaga, L.V.R., **15**-1415, **15**-1416, **15**-1430, **15**-1439, **15**-2390
Bonanni, M., **19**-1231
Bonato, M., **15**-0678
Bonaventura, M.M., **04**-0369
Bonazzola, L., **05**-0273
Bonačić-Koutecký, V., **07**-0001
Bonchev, D., **04**-0260
Bond, F.T., **17**-0270, **17**-0275
Bondarenko, T.N., **10**-1851
Bonde, S.E., **10**-1296
Bondlela, M., **10**-1380
Bondock, S., **16**-2089, **16**-2090
Bondybey, V.E., **15**-0488
Bonesi, S.M., **11**-0300
Bonet, J., **18**-0186
Bongini, A., **15**-1099
Bonham, R.A., **01**-0060, **01**-0061
Bonhoeffer, K.F., **19**-1764
Boniardi, O., **19**-0450
Bonilla, R.J., **15**-0526
Bonini, B.F., **10**-1495
Bonini, C., **10**-1150, **10**-1153, **10**-1172, **15**-1690, **19**-0898
Bonini, G., **11**-0497
Bonitatebus Jr., P.J., **18**-0770
Bonitatebus, P.J., **18**-0792
Bonitz, G.H., **16**-0405
Bonjoch, J., **15**-1240
Bonk, P.J., **06**-0016
Bonnat, M., **19**-1490
Bonne, D., **13**-0209
Bonne, F., **16**-0391
Bonneau, R., **04**-0469, **05**-0386
Bonnekessel, M., **10**-1330
Bonner, O.D., **16**-0040
Bonner, W.A., **14**-0408, **18**-0032, **18**-0083, **19**-1592
Bonnet, V., **13**-0319
Bonnet-Delpon, D., **10**-0296, **10**-0672, **10**-0929, **11**-0391, **15**-1753, **15**-1770, **16**-0863, **16**-0901, **19**-0863
Bonnett, R., **16**-0275, **18**-0877
Bonnichon, F., **05**-0354
Bonnier, J., **14**-0105
Bonnier, J.M., **13**-0748
Bonnin, J.P., **11**-0453
Bonrath, W., **07**-0116
Bonthrone, W., **19**-0254
Bonvicino, G.E., **13**-0773
Bonvino, V., **11**-0334
Bonzougou, Y., **16**-1926
Boogers, J.A.F., **15**-1131
Boojamra, C.G., **14**-0297
Boone, A.W., **06**-0064
Boone, J.R., **19**-0951, **19**-1060, **19**-1061, **19**-1062
Boons, G.-J., **10**-0604
Boord, C.E., **04**-0412
Booth, B.L., **10**-1839, **11**-0528
Booth, H., **04**-0338, **04**-0366, **04**-0367, **17**-0084
Booth, S., **10**-1790
Booth, S.E., **05**-0142
Boothe, R., **11**-0298
Boothe, T.E., **17**-0139
Boovanahalli, S.K., **10**-1117
Boozer, C.E., **10**-0211
Bopp, R.J., **10**-0114
Bora, U., **15**-1002
Borah, R., **16**-0358
Borate, H.B., **16**-1153
Borau, V., **13**-0576
Borbaruah, M., **19**-0934
Borch, R.F., **05**-0052, **16**-0361, **16**-1217, **19**-1178
Borchardt, A., **02**-0359
Borchardt, J.K., **17**-0031, **17**-0032
Borchert, A.E., **18**-0582
Bordeau, M., **12**-0320
Borden, G.W., **18**-0467
Borden, J.E., **18**-0567
Borden, W.T., **01**-0001, **02**-0216, **02**-0234, **04**-0470, **04**-0521, **04**-0522, **05**-0121, **05**-0239, **05**-0285, **05**-0286, **05**-0288, **05**-0332, **05**-0398, **10**-0047, **10**-0227, **15**-0562, **18**-0543, **18**-0630, **18**-0669, **19**-0766
Bordwell, F.G., **01**-0102, **01**-0103, **01**-0106, **02**-0141, **05**-0105, **05**-0138, **05**-0245, **05**-0246, **05**-0378, **08**-0018, **08**-0051, **08**-0056, **08**-0084, **08**-0141, **08**-0217, **09**-0060, **10**-0077, **10**-0219, **10**-0222, **10**-0303, **10**-0305, **10**-0331, **10**-0333, **10**-1602, **17**-0003, **17**-0039, **17**-0048, **17**-0052, **17**-0054, **17**-0057, **17**-0073, **17**-0125, **17**-0221, **17**-0344, **17**-0346, **17**-0348, **17**-0353, **18**-0198, **19**-1616
Borecka, B., **03**-0172
Boregeaud, R., **15**-0170
Borg-Karlson, A.-K., **10**-0999
Borgen, G., **04**-0392
Borgmann, C., **15**-1481
Borhan, B., **15**-1673, **19**-0341, **19**-0396, **19**-0676
Borisenko, A.A., **15**-0759
Borisov, A.E., **05**-0135
Borisov, A.V., **15**-0021
Borkar, S.D., **19**-0559
Borkent, J.H., **04**-0070

Borkowski, M., **09**-0009
Born, D., **04**-0437
Born, R., **15**-0357
Börner, A., **15**-0609, **16**-0344, **16**-0373, **19**-1158
Borodin, A., **14**-0424
Borodkin, G.I., **15**-0623, **18**-0006, **18**-0011
Borodkin, V.S., **12**-0670
Borosky, G.L., **13**-0061, **18**-0095
Borredon, E., **10**-0587
Borredon, M.E., **10**-0819
Bors, D.A., **08**-0060
Borths, C.J., **15**-2051
Bortolini, O., **15**-1791
Boruah, A., **10**-0591, **10**-1394, **15**-1018, **17**-0384, **19**-1268, **19**-1694
Boruah, M., **17**-0464, **19**-1248
Boruah, R.C., **15**-1002
Boruah, A., **16**-1902, **18**-0313
Borčić, S., **10**-0134
Bos, H., **10**-0711
Bos, H.J.T., **15**-0216, **15**-0217, **16**-0209
Bos, W., **10**-1614
Bosc, J., **10**-1524
Bosch, A., **18**-0872, **18**-0873
Bosch, A.I., **18**-0322
Bosch, E., **11**-0119, **16**-2083, **19**-0272
Bosch, I., **16**-1794, **19**-1272
Bosch, R.J., **04**-0349, **05**-0339, **10**-1183
Boschetto, D.J., **12**-0013
Bosco, J.W.J., **16**-1696
Bosco, M., **10**-0931, **10**-1064, **11**-0457, **15**-1018, **15**-1105, **15**-1167, **15**-1170, **15**-1289, **16**-0521, **16**-0615, **16**-1618, **19**-0997
Bose, A.K., **07**-0116, **07**-0105, **10**-1599
Bose, D.S., **10**-1030, **16**-0062, **16**-0077, **16**-0131, **16**-0328, **16**-1171, **16**-1580, **17**-0441, **17**-0465, **17**-0467, **17**-0471, **17**-0483, **19**-0212, **19**-0772
Bose, G., **10**-0561
Bosica, G., **12**-0686, **15**-1005, **15**-1033, **16**-0113, **16**-0255, **16**-0808, **16**-1156
Bosma, R.H.A., **18**-0826
Bosman, C., **15**-1855
Bosnich, B., **04**-0150, **04**-0151, **12**-0079, **15**-1361, **15**-1366, **16**-1080, **16**-1473, **18**-0689, **19**-1759
Bosret, J., **16**-0486
Bossard, F., **10**-1688
Bossart, M., **14**-0391, **18**-0056
Bosser, G., **17**-0367
Bosshard, H., **18**-0132
Bossio, M.R., **15**-0361
Boswell Jr., G.A., **10**-1078, **16**-0447
Boswell, C.J., **10**-0253
Bothe, H., **04**-0431
Bothner-By, A.A., **02**-0291
Botoshansky, M., **05**-0263
Bott, K., **10**-0391
Bott, R.W., **11**-0011
Botta, M., **07**-0119, **10**-0901
Bottalico, D., **10**-1770
Bottaro, J.C., **12**-0709
Böttcher, A., **16**-1918
Botteghi, C., **15**-1486
Botteron D.G., **17**-0143
Bottini, A.T., **04**-0475, **10**-0262, **10**-0854, **13**-0091
Bottino, A., **04**-0162
Bottino, F.A., **19**-1714
Bottle, R.T., appendixA-0001
Botto, R.E., **10**-0191
Bottoni, A., **05**-0121, **15**-2211, **15**-2336, **16**-0750
Bouab, O., **10**-0537
Bouas-Laurent, H., **10**-1794
Bouaziz, Z., **07**-0091
Boucard, V., **18**-0809
Bouchez, L.C., **16**-2168
Bouchoule, C., **16**-2052
Bouchu, D., **15**-1065
Bouda, H., **10**-0819
Boudakian, M.M., **10**-0238
Boudin, A., **12**-0593
Boudjouk, P., **01**-0011, **07**-0080, **07**-0086, **07**-009, **10**-1226, **15**-0175, **15**-0586, **16**-0814, **16**-2003
Boudreaux, G.J., **17**-0350
Boué, S., **12**-0040
Bougauchi, M., **15**-1808
Bouguir, F., **19**-1021
Bouhlel, E., **16**-0812
Bouillon, G., **10**-0746
Bouillon, J.-P., **16**-1062
Bouinidane, K., **19**-1796
Bouis, P.A., **05**-0092
Boukhal, H., **15**-1001
Boukherroub, R., **15**-0472, **19**-1403
Boulaajaj, S., **15**-1001
Bouloc, N., **11**-0423
Boumizane, K., **16**-0453
Bounds, P.L., **12**-0059
Bouquant, J., **16**-1062
Bouquillon, S., **19**-0218
BourBouz, S., **16**-0646
Bourcier, S., **04**-0096
Bourdelande, J.L., **15**-1785
Bourdon, F., **16**-1730
Bourdon, J., **15**-1770
Bourgain, M., **10**-1529, **10**-1530, **10**-1766, **10**-0741
Bourgois, J., **10**-0265
Bourguet, E., **18**-0156
Bourhis, M., **10**-1524
Bourn, A.J.R., **04**-0323
Bourns, A.N., **06**-0067, **13**-0018, **17**-0059, **17**-0236
Bousquet, C., **15**-1835
Boussu, M., **16**-1930
Boustany, K.S., **19**-0871
Boutagy, J., **16**-1306
Boutin, R.H., **18**-0272
Boutonnet, F., **15**-0053
Bouvier, J.-P., **15**-1245
BouzBouz, S., **18**-0781, **18**-0786
Bouzide, A., **15**-0965, **15**-0971, **16**-2157, **19**-1384
Bovenkamp, J.W., **03**-0113, **18**-0250
Bovey, F.A., **04**-0323
Bovicelli, P., **10**-0685, **16**-0443, **17**-0213
Bovin, Y., **16**-2132
Bowden, K., **01**-0042, **02**-0425, **02**-0426, **08**-0048, **08**-0126, **15**-0047, **16**-1594, **19**-0074
Bowe, C., **08**-0147
Bowe, M.D., **05**-0141
Bowen, C.T., **10**-0082
Bowen, J.P., **03**-0012
Bowen, P., **18**-0872
Bower, J., **15**-2426
Bower, T.R., **15**-0004, **15**-0033
Bowers Jr., J.R., **16**-0530
Bowers, A., **19**-0074
Bowers, C.W., **03**-0102
Bowers, K.W., **15**-0543
Bowers, M.T., **08**-0219, **08**-0223, **08**-0224
Bowles, A.J., **14**-0044
Bowles, D.M., **18**-0490
Bowlin, H.B., **18**-0559
Bowlus, S.B., **16**-1193
Bowman, N.S., **06**-0069, **18**-0179
Bowman, P.S., **08**-0086
Bowman, W.R., **10**-1483, **10**-1603, **15**-1277, **16**-1506, **19**-1533
Bowry, V.W., **14**-0075, **14**-0084
Box, V.G.S., **04**-0366
Boxwell, C.J., **15**-0531
Boy, J., **01**-0065

Boyall, D., **16**-0552
Boyd R.H., **08**-0116
Boyd, D.R., **04**-0038, **04**-0136, **18**-0645
Boyd, G.V., **15**-0038, **15**-0961
Boyd, R.H., **08**-0032, **15**-0028
Boyd, R.J., **01**-0029
Boyd, S.D., **10**-1484
Boyd, S.E., **03**-0184, **03**-0191
Boydston, A.J., **02**-0290
Boyer, B., **10**-0646, **19**-0951, **19**-1060
Boyer, J.H., **10**-1032, **12**-0086, **12**-0707, **12**-0708, **12**-0713, **13**-0722, **15**-0397, **18**-0264, **19**-0763, **19**-0776
Boyer, L.E., **18**-0194
Boyer, R.F., **18**-0557
Boykin, D.W., **13**-0480, **13**-0501
Boyle Jr., W.J., **08**-0141, **15**-0024
Boyle, B.A., **18**-0872
Boyle, P.H., **04**-0156, **04**-0157
Boyles, D., **08**-0147
Boynton, W.A., **10**-0253
Bozell, J.J., **13**-0361
Braca, G., **15**-1375
Brace, N.O., **10**-0970
Brackenridge, I., **10**-0630
Brackman,W., **14**-0353
Bradamante, S., **02**-0143
Bradamanti, S., **05**-0115
Bradbury, D., **11**-0658
Braddock, D.C., **10**-0717, **10**-0994, **11**-0137, **11**-0423, **16**-0759, **16**-1416, **18**-0793, **19**-0115
Braddon, D.V., **10**-0170
Bradley, J., **05**-0380, **14**-0033, **14**-0328
Bradley, M., **10**-1790, **15**-1690, **19**-0797
Bradley, W.A., **10**-0077
Bradshaw, J.S., **03**-0101, **03**-0105, **03**-0148, **04**-0163, **04**-0177, **13**-0133, **14**-0399, **16**-0219, **19**-1473, **19**-1577
Bradshaw, R.W., **10**-0982
Bradsher, C.K., **11**-0392, **11**-0393, **12**-0615
Brady, D.G., **15**-0049
Brady, J.D., **11**-0021
Brady, W.T., **15**-0265, **15**-2178, **15**-2184, **15**-2185, **15**-2186, **15**-2213, **15**-2214, **15**-2216, **16**-2108, **17**-0168, **17**-0170
Braenden, J.E., **19**-0457
Braendlin, H.P., **11**-0224
Braga, A.L., **10**-0785, **12**-0290, **12**-0294, **15**-0216, **15**-0291, **15**-0944, **15**-1325, **16**-0687
Bragin, J., **04**-0436
Bragole, R.A., **18**-0613
Braier, A., **15**-2443
Braig, W., **10**-1312
Braillon, B., **16**-0263
Braish, T.F., **15**-0040
Braisted, A.C., **18**-0604
Bram, G., **10**-0340, **10**-0489, **10**-0490, **10**-0699, **10**-1047, **10**-1787, **16**-1689, **17**-0307
Brammer Jr., L.E., **05**-0216
Brammer, C., **15**-1982
Brammer, L., **01**-0052, **01**-0070, **02**-0031
Branca, J.C., **05**-0378
Branca, S.J., **04**-0443
Branchadell, V., **15**-2244, **15**-2291
Branchaud, B.P., **17**-0205
Branco, L.C., **09**-0116, **15**-1703
Branco, P.S., **15**-1907
Brand, D.J., **04**-0019
Brand, M., **12**-0138, **15**-1519, **15**-1545
Brand, W.W., **13**-0773
Branda, N.R., **04**-0072
Brandänge, S., **11**-0335, **19**-1332
Brandenberger, S.G., **19**-0418
Brandes, B.D., **15**-1829
Brandes, E., **18**-0710
Brandes, E.B., **18**-0667
Brandi, A., **17**-0449, **19**-0774
Brandl, M., **06**-0076, **19**-0065
Brandon, R.W., **05**-0328
Brandsma, L., **10**-0230, **10**-0826, **10**-0999, **10**-1726, **12**-0396, **12**-0421, **12**-0483, **15**-0216, **15**-0217, **15**-0502, **15**-0532, **15**-0545, **16**-1898
Brändström, A., **10**-0453
Brandt, S., **10**-0178
Brandvold, T.A., **15**-1882
Brandã, R.F., **16**-0276
Brannen Jr., W.T., **10**-0303
Brannock, K.C., **10**-1621, **15**-2189, **16**-0290
Brant, J.B., **19**-0714
Branton, G.R., **18**-0572
Brard, L., **15**-1871
Bräse, S., **10**-0753, **10**-1488, **16**-0687
Brasen, W.R., **19**-0836
Braslavsky, S.E., **07**-0001, **07**-0011
Brassel, B., **18**-0567
Bratcher, M.S., **02**-0360
Bratovanov, S., **16**-0487
Bratovanov, S.S., **15**-1125
Bratsch, S.G., **01**-0029
Braude, E.A., **05**-0135, **08**-0018, **08**-0040, **15**-0849, **19**-0023
Brauman, J.I., **02**-0348, **05**-0106, **05**-0123, **08**-0014, **08**-0077, **08**-0, **08**-0224, **08**-0233, **08**-0234, **10**-0020, **10**-0336, **10**-0353, **10**-0354, **10**-0359, **10**-0413, **10**-1813, **12**-0664, **19**-0460, **19**-0467
Braun, A., **15**-1620
Braun, A.M., **14**-0161
Braun, H., **16**-1378
Braun, J.B., **13**-0543
Braun, M., **10**-1456, **15**-1841, **16**-1013, **16**-1031, **16**-1189
Braun, M.P., **12**-0260
Braun, R., **15**-2032
Brauner, J., **10**-1546
Braunstein, D.M., **19**-1235
Braunstein, P., **12**-0742
Braunton, A., **12**-0124
Braverman, S., **15**-2023, **18**-0738
Bravo, A., **14**-0138
Bravo, J.A., **03**-0200
Bravo, J.L., **04**-0300, **15**-2004
Bravo-Borja, S., **19**-1523
Bravo-Zhivotovskii, D., **05**-0263
Bray, C.D., **10**-0934
Bray, L.E., **12**-0013
Bray, T., **07**-0102
Bray, T.L., **15**-2022
Bray, T.M., **05**-0260
Brayer, J.-L., **10**-1424, **13**-0727, **13**-0728
Brazier, C.R., **05**-0399
Brazis, N.J., **18**-0789
Brazzillo, J., **18**-0194
Breau, L., **16**-1340
Breault, G.A., **15**-2082
Breaux, E.J., **07**-0026
Brebion, F., **10**-1454
Breccia, A., **07**-0105
Brechbiel, M., **14**-0086, **16**-1481, **16**-1485, **18**-0746, **18**-0750
Brechbühler, H., **10**-0723
Brechot, P., **15**-1795
Breder, C.V., **11**-0259
Breen, P.J., **04**-0267
Bregadze, V.I., **13**-0263, **13**-0660
Breger, I.K., **17**-0092
Bregman, J., **02**-0274, **02**-0292

Breinbauer, R., **13**-0548, **18**-0777
Breindl, C., **13**-0162, **15**-0314, **15**-0320
Breit, B., **15**-1137, **15**-1481, **15**-1491
Breitbeil, F.W., **15**-0133
Breitmaier, E., **12**-0536, **15**-2061
Bremer, M., **01**-0054
Bremeyer, N., **15**-0420, **15**-1007
Bremner, D.H., **07**-0084, **15**-1565
Bremner, J.B., **15**-2235
Brenek, S.J., **15**-0497, **15**-0663
Breneman, C., **04**-0278
Breneman, C.M., **02**-0041, **10**-1332, **12**-0560
Brener, L., **15**-2199, **18**-0500, **18**-0638
Breuer, Th., **08**-0084
Brenn, J., **03**-0124
Brennan, J., **16**-1342
Brennan, P.E., **15**-1958
Brennen, C.E., **07**-0066, **07**-0069
Brenner, E., **13**-0198, **13**-0200
Brenner, S., **15**-0548
Breslow, D.S., **15**-1494
Breslow, R., **02**-0155, **02**-0197, **02**-0198, **02**-0203, **02**-0209, **02**-0223, **02**-0226, **02**-0230, **02**-0231, **02**-0232, **02**-0233, **02**-0234, **02**-0235, **02**-0236, **02**-0237, **03**-0174, **08**-0075, **09**-0091, **11**-0052, **15**-2029, **16**-1496, **18**-0161, **18**-0204, **18**-0495, **18**-0503, **18**-0573, **19**-0062, **19**-0065, **19**-0601, **19**-0602, **19**-0603, **19**-1309
Bresson, A., **15**-1578
Brestensky, D.M., **16**-1073
Breton, G.W., **15**-0167
Brett, A.M., **02**-0028
Brettschneider, H., **05**-0231
Breuckmann, R., **15**-2232
Breuer, E., **05**-0255, **12**-0515, **16**-2160, **17**-0343, **18**-0287
Breuer, K., **15**-1368, **16**-0724
Breuer, S.W., **14**-0394
Breuker, K., **01**-0087
Breuzard, J., **15**-0865
Brewer, R.G., **01**-0092
Brewster, A.G., **19**-0267
Brewster, J.H., **04**-0023, **04**-0102, **04**-0127, **04**-0131, **04**-0146, **15**-0597, **18**-0385
Briand, S., **12**-0666, **16**-0514
Bribes, J.L., **05**-0077, **10**-0205
Brice, J.L., **10**-0980, **15**-0334
Brichford, N.L., **16**-0584
Brickman, M., **11**-0043
Bricout, H., **10**-0913
Bridge, A., **16**-2107
Bridge, A.W., **19**-1129
Bridges, A.J., **15**-2044
Bridon, D., **14**-0420, **19**-0437
Bridson, J.N., **02**-0067, **02**-0068, **02**-0281, **10**-1764, **12**-0153
Brieger, G., **10**-0488, **15**-0518, **15**-1980, **15**-2080, **17**-0178
Briegleb, G., **12**-0088
Briehl, H., **04**-0476
Brielmann, H.L., **15**-0386
Brienne, M., **04**-0182
Brienne, M.J., **04**-0096
Brier, P.N., **04**-0277
Briggs, A.J., **16**-0030
Briggs, E.M., **10**-0995
Briggs, J.P., **08**-0224, **08**-0225, **08**-0226
Briggs, W.S., **17**-0125
Brilkina, T.G., **12**-0432, **12**-0438, **13**-0224
Brill, T.B., **16**-1309
Brill, W.F., **10**-0291
Brillon, D., **10**-1600
Brilmyer, G., **19**-0623
Brimble, M.A., **10**-1274, **15**-1682, **18**-0807
Brinchi, L., **10**-0407, **10**-0701
Brinck, T., **18**-0352
Brindell, G.D., **18**-0066
Bringmann, G., **13**-0237, **13**-0456, **19**-1540
Brinich, J.M., **10**-0117
Brinkman, G.A., **11**-0312
Brinkman, H.R., **19**-1197
Brinkman, M.R., **05**-0219
Brinkmann, A., **19**-1155
Briody, J.M., **15**-0290, **15**-0368
Briody, R.G., **10**-0068, **10**-0069
Brion, J.-D., **13**-0325, **13**-0559
Brisbois, R.G., **12**-0220, **13**-0543
Brittain, H.G., **04**-0117
Brittain, J., **10**-0816
Brittain, J.M., **11**-0227
Brittain, T.J., **14**-0269
Brittain, W.J., **10**-0200
Britten, A.Z., **10**-1676
Britton Jr., G.H., **17**-0017
Britton, T.C., **12**-0221, **12**-0230
Brix, B., **12**-0550
Brixius, D.W., **19**-0436
Brizius, G., **18**-0828
Brizzolara, A., **10**-1674, **10**-1678
Broaddus, C.D., **12**-0057, **12**-0400
Broadhurst, A.T., **12**-0040
Broadhurst, M.J., **02**-0303
Brocarrd, J., **16**-0687
Brocchetta, M., **16**-1705
Broch, N.C., **11**-0424
Bröcher, D.J., **15**-2443
Brochu, C., **15**-2345
Brochu, M.P., **12**-0124
Brock, C.P., **02**-0366, **16**-2088
Brockington, J.W., **17**-0133
Brockington, R., **05**-0021
Brockmann Jr., H., **04**-0144
Brocks, J.J., **01**-0107, **05**-0267
Brocksom, T.J., **12**-0245, **18**-0676
Brockway, N.M., **05**-0347
Brod, A.O., **10**-0727
Brod, L.H., **10**-0534
Brodhag, A.E., **19**-0836
Brodie, B.B., **14**-0202
Brodsky, B.H., **19**-0499
Broeckaert, L., **07**-0082
Broekhof, N.L.J.M., **16**-1318
Brogan, J.B., **15**-2352
Broger, E.A., **15**-0598
Broggini, G., **15**-1930
Broggini, G., appendixA-0032
Brohm, D., **18**-0777
Brois, S.J., **04**-0036
Brokaw, M.L., **08**-0059
Brokhovetsky, D.B., **11**-0321
Broline, B.M., **18**-0567
Bromilow, J., **09**-0047, **09**-0055
Bromley, D., **11**-0229, **14**-0431
Bromley, K., **16**-1594
Bronson, J.J., **18**-0585
Brönstrup, M., **12**-0608
Brook, A.G., **01**-0009, **01**-0011, **18**-0898, **18**-0899
Brook, M.A., **04**-0131, **14**-0204, **16**-0147, **16**-1667, **18**-0683
Brook, P.R., **15**-2187, **15**-2210, **15**-2213, **15**-2215, **18**-0559
Brookes, P., **13**-0471
Brookes, P.C., **17**-0216
Brookhart, M., **10**-0131, **10**-0132, **10**-0156, **15**-1900, **15**-2287, **15**-2288, **15**-2297, **15**-2356, **19**-0043
Brooks, C.A., **15**-0583
Brooks, C.D., **19**-0393
Brooks, D.W., **10**-1089
Brooks, M.A., **18**-0062
Brophy, J.E., **18**-0534
Broster, F.A., **14**-0394
Brougham, P., **15**-1730
Broutin, P.-E., **11**-0295

Brouwer, C., **10**-1784
Brouwer, D.M., **05**-0015, **08**-0019, **08**-0023, **11**-0004, **12**-0048, **18**-0007, **18**-0008, **18**-0027, **18**-0029, **18**-0048
Browej, E.I., **16**-1355, **16**-1357
Brower, H.E., **17**-0067
Brower, K.R., **14**-0132, **17**-0067
Brown, B.L., **04**-0393
Brown, C.A., **12**-0067, **15**-0404, **15**-0432, **15**-1114, **16**-2026, **19**-1068
Brown, C.W., **19**-0338
Brown, D., **10**-0826
Brown, D.E., **04**-0289
Brown, D.F., **17**-0133
Brown, D.H., **13**-0497
Brown, D.J., **15**-0406
Brown, D.J., **15**-2185
Brown, D.S., **15**-1429, **19**-0126
Brown, D.W., **16**-2108
Brown, E., **16**-1713
Brown, E.C., **17**-0203, **18**-0639
Brown, E.S., **15**-1499, **15**-1504
Brown, E.V., **19**-1790
Brown, F.J., **10**-0079
Brown, F.K., **15**-1939, **15**-2090
Brown, G.R., **02**-0312, **19**-1286
Brown, G.W., **10**-0995
Brown, H.C., **04**-0192, **05**-0092, **06**-0074, **08**-0018, **08**-0040, **08**-0179, **08**-0190, **09**-0004, **09**-0006, **09**-0008, **09**-0009, **09**-0020, **09**-0033, **10**-0128, **10**-0133, **10**-0157, **10**-0170, **10**-0177, **10**-0179, **10**-0182, **10**-0198, **10**-0320, **10**-1160, **10**-1377, **10**-1415, **10**-1417, **10**-1715, **10**-1745, **10**-1746, **10**-1747, **10**-1749, **10**-1750, **10**-1751, **10**-1752, **10**-1753, **10**-1754, **10**-1755, **10**-1756, **10**-1757, **10**-1761, **10**-1764, **11**-0021, **11**-0024, **11**-0051, **11**-0081, **11**-0082, **11**-0089, **11**-0090, **11**-0092, **11**-0318, **11**-0373, **11**-0374, **11**-0600, **11**-0648, **12**-0013, **12**-0427, **12**-0434, **12**-0442, **12**-0443, **12**-0447, **12**-0453, **12**-0487, **12**-0488, **12**-0489, **12**-0490, **12**-0492, **12**-0494, **12**-0515, **12**-0516, **12**-0518, **12**-0519, **12**-0557, **14**-0392, **14**-0393, **14**-0395, **14**-0396, **15**-0115, **15**-0116, **15**-0117, **15**-0187, **15**-0259, **15**-0260, **15**-0432, **15**-0491, **15**-0493, **15**-0560, **15**-0636, **15**-0640, **15**-0641, **15**-0642, **15**-0643, **15**-0644, **15**-0645, **15**-0646, **15**-0647, **15**-0648, **15**-0649, **15**-0650, **15**-0651, **15**-0653, **15**-0654, **15**-0658, **15**-0659, **15**-0660, **15**-0665, **15**-0666, **15**-0669, **15**-0670, **15**-0672, **15**-0673, **15**-0674, **15**-0675, **15**-0677, **15**-0679, **15**-0683, **15**-0684, **15**-0685, **15**-0688, **15**-0689, **15**-0690, **15**-0692, **15**-0693, **15**-1183, **15**-1184, **15**-1185, **15**-1186, **15**-1187, **15**-1188, **15**-1189, **15**-1192, **15**-1634, **16**-0493, **16**-0544, **16**-0697, **16**-0699, **16**-0706, **16**-0707, **16**-0996, **16**-0997, **16**-1018, **16**-2059, **17**-0015, **17**-0087, **17**-0088, **17**-0090, **17**-0100, **17**-0109, **17**-0321, **18**-0068, **18**-0105, **18**-0106, **18**-0107, **18**-0252, **18**-0254, **18**-0420, **18**-0421, **18**-0422, **18**-0423, **18**-0424, **18**-0425, **18**-0426, **18**-0429, **18**-0430, **18**-0431, **18**-0433, **18**-0435, **18**-0436, **18**-0437, **18**-0438, **18**-0439, **18**-0441, **18**-0442, **18**-0443, **18**-0444, **18**-0447, **18**-0448, **18**-0450, **18**-0453, **18**-0455, **19**-0903, **19**-0949, **19**-0993, **19**-0994, **19**-1016, **19**-1018, **19**-1053, **19**-1054, **19**-1059, **19**-1077, **19**-1086, **19**-1091, **19**-1096, **19**-1107, **19**-1115, **19**-1167, **19**-1182, **19**-1260, **19**-1292, **19**-1293, **19**-1342, **19**-1379, **19**-1490, **19**-1496, **19**-1527, **19**-1634, **19**-1642
Brown, H.L., **15**-1046
Brown, J., **02**-0232, **03**-0172
Brown, J.D., **16**-1908
Brown, J.E., **18**-0387, **18**-0733
Brown, J.M., **02**-0298, **04**-0061, **05**-0126, **12**-0276, **12**-0580, **12**-0597, **13**-0393, **13**-0427, **13**-0440, **15**-0427, **15**-0444, **15**-0700, **15**-1478, **18**-0615, **18**-0616
Brown, L.R., **18**-0268
Brown, M.G., **02**-0036
Brown, M.J., **15**-2180, **16**-2094
Brown, M.S., **19**-1088
Brown, P.B., **15**-2254
Brown, R F.C., **18**-0520
Brown, R., **17**-0395
Brown, R.A., **15**-0614, **16**-0119
Brown, R.D., **02**-0191, **13**-0047
Brown, R.E., **15**-1446
Brown, R.F.C., **05**-0294, **05**-0383, **15**-2086, **15**-2231, **18**-0519, **18**-0520
Brown, R.K., **18**-0724, **19**-1390
Brown, R.S., **08**-0223, **15**-0008, **15**-0012, **15**-0022, **15**-1523, **16**-1595, **16**-1596
Brown, R.T., **12**-0654
Brown, R.W., **19**-0129
Brown, S.H., **14**-0296
Brown, S.M., **15**-1721, **19**-0122, **19**-0123
Brown, S.N., **19**-0214
Brown, S.P., **12**-0124
Brown, T.H., **11**-0518
Brown, T.L., **05**-0148, **05**-0149, **05**-0152
Brown, W., **12**-0370
Brown, W.G., **15**-0561, **19**-0931
Brownawell, M., **18**-0751
Brownawell, M.L., **11**-0579, **18**-0749
Brownbridge, P., **12**-0311, **15**-1912, **16**-1233, **18**-0032
Browne, A.R., **02**-0173, **04**-0442
Brownell, R., **19**-0250
Brownhill, A., **15**-0981
Browning, R.G., **12**-0367, **13**-0228
Brownlee, R.T.C., **09**-0047, **09**-0051, **09**-0055
Brownlee, T.H., **17**-0084
Brownlie, G., **18**-0111
Brownstein, S., **04**-0502, **11**-0451, **11**-0572, **11**-0575, **15**-1652
Broxterman, Q.B., **16**-0864, **19**-1484
Broxton, T.J., **16**-1570, **16**-1571, **17**-0072, **19**-1569, **19**-1573
Bruce, D.W., **10**-1296
Bruce, M.I., **02**-0166, **03**-0083, appendixA-0037
Bruch, M.D., **15**-1988
Bruck, A., **03**-0041
Bruck, D., **05**-0052, **11**-0016
Bruckenstein, S., **08**-0007, **08**-0039
Bruckner, V., **09**-0013
Brückner, C., **19**-0196
Brückner, D., **16**-1291
Brückner, R., **18**-0735
Brückner, S., **04**-0038
Brugger, W., **16**-2051
Bruggink, A., **13**-0575, **15**-0043
Bruice, P.Y., **12**-0095, **12**-0096
Bruice, T.C., **04**-0252, **10**-0371, **10**-0372, **12**-0095, **15**-1743,

16-0020, **16**-0025, **16**-0026, **16**-0034, **16**-1571, **16**-1845, **16**-1846, **16**-1847
Bruin, J.W., **12**-0585
Brummond, K.M., **12**-0151, **15**-0834, **15**-0879, **15**-1444, **15**-1445, **15**-1450
Brun, C., **15**-2096
Brun, P., **12**-0074, **15**-0999, **15**-1923, **15**-2326
Brundle, C.R., **01**-0013, **01**-0015, **01**-0016
Brune, H.A., **18**-0462
Bruneau, C., **10**-1463, **15**-0279, **15**-0281, **15**-0428, **15**-0835, **16**-0436, **18**-0814
Brunel, J.M., **10**-1155, **15**-1137, **16**-1422, **19**-0823, **19**-1032
Brunel, Y., **15**-1857, **16**-1275
Brunelle, D.J., **10**-1340, **10**-1351, **10**-1370, **10**-1436, **15**-1087, **16**-1652, **16**-1655
Brunelle, P., **10**-0124
Brunelle, W.H., **19**-0364
Bruner, H.S., **16**-0193
Brunet, J., **10**-0262, **10**-1810, **11**-0656, **13**-0613
Brunet, J.-J., **10**-0460, **11**-0646, **15**-1386, **15**-1389
Brungardt, B., **10**-0178
Bruni, R., **19**-0872
Brunie, J., **12**-0081
Brunner, H., **04**-0146, **04**-0149, **04**-0150, **05**-0231, **15**-0597, **19**-1241
Brunner, M., **15**-1466, **16**-1918
Bruno, F., **14**-0418
Bruno, J.J., **15**-0501
Brunow, G., **16**-1214
Brunton, S.A., **15**-1253
Brüntrup, G., **16**-1000, **17**-0412, **17**-0414, **17**-0416
Brunvoll, J., **02**-0120, **02**-0272
Brus, L.E., **11**-0565
BrusJ., **04**-0092
Brusova, G.P., **18**-0250
Brutcher Jr., F.V., **15**-1683
Bruyere, D., **15**-0806
Bruylants, A., **14**-0116, **14**-0121, **16**-0098
Bruylants, P., **10**-1491
Bruza, K.J., **15**-1349, **15**-1350
Bruzinski, P.R., **15**-2297
Bryan, C.J., **11**-0305
Bryan, V.J., **16**-1906
Bryans, J.S., **15**-1254
Bryant, G.L., **13**-0134
Bryant, J.A., **10**-1307
Bryany, J.A., **03**-0121
Bryce, M.R., **13**-0037, **15**-1996
Bryce-Smith, D., **10**-1316, **11**-0369, **12**-0411, **12**-0412, **13**-0651, **14**-0437, **18**-0493, **19**-1347
Brycki, B., **10**-0387
Brycki, B.E., **10**-0001, **10**-0084
Bryker, W.J., **13**-0716
Brylikowska-Piotrowicz, J., **10**-0995
Brylikowska-Piotrowicz, J., **10**-0995
Bryson, T.A., **10**-1711, **16**-0405
Brzezinski, L.J., **16**-0797
Brząszcz, M., **19**-0707
Bu, J., **11**-0396
Bu, X.R., **16**-1438
Bu, Y.-P., **16**-1092
Buback, M., **13**-0380
Bublitz, D.E., **02**-0166, **11**-0063, **12**-0562, **19**-1475
Bubnov, Y.N., **16**-1969, **18**-0548
Bubnov, Yu.N., **16**-0697, **16**-1970
Bucciarelli, M., **04**-0038
Büch, H.M., **15**-2284
Buchan, C., **10**-1859
Buchanan, D.H., **12**-0013
Buchanan, D.N., **15**-2113
Buchanan, G.L., **04**-0491, **12**-0645, **12**-0667, **15**-1046
Buchanan, G.W., **02**-0244, **03**-0113, **04**-0336
Buchanan, J.G.S., **19**-1435
Buchardt, O., **04**-0068, **04**-0154, **04**-0155
Buchbauer, G., **16**-0195
Buchecker, C., **17**-0507
Bucher, B., **16**-2161
Bucher, G., **05**-0207
Buchholz, B., **10**-1563
Buchholz, S., **12**-0030, **19**-1022
Büchi, G., **10**-0661, **15**-0346, **15**-2243, **15**-2244, **18**-0407, **19**-0451
Büchi, G.H., **10**-0687
Büchi, H., **10**-0723
Buchina, I.K., **11**-0607
Buchman, O., **10**-1822, **18**-0143, **19**-0661
Büchner, W., **12**-0691
Buchneva, L.M., **09**-0034
Buchstaller, H.P., **16**-1786
Buchwald, G., **14**-0235
Buchwald, S.L., **03**-0115, **10**-1405, **10**-1635, **11**-0182, **12**-0523, **13**-0117, **13**-0118, **13**-0123, **13**-0124, **13**-0138, **13**-0174, **13**-0175, **13**-0176, **13**-0177, **13**-0178, **13**-0179, **13**-0182, **13**-0183, **13**-0184, **13**-0185, **13**-0188, **13**-0189, **13**-0198, **13**-0201, **13**-0202, **13**-0205, **13**-0207, **13**-0212, **13**-0226, **13**-0228, **13**-0229, **13**-0232, **13**-0258, **13**-0275, **13**-0357, **13**-0473, **13**-0508, **13**-0533, **13**-0539, **13**-0575, **13**-0583, **13**-0587, **13**-0593, **15**-0425, **15**-0430, **15**-0476, **15**-0592, **15**-0593, **15**-0594, **15**-0708, **15**-0773, **15**-0812, **15**-0973, **15**-1424, **15**-1439, **15**-1465, **15**-1482, **15**-1505, **16**-1311, **16**-1348, **18**-0726, **19**-1133, **19**-1154, **19**-1163, **19**-1472
Buck, C.J., **18**-0050
Buck, H.M., **07**-0015, **10**-0152, **10**-1252
Buck, J.S., **16**-1493
Buck, P., **13**-0003, **17**-0311
Buckingham, A.D., **04**-0126
Buckingham, J., **04**-0096, **16**-0302
Buckl, K., **18**-0506
Buckle, M.J.C., **12**-0004
Buckles, R.E., **15**-0014, **15**-1539, **19**-0838
Buckley, B., **15**-1782
Buckley, B.R., **15**-1782
Buckley, P., **04**-0282
Buckley, P.D., **17**-0065
Buckmelter, A.J., **14**-0080
Buckner, J.K., **10**-0071
Buckwalter, B., **10**-1726
Buckwalter, B.L., **10**-1511
Bucsi, I., **11**-0119
Buda, A.B., **02**-0072, **04**-0504, **18**-0483
Būda, V., **10**-0999
Buddenbaum, W.E., **06**-0080
Budhai, L., **19**-0488
Budzelaar, P.H.M., **16**-0833
Buehler, C.A., **11**-0046, **11**-0224, **11**-0423, **11**-0534
Buehler, E., **10**-0770
Buehler, N.E., **18**-0853
Buenker, R.J., **07**-0015
Buess, C.M., **02**-0135
Bug, T., **10**-0355, **10**-0407
Bugaenko, L.T., **05**-0211
Bugatti, V., **19**-0823
Bugl, M., **18**-0764
Bühl, H., **04**-0472
Bühl, M., **04**-0137, **15**-2293
Buhler, J.D., **16**-0515
Bühler, R.E., **14**-0119
Bui, T., **16**-0415, **16**-1036, **16**-1068

Bui-The-Khai, **10**-0900, **10**-0916
Buijsman, R.C., **18**-0771
Buiry, P.J., **13**-0424
Buisson, P., **15**-0404
Buist, G.J., **16**-2126, **19**-0327
Bujok, R., **10**-1043
Bulat, H., **13**-0480
Bulbule, V.J., **16**-1152, **16**-1153, **16**-1683
Bulgarevich, S.B., **08**-0149
Bull, H.G., **10**-0520
Bull, S.D., **10**-1640, **19**-1515, **19**-1625
Bullen, J.V., **11**-0104
Bullock, R.M., **15**-0515
Bullock, V.R., **04**-0309
Bulman, A., **18**-0715
Bulten, E.J., **15**-0522
Bulthuis, J., **04**-0283
Bumagin, N.A., **10**-1306, **10**-1400, **10**-1782, **10**-1846, **12**-0526, **13**-0514, **13**-0526, **13**-0534, **13**-0601, **13**-0602, **13**-0619, **14**-0384
Bumgardner, C.L., **12**-0160, **13**-0767, **19**-1517
Bunce, N.J., **05**-0208, **14**-0097, **14**-0118, **14**-0145, **14**-0438, **18**-0891
Bunce, R.A., **10**-1585
Buncel, E., **05**-0099, **05**-0110, **05**-0110, **05**-0130, **05**-0145, **05**-0198, **05**-0199, **05**-0378, **08**-0014, **08**-0065, **08**-0066, **08**-0133, **10**-0358, **10**-0362, **10**-0364, **10**-0365, **10**-0368, **10**-0369, **10**-0372, **10**-0408, **10**-0449, **10**-0451, **10**-1447, **10**-0688, **10**-1656, **12**-0390, **12**-0415, **12**-0639, **13**-0003, **13**-0005, **13**-0008, **13**-0009, **13**-0032, **16**-0015, **16**-1013, **16**-2146, **18**-0739, **18**-0880, **18**-0881, **18**-0883, **18**-0886, **18**-0887, **18**-0889
Buncel, I.M., **11**-0543
Bunch, B., **10**-0209
Bundel', Yu.G., **10**-1087, **15**-0030, **18**-0028, **18**-0035, **18**-0046
Bunina-Krivorukova, L.I., **18**-0713
Bunlaksananusorn, T., **15**-0375, **15**-0901
Bunnell, R.D., **15**-0325
Bunnelle, W.H., **16**-0449
Bunnett, J.F., **06**-0035, **06**-0036, **06**-0053, **06**-0058, **08**-0003, **08**-0127, **08**-0130, 09-II-0002, **10**-0063, **11**-0278, **11**-0611, **11**-0614, **11**-0641, **11**-0642, **12**-0685, **13**-0003, **13**-0012, **13**-0013, **13**-0015, **13**-0042, **13**-0043, **13**-0051, **13**-0052, **13**-0055, **13**-0059, **13**-0073, **13**-0086, **13**-0088, **13**-0141, **13**-0164, **13**-0248, **13**-0574, **13**-0588, **13**-0589, **13**-0590, **13**-0596, **13**-0597, **13**-0755, **13**-0776, **16**-1845, **16**-1846, **16**-1850, **17**-0003, **17**-0035, **17**-0057, **17**-0069, **17**-0073, **17**-0086, **17**-0091, **17**-0101, **19**-1376, **19**-1569
Buntain, G.A., **18**-0344, **18**-0346
Bunting, J.W., **08**-0044, **17**-0053
Bunton, C.A., **06**-0088, **10**-0060, **10**-0422, **10**-0516, **10**-0529, **11**-0572, **11**-0575, **13**-0019, **15**-1790, **16**-0016, **16**-1596, **19**-0311, **19**-0327
Bunton, L.A., **10**-0407
Bunyan, P.J., **19**-1747
Bunz, U.H.F., **18**-0828
Bünzli, J., **02**-0294
Buono, G., **10**-1155, **15**-0602, **15**-1137, **19**-1032
Buonora, P., **15**-2119
Buonora, P.T., **16**-0991
Bur, S., **16**-0399
Bur, S.K., **15**-2000, **19**-1777
Burawoy, A., **03**-0039
Burch, R.R., **15**-0446
Burchard, T., **19**-0061
Burden, F.R., **02**-0191
Burdett, J.K., **01**-0001
Burdisso, M., **15**-1951
Burditt, A.M., **06**-0039, **16**-2073
Burdon, J., **19**-1466
Burdon, M.G., **11**-0516
Bureau, C., **03**-0125
Burfield, D.R., **14**-0222
Burfitt, I.R., **10**-1511
Burford, S.C., **15**-0952
Burg, D.A., **15**-1978
Burgard, A., **18**-0259
Burger, E.C., **18**-0675
Burger, G., **04**-0174
Burger, T.F., **17**-0255
Burger, U., **15**-2108, **15**-2282, **18**-0477, **18**-0651
Burgess, E.M., **10**-0907, **16**-0028
Burgess, J., **06**-0057, **10**-0034
Burgess, K., **07**-0118, **15**-0199, **15**-0200, **15**-0425, **15**-0656, **15**-0696, **15**-0697, **15**-0700, **15**-1741
Burgess, L.E., **10**-1208
Burghard, H., **19**-1713
Burgos, C., **11**-0356
Burgoyne, W., **19**-1295
Burgstahler, A.W., **15**-0781, **19**-1098
Burham, R.L., **15**-1539
Burini, A., **15**-0848
Burk, M.J., **10**-0582, **15**-0429, **15**-0598, **15**-0606, **19**-0061, **19**-1028, **19**-1134
Burk, P.L., **15**-2201
Burka, L.T., **18**-0070
Burkart, M., **10**-0728
Burke, J.J., **08**-0033, **08**-0118
Burke, J.P., **10**-1454
Burke, L.A., **02**-0054
Burke, M.C., **12**-0398
Burke, S.D., **12**-0350, **15**-2261, **18**-0871
Burkert, U., **01**-0053, **04**-0406, **04**-0495
Burkett, H., **11**-0610
Burkhardt, E.R., **12**-0600
Burkoth, T.L., **02**-0248, **02**-0250
Burkus, T., **16**-2037
Burlak, N., **02**-0331
Burlingame, A.L., **12**-0109
Burlingame, T.G., **04**-0255
Burmakov, A.I., **16**-0448
Burmeister, J.L., **15**-0406
Burn, D., **12**-0306
Burnell, D.J., **15**-2062
Burnell-Curty, C., **16**-1802, **16**-1837
Burnett, D.A., **15**-1247
Burnett, E., **16**-0405
Burns, C.L., **10**-1331
Burns, S.E., **10**-1585
Burns, S.J., **17**-0189
Burns, T.P., **12**-0599
Burpitt, R.D., **15**-2212, **16**-0290
Burrell, R.C., **18**-0079, **18**-0582
Burri, P., **13**-0028, **13**-0748
Burrous, M.L., **15**-0549
Burrows, C.J., **15**-1909
Burrows, E.P., **19**-0748
Bürstinghaus, R., **15**-1114
Burt, R.A., **10**-0571
Burton, A., **16**-0491
Burton, D.J., **05**-0346, **14**-0313, **16**-1282, **16**-1888
Burton, G., **10**-0978
Burton, J., **15**-1133
Burton, K., **15**-1006
Burton, K.A., **05**-0298
Burton, N.A., **02**-0418, **18**-0709

Burton, P.E., **18**-0053
Burwell Jr., R.L., **15**-0451, **15**-0453, **15**-0456
Bury, A., **10**-0378
Busch, P., **17**-0521, **17**-0522, **17**-0524
Buschek, J.M., **15**-0012
Buschhoff, M., **12**-0376
Buschmann, E., **10**-1621
Buschmann, J., **04**-0379, **18**-0637
Buschmann, N., **18**-0774, **18**-0781
Bush Jr., J.B., **15**-1921
Bushby, R.J., **12**-0065
Bushell, A.W., **18**-0101
Bushman, D.G., **17**-0065
Bushmelev, V.A., **11**-0013
Bushweller, C.H., **04**-0261, **04**-0316, **04**-0325, **04**-0330, **04**-0331, **04**-0350, **04**-0351, **04**-0354
Buss, D.R., **04**-0156
Buss, E., **15**-1573
Buss, V., **05**-0002, **05**-0050, **05**-0076, **05**-0083, **15**-0630
Bussell, G.E., **06**-0035
Büssemeier, B., **15**-2431
Bussman, W., **04**-0163
Bussolari, J., **16**-1322
Bussolari, J.C., **13**-0479
Bustamante, J.M., **15**-1710
Buston, J.E.H., **18**-0398, **18**-0399
Busujima, T., **16**-1081, **16**-1086, **16**-1121, **16**-1122
Butcher, S.S., **04**-0296
Butchko, M.A., **05**-0353
Buteiko, Zh.F., **10**-1318
Butenschön, H., **15**-2364
Butin, K.P., **05**-0100, **08**-0013, **08**-0014, **12**-0043, **12**-0045
Butler, A.B., **11**-0110
Butler, A.R., **01**-0042, **11**-0283, **13**-0687, **16**-1517, **16**-1744, **16**-1845, **19**-0748
Butler, D.N., **15**-0093, **15**-0516
Butler, J.R., **13**-0166
Butler, K.E., **02**-0310
Butler, R., **11**-0307
Butler, R.N., **05**-0054, **13**-0657, **13**-0695, **13**-0742, **14**-0206, **14**-0250, **14**-0256, **15**-0188, **18**-0307, **19**-0763
Butova, E.D., **14**-0142
Butskus, P.F., **15**-1986
Butskus, P.F., **17**-0104
Butsugan, Y., **10**-1512, **16**-0645, **16**-0678, **16**-0816, **16**-0874, **16**-1393
Butt, G., **01**-0042
Butte, W.A., **12**-0392
Buttenberg, W.P., **17**-0326
Butters, M., **11**-0142
Buttery, R.G., **05**-0377
Button, M.A.C., **18**-0610
Buu-Hoï, N.P., **11**-0655
Buvet, R., **19**-0748
Buynak, J.D., **16**-0697
Buys, H.R., **04**-0317, **04**-0354, **04**-0365
Buza, M., **15**-1536
Buzard, D.H., **13**-0237
Buzás, A., **16**-2071
Buzbee, L.R., **13**-0101
Buzby, J.H., **19**-0751
Buzek, P., **10**-0208
Bydlinski, G.A.S., **15**-2339
Byeon, S.-H., **19**-0800
Byers, G.W., **17**-0527
Byk, S.Sh., **03**-0164
Bykhovskaya, M.Sh., **15**-0045
Byrd, L.R., **15**-0112
Byrne, C.J., **09**-0030
Byrne, J.J., **16**-1456
Byrne, K., **04**-0106
Byrne, M.P., **03**-0102, **17**-0228
Byrne, N.E., **16**-2082
Bystrom, S.E., **15**-1867, **14**-0252, **17**-0380
Bytschkov, I., **15**-0348, **15**-0355
Bzowej, E.I., **16**-1349

Cabaleiro, M.C., **17**-0052
Caballero, A., **12**-0366, **15**-2299
Caballero, G.M., **10**-0540
Cabaret, D., **16**-0540
Cabello, J.A., **15**-0574
Cabera, S., **10**-1454
Cabeza, I., **16**-0687
Cabezas, J.A., **16**-0475
Cabiddu, S., **01**-0104
Cablewski, T., **11**-0191
Cabrera, A., **10**-1247, **15**-0579
Cabrera, C.R., **15**-0652
Cabrera, G., **17**-0188
Cabrera, S., **16**-0687, **16**-0688
Cabri, W., **04**-0196, **13**-0360, **13**-0395, **13**-0418, **19**-1374, **19**-1680
Cacace, F., **10**-0260, **11**-0098, **11**-0311, **13**-0752
Caccamese, S., **04**-0162
Cacchi, S., **10**-1848, **13**-0149, **13**-0230, **13**-0407, **13**-0608, **13**-0609, **15**-0245, **15**-0848, **15**-1199, **16**-1459, **16**-1984, **19**-1131, **19**-1374
Cacciapaglia, R., **10**-0343
Cadamuro, S., **10**-1866
Caddick, S., **07**-0105, **07**-0110, **07**-0116, **13**-0480, **19**-1171
Cadilhac, C., **13**-0709
Cadiot, P., **14**-0301, **14**-0314, **18**-0828
Cadogan, J.I.G., **10**-1097, **10**-1099, **13**-0743, **13**-0745, **14**-0353, **15**-0016, **15**-0050, **15**-1355, **15**-1357, **15**-1357, **15**-2261, **15**-2322, **16**-1255, **16**-1306, **16**-1323, **17**-0337, **18**-0469, **18**-0470, **19**-1420, **19**-1424, **19**-1546, **19**-1568, **19**-1603, **19**-1747
Cadot, C., **15**-0638, **15**-0664
Cady, G.H., **03**-0164
Cafferata, L.F.R., **10**-0284
Cagle, P.C., **12**-0352
Caglioti, L., **16**-1459, **19**-1510
Cahard, D., **12**-0133
Cahiez, G., **10**-1245, **10**-1298, **10**-1301, **10**-1329, **10**-1343, **10**-1373, **10**-1395, **10**-1413, **12**-0314, **13**-0313, **13**-0334, **15**-0952, **15**-0954, **15**-0955, **16**-0565, **16**-0817, **16**-1907
Cahn, R.S., **04**-0098
Cai, D., **13**-0237, **15**-0440
Cai, J., **04**-0358, **04**-0375, **16**-0777
Cai, K., **19**-0568
Cai, M.-Z., **10**-1327, **10**-1852, **13**-0610
Cai, Q., **10**-0979, **13**-0117, **13**-0202
Cai, W., **15**-0663
Caiazzo, A., **11**-0355
Caille, S.Y., **11**-0029
Caillot, F., **13**-0490
Cain, C.M., **12**-0108
Cain, E.N., **14**-0045, **16**-0248, **19**-0445
Cain, G.A., **19**-1356
Cain, M.E., **10**-0792
Caine, D., **10**-1609, **10**-1653, **12**-0240, **12**-0418, **15**-0517, **16**-0994, **17**-0409
Cainelli, G., **12**-0585, **15**-1667, **15**-2056, **16**-0499, **16**-0500, **16**-0506, **16**-0976, **19**-0071, **19**-0098, **19**-0259, **19**-0387, **19**-0391, **19**-0417, **19**-0455, **19**-0695
Caira, M.R., **03**-0169
Cairncross, A., **11**-0616, **13**-0460, **15**-2205
Cairns, T.L., **15**-2227, **15**-2228, **15**-2279, **15**-2327, **16**-0205
Cais, M., **03**-0083, **15**-1517, **16**-1891

Cajthami, C.E., **08**-0203
Calabrese, J.C., **12**-0365, **12**-0629, **15**-0696
Calabrò, G.P., **15**-1136
Calder, G.V., **08**-0078, **13**-0047
Calder, I.C., **02**-0272, **02**-0324, **02**-0326, **02**-0328
Calderari, G., **15**-1042
Calderbank, K.E., **02**-0140
Calderon N., **18**-0756, **18**-0758, **18**-0760, **18**-0762, **18**-0824, **18**-0836
Calderón, O., **16**-1192
Calderwood, D.J., **16**-1954
Caldin, E.F., **06**-0062
Caldwell, D., **04**-0268
Caldwell, D.J., **04**-0126
Caldwell, G., **08**-0232, **10**-0271, **10**-0416
Caldwell, J.J., **15**-1928
Caldwell, M., **19**-0851
Caldwell, R.A., **05**-0289, **06**-0079, **07**-0048, **08**-0071, **15**-2252
Calet, S., **17**-0223
Calhorda, M.J., **03**-0046, **03**-0056
Calimano, E., **13**-0306
Calkins, T.L., **15**-2363, **18**-0487, **18**-0488
Callaghan, O., **15**-1269
Callahan, J.H., **02**-0356
Callier, A.-C., **15**-0385
Calloway, N.O., **11**-0318
Calmes, M., **11**-0464, **19**-1032
Calmon, J.P., **16**-1570
Calo, V., **10**-1530, **13**-0399
Calò, V., **13**-0415
Calter, M.A., **16**-1028
Calverley, M.J., **10**-0992
Calvert, J.G., **07**-0001, **07**-0027, **07**-0038, **07**-0044, **07**-0065, **19**-1687
Calvert, R.L., **02**-0140
Calves, J., **05**-0021
Calvin, M., **04**-0068, **04**-0155
Calvo, R.L., **15**-2432
Calzada, J.G., **10**-1764
Calō, V., **10**-0819
Camaggi, G., **18**-0493
Camaioni, D.M., **11**-0540, **19**-0255, **19**-0608
Camarena, R., **16**-2063
Cambie, R.C., **12**-0161, **14**-0431, **15**-1557, **15**-1589, **15**-1603, **15**-1604, **15**-1626, **15**-1631, **15**-1686
Cambillau, C., **10**-0490
Cambron R.T., **18**-0061
Cameron A.G., **18**-0677
Cameron D.K., **15**-0016
Cameron G.S., **12**-0071
Cameron K.S., **04**-0382
Cameron R.E., **19**-0109
Cameron, T.S., **05**-0144, **19**-0121
Cami-Kobeci, G., **10**-0897
Caminati, W., **03**-0031
Caminiti, R., **15**-1751
Cammers-Goodwin, A., **04**-0269
Camp, D., **10**-0702
Camp, R.L., **15**-1804
Campagne, J.-M., **13**-0470, **16**-1112, **16**-1113
Campaigne, E., **16**-0002, **16**-0203
Campaigne, E., **16**-0206
Campana, C.F., **01**-0011
Campbell Jr., B.N., **11**-0358
Campbell Jr., J.B., **10**-1377, **10**-1752, **14**-0395, **15**-0688, **15**-0690
Campbell, A., **18**-0010
Campbell, A.L., **10**-1187, **12**-0571
Campbell, D.H., **15**-1879
Campbell, D.S., **16**-1571
Campbell, E.J., **10**-1546, **19**-0970, **19**-0972, **15**-1429
Campbell, G., **16**-1561
Campbell, G.A., **11**-0275
Campbell, J.R., **10**-1158, **13**-0132
Campbell, J.R., **19**-0408
Campbell, M.L., **08**-0037
Campbell, M.M., **15**-1565
Campbell, M.S., **02**-0075
Campbell, P., **11**-0052
Campbell, T.W., **16**-2068, **16**-2069
Campelo, J.M., **15**-0191, **15**-0454, **15**-0574
Campi, E., **15**-1486
Campi, E.M., **15**-1493, **15**-1685
Campillo, M., **19**-1022
Campillo, N., **08**-0012
Campion, A., **02**-0218
Campo, M.A., **13**-0612, **15**-0919
Campos, K., **05**-0216
Campos, K.R., **15**-0440, **15**-0604, **15**-2064, **18**-0719
Campos, P.J., **12**-0486, **15**-1546, **15**-1547, **15**-2416, **18**-0592, **19**-1706, **19**-1706
Camps, F., **10**-0602, **10**-1089, **10**-1798, **15**-1545, **18**-0804
Camps, M., **15**-0268, **15**-0290, **16**-1573
Camps, P., **04**-0369, **04**-0490
Canali, L., **15**-1823
Canary, J.W., **02**-0237
Cancho, Y., **15**-0916
Candiani, I., **13**-0360, **13**-0395, **13**-0418
Candlin, J.P., **15**-0401, **19**-0873
Candran, N., **15**-0834
Candy, J.-P., **05**-0383, **19**-0042
Cane, D.E., **10**-1594, **16**-1316
Canepa, C., **15**-1731
Canet, J,-L., **19**-1730
Cañibano, V., **11**-0268
Canivet, P., **08**-0019
Canle, L.M., **08**-0081
Cann, P.F., **17**-0046
Cannizzaro, C.E., **03**-0066, **15**-0267
Cannizzo, L.F., **16**-1347
Cannon, J.F., **15**-0354, **15**-1614
Cano, A.C., **16**-2063
Canonne, P., **16**-0517, **16**-0953, **16**-1935
Cant, P.A.E., **15**-2232
Cantacuzène, J., **16**-0285
Cantagalli, G., **15**-1167
Cantello, B.C.C., **19**-0438
Cantlin, R.J., **12**-0091
Cantone, A., **16**-2143
Cantow, H., **04**-0290
Cantrill, S.J., **03**-0185, **03**-0186
Cantu, A.A., **13**-0747
Cao, C., **15**-0352, **16**-1433
Cao, G.-Q., **16**-1081
Cao, P., **10**-0978, **15**-0775
Cao, R., **15**-1125
Cao, W., **16**-1172
Cao, Y., **05**-0369
Cao, Y.-Q., **10**-0627, **10**-1788
Capan, E., **16**-1422
Capdevielle, P., **11**-0539, **19**-0279, **19**-0436
Capitò, E., **10**-1495
Capitosti, G.J., **05**-0351
C? aplar, V., **04**-0146, **15**-0597
Caple, R., **15**-2024
Capobianco, A.M., **17**-0092
Capon, B., **02**-0393, **02**-0402, **10**-0102, **10**-0420, **10**-0534, **12**-0097, **16**-0027, **16**-0032
Caporusso, A.M., **15**-0363
Capozzi, F., **15**-1607
Capozzi, G., **15**-0021, **15**-1607, **15**-1845, **19**-0791, **19**-0849
Cappelli, F.P., **06**-0086
Capperucci, A., **15**-1068, **16**-0217
Capponi, M., **02**-0381, **02**-0412, **15**-0215
Capraro, D., **15**-1526

Caprentier, J.-F., **13**-0626
Capretta, **13**-0491
Capson, T.L., **18**-0280
Caputo, J.A., **19**-0410
Caputo, R., **10**-1151, **16**-0147, **17**-0199
Caputo, T.D., **16**-0785
Capwell, R.J., **04**-0378
Caramella, P., **15**-0080, **15**-1946, **18**-0590
Carballares, S., **16**-1239
Carballeira, J.D., **19**-1022
Carboni, B., **12**-0518, **16**-0703
Carda, M., **16**-0996
Cardamone, R., **12**-0261
Cardellicchio, C., **16**-1929
Cardellina, J.H.I., **18**-0204
Cardenas, R., **10**-0232
Cárdenas, D.J., **12**-0276, **15**-0818
Cardi, N., **19**-1419
Cardillo, G., **15**-1099, **15**-1317, **15**-1584, **19**-0010, **19**-0071, **19**-0090, **19**-0098, **19**-0259, **19**-0387, **19**-0417, **19**-0455, **19**-0695, **19**-0732
Cardin, D.J., **18**-0837
Cardinale, G., **19**-0057, **19**-0352
Cardomone, R., **13**-0471
Cardona, F., **17**-0449, **19**-0767, **19**-1231
Cardona, L., **16**-1528
Cardona, R., **15**-2117
Cardoso, S.P., **11**-0119
Carducci, M., **15**-1889
Carenzi, D., **13**-0228
Caress, E.A., **17**-0090
Carey, E., **17**-0052
Carey, F.A., **04**-0131, **10**-0060, **17**-0342, **19**-1345
Carey, J.G., **13**-0712
Cargill, R.L., **15**-2242, **18**-0467
Cargioli, J.D., **08**-0023
Cargle, V.H., **18**-0590
Carhart, R.E., **04**-0129
Cariou, K., **15**-0834
Carles, J., **19**-0379
Carless, H.A., **07**-0044
Carless, H.A.J., **15**-1721, **16**-2083, **16**-2083, **16**-2084
Carlier, P.R., **04**-0193, **05**-0195, **08**-0210, **15**-1826
Carlin, R.B., **18**-0744
Carlone, A., **10**-0931
Carloni, S., **19**-0532
Carlqvist, P., **18**-0352
Carlsen, P., **10**-0766
Carlsen, P.H.J., **11**-0280, **14**-0441, **19**-0590
Carlsmith, L.A., **13**-0038, **13**-0079
Carlson, B.A., **18**-0426
Carlson, R., **15**-0499, **15**-2039, **16**-0289, **16**-0290, **19**-1791
Carlson, R.G., **15**-1585, **15**-2080
Carlson, R.M., **17**-0361
Carlson, S.C., **10**-1482, **19**-1531, **19**-1531
Carlson, T.A., **01**-0013
Carlsson, D.J., **14**-0164
Carman, R.M., **10**-1054
Carmeli, M., **10**-1003
Carmichael, A.J., **13**-0415
Carmichael, G., **17**-0504
Carmody, M.J., **02**-0172, **15**-2232
Carnahan Jr., J.C., **05**-0067, **17**-0334
Carnahan, E., **07**-0040
Carneiro, J.W., **10**-0206
Carneiro, J.W. de M., **10**-0208
Carnell, A.J., **04**-0199, **15**-1771
Carninji, J.J., **15**-0807
Caro, B., **19**-0951, **19**-1060
Caron H., **16**-0517
Caron M., **10**-0496, **15**-1564
Caron, S., **13**-0591
Caronna, T., **14**-0344, **14**-0347
Caroon, J.M., **16**-1709
Carothers, W.H., **19**-1174
Carpenter, B.K., **02**-0217, **02**-0218, **06**-0030, **15**-2402, **18**-0502, **18**-0562, **18**-0669
Carpenter, G.B., **05**-0191, **10**-0342
Carpenter, J.G.D., **01**-0087
Carpenter, T.C., **10**-1191
Carpentiere, J.-F., **13**-0627
Carpino, L.A., **17**-0357
Carpita, A., **10**-0790, **13**-0473, **13**-0536
Carr, C.S., **13**-0782
Carr, D.B., **15**-1150
Carr, G., **18**-0359
Carr, M.D., **12**-0072
Carr, R.V.C., **15**-1997
Carrasco, M.C., **19**-1438
Carrasco, N., **08**-0083
Carrasquillo, A., **18**-0346
Carrea, G., **15**-1758, **19**-0759, **19**-0824
Carreaux, F., **16**-0703
Carrée, F., **10**-0925
Carreira, E.M., **15**-0345, **15**-0591, **15**-1939, **16**-0551, **16**-0552, **16**-0758, **16**-0760, **16**-0888, **16**-0928, **19**-1056
Carreira, L.A., **04**-0385
Carreño, M.C., **11**-0268, **19**-1497
Carretero, J.C., **10**-0487, **10**-1454, **12**-0262, **13**-0358, **15**-1070, **15**-1129, **15**-1418, **15**-2063, **15**-2148, **16**-0687, **16**-0688
Carreyre, H., **11**-0536
Carrick, P.G., **05**-0399
Carrié, D., **15**-2305
Carrié, R., **12**-0518
Carrigan, .D., **16**-1671
Carrigan, M.D., **16**-0172
Carrillo, J.R., **07**-0121
Carrillo, J.R., **10**-0973
Carringan, M.D., **10**-0544
Carrington, A., **15**-0543
Carrión, A.E., **18**-0123
Carriuolo, J., **16**-1846
Carroll, A.R., **19**-1713
Carroll, F.I., **11**-0488
Carroll, F.I., **15**-0552
Carroll, M.A., **13**-0407, **13**-0492
Carroll, M.F., **18**-0673
Carroll, P., **16**-0646
Carroll, P.J., **10**-1454, **15**-2061, **19**-0823
Carroll, T.X., **02**-0056, **08**-0171
Carrupt, P., **15**-2238
Carruthers, W., **04**-0494, **10**-1575, **15**-0401, **15**-0961, **15**-1932, **15**-1980, **15**-2166, **18**-0864
Čársky, P., **08**-0170
Carson, A.S., **04**-0234
Carson, F.W., **18**-0737
Carson, K.G., **16**-0362
Carson, M.W., **15**-0878
Carson, M.W., **15**-1226
Carson, R.J., **11**-0332
Carswell, E.L., **16**-1107
Cartaya-Marin, C.P., **16**-1483
Carter Jr., T.P., **19**-0361
Carter, C., **16**-1021
Carter, C.A.G., **12**-0533, **13**-0628
Carter, D.S., **12**-0352, **13**-0652
Carter, E.A., **18**-0091
Carter, G.E., **10**-0434, **10**-0437, **10**-0438, **16**-1512
Carter, J.C., **17**-0247
Carter, J.V., **10**-0077
Carter, P., **10**-0123, **10**-0134
Carter, P.L., **16**-2113
Carter, R.E., **06**-0074
Carter, R.L., **04**-0186, **15**-0004
Carter, T.L., **15**-0033
Carter, W.L., **18**-0170

Carter, W.P.L., **19**-0385, **19**-0386
Carter, L.G., **10**-1730
Cartledge, F.K., **12**-0001
Caruso, A.J., **13**-0134
Caruso, T.C., **03**-0102, **10**-1649
Carvalho, E., **12**-0709
Carver, D.R., **13**-0052
Carver, J.R., **19**-0470
Casaarini, D., **04**-0416
Casadei, M.A., **12**-0752
Casadevall, A., **10**-0083
Casadevall, E., **10**-0083
Casado, A.L., **12**-0280
Casado, F., **13**-0066
Casado, J., **12**-0703
Casagrande, B., **16**-1177, **18**-0193
Casanova Jr., J., **14**-0417
Casanova, J., **04**-0169, **04**-0387, **04**-0436, **16**-1571, **17**-0272, **17**-0450, **19**-0442
Casapieri, P., **10**-0084
Casares, A., **15**-1176
Casarini, D., **04**-0059, **04**-0060, **04**-0087, **04**-0315
Casarrubios, L., **15**-1430, **15**-1436, **15**-1438, **15**-1441, **15**-1900
Casas, J., **16**-0414, **16**-1036, **19**-0384
Casati, S., **16**-1687
Case, R., **18**-0502
Caselli, A., **16**-0573
Čásenský, B., **19**-0010
Caserio, M.C., **10**-0635, **15**-0106, **15**-0112, **15**-1853, **15**-1914, **15**-2222
Casewit, C.J., **04**-0397
Casey, C.J., **18**-0778
Casey, C.P., **07**-0049, **10**-1436, **12**-0076, **14**-0377, **14**-0378, **15**-1170, **18**-0836
Casey, M., **10**-1487, **16**-0687
Casi, G., **10**-0883
Casini, G., **11**-0334
Casiraghi, G., **11**-0385, **11**-0388, **11**-0491, **16**-0984
Caskey, D.C., **08**-0079
Casnati, G., **11**-0385, **11**-0388, **11**-0491, **11**-0497, **12**-0118
Cason, J., **10**-1072, **16**-0836, **16**-0956, **16**-1901, **16**-1929
Caspar, M.L., **18**-0053
Caspi, E., **19**-0408
Cassar, L., **10**-1841, **13**-0281, **13**-0387, **13**-0598, **15**-1381, **15**-2201, **18**-0839
Casselman, A.A., **18**-0250
Cassidy, J., **15**-0656
Cassimatis, D., **11**-0453
Cassis, F.A., **11**-0367
Casson, A., **04**-0240
Cast, J., **18**-0412
Castagnetti, E., **11**-0040
Castaldi, G., **18**-0193, **19**-0963
Castañer, J., **05**-0256, **16**-1384
Castanet, A.-S., **11**-0295, **13**-0554
Castanet, Y., **13**-0626, **13**-0627, **15**-1381, **15**-1454
Castaño, A.M., **10**-1472
Castedo, L., **14**-0310, **15**-0827, **15**-2389, **18**-0782, **18**-0791
Castejon, H., **04**-0321
Castellano, G., **19**-0515
Castellano, R.K., **03**-0071
Castellino, S., **16**-0492, **16**-0743
Castellnou, D., **16**-0689
Castello, C., **16**-1036
Castells, J., **16**-1496
Castillon, S., **18**-0278, **10**-1459, **15**-1481
Castle, G.H., **10**-0604
Castle, K., **15**-0275
Castle, L., **14**-0204
Castro, A., **12**-0700, **12**-0703
Castro, A.M.M., **10**-1800, **15**-1334, **15**-2150, **16**-0803, **18**-0653
Castro, B., **10**-0908, **12**-0590, **12**-0590
Castro, B.R., **10**-1097
Castro, C., **02**-0339
Castro, C.E., **13**-0534, **16**-1898
Castro, E.A., **13**-0110, **16**-0104
Castro, I., **19**-0120
Castro, I.G., **15**-0331, **15**-0351
Castro, J.C., **07**-0118
Casu, A., **19**-0845
Casy, G., **15**-0606, **19**-1022
Catak, S., **18**-0568
Catalan, J., **08**-0228, **10**-0282
Catalán, J., **08**-0125, **08**-0131
Catalane, D.B., **10**-0995
Cate, L.A., **10**-0589, **16**-2171
Catelani, G., **15**-0125
Catellani, M., **13**-0228, **13**-0508
Cathcart, R.C., **18**-0250
Catheline, A., **16**-1999
Catino, A.J., **19**-0578
Cativiela, C., **15**-2038, **15**-2063
Cattania, M.G., **10**-0242
Catteau, J.-P., **10**-0555
Catto, B.A., **18**-0391
Caubere, P., **10**-0262, **10**-1243, **13**-0080, **13**-0462, **13**-0573, **13**-0613, **14**-0401, **19**-0010, **19**-1580
Cauble, D.F., **16**-0701, **16**-0704, **16**-0720
Cauci, S., **16**-1712
Caughlan, C.N., **16**-1302
Caulier, T., **07**-0082
Caulton, K.G., **15**-1904, **15**-2406
Cava, M.P., **02**-0208, **16**-0213, **17**-0517, **18**-0513
Cavaleiro, J.A.S., **07**-0121
Cavallo, L., **15**-1832, **18**-0833
Cavazza, M., **04**-0063, **04**-0155, **17**-0116
Cavazzini, M., **19**-0185, **19**-1776
Cave G.W.V., **09**-0084, **09**-0120
Cavé, A., **10**-1051, **16**-0402
Cavicchioni, G., **10**-0502
Cawley, J.J., **10**-0526
Cawse, J.N., **10**-1813
Cayen, C., **12**-0325
Cayón, E., **13**-0064
Cazaux, M., **12**-0303
Cazeau, P., **12**-0316, **12**-0320
Cazes, B., **15**-1445, **15**-1612
Cazes, J., **13**-0734, **14**-0105
Cazianis, C.T., **18**-0192, **19**-0974
Cazin, B., **14**-0231
Cazin, C.S.J., **13**-0473
Ceasar, G.P., **02**-0228
Ceccacci, F., **04**-0052
Ceccarelli, C., **03**-0025
Ceccherelli, P., **10**-0563, **19**-0668
Cecchetto, A., **19**-0181, **19**-1047
Ceccon, A., **10**-0084, **17**-0077
Cee, V.J., **04**-0140
Cefalo, D.R., **18**-0822
Čeković, Z., **14**-0206, **14**-0210, **14**-0211, **14**-0212, **19**-0006, **19**-0064
Celani, P., **18**-0847
Celewicz, L., **18**-0482
Cella, J.A., **10**-1510
Cellura, R.P., **15**-2282
Cenini, S., **12**-0748, **19**-1748
Cense, J.M., **18**-0118
Ceppi, E., **01**-0044
Ceré, V., **04**-0470, **18**-0727, **16**-0926
Cereda, E., **16**-1258
Cerero, S. de la M., **11**-0471
Cereti, A., **15**-0899
Cerezo, A. de F., **10**-0791
Cerezo, A.d.F., **10**-1400
Cerfontain, H., **08**-0028, **08**-0029, **11**-0199, **11**-0203, **11**-0204, **11**-0205, **11**-0206,

11-0207, **11**-0208, **11**-0210, **11**-0626, **11**-0627, **11**-0631, **13**-0774
Cerichelli, G., **11**-0654, **13**-0480, **16**-0163
Cerioni, G., **03**-0125
Cermola, F., **15**-1941
Černý, M., **19**-0880, **19**-1066, **19**-1507
Cerreta, F., **16**-0217
Cerritelli, S., **12**-0083
Cerreti, A., **14**-0071
Ceruti, M., **16**-1284
Cerveau, G., **12**-0593
Červený, L., **15**-0401, **19**-0956
Cervera, M., **13**-0066
Červinka, O., **10**-1674
Cesa, M.C., **15**-1170
César, V., **19**-1046
Cesare, V., **11**-0253
Cesati III, R.R., **15**-0868
Ceschi, M.A., **16**-0233
Cessac, J., **02**-0210
Cessna, A.J., **18**-0024
Cesta, M.C., **16**-1865
Cesti, P., **04**-0196
Cetinkaya, B., **18**-0837
Cevasco, G., **16**-1571
Cevidalli, G., **18**-0493
Cha, D.Y., **15**-1660
Cha, H.T., **14**-0356
Cha, J.H., **10**-1549
Cha, J.K., **11**-0060, **15**-1688
Cha, J.S., **19**-0992, **19**-1096, **19**-1104, **19**-1105, **19**-1107, **19**-1109, **19**-1113, **19**-1114, **19**-1183, **19**-1642
Cha, K.L., **12**-0356
Cha, Y., **05**-0335
Chaabouni, R., **12**-0223
Chabardes, P., **12**-0082
Chabaud, B., **10**-0789, **19**-0473, **19**-0474
Chaboche, C., **10**-1343
Chadha, P., **04**-0304
Chadwick, D., **11**-0423
Chadwick, D.J., **03**-0059
Chadwick, S.T., **13**-0642, **13**-0643
Chafetz, H., **12**-0303
Chahal, N., **15**-0164
Chahboun, R., **15**-0578, **16**-1618, **17**-0155, **19**-0316, **19**-0355, **19**-0940
Chai, Y., **18**-0680
Chaiez, G., **12**-0499
Chaigne, F., **15**-1975
Chaiken, I.N., **16**-1823
Chaikin, S.W., **19**-0931
Chaikovskii, V.K., **11**-0294
Chaisupakitsin, M., **11**-0506
Chakrabarti, D., **15**-1217
Chakrabarti, P., **04**-0295
Chakrabartty, S.K., **12**-0671
Chakraborti, A.K., **10**-0720, **10**-0923, **10**-0926, **16**-0324, **16**-1529, **16**-1618, **19**-0411
Chakraborty, A., **16**-1606, **16**-1750
Chakraborty, R., **15**-0191, **19**-0937
Chakraborty, U.R., **18**-0838
Chakrapani, H., **15**-0818, **15**-0820
Chalais, S., **18**-0183
Chalfont, G.R., **14**-0329
Chalk, A.J., **13**-0423, **15**-1477
Challis, B.C., **10**-0972, **11**-0110, **11**-0162, **11**-0163, **12**-0699, **12**-0702, **12**-0704, **13**-0687, **13**-0696, **16**-0385, **16**-1588, **16**-1868, **18**-0879, **19**-0748, **19**-1486
Challis, J.A., **10**-0972, **12**-0699, **16**-0385, **16**-1868, **19**-1486
Challis, J.C., **16**-1588
Challis, M.S., **16**-1744
Chaloner, P.A., **15**-0427, **15**-0972
Chaly, T., **16**-0147
Chamberlain, N.C., **19**-1410
Chamberlain, P., **15**-0187
Chamberlain, P.H., **15**-0016
Chamberlin, A.R., **17**-0275, **17**-0276
Chamberlin, R.M., **15**-0584
Chambers, D.J., **19**-1569
Chambers, E.J., **04**-0345
Chambers, M.R.I., **13**-0282
Chambers, R., **16**-2108
Chambers, R.A., **10**-1185
Chambers, R.D., **11**-0314, **12**-0135, **13**-0075, **15**-0070, **15**-0072, **15**-0248, **15**-0317, **16**-0454
Chambers, V.C., **10**-0316
Chambers, W.T., **10**-0191
Chambers-Asman, D.M., **12**-0362
Chambron, J.-C., **03**-0181, **03**-0201
Chamness, J.T., **18**-0742
Chamorro, E., **15**-1545
Chamot, E., **02**-0173
Champagne, P., **19**-0654
Chan, A.S.C., **10**-1453, **10**-1454, **15**-0413, **15**-0519, **15**-0604, **15**-0613, **15**-1125, **15**-1133, **15**-1136, **15**-1138, **15**-1147, **15**-1480, **15**-1509, **15**-1844, **15**-1902, **16**-0549, **16**-0680, **16**-0687, **16**-0691, **18**-0154, **19**-1028, **19**-1031, **19**-1035, **19**-1042
Chan, C., **16**-1621
Chan, D.M.T., **10**-0977
Chan, E.D., **18**-0272
Chan, H., **04**-0494
Chan, H.-L., **19**-0534
Chan, K.-Y., **15**-1903
Chan, K.S., **13**-0242, **15**-1885
Chan, M.C.W., **19**-0618
Chan, P.-M., **19**-0746
Chan, R.P.K., **19**-1131
Chan, T., **02**-0243, **16**-1232, **18**-0394
Chan, T.-H., **10**-1225, **16**-0591, **16**-1906
Chan, T.-L., **04**-0081
Chan, T.C., **16**-0648
Chan, T.H., **10**-0505, **10**-0805, **10**-0818, **12**-0477, **15**-1762, **15**-1803, **16**-0147, **16**-0591, **16**-0594, **16**-0602, **16**-0639, **16**-0648, **16**-0655, **16**-0660, **16**-0874, **16**-0880, **16**-0881, **16**-1195, **16**-1235, **16**-1667, **19**-0502, **19**-1598
Chan, T.Y., **15**-2082
Chan, W.-K., **15**-1746, **15**-1773
Chan, W.H., **11**-0092, **16**-1811, **17**-0234
Chan, W.L., **15**-1147, **16**-0549
Chan, W.Y., **16**-1240
Chanan, H., **10**-1256
Chance, J.M., **02**-0072
Chand, P.K., **16**-0065, **16**-0749, **16**-1531
Chanda, B.M., **15**-1898
Chandake, S.I., **16**-1701
Chandler, M., **08**-0147
Chandler, W.D., **08**-0036, **19**-0740
Chandra, A.K., **03**-0033
Chandra, K.L., **11**-0341, **16**-0171
Chandra, P.P., **04**-0454
Chandra, S., **01**-0077
Chandraiah, L., **19**-1237
Chandrakumar, K.R.S., **18**-0212
Chandrasakar, R., **13**-0770
Chandrasekar, S., **19**-1453
Chandrasekaran, S., **10**-0834, **11**-0322, **15**-0192, **15**-0193, **15**-0665, **15**-1844, **16**-0267, **16**-1668, **16**-1719, **16**-1741, **19**-0560, **19**-0576, **19**-0731, **19**-0735, **19**-0938, **19**-0948, **19**-1658

Chandrasekhar, J., **05**-0101, **05**-0124, **10**-0017, **10**-0021, **10**-0184, **16**-0007, **18**-0002
Chandrasekhar, M., **10**-0962, **19**-0167
Chandrasekhar, S., **10**-0683, **10**-0958, **10**-1123, **13**-0405, **15**-0403, **15**-0438, **16**-0093, **16**-0355, **16**-0744, **16**-0780, **16**-0784, **16**-1181, **16**-1404, **16**-1618, **18**-0289, **18**-0319, **18**-0333, **19**-0692, **19**-1117, **19**-1237, **19**-1521, **19**-1555
Chandrasekharan, J., **15**-0653, **19**-1059
Chandrashekar, G., **15**-0403
Chandrashekar, G., **15**-0438
Chandrashekar, V., **19**-1032, **19**-1035
Chandrassekhar, S., **18**-0326
Chaney, M.O., **12**-0224
Chang, C., **19**-0452
Chang, C.-L., **18**-0152
Chang, C.-W., **16**-1438
Chang, C.J., **08**-0064
Chang, C.T., **13**-0465
Chang, D., **19**-0544, **19**-0545, **19**-0546
Chang, D.-H., **15**-0930
Chang, D.C.K., **10**-0305
Chang, D.W.L., **07**-0054
Chang, F.-R., **16**-1671
Chang, F.C., **16**-2151
Chang, G., **10**-1099
Chang, H.-M., **13**-0383, **13**-0432, **15**-0933, **16**-0732
Chang, H.-T., **15**-1864
Chang, H.S., **19**-0231
Chang, H.W., **02**-0155, **02**-0198, **02**-0236
Chang, J., **11**-0092
Chang, J.C., **18**-0495
Chang, J.S., **16**-2108
Chang, K., **12**-0717
Chang, K.Y., **16**-1994
Chang, L.-B., **15**-1270
Chang, L.W., **11**-0111
Chang, L.Y., **15**-1679
Chang, M.H., **10**-1516, **10**-1549
Chang, S., **10**-0063, **10**-0178, **10**-1471, **13**-0567, **15**-1152, **15**-1177, **15**-1374, **15**-1406, **16**-0599, **17**-0436, **18**-0788, **18**-0789, **19**-0120
Chang, S.-Y., **15**-1218
Chang, T.C.T., **10**-1634
Chang, V.H., **15**-1198
Chang, V.S., **19**-0388, **19**-0403
Chang, Y., **01**-0011, **15**-0422, **16**-1155
Chang, Y.M., **16**-0352
Chang, Y.W., **19**-0250
Chanon, F., **05**-0313
Chanon, M., **05**-0313, **10**-0090, **10**-0092, **10**-0443, **13**-0052
Chanson, E., **16**-2004
Chanumathi, N., **10**-0927
Chanysheva, I.R., **10**-0278
Chao, B., **17**-0365
Chao, C.S., **13**-0465
Chao, D.-Y., **15**-1507
Chao, I., **10**-0275
Chao, L., **16**-0524, **16**-0963
Chao, L.C.F., **19**-0583
Chao, W., **18**-0817
Chao, Y.L., **10**-1179
Chaouchi, M., **13**-0109
Chaouk, H., **15**-1493
Chapaneri, K., **16**-0138
Chapdelaine, M.J., **15**-1090
Chapleo, C.B., **10**-0228
Chapleur, Y., **15**-1225
Chaplinski, V., **05**-0320
Chapman, C.J., **11**-0423, **15**-1024, **15**-1132, **19**-1155
Chapman, D., **15**-1176
Chapman, K.T., **10**-1640, **15**-2063, **16**-1144, **19**-0132, **19**-0241, **19**-1056
Chapman, N.B., **08**-0136, **08**-0149, **09**-0016, **09**-0019, **09**-0020, **09**-0038, **09**-0058, **09**-0061, **09**-0078, **10**-0350, **10**-0443, **10**-0495
Chapman, O.L., **02**-0212, **04**-0320, **04**-0477, **04**-0479, **05**-0388, **07**-0044, **13**-0047, **15**-2235, **16**-2083, **18**-0227, **18**-0467
Chapman, R.D., **12**-0709
Chapman, R.G., **03**-0173
Chapman, R.W., **12**-0469
Chappell, I.P., **15**-0970
Chapuis, C., **10**-1640
Chaquin, P., **11**-0226, **15**-2102
Chardon, C., **15**-2406
Charette, A.B., **10**-0705, **15**-0489, **15**-2337, **15**-2339, **15**-2340, **15**-2342, **15**-2345, **16**-0222, **16**-0223, **16**-1704
Charewicz, W.A., **03**-0107
Charkraborti, A.K., **10**-0925
Charles, G., **10**-1524, **16**-0356
Charles, K.R., **08**-0118
Charles, N.R., **15**-2438
Charles, R., **04**-0209
Charleson, D.A., **19**-0479
Charlton, J.L., **07**-0054, **15**-2002, **15**-2061
Charman, H.B., **12**-0017
Charnsangavej, C., **15**-2298
Charonnat, J.A., **15**-1069
Charpentier, P., **10**-0952
CharpentierMorize, M., **10**-0295, **10**-0296, **10**-0485, **11**-0391, **18**-0208
Charpiot, B., **13**-0581, **10**-0920
Charruault, L., **15**-0977
Charton, B., **14**-0107
Charton, M., **04**-0421, **05**-0068, **09**-0016, **09**-0031, **09**-0032, **09**-0038, **09**-0039, **09**-0041, **09**-0047, **09**-0051, **09**-0056, **09**-0060, **09**-0064, **09**-0068, **09**-0070, **09**-0071, **09**-0078, **09**-0080, **10**-0282, **13**-0027, **14**-0107, **15**-0128, **15**-0628, **17**-0088
Charushin, V.N., **13**-0638
Chary, K.P., **10**-1140, **19**-1208, **19**-1257, **19**-1259, **19**-1547, **19**-1640
Chase, C.R., **10**-0232
Chase, E., **15**-1268
Chassaing, C., **16**-1774
Chassaing, G., **05**-0138
Chassin, C., **19**-1338
Chastrette, M., **10**-0443, **10**-1134, **16**-0516, **16**-0954
Chataigner, I., **16**-1417
Chatani, N., **10**-1196, **10**-1862, **11**-0332, **11**-0414, **11**-0463, **12**-0543, **13**-0532, **15**-0755, **15**-0777, **15**-0830, **15**-0831, **15**-0920, **15**-1473, **15**-2443, **16**-1977, **16**-1978, **19**-1508
Chateauneuf, J., **05**-0297
Chatgilialoglu, C., **05**-0310, **10**-1209, **14**-0018, **14**-0019, **14**-0081, **15**-0067, **15**-0752, **15**-1196, **15**-1219, **17**-0138, **19**-1403, **19**-1419
Chattaraj, P.K., **08**-0155, **15**-2104
Chattaway, F.D., **14**-0010
Chatterjee, A., **19**-1672
Chatterjee, A.K., **10**-0554, **16**-1528, **18**-0778, **18**-0781
Chatterjee, B.G., **10**-1599
Chatterjee, S.K., **19**-1491
Chatterton, C., **10**-1457
Chattopadhyay, A., **16**-0825
Chattopadhyay, S., **19**-1022, **19**-1708, **19**-1716
Chattopadhyaya, J.B., **16**-0249, **18**-0330
Chatziiosifidis, I., **10**-1797
Chatzopoulos, M., **16**-1573
Chauder, B., **10**-1284, **13**-0641
Chaudhari, B.A., **19**-0155

Chaudhari, R.V., **13**-0203, **15**-1378, **19**-1186
Chaudhari, S.S., **10**-1067, **17**-0430
Chaudhary, K., **16**-0567
Chaudhary, S., **10**-1624
Chaudhary, S.S., **10**-0964
Chaudhuri, N., **05**-0377
Chaudhuri, P., **03**-0115, **14**-0321
Chaudhuri, S.K., **10**-1587
Chaudjuri, S.K., **19**-0683
Chaudret, B., **10**-1459
Chauhan, K., **18**-0642
Chauhan, K.K., **15**-2131
Chauhan, P.M.S., **10**-0861, **11**-0225
Chauhan, S., **17**-0368, **19**-0924
Chauhan, S.M.S., **13**-0105, **15**-1763, **19**-0072
Chaumeil, H., **13**-0521
Chauncy, B., **13**-0741
Chauret, D.C., **10**-1541
Chavan, S.P., **10**-0569, **15**-2007, **16**-0051, **16**-0243, **16**-1679, **16**-1701, **18**-0212, **19**-0703
Chavant, P., **16**-0817
Chavant, P.Y., **16**-0907, **16**-0928, **16**-1456
Chavarot, M., **16**-1456
Chavasiri, W., **19**-0612
Chavez, D.E., **15**-2149
Chawla, H.P.S., **15**-0436
Chawla, R., **14**-0171
Chayangkoon, P., **04**-0088
Chaykovsky, M., **16**-1273, **16**-1377, **16**-1403
Che, B.-H., **10**-1788
Che, C.-M., **15**-1746, **15**-1773, **15**-1903, **15**-2295, **19**-0549, **19**-0550, **19**-0618, **19**-0746
Che, D., **04**-0161
Chebolu, V., **14**-0118
Cheboub-Benchaba, K., **15**-2003
Chechik, V.O., **10**-0493
Cheema, Z.K., **18**-0100
Cheeseman, J.R., **04**-0015, **04**-0118
Cheeseman, J.R., **04**-0278
Cheikh, R.B., **12**-0223
Chekhuta, V.G., **09**-0048
Chekulaeva, I.A., **15**-0047, **15**-0348
Chelius, E.C., **05**-0057, **15**-0139
Chellamani, A., **19**-0831
Chellé-Regnaut, I., **19**-0122, **19**-0123
Chemat, F., **16**-0122, **16**-1577
Chemla, F., **05**-0139, **16**-0389, **19**-0508
Chen, A., **05**-0103, **08**-0062, **15**-1394
Chen, B., **13**-0413, **19**-0501, **19**-1633
Chen, B.-L., **07**-0051
Chen, C., **11**-0073, **13**-0012, **13**-0326, **13**-0430, **16**-0549, **16**-0552, **16**-0811, **19**-1020
Chen, C.-T., **03**-0200, **08**-0169
Chen, C.-y., **13**-0236, **13**-0272
Chen, C.H.-T., **13**-0475
Chen, D., **15**-1896, **16**-0798
Chen, D.-J., **16**-0082
Chen, E.N., **19**-0444
Chen, F., **19**-0402
Chen, F.-E., **16**-0095, **16**-0323, **16**-0342, **18**-0798, **19**-1627
Chen, F.-X., **16**-1433, **16**-1438
Chen, F.M.F., **18**-0722
Chen, G., **05**-0260, **10**-1453, **10**-1454, **16**-0549, **18**-0362
Chen, G.-F., **05**-0326
Chen, H., **10**-1421, **10**-1453, **13**-0528, **15**-0428, **15**-0604, **15**-0834, **15**-1445, **15**-1691, **15**-1885, **15**-2301, **19**-1028
Chen, H.E., **16**-0318
Chen, H.G., **16**-2056
Chen, H.K., **15**-1080
Chen, H.Y., **18**-0758, **18**-0762
Chen, J., **03**-0001, **04**-0269, **10**-0801, **10**-1608, **13**-0365, **15**-0578, **15**-1405, **15**-1456, **15**-1773, **16**-1995, **19**-0688, **19**-0767, **19**-1533
Chen, J.S., **15**-0967
Chen, J.-P., **16**-0631
Chen, J.-X., **13**-0628
Chen, J.-x., **12**-0533
Chen, J.C., **15**-0649
Chen, K., **04**-0400, **15**-1666, **16**-0777, **16**-0788
Chen, K.S., **05**-0281, **14**-0044, **18**-0081
Chen, K.X., **15**-1826
Chen, L., **04**-0178, **07**-0118, **13**-0206, **15**-0789, **15**-1153, **15**-1271, **16**-0297
Chen, M., **10**-1857, **15**-2409
Chen, M.-F., **16**-0094
Chen, M.C., **16**-1511, **16**-1558
Chen, M.H., **19**-1077
Chen, M.S., **19**-0539
Chen, N., **15**-0164
Chen, N.Y., **11**-0052
Chen, P., **10**-0864, **15**-1223, **18**-0833
Chen, Q., **10**-1309, **13**-0362, **16**-0908, **19**-1374
Chen, R., **02**-0120, **15**-1741, **16**-0397, **16**-1612, **19**-1263
Chen, R.H.K., **16**-1251
Chen, R.S., **02**-0272
Chen, S., **15**-0604, **16**-1862
Chen, S.-F., **16**-1784
Chen, S.-L., **02**-0281, **16**-1111
Chen, S.M., **15**-1480
Chen, T., **05**-0216, **05**-0350, **15**-1679, **19**-0831
Chen, T.-H., **03**-0005
Chen, W., **10**-1457, **13**-0496, **13**-0571, **15**-1488, **15**-1843
Chen, W.M., **18**-0134
Chen, X., **08**-0100, **08**-0214, **14**-0239, **19**-0538, **19**-1032
Chen, X.-M., **16**-0691, **16**-1012
Chen, Y., **02**-0367, **12**-0087, **13**-0272, **15**-1331, **15**-1759, **16**-1371, **16**-1626, **16**-1627, **16**-1947, **19**-0576
Chen, Y.-C., **13**-0401, **15**-0519, **15**-0575, **19**-1042
Chen, Y.-J., **16**-1092, **19**-0346, **19**-0804
Chen, Y.-Y., **03**-0123
Chen, Y.J., **16**-0875, **18**-0362
Chen, Z., **02**-0354, **16**-0552, **16**-0552, **16**-1644
Chen, Z.-C., **10**-0701, **10**-0869, **10**-1425, **10**-1475, **11**-0188, **11**-0241, **11**-0499, **13**-0145, **13**-0320, **13**-0356, **16**-0082, **16**-1170, **16**-1279, **16**-1773, **19**-0209, **19**-0528
Chen, Z.-N., **04**-0191
Chen, Z.-R., **18**-0820
Chen, Z.C., **13**-0437
Chen,M., **15**-1403
Chen,Y., **11**-0358
Chen, M.-F., **16**-0063
Chendke, P.K., **07**-0067
Chênevert, R., **11**-0052, **11**-0594
Chênevert, R., **19**-0922
Cheng, A.K., **18**-0642
Cheng, C., **16**-0278
Cheng, C.-c., **08**-0109
Cheng, C.-H., **13**-0383, **13**-0432, **13**-0553, **15**-0283, **15**-0761, **15**-0933, **15**-1145, **15**-2373, **15**-2381, **15**-2387, **16**-0577, **16**-0732
Cheng, C.H., **13**-0259, **13**-0465
Cheng, D., **15**-0840, **15**-0979
Cheng, D.-P., **16**-0082
Cheng, G., **16**-1371
Cheng, H.-S., **16**-0610
Cheng, H.N., **15**-0969

Cheng, J., **10**-0219, **13**-0179, **13**-0558, **13**-0571, **14**-0372
Cheng, J.-P., **01**-0102, **14**-0060, **16**-0767, **16**-0774, **16**-0777, **16**-1036
Cheng, J.P., **05**-0246
Cheng, K.-F., **16**-1074
Cheng, K.-m., **10**-0219
Cheng, K.-W., **19**-0618
Cheng, L., **10**-0285
Cheng, P., **08**-0108
Cheng, T., **15**-0654
Cheng, W., **13**-0471
Cheng, W.-C., **19**-0746
Cheng, X., **15**-0339
Cheng, Y., **16**-0323, **18**-0120
Cheng, Y.-H., **01**-0109
Cheng, Y.M., **12**-0354, **12**-0376
Chenier, J.H.B., **14**-0045, **14**-0218
Chenier, P.J., **10**-0151, **18**-0194
Chens, H., **15**-1691
Cheong, P.H.-Y., **16**-1029
Cheprakov, A.V., **11**-0287, **11**-0297
Cheramie, J., **16**-1021
Cherednichenko, L.V., **12**-0710
Cherepanov, I.A., **10**-1087
Chérest, M., **04**-0139
Cherkaoui, H., **19**-0222
Cherkasov, R.A., **16**-0213
Cherkasova, E.M., **16**-0031
Cherkinski, M., **15**-2023
Cherluck, R.M., **16**-0966
Chermprapai, A., **10**-1184
Chern, C., **10**-0743, **19**-0098
Chern, M.-S., **11**-0397
Cherng, C.-D., **15**-1218
Chernick, E.T., **17**-0325
Chernov, A.N., **15**-0280
Cherry, W., **07**-0019, **07**-0021
Chervin, I.I., **04**-0036, **04**-0039, **04**-0042
Chervin, I.T., **11**-0180
Cheskis, B.A., **19**-0091
Chesney, A., **15**-1285
Chesnokov, A.A., **16**-1391
Chesnokova, A.E., **16**-2066
Chesnut, D.B., **02**-0255
Chetri, A.B., **19**-0697
Chettle, S.J., **19**-1097
Chetverikov, V.P., **10**-1583
Cheung, A.W-H., **19**-1403
Cheung, C.K., **16**-0006
Cheung, H.K.Y., **14**-0097
Cheung, K.-K., **15**-0867, **15**-1768, **15**-1773
Cheung, M.F., **16**-1556
Cheung, Y., **14**-0194
Chevalier, P., **18**-0761
Chevallier, F., **19**-0905
Chevli, D.M., **10**-0114
Chevrier, B., **11**-0424, **11**-0454
Chhabra, B.R., **19**-0469, **19**-0471
Chhatriwalla, A., **16**-0591
Chhibber, M., **19**-0096
Chi, D.Y., **10**-0411, **10**-0501, **10**-1117, **11**-0640, **15**-1834, **19**-0260
Chi, Y., **16**-0344
Chi, Z., **16**-0649
Chia, L.H.L., **04**-0292
Chiacchiera, S.M., **13**-0013
Chiacchio, U., **16**-0049
Chianelli, D., **10**-1306, **13**-0103, **13**-0132, **13**-0132
Chiang, C., **18**-0231, **19**-0354, **19**-0371
Chiang, C.C., **02**-0258, **02**-0274
Chiang, G.C.H., **13**-0204
Chiang, J.P., **15**-1753
Chiang, S., **15**-0674
Chiang, Y., **02**-0383, **02**-0386, **02**-0388, **02**-0389, **08**-0057, **08**-0118, **10**-0530, **10**-0536, **10**-0571, **11**-0110, **12**-0084, **12**-0097, **12**-0100, **12**-0101, **15**-0025, **15**-0079, **15**-0215
Chiao, W., **17**-0027
Chiappe, C., **10**-0411, **11**-0242, **15**-0012, **15**-0014, **15**-0022, **15**-1515, **15**-1522, **15**-1524, **15**-1526
Chiara, J.L., **19**-1680
Chiarelli, R., **05**-0258
Chiarini, M., **11**-0654, **13**-0480, **16**-0163, **16**-0279
Chiarotto, I., **16**-0436
Chiba, K., **10**-0716, **11**-0328, **15**-0241, **15**-1061, **15**-1508, **19**-1375
Chiba, N., **10**-0584
Chiba, T., **10**-1558, **16**-1459
Chichilla, R., **16**-1786
Chick, J.E., **16**-0886
Chickos, J.S., **04**-0462
Chidambaram, N., **15**-0192, **19**-0576
Chidara, S., **16**-0616
Chiechi, R.C., **02**-0289
Chieffi, A., **10**-1635, **13**-0583, **13**-0587
Chieffi, G., **15**-2244
Chien, C.-T., **16**-1359, **16**-1360
Chien, Y.-Y., **12**-0459
Chiericato Jr., G., **19**-0579
Chiesa, A., **11**-0505
Chiev, K.P., **16**-0868
Chihal, D.M., **18**-0859
Chihara, T., **10**-0627, **10**-0636, **15**-0265, **16**-0260
Chikamatsu, H., **02**-0070
Chikami, Y., **15**-0174
Chikinev, A.V., **11**-0013
Childers Jr., W.E., **19**-0699
Childs, R.F., **02**-0348, **02**-0350, **02**-0351, **05**-0050, **07**-0044, **15**-2257, **18**-0540
Chilingaren, A.C.R., **18**-0178
Chimishkyan, A.L., **16**-1855
Chimni, S.S., **16**-0590, **16**-0592
Chin, C.-P., **10**-0440
Chin, C.S., **02**-0403
Chin, J., **16**-0018
Chinchilla, R., **16**-1784
Ching, C.B., **11**-0396
Ching, W., **16**-1445
Ching-Yun, C., **16**-0041
Chini, M., **10**-0663, **10**-0814, **10**-0954, **10**-1150
Chinn Jr., J.W., **05**-0152
Chinn, L.J., **14**-0214, **19**-0011, **19**-0693
Chinn, L.J.S., **19**-0453
Chinn, M.S., **12**-0352
Chiocconi, A.A., **10**-0868
Chiola, V., **10**-0291
Chiou, B.L., **18**-0440
Chirik, P.J., **15**-0629
Chirinko Jr., J.M., **10**-1690
Chirskaya, M.V., **15**-1574
Chisholm, J.D., **15**-1154, **16**-1652
Chisholm, M.H., **19**-1718, **19**-1725
Chistyakov, A., **14**-0139
Chitnavis, A., **19**-0112
Chittari, P., **15**-1694
Chittattu, G., **14**-0406, **19**-1589
Chitwood, J.L., **10**-0202, **16**-2113
Chiu, P., **16**-1074, **19**-1386
Chiu, R.-T., **15**-1246
Chiu, S.-H., **03**-0185, **03**-0187, **03**-0189
Chiurdoglu, G., **04**-0350, **03**-0180, **03**-0192, **04**-0261, **05**-0076
Chiusoli, G.P., **15**-1381
Chiusoli, G.P., **10**-1841
Chivers, T., **05**-0103, **08**-0062
Chivers, T., **12**-0586
Chizhov, B.A., **19**-0091
Chizhova, N.V., **16**-0258
Chloupek, F.J., **16**-0033
Chmurny, G.N., **12**-0013
Chmurzyński, L., **08**-0082, **19**-1021
Chng, S.-S., **16**-0610

Cho, B.P., **13**-0153
Cho, B.R., **17**-0093, **17**-0094
Cho, B.T., **16**-0359, **16**-0693, **19**-1016, **19**-1031, **19**-1078
Cho, C.-C., **16**-1359
Cho, C.-G., **11**-0171, **12**-0295, **16**-1743
Cho, C.-H., **10**-1489
Cho, C.-W., **16**-1975
Cho, C.H., **16**-1998
Cho, C.S., **10**-1500, **10**-1626, **13**-0328, **13**-0599, **15**-1159, **16**-2120
Cho, D.H., **15**-1203, **16**-1749, **19**-1403, **19**-1404, **19**-1470, **19**-1474
Cho, H.-N., **18**-0768
Cho, I.H., **19**-0137
Cho, I.S., **10**-1016
Cho, J.H., **10**-0858, **18**-0777
Cho, M.H., **11**-0613
Cho, M.S., **10**-1156, **16**-0554
Cho, S., **17**-0166
Cho, S.-D., **10**-0795, **19**-0523
Cho, S.H., **10**-0588, **10**-0694
Cho, Y., **18**-0274
Cho, Y.J., **16**-0351, **19**-1324, **19**-1751
Cho, Y.S., **10**-1194, **10**-1516, **10**-1549, **16**-0605, **19**-1188, **19**-1222, **19**-1512
Chobe, P., **18**-0402
Chodkiewicz, W., **14**-0301, **14**-0311, **14**-0314
Chodowska-Palicka, J., **11**-0618
Chodroff, S.D., **05**-0279
Choe, J., **19**-0376, **19**-0378
Choghamarani, A.G., **12**-0705
Choguill, H.S., **11**-0639
Choi, B.Y., **19**-0574
Choi, D.S., **15**-1436, **15**-1439
Choi, E., **15**-1152, **19**-0120
Choi, E.B., **17**-0528
Choi, H., **11**-0640, **15**-1138, **19**-0800
Choi, H.K.J., **05**-0358
Choi, H.Y., **19**-0260
Choi, J., **15**-0495, **15**-0503, **16**-0360, **16**-1535, **19**-1209, **19**-1299
Choi, J.-H., **19**-0332, **19**-0496
Choi, J.-K., **10**-1166, **15**-1247
Choi, J.H., **11**-0325
Choi, J.S., **10**-1453
Choi, J.Y., **15**-1136
Choi, K.H., **16**-1994, **19**-1550, **19**-1611, **19**-1612
Choi, K.I., **10**-1549, **16**-0605, **19**-1188, **19**-1222, **19**-1549, **19**-1550, **19**-1611
Choi, M., **15**-1438
Choi, M.C.K., **10**-1454, **15**-0519, **16**-0687, **19**-1042
Choi, M.J., **13**-0480
Choi, M.K.W.C., **19**-0178
Choi, N., **18**-0519
Choi, S., **15**-1834, **16**-1143, **16**-1147, **16**-1228, **18**-0175, **18**-0176, **19**-0800
Choi, S.-B., **15**-0586
Choi, S.-C., **10**-1408, **13**-0340, **13**-0623, **18**-0246
Choi, S.-Y., **05**-0306, **05**-0308, **05**-0310, **14**-0068, **14**-0070
Choi, S.U., **11**-0374
Choi, S.Y., **05**-0308
Choi, S.Y., **14**-0026
Choi, T.-L., **18**-0778, **18**-0781, **18**-0785, **18**-0795
Choi, W., **16**-1024
Choi, W.-K., **13**-0190
Choi, W.-W., **19**-0534
Choi, Y., **10**-0694, **19**-0459, **19**-0524
Choi, Y.H., **15**-1136
Choi, Y.J., **16**-2167
Choi, Y.K., **15**-1439, **19**-1160
Choi, Y.M., **19**-1086, **19**-1167, **19**-1490, **19**-1086, **19**-1091
Chong, A.O., **15**-1859, **15**-1876
Chong, J.A., **04**-0496, **10**-0044
Chong, J.M., **10**-0496, **10**-1062, **10**-1276, **10**-1461, **10**-1473, **10**-1541, **10**-1542, **15**-1124, **16**-0467, **16**-0699
Chong, Y.H., **15**-1371
Chono, M., **12**-0745
Chono, N., **15**-1254
Choo, D.J., **10**-0940
Choo, J., **04**-0352
Choony, N., **15**-0962
Chopade, P.R., **19**-0989
Choppin, S., **13**-0647
Chorbadjiev, S., **10**-0833
Chordia, M.D., **15**-1535, **15**-2074
Chorev, M., **03**-0203
Chortyk, O.T., **18**-0337
Chotii, K.Yu., **09**-0048
Chou, C.S., **19**-0109
Chou, F.E., **02**-0413
Chou, M.-C., **16**-1784
Chou, M.-Y., **12**-0459
Chou, P.K., **05**-0135
Chou, S., **10**-1290, **10**-1291
Chou, S.-S.P., **15**-2120
Chou, S.P., **12**-0498
Chou, T., **10**-0504, **12**-0572, **15**-2087
Chou, T.-C., **16**-0336
Chou, W., **15**-0502
Chou, W.-C., **16**-1784
Choucair, B., **16**-0878
Choudary, B.M., **10**-0752, **10**-0943, **11**-0214, **11**-0644, **15**-0270, **15**-1001, **15**-1669, **16**-0383, **16**-0616, **19**-0219, **19**-0781
Choudhary, M.I., **10**-0860, **10**-1081
Choudhary, V.R., **11**-0423, **13**-0410, **15**-1887
Chouhan, G., **16**-0233
Chounan, Y., **10**-0234
Chouraqui, G., **15**-2386
Chow, A., **04**-0312, **05**-0155, **05**-0185
Chow, D., **16**-2059
Chow, H.-F., **13**-0478
Chow, J., **12**-0228
Chow, L., **18**-0160
Chow, W.Y., **02**-0080
Chow, Y., **16**-0033
Chow, Y.L., **11**-0184, **14**-0187, **14**-0188, **15**-1610
Chowdari, N.S., **10**-0752, **11**-0214, **15**-1669, **16**-0877, **16**-0917
Chowdhury, C., **16**-1915
Chowdhury, S., **14**-0425
Choy, N., **18**-0487
Choy, W., **04**-0148, **16**-1014, **16**-1018, **16**-1050
Chrétien, J.R., **15**-0097
Chrisman, W., **16**-0057, **19**-0026, **19**-0161, **19**-1045
Christ, W.J., **15**-1688
Christen, D., **04**-0467
Christensen, C., **16**-1160
Christensen, J.J., **03**-0101, **03**-0105, **03**-0108, **04**-0163
Christensen, L.W., **12**-0208, **15**-1598
Christenson, B., **15**-1094, **15**-1170, **15**-1170
Christiaens, L., **10**-0798
Christian, B., **10**-0481
Christianson, D.W., **04**-0454
Christl, M., **02**-0084, **10**-0379, **18**-0651
Christman, D.R., **16**-2142
Christmann, K., **16**-1329
Christmann, K.-F., **16**-1330
Christmann, K.F., **16**-1297
Christmann, M., **16**-1112
Christoffers, J., **10**-1576, **15**-1021, **15**-1040, **19**-0489, **19**-0490
Christol, H., **10**-0179, **10**-0789, **15**-1376

Christophy, E., **07**-0046
Christy, M.E., **04**-0206
Christy, P.F., **11**-0029
Chrzanowska, M., **16**-0858
Chu, C., **12**-0560
Chu, C.-M., **13**-0753
Chu, C.C.C., **10**-1685
Chu, F., **10**-0610, **10**-0730, **16**-0199
Chu, K., **18**-0458
Chu, K.C., **12**-0031
Chu, M., **16**-0543
Chu, S., **15**-2107, **18**-0478
Chu, W.K.C., **08**-0059
Chua, P., **16**-0222, **16**-1704
Chuah, G., **19**-0971
Chuang, C., **15**-0105
Chuang, L., **14**-0095
Chuang, T., **19**-0452
Chuang, T.-H., **10**-0866
Chuaqui, C., **10**-0372
Chuard, R., **15**-0664
Chuchani, G., **11**-0037, **11**-0367, **17**-0131, **17**-0145
Chuche, J., **15**-0247
Chudek, J.A., **16**-0262
Chuit, C., **10**-0208, **12**-0499, **12**-0593, **15**-0954, **15**-1062
Chukovskaya, E.C., **15**-1640
Chukovskaya, E.Ts., **10**-1233
Chumakov, L.V., **15**-0021
Chun, Y.S., **19**-1031
Chung, B.C., **10**-1096, **13**-0252
Chung, B.Y., **10**-1016, **10**-1516, **16**-0634, **19**-1222, **19**-1655
Chung, C.-M., **15**-1203, **19**-1470
Chung, D.S., **10**-0019
Chung, E.-A., **16**-1975
Chung, F., **11**-0648
Chung, H.-A., **16**-1866
Chung, K.-G., **13**-0513
Chung, K.H., **17**-0426
Chung, M., **15**-1852
Chung, R.P., **16**-1570
Chung, S., **11**-0648, **15**-0571, **19**-0137, **19**-1339, **19**-1340, **19**-1765
Chung, S.K., **15**-1106
Chung, S.Y., **09**-0021, **10**-0304
Chung, Y.K., **15**-1411, **15**-1423, **15**-1431, **15**-1432, **15**-1436, **15**-1438, **15**-1439, **15**-1993, **19**-1042, **19**-1044
Chupakhin, O.N., **13**-0220, **13**-0638
Chupp, J.P., **16**-0274
Chuprakov, S., **15**-0843
Church, D.F., **14**-0093, **19**-0353, **19**-0356
Churchill, M.R., **03**-0083, **12**-0359, **15**-2302, **18**-0829
Churchill, R.M., **15**-2432
Chuvatkin, N.N., **10**-0759, **14**-0135, **15**-1544, **16**-0449
Chwang, A.K., **05**-0087
Chwang, W.K., **10**-0572
Chylińska, J.B., **19**-0365
Ciabattoni, J., **02**-0202, **02**-0203, **15**-1786
Ciaccio, J.A., **10**-1150, **10**-1792
Ciamician, G., **15**-2243
Ciappenelli, D.J., **12**-0392
Ciattini, P.G., **10**-0226, **13**-0608, **19**-1374
Ciavarri, J.P., **16**-0665
Cicchi, S., **17**-0449, **19**-0307, **19**-0774, **19**-1231
Cid, J.M., **10**-0856
Cieplak, A.S., **15**-0120, **15**-0121
Cieplak, P., **04**-0357
Ciganek, E., **15**-1986, **15**-2075, **15**-2282, **15**-2321, **15**-2322, **16**-0958, **17**-0259, **18**-0469, **18**-0470, **18**-0643
Cilento, G., **14**-0229, **15**-2157, **15**-2159
Ciliberti, L., **16**-1091
Ciminale, F., **15**-1167, **15**-1170
Cimiraglia, R., **11**-0172
Cingolani, G.M., **11**-0334
Cinquini, M., **04**-0029, **04**-0047, **05**-0138, **10**-0305, **12**-0185, **15**-1697, **16**-1118
Cintas, P., **03**-0210, **04**-0004, **04**-0300, **04**-0303, **15**-2004, **15**-2097, **16**-0586
Cintrat, J.-C., **12**-0272
Cioffari, A., **12**-0436
Cioffi, C.L., **13**-0522
Cioffi, N., **13**-0399
Ciorba, V., **02**-0093
Ciorba, V., **02**-0288
Ciro, S.M., **05**-0028
Cisneros, A., **19**-0317
Cistone, F., **15**-0638, **19**-1295, **19**-1522
Ciszewski, J.T., **15**-0352
Citterio, A., **11**-0185, **11**-0508, **13**-0582, **14**-0340, **14**-0344, **14**-0348, **14**-0363, **15**-1199
Ciuffarin, E., **08**-0058, **16**-2138, **16**-2144, **16**-2145
Ciuffreda, P., **16**-1687
Ciufolini, M.A., **02**-0355, **15**-1065, **16**-2082, **16**-2088, **16**-2132
Ciula, R.P., **04**-0435
Cividino, P., **15**-1009
Clabo Jr., D.A., **02**-0062
Claesson, A., **10**-1529, **19**-1321
Claisen, L., **16**-1131, **18**-0664
Clapham, B., **12**-0271
Clar, E., **02**-0119, **02**-0136
Claramunt, R.M., **02**-0423
Clardy, J., **02**-0353, **12**-0678
Clardy, J.C., **15**-1712
Clarembeau, M., **10**-0826
Claremon, D.A., **17**-0462
Clarendon, N.B., **09**-0016
Claridge, R.P., **11**-0123
Claridge, T.D.W., **13**-0427
Clark J.H., **09**-0084
Clark Jr., B.C., **02**-0350, **10**-0129, **10**-0131
Clark, A.J., **14**-0071, **15**-1232, **15**-1278, **16**-2107
Clark, B.C., **18**-0105
Clark, B.M., **16**-1340
Clark, C.G., **13**-0209, **13**-0231
Clark, C.T., **14**-0202, **15**-1322, **16**-1944
Clark, D.H., **12**-0258
Clark, D.L., **15**-0502
Clark, D.R., **10**-1814, **16**-0456
Clark, D.T., **02**-0231, **10**-0181
Clark, D.T., **10**-0206
Clark, F.R.S., **13**-0462
Clark, G.M., **16**-0043, **18**-0201
Clark, G.R., **02**-0201
Clark, G.W., **04**-0435
Clark, I.D., **12**-0040
Clark, J.D., **18**-0565, **18**-0667
Clark, J.H., **10**-0697, **10**-0713, **10**-1047, **13**-0147, **13**-0256, **13**-0257, **13**-0752, **18**-0359
Clark, J.S., **12**-0370
Clark, K.B., **01**-0101
Clark, L.W., **12**-0638
Clark, M., **04**-0398
Clark, M.T., **11**-0593
Clark, R.D., **17**-0361
Clark, R.F., **16**-0446
Clark, R.G., **01**-0003
Clark, T., **01**-0001, **02**-0007, **02**-0014, **02**-0020, **05**-0326, **14**-0076
Clarke, C.T., **10**-0992
Clarke, E.D., **08**-0101
Clarke, E.M., **02**-0390
Clarke, G.M., **18**-0039
Clarke, H.L., **03**-0083
Clarke, J.K.A., **15**-0451
Clarke, M., **18**-0370
Clarke, M.J., **12**-0643
Çizmeciyan, D., **08**-0213
Clarke, M.L., **10**-1463, **15**-1397
Clarke, M.T., **05**-0151, **05**-0196
Clarke, P.A., **16**-1621
Clarke, R.L., **04**-0320

Clarke, T.C., **10**-0254, **10**-0257
Clarkson, D., **02**-0004, **02**-0007
Clary, D.C., **10**-0345
Clary, D.W., **11**-0215
Clase, J.A., **10**-0604
Classon, B., **10**-1089
Claus, P., **11**-0518
Claus, R.E., **19**-0352
Clausen, K., **16**-0212, **16**-0220
Clausen, T.P., **10**-0182
Clausius, K., **18**-0725
Claver, C., **10**-1454, **10**-1459, **15**-1136, **15**-1136, **15**-1491, **15**-1492, **18**-0278
Clavier, H., **18**-0771
Clawson, L., **10**-0108, **16**-1348
Clayden, J., **13**-0289, **13**-0316
Clayman, L., **10**-0418
Clayton Jr., T.W., **15**-0707
Clayton, J.W., **10**-0210
Clayton, T.L., **15**-1057
Cleary, D.G., **10**-0794, **10**-1557
Cleator, E., **15**-1316
Clegg, W., **15**-1791
Clemens, A.H., **10**-0219, **11**-0107
Clemens, I., **10**-1790
Clement, A., **15**-1785, **18**-0222
Clément, G., **19**-1421
Clément, J., **10**-1820
Clemente, F.R., **04**-0303, **15**-2097, **15**-2150, **16**-1029
Clementi, S., **11**-0279
Clementi, S., **17**-0033
Clennan, E.L., **14**-0239, **15**-0149, **15**-1766, **15**-2151, **15**-2159
Clerici, A., **14**-0094, **16**-0009, **16**-0141, **19**-0255, **19**-0991, **19**-1657, **19**-1658, **19**-1663, **19**-1665
Clerici, L., **19**-1665
Cléry, P., **12**-0314
Cleve, N.J., **16**-1557
Clifford, A.A., **09**-0107, **13**-0407, **13**-0426, **14**-0319, **15**-2036
Clifford, P.R., **10**-0383
Clifford, R.P., **18**-0169
Clift, S.M., **16**-1348, **16**-1367
Clikeman, R.R., **04**-0349
Cline Jr., R.E., **07**-0071
Clinet, J.C., **15**-1236
Clippinger, E., **10**-0055, **10**-0066, **10**-0174
Clive, D.L.J., **10**-0049, **12**-0245, **14**-0406, **17**-0293, **19**-1589
Cloarec, J.-M., **15**-0489
Cloke, G.N., **13**-0480
Cloonan, M.O., **15**-1277
Clos, N., **04**-0146, **15**-0597
Closs, G.L., **02**-0196, **04**-0464, **05**-0219, **05**-0219, **05**-0327, **05**-0328, **05**-0330, **05**-0379, **10**-1314, **12**-0385, **15**-2308, **15**-2317, **17**-0507, **17**-0509, **18**-0388
Closs, L.E., **12**-0385
Closson, A., **15**-1670
Closson, W.D., **10**-0133, **10**-0134, **10**-0136, **17**-0334, **19**-1277
Clough, R.L., **04**-0510
Clouse, A.O., **10**-0262
Clowes, G.A., **11**-0411
Clunie, J.C., **16**-0037
Coates, G.E., **02**-0171, **05**-0145, **12**-0001
Coates, G.W., **10**-1552
Coates, R.M., **10**-0148, **10**-1653, **15**-1091, **18**-0107, **18**-0111, **18**-0506
Coates, W.M., **19**-0081
Coble, H.D., **16**-0193
Cobley, C.J., **16**-0431
Coche, L., **19**-0955
Cochran, J.C., **11**-0481
Cocivera, M., **16**-0318, **17**-0035, **17**-0116
Cockerill, A.F., **10**-0393, **10**-0520, **16**-0315, **16**-1293, **17**-0003, **17**-0007, **17**-0037, **17**-0039, **17**-0057, **17**-0063, **17**-0065, **17**-0084, **17**-0101, **17**-0103, **17**-0174, **17**-0245, **17**-0387, **19**-0252, **19**-0835
Cocks, A.T., **15**-2232, **17**-0122
Coe, D.E., **15**-1917
Coe, G.R., **12**-0569
Coe, P.L., **19**-1725
Coelho, F., **16**-0776
Coenen, J.W.E., **06**-0037
Coetzee, J.F., **06**-0087, **08**-0116, **08**-0126
Coffey, D.S., **12**-0406
Coffey, P.E., **15**-1817
Coffi-Nketsia, S., **10**-0733
Coffinet, D., **16**-1328
Cofré, P., **19**-0609
Cogdell, T.J., **10**-0134
Cogen, J.M., **05**-0322
Coggins, P., **12**-0105
Cogolli, P., **13**-0135
Cohen, G.M., **15**-2209
Cohen, H., **19**-0440
Cohen, J.F., **10**-1636
Cohen, L.A., **19**-1087
Cohen, M., **19**-0248
Cohen, M.D., **09**-0012
Cohen, M.H., **18**-0697
Cohen, N., **01**-0090
Cohen, R.J., **10**-0826
Cohen, S., **03**-0124, **14**-0079
Cohen, S.G., **07**-0032, **07**-0033, **14**-0454, **19**-1688
Cohen, T., **10**-0212, **10**-0395, **10**-1242, **11**-0615, **11**-0616, **12**-0386, **13**-0114, **13**-0459, **13**-0703, **13**-0749, **14**-0410, **14**-0412, **14**-0413, **14**-0414, **15**-0840, **15**-0979, **15**-1109, **15**-2044, **16**-0645, **16**-1410, **16**-1729, **16**-1955, **17**-0186, **18**-0235, **18**-0576, **19**-0644
Cohen, Y., **02**-0332, **10**-0457
Cohen, Z., **19**-0454
Cohn, G., **12**-0463
Cohn, M., **16**-0038
Cohrs, C., **02**-0084
Coisne, J.M., **12**-0416
Coke, J.L., **10**-0162, **17**-0007, **17**-0015, **17**-0017, **17**-0020, **17**-0022, **17**-0023
Colacot, T.J., **13**-0502
Colagioia, S., **16**-1865
Colapret, J.A., **16**-1195
Colard, N., **15**-1856
Colasson, B., **19**-1028
Colaux-Castillo, C., **15**-1708
Colb, A.L., **13**-0286
Colborn, R.E., **15**-2402, **15**-2403
Colbry, N.L., **16**-0349
Colby, D.A., **03**-0134
Colcha, W., **04**-0477
Colclough, T., **12**-0466
Coldham, I., **15**-0887, **18**-0398, **18**-0399, **18**-0419
Cole, C.M., **15**-0548
Cole, E.R., **14**-0260
Cole, L.L., **10**-0417, **10**-1066
Cole, S.J., **19**-1301
Cole, S.M., **15**-0307
Cole, T., **05**-0273
Cole, T.E., **12**-0516, **15**-0642, **15**-0643, **15**-0645, **18**-0422, **18**-0453
Coleman III, D.T., **19**-1762
Coleman, D., **10**-1319
Coleman, K.S., **19**-0120
Coleman, M.J., **17**-0343
Coleman, R.A., **15**-0692, **18**-0438, **18**-0439
Colens, A., **16**-1879
Coles, C.J., **10**-0083
Coles, J.A., **05**-0135
Coliboeuf, M., **16**-0863
Colins, C.C., **06**-0045
Coll, J., **10**-0602
Collazo, L.R., **10**-1182

Collet, A., **03**-0141, **04**-0009, **04**-0156, **04**-0156, **04**-0182
Collet, S., **13**-0352
Colley, A.M., **13**-0134
Collier, T.L., **04**-0136
Collier, T.R., **19**-1617
Collin, J., **10**-0925, **10**-1015, **10**-1867, **15**-2119, **16**-1082, **16**-2002, **19**-0967
Collings, B.A., **06**-0013
Collington, E.W., **10**-1734
Collingwood, S.P., **10**-1089
Collins, C., **18**-0041, **18**-0746
Collins, C.H., **15**-0032, **17**-0140
Collins, C.J., **06**-0038, **06**-0069, **10**-0079, **10**-0389, **10**-0395, **10**-0395, **15**-0137, **17**-0326, **18**-0001, **18**-0016, **18**-0022, **18**-0040, **18**-0056, **18**-0100, **18**-0124, **18**-0177, **18**-0179, **19**-1172, **19**-1499
Collins, G.R., **14**-0268
Collins, J.A., **18**-0040
Collins, J.C., **19**-0079
Collins, J.J., **18**-0617, **18**-0695
Collins, S., **16**-1087, **16**-1972
Collins, S.K., **04**-0082, **14**-0324
Collis, M.P., **18**-0826
Colllins, C.J., **19**-1498
Collman, J.C., **18**-0835
Collman, J.P., **03**-0083, **10**-1251, **10**-1332, **10**-1810, **10**-1812, **10**-1813, **10**-1814, **10**-1841, **10**-1843, **10**-1844, **13**-0394, **14**-0443, **15**-0406, **15**-1477, **15**-1479, **15**-2292, **15**-2403, **15**-2405, **19**-0460
Collum, D.B., **05**-0182, **05**-0188, **05**-0195, **08**-0199, **08**-0201, **08**-0202, **08**-0203, **08**-0204, **08**-0205, **08**-0206, **08**-0207, **10**-0867, **12**-0090, **12**-0268, **12**-0335, **12**-0422, **13**-0642, **13**-0643, **16**-0977, **16**-1862
Collumeau, A., **08**-0018
Colmegna, A., **15**-1758
Colobert, F., **11**-0295, **13**-0554
Colombo, L., **12**-0230, **16**-1077
Colon, C., **13**-0157
Colon, I., **13**-0462
Colonge, J., **12**-0081
Colonna, S., **04**-0029, **04**-0048, **05**-0138, **10**-0305, **12**-0185, **15**-1758, **15**-1814, **19**-0759, **19**-0799, **19**-0824
Colpa, J.P., **15**-0515
Colquhoun, H.M., **10**-1832, **12**-0074, **15**-0401
Colter, A.K., **05**-0088
Colussi, A.J., **07**-0073, **07**-0074
Colvin, E.W., **12**-0311, **12**-0509, **16**-1232, **16**-1233, **16**-1238
Comasseto, J.V., **10**-0785, **12**-0290, **12**-0291, **15**-1077, **16**-0582, **19**-1425
Combellas, C., **13**-0058, **13**-0089, **13**-0127, **13**-0343
Combs, A.P., **13**-0209
Comelles, J., **15**-1022
Comely, A.C., **15**-1440
Comes-Franchini, M., **10**-1495
Comesse, S., **15**-1029
Comfort, D.R., **16**-0401
Comins, D.L., **11**-0068, **12**-0330, **12**-0419, **12**-0534, **13**-0653, **15**-0583, **16**-1956
Comisarow, M., **16**-1567
Comisarow, M.B., **05**-0083, **10**-0165, **10**-0166
Comisso, G., **04**-0146, **15**-0597
Commercon, A., **10**-1529, **10**-1530
Commerçon-Bourgain, M., **15**-1062
Commeyras, A., **05**-0077, **10**-0205, **12**-0599, **16**-0123, **18**-0108
Compagnon, P.L., **16**-0120, **16**-0196
Compain, P., **15**-0221
Company, M.D., **15**-1224, **15**-1718
Conant, J.B., **10**-0303
Conaway, R., **11**-0298
Concellón, C., **10**-1167
Concellón, J.M., **10**-1167, **15**-2346, **16**-0500, **16**-0501, **17**-0163, **17**-0167, **17**-0214, **17**-0398, **17**-0400, **19**-0906
Concepcion, A.B., **12**-0368, **19**-0965
Concepción, J.I., **14**-0208
Concolino, T., **16**-0154
Condo, A., **16**-0977
Condon, F.E., **08**-0221, **11**-0023, **11**-0347
Condon, S., **13**-0342, **15**-1163
Condon-Gueugnot, S., **15**-0838, **15**-2273
Condroski, K.R., **15**-1737
Confalone, P.N., **13**-0272, **15**-1932
Conggui, Y., **10**-0592
Conia, J.M., **10**-0540, **12**-0155, **15**-0961, **15**-2329, **15**-2350, **16**-1938, **18**-0159, **18**-0209, **18**-0553, **18**-0671
Coniglio, S., **16**-1865
Conlan, D.A., **18**-0587
Conley, R.A., **15**-0549, **19**-1798
Conley, R.T., **17**-0450, **17**-0451, **17**-0454, **18**-0256, **18**-0337
Conlon, E.H., **16**-0099
Conlon, L.E., **10**-0661
Connell, R., **12**-0216
Connell, R.D., **15**-1693
Connolly, D.J., **13**-0424
Connolly, J.P., **15**-1314
Connolly, J.W., **03**-0159
Connon, S.J., **16**-0770, **16**-0778, **18**-0781, **18**-0792
Connor, D.S., **04**-0435, **10**-1240
Connor, J.A., **13**-0269, **13**-0280
Connor, J.K., **10**-0395
Connor, T.M., **01**-0032
Connors, K.A., **06**-0043, **06**-0052, **06**-0053, **09**-0016
Conon, S.J., **18**-0800
Conover, W.W., **15**-1804
Conrad, N.D., **18**-0656
Conroy, H., **18**-0659
Consani, K.A., **09**-0096
Considine, W.J., **12**-0591
Consiglio, G., **04**-0149, **10**-1455, **10**-1511, **15**-1489, **15**-1491
Consolandi, E., **16**-1118
Consoli, G.M.L., **03**-0127, **03**-0128, **04**-0066
Consorti, C.S., **09**-0110, **13**-0401
Constabel, F., **16**-2131
Constantieux, T., **15**-1137
Constantinou-Kokotou, V., **16**-1620
Conte, V., **15**-1526
Contento, M., **15**-1667, **19**-0391
Conticello, V.P., **15**-1871
Continetti, R.E., **08**-0216
Contreras, R., **10**-0031, **10**-0032, **15**-1999, **15**-2099, **15**-2104
Convers, E., **16**-1654
Conway, B.E., **14**-0415
Cook Jr., J.A., **10**-0165, **10**-0166
Cook, A.G., **10**-1674, **10**-1682, **12**-0086, **14**-0255, **15**-2188, **16**-0103, **16**-0287, **16**-0942, **19**-0047, **19**-1140
Cook, D., **11**-0453, **17**-0072
Cook, F., **17**-0269
Cook, F.B., **17**-0280
Cook, F.L., **03**-0102
Cook, G.K., **17**-0333
Cook, G.R., **18**-0608
Cook, J.M., **11**-0400
Cook, M.J., **04**-0333
Cook, R.S., **11**-0083
Cook, W.J., **19**-0104

Cooke Jr., M.P., **10**-1809, **10**-1816, **15**-0882, **15**-1110, **15**-1117, **16**-0966, **16**-1927, **17**-0015, **17**-0017, **19**-1529
Cooke, D.W., **15**-0409, **15**-0574
Cooke, F., **16**-1241
Cooke, G., **13**-0504
Cooke, G.A., **16**-1563
Cooke, T.W., **17**-0092
Cookson, P.G., **10**-0741
Cookson, R.C., **02**-0211, **15**-1393, **15**-2116, **17**-0015, **17**-0495, **18**-0204, **18**-0564, **18**-0855
Cookson, R.F., **08**-0006
Cooksy, A.L., **05**-0306, **14**-0084
Cooley, J.H., **10**-1186, **10**-1189
Cooley, N.A., **12**-0276
Coombes, R.G., **11**-0029, **11**-0083, **11**-0094, **11**-0096, **11**-0204
Coombs, R.V., **10**-1653
Coon, C.L., **11**-0139, **19**-0769
Cooney, B.T., **02**-0372
Cooney, J.J.A., **13**-0316
Cooney, J.V., **07**-0080, **16**-1541
Cooney, M.J., **02**-0353
Cooper, A., **18**-0743
Cooper, A.I., **09**-0101
Cooper, A.J.L., **16**-2136
Cooper, C.F., **13**-0693
Cooper, C.N., **18**-0022, **18**-0102
Cooper, D.L., **02**-0006, **02**-0014, **02**-0121, **15**-1953, **15**-1954
Cooper, G.D., **12**-0554, **19**-1570
Cooper, J., **14**-0044
Cooper, J.S., **10**-0418
Cooper, K.A., **10**-0330, **17**-0034, **17**-0118, **17**-0121
Cooper, M.A., **02**-0127
Cooper, M.S., **15**-1730
Cooper, N.J., **18**-0597
Cooper, P.J., **15**-0089, **15**-0653
Cooper, R.A., **05**-0218, **05**-0221, **10**-1314, **12**-0627
Cooper, R.M., **13**-0748
Cooper, T.A., **10**-1227
Coote, M.L., **01**-0112
Coote, S.J., **15**-0778, **16**-0472
Cope, A.C., **04**-0074, **04**-0167, **04**-0223, **04**-0457, **10**-0013, **14**-0040, **14**-0212, **17**-0243, **17**-0248, **17**-0249, **17**-0250, **17**-0258, **17**-0259, **18**-0050, **18**-0053, **18**-0085, **18**-0596, **18**-0674, **19**-1733
Copéret, C., **15**-1753
Copley, S.D., **18**-0658
Coppe, M., **19**-0120
Coppola, G.M., **04**-0135, **04**-0481, **10**-0231, **10**-0541, **15**-0106, **15**-0443, **15**-2183, **16**-2091, **17**-0378, **18**-0171, **18**-0695
Coppolino, A., **16**-1065
Coratti, A., **18**-0356
Corbally, R.P., **04**-0234
Corbiau, J.L., **14**-0121
Corbin, V.L., **15**-1080
Corcoran, J.W., **16**-1651
Corcoran, R.J., **19**-0065
Cordes, E.H., **10**-0520, **10**-0525, **16**-0100, **16**-1445
Córdoba, R., **16**-1429
Córdova, A., **16**-0413, **16**-0414, **16**-0917, **16**-1036, **16**-16, **19**-0506
Corella, J.A., **19**-1031
Corelli, F., **07**-0119
Corey, D.E., **04**-0175
Corey, E.J., **04**-0169, **05**-0138, **10**-0227, **10**-0229, **10**-0233, **10**-0559, **10**-0613, **10**-0743, **10**-1104, **10**-1144, **10**-1252, **10**-1253, **10**-1255, **10**-1288, **10**-1334, **10**-1338, **10**-1364, **10**-1369, **10**-1594, **10**-1652, **10**-1693, **10**-1697, **10**-1699, **10**-1701, **10**-1707, **10**-1708, **10**-1842, **12**-0313, **14**-0417, **15**-0486, **15**-1042, **15**-1066, **15**-1071, **15**-1080, **15**-1092, **15**-1118, **15**-1170, **15**-1173, **15**-1342, **15**-1585, **15**-1665, **15**-1684, **15**-1693, **15**-1693, **15**-1696, **15**-1741, **15**-1807, **15**-1826, **15**-1921, **15**-2012, **15**-2058, **15**-2064, **15**-2065, **15**-2158, **15**-2185, **15**-2294, **16**-0224, **16**-0232, **16**-0246, **16**-0248, **16**-0254, **16**-0498, **16**-0706, **16**-1025, **16**-1048, **16**-1051, **16**-1057, **16**-1123, **16**-1143, **16**-1147, **16**-1194, **16**-1228, **16**-1251, **16**-1273, **16**-1285, **16**-1289, **16**-1316, **16**-1316, **16**-1317, **16**-1328, **16**-1328, **16**-1329, **16**-1377, **16**-1378, **16**-1403, **16**-1436, **16**-1452, **16**-1458, **16**-1490, **16**-1652, **16**-1655, **16**-2035, **17**-0239, **17**-0240, **17**-0324, **17**-0338, **17**-0339, **17**-0341, **17**-0342, **17**-0419, **18**-0109, **18**-0450, **18**-0551, **18**-0684, **19**-0080, **19**-0081, **19**-0442, **19**-0577, **19**-0599, **19**-0650, **19**-0659, **19**-0754, **19**-0775, **19**-1031, **19**-1366, **19**-1658
Corey, P.E., **15**-1768
Corley, R.C., **05**-0304
Corma, A., **16**-1440, **19**-0969
Cormier, R.A., **19**-1459
Cornejo, J.J., **19**-0281
Cornélis, A., **11**-0141, **11**-0142
Cornelisse, J., **13**-0057, **19**-1219
Cornforth, J.W., **04**-0253, **15**-1558
Cornils, B., **10**-1837, **13**-0394, **15**-1381, **15**-1477
Cornwell, M.J., **13**-0130
Corral, J., **19**-0515
Correa, M., **13**-0480
Correa, P.E., **19**-0801
Correi, V.R., **19**-1425
Correia, C.F., **01**-0098
Correia, C.R.D., **13**-0425, **15**-2177
Correia, J.S., **10**-1072
Correia, R., **10**-0703, **13**-0637
Corrette, C.P., **15**-0746, **15**-0976
Corrigan, J.R., **19**-0081
Corriu, R., **11**-0422, **11**-0451, **15**-0024, **15**-0290
Corriu, R.J.P., **04**-0026, **10**-1303, **11**-0029, **12**-0270, **12**-0593, **19**-1099
Corsaro, A., **16**-0049, **16**-0242
Corset, J., **05**-0138, **15**-1001
Corsi, M., **17**-0449, **19**-0307
Corson, F.P., **10**-0262
Cortés, D.A., **02**-0234, **19**-0109
Cortez, C.N., **15**-0544
Cortez, G.S., **16**-2075
Cory, R.M., **15**-2210
Coryn, M., **16**-1469
Cosa, J.J., **11**-0594
Cosgrove Jr., W.R., **03**-0159
Coşkun, N., **16**-0334
Cosmo, R., **04**-0510
Cosp, A., **18**-0363, **16**-1015
Cossar, J., **08**-0054, **08**-0057, **12**-0672, **12**-0676, **16**-0993
Cossé-Barbi, A., **04**-0295
Cossey, K.N., **16**-1707
Cossio, F.P., **16**-0832, **10**-1141, **15**-1944, **15**-1947, **15**-1947, **15**-2055, **15**-2109
Cossu, S., **15**-0324
Cossy, J., **05**-0299, **10**-0562, **10**-0925, **10**-0960, **12**-0249, **13**-0323, **13**-0586, **15**-0318, **15**-0633, **15**-0638, **15**-0664, **15**-0965, **15**-0971, **15**-2238, **16**-0009, **16**-0646, **16**-0747, **16**-1475, **16**-1492, **16**-1655, **16**-1806, **16**-1961, **18**-0318, **18**-0781, **18**-0786, **18**-0812, **19**-0014, **19**-0265, **19**-1042

Costa, A., **13**-0021, **16**-1686, **18**-0308
Costa, A.L., **16**-0750
Costa, A.M., **15**-0302, **19**-1272
Costa, I.M., **16**-0293
Costa, M., **12**-0734
Costa, P.R.R., **16**-1120
Costain, C.C., **01**-0071
Costanza, A., **10**-0148
Costas, M., **15**-1666
Coste, J., **10**-0179
Costello, A.M., **16**-1869
Costentin, C., **05**-0303, **13**-0052
Costero, A.M., **13**-0046, **16**-1289
Costisella, B., **16**-1002, **19**-1771
Costopanagiotis, A., **16**-1579
Cosyns, J., **15**-0424
Cota, D.J., **16**-2053
Cote, P.N., **18**-0056
Cotelle, P., **10**-0555, **18**-0382
Cott, P., **15**-1905
Cottard, F., **05**-0301
Cotterrell, G., **15**-1080
Cottier, L., **10**-1100
Cotton, F.A., **01**-0008, **03**-0084, **04**-0377
Cottrell, C.E., **02**-0241, **04**-0193, **05**-0171, **18**-0621
Cottrell, F.D., **04**-0436
Couderet, G., **19**-1627
Coudert, G., **10**-0911
Couffignal, R., **16**-2015
Coughlan, N., **15**-1529
Coulson, C.A., **02**-0004, **02**-0007, **02**-0008, **02**-0026, **02**-0033, **02**-0115, **04**-0419
Coulson, J., **11**-0589
Coulston, K.J., **18**-0519, **18**-0520
Coulter, J.M., **19**-1526
Coumbarides, G., **12**-0108
Councler, C., **12**-0461, **12**-0462
Courgeon, T., **12**-0518
Courmarcel, J., **19**-1045
Court, J., **14**-0105, **19**-1037
Court, J.J., **16**-1967
Courtieu, J., **19**-0699
Courtneidge, J.L., **05**-0300, **05**-0318, **13**-0658
Courtney, J.L., **19**-0010
Courtois, G., **12**-0033
Cousins, K.R., **18**-0692
Cousins, R.P.C., **12**-0108
Cousseau, J., **15**-0174
Coussemant, F., **15**-0024, **16**-0346, **16**-1464, **16**-1467, **16**-1469, **16**-1470
Couto, A., **08**-0125, **08**-0131
Coutts, I.G.C., **12**-0362, **18**-0272
Couture, A., **16**-1321
Couture, C., **13**-0269
Couture, P., **05**-0384
Couture, Y., **15**-1611
Couturier, D., **13**-0735, **18**-0382
Couturier, M., **15**-0497
Couty, F., **10**-1493, **16**-0486
Couve-Bonnaire, S., **13**-0626, **13**-0627
Couvillon, T.M., **18**-0085
Covell, J., **18**-0855
Coverdale, A.K., **10**-0424
Covey, W.D., **11**-0028
Cowan, D., **12**-0575
Cowan, D.O., **07**-0005
Cowan, P.J., **16**-2006
Cowdrey, W.A., **10**-0003, **16**-1562
Cowell, G.W., **17**-0496
Cowen, K.A., **16**-0361
Cowley, A.H., **01**-0009
Cox, B.G., **06**-0064
Cox, D., **05**-0020
Cox, D.P., **15**-2312, **18**-0126
Cox, E.D., **11**-0400
Cox, G.R., **15**-1080
Cox, G.S., **07**-0039
Cox, J.D., **01**-0093, **01**-0094, **01**-0099
Cox, J.L., **14**-0260
Cox, J.M., **18**-0816
Cox, R.A., **08**-0038, **08**-0116, **08**-0119, **08**-0129, **16**-1059, **18**-0739, **18**-0881, **18**-0886, **18**-0887, **18**-0889
Cox, R.H., **10**-1317
Cox, P.J., **10**-1639
Coxon, J.M., **07**-0001, **08**-0071, **15**-0123, **15**-0134, **15**-0138, **15**-2232, **16**-0495, **16**-0645, **17**-0035
Coyle, J.D., **07**-0001, **07**-0013, **07**-0041, **07**-0044, **15**-2235, **16**-2083
Coyle, J.J., **05**-0379
Coyne, E.J., **16**-1271
Cozens, F.L., **05**-0011
Cozzi, F., **04**-0047, **05**-0138, **15**-1697, **16**-1118
Cozzi, P., **16**-1032
Cozzi, P.G., **15**-0425, **16**-1118, **16**-1434
Crabb, T.A., **04**-0354
Crabbé, P., **04**-0268, **10**-1429, **10**-1434, **16**-0580, **16**-0580
Crabtree, R.H., **02**-0042, **14**-0296, **14**-0297, **15**-0418, **15**-0462, **15**-0847, **17**-0301, **18**-0834, **19**-0061, **19**-0970
Craft, J., **02**-0364
Cragg, G.M.L., **10**-1749, **15**-0636, **15**-0646, **18**-0420, **19**-0882, **19**-0889, **19**-0896, **19**-0992
Craig, D., **15**-1980, **15**-2083, **16**-1236, **16**-1239
Craig, D.P., **04**-0007
Craig, J.C., **18**-0195, **19**-0674, **19**-1128, **19**-1131
Craig, N.C., **15**-0488
Craig, R.A., **04**-0412
Craig, S.L., **10**-0413, **15**-0167
Crain, D.L., **18**-0825
Cram, D.G., **17**-0099
Cram, D.J., **02**-0061, **02**-0212, **03**-0101, **03**-0117, **03**-0121, **03**-0142, **03**-0154, **03**-0171, **03**-0172, **04**-0137, **04**-0163, **04**-0164, **04**-0177, **05**-0099, **05**-0135, **05**-0137, **05**-0138, **08**-0013, **08**-0047, **08**-0062, **08**-0074, **10**-0006, **10**-0127, **10**-0153, **10**-0155, **10**-0156, **10**-0161, **10**-1307, **12**-0028, **12**-0029, **12**-0030, **12**-0031, **12**-0057, **12**-0063, **12**-0064, **12**-0682, **15**-0437, **16**-0490, **16**-2141, **17**-0081, **17**-0099, **17**-0261, **18**-0012, **18**-0028, **18**-0031, **18**-0035, **18**-0094, **18**-0258, **18**-0258, **19**-1432, **19**-1616, **19**-1734, **19**-1735
Cram, J.M., **02**-0061, **03**-0101, **04**-0177, **10**-0006, **12**-0029
Cramer III, R.D., **04**-0398
Cramer, C.J., **04**-0367, **05**-0410, **10**-0337
Cramer, J., **19**-0436
Cramer, P., **15**-0222
Cramer, R., **12**-0075, **15**-0794
Crameri, Y., **15**-0598
Cramp, S.M., **16**-1312
Crampton, M.R., **03**-0049, **08**-0043, **13**-0009, **13**-0019
Crandall, J.K., **02**-0204, **10**-1842, **15**-1804, **15**-1805, **17**-0206, **18**-0205, **19**-1321
Crane, L.J., **04**-0150, **04**-0171
Crank, G., **14**-0260
Crans, D.C., **04**-0208
Cravero, R.M., **02**-0404
Craw, J.S., **18**-0667
Crawford, J.T., **11**-0363, **19**-0206
Crawford, K.R., **13**-0233
Crawford, M., **16**-1211
Crawford, R.J., **10**-0122

Crawford, T.D., **02**-0252
Crawley, M.L., **10**-1446
Craze, G., **10**-0533, **16**-1936
Creary, X., **05**-0245, **05**-0338, **05**-0353, **10**-0038, **10**-0148, **10**-0178, **10**-0296, **10**-0297, **10**-0299, **10**-0306, **10**-0436, **13**-0141, **13**-0597, **14**-0089
Credi, A., **03**-0184
Creed, D., **15**-2252
Creedon, S.M., **17**-0478
Creese, M.W., **17**-0125
Cregar, P.L., **10**-1690, **10**-1692
Cregge, R.J., **10**-1614
Crelier, A.M., **10**-0262
Cremer, D., **02**-0207, **04**-0395, **04**-0402, **04**-0416, **04**-0420, **16**-1022
Cremers, J.G.O., **16**-0687
Cresp, T.M., **02**-0093, **02**-0298
Crespo, R., **02**-0185
Creswell, C.J., **03**-0067
Crettaz, R., **10**-1847
Cretton, A., **02**-0402
Crévisy, C., **19**-0120
Crews, A.D., **13**-0157
Crews, P.O., **02**-0163
Crich, D., **10**-0894, **12**-0655, **15**-1241, **15**-1249, **15**-1284, **17**-0293, **18**-0059, **18**-0061, **19**-0177, **19**-0436, **19**-1413
Cridland, A., **17**-0211
Criegee, R., **15**-1656, **15**-2255, **18**-0372, **18**-0471, **18**-0472, **18**-0494, **19**-0325, **19**-0326, **19**-0359, **19**-0361, **19**-0372
Crimmin, M.J., **18**-0761
Crimmins, M.T., **15**-2241, **16**-0567, **16**-1146, **19**-1403
Crimmins, T.F., **10**-1605, **18**-0120
Cripe, T.A., **05**-0378
Cripe, T.H., **05**-0246
Crisp, C.T., **18**-0826
Crisp, G.T., **12**-0256, **13**-0418
Crispino, G.A., **15**-1658, **15**-1693, **15**-1693, **15**-1704
Crist, D.R., **11**-0274
Cristau, H.J., **10**-0789, **13**-0578
Cristol, S.J., **10**-0066, **10**-1089, **14**-0428, **15**-0115, **15**-0136, **15**-2242, **17**-0011, **17**-0016, **17**-0395, **18**-0066
Crivello, J.V., **15**-0148
Croatt, M.P., **15**-1421
Crocker, M.J., **07**-0069
Croft, A.P., **03**-0174, **17**-0031
Croizy, J.F., **15**-0797
Crombie, L., **16**-1246
Cromer, F., **02**-0364
Cromer, R.A., **18**-0676
Cromwell, N.H., **04**-0422
Cron S., **19**-1509
Cronin, M.F., **06**-0045
Crookes, M.J., **12**-0198
Crooks III, W.J., **19**-1360
Crooks, J.E., **08**-0096
Crosby, D., **19**-1533
Crosby, J., **04**-0134
Crosignani, S., **10**-1105, **16**-1642, **16**-1643, **16**-1786
Cross, G.A., **10**-1304
Cross, M.J., **15**-0249
Cross, R.J., **02**-0365, **15**-2070
Cross, R.M., **17**-0234
Cross, R.T., **19**-0438
Crossland, I., **16**-0532
Crossland, R.K., **10**-0382
Crotti, C., **12**-0748
Crotti, P., **10**-0663, **10**-0814, **10**-0953, **10**-0954, **10**-1150, **10**-1564
Crounse, N.N., **11**-0479
Crouse, B., **16**-0901
Crouse, G.D., **15**-1997
Crousse, B., **10**-0929, **15**-1770, **16**-0863
Crout, D.H.G., **11**-0083
Crowe, D.F., **17**-0418
Crowe, W.E., **18**-0759, **19**-1133
Crowley, H.K., **17**-0478
Crowley, J.I., **16**-1817, **16**-1823, **16**-2024
Crowley, K.J., **15**-2235, **18**-0471
Crowley, P.B., **16**-1271
Crowley, P.J., **01**-0087
Crozet, M.P., **10**-1227
Crozier, R.F., **15**-1932
Crudden, C.M., **15**-1773, **15**-0421, **15**-1394
Crudden, C.M., **15**-1672
Cruickshank, D.W.J., **02**-0122
Crum, L.A., **07**-0075, **07**-0069
Crumbliss, A.L., **12**-0621
Crumine, D.S., **18**-0862
Crump, R.A.N.C., **04**-0079
Crumrine, D.S., **16**-0999
Cruse, R.W., **14**-0200
Cruse, R.W., **14**-0200
Crutchfield, M.M., **19**-0255
Cruz, G., **15**-0652
Cruz, R., **04**-0333
Cruz, R.P.A., **11**-0437, **11**-0438
Cruz, S.G., **16**-1348
Cruz-Almanza, R., **15**-1244, **18**-0232
Cryberg, R.L., **05**-0412
Csákÿ, A.G., **16**-1429, **18**-0781
Cserr, R., **12**-0457
Csizmadia, I.G., **02**-0089, **04**-0047, **04**-0285, **05**-0119, **05**-0121, **10**-0771, **12**-0087, **15**-0021, **16**-1402, **18**-0226
Csjernyik, G., **19**-0221
Csuhai, E., **19**-0612, **19**-0613, **19**-0614
Csuk, R., **15**-0520, **16**-0813, **19**-1645
Cuadro, A.M., **12**-0271, **13**-0544
Cubbage, J.W., **17**-0284
Cubero, E., **03**-0075, **03**-0076, **03**-0079
Cuerva, J.M., **15**-1233, **19**-0355
Cuervo, H., **16**-0501
Cueto, O., **12**-0435
Cuevas, G., **04**-0359, **04**-0364, **04**-0372
Cui, C., **11**-0557
Cui, D.-M., **11**-0418, **11**-0442, **15**-1135
Cui, M., **15**-1826
Cui, P., **16**-0150
Cui, W., **13**-0180, **16**-1713, **19**-1660
Cui, X., **10**-0768, **10**-1199, **10**-1453, **10**-1454, **15**-0425, **15**-0519, **15**-0575, **15**-2127, **16**-0865, **16**-1037
Cui, Y., **15**-1904, **19**-0174
Culkin, D.A., **13**-0583
Cullen, E., **13**-0758
Cullen, W.R., **02**-0241
Cullis, C.F., **19**-0069
Cullis, P.M., **04**-0031, **18**-0370
Culmann, J., **12**-0049
Culvenor, C.J., **17**-0225
Cummerson, D.A., **15**-1730
Cummings, D.L., **03**-0067
Cummings, T.F., **16**-0400
Cummins, J.M., **12**-0382
Cundall, R.B., **15**-2239, **16**-0119
Cundari, T.R., **08**-0219
Cunico, R.F., **12**-0069, **16**-0477, **16**-1995
Cunningham Jr., A.F., **04**-0443
Cunningham, A., **16**-0632
Cunningham, I.D., **15**-0981, **16**-2126
Cunningham, I.M., **12**-0034
Cunningham, M., **18**-0338
Cunsolo, F., **03**-0128, **04**-0066, **04**-0162
Cunsolo, G., **15**-1136
Cuny, G.D., **15**-1482
Cuong, N.K., **19**-0279
Cupone, G., **10**-1123
Cuppen, T.J.H.M., **18**-0515

Curci, R., **15**-1743, **15**-1766, **15**-1766, **15**-1768, **15**-2164, **19**-0010, **19**-0255, **19**-0301, **19**-0514, **19**-0615, **19**-0760, **19**-0834, **19**-0235
Curerva, J.M., **16**-0646
Curillon, C., **10**-1277
Curini, M., **10**-0563, **10**-0925, **12**-0723, **15**-1365, **15**-1625, **16**-0149, **16**-1842, **19**-0668, **19**-1726
Curl, R.F., **02**-0355
Curphey, T.J., **10**-0380, **10**-1685, **15**-1785, **16**-0215, **16**-1675
Curran, A.C.W., **15**-1046
Curran, D.P., **10**-0095, **10**-0703, **10**-0704, **10**-0975, **10**-1209, **12**-0263, **12**-0264, **12**-0276, **14**-0001, **14**-0035, **14**-0100, **15**-0065, **15**-0078, **15**-1197, **15**-1201, **15**-1218, **15**-1245, **16**-2161, **19**-1333, **19**-1686
Curran, E.L., **10**-0114
Currie Jr., J.O., **16**-0233, **18**-0395
Curriev Jr., Y.O., **10**-1693
Curry, M.J., **10**-0659
Curti, R., **16**-1865
Curtin, D.Y., **04**-0182, **04**-0187, **05**-0135, **17**-0127, **18**-0056
Curtis, E.A., **16**-0966
Curtis, M.D., **15**-1116
Curtis, R.F., **14**-0316
Curtis, V.A., **10**-0384, **10**-0385, **10**-0724
Curtiss, L.A., **01**-0052, **03**-0007
Cusack, K.P., **16**-2172
Cusack, N.J., **19**-1436
Cushnyr, B., **19**-0529
Cussans, N.J., **10**-0558
Cuvigny, T., **10**-1656, **12**-0693, **16**-2152, **17**-0448, **19**-0478
Cuyegkeng, M.A., **04**-0508
Cuzens, j.R., **19**-1172
Cvetanović, R.J., **05**-0333, **15**-2236, **15**-2247, **15**-2247, **19**-0357
Cvetković, M., **19**-0064
Cybulski, M., **19**-1553
Cynkowski, T., **02**-0352
Cyr, C.R., **12**-0076
Cyr, D.R., **10**-1542
Cyr, J.S., **16**-1021
Cyranski, M.K., **02**-0068, **02**-0092, **02**-0188, **02**-0092
Cyrański, M.K., **02**-0137
Cyvin, B.N., **02**-0120, **02**-0272
Cyvin, S.J., **02**-0119, **02**-0120, **02**-0272
Cywin, C.L., **16**-1048
Cywinski, N.F., **15**-1358
Czaja, R.F., **15**-0054, **15**-0126
Czarnik, A.W., **16**-1702, **16**-1823
Czarnocki, Z., **02**-0092
Czech, B.P., **03**-0107, **10**-0470
Czekay, G., **19**-0064
Czekelius, C., **15**-0591
Czernecki, S., **10**-0229, **12**-0605, **19**-0081
Czira, G., **17**-0209
Czopp, M., **16**-0950
Czuba, L.J., **12**-0328
Czugler, M., **03**-0156, **15**-1001

D'Accolti, L., **19**-0235, **19**-0301, **19**-0514, **19**-0615
D'Achille, R., **10**-1172
D'Agostino, J., **07**-0054
D'Alessandro, F., **16**-1865
D'Alliessi, D.G., **15**-2065
D'Ambrosi, A., **15**-1822
d'Angelo, J., **10**-1647, **10**-1662, **12**-0103, **15**-1044, **15**-1045, **15**-1301, **15**-2234, **16**-1120
D'Annibale, A., **14**-0071, **15**-0899, **15**-1258, **15**-1855, **15**-1922, **15**-1924
D'anniballe, G., **16**-1865
D'Ascoli, R., **19**-0732
D'Auria, M., **11**-0285, **15**-1558, **19**-0080, **19**-0732, **19**-0735
D'az-Ortis, A., **07**-0121
D'Elia, V., **16**-1865
D'Ettole, A., **16**-1929
d'Incan, E., **10**-0217
D'Rozario, P., **16**-2143
D'Silva, R.M., **17**-0139
D'Souza, M.J., **10**-0154
D'Souza, V.T., **15**-1852
D'Souza, C.J.E., **04**-0313
D'yachenko, A.I., **05**-0370, **13**-0037
D'yakonov, I.A., **02**-0196, **02**-0205, **18**-0634
da Costa, J.C.S., **19**-1088
da Costa, R.C., **19**-1221
da Rocha, S.R.P., **09**-0097
da Rosa, R.G., **13**-0481
da Silva, F.C., **16**-0831
da Silva, M.F., **19**-1221
da silva, F.M., **15**-0997
Da, C. **16**-0687
Da, C.-s., **16**-0549, **16**-0687
Daasbjerg, K., **08**-0072, **10**-0091
Daasvatn, K., **03**-0106
Dabbagh, G., **10**-1319, **10**-1357, **12**-0560, **16**-0848
Dabdoub, M.J., **15**-0313, **15**-1551, **16**-0583
Dabdoub, V.B., **15**-1551, **16**-0583
Dabin, G., **10**-0700
Dabkowska, I., **08**-0087
Dabora, S.L., **15**-0409, **15**-2022
Dadali, V.A., **16**-2170
Dadjour, D.F., **12**-0040
Daeuble, J.F., **15**-2032
Dafaye, J., **17**-0335
Dafforn, G.A., **10**-0283, **10**-0420
Dagani, D., **15**-2269
Dagani, R., **07**-0112
Dagonneau, M., **16**-0528
Dahan, A., **15**-1433
Dahiya, R., **16**-0271, **16**-0375, **19**-0089, **19**-0207, **19**-1112
Dahl, A.R., **15**-0136
Dahl, M., **12**-0419
Dahlberg, D.B., **17**-0056
Dahlen, A., **10**-1123, **15**-0478, **15**-0924, **19**-0985, **19**-1704
Dahlgren Jr., G., **03**-0067
Dahlgren, L., **06**-0074
Dahlman, O., **19**-1332
Dahmen, A., **18**-0497
Dahmen, S., **10**-0753, **10**-1488, **16**-0549
Dahn, H., **10**-0519, **18**-0126
Dai, C., **13**-0435, **13**-0480
Dai, G., **15**-0919, **15**-2396
Dai, H., **10**-1453
Dai, H.-F., **16**-0342, **18**-0798
Dai, J., **13**-0491, **19**-1024
Dai, L., **15**-0657, **16**-0991
Dai, L., **19**-1090
Dai, L.-X., **10**-0674, **10**-0675, **10**-0924, **10**-1173, **10**-1468, **10**-1571, **16**-0851, **16**-0871, **16**-0911 **16**-1326
Dai, M., **13**-0365, **15**-1405
Dai, P., **19**-1423
Dai, R., **16**-1768
Dai, S., **15**-2219
Dai, W.-M., **16**-1258
Dai, Z., **19**-0823
Daibuzono, K., **15**-1238
Daignault, R.A., **19**-1475
Daikai, K., **15**-1300
Daikawa, N., **16**-0661
Dailey, B.P., **01**-0057, **02**-0127, **02**-0228
Dailey, W.P., **04**-0428, **04**-0431, **05**-0365
Daily, J.W., **07**-0066
Dainty, R.F., **11**-0548
Dairokuno, T., **10**-0154
Dais, P., **09**-0052

Dakamin, M.G., **11**-0566
Dakarapu, R., **11**-0438
Dake, G.R., **15**-0396, **15**-0822, **18**-0134
Dakin, L.A., **10**-0564
Dakka, G., **10**-1073
Dakka, J., **10**-0699
Dakternieks, D., **12**-0614
Dal Pozzo, R., **15**-1170
Dalcanale, E., **19**-0699
Dale, J., **01**-0007, **03**-0106, **03**-0107, **04**-0261, **04**-0350, **04**-0387, **04**-0392, **04**-0502, **16**-0540
Dale, J.A., **04**-0105, **04**-0206
Dale, J.W., **15**-2426
Dalessandro, J., **19**-1295
Dalgaard, L., **16**-1252
Dalili, S., **13**-0208, **15**-0021
Dalko, P.I., **15**-0638, **15**-0664, **19**-1042
Dall'Acqua, F., **09**-0104
Dalla Croce, P., **10**-0992
Dallavalle, S., **19**-0824
Dallemer, F., **16**-2002
Dalley, N.K., **04**-0163, **04**-0177
Dallinger, D., **07**-0121
Dalman, G.W., **13**-0091
Dalmolen, J., **16**-0864
Dalpozzo, R., **10**-0545, **10**-1123, **15**-0875, **15**-1167, **16**-1618
Dalrymplem D.L., **18**-0654
Dalton, A.M., **12**-0373
Dalton, D.M., **19**-1055
Dalton, D.R., **15**-0016, **15**-1562
Dalton, D.R., **15**-1562
Dalton, J.C., **07**-0025, **07**-0044, **07**-0046, **15**-2235
Dalvi, P.V., **15**-2018
Daly, A.M., **15**-1773, **15**-1835
Daly, W.H., **16**-0289
Dalzell, H.C., **14**-0378
Damavandi, J.A., **19**-0034
Damayanthi, Y., **19**-1268
Dämbkes, G., **16**-1498
Dambrin, V., **10**-1688
Damiano, J., **07**-0080
Damin, B., **15**-1566
Damm, L., **12**-0035
Damm, W., **05**-0242, **14**-0057, **14**-0092, **15**-0066
Dammel, R., **16**-0263
Damodharan, L., **03**-0003
Damrauer, R., **05**-0106, **05**-0380, **08**-0079
Dams, R., **19**-1714, **19**-1718, **19**-1727
Dan'kov, Yu.V., **15**-0010
Danca, D.M., **15**-1272
Dance, I., **03**-0209
Dance, I.G., **03**-0155
Danda, H., **16**-1025
Danda, Y., **13**-0450
Dandapani, S., **10**-0703, **10**-0704
Danehy, J.P., **19**-1639
Danen, W.C., **05**-0279, **10**-0089, **14**-0048, **14**-0099, **15**-1610
Daney, M., **10**-1794
Danforth, R.H., **13**-0099
Dang, H.-S., **15**-0754, **15**-1353, **15**-1367
Dangat, V.T., **11**-0273
Danheiser, R.L., **10**-1232, **12**-0220, **12**-0373, **12**-0525, **15**-2036, **18**-0488, **18**-0585, **18**-0586, **19**-1658, **15**-2125
Danhui, Y., **16**-0840
Daniel, C., **15**-0463
Daniel, H., **17**-0254
Daniel, K.L., **12**-0370
Daniel, T., **11**-0231, **11**-0234, **11**-0237, **11**-0426
Danieli, B., **16**-0687
Danielmeier, K., **14**-0415
Daniels, R., **15**-0080
Daniewski, A.R., **10**-0395
Danikiewicz, W., **13**-0672
Danilova, N.A., **14**-0383
Danilova, T.I., **16**-0687
Danion, D., **13**-0352
Danion-Bougot, R., **13**-0352
Danishefsky, S., **15**-0144, **15**-2003, **15**-2045, **15**-2126
Danishefsky, S.J., **19**-0756
Danjo, H., **15**-1335
Danks, T.N., **15**-0619, **16**-0282
Dankwardt, J.W., **13**-0312
Dannenberg, J.J., **05**-0240, **10**-0209 **14**-0007, **18**-0083
Danno, S., **13**-0420
Danova, B.V., **16**-0198
Danovich, D., **05**-0263
Dantale, S.W., **16**-1679, **19**-0703
Dao, L.H., **10**-0301
Daplozzo, R., **19**-0997
Dapurkar, S.E., **19**-1074
Darba, P., **04**-0514, **10**-0276
Darbre, T., **16**-1036
Darby, A.C., **11**-0307
Darby, N., **02**-0248, **18**-0487
Darcel, C., **19**-0789
Darchen, A., **12**-0716
Darcy, M.G., **19**-0751
Dardis, R.E., **16**-0405
Dardoize, F., **10**-1689
Dargel, T.K., **15**-2335
Darling, S.D., **17**-0391
Darowska, M., **08**-0087
Darrin, M., **19**-0620
Darses, S., **10**-1424, **12**-0334, **13**-0727, **13**-0728, **13**-0729, **15**-1132
Darville, K., **19**-0939
Darwish, D., **17**-0069
Das Gupta, T.K., **15**-1927
Das, A., **10**-0812, **17**-0212, **17**-0374
Das, A.R., **16**-0578, **19**-0895, **19**-0944
Das, B., **15**-0565, **15**-1141, **16**-0322, **16**-0333, **16**-1526, **16**-1527, **16**-1532, **16**-1638, **16**-1647, **16**-1700, **17**-0442
Das, B.C., **15**-1123
Das, D., **16**-1951
Das, G., **16**-1010
Das, J., **15**-1023, **15**-1684, **16**-1043, **19**-0731
Das, J.P., **14**-0285, **14**-0426
Das, K.K., **16**-1768
Das, N.B., **10**-1013
Das, P., **13**-0489, **15**-0618
Das, P.J., **19**-0697
Das, S., **15**-1123, **15**-1295, **16**-1055, **16**-1741, **19**-0652, **19**-0681
Das, U., **10**-0929
Dasent, W.E., **15**-0083
Dasgupta, S.K., **13**-0387
Daşkapan, T., **13**-0188
Daskapan, T., **15**-0878
Datar, R., **16**-0860
Date, S.K., **18**-0212
Datta Gupta, A., **15**-2297, **19**-0535
Datta, A.P., **11**-0459
Datta, D., **09**-0074
Datta, I., **12**-0215
Datta, M., **16**-0241
Daub, G.H., **16**-1139
Daub, G.W., **18**-0676
Daub, J., **18**-0643
Dauban, P., **15**-1903, **15**-1904
Dauben Jr., H.J., **02**-0100, **02**-0155, **02**-0173, **14**-0178, **14**-0181, **19**-0446
Dauben, P., **15**-1902
Dauben, W.G., **04**-0422, **04**-0443, **05**-0322, **07**-0039, **10**-0202, **15**-0988, **15**-2242, **16**-0148, **16**-1281, **17**-0271, **18**-0463, **18**-0464, **18**-0467, **18**-0485, **18**-0486, **18**-0535, **18**-0537, **18**-0842, **18**-0, **18**-0856
Daunis, J., **11**-0464
Dauphin, G., **15**-1578

Daus, K.A., **15**-0167
Dauvergne, J., **15**-1435
Davankov, V.A., **04**-0173
Dave, B., **13**-0170
Dave, H.R., **16**-1770
Dave, P.R., **15**-2068, **16**-1768
Dave, V., **15**-2264, **18**-0241
Davenport, D., **04**-0282
Daverio, P., **19**-1036
Daves Jr., G.D., **13**-0372, **13**-0374
Davey, P.N., **15**-0974, **15**-0986
Daviaud, G., **15**-1086
Davico, G.E., **02**-0024
David, D.E., **05**-0269
David, M., **15**-1029
Davidov, P., **19**-0362
Davidovich, Yu.A., **10**-0522, **16**-1816
Davids, K.L., **04**-0393
Davidson, D., **16**-1869
Davidson, E.R., **02**-0216, **05**-0121, **05**-0285, **05**-0288, **05**-0332 **18**-0627
Davidson, E.W., **15**-0548
Davidson, F., **12**-0365
Davidson, M., **16**-1470, **16**-1464, **16**-1467, **16**-1469
Davidson, M.H., **15**-0246
Davidson, M.M., **18**-0709
Davidson, N., **05**-0273
Davidson, R.B., **04**-0163, **04**-0298, **04**-0419
Davidson, R.S., **12**-0658, **14**-0062, **15**-2253
Davidson, W.R., **08**-0191
Davidsson, Ö., **08**-0208, **16**-0490, **16**-0979, **03**-0057
Davie, C.P., **12**-0373
Davies, **04**-0164
Davies, A.G., **04**-0358, **04**-0375, **05**-0209, **05**-0316, **05**-0318, **10**-0688, **10**-0741, **11**-0077, **12**-0436, **12**-0436, **12**-0447, **13**-0658, **14**-0244, **15**-0975
Davies, A.P., **10**-1089, **12**-0654
Davies, D.G., **12**-0681
Davies, D.I., **10**-1320, **14**-0001, **14**-0010, **14**-0012, **14**-0106, **14**-0108, **15**-1232, **15**-1584, **19**-0434, **19**-0438
Davies, D.T., **15**-1929
Davies, H.M., **12**-0359, **15**-2303
Davies, H.M.L., **12**-0218, **12**-0359, **12**-0360, **12**-0361, **12**-0371, **15**-2296, **15**-2297, **15**-2298, **15**-2302, **15**-2303, **15**-2432, **16**-1390
Davies, I.W., **09**-0105, **13**-0385, **15**-0364, **15**-0755, **19**-1148
Davies, J.A., **10**-1841, **15**-1375, **15**-1477
Davies, J.E., **03**-0101, **03**-0105, **03**-0119, **03**-0141 **03**-0155, **03**-0157, **03**-0162, **03**-0164, **03**-0166, **03**-0167, **03**-0174, **03**-0175, **03**-0177
Davies, J.E.D., **03**-0210
Davies, J.W., **18**-0344
Davies, M., **15**-0268
Davies, M.H., **08**-0141
Davies, M.W., **15**-2411
Davies, N.R., **12**-0074
Davies, R.V., **16**-0434, **16**-1954
Davies, S.G., **02**-0044, **10**-1511, **10**-1640, **19**-1515, **19**-1625
Davies, T.M., **10**-0285
Davies, W., **17**-0225
Davis Jr., J.C., **03**-0040
Davis Jr., J.H., **16**-1069, **16**-1170
Davis, A.B., **13**-0019
Davis, A.P., **16**-0746
Davis, B.A., **16**-0367
Davis, B.H., **17**-0158
Davis, B.R., **19**-1427, **19**-1436
Davis, C.B., **16**-1870
Davis, D.D., **04**-0127, **04**-0146, **12**-0007, **12**-0012, **15**-0597
Davis, F.A., **04**-0028, **12**-0130, **12**-0138, **12**-0440, **16**-0853, **19**-0480, **19**-0498, **19**-0500, **19**-0501, **19**-0736, **19**-0823, **19**-0827, **19**-0830
Davis, G.A., **16**-2084
Davis, G.T., **16**-1845, **16**-1846, **16**-1850, **17**-0069
Davis, H.A., **19**-1390
Davis, J.H., **18**-0650
Davis, M., **04**-0317
Davis, M.E., **15**-1478
Davis, P., **04**-0197
Davis, P.D., **10**-1824
Davis, R., **10**-1798
Davis, R., **15**-1641
Davis, R.C., **19**-0662
Davis, R.E., **17**-0221
Davis, R.F., **18**-0638
Davis, R.M., **15**-0016
Davis, S., **14**-0146, **19**-0109
Davis, T.A., **19**-0989
Davis, T.C., **15**-2063
Davis, T.J., **16**-0646
Davis, T.P., **16**-0213
Davis, V.C., **15**-1932
Davis, W.M., **18**-0836
Davister, M., **11**-0348
Davoli, P., **16**-2122
Davoust, D., **17**-0315
Davy, H., **16**-0227
Dawes, H.M., **03**-0028
Dawes, K., **07**-0044
Dawson, B.T., **12**-0601, **16**-1899
Dawson, I.M., **11**-0544, **11**-0552
Dawson, L.R., **08**-0231
Dawson, M.I., **10**-1289
Day, A., **03**-0210
Day, A.C., **15**-2105, **16**-0300, **16**-2074
Day, A.I., **03**-0209
Day, A.R., **19**-0977
Day, J.C., **14**-0185, **14**-0188
Dayagi, S., **16**-0266, **19**-0280
Daynard, T.S., **19**-1729
Dayrit, F.M., **15**-1150, **15**-1151
Dayton, D.C., **05**-0269
De Angelis, F., **10**-0901, **10**-0916
De Bakker, C., **16**-1918
De Bernardinis, S., **19**-1374
De Boer, C.D., **18**-0628
De Boos, G.A., **19**-0996
De Borggraeve, W., **07**-0121
De Cock, C., **15**-2182, **15**-2222
De Felippis, J., **04**-0469
De Giovani, W.F., **19**-0579
De Jong, F., **03**-0101
De Kimpe, N., **10**-0293, **10**-0873, **10**-1233, **12**-0110, **15**-2261, **16**-1224, **16**-1354, **19**-0041, **19**-1328
De Lombart, S., **16**-0486
De Luca, L., **10**-1091
De Lucchi, O., **15**-1998, **17**-0502, **18**-0853, **19**-0443, **19**-1778
De Lue, N.R., **12**-0487, **12**-0488, **12**-0489
De Maria, P., **10**-0264, **12**-0083
De Meese, J., **16**-1390
De Meio, G.V., **13**-0264
De Micheli, C., **15**-1932, **15**-1943
De Mico, A., **15**-1558
De Munary, S., **10**-1179
De Nino, A., **10**-0545, **10**-1123, **15**-0875, **16**-1618
De Poorter, B., **19**-0456
De Rose, V.T., **15**-1741
De Santis, A., **08**-0129
De Shazo, M., **11**-0041
De Tar, D.F., **06**-0010, **09**-0066, **14**-0033, **14**-0105, **16**-0015
De Valois, P.J., **11**-0636
de Alaniz, J.R., **15**-1370, **19**-0704

de Armas, J., **15**-0864, **15**-0868
de Boer, H.J.R., **02**-0063, **12**-0613
de Boer, T.J., **10**-0317, **13**-0074, **16**-0043, **17**-0497, **19**-1755
de Bruin, T.J.M., **15**-1418, **15**-1453
de Cremiers, V.A., **13**-0504
de Diego, C., **19**-1350
de Dios, A., **10**-1246
de Echagüen, C.O., **15**-2100
de Faria, A.R., **15**-2177
de Fays, L., **08**-0189, **15**-2004
de Filippis, A., **13**-0323, **13**-0586
de França, K.W.R., **13**-0304
de Frutos, Ó., **13**-0378, **15**-2392
de Groot, A., **17**-0296
de Gunst, G.P.
de Haan, J.W., **10**-0152, **18**-0566
de Heer, M.I., **01**-0104
de Jeso, B., **02**-0421
de Jonge, A.P., **16**-1650
de Jonge, C.R.J., **19**-0010
de Julien de Zélicourt, Y., **02**-0294
de K. Haynes, A.K., **19**-1171
de Kanter, F.J.J., **02**-0062
de Klein, W.J., **15**-1356
de Koning, A.J., **11**-0655
de Koning, C.D., **18**-0786
de la Cruz, P., **07**-0112, **16**-1174, **18**-0322
de la Hoz, A., **07**-0112, **07**-0121, **15**-2022
de la Mare, P.B.D., **02**-0367, **09**-0027 **10**-0001, **10**-0222, **11**-0005, **11**-0064, **11**-0119, **11**-0224, **11**-0227, **11**-0271, **15**-0001, **15**-0068, **15**-0073, **15**-1511, **15**-1581, **17**-0069, **17**-0080
de la Pradilla, R.F., **10**-1246, **18**-0488
de la Rosa, J.C., **13**-0358
de la Vega, F., **11**-0260
de Lange, B., **07**-0061, **16**-0864
de Leon, S., **11**-0327, **15**-2398
de Lera, A.R., **13**-0518
de Ligny, C.L., **09**-0057
de los Santos, J.M., **16**-0304
De Luca, L., **07**-0042, **12**-0730, **16**-1703, **16**-1790, **16**-1948, **19**-0171, **19**-0186, **19**-0677
de M. Carneiro, J.W., **05**-0078, **11**-0119
de Manderola, O.B., **16**-2064
de Mattos, M.C.S., **15**-0178, **15**-1576
de Mayo, P., **02**-0181, **05**-0125, **05**-0383, **07**-0046, **07**-0054, **11**-0594, **14**-0229, **15**-1224, **15**-2157, **16**-0218, **18**-0001, **18**-0002, **18**-0054, **18**-0094, **18**-0104, **18**-0168, **18**-0194, **18**-0263, **18**-0284, **18**-0335, **18**-0338, **18**-0373, **18**-0420, **18**-0464, **18**-0573, **18**-0628, **18**-0745, **18**-0849, **18**-0856, **18**-0860, **18**-0863, **18**-0898, **19**-1001
de Meijere, A., **04**-0339, **04**-0416, **05**-0086, **05**-0315, **05**-0320, **05**-0351, **12**-0274, **12**-0744, **13**-0380, **13**-0418, **15**-2413, **18**-0087, **18**-0528, **18**-0571, **18**-0590, **18**-0630, **19**-1400
de Mendoza, J., **19**-1173
de Meyer-van Duyse, A., **09**-0047
de Nooy, A.E.J., **19**-0195
de O. Jardim, A.H., **16**-0831
de O.Viera, T., **15**-1770
de Oliveira, P.S.M., **19**-1088
de Oliveira-Neto, J., **16**-1324
de Parrodi, C.A., **10**-1162, **16**-0688
de Petris, G., **11**-0098
de Rossi, R.H., **11**-0558, **11**-0594, **13**-0014, **13**-0052, **13**-0589
de Rosso, C.R.S., **19**-0367
de Ryck, P.H., **12**-0506
de S. Santos, E., **16**-0831
de Sá, A.C.P.F., **10**-0828
de Sanabia, J.A., **18**-0123
de Savignac, A., **10**-1006
de Sousa, S.E., **17**-0218
de Souza Barboza, J.C., **15**-1142
de Souza, R.F., **09**-0110, **15**-0798
de Souza-Barboza, J.C., **12**-0609, **16**-0479
de V.F. Neder, A., **11**-0437
de Vincente, J., **16**-1371
de Vires, J.G., **15**-1131
de Visser, S.P., **14**-0079
de Vos, M.J., **16**-0486
de Vries, A.H.M., **13**-0369, **15**-1131, **15**-1136, **16**-0787
de Vries, E.F.J., **04**-0092
de Vries, J.G., **13**-0369, **15**-0604, **15**-1741, **16**-0431
de Waard, E.R., **12**-0189
de Wit, P., **11**-0199
de Wolf, W.E., **02**-0062, **02**-0063, **10**-0317, **15**-2282, **18**-0649
De, A., **16**-0097, **16**-1174, **16**-1192
De, N.C., **15**-0195
De, P., **16**-0061, **16**-0062
De, S., **16**-0061, **16**-0062
De, S.K., **03**-0054, **16**-0056, **16**-0070, **16**-0142, **16**-0234, **16**-1441, **18**-0310, **18**-0311
De-xiang, W., **15**-2105
Deacon, G.B., **12**-0045, **12**-0279, **12**-0659
Deacon, G.B., **15**-1685
Deady, L.W., **10**-0854, **10**-0890, **10**-1188
Deady, L.W., **16**-1517
Deak, H.L., **18**-0584
Deakyne, C.A., **03**-0001
Dean, C.L., **15**-0021
Dean, D.K., **16**-0777
Dean, F.H., **15**-1544
Deans, F.B., **11**-0085
Dear, R.E.A., **11**-0636
Deardorff, D.R., **10**-0734
Deardorff, J.D., **19**-1313
Deaton-Rewoliwski, M.V., **19**-1626
Deb, A.C., **18**-0668
Deb, K.K., **03**-0040
Debenham, S.D., **10**-1453
Deberly, A., **16**-0493, **16**-0683, **19**-0954
DeBoef, B., **15**-0727, **15**-2445
DeBoer, A., **15**-0054, **15**-0126
DeBoer, C.D., **14**-0183
DeBoer, C.D., **15**-2239
DeBoos, G.A., **11**-0136, **11**-0231
DeBruin, K.E., **15**-0196
DeBruin, K.R., **15**-0133
DeBruyn, D.J., **16**-0181
Deb, F., **18**-0225
DeBuyck, L., **12**-0123, **12**-0152
DeCamp, M.R., **18**-0621
DeCarlo, V.J., **16**-2071
Dechoux, L., **12**-0107
Dechoux, L., **17**-0207
Decken, A., **19**-1609
Declerq, J., **16**-1224
Declerzq, J.-P., **18**-0156
Decock-Le Révérend, B., **18**-0634
Decodts, G., **17**-0307
DeCorso, A.R., **15**-1569
Decorzant, R., **10**-1653
Decouzon, M., **08**-0087, **19**-1245
Dedeoglu, E., **11**-0096

Dedov, A.G., **14**-0198
Dedov, A.G., **15**-0521
Deeth, R.J., **13**-0427
Deets, G.L., **19**-0440
Deetz, M.J., **04**-0311
Defay, N., **04**-0068
DeFrees, D.J., **06**-0072, **08**-0235, **10**-0185, **10**-0186, **10**-0201
Deganello, G., **15**-0439
Degani, I., **10**-1866
Degani, I., **16**-1284, **19**-1509
Degani, Y., **16**-0266, **19**-0280
Degen, H.-G., **15**-1791, **15**-1807, **15**-1812
Degen, P., **15**-1172
Degenhardt, C.R., **10**-0077
Degenkolb, P., **12**-0264
Deger, H.M., **02**-0333
Degering, E.F., **19**-1249
Deghenghi, R., **16**-1697
Degl'Innocenti, A., **15**-1068, **16**-0217, **16**-1148, **17**-0209
Deglise, X., **12**-0725
Degnan, A.P., **15**-2138
DeGonia, D.J., **13**-0742
Degorre, F., **10**-0368
DeHaan, F.P., **11**-0028, **11**-0092
Dehaen, W., **07**-0118, **07**-0119, **07**-0121, **15**-2022
Dehaen, W., **13**-0547
Dehghani, A., **12**-0330
Dehmlow, E.V., **10**-0453, **10**-0458, **10**-0466, **10**-0716, **12**-0654
Dehmlow, E.V., **15**-2172, **15**-2213, **15**-2278, **19**-0337
Dehmlow, S.S., **10**-0453
Dehn, R.L., **17**-0418
Dehnicke, K., **04**-0437, **15**-1624
DeHoff, B., **10**-1345
Deitch, J., **16**-2015
Deiter, S.A., **18**-0802
DeJong, F., **04**-0164
Dejroongruang, K., **02**-0353
Deka, N., **16**-0233
Dekerckheer, C., **07**-0076
Dekker, J., **16**-0833
Dekkers, H.P.J.M., **04**-0216
Del Bene, J.E., **03**-0042
Del Re, G., **02**-0013
Del Valle, L., **10**-1439
del Campo., C., **18**-0141
del Villar, A., **10**-1438
DeLaat, A.M., **03**-0047
DeLacierva, C.O., **15**-0806
Delacroix, A., **15**-0346
Delacroix, T., **16**-1907
Delahunty, C., **09**-0066
Delair, P., **19**-1663
Delaney, E., **16**-1828
Delapierre, G., **15**-1137
Delas, C.
Delaude, L., **11**-0142
Delaumeny, M., **10**-1529
Delavarenne, S.Y., **12**-0483
Delay, F., **10**-0226, **19**-1292
DeLeon, E.L., **04**-0321
Deleuze, M.S., **03**-0196
Deleuze, M.S., **10**-0854
Delfly, M., **11**-0550
Delgado, A., **12**-0678
Delgado, A., **15**-0827, **15**-0916, **16**-0672, **16**-1759, **18**-0791
Delgado, F., **16**-2063, **19**-0089
Delgado, M., **18**-0820
Delgass, W.N., **06**-0037
Delguzzo, L., **10**-0109
Delker, G.L., **11**-0028
Dell'Anna, G., **16**-0861
Dell'Erba, C., **08**-0168, **17**-0056
Dell, C.P., **18**-0680
Dell, S., **10**-0721
Della, E.W., **04**-0433, **05**-0080, **05**-0082, **10**-0045, **10**-0368
Della, E.W., **12**-0655, **14**-0434
Della Sala, G., **15**-0232, **15**-1741
Dellacoletta, B.A., **14**-0452
Dellaria Jr., F.F., **16**-1728, **19**-1567
Dellaria Jr., J.F., **13**-0733, **14**-0354
Dellaria, J.F., **12**-0230
Delmas, M., **10**-0819, **11**-0481
Delmas, M., **16**-1324
Delmon, B., **17**-0176
Delogu, G., **11**-0376
DeLong, G.T., **05**-0196
Delong, M.N., **15**-1029
deLong, M., **15**-2439
Delorme, D., **10**-0614
Delorme, D., **16**-1326
Delplancke, J.-L., **16**-0578
DeLucca, J.P., **12**-0377
DeLucchi, O., **15**-0324
DeLue, N.R., **18**-0436
DelZotto, A., **17**-0267
Dem'yanov, N.Ya., **04**-0465
Dem'yanov, P.I., **10**-0490
Demange, L., **15**-0153
DeMarco, A.M., **18**-0302
DeMaria, P., **08**-0168
DeMario, D.R., **14**-0312
Demay, S., **15**-0682
Dembech, P., **12**-0045
Dembinski, R., **10**-0703
Dembitsky, V.M., **15**-1758
Dembofsky, B.T., **04**-0110
Demchuk, D.V., **04**-0360
Demchuk, K.J., **08**-0036
Demchuk, O.M., **18**-0811
DeMello, N.C., **15**-1737
DeMember, J.R., **05**-0023, **05**-0077, **10**-0187, **10**-0205, **12**-0342, **18**-0108
Demers, J.P., **12**-0013, **15**-1939
Demerseman, B., **10**-1463
Demerseman, P., **11**-0550, **13**-0098
Demicheli, G., **16**-1151
DeMico, A., **19**-0204, **19**-1770
Deming, P.H., **15**-1776
Demir, A.S., **13**-0349, **14**-0258, **15**-1042, **16**-0986, **16**-1500, **16**-2065, **17**-0215, **19**-0494, **19**-0511
DeMira, M., **18**-0370
Demirtas, I., **08**-0081
Demisch, W.H., **10**-0150
Demko, Z.P., **15**-1865
Demonceau, A., **10**-0638, **15**-1643, **15**-1959
Demoute, J.-P., **10**-1424, **13**-0727, **13**-0728
Dempsey, B., **08**-0018, **08**-0160
Demuth, M., **15**-2235, **18**-0857, **18**-0860, **18**-0863
Demuynck, M., **16**-0206
den Hertog, H.J., **13**-0049
Denekamp, C., **15**-2219
Denes, A.S., **16**-1468
DeNet, R.W., **10**-1582
Deng, G., **03**-0123
Deng, G.-J., **15**-0604, **15**-0613, **16**-0691, **16**-1012
Deng, H., **16**-1439
Deng, J.-G., **15**-0519, **15**-0575, **19**-1042, **19**-1043
Deng, L., **15**-1004, **15**-1331, **15**-1827, **16**-1443, **16**-1626, **16**-1627
Deng, L.X., **15**-1202
Deng, M.-Z., **10**-1421, **12**-0282, **13**-0347, **13**-0528
Deng, M.-z., **10**-1419, **12**-0281, **13**-0500
Deng, Q., **15**-0963, **15**-2017
Deng, W., **13**-0138
Deng, X.-M., **16**-1394, **16**-1852
Deng, Y., **13**-0482, **15**-0719, **16**-0067, **16**-0152, **18**-0317
Deniau, E., **16**-1321
Denis, G., **11**-0481
Denis, G.I., **17**-0104
Denis, J., **02**-0412, **05**-0039
Denis, J.M., **15**-2329, **16**-0263, **12**-0724, **17**-0199, **17**-0200, **17**-0222, **19**-1620
Denis, P., **15**-0797

Denis, R.C., **15**-0053
Denise, B., **12**-0583, **16**-0540
Denisenko, S.N., **04**-0039
Denisov, E.T., **14**-0023
Denk, M.K., **05**-0348
Denmark, S.E., **10**-1155, **10**-1642, **13**-0341, **13**-0390, **13**-0448, **13**-0504, **13**-0567, **13**-0634, **15**-0917, **15**-1178, **15**-1766, **15**-1768, **15**-1773, **15**-2334, **15**-2337, **16**-0494, **16**-0585, **16**-0643, **16**-0743, **16**-0858, **16**-0924, **16**-1022, **16**-1046, **16**-1080, **16**-1097, **16**-1110, **16**-1126, **16**-2129, **18**-0681, **19**-1154
Denney, D.B., **12**-0438, **14**-0263, **14**-0264
Denney, D.Z., **12**-0438, **14**-0263, **14**-0264
Dennis, N., **04**-0362, **15**-2122, **15**-2139
Denniston, A.D., **05**-0121
Denny, R.W., **14**-0227, **14**-0236, **15**-2151
Deno, N.C., **05**-0034, **05**-0035, **05**-0038, **05**-0043, **05**-0048, **05**-0049, **05**-0050, **05**-0061, **05**-0062, **05**-0071, **05**-0075, **08**-0022, **08**-0035, **08**-0121, **09**-0047, **09**-0050, **10**-0803, **12**-0148, **12**-0303, **12**-0724, **14**-0065, **14**-0149, **14**-0151, **14**-0152, **14**-0153, **14**-0154, **14**-0158, **18**-0367, **18**-0865, **19**-0411, **19**-0462, **19**-0663, **19**-0691
Denson, D.D., **17**-0524, **19**-0379
Dent III, W.H., **15**-1733
Dent, A.L., **15**-0405
Denyer, C.V., **10**-0049
Denzel, T., **16**-1344
DePalma, V.M., **05**-0130
Depew, M.C., **05**-0314
Depew, R.E., **03**-0208
Depezay, J., **16**-1057
Depezay, J.C., **10**-1662
DePomar, J.C.J., **12**-0563
Deprèle, S., **15**-0378, **15**-0379
Depriest, R.N., **10**-0618
DeProft, F., **13**-0048
DePue, J.S., **10**-0867
DePuy, C.H., **02**-0024, **05**-0106, **10**-0267, **10**-0318, **10**-0368, **12**-0219, **15**-0131, **15**-0133, **15**-0135, **17**-0008, **17**-0015, **17**-0066, **17**-0099, **17**-0140, **17**-0141, **17**-0183, **17**-0229, **17**-0235, **17**-0258, **17**-0280, **18**-0504, **18**-0507
Derdour, A., **16**-1832
Dere, R.T., **15**-1016
Derenberg, M., **12**-0681
Derendyaev, B.G., **18**-0035
Derevitskaya, V.A., **16**-1673
Derfer, J.M., **04**-0412
Derguini-Boumechal, F., **10**-1294, **10**-1536
Dérien, S., **15**-0813, **15**-1388
Dermer, O.C., **10**-0494, **10**-0673, **10**-0872, **10**-0955, **14**-0127, **15**-1883, **17**-0360, **18**-0580
Dernell, W., **16**-1956
Derome, A.E., **19**-1558
Derrien, N., **19**-1034
Dershem, S.M., **14**-0089
DeRussy, D.T., **04**-0193, **18**-0621
Dervan, P.B., **15**-2096, **17**-0199, **18**-0589, **18**-0629
Des Roches, D., **18**-0143
des Abbayes, H., **10**-1820, **10**-1845
Desai, B., **15**-0619, **18**-0773
Desai, D.G., **17**-0429, **19**-0979, **19**-0988
Desai, L., **19**-0513
Desai, M.C., **18**-0443
Desai, N.B., **16**-1262, **16**-1289
Desai, P., **18**-0297
Desai, U.V., **11**-0249, **16**-1157
Desai, V.R., **18**-0068
Desbène, P., **11**-0226
Deschamps, N.M., **15**-1421, **15**-1422
Descotes, G., **18**-0761
Deselnicu, M.I., **10**-1331
Deshayes, H., **19**-1412
Deshayes, K., **03**-0172
Deshayes, S., **10**-0468
Deshmukh, A.R.A.S., **10**-1027, **19**-1273
Deshmukh, R.R., **13**-0415, **16**-1153
DeShong, P., **10**-0703, **10**-1212, **13**-0510, **13**-0520, **13**-0631, **13**-0632, **13**-0635, **13**-0637, **15**-1932
Deshpande, A.K., **05**-0361, **19**-1339
Deshpande, M.S., **16**-1864
Deshpande, R.M., **19**-1186
Deshpande, V.H., **10**-0660, **15**-1294, **16**-1152, **16**-1153, **16**-1683, **19**-0960
DeSimone, J., **10**-0412
Desimoni, G., **15**-0961, **15**-1043, **15**-2122, **15**-2179, **18**-0708
Desio, P.J., **16**-0562
Desiraju, G.R., **03**-0070, **08**-0011
Deskus, J., **10**-0864, **16**-1932
Deslongchamps, P., **04**-0363, **10**-0538, **10**-1600, **15**-1980, **16**-0030
Desmaële, D., **10**-0873, **15**-1045, **15**-1301, **16**-1120
Desmarets, C., **13**-0199
Desmaris, L., **10**-1100
DesMarteau, D.D., **11**-0314
Desmond, K.M., **14**-0183
Desmond, R., **19**-0673
Desmurs, J.-R., **10**-0925, **10**-0960, **11**-0220, **18**-0812
DeSouza, D.J., **14**-0352
DeSouza, M.V.N., **19**-1088
Despres, L., **16**-1813
Dess, D.B., **19**-0198
Dessanti, F., **19**-1537, **15**-1921, **19**-0436
Dessole, G., **10**-1495
Dessy, R.E., **05**-0103, **08**-0062, **12**-0002, **12**-0040, **12**-0569
DeStephano, J.P., **16**-0516
Destro, R., **02**-0260, **02**-0277, **02**-0285, **02**-0319, **13**-0010
Desvard, O.E., **10**-0284
DeTar, D.F., **04**-0514, **09**-0060, **09**-0073, **10**-0276, **14**-0033, **14**-0328, **19**-1569
Detomaso, A., **19**-0301, **19**-0760
Detoni, S., **03**-0008
Detre, G., **17**-0418
Detsina, A.N., **11**-0029, **11**-0088
Dettwiler, J.E., **16**-1965
Detty, M.R., **17**-0208
Deubel, D.V., **15**-1738, **19**-0233
Deuchert, K., **19**-0004
Deudon, S., **13**-0231
Deussen, R., **15**-1485
Deutch, J.E., **12**-0611
Deutsch, M., **19**-0823
Deutsch, P.P., **05**-0222
Dev, S., **15**-0436, **16**-0235, **19**-0348, **19**-0463
Dev, V., **04**-0475, **17**-0507, **17**-0509
Devaiah, V., **19**-1195
Devant, R.M., **16**-1189
Devaprabhakara, D., **14**-0395, **15**-0510, **15**-0512, **15**-0665
Devasagayaraj, A., **10**-1384, **10**-1828

DeVasher, R.B., **13**-0502
Devi, G., **16**-0882
Deville, C.G., **15**-1946
Devin, P., **15**-1273
DeVincentis, D., **10**-0508
Devine, P.N., **13**-0266
Devlin, F.J., **04**-0114, **04**-0118
DeVos, D.E., **19**-0120
Devos, A., **10**-1089
Devos, A., **16**-1879
Devrout, E., **02**-0260
Devynck, J., **10**-1854
Devynck, J., **12**-0341
Dewald, R.R., **19**-0962
Dewar, M.J.S., **02**-0190
Dewar, M.J.S., **01**-0001, **01**-0042, **02**-0005, **02**-0009, **02**-0013, **02**-0018, **02**-0019, **02**-0036, **02**-0115, **02**-0189, **02**-0218, **02**-0367, **03**-0082, **03**-0087, **05**-0332, **06**-0079, **08**-0171, **10**-0170, **10**-0179, **10**-0222, **11**-0017, **15**-0004, **15**-0033, **15**-0169, **15**-2090, **15**-2096, **15**-2098, **15**-2108, **18**-0477, **18**-0630, **18**-0669, **18**-0745
Dewey, R.S., **15**-0485
Dewhurst, B.B., **12**-0668
DeWitt, S.H., **16**-1823
Dewkar, G.K., **19**-0752
DeWolfe, R.H., **10**-0213, **10**-0214, **10**-0289, **10**-0520, **10**-0609, **10**-0658, **10**-1477, **10**-1519, **12**-0057, **16**-0160, **16**-1589, **18**-0471, **18**-0526, **18**-0569, **18**-0594
Dey, K., **13**-0616
Dey, S., **19**-0711
Deyà. P.M., **13**-0021
Deycard, S., **05**-0282
Deyerl, H.-J., **08**-0216
DeYoung, D.J., **01**-0011
DeYoung, S., **15**-0080
Deyrup, A.J., **05**-0075, **05**-0062, **08**-0115
Deyrup, C.L., **10**-0146, **10**-0149
Deyrup, J.A., **07**-0057, **16**-1231
Dhal, P.K., **15**-1694
Dhanabalasingam, B., **15**-1283
Dhanak, D., **16**-1835
Dhanoa, D., **10**-0179
Dhanoa, D.S., **16**-1895
Dhar, D.N., **15**-0071
Dhar, M.L., **17**-0105, **17**-0106, **17**-0118
Dhar, P., **10**-0834
Dhar, R.K., **16**-0997
Dhas, N.A., **15**-2023
Dhawan, S.N., **07**-0048
Dhillon, R.S., **15**-0620, **15**-0636, **15**-0694, **15**-0694, **18**-0441
Dhimane, H., **15**-1029
Dhokte, U.P., **15**-0675
Dhuru, S.P., **19**-1323
Di Bari, L., **04**-0120
Di Blasio, B., **08**-0024
Di Deo, M., **10**-1064
Di Fabio, R., **19**-0898
Di Furia, F., **19**-0834
Di Giorgio, V.E., **07**-0015
Di Giuseppe, S., **15**-2423, **16**-0163, **16**-0279
Di Silvestro, G.D., **04**-0038
Di Valentin, C., **15**-1944
Di Vona, M.L., **10**-0378, **19**-1465
di Cosmo, A., **13**-0415
di Maio, G., **02**-0272
Diab, Y., **19**-1245
Dial, C., **11**-0298
Dial, J.L., **11**-0271
Diamanti, J., **12**-0325
Diamond, C.J., **03**-0146
Diaper, D.G.M., **19**-0350, **19**-0351
Dias, A.K.B., **11**-0437
Dias, E.L., **15**-2356
Dias, H.V.R., **12**-0365, **12**-0367
Dias, J.R., **02**-0022, **02**-0116, **02**-0119, **19**-1467
Dias, S., **10**-0848
Diaz, A., **10**-0132, **10**-0152, **10**-0158
Diaz, A.F., **10**-0062
Diaz, C., **10**-0282
Díaz, D.D., **13**-0494
Díaz, M.J., **10**-0777
Díaz, M.R., **10**-1167
Díaz, N., **13**-0358
Díaz-Ortis, A., **15**-2022
Díaz-Ortiz, Á., **13**-0413
Díaz-Ortiz, A., **07**-0112
Díaz-Requejo, M.M., **12**-0366, **15**-2293, **15**-2299, **19**-0548
DiChenna, P.H., **15**-1903
Dick, A.R., **19**-0527
Dick, K., **03**-0152
Dick, K.F., **19**-0076
Dickason, W.C., **10**-0076, **10**-0078, **15**-0685, **18**-0424
Dicken, C.M., **15**-1932
Dickens, M.J., **10**-0473
Dickenson, G., **09**-0114
Dicker, I.B., **16**-1084
Dickerhoof, D.W., **05**-0152
Dickerman, S.C., **13**-0734, **14**-0105, **14**-0352
Dickerson, T.J., **16**-1045
Dickhaut, J., **14**-0057
Dickinson, C.L., **15**-0073
Dickinson, M.G., **11**-0335
Dickstein, J.I., **10**-0286, **15**-0079, **15**-1215
DiCosimo, R., **14**-0271
Didelot, M., **13**-0709
Didenko, Y.T., **07**-0070, **07**-0072
Didillon, B., **05**-0383, **19**-0042
Didiuk, M.T., **15**-0870, **17**-0187, **18**-0814
Dieck, H.A., **13**-0387
Diederich, F., **02**-0308, **02**-0356, **03**-0071, **03**-0112, **03**-0150, **03**-0152, **03**-0206, **13**-0536, **14**-0300, **16**-1496
Dieffenbacher, A., **15**-2213
Diego-Castro, M.J., **15**-2025
Diéguez, M., **10**-1454, **15**-1491
Diéguez, M. Ruiz, A., **15**-1136
Diehl, W., **16**-0329
Diehm, M., **04**-0073
Diels, G., **13**-0187
Diercks, R., **15**-2402
Diesen, J.S., **19**-1155
Dieter, J.W., **10**-1273
Dieter, R.K., **10**-0519, **10**-1273, **10**-1279, **10**-1717, **15**-0322, **15**-1084, **16**-0860, **16**-0961
Dietl, H.K., **10**-1621, **12**-0116
Dietrich, B., **03**-0119, **04**-0242, **04**-0244
Dietrich, C.O., **12**-0223
Dietrich, H., **05**-0153
Dietrich-Buchecker, C.O., **03**-0200, **03**-0206, **03**-0207, **19**-1743
Dietsche, M., **16**-1655
Dietsche, T.J., **02**-0045, **02**-0046, **10**-1448, **10**-1450
Dietz Jr., A.G., **13**-0114, **13**-0703
Dietz, F., **02**-0245
Dietze, P., **10**-0356
Dietze, P.E., **10**-0065, **10**-0083, **10**-0279
Dietzel, P., **13**-0641
Diez, C., **18**-0487
Díez, B.R., **10**-1362
Díez-Barra, E., **07**-0112, **10**-0973, **16**-1174, **18**-0322
DiFate, V.G., **10**-0198
Differding, E., **12**-0134
DiGiuseppe, S., **15**-0245
Dijksman, A., **19**-0181, **19**-0225
Dijkstra, G., **10**-0695
DiLabio, G.A., **02**-0024
Dill, K., **10**-0209, **18**-0083
Dillard, D.E., **10**-0114

Dilley, G.J., **04**-0124
Dilling, W.L., **15**-2166, **15**-2237, **15**-2241, **19**-0921
Dillinger, S., **12**-0293
Dillon, R.L., **08**-0041, **10**-0026
Dilworth, B.M., **19**-1780
DiMarino, J.-L., **18**-0324
Dimas, L., **16**-0962
DiMauro, E.F., **16**-0692
Dimbacher, T., **08**-0084
Dimitriadis, E., **19**-1395
Dimitrov, V., **16**-0487
Dimock, S.H., **10**-1375, **15**-1067
Dimonie, M., **18**-0756
Dimroth, K., **05**-0052, **10**-0430, **10**-0443, **10**-0445, **10**-0446, **10**-0447, **19**-0290
Dinadayalane, T.C., **02**-0360, **02**-0361
Dinan, F.J., **11**-0586, **17**-0458
Dinçtürk, S., **14**-0089
Diner, U.E., **19**-1390
Dinér, P., **08**-0208
Ding, J., **15**-0134
Ding, K., **10**-1453, **10**-1460, **13**-0237, **15**-2129, **15**-2148
Ding, Q.-P., **16**-1036
Ding, R., **16**-0875
Ding, S., **07**-0118, **18**-0767
Ding, Y., **05**-0287, **19**-1199
Ding, Z., **12**-0454, **13**-0108
Ding, Z.-d., **10**-1387, **19**-1035
Dingerdissen, U., **16**-0344, **16**-0373
Dingle, T.W., **02**-0280
Dinizo, S.E., **15**-0134, **19**-0662
Dinjus, E., **16**-0850
Dinner, A., **18**-0195
Dinnocenzo, J.P., **01**-0101, **18**-0587
Dinoi, A., **15**-1766, **19**-0301
Dinoi, A., **19**-0615
Diogo, H.P., **02**-0331
DiPietro, J., **15**-1358
DiProfio, P., **10**-0407
Dirk, S.M., **19**-0753
Dirkx, I.P., **13**-0074
Dirlam, J., **10**-0170
Discordia, R.P., **04**-0193, **16**-1833
Dishong, D.M., **03**-0101, **03**-0146
Distaso, M., **16**-1842
Distler, H., **10**-0836
Ditchfield, R., **02**-0028
Diter, P., **19**-0823
DiTommaso, D., **16**-0750
Ditrich, K., **13**-0094, **16**-1019, **16**-1022
Dittman Jr., W.R., **19**-1450
Dittmer, B., **05**-0138
Dittmer, D.C., **04**-0193, **15**-0021, **17**-0365
Dittmer, D.L., **16**-0656
Dittmer, H., **10**-0212
DiValentin, C., **15**-1944, **19**-0114
Diver, S.T., **15**-0805, **15**-0815, **18**-0788, **18**-0789
Diversi, P., **04**-0064, **18**-0825
Diwakar, M.M., **19**-1186
Dix, D.T., **05**-0171
Dix, L.R., **11**-0125
Dixneuf, P.H., **15**-0279, **15**-0281, **15**-0372, **15**-0813, **15**-0835, **16**-0436, **18**-0814
Dixon, D.A., **04**-0233, **08**-0223
Dixon, J.A., **10**-1318, **13**-0650
Dixon, J.E., **10**-0371
Dixon, J.M., **04**-0367
Dixon, N.J., **10**-1532
Dixon, T.A., **03**-0072
Diyabalanage, H.V.K., **12**-0367
Djakovitch, L., **13**-0400, **13**-0541
Djerassi, C., **04**-0021, **04**-0129, **15**-0574, **17**-0125, **17**-0224, **19**-0075, **19**-0155, **19**-0708, **19**-1462
Dmitrenko, O., **04**-0414, **04**-0415
Dmitrienko, G.I., **02**-0054
Dmitriev, D.E., **04**-0360, **16**-0153
Dmitriev, L.B., **15**-0867
Dmitrieva, L.G., **12**-0710
Dneprovskaia, E., **15**-1000
Dneprovskii, A.N., **14**-0065
Dneprovskii, A.S., **06**-0029, **14**-0097, **14**-0128, **14**-0158
do Amaral, A.T., **16**-1566
do Amaral, L., **16**-0308, **16**-0315, **16**-1445
Do, J.Y., **18**-0063
Do, Y., **18**-0789
Do, Y.-K., **15**-1472
Doad, G.J.S., **16**-1284
Doan, P.E., **10**-0448
Dobaeva, N.M., **11**-0101
Dobashi, S., **15**-2152
Dobashi, Y., **04**-0175
Dobbs, A.P., **15**-1248, **16**-1479
Dobi, P., **10**-0430, **10**-0444
Dobinson, F., **19**-0358
Dobkowski, J., **12**-0087
Dobler, M., **02**-0268, **04**-0041
Döbler, C., **15**-1764, **19**-0238
Dobronravov, P.N., **18**-0250
Dobrovolny, M., **02**-0204
Dobrynin, V.N., **10**-0494
Dobson, B., **10**-0060, **17**-0064
Dobson, H.K., **18**-0609
Doca, N., **16**-2071
Dockendorff, C., **15**-0557
Dockery, K.P., **18**-0061
Dockx, J., **10**-0453
Doctorovich, F., **05**-0361, **12**-0532, **13**-0618, **16**-0843, **19**-1339
Doda, K., **10**-0713, **16**-1503
Dodd, R.H., **15**-1902, **15**-1903, **15**-1904
Dodderel, D., **04**-0329
Dodge, R.P., **02**-0228
Dodonov, V.A., **12**-0438, **13**-0224
Dodson, R.M., **18**-0855
Dodsworth, D.J., **16**-1784, **16**-1786
Dodziuk, H., **04**-0101
Doecke, C.W., **04**-0442, **10**-0152
Doering, W. von E., **02**-0157, **05**-0377, **05**-0380, **05**-0386, **10**-0012, **12**-0063, **12**-0219, **12**-0349, **12**-0351, **12**-0375, **15**-2096, **15**-2222, **15**-2232, **15**-2311, **15**-2319, **18**-0191, **18**-0373, **18**-0590, **18**-0613, **18**-0621, **18**-0630, **18**-0633, **18**-0640, **19**-0164
Dogadina, A.V., **15**-1315, **16**-1309
Dogan, O., **10**-0876
Doherty, A.M., **19**-0068
Doherty, M.M., **10**-0132
Doherty, R.M., **03**-0015, **10**-0429, **10**-0432, **10**-0443, **10**-0448
Dohi, M., **10**-0074
Dohle, W., **10**-1329
Dohmaru, T., **19**-1468, **19**-1492
Dohner, B.R., **17**-0028
Döhnert, D., **05**-0285
Doi, H., **15**-1140, **15**-1297
Doi, J.T., **10**-1089, **19**-0850
Doi, M., **19**-1591
Dokawa, S., **16**-1496
DokTycz, S.J., **07**-0066
Dolak, T.M., **10**-1711
Dolan, S., **16**-1239
Dolata, D.P., **15**-2026
Dolbier Jr., W.R., **04**-0062, **05**-0306, **12**-0171, **14**-0072, **15**-0001, **15**-1212, **15**-2170, **15**-2219, **16**-0572, **16**-0809, **18**-0159, **18**-0461, **18**-0482, **18**-0509, **18**-0589, **18**-0628
Dolbier, D.W., **15**-2219

Dolbier, W.B., **18**-0563
Dolbier, W.R., **18**-0471
Dolby, L.J., **16**-1466, **19**-1410
Dolby-Glover, L., **13**-0254
Doldouras, G.A., **19**-1516
Dolenc, D., **12**-0126
Dolenko, A., **18**-0880, **18**-0889
Doleschall, G., **16**-1660, **19**-0440, **19**-0662, **19**-1128
Dolfini, J.E., **15**-0048
Dolhem, E., **10**-1811, **10**-1818
Doll, K.M., **09**-0103
Doll, R.J., **19**-0065
Dollat, J., **10**-1434
Dolle, R.E., **11**-0462, **15**-1958
Doller, D., **19**-0612, **19**-0614
Dollinger, H., **10**-1492, **10**-1716
Dollinger, L.M., **16**-1352
Dollinger, M., **18**-0630
Dolliver, D.D., **04**-0221
Dolman, S.J., **18**-0808
Dolphin, J.M., **16**-1208
Domae, T., **16**-1426
Domaille, P.J., **15**-1504
Domain, R., **08**-0219
Domalski, E.S., **01**-0093
Domalski, M.S., **15**-0860
Domareva-Mandel'shtam, T.V., **18**-0634
Dombrovskii, A.V., **13**-0732, **16**-1306
Dombrovskii, V.A., **16**-1306
Dombrowski, G.W., **01**-0101
Domeier, L.A., **04**-0164
Domen, K., **05**-0069
Domenick, R.L., **10**-0178
Domine, M.E., **19**-0969
Domingo, L., **16**-1496
Domingo, L.R., **15**-1984, **15**-1999, **15**-2057, **15**-2099, **15**-2120
Domingo, V.M., **16**-1384
Dominguez, R.M., **17**-0131, **17**-0145
Domínguez, E., **15**-1070, **16**-0372
Domínguez, G., **15**-1430, **15**-1436, **15**-1438, **15**-1441, **15**-1443
Dominguez-Fernandez, B., **15**-1770, **15**-1773
DoMinh, T., **15**-2213
Dommisse, R., **13**-0196
Dommisse, R.A., **13**-0174, **13**-0178
Donahue, N.M., **06**-0007
Donald, D.S., **18**-0039
Donaruma, L.G., **18**-0335
Donath, W.E., **04**-0382
Donati, D., **16**-2102
Donato, A., **19**-0960
Donde, Y., **18**-0689
Done, J.N., **10**-1320
Donetti, A., **19**-0450
Dong, C., **15**-1463, **19**-0180
Dong, D.C., **10**-0450
Dong, G., **10**-1497, **15**-1405, **16**-0556
Dong, L., **15**-1128
Dong, M., **14**-0188
Dong, Q., **10**-0948
Dong, T.-W., **15**-0508, **15**-0566, **16**-0663
Dong, X., **19**-1028
Dong, Y.-W., **15**-1034
Dong, Z.-M., **19**-0402
Dongare, M.K., **18**-0309
Dönges, R., **02**-0181
Donnelly, D.M.X., **12**-0520
Donnelly, S.J., **19**-1450
Donnoli, M.I., **04**-0114, **19**-0823
Donohoe, G., **16**-0191
Donohoe, T.J., **15**-0534, **15**-0536, **15**-1680
Donohue, J.A., **16**-1593
Donovan, D.J., **05**-0021, **05**-0090, **10**-0200
Donovan, T.A., **10**-1222
Donovan, W.H., **05**-0200
Donow, F., **04**-0174
Donzel, A., **16**-1845
Doomes, E., **17**-0346
Doorakian, G.A., **18**-0462
Döpp, D., **18**-0862
Doraiswamy, L.K., **07**-0085
Dorange, I., **15**-0832
Dordick, J.S., **19**-0232
Dore, M., **11**-0451
Dorff, P., **16**-1322
Dorfman, E., **18**-0373
Dorfman, L.M., **05**-0109
Doria, G., **15**-0469
Dorigo, A.E., **04**-0295
Doris, E., **10**-0887, **12**-0107, **13**-0584, **15**-0581, **17**-0207, **19**-0905
Dormer, P.G., **09**-0105, **13**-0504, **13**-0541, **13**-0606
Dorn, C.R., **11**-0381
Dorn, H.C., **02**-0364
Dornow, R., **15**-0101
Dorofeenko, G.N., **16**-0281
Dorofeev, A.S., **16**-0153, **19**-1691
Doron'kin, V.N., **13**-0676
Dorow, R.L., **12**-0230, **19**-0501
Dorr, H., **19**-0416
Dörr, M., **18**-0853
Dorrell, F.J., **12**-0021
Dorsch, H., **04**-0484
Dorsey, G.F., **16**-1556
Dorta, R., **19**-0432
Dorta, R.L., **17**-0154
Dorwin, E., **13**-0019
Dory, Y.L., **15**-1983
dos Santos, C., **19**-0367
dos Santos, L.M.F., **13**-0402
dos Santos, R.M.B., **01**-0098
Dossena, A., **12**-0118
Dostal, J.M., **17**-0052
Dostrovsky, I., **18**-0005
Dosunmu, M.I., **16**-0027
Doty, J.C., **15**-2252
Dötz, K.H., **15**-2417
Dou, H.-N., **19**-0082
Dou, H.J., **13**-0736, **13**-0743, **14**-0326
Doubleday Jr., C., **05**-0285, **10**-1370
Doubleday, W., **16**-0645
Doucet, H., **10**-0886, **10**-1420, **13**-0367, **13**-0399, **13**-0401, **13**-0445, **13**-0539, **13**-0541, **13**-0560, **16**-0642, **16**-1798
Doucet, R.J., **19**-0121
Douek, M., **02**-0233
Dougharty, K.W., **15**-0004, **15**-0033
Dougherty, D.A., **03**-0075, **11**-0019
Dougherty, T.J., **07**-0049
Dougherty, R.C., **01**-0001
Douglas, A.W., **18**-0723
Douglas, C.J., **10**-0997
Douglas, D.E., **06**-0039, **16**-2073
Douglas, J., **11**-0245
Douglas, J.E., **16**-1561
Douglas, K.T., **16**-1569, **16**-1571, **16**-1861
Douglas, T.A., **06**-0026
Douglass, D.C., **10**-0131
Douglass, J.E., **11**-0599
Douglass, M.R., **15**-1871
Doumaux Jr., A.R., **14**-0249, **19**-0588
Dounay, A.B., **13**-0378
Douraghi-Zadeh, K., **16**-2067
Doussot, J., **10**-1019, **12**-0340
Dow, R.L., **19**-0135
Dowd, P., **10**-1801, **15**-0963, **15**-1251, **18**-0175, **18**-0176, **18**-0246
Dowd, S.R., **10**-1683
Dowd, W., **10**-0430, **17**-0092
Dowden, **08**-0149
Dowdy, E.D., **15**-0335, **15**-0767, **16**-1828
Doweyko, A.M., **12**-0187

Dowle, M.D., **15**-1584
Dowling, J.P., **12**-0089, **12**-0417
Downey, C.W., **16**-1053, **16**-1145, **16**-1161
Downie, I.M., **19**-1305
Downing, J.W., **04**-0497, **04**-0498
Downing, S., **16**-0130
Dows, D.A., **04**-0378
DoxK.M., **03**-0121, **10**-1307
Doyarenko, M.N., **04**-0465
Doye, S., **13**-0117, **15**-0326, **15**-0348, **15**-0355
Doyle, D.L., **12**-0254
Doyle, G., **18**-0796
Doyle, M.J., **15**-2201, **18**-0837
Doyle, M.P., **10**-0756, **10**-1183, **11**-0265, **12**-0348, **12**-0352, **12**-0358, **12**-0368, **12**-0370, **13**-0716, **13**-0733, **14**-0209, **14**-0354, **15**-0471, **15**-0707, **15**-1480, **15**-2065, **15**-2266, **15**-2286, **15**-2292, **15**-2298, **15**-2302, **15**-2306, **15**-2355, **16**-0181, **18**-0242, **19**-0135, **19**-0251, **19**-0578, **19**-0665, **19**-1303, **19**-1450, **19**-1567
Doyle, T.D., **18**-0516
Doyon, J.B., **04**-0454
Dozias, M.-J., **16**-0144
Drăguțn, V., **18**-0756
Drabicky, M.J., **10**-0517
Drabowicz, J., **04**-0047, **10**-0841, **19**-0795, **19**-0822, **19**-0826, **19**-0853, **19**-1602
Draffehn, J., **09**-0043
Dräger, G., **16**-0429
Drâghici, C., **15**-2210
Drago, R.S., **03**-0018, **03**-0054, **08**-0219, **10**-0403, **10**-0448, **19**-0109
Dragovich, P.S., **19**-0894
Drahowzal, F.A., **11**-0316, **11**-0352
Drake, B.V., **15**-2116
Drake, C.A., **04**-0516
Drake, J., **12**-0091
Drake, R.A., **18**-0459
Dralants, A., **02**-0244
Dransfeld, A., **02**-0104, **18**-0593
Draper, J.D., **10**-0655
Draper, R.W., **19**-1186
Draper, T.L., **13**-0376
Drauz, K., **04**-0136, **10**-1033, **15**-0609, **19**-1022, **19**-1082
Drauz, K.-H., **15**-1813, **15**-1817
Drechsel-Grau, E., **15**-0101
Drechsler, K., **15**-2172
Dreher, E., **13**-0704
Dreiding, A.S., **04**-0040, **12**-0032, **15**-2213
Drent, E., **15**-1381
Drenth, W., **06**-0043, **15**-0218, **16**-1776, **16**-2125
Dresely, S., **16**-0493
Dreßel, B., **02**-0161
Drew, G.M., **04**-0340
Drew, R.M., **16**-0009
Drewello, T., **19**-0064
Drewer, R.J., **07**-0045
Drewes, R., **18**-0560
Drewes, S.E., **16**-0771, **16**-0772
Drexler, H.-J., **15**-0608, **15**-0609
Driessen, P.B.J., **10**-0152
Driggs, R.J., **10**-1377
Driver, M.S., **13**-0174, **13**-0175
Driver, T.G., **15**-0736
Drobnica, L., **16**-1755
Drommi, D., **10**-1453
Dronov, V.I., **16**-0398
Drowns, M., **10**-0981
Drozd, J.C., **19**-0404
Drozd, V.N., **10**-1483, **13**-0052, **13**-0775, **15**-0867
Drozdova, T.I., **15**-1608
Drtina, G.J., **10**-1150
Drucker, G.E., **02**-0141, **09**-0060
Druelinger, M., **10**-1661
Druelinger, M.L., **01**-0060
Druet, L.M., **08**-0038, **16**-1598
Druey, J., **18**-0392
Druliner, J.D., **15**-1504
Drumright, R.E., **04**-0422
Drury III, W.J., **12**-0124, **12**-0167, **15**-2180, **16**-2103, **19**-1273
Druzhkov, O.N., **12**-0620
Druzian, J., **16**-1863
Drygina, O.V., **15**-1932
Dryuk, V.G., **15**-1726, **15**-1731
Du Bois, J., **12**-0228, **12**-0229, **15**-1903
du Mesnil, F.-X., **15**-0796, **15**-2079
du Vigneaud, V., **19**-1514
Du, C.F., **13**-0310
Du, D.-M., **19**-1032
Du, H., **10**-1273, **15**-2148, **15**-2148
Du, P.C., **19**-0203
Du, W., **15**-0145
Du, X., **13**-0439, **15**-1181, **16**-1893
Duan, C.-y., **03**-0133
Duan, H., **19**-0241
Duan, H.-F., **19**-1028
Duan, J., **12**-0171
Duan, W.-S., **04**-0403
Duan, Y.-Z., **13**-0347
Duan, Z.F., **19**-0291
Dubac, J., **07**-0114, **10**-1092, **11**-0220, **11**-0423, **15**-0964, **16**-1091, **16**-2029, **19**-1318
Dubbaka, S.R., **13**-0243, **13**-0296, **16**-2168
Dubé, D., **10**-0996
Dubé, P., **15**-0497
Duboc, C., **10**-0350
DuBois, J., **19**-0499
Dubois, G., **15**-1729, **15**-1729
Dubois, J.E., **02**-0383, **04**-0295, **09**-0021, **09**-0059, **09**-0074, **10**-0170, **10**-1368, **10**-1370, **10**-1751, **11**-0010, **12**-0099, **12**-0303, **12**-0661, **14**-0418, **15**-0014, **15**-0016, **15**-0036, **15**-0068, **15**-0097, **16**-0514, **16**-0811, **16**-1014, **16**-1926, **16**-1929, **16**-1930, **16**-2040, **17**-0157, **18**-0035
Dubois, L.H., **12**-0607
Duboudin, F., **12**-0316
Duboudin, J.G., **15**-0862
Dubree, N.J.P., **13**-0652
Dubreuil, J.F., **15**-1949
Dubrova, L.N., **11**-0573
Dubuis, R., **15**-0436
Duce, P.P., **10**-0034
Ducep, J., **10**-1727, **12**-0388
Ducep, J.-B., **15**-2145
Ducep, J.B., **10**-1264, **10**-1706, **18**-0727
Duchêne, A., **10**-1419, **12**-0272, **12**-0297
Duchin, L., **07**-0080
Duchin, L., **16**-1541
Duclos Jr., R.I., **13**-0741
Ducom, J., **05**-0166, **12**-0583, **16**-0540
Ducoux, J.-P., **10**-1521
Ducray, R., **11**-0137
Dudás, J., **19**-1215
Duddeck, H., **04**-0458
Duddu, R., **15**-2068, **16**-1768
Duddy, N.W., **16**-1571
Dudek, C.M., **19**-1403
Dudfield, P., **10**-1641
Dudinskaya, A.A., **15**-1987
Dudley, G.B., **10**-0690
Dudman, C.C., **19**-1130
Dueno, E.E., **10**-0610, **10**-0730, **16**-0199
Duesler, E., **15**-2210
Duesler, E.N., **04**-0187, **13**-0784
Duetz, W., **19**-0543
Duetz, W.A., **19**-0544
Dufaux, R., **12**-0691

Duff, J.L., **10**-0098
Duff, K., **16**-0916
Duffey, D., **18**-0888
Duffey, D.C., **10**-0212
Duffey, M.O., **19**-1776
Duffin, H.C., **19**-0632
Duffley, R.P., **14**-0378
Duffy, J.A., **16**-1600
Dufková, L., **16**-0760
Dufresne,Y., **10**-0614
Dugave, C., **15**-0153
Duggan, M.E., **16**-0192
Duggan, P.J., **18**-0060
Dughera, S., **10**-1866
Duhaime, R.M., **12**-0080
Duhamel, L., **04**-0136, **10**-1269, **17**-0315
Duhamel, P., **04**-0136, **16**-0285, **16**-0286
Duhl-Emswiler, B.A., **16**-1324
Duijvestijn, M.J., **05**-0223
Duisberg, C., **11**-0380
Dujardin, R., **12**-0567
Duke, A.J., **15**-2213, **15**-2215, **17**-0421, **17**-0499, **17**-0502, **17**-0510, **17**-0516
Duke, C.V.A., **13**-0147, **13**-0256
Dull, D.L., **04**-0105
Dumas, F., **15**-1045, **16**-1078
Dumeunier, R., **16**-1618
Dumont, W., **15**-1114, **18**-0133, **18**-0235
Dumpis,Yu.Ya., **19**-1279
Dumsha, T.C., **16**-1593
Duñach, E., **15**-1236, **15**-1388, **16**-0850, **18**-0151, **19**-1384, **19**-1495
Duncan Jr., S., **11**-0371
Duncan, A.P., **15**-1136
Duncan, F.J., **05**-0333
Duncan, J.A., **18**-0611
Duncan, J.H., **05**-0187
Duncan, M.P., **19**-0480, **19**-0844
Duncan, P., **14**-0033
Duncan, P., **14**-0328
Duncan, S.M., **07**-0102, **15**-2022
Duncan, W.G., **15**-2219
Dunetz, J.R., **12**-0525
Dunford, H.B., **02**-0387
Dunitz, J.D., **02**-0228, **02**-0283, **03**-0045, **04**-0041, **04**-0295, **04**-0318, **04**-0387, **04**-0452, **04**-0453, **05**-0191, **05**-0192
Dunkelblum, E., **15**-0647, **15**-0650
Dunkin, I.R., **05**-0203
Dunlap, M.S., **19**-1676
Dunlap, N.K., **15**-1092
Dunlap, R.P., **06**-0076, **19**-1765
Dunlop, A.K., **03**-0160
Dunn, A.D., **15**-1943, **16**-0200, **16**-0433, **16**-1250
Dunn, G.E., **12**-0638
Dunn, J.A., **05**-0384
Dunn, K., **12**-0614
Dunne, A.M., **18**-0800
Dunne, E.C., **16**-1271
Dunne, K., **05**-0061, **18**-0748
Dünnebacke, D., **05**-0237
Dunnigan, D.A., **10**-1582
Dunning, J.E., **17**-0247
Dünnwald, T., **16**-1500, **16**-2065
Dunogues, J., **12**-0316, **12**-0428, **15**-1175, **16**-0743
Duong, T., **19**-0604
Dupau, P., **07**-0122
Dupont, J., **09**-0110, **13**-0297, **13**-0397, **13**-0401, **13**-0475, **15**-0798
Dupont, R., **10**-1454
Duprat, F., **14**-0231
Dupré, D., **13**-0342, **15**-1163
DuPriest, M.T., **10**-1728
Duprilot, J., **10**-1854
Dupuis, C., **19**-1622
Dupuis, D., **10**-1640
Dupuis, J., **19**-1532
Dupuy, C., **15**-1142
Dupuy, W.E., **10**-0203, **18**-0048
Duquesne, A., **12**-0465
Duraisamy, M., **05**-0356, **14**-0378
Duran, M., **02**-0154
Durand, R., **19**-0247
Durandetta, J.L., **10**-1738
Durandetti, M., **10**-1397, **13**-0304, **13**-0344, **16**-0570, **16**-0716
Durant, A., **16**-0578
Durbut, P., **15**-1795
Durden, D.A., **16**-0367
Durham, D.L., **14**-0232
Durham, L.J., **19**-0361
Durig, J.R., **04**-0382
Durr, R., **15**-0324
Dürr, H., **02**-0052, **02**-0243, **05**-0404, **07**-0045, **15**-2322, **18**-0469, **18**-0470, **18**-0643
Durrant, J.L.A., **15**-1641
Durst, H.D., **03**-0101, **10**-0462, **16**-0361
Durst, T., **04**-0220, **05**-0099, **05**-0110, **05**-0119, **05**-0145, **05**-0198, **05**-0199, **08**-0014, **10**-1447, **10**-1656, **12**-0183, **12**-0390, **12**-0415, **13**-0161, **16**-1013, **16**-1194, **16**-1195, **16**-1376, **16**-1379, **16**-2033, **18**-0143, **19**-0638, **19**-0842
Dushenko, G.A., **18**-0540
Dusich, C.L., **12**-0167
Dusold, L.R., **17**-0262
Duspara, P.A., **04**-0454
Dussault, P., **19**-0717
Dussault, P.H., **19**-1423
Dussin, G., **10**-1384
Dust, J.M., **14**-0089
Dustman, C.K., **05**-0099
Dustman, J.A., **19**-0525
Duthaler, R.O., **16**-0684
Dutheuil, G., **16**-1280
Dutler, H., **18**-0111
Dutler, R., **10**-0280
Dutly, A., **11**-0096
Dutra, G.A., **10**-1344
Dutron-Woitrin, F., **19**-1795
Dütsch, H.R., **14**-0093
Dutta, J., **15**-0480, **15**-0582
Dutta, M.P., **19**-1694
Dutta, P., **10**-1223, **16**-1524, **16**-1829
Dutta, V.P., **15**-1562
Duursma, A., **15**-1131, **15**-1138
Duval, D., **15**-0038
Duval, X., **04**-0136
DuVernet, R.B., **02**-0295
Dux III, F., **19**-1295
Dux, F.J., **10**-0803
Duygu, A.N., **16**-0986
Duynstee, E.F.J., **10**-0422
Dvolaitzky, M., **19**-1295
Dvorak, D., **16**-2100
Dvoretzky, I., **05**-0377, **12**-0383, **19**-0418
Dvorko, G.F., **10**-0033, **10**-0406
Dvornikova, E., **11**-0281
Dvořák, D., **15**-0918
Dwyer, F.G., **11**-0052
Dwyer, J., **15**-0970
Dyadyusha, G.G., **15**-0092
Dyall, L.K., **05**-0404
Dyatkin, B.L., **15**-0072
Dyatkina, M.E., **05**-0285
Dyck, J., **13**-0491
Dyckman, A.J., **15**-0775, **15**-0842
Dye, J.L., **15**-0540
Dyker, G., **13**-0338
Dykstra, R.R., **05**-0181
Dyson, P.J., **09**-0109, **15**-0525, **15**-0531
Dyumaev, K.M., **08**-0217
Dzhemilev, U.M., **10**-1438, **15**-0704, **15**-0706, **15**-2195, **15**-2429
Dzidic, I., **08**-0225
Dzielenziak, A., **19**-0138

Dzierba, C.D., **16**-1457
Dzyuba, S.V., **09**-0118

Eaborn, C., **11**-0011, **11**-0032, **11**-0045, **11**-0073, **11**-0084, **11**-0085, **12**-0045, **12**-0279, **12**-0476, **13**-0616
Eachus, S.W., **02**-0258
Eaddy, J.F., **16**-1780
Eadon, G., **19**-0213
Earl, G.W., **10**-0285
Earl, H.A., **10**-0378
Earle, M.J., **09**-0109, **13**-0415
Earle, R.B., **13**-0006
Early, T.R., **13**-0177, **13**-0407, **13**-0492
Easdon, J.C., **15**-0004, **15**-0033
Eash, K.J., **16**-0075, **16**-0172, **18**-0140
Eason, R.G., **02**-0071
East, S.P., **04**-0237
Eastham, J.F., **12**-0392, **18**-0001, **18**-0124, **18**-0177, **18**-0188
Eastment, P., **08**-0186
Eastmond, R., **14**-0317
Easton, C.J., **03**-0186, **14**-0097, **15**-0104, **15**-1939
Eastwood, F.W., **17**-0343, **18**-0519, **18**-0520, **18**-0688
Eaton, D.F., **07**-0039
Eaton, B.E., **15**-2363
Eaton, D.L., **15**-2394
Eaton, G., **12**-0654
Eaton, J.T., **16**-0137, **16**-1775
Eaton, P., **15**-2004
Eaton, P.E., **04**-0441, **04**-0443, **04**-0520, **07**-0064, **10**-0046, **11**-0155, **13**-0645, **15**-2238, **18**-0067, **18**-0528, **18**-0838, **18**-0839, **19**-0771
Eaton, S.S., **04**-0216
Eatough, D.J., **03**-0101
Ebata, K., **04**-0503, **04**-0518
Ebbesen, T.W., **18**-0225
Ebel, H.F., **05**-0099
Ebeling, G., **13**-0401
Eberbach, W., **15**-2196
Eberhard, J.K., **11**-0448
Eberhard, M.R., **13**-0401
Eberhardt, G.G., **12**-0392, **15**-0724
Eberhardt, W.H., **16**-0028
Eberius, K.W., **02**-0227
Eberle, M.K., **16**-1061, **16**-1922
Eberlein, T.H., **10**-0995
Eberlin, M.N., **11**-0071, **16**-1350, **18**-0655
Ebersberger, J., **11**-0350
Eberson, L., **06**-0027, **08**-0178, **11**-0101, **14**-0415, **19**-0004
Ebert, C., **17**-0152
Ebert, G.W., **10**-1222, **12**-0597
Ebert, H.M., **16**-1786
Ebine, S., **13**-0218
Ebitani, K., **15**-1745, **15**-1791, **16**-0149, **19**-0120
Ebner, M., **16**-1827
Ebrahim, S., **15**-1814
Ebrahimi, S., **10**-0809, **10**-0936, **16**-0175, **16**-0160, **16**-0166
Eby, P., **15**-0162
Eby, P.S., **19**-1729
Echavarren, A.M., **10**-1472, **12**-0276, **13**-0378, **13**-0523, **13**-0619, **15**-0776, **15**-0818, **15**-0820, **15**-2392, **19**-1173
Echegoyen, L., **05**-0212
Echevarren, E.M., **10**-1361
Echigo, Y., **10**-1089
Eck, D.L., **17**-0035
Eckart, M.D., **18**-0040
Ecker, J.R., **15**-1827
Ecker, R., appendixA-0023
Eckert, C.A., **10**-0411, **15**-0614, **15**-2096
Eckert, M., **19**-0238
Eckert-Maksić, M., **02**-0082, **02**-0348, **02**-0353, **11**-0078
Eckes, H., **15**-2047
Eckes, L., **05**-0067
Eckhardt, W., **01**-0044
Eda, T., **16**-1261
Eda, Y., **12**-0656
Edelstein, J., **04**-0080
Edens, M., **10**-0232
Eder, U., **16**-1072
Edgar, M., **04**-0314
Edge, D.J., **18**-0072
Edgecombe, K.E., **01**-0029
Edgington, D.N., **10**-0398
Edison, D.H., **17**-0006
Edman, C., **16**-0317
Edmison, M.T., **14**-0127
Edmonds, P., **07**-0067
Edmondson, P.B., **01**-0097
Edmondson, S.D., **13**-0193
Edward, J.T., **08**-0123, **08**-0164, **16**-0119, **19**-1469
Edwards Jr., W.R., **11**-0440, **16**-1937
Edwards, A., **08**-0147
Edwards, A.G., **10**-0430, **10**-0444
Edwards, A.J., **16**-1276
Edwards, B.E., **16**-0203, **16**-0206
Edwards, G.L., **15**-1685
Edwards, J.D., **12**-0348
Edwards, J.K., **16**-1172
Edwards, J.O., **10**-0348, **10**-0361, **10**-0363, **15**-1743, **15**-1766, **15**-1768, **15**-1786, **19**-0010, **19**-0255
Edwards, J.P., **15**-2334, **15**-2337, **16**-0924
Edwards, K., **15**-1677
Edwards, L.G., **15**-2441
Edwards, M.L., **10**-0899
Edwards, O.E., **10**-0268
Edwards, S.D., **18**-0815
Eeckhaut, A., **19**-1328
Eeshwaraiah, B., **15**-1340
Effenberger, F., **10**-0688, **10**-1033, **11**-0013, **11**-0046, **11**-0139, **11**-0216, **11**-0375, **11**-0434, **11**-0448, **11**-0508, **11**-0547, **13**-0083, **13**-0752
Effio, A., **16**-0318, **18**-0073
Efimova, I.V., **12**-0524, **15**-0372
Efraty, A., **02**-0227
Efros, L.S., **02**-0124
Ege, G., **17**-0507
Eggensperger, H., **10**-1075
Egger, K.W., **15**-0059, **15**-2210, **17**-0122, **17**-0495
Eggerding, D., **02**-0346
Eggers, M.D., **10**-0306
Eggestad, J., **03**-0107
Egi, M., **16**-1976
Egli, H., **19**-0470
Egli, M., **04**-0164
Egli, R.A., **11**-0650, **19**-1170
Egorochkin, A.N., **03**-0037, **09**-0020
Egorov, M.P., **13**-0008
Eguchi, K., **19**-1354
Eguchi, S., **10**-1322
Ehler, D.F., **19**-1505
Ehlers, A.W., **15**-2072
Ehlers, J., **04**-0175
Ehmann, W.J., **15**-0467
Eholzer, U., **17**-0479
Ehrenberg, M., **01**-0066
Ehrenkaufer, R.E., **16**-0371, **19**-1203
Ehrenson, S., **09**-0037, **09**-0047, **09**-0051, **09**-0054
Ehrentraut, A., **13**-0483
Ehrlich, P., **16**-1254
Ehrlich, S., **15**-0080
Eibach, F., **19**-0027
Eichberger, M., **15**-0314, **15**-0343
Eichel, W., **15**-0101
Eichelmann, H., **10**-0840
Eichenauer, H., **04**-0143, **16**-1032

Eicher, T., **02**-0204, **04**-0477, **16**-0464
Eichhorn, I., **16**-0140
Eickemeyer, D.B., **13**-0779
Eidenschink, R., **15**-1977
Éidus, Ya.T., **10**-1833, **12**-0731, **15**-1375, **18**-0422
Eierdanz, H., **15**-0094
Eigen, M., **08**-0097
Eigenmann, E.W., **17**-0117
Eigenmann, H.K., **14**-0058
Eikawa, M., **19**-0593
Eilbracht, P., **15**-0340, **15**-0341, **15**-1485
Eilers, F., **10**-1527
Eimer, J., **15**-2322, **18**-0469, **18**-0470
Einhorn, C., **10**-0473, **10**-1150, **15**-0190, **16**-0840, **19**-0189
Einhorn, J., **10**-0473, **13**-0098, **15**-0190, **16**-0840, **16**-0966, **19**-0189
Einstein, F.W.B., **02**-0241
Eis, M.J., **10**-1563
Eisch, J.J., **11**-0224, **12**-0001, **15**-0501, **15**-0703, **15**-0712, **15**-0861, **15**-0862, **15**-2403, **15**-2405, **16**-0273, **16**-0500, **18**-0402, **18**-0417
Eisele, D., **18**-0784
Eisele, G., **10**-1524
Eisen, M.S., **16**-0968
Eisenberg, R., **05**-0222
Eisenbraun, E.J., **16**-0989, **19**-0557, **19**-0558
Eisenhardt, W., **16**-2084
Eisenschmid, T.C., **05**-0222
Eisenstein, O., **01**-0048, **10**-0364, **15**-2406, **19**-1063
Eisenthal, R., **19**-0466, **19**-0630
Eisler, S., **17**-0325
Eissenstat, M.A., **10**-1653
Eiter, K., **17**-0303, **17**-0305
Ejiri, E., **02**-0296, **02**-0303, **02**-0304, **02**-0306, **02**-0328
Ek, F., **13**-0675, **13**-0725
Eklund, L., **15**-2039
Eklund, R., **18**-0352
Eksterowicz, J.E., **14**-0057
Ekwurieb, N.N., **19**-1128
El Ali, B., **12**-0748, **15**-0341, **15**-1385, **15**-1403, **15**-1466
El Bialy, S.A.A., **15**-1254
El Gaïed, M.M., **16**-0774
El Gharbi, R., **16**-1324
El Idrissi, M., **19**-0371
El Kaim, L., **16**-0396, **16**-1735, **19**-1255
El Zaizi, A., **11**-0646
El'yanov, B., **15**-0970
El-Alaoui, M., **02**-0383, **10**-0531, **15**-0251
El-Bassiouny, F.A., **16**-1141
El-Bouz, M., **15**-1112, **15**-1114
El-Din, A..M.N., **11**-0176
El-Din, G.N., **16**-1281
El-Dusouqui, O.M.E., **11**-0029
El-Fekky, T.A., **10**-1839
El-Ghanam, A., **15**-1403
El-Hiti, G.A., **11**-0276, **16**-0661, **19**-0996
El-Khrisy, E.A.M., **16**-0220
El-Mowafy, A.M., **19**-1523
El-Nasr, M.M.S., **05**-0378
El-Newaihy, M.F., **16**-1141
El-Quisairi, A.K., **15**-1534
El-Saidi, M., **05**-0394
El-Sayed, M.A., **07**-0024
El-Telbany, F., **19**-1494
Elad, D., **11**-0594, **15**-0050, **15**-1353, **15**-1354
Elam, C., **08**-0147
Elam, E.U., **16**-2080
Elangovan, A., **13**-0544
Elbl, K., **03**-0029
Eldin, S., **05**-0114, **12**-0060
Eldred, S.E., **16**-1732
Elemes, Y., **14**-0238, **14**-0240
Eleveld, M.B., **12**-0108, **16**-0490
Elgemeie, G.H., **15**-1720
Elgendy, S., **12**-0332
Elguero, J., **02**-0348, **02**-0415, **02**-0423, **08**-0012, **08**-0228, **19**-1350
Elia, R.J., **10**-0212
Elian, M., **15**-2210
Eliason, R., **10**-0571, **10**-0534
Eliel, E.L., **01**-0087, **03**-0203, **04**-0001, **04**-0017, **04**-0021, **04**-0098, **04**-0099, **04**-0100, **04**-0115, **04**-0116, **04**-0117, **04**-0126, **04**-0136, **04**-0137, **04**-0138, **04**-0141, **04**-0156, **04**-0157, **04**-0250, **04**-0253, **04**-0259, **04**-0261, **04**-0263, **04**-0274, **04**-0316, **04**-0337, **04**-0343, **04**-0350, **04**-0351, **04**-0354, **04**-0356, **04**-0, **04**-0359, **04**-0361, **04**-0362, **04**-0376, **04**-0381, **04**-0387, **04**-0424, **05**-0130, **06**-0041, **09**-0014, **10**-0108, **13**-0744, **14**-0025, **16**-0005, **16**-0493, **17**-0069, **19**-1064, **19**-1389, **19**-1475
Eliev, S., **19**-1063
Elings, J.A., **18**-0359
Elinson, M.N., **12**-0677, **16**-0153, **19**-1691
Eliseenkov, E.V., **06**-0029, **14**-0128
Eliseev, O.L., **10**-1851
Elix, J.A., **02**-0272, **02**-0326, **18**-0371
Elizarov, A.M., **03**-0189
Elkik, E., **16**-1215
Ell A.H., **19**-0221
Ellenberger, S.R., **15**-1712
Ellencweig, A., **04**-0366
Ellensohn, R.M., **16**-0582
Ellern, D.A., **02**-0363
Ellestad, K.E., **15**-0879
Ellingboe, J.W., **16**-1014
Ellinger, C.A., **10**-0907
Elliott, G.I., **13**-0579, **13**-0580
Elliott, J.D., **10**-0992
Elliott, R.C., **13**-0733
Elliott, R.L., **02**-0274
Elliott, S.P., **15**-2209, **15**-2221
Ellis, D.D., **04**-0249
Ellis, D.J., **15**-0525, **15**-0531
Ellis, G.P., **13**-0268
Ellis, J.E., **16**-1065
Ellis, R.J., **16**-1234, **16**-1237
Ellis, W.W., **16**-1473
Ellison, F.O., **01**-0002
Ellison, G.B., **01**-0025, **01**-0088, **02**-0024, **05**-0132, **05**-0269, **05**-0273, **10**-0491, **17**-0120
Ellison, J.J., **05**-0175
Ellman, J.A., **10**-0847, **15**-092, **15**-2065, **16**-0895, **16**-0896, **16**-1823, **19**-0829
Ellsworth, E.L., **10**-1355, **10**-1367, **10**-1375, **12**-0570, **15**-0708, **15**-1067, **15**-1082
Ellzey Jr., M.L., **02**-0128
Elmasmodi, A., **18**-0382
Elmore, S.W., **18**-0598
Elmorsy, S.S., **10**-1028
Elofson, R.M., **13**-0689, **13**-0740, **13**-0747
Elphimoff-Felkin, I., **19**-1361
Elpiner, I.E., **07**-0077
Elschenbroich, C., **05**-0145
Elsenbaumer, R.L., **16**-0540
Elsevier, C.J., **10**-1349, **10**-1363
Elsinger, F., **10**-1175
Elsom, L.F., **14**-0370, **14**-0371
Elson, I.H., **14**-0044
Elson, K.E., **10**-0705
Elvidge, J.A., **11**-0113, **16**-0426
Elving, P.J., **08**-0007, **08**-0039
Elworthy, T.R., **10**-1348, **15**-1344
Emami, R., **12**-0070
Emanuel, C.J., **14**-0070
Emch, J.D., **16**-1352

Emeric, G., **18**-0318
Emerschitz, T., **16**-0476
Emerson, G.F., **02**-0229
Emerson, M.T., **03**-0009
Emerson, T.R., **16**-0275
Emilsson, P., **13**-0415
Emme, I., **16**-0774
Emmerich, D.J., **12**-0294, **15**-0291
Emmons, W.D., **15**-1727, **16**-1305, **18**-0365, **19**-0766
Emrani, J., **18**-0677
Emrich, D.E., **15**-0960
Emrich, R., **04**-0437
Emrullahoglu, M., **13**-0349
Emsley, J., **03**-0010, **03**-0028, **03**-0043, **10**-0713, **16**-0456, **16**-1886
Enami, H., **12**-0547
Enayat, E.I., **16**-1141
Encarnación, L.A.A., **15**-2161
Encina, M.V., **07**-0047
Endate, K., **10**-1258
Enders, D., **04**-0143, **10**-0753, **10**-1592, **10**-1660, **10**-1661, **10**-1721, **15**-0994, **15**-1042, **15**-1347, **15**-1368, **15**-1810, **16**-0091, **16**-0724, **16**-0857, **16**-1032, **16**-1057, **16**-1190, **18**-0703, **19**-0501, **19**-1281, **19**-1683
Endo, K., **02**-0296, **15**-0893
Endo, M., **10**-1260, **11**-0245, **15**-1668
Endo, R., **04**-0212
Endo, T., **05**-0084, **19**-1670
Endo, Y.J., **04**-0276
Engbert, T., **10**-0317
Engberts, J.B.F.N., **02**-0406, **09**-0092, **10**-0445, **14**-0404, **15**-2008, **15**-2019, **15**-2029, **15**-2030, **15**-2035, **19**-1252, **19**-1587
Engdahl, C., **18**-0009
Engel, C.R., **16**-1697
Engel, J., **04**-0271
Engel, P.S., **05**-0292, **05**-0298, **05**-0310, **07**-0030, **14**-0002, **14**-0067, **14**-0074, **14**-0146, **17**-0508
Engeldinger, E., **03**-0179
Engelking, P.C., **05**-0132, **05**-0273, **05**-0399
Engelsma, J.W., **14**-0127
Engenito Jr., J.S., **11**-0191
Engesser, K.-H., **19**-0546
England, D.C., **15**-1503, **16**-0456
England, M.D., **18**-0406
England, W.P., **18**-0620
Engler, E.M., **10**-0281, **18**-0118
English Jr., J., **17**-0408
English, R.B., **03**-0200
Engman, A.M., **19**-1454
Engman, L., **15**-1239, **15**-1261, **17**-0380
Enholm, E.J., **15**-1051, **16**-0871, **19**-1010, **19**-1315, **19**-1697
Enikolopiyan, N.S., **10**-0494
Enisov, E.T., **14**-0195
Enkelmann, V., **11**-0419
Enomoto, K., **08**-0101, **16**-0209
Enomoto, M., **12**-0069
Enriquez-Rios, V., **10**-0893
Ensley, H., **12**-0251
Entelis, S.G., **16**-0190
Entreken, E.E., **19**-1091
Entwistle, I.D., **15**-0518, **19**-1102, **19**-1200, **19**-1223, **19**-1232
Epa, W.R., **12**-0269, **15**-0230, **19**-0481
Ephritikhine, M., **16**-0968, **19**-1727
Epifano, F., **10**-0563, **0**-0925, **12**-0723, **15**-1365, **15**-1625, **16**-0149, **16**-1842, **19**-0668, **19**-1726
Epiotis, N.D., **05**-0121, **15**-2044, **15**-2105
Epling, G.A., **15**-0538
Epple, G., **11**-0434
Epple, R., **07**-0122
Eppley, R.L., **13**-0650
Epshtein, L.M., **03**-0014, **08**-0217
Epstein, OL., **10**-1496
Epstein, W.W., **19**-0638
Equey, O., **10**-1550, **15**-1266, **17**-0218
Erashko, V.I., **10**-0483
Erdélyi, M., **13**-0547, **13**-0550
Erden, I., **16**-0066
Erdik, E., **10**-1292, **12**-0507, **12**-0555, **13**-0188
Erdman, J., **10**-0481
Erfort, U., **15**-1357
Erhan, S.Z., **09**-0103
Erhardt, J.M., **10**-1560
Erickson, A.S., **10**-1481
Erickson, B.W., **10**-0559, **16**-0248, **16**-0254, **16**-1816
Erickson, G.W., **10**-1661
Erickson, J.A., **15**-2238
Erickson, K.C., **16**-1670
Erickson, M.S., **02**-0360
Erickson, W.F., **15**-0860, **18**-0396
Erickson, W.R., **13**-0780
Ericsson, C., **15**-1239
Eriks, K., **05**-0088
Erikson, C.M., **08**-0050
Eriksson, M., **10**-1334, **10**-1365
Eriksson, S.O., **16**-1592
Erivanskaya, L.A., **19**-1373
Eriyama, Y., **01**-0011
Erker, G., **16**-0292, **16**-1300
Erker, T., **13**-0272
Erlandsson, P., **04**-0175
Erman, M.B., **16**-0340, **16**-2055
Erman, W.F., **10**-0269, **18**-0098
Ermanson, A.V., **12**-0506
Ermer, O., **02**-0216, **02**-0295, **04**-0504
Ermolaev, V.L., **07**-0028
Ernst, A.B., **15**-1921
Ernst, B., **10**-1089
Ernst, T.D., **11**-0179
Erra-Balsells, R., **11**-0300
Ershadi, A., **11**-0288
Ershov, B.A., **18**-0136
Ershov, V.V., **02**-0411, **02**-0413, **11**-0013, **18**-0187
Ertas, M., **16**-1014
Ervin, K.M., **10**-0016
Erykalov, Yu.G., **11**-0637
Érzyutova, E.I., **14**-0287
Esashi, Y., **19**-1368
Esashi, Y., **19**-1369
Escaffre, P., **15**-1381
Escale, F., **19**-1032
Escale, R., **02**-0424
Eschenmoser, A., **04**-0036, **04**-0041, **10**-0015, **10**-0723, **10**-1175, **12**-0035, **15**-0781, **15**-1927, **16**-0402, **16**-0404, **17**-0411, **17**-0418, **17**-0420, **19**-0250
Escher, I.H., **15**-1136
Eschner, M., **10**-0430
Escolano, C., **15**-1240
Escribano, A., **15**-1006, **19**-1497
Escudero-Salas, A., **19**-0261
Escudié, J., **01**-0009
Esfandiari, S., **19**-1410
Eshghi, H., **11**-0549, **16**-1646, **18**-0323
Eskandari, M.M., **10**-1165
Eskew, N.L., **10**-0900
Eslami, S., **16**-0234
Esmaeili, A.A., **11**-0288
Esmayilpour, K., **16**-1740
Espejo de Ochoa, O., **18**-0347
Espenson, J.H., **10**-0645, **12**-0013, **12**-0015, **16**-0085, **17**-0226, **19**-0074, **19**-0299, **19**-0509, **19**-0510, **19**-0715, **19**-0744
Espín, M., **13**-0066

Espinet, P., **12**-0280, **13**-0366
Espino, C.G., **12**-0228, **12**-0229
Esponet, P., **13**-0523
Esterbrook III, J., **12**-0124
Esteve Jr., R.M., **12**-0648
Esteves, P.M., **11**-0119, **11**-0236
Estrella-Jimenez, M., **18**-0792
Esumi, S.-i., **15**-2036
Eswarakrishnan, V., **12**-0402, **17**-0349
Etemad-Moghadam, G., **15**-1039
Etemadi, S., **19**-0148
Etheredge, S.J., **10**-1636, **15**-2126
Etlis, V.S., **15**-1966
Eto, M., **15**-0968
Etter, J.B., **16**-0823
Etter, M.C., **03**-0023, **03**-0035, **04**-0187
Etzemüller, J., **15**-1927
Eudy, N.H., **19**-1067
Eulaerts, O., **07**-0075, **07**-0080
Eulenberger, A., **15**-2278
Euler, K., **18**-0652
Euranto, E.K., **16**-1549, **16**-1557, **16**-1573
Eustace, S.J., **12**-0089, **12**-0417
Eustache, F., **19**-1042
Eustathopoulos, H., **13**-0748
Evain, E.J., **10**-1186, **10**-1189
Evano, G., **10**-1493
Evans Jr., E.A., **04**-0253
Evans Jr., S.A., **10**-0653, **10**-0900
Evans, A.C., **02**-0310
Evans, B.J., **19**-0850
Evans, C.A., **05**-0211
Evans, C.M., **16**-0030
Evans, D.A., **04**-0140, **10**-1638, **10**-1640, **10**-1726, **12**-0221, **12**-0230, **12**-0460, **15**-0580, **15**-0604, **15**-0656, **15**-0696, **15**-0698, **15**-1688, **15**-2063, **15**-2064, **15**-2297, **16**-0240, **16**-0733, **16**-0997, **16**-1003, **16**-1013, **16**-1015, **16**-1018, **16**-1053, **16**-1144, **16**-1145, **16**-1161, **16**-2180, **18**-0601, **18**-0737, **19**-0501, **19**-0968, **19**-1056
Evans, D.F., **05**-0165
Evans, E., **10**-0208
Evans, E.A., **11**-0113, **16**-1944
Evans, F.E., **04**-0389
Evans, G.L., **16**-0205
Evans, G.R., **15**-2102
Evans, J.C., **05**-0015
Evans, J.W., **10**-0847
Evans, M.A., **15**-2181
Evans, M.B., **10**-0792
Evans, P., **15**-1435
Evans, P.A., **10**-0607, **10**-0886, **10**-0903, **10**-1468, **10**-1469, **18**-0299, **19**-0054
Evans, R.D., **15**-1543, **19**-0733
Evans, R.J., **19**-0425
Evans, S.A., **04**-0362
Evans, S.V., **04**-0142
Evans, W.D., **14**-0130
Evans, W.G., **03**-0055
Evans, W.J., **02**-0254, **16**-0659
Evans, W.L., **05**-0071, **08**-0121
Evanseck, J.D., **10**-0020
Everett, J.R., **04**-0338
Everly, C.R., **14**-0043
Evers, M., **10**-0797, **10**-0798
Evstigneeva, R.P., **19**-1801
Evtushenko, N.Yu., **10**-0406
Ewing, D.F., **09**-0019
Ewing, G.J., **10**-0543
Ewing, M., **16**-1581
Exner, J.H., **12**-0412
Exner, O., **01**-0034, **01**-0035, **01**-0042, **02**-0058, **08**-0170, **08**-0171, **09**-0016, **09**-0020, **09**-0040, **11**-0087, **18**-0286
Eyer, M., **16**-1149
Eymann, W., **10**-0250
Eynde, J.J.V., **10**-0610
Eyring, H., **04**-0126, **04**-0268
Ezhaya, A., **19**-0450
Ezoe, A., **16**-0711
Ezquerra, J., **19**-1497

Fabbrini, M., **19**-0187
Faber, D., **18**-0087
Faber, K., **04**-0198, **10**-0703, **16**-1687, **19**-1022
Fabian, J., **07**-0003
Fabian, M.A., **04**-0375
Fabian, W., **02**-0223
Fabian, W.M.F., **02**-0425
Fabiano, E., **10**-0898
Fabienke, E., **16**-2158
Fabre, A., **14**-0298
Fabre, C., **12**-0695
Fabre, O., **07**-0082
Fabre, P., **12**-0341
Fabricius, D.M., **18**-0613
Fabrizi, G., **13**-0149, **13**-0230, **13**-0407, **15**-0245, **16**-1983, **18**-0356
Faburada, A.L., **10**-0481
Facchetti, A., **10**-1597
Facelli, J.C., **02**-0218
Fache, F., **10**-0605, **10**-0884, **10**-0976, **12**-0165, **16**-1778, **19**-0533
Fadaei, Z., **16**-1629
Fadel, A., **19**-1730
Fadel, R., **15**-0562
Fadini, L., **15**-1320, **19**-0221
Fagan, J.F., **10**-0060
Fagan, M.W., **01**-0087
Fagan, P.J., **15**-0820
Fager, J.H., **19**-0440
Fagerli, A.K., **02**-0431
Faghih, R., **04**-0206
Fagnou, K., **10**-0666, **13**-0441
Fahey, R.C., **06**-0083, **15**-0003, **15**-0005, **15**-0013, **15**-0019, **15**-0030, **15**-0031, **15**-0033
Fähndrich, B., **15**-2304
Fahrenholtz, S.R., **14**-0034, **17**-0090
Faid-Allah, H., **16**-0433
Faigl, F., **17**-0209
Fain, D., **12**-0666
Faïn, D., **10**-0170
Fainberg, A.H., **10**-0055, **10**-0066, **10**-0282, **10**-0419, **10**-0430
Fainzil'berg, A.A., **05**-0327, **10**-0483
Fairlamb, I.J.S., **13**-0480
Fairlie, D.P., **15**-1361, **19**-1759
Fairlie, J.C., **19**-1338
Fairweather, N., **14**-0035
Faita, G., **15**-0961, **18**-0708
Fajer, J., **11**-0313
Fajgar, R., **19**-0363, **19**-0381
Fakultatea, K., **16**-0832
Falbe, J., **10**-1837, **10**-1838, **15**-1375, **15**-1464, **15**-1477, **15**-1485
Falck, J.R., **10**-0795, **10**-1380, **10**-1420, **10**-1798, **13**-0346, **15**-0252, **16**-1181, **16**-1369, **16**-1381, **17**-0316, **19**-0523
Falgayrac, G., **15**-1163
Falguières, A., **16**-0646
Falk, F., **17**-0149
Falkehag, I., **19**-0269
Fall, M.J., **15**-2297
Fallah, A., **15**-0383
Faller, J.W., **10**-1466, **15**-0431, **15**-2065
Faller, P., **19**-0241
Fallis, A.E., **14**-0324
Fallis, A.G., **04**-0082, **15**-1222, **15**-1395, **15**-1854, **15**-1980, **15**-2058, **15**-2080, **16**-2032
Falomir, E., **16**-0996
Falorni, M., **19**-1073
Faltin, C., **16**-0770
Falvey, D.E., **05**-0409, **05**-0410
Familoni, O.B., **10**-1283, **13**-0326
Fan, B.-M., **19**-1028

Fan, C.-A., **13**-0162, **16**-0298, **19**-0082, **19**-1673
Fan, C.A., **18**-0134, **18**-0154, **18**-0157
Fan, D., **16**-1932
Fan, D.-p., **10**-0864
Fan, H., **15**-2268
Fan, J., **16**-1037
Fan, K., **15**-0966
Fan, O.-H., **16**-0691
Fan, Q.-H., **15**-0604, **16**-1012
Fan, Q.H., **15**-0613
Fan, R., **16**-2091, **19**-0535
Fan, R.-H., **10**-0578, **10**-0675, **10**-0958, **10**-1173, **10**-1573
Fan, W.-Q., **11**-0066
Fan, X., **16**-0684, **16**-1644
Fan, Y., **16**-1097, **16**-2129
Fañanas, F.J., **12**-0409
Fancelli, D., **13**-0582
Fang, G., **16**-0949, **18**-0800
Fang, J., **19**-0452
Fang, J.-M., **14**-0278, **16**-0336, **19**-1648, **19**-1670
Fang, L., **15**-1157
Fang, M.M., **07**-0070
Fang, W.-H., **15**-2333
Fang, W.-k., **18**-0298
Fang, X., **10**-0948, **16**-0745, **16**-0899, **16**-0912, **19**-0175, **19**-0679
Fang, Y., **10**-1675
Fanta, P.E., **13**-0455, **16**-2163
Fantin, G., **15**-1791, **19**-0232, **19**-0872
Fantoni, A.C., **03**-0031
Fanwick, P.E., **15**-0973
Fara, D.C., **10**-0215
Faraci, G., **11**-0262
Farah, B.S., **16**-0439
Farah, J.P.S., **10**-0529
Faraone, F., **10**-1453, **15**-1136
Farcas, S., **16**-1363
Fărcaşiu, D., **05**-0013, **06**-0021, **10**-0038, **10**-0083, **11**-0012, **18**-0046, **18**-0052, **18**-0118
Farhadi, S., **14**-0422
Farid, S., **01**-0101, **07**-0054, **15**-2252
Farina, M., **04**-0001
Farina, V., **12**-0256, **12**-0259, **12**-0267, **12**-0276
Farkas, L.V., **10**-0995
Farkas, M.E., **11**-0439
Farley, E.N., **02**-0327
Farlow, R.A., **18**-0220
Farmer, P.J., **05**-0253
Färnegårdh, K., **15**-1664
Farneth, W., **07**-0019, **07**-0021
Farnetti, E., **19**-0960
Farng, L.O., **16**-2146
Farnham, W.B., **10**-0190, **12**-0629, **18**-0842
Farnoux, C.C., **16**-0425
Farnsworth, M.V., **15**-0249, **15**-2441
Farnum, D.G., **02**-0197, **05**-0089, **10**-0182, **10**-0188, **15**-2172, **16**-2080
Farnum, W.B., **10**-0191
Farooq, O., **11**-0487, **12**-0341, **14**-0169, **17**-0169, **18**-0117
Farooq, S., **10**-0015
Farooqi, J.A., **11**-0608
Farquhar, D., **02**-0317
Farrall, M.J., **16**-1379
Farrant, G.C., **15**-2437
Farrar, A.C., **12**-0436
Farrar, W.V., **16**-0265
Farrell, P.G., **11**-0013, **17**-0064
Farrington, E.J., **13**-0440
Farrington, G., **07**-0044
Farrokhi, A., **19**-0080, **19**-0866
Farrugia, L., **16**-0760
Farthing, C.N., **16**-1276
Fasel, J., **18**-0855
Fasihi, J., **10**-0897
Fasihi, J., **16**-1615
Fassberg, J., **10**-0240
Fassina, V., **18**-0781
Fässler, R., **16**-0551, **16**-0928
Fastabend, U., **15**-2172
Fataftah, Z.A., **04**-0512
Fathi, R., **13**-0443, **13**-0548
Fatiadi, A.J., **03**-0097, **10**-1577, **10**-1785, **15**-0071, **15**-1657, **16**-1628, **19**-0010, **19**-0311
Fatiadi, K., **17**-0424
Fatland, A.W., **15**-2363
Fato, M., **18**-0847
Fattahi, A., **08**-0134
Fattal, E., **18**-0091
Fattuoni, C., **01**-0104
Faubl, H., **04**-0493
Faul, M.M., **10**-0857, **15**-2297
Faulconer, J.M., **12**-0706
Faulkner, D.J., **18**-0676
Faulks, S.J., **12**-0659
Faunce, J.A., **16**-1032
Fauré-Tromeur, M., **17**-0237
Faust, R., **02**-0023
Faustini, F., **10**-1179
Fausto, R., **04**-0297
Fauth, D.J., **15**-0417
Fauvarque, J., **12**-0583, **16**-0531, **16**-0540
Fava, A., **02**-0089, **04**-0470, **10**-0084, **16**-1402, **16**-2138, **18**-0727
Favero, L., **10**-0953, **10**-0954, **10**-1564
Favi, G., **15**-2174
Favini, G., **10**-0242
Favorskii, A., **18**-0178
Favre, A., **16**-1655
Favreau, D., **19**-1479
Fay, J.N., **15**-2034
Fazakerley, V., **05**-0165
Fazal, A.N., **10**-1469
Fazio, A., **15**-0361, **15**-0919, **15**-0304
Feast, W.J., **18**-0756
Feaster, J.E., **19**-1134
Featherman, S.I., **01**-0087
Fechter, M.H., **16**-1424
Fedder, J.E., **16**-1872
Fede, J.-M., **05**-0368, **12**-0346
Fedenok, L.G., **14**-0319
Fedin, V.P., **02**-0166
Fedor, L.R., **15**-0195, **16**-0020, **16**-0025, **17**-0046, **17**-0047, **17**-0052
Fedorov, A.Yu., **13**-0210
Fedorova, A.V., **15**-0222
Fedorovich, A.D., **18**-0526, **18**-0556
Fedoruk, N.A., **19**-1410
Fedoryński, M., **10**-1580
Fedrick, J.L., **13**-0071
Feducovich, S.K., **16**-0153, **19**-1691
Feeder, N., **02**-0076, **04**-0454
Feely, W., **17**-0182
Feenstra, R.W., **07**-0120
Fehlner, J.R., **14**-0161
Fehlner, T.P., **15**-0637
Fehr, C., **12**-0425, **16**-1928
Feig, G., **14**-0264
Feigel, M., **10**-0056
Feigl, F., **11**-0633
Feigon, J.F., **11**-0028
Feiler, L.A., **15**-2185, **15**-2186, **15**-2212, **15**-2216, **15**-2225
Feit, B., **05**-0135
Feit, I.N., **17**-0083, **17**-0092, **17**-0092, **17**-0101, **17**-0116
Feiten, H.-J., **19**-0543, **19**-0544, **19**-0546
Feitler, D., **16**-1799
Fel'dblyum, V.Sh., **15**-0790
Feld, D., **18**-0727
Felder, M., **19**-1149
Felder, P., **05**-0324
Feldman, D., **10**-0455
Feldman, J., **18**-0836
Feldmann, R., **15**-2437
Feldus, S., **08**-0175

Felix, D., **04**-0036, **12**-0035, **15**-1384, **15**-1927, **17**-0418, **17**-0420
Felix, L.A., **12**-0472
Felix, L.de A., **16**-0233
Felker, D. 8, **16**-1425
Felker, P.M., **03**-0072
Felkin, H., **04**-0139, **04**-0169, **10**-0208, **10**-1511, **15**-0861, **15**-0867, **18**-0413, **19**-0061
Felkin, H., **19**-1233
Fell, B., **12**-0480, **12**-0554, **15**-1484, **15**-1486
Fellenberger, K., **10**-1536, **18**-0510, **18**-0730
Fellmann, J.D., **10**-0916
Fellmann, P., **16**-1014
Fellous, R., **09**-0075
Fellows, C.A., **13**-0621
Felpin, F.-X., **16**-0578
Felt, G.R., **10**-0076
Felt, G.R., **10**-0078
Feltkamp, H., **04**-0264
Feltman, T.L., **11**-0371
Felton, S.M., **16**-1847
Femoni, C., **04**-0087, **16**-0926
Feng, A., **15**-1397
Feng, J.-C., **16**-0054, **19**-1090
Feng, L., **18**-0492
Feng, L.-C., **16**-1005, **16**-1108
Feng, M.S., **06**-0071
Feng, R.H.C., **14**-0040
Feng, S.-Q., **10**-0879
Feng, X., **15**-2127, **16**-0684, **16**-1427, **16**-1428, **16**-1433, **16**-1438, **16**-1438
Feng, Y., **01**-0111, **19**-1031, **19**-1039, **19**-1675
Feng, Y.-S., **10**-1864, **16**-0785, **16**-0789
Feng, Y.-Y., **16**-1173
Fenichel, L., **15**-1042
Fenoglio, D.J., **04**-0295
Fenselau, A.H., **19**-0160
Fensterbank, L., **15**-0834, **15**-1273
Fenteany, G., **13**-0111
Fentiman Jr., A.F., **10**-0140
Fentiman, A., **11**-0576
Fenton, G., **19**-1515, **19**-1625
Fenton, S.W., **14**-0040
Fenwick, A., **16**-2111
Fenwick, D.R., **13**-0261
Fenwick, J., **18**-0224
Fenzl, W., **15**-1183
Feoktistov, L.G., **19**-0955, **19**-1317
Ferappi, M., **11**-0334
Ferber, P.H., **10**-0134, **10**-0170
Ferguson, C.P., **01**-0087
Ferguson, D.C., **19**-0935
Ferguson, G., **02**-0060, **03**-0139
Ferguson, J.W., **18**-0036
Ferguson, L.N., **19**-0423
Ferguson, R., **18**-0872, **18**-0873
Ferguson, R.R., **14**-0297, **15**-0847
Fergusson, S.B., **10**-1861
Feringa, B.L., **04**-0205, **07**-0061, **10**-1374, **15**-0387, **15**-0604, **15**-1019, **15**-1103, **15**-1125, **15**-1131, **15**-1136, **15**-1138, **19**-0536
Ferland, J.M., **19**-1469
Fernádez, A., **15**-1006
Fernamberg, K., **05**-0352
Fernandes, E., **18**-0642
Fernandes, M.A., **18**-0786
Fernandes, R.A., **16**-0871, **16**-0911, **19**-0077
Fernandes, S.A., **18**-0655
Fernandex, X., **16**-0225
Fernándex-Fano, R., **16**-0501
Fernandez, E., **18**-0278
Fernandez, I., **19**-1250
Fernández, E., **15**-1481
Fernández, I., **16**-0073, **19**-0120
Fernández, J.M., **16**-1422
Fernández, M., **10**-1572
Fernández, R., **19**-0300
Fernández, S., **19**-0317
Fernández-Hernandez, J.M., **15**-2384
Fernández-Ibáñez, M.Á., **10**-1800
Fernández-Mateos, A., **10**-0133
Fernandez-Picot, I., **14**-0420
Fernández-Rivas, C., **12**-0276, **15**-0776
Fernández-Simón, J.L., **16**-0500
Fernelius, W.C., **04**-0098
Fernholt, L., **02**-0030, **03**-0050, **04**-0283, **04**-0317
Feroci, M., **10**-0785, **12**-0745, **12**-0752, **16**-0436
Ferraboschi, P., **15**-0520, **19**-1091
Ferraccioli, R., **13**-0228
Ferrand, E.F., **10**-0490
Ferrand, Y., **15**-2307
Ferrara, D.M., **11**-0092
Ferrara, M., **16**-0947, **16**-0949, **18**-0800
Ferraris, D., **16**-2105, **19**-1273
Ferraz, H.M., **18**-0210
Ferraz, H.M.C., **15**-0277, **15**-1770, **19**-0581, **19**-0594
Ferreira, A.B., **18**-0855
Ferreira, E.M., **15**-0592
Ferreira, J.T.B., **10**-0785, **16**-0583
Ferreira, J.T.B., **19**-1425
Ferreira, P., **19**-0192
Ferreira, V.F., **16**-0831
Ferreiro, M.J., **04**-0108
Ferrell, T.M., **19**-0377
Ferrer, M., **19**-0384
Ferrer, P., **16**-1289
Ferreri, C., **10**-1151, **10**-1209, **14**-0018, **15**-0067, **15**-1219, **16**-0147, **19**-1403
Ferrero, L., **19**-1245
Ferrier, B.M., **18**-0640
Ferrieri, R.A., **14**-0051
Ferrini, P.G., **17**-0504
Ferris, A.F., **17**-0453, **17**-0457, **19**-1174
Ferris, D.C., **08**-0219
Ferris, J.P., **12**-0647, **16**-1460
Ferrroud, C., **16**-0646
Fersht, A.R., **16**-0032
Fersht, A.R., **16**-1517
Ferstandig, L.L., **03**-0058
Ferwanah, A.-R.S., **13**-0636
Fessenden, R., **16**-1901
Fessenden, R.W., **02**-0101, **05**-0273, **05**-0280
Fessner, W., **05**-0085, **15**-2232, **19**-0068
Fétizon, M., **16**-0251
Fettes, A., **16**-1054
Fettouhi, M., **15**-1403
Fetzer, U., **17**-0479
Feuer, B.I., **12**-0234
Feuer, H., **07**-0053, **10**-0585, **10**-0640, **10**-0968, **10**-1001, **10**-1479, **11**-0119, **11**-0132, **12**-0207, **12**-0208, **12**-0713, **13**-0008, **13**-0074, **13**-0722, **15**-1004, **16**-0107, **16**-0397, **16**-1149, **17**-0113, **19**-0763, **19**-0776, **19**-1150, **19**-1227, **19**-1235, **19**-1532
Feuer, J., **15**-2044, **15**-2103
Feuerstein, M., **10**-0886, **13**-0367, **13**-0399, **13**-0401, **13**-0539, **13**-0560, **16**-1798
Feutrill, G.I., **10**-0799
Fevig, T.L., **15**-1197
Fey, P., **10**-1661
Fey, T., **19**-0190, **19**-0191
Feyen, P., **18**-0019
Feytmants-de Medicis, E., **16**-0098
Fiandanese, V., **10**-1325, **10**-1770, **16**-1924, **16**-1929, **17**-0031, **17**-0056
Fiaschi, R., **16**-0442, **17**-0188
Fiaud, J., **10**-1439

Fiaud, J.C., **04**-0136, **04**-0190
Fibiger, R., **10**-1022, **15**-0398
Fichter, K.C., **15**-0703
Ficini, J., **15**-2234, **18**-0687
Fickes, G.N., **15**-2078
Fidler, J., **04**-0128
Fiedler, C., **15**-2438
Fiedler, P., **01**-0042
Fiege, M., **16**-2090
Field, F.H., **10**-0184
Field, J.A., **19**-1022
Field, K.W., **10**-0395
Field, L., **16**-0229, **18**-0329
Field, L.D., **12**-0050, **12**-0341, **18**-0255, **19**-1598
Fieldhouse, R., **15**-2301, **16**-1383
Fielding, M.R., **15**-0197
Fields, D.B., **15**-1521
Fields, E.K., **12**-0354, **13**-0037, **15**-2075
Fields, J.D., **15**-1730, **18**-0895, **19**-0758
Fields, K.W., **12**-0398, **16**-1991, **18**-0229
Fields, R., **18**-0169
Fields, S.C., **12**-0469
Fields, T.R., **18**-0535
Fierke, C.A., **04**-0454
Fierman, M.B., **10**-0847
Fierz, H.E., **11**-0034
Fieser, L.F., **10**-0577, **15**-1531, **17**-0308, **19**-0071, **19**-1319, **19**-1428
Fieser, M., **10**-0577, **15**-1531, **17**-0308, **19**-0071, **19**-1428
Fife, T.H., **10**-0530, **10**-0531, **10**-0532, **10**-0533, **10**-0534, **10**-0536, **10**-0574, **16**-1936
Fife, W.K., **10**-0467, **16**-1712, **18**-0708
Fifolt, M., **10**-1604
Fifolt, M.J., **10**-1482
Figadere, B., **16**-0565, **10**-1051, **12**-0314, **13**-0308
Figeys, H.P., **02**-0093, **02**-0244, **12**-0416
Figge, L., **15**-2232
Figueras, F., **15**-1001, **15**-2038
Figuero, J.S., **16**-1352
Figuly, G.D., **12**-0402
Fihri, A., **13**-0541
Fiksdahl, A., **10**-0766
Filho, A.P.O., **11**-0124
Filho, E.P.S., **15**-0625, **16**-0804
Filimonov, V.D., **11**-0294
Filimonov, V.D., **19**-0743
Filipescu, N., **18**-0516
Filipp, N., **18**-0617
Filipp, N., **18**-0695
Filippi, J.-J., **16**-0225
Filippini, G., **02**-0163
Filippini, L., **11**-0508
Filippova, T.V., **15**-1798
Filippova, T.Yu., **14**-0198
Filler, R., **01**-0106, **08**-0163, **10**-1041, **11**-0313, **12**-0111 **19**-0110
Filley, J., **10**-0368, **10**-0491
Fillion, E., **11**-0332
Fillion, H., **07**-0091
Fillipi, G., **13**-0743
Filmore, K.L., **11**-0648
Filon, H., **16**-1908
Filzen, G.F., **18**-0059
Fina, N.J., **10**-0361, **10**-0363
Finch, A.F., **10**-0495
Finch, H., **19**-0264
Finch, M.A.W., **10**-0228
Findeis, M.A., **04**-0151
Findlay, P., **15**-0218
Finet, J., **12**-0520, **13**-0223, **13**-0224, **13**-0580, **13**-0581, **14**-0286, **14**-0331, **14**-0332, **19**-0010
Finet, J.-P., **13**-0210
Finger, A., **10**-0488
Fini, A., **07**-0105
Fink, D.M., **10**-0933, **10**-1232
Fink, M.J., **01**-0011
Fink, W.H., **06**-0064
Finkbeiner, H., **15**-1921
Finkbeiner, H.L., **12**-0554, **16**-1247, **16**-1247
Finke, J., **16**-1000
Finke, R., **10**-1251
Finke, R.G., **03**-0083, **10**-1332, **10**-1813, **10**-1841, **13**-0394, **14**-0443, **15**-0406, **15**-1477, **15**-1479, **15**-2292, **15**-2403, **18**-0835
Finkelhor, R.S., **16**-1408
Finkelstein, M., **19**-0586
Finkenbine, J.R., **10**-0818
Finlay, J., **10**-0576
Finlayson, A.J., **10**-0210
Finlayson, W.L., **10**-0890, **16**-1517
Finley, K.T., **15**-0039, **15**-1991, **17**-0062, **19**-1732
Finley, R.L., **10**-0530
Finn, J., **04**-0210, **04**-0211
Finn, J., **19**-0498
Finn, M.G., **13**-0494, **15**-1691, **15**-1731, **15**-1821, **15**-1824, **15**-1826
Finnegan, D.F., **18**-0779
Finnegan, R.A., **11**-0556, **12**-0400
Finney, N.S., **16**-0945
Finocchiaro, P., **03**-0166, **19**-1714
Finston, H.L., **08**-0001
Finzi, C., **13**-0582
Fiorani, T., **13**-0582
Fioravanti, S., **15**-1884, **15**-1889, **15**-1890
Fiorentino, M., **15**-1768, **19**-0301, **19**-0615
Fiorini, D., **12**-0686, **15**-1005, **15**-1033, **16**-0113, **16**-0327, **16**-0808
Fioshin, M.Ya., **14**-0418
Firestone, R.A., **02**-0002, **09**-0088, **10**-0477, **15**-1945, **15**-1945, **15**-2027, **18**-0659
Firl, J., **15**-2122
Firnberg, D., **14**-0161
Firouzabadi, H., **10**-0681, **10**-0708, **10**-0812, **10**-0848, **10**-1090, **10**-1106, **10**-1113, **10**-1807, **11**-0128, **11**-0138, **11**-0299, **16**-0160, **16**-0234, **16**-0238, **16**-1684, **17**-0156, **17**-0466, **19**-0080, **19**-0145, **19**-0148, **19**-0303, **19**-0762, **19**-0807, **19**-0865
Firouzbakht, M.L., **14**-0051
Firth, W.C., **14**-0428
Fisanick, G.J., **04**-0430
Fisch, A., **12**-0416
Fisch, M., **18**-0085
Fischer Jr., W.F., **10**-1350, **15**-1086
Fischer, A., **08**-0030, **11**-0054, **11**-0058, **11**-0083, **15**-2242, **18**-0034
Fischer, B., **19**-1614
Fischer, C., **13**-0611, **16**-0888
Fischer, C.M., **19**-0361
Fischer, E., **15**-0006
Fischer, G., **02**-0118, **04**-0209, **11**-0116, **15**-0488
Fischer, H., **05**-0100, **05**-0208, **05**-0218, **08**-0014, **11**-0563, **14**-0093, **15**-1211, **15**-2168, **18**-0055, **19**-0191
Fischer, H.P., **12**-0030, **17**-0452, **17**-0452, **17**-0456
Fischer, J.W., **04**-0442, **11**-0132
Fischer, K., **15**-0793, **16**-1400
Fischer, M., **11**-0594
Fischer, N.S., **16**-1401
Fischer, P.B., **11**-0105
Fischer, P.M., **13**-0442
Fischer, R., **15**-0799
Fischer, S., **16**-0576
Fischer, S.F., **07**-0022
Fischer, T., **15**-2041
Fischer, W., **17**-0405

Fish, A., **19**-0069
Fishbein, J.C., **13**-0771
Fishbein, R., **12**-0148, **12**-0724, **14**-0065, **14**-0154
Fishel, D.L., **16**-0309, **19**-0419
Fisher, A.J., **02**-0364
Fisher, A.M., **05**-0126
Fisher, C.L., **15**-1853
Fisher, F.J., **16**-0998
Fisher, G., **19**-0525
Fisher, G.B., **19**-1271
Fisher, J., **04**-0019
Fisher, J.J., **02**-0037
Fisher, K.D., **15**-1445
Fisher, L.E., **16**-1709
Fisher, M.J., **15**-2061
Fisher, R.D., **06**-0082, **10**-0059, **10**-0327, **10**-0430
Fisher, R.P., **18**-0429, **18**-0436, **18**-0444, **18**-0446, **18**-0451
Fisher, T.H., **14**-0049, **14**-0089
Fisher, W.F., **01**-0042
Fishman, J., **14**-0400, **19**-1579
Fitch, R.W., **19**-1194
Fitjer, L., **04**-0322, **04**-0326, **04**-0369
Fitzgerald, B.M., **18**-0722
Fitzgerald, P., **18**-0374
Fitzgerald, R., **01**-0041, **10**-0262
Fitzmaurice, N.J., **15**-1486
Fitzpatrick, J.D., **02**-0211, **02**-0229
Fitzroy, M.D., **15**-1685
Fix, S.R., **15**-0334
Fizet, C., **16**-0326
Flack, H.D., **02**-0402
Flack, K., **18**-0793
Flack, S.S., **10**-0732
Flaherty, A., **18**-0687
Flamarique, A.C.R., **10**-1800
Flamm-ter Meer, **04**-0294
Flammang, R., **04**-0486
Flanders, V.L., **10**-0973
Flaniken, J.M., **19**-1499
Flann, C.J., **18**-0665
Flautt, T.J., **12**-0400
Fleet, G.W.J., **19**-0934
Flego, M., **16**-1426
Fleischer, F., **04**-0437
Fleischer, R., **05**-0185
Fleischhauer, J., **15**-2001
Fleming, E.M., **16**-0770
Fleming, F.F., **10**-1669, **10**-1802, **12**-0548, **15**-1000, **15**-1101, **17**-0164, **17**-0165, **17**-0181
Fleming, I., **06**-0001, **10**-0688, **10**-1431, **10**-1650, **12**-0004, **12**-0035, **12**-0428, **13**-0418, **13**-0536, **15**-1175, **15**-1980, **15**-2103, **16**-0743, **16**-1601, **18**-0654
Fleming, J.J., **02**-0281
Fleming, M.J., **17**-0210
Fleming, M.P., **10**-1503, **14**-0428, **19**-1709, **19**-1714, **19**-1716, **19**-1719, **19**-1725, **19**-1727
Fleming, N.B., **11**-0488
Fleming, R.H., **15**-2183
Fleming, S.A., **16**-2088, **18**-0590
Flemming, S., **15**-0616, **15**-1058
Fletcher, B., **14**-0128
Fletcher, R.S., **09**-0006
Fletschinger, M., **08**-0084
Flippen, L.A., **10**-1522, **13**-0652, **16**-1033, **19**-0350
Fliszár, S., **05**-0092, **19**-0357, **19**-0365, **19**-0379
Flitsch, W., **02**-0282, **02**-0424, **16**-1342
Flo, C., **05**-0053, **10**-0520
Flogaus, R., **16**-1922
Flood, R.W., **15**-1813
Flood, S.H., **11**-0025, **11**-0026, **11**-0027, **11**-0347
Flood, T.C., **12**-0007, **17**-0329, **19**-1718
Florence, G.J., **19**-0688
Flores-López, L.-Z., **16**-1438
Flores-Santos, L., **10**-1454
Florez, J., **16**-1189
Florio, E., **15**-0538
Florio, S., **10**-1281, **16**-0473
Floris, B., **15**-0280
Florkin, M., **04**-0253
Floss, H.G., **04**-0021
Flosser, D.A., **10**-1085
Flowers II, R.A., **16**-0980, **19**-0984, **19**-0989, **19**-1145, **19**-1302, **19**-1671, **19**-1704
Floyd, D., **15**-1071
Floyd, D.M., **10**-1356
Floyd, R.J., **13**-0477
Flügge, J., **16**-1214
Flury, P., **10**-0175
Flygare, J.A., **16**-1243
Flynn Jr., J., **10**-0261
Flynn, B.L., **15**-2413
Flynn, D.L., **16**-1583, **16**-2072
Flynn, K.E., **04**-0470
Flynn, R., **13**-0574
Flynt, M.S., **16**-0301
Foá, M., **04**-0196, **13**-0281, **13**-0598, **13**-0613
Fobare, W.F., **11**-0265
Fobker, R., **12**-0625
Foces-Foces, C., **02**-0423
Fochi, M., **10**-1495
Fochi, R., **10**-1866, **16**-1284, **19**-1509
Fodor, G., **09**-0013, **10**-1191, **11**-0395, **11**-0399
Fogagnolo, M., **15**-1791, **19**-0232
Fogler, H.S., **07**-0067
Foglia, T.A., **10**-0698
Föhlisch, B., **16**-1922
Fok, C.C.M., **17**-0192
Fokin, A.A., **14**-0003, **14**-0142, **14**-0150
Fokin, A.V., **10**-0494, **10**-0817
Fokin, V.V., **07**-0122, **15**-1860
Foldi, V.S., **16**-2068
Folest, J., **10**-1308, **10**-1854
Folest, J.C., **10**-1228, **10**-1811
Foley, K.M., **19**-1504
Follet, M., **15**-0678
Folli, U., **02**-0058
Folliard, J.T., **16**-0106
Folsom, H.E., **02**-0360
Folsom, T.K., **16**-1670
Folting, K., **15**-2406
Fomina, L., **14**-0322
Fomina, V.I., **03**-0164
Fomine, S., **14**-0322
Fonck, G., **19**-0041
Fong, C.W., **12**-0479
Fong, F.K., **10**-0182
Fong, G.D., **19**-0382
Fong, W.M., **19**-0583
Fonguerna, S.J., **16**-1383
Fonken, G.J., **15**-2235, **18**-0462, **18**-0486
Fono, A., **15**-0285
Fonseca, M.T.H., **15**-0993
Font-Sanchis, E., **14**-0216
Fontaine, C., **04**-0206
Fontaine, E., **19**-1243
Fontaine, G., **12**-0242
Fontana, A., **08**-0168, **12**-0083
Fontana, F., **11**-0262, **14**-0120, **14**-0337, **14**-0338, **14**-0342, **14**-0343, **19**-0120, **19**-0181, **19**-0331, **19**-0588, **19**-0612, **19**-0614, **19**-1047
Fontana, R., **14**-0138
Fontenas, C., **18**-0401
Foos, J.S., **02**-0053, **19**-0685
Foote, C.S., **04**-0417, **14**-0230, **14**-0234, **14**-0236, **14**-0241, **14**-0244, **15**-0967, **15**-2158, **15**-2160
Foote, R.S., **16**-1057
Forbes, C.C., **04**-0311
Forbes, D.C., **16**-1069, **16**-1170, **16**-1382, **19**-1697
Forbes, E.J., **11**-0611

Forbes, I.T., **11**-0218
Forbes, W.F., **15**-0849
Forcato, M., **19**-0308
Forch, B.E., **02**-0334
Ford, A., **19**-1030, **19**-1032
Ford, F., **05**-0384
Ford, G.D., **16**-1383
Ford, G.P., **09**-0039
Ford, J.G., **15**-1434, **18**-0780, **18**-0792
Ford, P.C., **15**-0463
Ford, R.A., **04**-0331, **14**-0222
Ford, S.H., **10**-1767
Ford, W.T., **10**-0335, **12**-0030, **16**-1269, **17**-0068, **17**-0073, **17**-0075, **18**-0506
Foreman, M.I., **03**-0094, **15**-1417
Foresti, E., **04**-0059, **15**-0225, **18**-0073
Forestiere, A., **19**-0674
Forgione, P., **15**-1395
Forlani, L., **13**-0019, **16**-0272
Forman, M.A., **18**-0194
Formosinho, S.J., **05**-0378, **07**-0044, **08**-0104
Fornarini, S., **10**-0169, **10**-0260
Forni, A., **04**-0038, **16**-2122
Forrest, J., **13**-0458
Forrest, T.P., **18**-0722
Forrester, A.R., **05**-0226, **05**-0341
Forrester, J.L., **15**-1539
Forsén, S., **02**-0379, **02**-0411
Forslund, R.E., **19**-0578
Forster, M., **19**-0386
Förster, H., **04**-0271, **04**-0509
Förster, S., **10**-1033
Forsynth, C.J., **19**-0688
Forsyth, D.A., **04**-0035, **10**-0167, **10**-0178, **10**-0187, **11**-0015
Forsythe, G.D., **15**-0548
Fort Jr., R.C., **05**-0079
Fort Jr., R.C., **05**-0083, **05**-0239, **05**-0279, **08**-0233, **10**-0011, **10**-0041, **12**-0009, **14**-0101, **18**-0018
Fort, A.W., **18**-0204
Fort, Y., **10**-1243, **13**-0198, **13**-0199, **13**-0200, **13**-0462, **13**-0646, **13**-0647, **14**-0401, **19**-1312, **19**-1580
Forth, M.A., **19**-1225
Fortier, S., **03**-0113
Fortunak, J.M., **19**-1017, **19**-1054
Foscolos, G., **16**-0517
Foscolos, G.B., **16**-0953
Fosheé, D.O., **09**-0078
Foss, F.D., **16**-0015
Foss, R.P., **07**-0023, **19**-1689
Fossel, E.T., **18**-0640
Fossey, J.S., **16**-1432
Foster, G., **19**-0423
Foster, G.P., **16**-2137
Foster, K., **12**-0370
Foster, R., **03**-0080, **03**-0094, **03**-0096, **13**-0008, **16**-0262
Foster, R.F., **05**-0106, **12**-0664
Foster, T.F., **15**-0409
Fosty, R., **12**-0015
Foti, C.J., **15**-1730
Foti, F., **15**-1937
Fotuhi, L., **10**-0665
Fouad, F.M., **17**-0064
Foubelo, F., **12**-0409
Foubelo, F., **16**-0854
Foubister, A.J., **19**-1286
Fougherty, D.A., **03**-0075
Foulon, J.P., **15**-1062
Fountain, K.R., **06**-0015
Fouquet, E., **10**-1410, **16**-1504
Fouquet, G., **10**-1312
Four, P., **15**-1170, **19**-1100
Fournier, F., **15**-1452
Fournier, J., **16**-0436
Fournier, L., **16**-0228
Fournier, P., **10**-1368
Fournioux, X., **10**-1437
Fowler, C.B., **16**-0961
Fowler, F.W., **15**-1633, **16**-0543, **18**-0687
Fowler, J.S., **10**-0841
Fowler, P.W., **02**-0083
Fowler, R., **16**-0405
Fowley, L.A., **15**-0418
Fox, A.S., **19**-0467
Fox, B.G., **19**-0241
Fox, B.L., **18**-0344
Fox, D.L., **10**-0826
Fox, D.N.A., **16**-1088, **16**-1090
Fox, D.P., **17**-0326
Fox, J.M., **10**-1635, **13**-0583
Fox, J.P., **15**-0198
Fox, M.A., **15**-1298, **15**-2117
Fox, R.C., **04**-0458
Fox, R.J., **16**-0886
Fraancoeur, S., **15**-2342
Frabboni, B., **18**-0847
Frach, R., **17**-0476
Fradera, X., **02**-0154
Fraenkel, G., **04**-0312, **05**-0150, **05**-0155, **05**-0171, **05**-0185, **05**-0187, **06**-0056, **16**-0441
Fraenkel, R., **19**-0381
Fraga, S.A., **15**-1939
Fraile, A.G., **11**-0471, **16**-2057
Fraile, J.M., **15**-2305, **16**-0689
Fraisse, P.L., **10**-1471
Frajerman, C., **18**-0413
Framery, E., **10**-1453
Francalanci, F., **04**-0196, **13**-0613, **19**-1374
France, M.B., **15**-1701
France, S., **12**-0167, **15**-2180, **16**-2106, **17**-0318
Francesch, C., **16**-1215
Franciò, G., **15**-1136
Francis, A.W., **11**-0349, **15**-0009
Francisco, C.G., **14**-0208
Franck, X., **13**-0308
Franck-Neumann, M., **15**-2096, **17**-0507
Francl, M.M., **10**-0110
Franco, D., **19**-1495
Frank, D.L., **10**-0171
Frank, F.J., **19**-0079
Frank, H., **05**-0217
Frank, R.M., **01**-0043
Franke, F.P., **14**-0043
Franke, J., **03**-0101
Franke, W., **05**-0067, **17**-0252, **17**-0311
Frankel, J.J., **19**-1368
Frankel, M.B., **10**-0968
Franken, E., **04**-0501
Franklin, N.C., **04**-0264
Franklin, N.C., **17**-0084
Frantz, D.E., **15**-0662, **16**-0551, **16**-0552, **16**-0928
Franz, A.K., **15**-0736
Franz, L.H., **02**-0164
Franz, R., **05**-0402
Franz, R.A., **12**-0736
Franzen, V., **05**-0380, **11**-0316, **19**-0653
Franzén, R., **13**-0409, **13**-0485
Franzén, R.G., **16**-0465
Fränzl, H., **19**-0221
Franzus, B., **10**-1099, **18**-0559
Fraser, A.R., **15**-2202
Fraser, J.R., **03**-0172
Fraser, M.E., **03**-0113
Fraser, R.R., **04**-0208, **10**-1656, **11**-0116, **12**-0114
Fraser-Reid, B., **10**-0537, **16**-0009
Frater, G., **18**-0224, **18**-0705
Frattini, S., **16**-1258
Frauenkron M., **15**-2298
Frauenrath, H., **16**-1195
Fravel Jr., H.G., **18**-0535
Fray, G.I., **02**-0239
Frazén, J., **15**-0832
Frazier Jr., R.H., **19**-0848
Frazier, H.W., **16**-1222
Frazier, K.A., **19**-1468

Freccero, M., **15**-1731, **15**-1733, **15**-1736, **15**-1944, **19**-0519
Fréchet, J.M.J., **12**-0534, **13**-0217, **16**-1379, **16**-1822, **16**-1822
Fréchette, M., **08**-0191
Fredenhagen, H., **19**-1764
Fredereiksen, M.U., **02**-0192
Frederick, M.O., **10**-0997
Fredriksen, S.B., **03**-0107
Freed, K.F., **07**-0020
Freedman, H.H., **02**-0206, **05**-0040, **05**-0076, **18**-0462, **19**-0660
Freedman, L.D., **13**-0166
Freeman, F., **10**-1577, **15**-0001, **15**-1679, **15**-1679, **19**-0713, **19**-0714
Freeman, H.S., **13**-0166
Freeman, J.P., 09-II-0006, **19**-1517
Freeman, N.J., **03**-0028
Freeman, P.K., **12**-0578, **15**-0057, **15**-2185, **15**-2196
Freeman, R., **14**-0327
Freeman, R.C., **15**-0369
Freeman, W.A., **03**-0210
Freeman, W.R., **14**-0148
Freenor, F.J., **10**-1135
Freerksen, R.W., **19**-1422
Freiberg, D.A., **16**-0160, **16**-1671
Freidlin, V.I., **16**-1470
Freidlina, R.Kh., **05**-0211, **10**-1233, **15**-1640, **18**-0054, **18**-0069, **18**-0080, **18**-0080, **18**-0084
Freiesleben, W., **12**-0074, **14**-0259, **15**-0792, **19**-0718
Freifelder, M., **15**-0401, **19**-1175
Freilich, S.C., **16**-2087
Freire, A., **08**-0081
Freiser, B.S., **11**-0101
Frejd, T., **10**-1381
Frejd, T., **13**-0675, **13**-0725, **15**-2085
Frelek, J., **04**-0119
Fremaux, B., **16**-1467
French, M.A., **03**-0052
Frenette, R., **10**-0620, **12**-0348
Frenkel, A.D., **18**-0879
Frenking, G., **10**-1333, **15**-1696, **15**-1738, **19**-1727
Frennesson, D.B., **10**-0855
Frensdorff, H.K., **03**-0101
Frenz, B.A., **04**-0377
Frère, S., **11**-0382
Frese, E., **16**-1397
Freskos, J., **10**-1272
Fressigne, C., **05**-0178, **08**-0198, **16**-0470
Fretwell, P., **15**-0878
Fretz, E.R., **18**-0107
Freudenberger, J.H., **19**-1662, **19**-1663
Frey Jr., F.W., **10**-1320
Frey, D., **10**-1124
Frey, E.J., **15**-0714
Frey, H., **10**-0998
Frey, H.M., **04**-0413, **05**-0332, **05**-0339, **05**-0366, **05**-0380, **12**-0378, **15**-2230, **15**-2232, **15**-2265, **15**-2309, **18**-0168, **18**-0551, **18**-0572
Frey, J., **02**-0399, **12**-0083
Frey, L.F., **13**-0272
Frey, P.A., **03**-0022
Frey, T.G., **15**-0047
Fricke, H., **15**-2323
Frid, M., **10**-1405
Friderichsen, A.V., **05**-0269
Fridkin, M., **16**-1816
Fridman, A.L., **10**-1722, **12**-0699, **16**-2047, **19**-1284
Fried, A., **19**-0050
Fried, H.E., **02**-0141, **09**-0060
Fried, J., **10**-1767
Fried, J.H., **15**-0074
Friedel, R.A., **15**-0549
Friederang, A., **15**-1632
Friedl, T., **12**-0421
Friedman, B.S., **11**-0316
Friedman, L., **05**-0387, **05**-0389, **10**-0203, **10**-0393, **10**-1786, **12**-0349, **15**-2075, **17**-0269, **17**-0280, **19**-0419
Friedman, M., **15**-0076
Friedman, N., **05**-0035, **05**-0050
Friedrich, A., **18**-0554, **18**-0559
Friedrich, E., **16**-1032
Friedrich, E.C., **10**-0315, **15**-2332, **15**-2341
Friedrich, H.B., **19**-0143
Friedrich, K., **10**-1785, **15**-1499, **15**-1499, **16**-1421, **17**-0148, **17**-0424, **17**-0458
Friedstad, G.K., **16**-0932
Friege, H., **15**-2096
Friend, C.L., **15**-0311
Friend, C.M., **14**-0408, **19**-0015, **19**-1592
Friesen, D., **04**-0283
Friestad, G.K., **16**-0936
Frigerio, M., **19**-0198, **19**-0199
Friguelli, F., **10**-0672
Frim, R., **04**-0071
Frimer, A.A., **14**-0227, **14**-0228, **14**-0241, **15**-2156, **15**-2159
Frings, M., **03**-0124
Fringuelli, F., **02**-0149, **10**-0672, **10**-0944, **10**-1167, **15**-1681, **15**-1819, **15**-1985, **15**-2003, **15**-2006, **19**-1258, **10**-1152
Frisbee, A.R., **16**-1820
Frisch, A.C., **10**-1297
Frisch, H.L., **03**-0199
Frisch, M.A., **04**-0320
Frisch, M.J., **04**-0118
Frisell, C., **12**-0438
Frison J.-C., **18**-0361
Frisque-Hesbain, A., **10**-1089, **16**-1879
Fristad, W.E., **14**-0421, **15**-1715, **15**-1882, **15**-1921, **19**-0436, **19**-0852
Fritch, P.C., **10**-0235
Fritsch, P., **17**-0326
Fritz, H., **03**-0194, **04**-0294, **08**-0084, **11**-0469, **16**-0326
Fritz, H.L., **12**-0015
Fritz-Langhals, E., **05**-0253
Fritzberg, A.R., **18**-0205
Fritzen, E., **10**-1291
Fritzsche, G., **18**-0631
Fröch, S., **16**-1019
Frochi, M., **10**-0716
Froech, S., **16**-1022
Froehner, S., **10**-0529
Froemsdorf, D.H., **17**-0066, **17**-0092, **17**-0140, **17**-0280
Frøhaug, Az., **19**-0590
Fröhlich, H., **11**-0642
Fröhlich, R., **02**-0161, **16**-1300
Frohn, M., **15**-1767, **15**-1768
Frohning, C.D., **15**-1381
Frölich, R., **16**-2083
Frolov, A.N., **14**-0358
Froment, F., **05**-0138, **15**-1001
Frommeld, H.D., **16**-1056, **19**-1557
Fronczek, F.R., **19**-0952
Frontera, A., **12**-0389, **13**-0021
Frontier, A.J., **15**-0850
Frost II, K.A., **04**-0475, **10**-0262
Frost, C.G., **11**-0200, **11**-0217, **11**-0423, **13**-0194, **15**-1024, **15**-1132, **15**-2131, **16**-1982
Frost, H.N., **13**-0177, **16**-1581
Frost, L.N., **16**-1570
Frost, R.M., **10**-1296
Froudakis, G., **15**-1219
Frøyen, P., **16**-1338, **16**-1339
Fruchart, J.-S., **12**-0103
Fruchey, O.S., **10**-0226
Fruit Jr., R.E., **05**-0049, **19**-0663
Fruit, C., **12**-0239
Frullanti, B., **19**-0532
Fry Jr., F.S., **02**-0416

Fry, A., **06**-0040, **10**-0224, **15**-0018, **15**-0653, **17**-0003, **17**-0006, **17**-0058, **17**-0058, **17**-0128, **18**-0177, **18**-0179, **18**-0182, **18**-0374, **19**-1334
Fry, A.J., **07**-0080, **10**-0190, **11**-0659, **14**-0415, **16**-2059, **17**-0371, **18**-0125, **19**-0446, **19**-1228, **19**-1317, **19**-1334, **19**-1449, **19**-1691
Fry, D.F., **16**-0961, **19**-1502
Fry, J.L., **10**-0057, **10**-0279, **10**-0280, **10**-0281, **18**-0023, **18**-0026, **18**-0045, **18**-0048, **19**-0910, **19**-1450, **19**-1742
Fry, K., **11**-0142
Fry, M.A., **19**-0436
Frydrych-Houge, C.S.V., **19**-1717
Frye, L.L., **16**-2172
Fryhle, C.B., **10**-0798
Fryzuk, M.D., **04**-0150, **04**-0151
Fu, C.-G., **10**-0553
Fu, C.C., **19**-1128
Fu, D.-K., **16**-1357
Fu, F., **10**-1453
Fu, G.C., **10**-1155, **10**-1384, **10**-1406, **10**-1422, **12**-0270, **12**-0299, **12**-0363, **13**-0294, **13**-0299, **13**-0350, **13**-0351, **13**-0364, **13**-0367, **13**-0435, **13**-0480, **13**-0539, **13**-0635, **15**-0368, **15**-0580, **15**-0656, **15**-0689, **15**-0696, **15**-1274, **15**-1369, **16**-0793, **16**-1502, **16**-1941, **16**-2104, **18**-0759, **18**-0796, **19**-0220, **19**-1261, **19**-1407, **19**-1681
Fu, H., **16**-0095, **16**-0323
Fu, I.-P., **16**-1438
Fu, J., **16**-0585
Fu, P.-F., **15**-1870
Fu, P.P., **19**-0012
Fu, S.S., **15**-0046
Fu, X., **05**-0367, **12**-0285
Fu, X.Y., **15**-0463
Fu, Y., **10**-1386, **15**-0604, **15**-1136, **16**-1920, **19**-1028
Fu, Z., **12**-0275, **13**-0424
Fu, G.C., **19**-1682
Fuchibe, K., **11**-0649, **15**-2377
Fuchicello, A., **02**-0359
Fuchigami, T., **11**-0328, **14**-0143, **10**-1783, **10**-1854, **19**-1177, **19**-1493
Fuchs, B., **04**-0366, **04**-0380
Fuchs, H., **04**-0046
Fuchs, J.R., **19**-1671
Fuchs, P.L., **10**-1773, **13**-0378, **15**-0040, **16**-0092, **16**-0221, **16**-0246, **16**-0247, **16**-1289, **16**-1820, **17**-0195
Fuchs, R., **10**-0333, **10**-0417, **10**-1066, **19**-0410
Fudesaka, M., **19**-0161, **19**-0176
Fueno, T., **04**-0011, **10**-0571, **15**-0107, **15**-1600, **15**-2117
Fuentealba, P., **15**-2104
Fuentes, A., **19**-1762
Fuest, M., **10**-1324
Fugami, K., **13**-0439
Fuhlendorff, R., **10**-0092
Fuhrman, G., **10**-1285
Fuji, K., **03**-0130, **10**-0798, **10**-0800, **10**-1463, **15**-1448
Fuji, Z., **02**-0120
Fujibayashi, T., **16**-0609
Fujieda, Y., **17**-0241
Fujihara, H., **10**-0464
Fujihara, H., **16**-0866, **16**-0894
Fujii, A., **16**-0408, **16**-1444, **16**-1657, **19**-1005
Fujii, J., **10**-0886
Fujii, K., **16**-1282, **16**-1314
Fujii, N., **10**-0234, **15**-0394, **15**-0922
Fujii, S., **15**-2351
Fujii, T., **05**-0206, **10**-0905, **10**-1214, **14**-0191, **16**-0751
Fujikura, R., **16**-1708
Fujikura, Y., **19**-0461
Fujimatsu, H., **16**-0711
Fujimori, C., **19**-1781, **19**-1783
Fujimori, M., **10**-1306, **12**-0278
Fujimoto, E., **03**-0051
Fujimoto, E.K., **10**-0350, **10**-0425
Fujimoto, H., **15**-1206, **15**-2049, **15**-2103, **15**-2107, **18**-0478, **18**-0622
Fujimoto, K., **11**-0542, **16**-0737, **16**-2092, **18**-0732
Fujimoto, S., **12**-0547
Fujimoto, T., **03**-0149, **15**-2383, **19**-1699
Fujimura, T., **10**-1358, **13**-0595
Fujimura, Y., **15**-1387
Fujinami, T., **16**-0434, **17**-0487, **19**-0922
Fujino, T., **15**-0056
Fujio, M., **08**-0223, **10**-0063, **10**-0154, **10**-0169, **10**-0170, **10**-0273, **10**-0274, **10**-0311, **10**-0403, **10**-0440, **10**-0441, **10**-0442, **11**-0172
Fujioka, H., **18**-0139
Fujioka, S., **15**-1001, **15**-1004, **16**-1036, **18**-0363
Fujioka, T., **15**-1267
Fujisaki, S., **10**-0796, **11**-0244, **12**-0120, **12**-0721, **12**-0722
Fujisawa, T., **10**-1154, **10**-1511, **15**-1607, **15**-2298, **16**-0923, **16**-1929, **19**-1021, **19**-1072, **19**-1108
Fujisawa, Y., **15**-2304
Fujise, Y., **15**-2116
Fujishima, A., **16**-1245
Fujishima, H., **15**-1191
Fujita, A., **15**-0585, **15**-0589
Fujita, E., **04**-0136, **10**-0798, **10**-0800, **16**-0232
Fujita, H., **10**-0874, **15**-0321
Fujita, K., **10**-1625, **15**-0558, **15**-1265, **15**-1420, **16**-1116, **18**-0011
Fujita, K.-i., **10**-0882, **10**-0905, **11**-0357, **13**-0663, **19**-0690
Fujita, M., **03**-0193, **03**-0197, **05**-0111, **07**-0083, **07**-0098, **10**-0730, **12**-0484, **12**-0695, **14**-0071, **15**-0056, **15**-0839
Fujita, N., **16**-0086
Fujita, R., **10**-1454
Fujita, S., **02**-0303, **02**-0304, **02**-0306, **02**-0328, **04**-0257, **04**-0258, 09-II-0001
Fujita, S., **19**-1781
Fujita, T., **08**-0169, **09**-0078, **10**-0827, **10**-1453, **13**-0482, **16**-0687, **17**-0373
Fujita, Y., **19**-0653
Fujitsuka, H., **15**-2197
Fujiwara, F.Y., **03**-0052
Fujiwara, I., **10**-0796
Fujiwara, K., **15**-2069, **16**-1167
Fujiwara, M., **10**-0074, **10**-1014, **11**-0476, **12**-0317, **15**-0820, **15**-1379
Fujiwara, N., **15**-0938
Fujiwara, S.-i., **14**-0013, **16**-0437
Fujiwara, T., **10**-1205, **10**-1215, **15**-0885, **15**-0914, **16**-0452, **16**-1357, **16**-1358
Fujiwara, Y., **03**-0078, **10**-0712, **10**-1169, **11**-0331, **11**-0493, **11**-0505, **12**-0605, **13**-0040, **13**-0360, **13**-0420, **13**-0447, **15**-1165, **15**-1330, **18**-0363, **19**-1649, **19**-16, **19**-1707, **19**-1718
Fujiwra, H., **15**-0839
Fujiyama, R., **10**-0207, **10**-0311, **16**-1435
Fukamachi, S., **10**-0716
Fukata, G., **11**-0595
Fukazawa, Y., **04**-0270, **13**-0781

Fukazawa, Y., **16**-2025
Fuks, R., **10**-1681, **15**-1964, **15**-1992, **15**-2233, **15**-2308, **15**-2362, **16**-0198
Fukuda, E.K., **16**-1568
Fukuda, K., **10**-0788, **19**-0650
Fukuda, M., **11**-0328
Fukuda, T., **10**-1454, **13**-0648, **15**-2298, **16**-2127
Fukuhara, H., **16**-0892
Fukuhara, J., **10**-1044
Fukuhara, T., **10**-1084, **10**-1148, **10**-1836, **11**-0358, **13**-0705, **13**-0718, **15**-0168, **15**-1520, **15**-1548
Fukui, K., **12**-0087, **15**-2103, **15**-2107, **18**-0476, **18**-0478, **18**-0622
Fukui, S., **19**-1781, **19**-1783
Fukuma, T., **16**-0664, **16**-0765, **16**-1426
Fukumoto, K., **15**-0785, **19**-0667
Fukumoto, T., **12**-0718, **16**-1667, **16**-2142, **18**-0884
Fukumoto, Y., **10**-1862, **15**-2443
Fukunaga, J.Y., **15**-2209, **18**-0537
Fukunaga, K., **17**-0369
Fukunaga, R., **02**-0052
Fukunaga, T., **02**-0113
Fukuoka, K., **13**-0441
Fukuoka, S., **12**-0745
Fukushima, A., **16**-1289
Fukushima, D., **19**-0871
Fukushima, H., **04**-0177, **10**-1827
Fukuta, Y., **15**-1474, **19**-0881
Fukutani, Y., **15**-2344
Fukuto, J.M., **12**-0012, **12**-0022
Fukuyama, T., **11**-0463, **13**-0202, **13**-0557, **16**-1990, **18**-0678
Fukuyama, T., **19**-1116
Fukuyo, E., **10**-0691
Fukuzawa, S., **04**-0459, **15**-0912, **15**-1716, **15**-2065, **18**-0245, **19**-0471, **19**-0922
Fukuzawa, S.-i., **15**-2036, **16**-0829, **19**-0985, **19**-0986
Fukuzumi, K., **18**-0761
Fukuzumi, S., **12**-0025, **15**-0022, **16**-1415
Fulford, S.Y., **16**-0774
Fuller, C.E., **10**-1361
Fuller, D.J., **05**-0188, **08**-0205, **14**-0027, **14**-0062
Fuller, G., **15**-1518
Fuller, J.C., **19**-0939, **19**-0953, **19**-1154
Fuller, S.E., **04**-0512, **14**-0153
Fullerton, T.J., **02**-0045, **02**-0046, **10**-1448, **10**-1450
Fulop, F., **02**-0429, **02**-0430
Fulton, J.R., **16**-1371
Fulton, R.P., **19**-1417
Funabashi, Y., **15**-1092, **16**-0522
Funabiki, K., **15**-1545
Funabiki, T., **14**-0201, **15**-0417, **15**-1504
Funabashi, K., **16**-0687
Funaki, T., **02**-0069
Funakoshi, K., **15**-0985
Funakoshi, S., **16**-1134, **16**-2018
Funaro, J.M., **16**-2172
Funato, M., **10**-1206
Funatsu, M., **15**-0778
Funderburk, L.H., **06**-0062
Fünfschilling, P.C., **15**-0135
Fung, A.P., **10**-0649, **18**-0325, **19**-0691
Fung, N.Y.M., **19**-1001
Fung, S., **11**-0391
Fung, S.H.C., **19**-0583
Funhoff, D.J.H., **02**-0308
Funk, B., **05**-0321
Funk, R.L., **10**-1710, **10**-1726, **15**-0879, **17**-0170
Furber, M., **15**-0952
Furet, N., **12**-0249, **15**-0633
Furin, G.G., **11**-0339, **18**-0883
Furkawa, I., **10**-1453
Furlani, T.R., **15**-2029
Furmanova, N.G., **02**-0410
Furness, K., **18**-0296, **18**-0297
Furrow, S.D., **15**-1558
Furst, A., **19**-1752
Furst, G.T., **16**-0849
Fürstner, A., **10**-1299, **10**-1330, **11**-0427, **13**-0311, **13**-0472, **15**-0475, **15**-0776, **15**-0818, **15**-0965, **16**-0809, **16**-0813, **18**-0772, **18**-0797, **18**-0814, **18**-0828, **19**-1645, **19**-1715, **19**-1722, **19**-1723, **19**-1724
Furstoss, R., **10**-0582, **18**-0842
Furubayashi, T., **15**-1184
Furuhashi, K., **10**-1203
Furuhata, K., **04**-0390
Furuhata, T., **10**-0785
Furukawa, A., **18**-0139
Furukawa, I., **10**-0886, **19**-1093
Furukawa, J., **04**-0011, **10**-0571, **15**-2117, **15**-2198, **15**-2327, **15**-2341, **16**-0562
Furukawa, N., **10**-0464, **10**-1098, **13**-0082, **13**-0101, **15**-1892, **17**-0135, **18**-0261, **19**-0852, **19**-1618
Furukawa, S., **15**-0558
Furumai, S., **19**-1604
Furuno, H., **15**-1300, **16**-0630
Furusaki, A., **13**-0010
Furusawa,O., **13**-0752
Furusho, Y., **03**-0182
Furuta, H., **11**-0172
Furuta, K., **10**-1637, **14**-0208, **14**-0213, **15**-2063, **16**-0645, **16**-1047, **16**-1051, **16**-1418
Furuta, T., **15**-0608
Furutani, H., **19**-1021
Furuya, T., **19**-0541
Furuyama, S., **15**-0059
Furxhi, E., **15**-1222
Fusco, C., **19**-0235, **19**-0301, **19**-0514, **19**-0615
Fusco, R., **18**-0714
Fuso, F., **10**-0175
Fuson, R.C., **02**-0398, **12**-0094, **15**-1166, **19**-1095, **19**-1122
Fustero, S., **16**-1413
Futamata, M., **10**-0881
Futamura, J., **18**-0139
Fwu, S.-L., **15**-0941
Fyfe, C.A., **11**-0016, **13**-0008, **13**-0090, **16**-0318
Fyfe, M.C.T., **03**-0186

Gaasbeek, C.J., **05**-0031, **10**-0184
Gabbi, C., **19**-0828
Gabe, E.J., **04**-0502
Gabhe, S.Y., **13**-0094
Gable, C.M., **03**-0160
Gable, K.P., **15**-1656, **15**-1696, **15**-2402
Gable, K.P., **17**-0203
Gabriel, A.O., **16**-1419
Gabriel, C., **07**-0108
Gabriel, S., **07**-0108
Gabriele, B., **12**-0734, **15**-0243, **15**-0304, **15**-0361
Gabrielsen, B., **10**-0081
Gacem, B., **16**-1636
Gacon, A., **19**-1255
Gadallah, F.F., **13**-0740, **13**-0747
Gadamasetti, G., **10**-1674
Gadamasetti, K.G., **15**-2282
Gadberry, J.F., **15**-0005
Gade, L.H., **19**-1046
Gademann, K., **15**-2149
Gadgil, V.R., **18**-0642
Gadhwal, S., **10**-0591, **16**-0395, **19**-1433

Gadras, A., **13**-0578
Gadre, S.R., **15**-0099
Gadru, K., **10**-0101
Gadzikwa, T.L., **13**-0543
Gaemi, E., **11**-0134
Gaetano, K., **11**-0298
Gaffney, A., **17**-0074
Gaffney, A.H., **17**-0031
Gaffney, P.R.J., **04**-0348
Gage, J.R., **10**-0888
Gaggero, N., **15**-1758, **19**-0799, **19**-0824
Gagné, M.R., **15**-0419, **15**-1868, **15**-1869, **15**-1871, **16**-1680, **19**-0968
Gagnier, R.P., **10**-1239
Gagnier, S.V., **15**-1408
Gagnon, J.L., **19**-0321
Gagosian, R.B., **18**-0202, **18**-0205, **18**-0236
Gai, F., **12**-0087
Gai, Y., **13**-0315, **15**-2008, **17**-0287
Gailbreath, B.D., **10**-0022
Gais, H., **05**-0143
Gais, H.-J., **04**-0181, **10**-0840
Gaisberger, R.P., **16**-1424
Gajare, A.S., **10**-0660, **11**-0255, **13**-0177, **16**-1683
Gajek, K., **18**-0614
Gajewski, J.J., **02**-0232, **15**-2090, **15**-2094, **16**-0584, **18**-0070, **18**-0471, **18**-0526, **18**-0567, **18**-0589, **18**-0591, **18**-0601, **18**-0621, **18**-0623, **18**-0630, **18**-0634, **18**-0656, **18**-0669, **18**-0677, **18**-0708, **18**-0709, **18**-0710
Gakh, A.A., **10**-0323
Gal, C., **14**-0134, **14**-0136
Gal, G., **11**-0399
Gal, J., **01**-0051, **03**-0016, **08**-0076, **08**-0146
Gal, J.-F., **08**-0087
Gal, V.M.S., **08**-0104
Galabi, S., **16**-2178
Galabov, B., **04**-0307, **16**-1844
Galaev, I.U., **04**-0151
Galán, A., **19**-1173
Gale, L.H., **04**-0328, **12**-0505
Galema, S.A., **07**-0107
Galili, N., **15**-2298
Galindo, F., **14**-0069, **16**-2081
Galindo, J., **16**-1928
Gall, J.S., **10**-0070, **10**-0334
Gall, M., **10**-1649, **10**-1652, **12**-0328, **12**-0420, **16**-2011
Gallagher, D.W., **19**-0350
Gallagher, M.E., **02**-0323
Gallagher, M.J., **04**-0044, **12**-0579
Gallagher, S.P., **18**-0255
Gallagher, S.S., **18**-0473
Gallagher, T., **15**-0364
Gallagher, W.P., **12**-0258, **12**-0266, **13**-0563
Galland, B., **15**-0012
Galland, J.-C., **15**-0774, **15**-0977, **18**-0812
Gallardo, I., **11**-0192, **13**-0007, **13**-0064, **13**-0066, **13**-0158
Galle, D., **16**-1013
Galle, J.E., **15**-2405
Gallego, A.M., **12**-0280
Gallego, C.H., **16**-1348
Galletero, S., **16**-0073
Galletti, P., **15**-2056, **16**-0976
Galley, M.W., **11**-0107
Galli, C., **04**-0386, **05**-0241, **06**-0012, **10**-0266, **10**-0709, **11**-0308, **13**-0060, **13**-0063, **13**-0590, **14**-0350, **14**-0352, **19**-0187
Galli, E., **15**-1758
Galli, R., **14**-0153, **14**-0347, **15**-1882
Gallina, C., **10**-0226, **10**-1438
Gallivan Jr., R.M., **15**-0669
Gallivan, J.P., **11**-0019
Gallo, E.A., **03**-0068
Gallo, R., **09**-0065, **09**-0068
Gallopo, A.R., **15**-1768
Gallucci, J.C., **12**-0348, **15**-0105
Gallucci, R.R., **12**-0139
Gallulo, V., **16**-0962
Galluzzo, D.J., **16**-1352
Galonić, D., **10**-1562
Galpin, J.D., **18**-0608
Galton, S.A., **19**-1436
Galvagno, S., **19**-0960
Gálvez, J., **17**-0485
Gama, A., **16**-1438
Gamasa, M.P., **19**-1762
Gamba, A., **18**-0708
Gambaro, M., **15**-1662
Gambaryan, N.P., **16**-0041
Gamber, G.G., **15**-1422, **15**-2435
Gambill, C.R., **16**-2162
Gamboni, R., **19**-0475
Gamez, P., **10**-0925, **19**-0183
Gammill, R.B., **15**-0561
Gammon, J., **12**-0465, **12**-0467
Gamsey, S., **13**-0172
Ganapathy, S., **18**-0061
Ganboa, I., **16**-0339
Ganchegui, B., **12**-0329, **19**-0218
Gancher, E., **19**-0349
Gande, M.E., **18**-0669
Gandler, J.R., **13**-0012, **17**-0003, **17**-0052
Gandolfi, C.A., **10**-1179
Gandolfi, R., **15**-1731, **15**-1733, **15**-1736, **15**-1932, **15**-1943, **15**-1944, **15**-1951, **19**-0114, **19**-0232, **19**-0519
Gandon, V., **15**-0881, **15**-2400, **16**-0856, **16**-1115, **16**-1411
Gandour, R.D., **15**-1840
Gandour, R.W., **02**-0352, **15**-1946
Ganellin, C.R., **04**-0074, **04**-0167
Ganem, B., **10**-0497, **10**-0624, **10**-0731, **10**-0988, **10**-1563, **15**-0404, **15**-0571, **16**-1862, **17**-0282, **18**-0669, **19**-0170, **19**-0757, **19**-1168, **19**-1206
Ganesan, K., **16**-0997
Ganesan, R., **16**-0191
Ganesh, K.N., **19**-0584
Ganesh, Y.S.S., **11**-0394, **19**-1214
Ganguli, S., **10**-0368
Ganguly, B., **16**-0007
Ganguly, N.C., **16**-0061, **16**-0062, **16**-0241
Ganguly, R.N., **18**-0344
Ganguly, S., **15**-0084
Gani, V., **16**-1593, **16**-1594
Ganin, E., **19**-0622
Ganis, P., **02**-0283
Gano, J., **04**-0479
Gansäuer, A., **16**-0646, **19**-1665
Ganter, C., **18**-0118
Gantzel, P., **03**-0200
Gantzel, P.K., **02**-0271
Ganushchak, N.I., **13**-0731
Ganz, C., **15**-0187
Ganzer, D., **13**-0119
Ganzer, G.A., **04**-0497
Gao, D., **15**-2013, **15**-2015
Gao, F., **16**-0397
Gao, G., **15**-0740, **15**-0841, **16**-0549, **19**-0174
Gao, G.-Y., **15**-1898
Gao, H., **15**-0422, **15**-1843, **16**-1155
Gao, J., **10**-0018, **15**-2029, **18**-0667
Gao, J.J., **16**-0785, **16**-2088
Gao, L., **10**-0833, **16**-1155
Gao, L.X., **15**-0272
Gao, Q., **15**-0891, **16**-1047, **16**-1418
Gao, S., **15**-1137, **19**-0277
Gao, W., **15**-0237, **15**-0395

Gao, W.-Z., **15**-0244
Gao, X., **19**-0334
Gao, Y., **10**-0498, **10**-0819, **10**-1018, **15**-1822, **19**-0902, **19**-1032
Gaoni, Y., **02**-0272, **02**-0273, **02**-0287, **02**-0291, **02**-0324
Gapinski, R.E., **16**-1729
Garapon, J., **15**-1566
Garau, C., **13**-0021
Garavelas, A., **15**-0264
Garavelli, M., **18**-0847
Garay, R.O., **17**-0052
Garbarino, G., **17**-0056
Garbarino, J.A., **16**-2058
Garber, S.B., **18**-0800, **18**-0823
Garbisch Jr., E.W., **12**-0141, **13**-0012, **13**-0086, **19**-1368
Garbuzova, I.A., **02**-0254
Garcia, A., **15**-0454, **15**-0574
Garcia, B., **16**-1528
Garcia, B.A., **10**-1048
Garcia, C.F., **15**-2298
Garcia, E., **10**-1694, **14**-0390
Garcia, H., **16**-1440
Garcia, I.F., **16**-0632
Garcia, J., **16**-0708, **16**-1857
Garcia, L.A., **15**-1945
García, B., **08**-0118, **12**-0486
García, C., **16**-0687, **16**-0688
García, D., **13**-0544
García, G.V., **15**-0873
García, J.I., **15**-2038, **15**-2054, **15**-2059, **15**-2305
García, J.M., **15**-1310
García, M.C., **15**-1334
García, O., **19**-0089
García, T., **16**-1664
Garcia-Blanco, F., **10**-0282
García-Expósito, E., **15**-2244
Garcia-Garibay, M., **04**-0142
García-Gómez, G., **15**-0998
García-Granda, S., **10**-1167, **15**-2289
Garcia-Ochoa, S., **10**-1530
García-Raso, A., **13**-0299
García-Ruano, J.L., **11**-0268
Garcia Ruano, J.L., **15**-2063, **10**-0487
García Ruano, J.L.G., **19**-1497
Garcia-Slanga, B.J., **13**-0737
García-Yebra, C., **10**-1463
Garcias, X., **13**-0237
Gardano, A., **13**-0613
Gardelli, C., **10**-0663, **10**-1150, **10**-1564, **10**-1640
Gardette, M., **15**-0949
Gardiner Jr., W.C., **06**-0043
Gardini, G.P., **14**-0155, **14**-0341, **14**-0344
Gardlik, J.M., **04**-0086
Gardner, H.C., **15**-0859
Gardner, J.N., **19**-1615
Gardner, P.D., **04**-0483, **15**-0510
Gardossi, L., **17**-0152
Gareau, Y., **10**-0816
Gareau, Y., **15**-0301
Gareev, G.A., **10**-0661
Garegg, P.J., **10**-1096
Garg, C.P., **15**-0665
Garg, P., **18**-0146
Gargalak Jr., J., **12**-0290
Gargo, J.V.S., **19**-0232
Gariano Jr., P., **10**-0727
Gariano, A., **10**-0727
Garibina, V.A., **16**-1309
Garigipati, R.S., **16**-0428
Garkusha, O.G., **02**-0254
Garley, M., **10**-0750
Garner, A.Y., **15**-2311
Garner, C.M., **15**-0674, **16**-1422
Garner, C.S., **12**-0008
Garner, L.A., **18**-0874
Garner, P., **10**-0876, **15**-2029
Garnett, I., **15**-1782
Garnett, J.L., **11**-0116, **11**-0117, **11**-0118
Garnier, B., **18**-0209
Garnier, L., **10**-1821
Garnovskii, A.D., **08**-0149, **15**-1932
Garratt, D.G., **15**-0001, **15**-0021, **15**-0026, **15**-0087
Garratt, P.G., **02**-0272
Garratt, P.J., **02**-0093, **02**-0103, **02**-0248, **02**-0255, **02**-0272, **02**-0274, **02**-0288, **02**-0305, **02**-0326, **02**-0350, **04**-0516
Garrell, R.L., **03**-0185
Garrett, C.E., **15**-0689
Garrido, F., **13**-0608
Garrigues, B., **15**-2022
Garrison, B.J., **07**-0015
Garrone, A., **19**-0116
Garrou, P.E., **10**-0916
Garsky, V., **15**-0969
Garst, J.F., **10**-1317, **12**-0436, **12**-0611, **15**-0515, **15**-1497, **16**-0536, **16**-2027, **18**-0415, **18**-0416
Garst, M.E., **15**-2433, **19**-1410
Garver, L.C., **12**-0212
Garvey, D.S., **10**-0948, **19**-0175, **04**-0133, **19**-0679
Garwood, D.C., **10**-0006
Garwood, R.F., **11**-0589
Gary, T., **11**-0120
Garza, T., **15**-2170
Garzya, V., **11**-0218
Gasanov, R.G., **05**-0211
Gasc, M.B., **15**-0314, **15**-0327
Gasch, C., **19**-0300
Gaset, A., **10**-0819, **11**-0481, **16**-1324
Gash, D.M., **04**-0213
Gasol, V., **10**-1089, **10**-1798, **15**-1545
Gaspar, P.P., **05**-0327, **12**-0051, **12**-0063, **15**-2316
Gaspard-Iloughmane, H., **10**-1092
Gasparrini, F., **04**-0059, **13**-0407, **19**-1510
Gassman, P.G., **04**-0233, **04**-0246, **05**-0411, **05**-0412, **10**-0132, **10**-0138, **10**-0140, **10**-0143, **10**-0148, **10**-0151, **10**-0281, **10**-0294, **10**-0300, **10**-0969, **10**-1589, **11**-0275, **11**-0519, **11**-0520, **12**-0241, **12**-0679, **15**-0307, **15**-2092, **15**-2203, **15**-2204, **15**-2206, **16**-1537, **16**-1586, **17**-0189, **18**-0344, **18**-0346, **18**-0840, **18**-0, **18**-0844, **18**-0846, **19**-1319, **19**-1320
Gastaldi, S., **17**-0138, **19**-1306
Gastaminza, A., **11**-0041
Gasteiger, J., **01**-0094, **02**-0057, **15**-0547
Gastner, T., **16**-0871
Gaston, L.K., **19**-1734
Gatehouse, B.M., **12**-0279
Gates, M., **10**-0171
Gathergood, N., **16**-0899, **16**-0912
Gati, A., **04**-0504, **15**-2365
Gati, E., **04**-0188
Gatri, R., **16**-0774
Gatto, V.J., **03**-0101, **03**-0146
Gattuso, M.J., **02**-0101
Gau, G., **08**-0014
Gau, H.-M., **16**-0674, **16**-0687
Gaudemar, M., **10**-1643, **10**-1689, **16**-0809, **16**-0836
Gauder, S., **19**-1241
Gaudry, M., **16**-0403
Gaugler, R.W., **08**-0022
Gaul, J.M., **19**-1504
Gaul, M.D., **15**-2032
Gault, Y., **04**-0169
Gäumann, T., **15**-0450
Gaunt, M.J., **15**-0163, **15**-1007, **15**-1305, **18**-0905
Gaur, S., **12**-0105
Gautam, V.K., **15**-0694
Gauthier Jr., D.R., **13**-0266, **13**-0504, **16**-0758, **16**-0760
Gauthier, J.Y., **16**-1730
Gauthier, R., **16**-0954

Gauthier, S., **13**-0217
Gautier, A., **10**-0549, **19**-0122
Gautier, E.C.L., **10**-0542
Gautier, J., **16**-0425
Gavard, J., **11**-0550
Gavaskar, K.V., **15**-0884
Gavazza, F., **16**-1983
Gavenonis, J., **16**-0632
Gavezzotti, A., **01**-0007, **01**-0072
Gaviña, F., **13**-0046, **16**-1289
Gavrilenko, V.V., **12**-0481, **19**-1115
Gavuzzo, E., **04**-0066
Gawienowski, J.J., **07**-0081
Gawinecki, R., **12**-0085
Gawley, R.E., **09**-0082, **10**-1725, **12**-0003, **13**-0291, **16**-1064, **17**-0450, **18**-0306
Gawronska, K., **05**-0356
Gawronski, J., **05**-0356
Gawro\O(n,')ski, J., **04**-0113
Gayathri, K.U., **14**-0308
Gaylord, N.G., **19**-1070, **19**-1083, **19**-1486
Gayton-Garcia, R., **12**-0406
Gázguez, J.L., **08**-0158
Gazit, A., **10**-0244, **10**-0245
Gazzolo, F.H., **13**-0006
Ge, C.-S., **15**-2268
Gebicki, J., **03**-0165
Gebicki, J.M., **05**-0210
Gebreyes, K., **17**-0349
Gebrian, J.H., **02**-0256, **02**-0258
Gedanken, A., **15**-2023, **19**-0158
Gedye R., **07**-0101, **15**-0012
Gedye, R.N., **07**-0101
Gee, K.R., **18**-0601, **18**-0708
Geels, E.J., **12**-0717
Geer, R.P., **17**-0139
Geerlings, P., **13**-0048
Geetha, V., **15**-1035
Gehret, J-C.E., **15**-2282
Geib, A.D., **15**-1445
Geib, G.D., **16**-1348
Geib, S.J., **15**-1444
Geiger, C.C., **10**-0178
Geiger, M., **04**-0119
Geis, O., **13**-0182
Geise, B., **19**-1532
Geise, H.J., **04**-0283, **04**-0317, **19**-1714, **19**-1718
Geise, H.Y., **19**-1727
Geisel, M., **14**-0433
Geisel, M., **17**-0406
Geisler, V.J., **11**-0120
Geiss, W., **05**-0322
Geissler, M., **05**-0131
Geissman, T.A., **19**-1754
Geke, J., **11**-0139
Gelalcha, F.G., **19**-0211
Gelas-Mialhe, Y., **10**-1216, **16**-0329
Geletii, Y.V., **19**-0614
Geller, B.A., **10**-0915, **11**-0573
Geller, L.E., **18**-0870
Geller, T., **15**-1813, **15**-1816
Gellert, E., **13**-0741
Gellibert, F., **10**-1110
Gellman, S.H., **16**-1732
Gelman, D., **11**-0360, **13**-0322, **16**-0891, **16**-1311
Gelman, S.H., **03**-0068
Gelo Pujic, M., **18**-0362
Gelpke, A.E.S., **13**-0237
Geltz, Z., **08**-0119
Gemal, A.L., **19**-0922, **19**-0941
Gendreau, Y., **10**-1530
Geneste, J., **15**-1578
Geneste, P., **10**-0148, **19**-0247
Genêt, J.-P., **10**-0226, **10**-1424, **12**-0334, **12**-0508, **13**-0727, **13**-0728, **13**-0729, **15**-0774, **15**-0932, **15**-0977, **15**-1125, **15**-1132, **19**-1028, **19**-1622
Geng, B., **12**-0270, **16**-0697
Geng, F., **16**-1904, **18**-0407, **18**-0409
Geng, Z., **16**-1074
Genin, E., **15**-0932
Gennari, C., **12**-0230, **16**-1032, **16**-1051, **16**-1077, **16**-1417
Gennaro, A., **10**-1854
Gennet, D., **16**-1290
Genov, D.G., **18**-0764
Genski, T., **15**-1791
Gensler, W.J., **15**-0501
Gent, B.B., **17**-0084
Gentile, A., **11**-0185, **14**-0340
Gentili, P., **10**-0266, **13**-0060, **13**-0063, **19**-0187
Gentilucci, L., **06**-0032, **15**-1317
Gentric, E., **03**-0015
Geoffroy, M., **19**-0964
Geoffroy, O.J., **19**-1538
Geoghegan Jr., P.J., **15**-0187
Georg, G.I., **16**-1784, **18**-0777, **11**-0433
George, A.V., **15**-2027
George, M.V., **07**-0062, **07**-0063, **15**-1295, **18**-0471, **19**-0010
George, P., **02**-0028, **15**-2145
George, R.S., **16**-0513
George, T.G., **15**-1532, **15**-1599, **15**-1624
Georghiou, P.E., **19**-1294
Georgiadis, G.M., **18**-0901
Georgiadis, R., **08**-0238
Georgoulis, C., **10**-0224, **10**-0229, **12**-0605, **19**-0081
Geraci, C., **03**-0123, **03**-0128, **03**-0139, **04**-0066, **04**-0092
Geraghty, N.W.A., **15**-0720
Gérard, L., **18**-0014
Gerasimova, E.S., **18**-0293
Gerber, G.E., **16**-1669
Gerdes, J.M., **16**-0148
Gerdes, P., **15**-1347
Gerdil, R., **03**-0155
Gerecs, A., **11**-0546
Gerhardt, G., **06**-0015
Gerhardt, H., **16**-1820
Geri, R., **15**-0363
Géribaldi, S., **15**-0038
Gerisch, M., **16**-0947
Gerlach, A., **15**-1694
Gerlach, H., **03**-0203, **16**-1652
Germain, A., **05**-0060, **11**-0455
Germain, G., **04**-0460
German, A.L., **16**-1698
German, L., **11**-0310, **12**-0111, **14**-0131
German, L.S., **15**-0072, **15**-1622
Germani, R., **10**-0407, **10**-0701, **15**-1681, **15**-1819
Germon, C., **10**-1525
Gernon, M., **12**-0402
Gero, A., **02**-0385
Gerrard, W., **08**-0078, **08**-0238, **12**-0466, **17**-0230
Gerratt, J., **02**-0006, **02**-0121, **15**-1953
Gerrits, P.J., **16**-1423
Gersch, B., **03**-0116
Gershtein, N.A., **11**-0637
Gersmann, H.R., **12**-0310, **14**-0226
Gerson, F., **05**-0313, **05**-0315, **05**-0319, **05**-0320, **05**-0324
Gerstenberger, M.R.C., **14**-0129
Gerstmans, A., **11**-0142
Gerth, D.B., **17**-0508
Gesche, P., **18**-0480
Gesenberg, K.D., **12**-0151
Geske, D.H., **05**-0208
Geslin, M., **19**-1243
Gessler, S., **18**-0774
Gesson, J., **11**-0533
Gesson, J.-P., **15**-0718
Gestmann, D., **04**-0434
Getman, D., **18**-0574
Gettwert, V.J., **11**-0147
Getzler, Y.D.Y.L., **10**-1552
Geuss, R., **05**-0171
Gevergyan, V., **15**-0803
Gevorgyan, G.A., **16**-0392, **16**-0393

Gevorgyan, V., **10**-1432, **10**-1432, **10**-1784, **13**-0309, **15**-0244, **15**-0356, **15**-0738, **15**-0771, **15**-0843, **15**-0854, **15**-2357, **15**-2363, **15**-2372, **15**-2379, **19**-1451
Gewald, K., **16**-1413
Geyer, E., **04**-0193
Ghadir, K.D.F., **01**-0042
Ghaemi, E., **11**-0127, **11**-0134, **12**-0698
Ghaffarzadeh, M., **19**-1147
Ghanbarpour, A., **06**-0082, **17**-0062
Ghannam, A., **18**-0900
Ghasemzadeh, Z., **19**-0092
Ghassemzadeh, M., **16**-0063, **16**-0145, **19**-0101, **19**-0147, **19**-0150, **19**-0153
Ghatak, A., **16**-2097, **19**-0119, **19**-1648
Ghatak, U.R., **19**-0411, **19**-1467
Ghattas, A.A.G., **16**-0220
Ghazi, I., **10**-1164
Ghelfenstein, M., **18**-0416
Ghelfi, F., **12**-0114, **12**-0115, **12**-0119, **12**-0123, **12**-0152, **15**-1527, **15**-1602, **19**-0828
Ghenciulescu, A., **19**-0631
Gheorghiu, M.D., **15**-2210
Ghiaci, M., **10**-1131, **11**-0238, **16**-0078, **18**-0321
Ghirardelli, R.G., **17**-0042
Ghiro, E., **15**-0053
Ghodrati, K., **16**-0053, **16**-0245
Gholizadeh, M., **19**-0080, **19**-0866
Ghoneim, N., **07**-0032
Ghorai, M.K., **15**-1217
Ghorbani, M., **15**-1755
Ghoroku, K., **13**-0448
Ghorpade, S.R., **16**-1737
Ghosal, S., **14**-0385
Ghose, B.N., **14**-0317
Ghosez, L., **08**-0189, **10**-1089, **15**-2004, **15**-2011, **15**-2032, **15**-2146, **15**-2147, **15**-2183, **15**-2184, **15**-2212, **15**-2213, **16**-1879, **18**-0509
Ghosh, A.C., **16**-1176
Ghosh, A.K., **16**-0027, **18**-0797
Ghosh, K., **11**-0418
Ghosh, K., **13**-0531, **16**-0841, **16**-1983, **19**-1110
Ghosh, M., **18**-0698
Ghosh, P.K., **11**-0296
Ghosh, R., **16**-1606, **16**-1750
Ghosh, S., **11**-0389, **12**-0215, **17**-0450, **17**-0451, **18**-02, **18**-0698
Ghosh, S.K., **16**-1126
Ghribi, A., **10**-1520
Giacobbe, T.J., **14**-0257
Giacomelli, G., **07**-0042, **10**-1091, **12**-0730, **16**-1703, **16**-1790, **16**-1948, **19**-0171, **19**-0186, **19**-0677
Giacomello, P., **11**-0311
Giacomini, D., **15**-2056, **16**-0976
Giam, C., **13**-0617
Giamalva, D., **19**-0353
Giamalva, D.H., **12**-0348
Giambastiani, G., **10**-1449
Gianeti, T.R., **15**-0313
Giang, Y.F., **17**-0168, **17**-0170
Giangiordano, M.A., **16**-0853
Gianni, M.H., **04**-0261, **04**-0350, **04**-0354
Giannotti, C., **14**-0332
Gianotti, M., **15**-1317
Giansiracusa, J.J., **10**-0182
Giardello, M.A., **15**-1871
Giarlo, G., **10**-1002
Gibbard, H.C., **02**-0267
Gibbons, C.S., **04**-0450
Gibbons, T., **11**-0123
Gibbs, D.E., **19**-1240
Gibbs, H.W., **11**-0055
Gibbs, R.A., **16**-0142, **16**-1441
Gibby, J.E., **15**-2441
Gibe, R., **12**-0364
Giberson, C.B., **02**-0270
Gibian, M.J., **05**-0304
Giblin, G.M.P., **19**-0685
Giboreau, P., **15**-2022
Gibson, C.P., **14**-0377
Gibson, D., **13**-0280
Gibson, D.T., **15**-1721, **15**-1722, **15**-1723, **15**-1724
Gibson, L.L., **18**-0676
Gibson, M.S., **10**-0852, **10**-0982, **15**-0314
Gibson, S.E., **13**-0364, **15**-1417, **15**-1440
Gibson, T.L., **11**-0378
Gibson, V.C., **18**-0756
Gidaspov, B.V., **10**-1035, **11**-0138, **12**-0710, **12**-0711, **18**-0291, **18**-0305, **19**-0786
Gidley, G.C., **14**-0138, **17**-0084
Giebel, D., **11**-0427
Gielen M., **04**-0027, **12**-0015, **12**-0040
Gielen, M., **15**-2407
Gieren, A., **04**-0467
Giersch, W., **19**-0314
Giese, B., **05**-0242, **05**-0273, **05**-0294, **05**-0378, **14**-0001, **14**-0056, **14**-0057, **14**-0092, **14**-0123, **14**-0286, **15**-0050, **15**-0052, **15**-0066, **15**-0091, **15**-0100, **15**-0127, **15**-0752, **15**-1193, **15**-1196, **15**-1197, **15**-1214, **15**-1353, **15**-1357, **15**-2314, **18**-0077
Giese, C.M., **15**-2318
Giese, R.W., **19**-0337
Giese, S., **15**-0852, **15**-0853, **15**-1412
Giesen, F.L.L., **11**-0351
Gieson, V., **10**-1324
Giessert, A.J., **15**-0815, **18**-0788, **18**-0789
Giessner-Prettre, C., **05**-0178, **08**-0198, **16**-0470
Giffney, J.C., **11**-0125
Gigante, B., **16**-1440
Giger, U., **15**-2331
Giglio, E., **03**-0167
Giguere, R.J., **07**-0102, **07**-0105, **10**-0471, **12**-0634, **15**-2022
Giguère, P.A., **04**-0282
Gil, G.S., **15**-0878
Gil, P., **13**-0046
Gil, R., **10**-0925, **15**-1161, **15**-2033
Gil, S., **12**-0004, **19**-0840
Gil-Av, E., **04**-0169, **04**-0170, **04**-0175, **04**-0209, **18**-0462
Gilabert, D.M., **19**-0282
Gilardi, R., **15**-2068
Gilardi, R.D., **16**-1768
Gilbert, A., **15**-2439, **18**-0493
Gilbert, B., **08**-0113
Gilbert, B.A., **10**-1192
Gilbert, B.C., **05**-0208, **05**-0345, **10**-1225, **14**-0146, **14**-0352, **15**-1254
Gilbert, D.P., **15**-0307
Gilbert, E.E., **11**-0198, **11**-0209, **11**-0631, **12**-0255, **13**-0093, **14**-0272, **14**-0360, **16**-0385, **16**-0439, **19**-0791, **19**-0794
Gilbert, H.F., **16**-0010
Gilbert, J.C., **04**-0478, **12**-0348, **15**-2200, **15**-2208, **18**-0092, **18**-0590, **18**-0692
Gilbert, K.E., **18**-0629, **19**-0766
Gilbert, L., **19**-1056
Gilbert, R.P., **10**-0253
Gilbertson, R.D., **05**-0064
Gilbertson, S.R., **15**-2445, **12**-0275, **13**-0424, **15**-0425, **18**-0764, **18**-0831

Gilchrist, J.H., **08**-0203, **08**-0205, **12**-0422
Gilchrist, M., **10**-0357, **16**-0019
Gilchrist, T.L., **02**-0267, **05**-0327, **13**-0037, **15**-1894, **15**-2103, **15**-2133, **15**-2166, **18**-0471
Gilday, J.P., **12**-0403, **12**-0665, **12**-0683, **12**-0684
Gilde, H., **14**-0415, **14**-0419
Giles, P.R., **16**-0799, **19**-0122, **19**-0123
Giles, W.B., **15**-2103
Gilheany, D.C., **15**-1691
Gilheany, D.G., **15**-1773, **15**-1835, **16**-0488, **16**-1271
Gilkerson, T., **19**-1223
Gill, G.B., **15**-0789, **15**-1271, **15**-2103, **16**-1486
Gill, N.S., **15**-1046
Gille, B., **16**-1475
Gilles, J., **02**-0291, **02**-0298, **02**-0324, **18**-0637
Gillespie, K.M., **15**-1885, **15**-1905
Gillespie, R.J., **05**-0021, **05**-0023, **08**-0015, **08**-0016, **11**-0153
Gilley, C.B., **19**-0686
Gillie, A., **12**-0278
Gillies, C.W., **19**-0345, **19**-0354, **19**-0361, **19**-0379
Gillies, J.Z., **19**-0361
Gillingham, D.G., **18**-0823
Gillis, D.J., **15**-0515
Gillmore, A.T., **10**-0621
Gilman, H., **04**-0013, **10**-1285, **12**-0001, **13**-0042, **16**-1893
Gilman, N.W., **14**-0276, **18**-0621, **18**-0688
Gilmor, W.F., **18**-0196
Gilmore, N.J., **19**-1031
Gilow, H.M., **11**-0041, **11**-0273
Gimbert, Y., **15**-1418, **15**-1437, **15**-1452, **15**-1453
Gimbert, Y., **16**-1321
Gimeno, J., **15**-0194
Gimisis, T., **19**-1403
Gimisis, Z.T., **15**-1219
Gimzewski, J.K., **08**-0234
Ginah, F.O., **10**-1222
Ginak, A.I., **15**-0001
Gingras, M., **10**-0505, **10**-0745, **10**-0776, **10**-0805
Ginj, M., **16**-0687
Ginodman, L.G., **13**-0154
Ginos, J.Z., **16**-2136
Ginsburg, D., **04**-0431, **15**-0992, **15**-2115
Ginsburg, G.S., **07**-0080
Ginzburg, B.M., **13**-0067
Giordano, C., **11**-0607, **14**-0120, **14**-0348, **18**-0193, **19**-0963
Giordano, F., **15**-1941
Giordano, L., **15**-1741
Giorgio, E., **16**-0687
Giovani, E., **10**-0814
Giovannini, P.P., **19**-0232
Giovannini, R., **10**-1384, **19**-1586
Gipe, B.T., **15**-0004, **15**-0033
Gipson, J.D., **16**-0704
Giralt, E., **13**-0504
Girard, C., **15**-2329, **18**-0708, **19**-1056
Girard, J.-P., **18**-0156
Girard, J.P., **15**-1685
Girard, P., **17**-0202
Girdhar, R., **10**-0294
Giri, V.S., **19**-1431, **19**-1487
Giridhar, D., **16**-0149
Girotti, R., **16**-0601
Giroux, A., **10**-1858
Girreser, U., **02**-0312
Gisdakis, P., **15**-1734, **15**-1738, **15**-1934, **19**-0114
Gissot, A., **13**-0290, **13**-0639, **15**-1939, **16**-0115
Gitlin, L.F., **17**-0092
Gitlitz, M.H., **12**-0591
Gittos, M.W., **16**-0434
Giudicelli, M.B., **10**-1044
Giuffrida, D., **02**-0312
Giuliani, A., **16**-0615
Giuliano, C., **10**-1153
Giumanini, A.G., **10**-1716, **12**-0701, **13**-0759, **16**-1712, **18**-0380, **18**-0387
Giunta, N., **15**-1685
Givens, R.S., **07**-0050, **17**-0499, **17**-0515, **18**-0641
Gjuranovič, Ž., **10**-0142
Gladfelter, E.J., **14**-0153
Gladfelter, W.L., **12**-0742
Gladiali, S., **15**-1492, **16**-1225
Gladys, J.A., **19**-0909, **19**-1455
Gladysheva, F.N., **15**-1966
Gladysz, J.A., **12**-0352, **16**-1422, **17**-0190, **19**-1055
Glänzer, B.I., **15**-0520
Glapski, C., **15**-1049
Glaser, P.B., **15**-0729
Glaser, R., **05**-0068, **13**-0005, **13**-0023, **13**-0027
Glasfeld, A., **04**-0252
Glasovac, Z., **02**-0082
Glass, L.E., **10**-0176, **16**-1570
Glass, R.S., **04**-0354, **04**-0387, **16**-0432
Glass, T., **02**-0364
Glasson, W.A., **10**-0357
Glatzhofer, D.T., **16**-1707
Glave, W.R., **17**-0052
Glaze, W.H., **12**-0013
Glazer, E.A., **18**-0347
Glazunova, E.M., **16**-1186
Gleason, J.D., **16**-1457
Gleason, J.G., **12**-0174, **19**-0871, **19**-1425
Gleason, J.L., **15**-0809, **15**-0835
Gleave, D.M., **16**-1026
Glebova, E.V., **16**-0422
Gledhill, A.P., **19**-1566
Gleich, A., **04**-0243
Gleicher, G.J., **02**-0036, **14**-0104, **14**-0121, **15**-0101, **18**-0116
Gleiter, R., **02**-0052, **02**-0180, **02**-0353, **03**-0060, **04**-0249, **04**-0427, **04**-0490, **05**-0050, **11**-0508, **14**-0244, **15**-1447, **15**-2115, **18**-0631
Gleiter, R.J., **16**-1918
Glendening, E.D., **02**-0023
Glenn, A.G., **14**-0078, **18**-0075
Glenn, R., **16**-0030
Glick, A.H., **16**-2085
Glick, H.C., **05**-0363
Glick, M.D., **15**-0280
Glick, R., **09**-0047
Glick, R.E., **09**-0054
Glidewell, C., **02**-0133
Glineur, M., **18**-0509
Glink, P.T., **03**-0186
Glöckner, H., **02**-0236
Gloe, K., **03**-0139
Gloor, B.F., **13**-0588
Glorius, F., **10**-1471, **15**-2435
Glover, B., **13**-0305, **13**-0649
Glover, C., **16**-0138
Glover, I.T., **18**-0040
Glover, S.A., **15**-1259, **15**-1575
Glowinski, R., **14**-0384
Glukhovtsev, M.N., **02**-0092, **02**-0209, **02**-0231, **02**-0288, **05**-0327
Glushkov, R.G., **10**-0380
Glushkov, R.G.I., **10**-0686
Glyde, E., **02**-0371
Gmouth, S., **11**-0431
Gnanadesikan, V., **15**-1741
Gnanapragasam, N.S., **11**-0305
Gnanasekaran, C., **19**-0831
Gnedin, B.G., **16**-2143
Gnonlonfoun, N., **15**-0782
Goacolou, K., **15**-1782
Goble, M.P., **16**-1578
Goblyos, A., **02**-0429
Goda, K., **10**-1207, **15**-0735

Godat, M., **10**-0465
Goddard II, W.A., **15**-2300
Goddard III, W.A., **02**-0216, **05**-0332, **15**-2105
Goddard, J.-P., **15**-0701
Goddard, J.D., **15**-2089
Godefroi, E.F., **19**-1397
Godel, T., **10**-1641
Godet, T., **16**-2132
Godfrey, A.G., **17**-0282, **19**-0170
Godfrey, C.R.A., **19**-0058, **19**-1410
Godfrey, I.M., **18**-0371
Godfrey, M., **05**-0378, **08**-0171, **11**-0083
Godfrey, P.D., **13**-0047
Godjoian, G., **19**-1126
Godleski, S., **04**-0206
Godleski, S.A., **18**-0115
Godovikova, T.I., **13**-0687
Godschalx, J., **10**-1260
Godschalx, J.P., **10**-1824
Godt, A., **03**-0198
Goedecke, E., **02**-0181
Goedicke, C., **04**-0068
Goedken, V., **05**-0356, **18**-0019
Goel, A.B., **10**-0089, **10**-0772, **15**-0948, **15**-0948, **17**-0177
Goel, O.P., **16**-2056
Goel, S.C., **18**-0121
Goem G.L., **15**-0253
Goering, H.L., 170, **05**-0138, **10**-0063, **10**-0064, **10**-0068, **10**-0069, **10**-0134, **10**-0216, **10**-0217, **10**-1429, **10**-1430, **10**-1437, **10**-1509, **10**-1656, **14**-0263, **15**-0054, **15**-0057, **15**-0124, **18**-0708
Goerlich, J.R., **12**-0365
Goerner Jr., R.N., **18**-0056
Goetschel, C.T., **18**-0056
Goggiamani, A., **13**-0149, **13**-0230, **13**-0609, **16**-1983, **18**-0356
Gogia, A., **19**-0813
Gogoi, B.J., **16**-0882
Gogoi, P., **19**-0230
Gogoll, A., **13**-0550, **13**-0547
Gogonea, V., **02**-0338
Goh, S.-H., **16**-0590
Goh, S.H., **11**-0648
Gohain, M., **09**-0107
Goicoechea-Pappas, M., **10**-1725
Going, R., **12**-0139
Goj, L.A., **15**-0764
Gojo, T., **10**-0811
Gokcek, D.Y., **16**-1652
Gokel, G.W., **03**-0088, **03**-0101, **03**-0104, **03**-0117, **03**-0146, **04**-0164, **10**-0453, **10**-0610, **10**-0696, **10**-0784, **10**-0967, **10**-1047, **10**-1619, **10**-1787, **13**-0691, **13**-0737, **15**-2274, **16**-1255, **16**-2128, **16**-2133, **17**-0479, **19**-1564
Gokhale, A.S., **19**-0538
Göksu, S., **10**-0939, **19**-0392
Gol’dberg, Yu.Sh., **15**-2274
Gol’dfarb, Ya.L., **04**-0451, **04**-0456
Gol’ding, I.R., **13**-0534
Gol’dshtein, I.P., **03**-0001
Golan, O., **04**-0326, **04**-0344
Golborn, P., **11**-0073
Gold, H., **10**-0519, **13**-0413
Gold, M.R., **10**-0897
Gold, P.M., **15**-0561
Gold, V., **05**-0002, **05**-0006, **05**-0070, **06**-0047, **06**-0087, **10**-0119, **11**-0110, **12**-0412, **13**-0009, **15**-0024, **16**-1517, **16**-1886, **19**-1063, **08**-0019
Goldacre, R.J., **05**-0043
Goldberg, B.J., **10**-0209
Goldberg, G.M., **12**-0431
Goldberg, I., **01**-0067, **03**-0156
Goldberg, N.L., **10**-0711
Goldberg, S.I., **04**-0136, **17**-0126
Goldberg, S.Z., **02**-0254
Goldblum, A., **04**-0071, **16**-2160
Golden, D.M., **05**-0265, **15**-0059
Golden, J.T., **11**-0574
Golden, R., **01**-0042
Goldenberg, W.S., **05**-0177, **05**-0181
Goldfinger, P., **14**-0182
Goldfuss, B., **15**-0702
Goldhamer, D.M., **15**-0048
Golding, B.T., **10**-0898, **10**-1089, **12**-0657, **18**-0615
Golding, G.M., **13**-0484
Golding, P., **10**-0764
Golding, P.D., **11**-0587
Goldman, A.S., **19**-0050, **19**-0061
Goldman, B.E., **16**-1484
Goldman, E.W., **15**-2297
Goldman, G., **11**-0214, **11**-0416
Goldman, G.K., **02**-0377
Goldman, I.M., **15**-2243
Goldman, L., **19**-0160, **19**-0163
Goldman, M., **04**-0170
Goldman, N., **10**-1653
Goldmann, A., **04**-0437
Goldring, W.P.D., **18**-0797
Goldsmith, B., **19**-1295, **19**-1522
Goldsmith, E.A., **18**-0048
Goldsmith, M.D., **12**-0370
Goldstein, M.J., **02**-0254, **18**-0621, **18**-0623
Goldwhite, H., **11**-0593, **15**-0074
Goliński, J., **13**-0670, **19**-0778
Goll, J.M., **11**-0332
Goller, E.J., **04**-0138, **16**-0005
Gollnick, K., **14**-0227, **14**-0235, **14**-0241, **14**-0241, **15**-2151
Golobish, T.D., **04**-0428
Golobov, Y.G., **19**-1273
Golod, E.L., **11**-0029, **11**-0138, **12**-0711
Gololobov, Yu.G., **16**-1403
Golovina, Z.P., **16**-0031
Golse, R., **10**-1524
Golubeva, I.A., **16**-0422
Golubkin, L.N., **11**-0044
Gölz, H.-J., **02**-0261
Gomaa, M.A.-M., **11**-0176
Gomberg, M., **05**-0003, **05**-0229
Gomes de Mesquita, A.H., **05**-0088
Gomes, A.K., **15**-0997
Gomes, P., **10**-1442, **13**-0337, **15**-1162
Gómez Aranda, V., **15**-1875
Gomez, J., **08**-0131, **10**-1110
Gómez, A.M., **10**-1530, **15**-1224
Gómez, A.M., **15**-1718
Gómez, B., **15**-2104
Gómez, C., **15**-2346
Gómez, J., **08**-0125
Gómez, J.L., **17**-0485
Gómez, M., **10**-1454, **10**-1459
Gomez-Bengoa, E., **15**-0870, **13**-0131, **15**-1310
Gómez-Escalonilla, M.J., **13**-0516
Gómez-Lara, J., **19**-0261
Gómez-López, M., **03**-0191
Gómez-Lor, B., **13**-0378
Gómez-Parra, V., **10**-0729
Gommermann, N., **16**-0889
Gompper, R., **02**-0221, **02**-0222, **02**-0224, **02**-0236, **10**-0484, **15**-2224, **18**-0632
Gomtsyan, A., **16**-1965, **16**-1966
Goncharov, A.N., **16**-0015
Gondai, T., **15**-0626
Gong, H., **16**-0094
Gong, L., **10**-1453, **10**-1454, **13**-0482, **19**-1265

Gong, L.-Z., **15**-1128, **16**-0865, **16**-1037
Gong, W.H., **13**-0378, **13**-0389, **13**-0421
Gong, Y., **07**-0118, **07**-0119, **13**-0503
Gonikberg, E.M., **15**-0970, **19**-1019
Gonsalves, A.M. d'A.R., **15**-2133
Gonthier, E., **13**-0548, **18**-0777
Gonzalez, D., **15**-1724, **15**-2231
Gonzalez, J., **16**-1786
Gonzalez, M.A., **10**-1725
Gonzalez, T., **10**-0462
González, E., **16**-1192
González, C., **11**-0268
González, J., **16**-2112
González, J.J., **13**-0378
González, J.M., **10**-0669, **14**-0141, **15**-0357, **15**-1546, **15**-1547
González, R., **15**-1006
González, R.R., **10**-0133, **19**-0336
González-Bobes, F., **14**-0141
González-Nilo, F., **08**-0083
González-Nuñez, M.E., **19**-0515, **15**-1199, **19**-0799
Gonzalez-Outeirino, J., **04**-0348
González-Sierra, M., **02**-0404
González-Zamora, E., **15**-0415
Gonzálwz, G., **11**-0268
Gonzlez, A.M., **15**-0584
Gonçalves, S.M.C., **10**-0828, **12**-0142
Goo, Y.M., **16**-0136
Gooch, E.E., **12**-0492
Good, G.M., **15**-1475
Goodacre, P.R., **14**-0351
Goodale, J.W., **07**-0079, **07**-0088
Goodall, K., **15**-1254
Goodarzi, M., **19**-0084
Goodby, J.W., **10**-1296
Goode, E.V., **01**-0036
Goode, N.C., **04**-0240
Goodenough, K.M., **19**-1395
Goodenough-Lashua, D.M., **04**-0313
Gooding, O.W., **16**-0363, **16**-1746
Goodlett, V.W., **15**-2185, **15**-2189, **15**-2212
Goodman, J.L., **01**-0101, **05**-0374, **05**-0386, **15**-2324
Goodman, J.M., **16**-0783, **16**-1018, **16**-1032, **16**-1051, **16**-1384
Goodman, L., **10**-1119, **17**-0220
Goodman, M., **03**-0203
Goodman, R.M., **16**-0186
Goodman, S.N., **07**-0123
Goodwin, T.H., **02**-0004, **02**-0007
Goodwin, T.H., **04**-0419
Goon, D.J.W., **17**-0035, **18**-0891
Goon, S., **11**-0466
Goosen, A., **14**-0214, **15**-1575, **18**-0868
Goossen, L.J., **15**-0278
Gooßen, L.J., **13**-0454, **13**-0531, **13**-0636, **16**-0841, **16**-1983, **17**-0228, **19**-1110
Gopal, D., **15**-1117
Gopal, H., **19**-0434
Gopalaiah, K., **18**-0319, **18**-0326
Gopalakrishnan, G., **16**-0102
Gopalan, A.D., **09**-0098
Gopalan, A.S., **15**-0788
Gopalan, R., **12**-0147
Gopinath, R., **16**-0149, **19**-0702
Gopius, E.D., **18**-0044, **18**-0250
Goralski, C.T., **10**-0923, **15**-0670, **15**-0671, **15**-1598, **19**-0953, **19**-1154, **19**-1172, **19**-1527
Gorb, L., **12**-0087, **17**-0206
Görbitz, C.H., **03**-0035
Gorczyca, A.M., **04**-0221
Gordeichuk, S.S., **12**-0709
Gordi, Z., **18**-0323
Gordillo, B., **04**-0361
Gordillo, R., **15**-2097, **15**-2150, **16**-1029
Gordin, M.B., **18**-0028
Gordon, A.J., **14**-0222, **15**-0129
Gordon, C.M., **16**-0629
Gordon, G., **18**-0672
Gordon, I.M., **16**-2140
Gordon, J.E., **10**-0335
Gordon, J.W., **15**-0022
Gordon, K.M., **17**-0290, **19**-0600
Gordon, M., **14**-0212, **17**-0388
Gordon, M.D., **15**-2044
Gordon, M.S., **01**-0009, **01**-0010
Gordon, P.E., **19**-1449
Gordon, P.F., **07**-0003, **11**-0166
Gordon, R.J., **18**-0499
Gordon, R.S., **13**-0407, **13**-0492
Gordon, S., **02**-0127
Gore, J., **10**-1435
Gore, P.H., **11**-0073, **11**-0416, **11**-0452, **11**-0607, **11**-0608
Goré, J., **10**-0547, **10**-1349, **15**-0221, **15**-0511, **15**-1612, **15**-2212
Gorelik, M.V., **02**-0093, **11**-0582
Goren, Z., **04**-0344
Gorenstein, D.G., **13**-0030, **16**-0030
Gori, D., **16**-0779
Gorkom, M., **04**-0256
Gorlier, J., **15**-1074
Görlitz, M., **18**-0643
Gorman, A.A., **14**-0228, **15**-2156
Gorman, D.B., **15**-2092, **15**-2141
Gorman, J.A., **04**-0309
Görner, H., **07**-0054
Gorsane, M., **15**-1862, **19**-1056
Gorsuch, S., **10**-1274
Gorton, P.J., **15**-0181
Gortva, A.M., **18**-0567
Gosain, R., **15**-1253
Gosavi, R.K., **18**-0224, **18**-0226
Gosberg, A., **15**-1125, **15**-1134
Goshaev, M., **13**-0455
Gosmini, C., **10**-1442, **13**-0337, **15**-1162, **16**-1908
Gosney, A.P., **11**-0164
Gosney, I., **02**-0090, **15**-0016, **15**-2322, **16**-1323, **18**-0469, **18**-0470
Gosselain, P.A., **14**-0182
Gosselck, J., **10**-1599
Gosselin, P., **10**-0366
Gosser, L., **12**-0030
Gössler, W., **07**-0103
Gotanda, K., **12**-0252, **14**-0008
Gotebiowski, A., **04**-0135
Gothelf, A.S., **11**-0387
Gothelf, K.V., **15**-1960, **16**-0920, **16**-1164
Goti, A., **17**-0449, **19**-0307, **19**-0767, **19**-0774, **19**-1231
Goto, D., **10**-1854
Goto, H., **19**-1667
Goto, K., **03**-0135, **08**-0187, **16**-0670
Goto, M., **10**-0154, **10**-0170, **10**-0441
Goto, N., **10**-0154, **10**-0440
Goto, T., **15**-1092, **16**-0329
Gotor, V., **16**-1413, **19**-1022
Gotou, H., **02**-0317
Gotou, T., **15**-0933, **17**-0381
Gott, P.G., **15**-2185, **15**-2190
Gotta, M.F., **10**-0355
Gottardi, W., **11**-0251
Gottarelli, G., **04**-0187
Gotteland, J., **15**-1975
Göttker-Schnetmann, I., **19**-0043
Göttlich, R., **15**-0323, **15**-1568

Gottlieb, H., **19**-0158
Gottschalk, T., **16**-1416
Gotō, H., **04**-0275
Goubitz, K., **11**-0615
Goud, P.R., **16**-0328, **17**-0483
Goudgaon, N.M., **12**-0444, **12**-0514, **12**-0517
Goudmand, P., **18**-0634
Gough, R.G., **10**-1318
Gouin, L., **15**-0174
Gould, A.E., **18**-0488
Gould, E.S., **15**-1795
Gould, E.S., **19**-0787
Gould, F.E., **17**-0457, **19**-1174
Gould, I.R., **01**-0101, **05**-0335, **15**-2312, **17**-0515
Gould, K.J., **18**-0457
Goumont, R., **08**-0172
Goumont, T., **13**-0005
Goure, W.F., **10**-1824
Gourevitch, D.N., **15**-1959
Gouverneur, V., **15**-0229, **15**-1563, **18**-0818
Goux, C., **10**-0802
Goux-Henry, C., **10**-1453
Govande, C.A., **19**-0703
Gover, T.A., **14**-0137
Govind, N., **18**-0091
Govindachari, T.R., **11**-0400
Govindan, C.K., **19**-0356
Gowda, A.S.P., **19**-1201
Gowda, D.C., **19**-1153, **19**-1201, **19**-1205, **19**-1216, **19**-1749
Gowda, S., **19**-1153, **19**-1201, **19**-1216
Gowenlock, B.G., **12**-0706, **15**-1616
Gowland, F.W., **19**-1063
Gozzi, C., **13**-0301, **16**-1778
Gozzo, A., **19**-1791
Gozzo, F., **18**-0493
Gozzo, F.C., **11**-0071, **18**-0655
Grabacia, S., **18**-0773
Grabner, G., **05**-0354
Graboski, G.G., **16**-1149
Grabowski, E.J.J., **04**-0197, **15**-0615, **15**-1038, **18**-0302, **19**-0673, **19**-0678
Grabowski, J., **10**-0312
Grabowski, J.J., **10**-0368, **17**-0120, **18**-0601
Grabowski, S., **07**-0048
Grachev, M.A., **15**-1652
Gracheva, E.P., **15**-0049, **15**-0295
Gracheva, R.A., **04**-0144
Gracias, V., **18**-0297
Graczyk, D.G., **10**-0078
Gradl, S.N., **15**-0850, **16**-0688
Graefe, J., **15**-0222
Graf, E., **03**-0118
Graf, N.A., **15**-2210
Graf, R., **16**-2110, **16**-2111
Gragerov, I.P., **10**-1317, **13**-0746, **19**-0630, **19**-0755, **19**-1570
Graham, A., **12**-0198
Graham, A.E., **10**-0542, **16**-0234
Graham, G.R., **15**-2431
Graham, J., **11**-0153
Graham, S.H., **19**-1244
Graham, W.D., **15**-2282
Grahn, W., **15**-0094
Graiver, D., **03**-0194
Grajewski, J., **04**-0113
Grakauskas, V., **11**-0310, **11**-0311, **12**-0212, **12**-0728, **14**-0436
Gramaccioli, C.M., **02**-0285, **13**-0010
Gramain, J.-C., **10**-1216
Gramstad, T., **11**-0337
Gran-Masse, H., **12**-0103
Graña, P., **05**-0186
Grananderr, J., **16**-0470
Grand, A., **05**-0262
Grand, E., **15**-2143
Granander, J., **08**-0208
Grandberg, I.I., **17**-0446, **18**-0691, **18**-0714
Grandbois, E.R., **19**-1014
Grandclaudon, P., **16**-1321
Grandi, M., **11**-0409
Grandi, R., **12**-0114, **12**-0119, **19**-0828
Grandolini, G., **02**-0149
Granger, M.-C., **16**-0471
Granger, M.R., **08**-0025
Granger, R., **15**-1685
Granik, V.G., **04**-0461, **10**-0380, **10**-0686, **10**-1674, **16**-0425
Granito, C., **16**-2050
Granoth, I., **15**-0498
Grant, A.A., **18**-0125
Grant, D.M., **02**-0218, **03**-0077, **04**-0163
Grant, E.H., **07**-0108
Grant, H.M., **08**-0038
Grant, J.L., **08**-0075
Grant, R.W., **18**-0397
Gras, J., **10**-0613, **15**-2187
Gras, J.L., **15**-2212
Grasa, G.A., **13**-0192, **13**-0300, **13**-0480, **16**-1682, **16**-1695
Grashey, R., **15**-1932, **15**-1980, **15**-2166, **15**-2261
Grass, F., **12**-0670
Grasselli, P., **12**-0585, **16**-0499, **16**-0500
Grassi, G., **15**-1937
Grätz, W., **10**-1536
Grau, G., **14**-0320
Graul, S.T., **05**-0101, **05**-0107, **12**-0641
Gravaatt, E.C., **18**-0893
Gravel, D., **15**-0053, **16**-1834
Gravel, M., **16**-0699, **16**-0705
Gravestock, M.B., **15**-0784
Gray, B.L., **18**-0800
Gray, D., **11**-0298
Gray, D.L.F., **17**-0297
Gray, P., **14**-0110
Gray, T.A., **18**-0482
Gray, W.K., **09**-0106
Graybill, B.M., **11**-0215
Grayshan, R., **10**-1701, **10**-1702
Grayson, J.I., **15**-2003
Grayston, M.W., **10**-1503, **18**-0169
Graziani, M., **11**-0478, **19**-0960
Graziano, M.L., **15**-1941
Grazini, M.V.A., **12**-0371
Grdina, M.J., **14**-0237, **14**-0241
Grdinic, M., **15**-0095
Gream, G.E., **10**-0134, **10**-0170, **10**-0173, **19**-0438, **19**-1738
Greasley, P.M., **11**-0011
Grebenik, P., **02**-0171
Grech, E., **03**-0013
Greck, C., **12**-0508
Gree, R., **19**-0194, **19**-0120, **19**-0222
Greeley, R.H., **02**-0250
Green III, F.R., **16**-0112
Green, B., **16**-1438, **19**-1467, **19**-1469
Green, B.S., **04**-0164, **04**-0165, **09**-0012
Green, D.L.C., **05**-0099, **10**-0482
Green, D.P., **05**-0181, **12**-0629
Green, D.T., **15**-1558
Green, G.M., **15**-2290
Green, J., **08**-0147, **16**-1876, **18**-0686
Green, L., **10**-1284, **13**-0641, **13**-0641
Green, M., **10**-0357, **15**-2431, **17**-0457
Green, M.L.H., **02**-0171, **03**-0083, **05**-0145, **12**-0001
Green, M.M., **18**-0872
Green, M.P., **15**-0900
Green, N.S., **12**-0092
Green, R., **15**-1675
Green, R.D., **03**-0045

Greenberg, A., **02**-0204, **04**-0402, **04**-0409, **04**-0424, **18**-0113, **18**-0646
Greenblatt, J., **04**-0032
Greene Jr., G.H., **01**-0042
Greene Jr., J.L., **17**-0139
Greene, A.E., **15**-1418, **15**-1437, **15**-1452, **15**-1453, **19**-1462
Greene, D.J., **15**-0604
Greene, F.D., **10**-0748, **15**-1804, **17**-0099, **18**-0070, **18**-0203
Greene, J.L., **18**-0180
Greene, R.M.E., **18**-0836
Greene, T.W., **10**-0613, **10**-0895, **10**-0895, **16**-1761
Greenfield, H., **15**-0461
Greenhalgh, C., **13**-0019
Greenhall, M.P., **12**-0135
Greenlee, K.W., **04**-0412, **15**-0505
Greenlimb, P.E., **16**-1282
Greenman, K.L., **15**-0393
Greenspoon, N., **15**-0572, **19**-0920
Greenwald, R., **16**-1273
Greenwood, F.L., **19**-0361, **19**-0376
Greer, A., **15**-0967
Greer, S., **19**-1053
Greeves, N., **10**-0600, **16**-0487, **16**-0494, **16**-0624, **16**-0871, **16**-1439
Grega, K.C., **19**-0333
Gregor, I.K., **11**-0116
Gregoriou, G.A., **10**-0079
Gregory, B.J., **10**-0079, **18**-0332, **18**-0336
Gregory, C.D., **10**-1332
Gregory, M.J., **10**-0372, **11**-0611
Gregory, P., **07**-0003, **11**-0166
Gregory, R.J., **18**-0893
Gregory, T.A., **07**-0021
Gregson, M., **10**-1058, **10**-1259
Grehn, L., **10**-0992
Greiciute, D., **15**-1601
Greico, P.A., **18**-0710
Greidanus, G., **12**-0533, **13**-0628
Greig, C.C., **11**-0058
Greig, I.R., **15**-2071
Greigger, B.A., **19**-0411
Greijdanus, B., **15**-1806
Greiner, A., **17**-0149, **18**-0318
Greinert, R., **19**-0366
Greisbeck, A.G., **16**-2089
Greisinger, R., **18**-0557
Grekov, A.P., **10**-0361, **10**-0363
Grela, K., **18**-0781, **18**-0800, **18**-0811, **18**-0828, **19**-1740
Grelbig, T., **01**-0096
Grelier, S., **13**-0077
Grell, E., **03**-0116
Grellier, M., **10**-0875
Grellier, P.L., **03**-0015, **10**-0443, **12**-0002, **12**-0040, **12**-0424, **12**-0431, **12**-0482, **12**-0504, **12**-0551
Gremaud, D., **15**-2257
Gremyachinskiy, D.E., **16**-0673
Grendze, M.P., **10**-0189
Grenier, L., **12**-0348
Grenon, M., **16**-0223, **06**-0088
Gresser, M.J., **16**-1848
Gretz, E., **14**-0261
Greunig, H., **19**-0366
Greuter, H., **15**-2178, **16**-1393
Grev, R.S., **04**-0279
Grey, R.A., **16**-1903
Grgurina, I., **10**-0916
Gribble, G.W., **11**-0652, **13**-0504, **15**-0499, **16**-0137, **16**-0356, **16**-0374, **16**-1775, **19**-0935, **19**-1351, **19**-1444
Gribchenko, E.A., **13**-0720
Grice, P., **10**-0604, **19**-1130
Gridnev, I.D., **15**-0596, **15**-1920, **18**-0548
Griebe, D., **03**-0152
Griebenow, N., **16**-0580
Grieco, C., **10**-0268
Grieco, P.A., **10**-1058, **10**-1259, **12**-0246, **12**-0350, **13**-0543, **15**-0253, **15**-2029, **15**-2032, **15**-2261, **16**-1408, **16**-1583, **17**-0293, **18**-0364, **18**-0565, **18**-0667
Griengl, H., **16**-1424, **16**-1461, **16**-2015
Grier, M.C., **16**-0640
Griesbaum, K., **15**-0030, **15**-0106, **15**-0110, **15**-0297, **19**-0352, **19**-0366
Griesbeck, A., **15**-1841
Griesbeck, A.G., **12**-0101, **16**-2086, **16**-2087, **16**-2090
Griesinger, C., **05**-0184
Grieve, D.M.A., **16**-0027
Griffin, D., **11**-0200
Griffin, G.W., **04**-0441, **18**-0855, **18**-0859
Griffin, J.H., **12**-0352
Griffin, R.G., **05**-0224
Griffin, R.N., **12**-0648
Griffith, J.R., **16**-0194
Griffith, R.C., **04**-0286
Griffith, W.P., **19**-0123, **19**-0394
Griffiths, D.V., **10**-0955
Griffiths, D.W., **03**-0174
Griffiths, J., **07**-0003
Griffiths, J.G., **15**-2210
Griffiths, P.A., **15**-2239
Grigat, E., **10**-0615, **10**-0616
Grigg, R., **02**-0303, **10**-0900, **10**-1243, **15**-0806, **15**-0878, **15**-1476, **15**-1942, **19**-0708
Grigina, I.N., **16**-1186
Grignon-Dubois, M., **12**-0303
Grigor, B.A., **08**-0030
Grijzen, Y., **06**-0032
Griller, D., **01**-0089, **05**-0202, **05**-0208, **05**-0308, **05**-0345, **14**-0049, **14**-0077, **14**-0097, **14**-0146, **18**-0073, **19**-1533
Grilli, S., **04**-0087
Grillot, G.F., **11**-0590
Grim, S.O., **16**-1282
Grima, P.M., **07**-0099
Grimaud, J., **18**-0033
Grimaud, L., **16**-0396, **16**-1735
Grimeau, J., **12**-0014
Grimes, K.D., **19**-1313
Grimes, P., **12**-0406
Grimm, B., **18**-0571
Grimm, K.G., **16**-0240
Grimm, R.A., **14**-0408, **19**-1592
Grimme, W., **02**-0259, **04**-0467, **15**-2219, **18**-0552
Grimmelikhuysen, J.C., **19**-0352, **19**-0368
Grimmond, B.J., **15**-2065
Grinblat, J., **10**-0025
Grinter, R., **02**-0171
Grisdale, E.E., **10**-0333
Grisdale, P.J., **01**-0042
Grishin, Yu.K., **15**-0280
Grisso, B.A., **16**-1032
Grissom, J.W., **15**-2363, **18**-0487, **18**-0488
Griswold, A.A., **18**-0467
Gritter, R.J., **10**-0494
Grivas, J.C., **16**-0427
Grob, C.A., **01**-0042, **01**-0043, **01**-0044, **09**-0041, **10**-0173, **10**-0175, **10**-0177, **10**-0248, **10**-0251, **14**-0102, **14**-0433, **15**-0034, **17**-0403, **17**-0404, **17**-0405, **17**-0406, **17**-0407, **17**-0452, **17**-0456, **17**-0457
Gröbel, B., **10**-0558, **10**-1666
Groen, M.B., **04**-0186
Groenewege, M.P., **08**-0024
Groenewegen, F., **10**-1620
Grogan, M.J., **15**-1665, **16**-1458
Gröger, H., **16**-1422, **16**-1448, **19**-1022
Groh, B.L., **12**-0259

Grohmann, K., **02**-0272, **18**-0642
Gron, L.U., **13**-0403
Grondin, J., **12**-0599
Grondin, R., **15**-0384
Gronert, S., **05**-0106, **05**-0150 **10**-0267, **10**-0307
Gronheid, R., **05**-0065, **12**-0484
Gronowitz, S., **12**-0512
Gros, C., **04**-0096
Gros, E.G., **10**-0540
Gros, G., **15**-0375
Gros, P., **13**-0647
Grosjean, D., **15**-0068
Grosjean, F., **19**-1692
Grosjean, M., **04**-0268
Gross, A.W., **10**-1652, **12**-0313, **15**-1921, **19**-0754
Gross, B., **12**-0605
Gross, B.H., **19**-1313
Gross, E., **16**-1797, **16**-1816, **16**-2133
Gross, E.K.M., **10**-1208
Gross, G., **04**-0476, **04**-0486
Gross, H., **10**-0292, **11**-0488, **11**-0489
Gross, K.C., **08**-0175
Gross, M.F., **15**-0429
Gross, M.L., **11**-0031
Gross, P.H., **16**-0673
Gross, T., **16**-0344
Grosse, D., **16**-1889
Grossert, J.S., **05**-0144
Grossi, L., **05**-0215, **13**-0011, **15**-1167
Grossman, N., **18**-0186
Grossman, R.B., **15**-0773, **15**-1029, **15**-1041
Grosu, I., **02**-0428, **04**-0076
Grotemeier, G., **10**-1640
Groth, P., **02**-0346, **03**-0107
Groth, U., **16**-0576, **19**-1654
Groth, U.M., **15**-0878
Grotjahn, D.B., **08**-0197, **15**-0213
Groundwater, P.W., **15**-1940
Grout, A., **17**-0061
Groutas, W.C., **16**-1425
Grove, D.I., **02**-0362
Grove, D.M., **10**-1438
Grovenstein Jr., E., **05**-0145, **11**-0305, **11**-0620, **12**-0688, **18**-0094, **18**-0120, **18**-0121, **18**-0122
Grover, R., **04**-0304
Grover, V., **10**-0720
Grover, V.K., **10**-0606
Groves, E.E., **12**-0302
Groves, J.K., **15**-1648
Groves, J.T., **02**-0197, **14**-0082, **15**-1892, **19**-0464, **19**-0465
Groves, K., **18**-0503
Groves, L.G., **02**-0368
Groves, P.T., **14**-0288
Grozinger, K., **11**-0398
Grubber, M.J., **18**-0508
Grubbs, E.J., **01**-0041
Grubbs, R., **02**-0226
Grubbs, R.H., **15**-2201, **16**-1002, **16**-1347, **16**-1348, **18**-0755, **18**-0756, **18**-0759, **18**-0766, **18**-0767, **18**-0769, **18**-0778, **18**-0781, **18**-0785, **18**-0792, **18**-0794, **18**-0795, **18**-0796, **18**-0801, **18**-0805, **18**-0820, **18**-0832, **18**-0833, **18**-0836
Gruber, A.S., **13**-0397
Gruber, J.M., **19**-0479
Gruber, W., **18**-0011
Grubmüller, P., **12**-0687
Gruen, L.C., **11**-0110
Gruetzmacher, G., **11**-0520
Grugier, J., **16**-1999
Grünanger, P., **15**-1932
Gründemann, E., **04**-0039
Grundke, H., **18**-0420
Grundmann, C., **19**-1556, **19**-1557
Grundon, M.F., **13**-0773, **17**-0446
Grundy, J., **10**-0718
Grüner, H., **15**-2255, **18**-0494
Grunewald, G.L., **10**-0993, **18**-0641
Gruntz, U., **10**-0725, **10**-0850
Grunwald, E., **03**-0009, **06**-0004, **06**-0043, **08**-0220, **09**-0016, **10**-0282, **10**-0422, **10**-0427, **16**-0156, **16**-0157
Grunwell, J.R., **15**-1171
Gruseck, U., **18**-0582
Gruszecka, E., **18**-0751, **18**-0891
Grutladauria, M., **15**-0224, **15**-0439
Grutzner, J.B., **05**-0126, **05**-0134, **12**-0102, **12**-0208, **15**-1512
Gruzdneva, V.N., **09**-0034, **18**-0044
Grynszpan, F., **03**-0124
Grzyb, J.A., **16**-1803
Gschrei, C.J., **15**-0331
Gschwend, H.W., **10**-1284, **12**-0388, **13**-0641
Gschwind, R.M., **08**-0088
Gstöttmayr, C.W.K., **10**-1303
Gu, C., **19**-0253
Gu, D., **19**-0517, **19**-0792
Gu, H., **19**-1120
Gu, J., **19**-1230
Gu, P.M., **19**-1042
Gu, S., **15**-0867
Guan, X.-P., **16**-1768
Guanti, G., **12**-0230, **16**-1571, **16**-2146
Guardeño, R., **15**-0454
Guari, Y., **13**-0177
Guarna, A., **10**-1414, **12**-0283, **16**-0687, **19**-1022
Guarnieri, A., **05**-0241, **13**-0060
Guay, D., **15**-0783, **16**-1372, **16**-2180
Gubelt, C., **12**-0480
Guchhait, S.K., **13**-0386, **15**-0480, **15**-0582, **17**-0372, **19**-1336
Gudipati, M.S., **16**-2090
Gudkov, B.S., **15**-0447, **15**-0450
Gudkova, A.S., **18**-0250
Gudkova, I.P., **04**-0169, **04**-0209
Gudmundsdottir, A.D., **05**-0402
Gudmundsson, B.O., **05**-0177, **05**-0181
Gudnason, P.I., **04**-0371
Guella, F., **10**-0242
Guemas, J., **16**-0209, **15**-0024, **15**-0268, **15**-0290
Guerin, D.J., **15**-1318
Guérin, B., **15**-1245, **15**-1281
Guérin, C., **04**-0026
Guerra, F.M., **14**-0177, **15**-0284
Guerra, I.M., **15**-1710
Guerra, M., **01**-0110, **15**-1219
Guerreiro, M.C., **19**-0611
Guerrero, A., **10**-1089, **10**-1798, **15**-1545
Guerrieri, F., **10**-1841, **15**-1381
Guertin, D.L., **19**-0779
Guertin, K.R., **19**-0502, **19**-0814
Guest, J.M., **18**-0667
Guette, C., **11**-0226
Guette, J., **11**-0261
Guetté, J., **04**-0209, **04**-0214, **04**-0214
Gugel, H., **04**-0472
Guggenberger, L.J., **05**-0159
Guggisberg, A., **16**-1858
Guha, S., **19**-0982
Guibe, F., **10**-0340, **10**-0489, **19**-1100
Guibé, F., **18**-0809
Guibé-Jampel, E., **18**-0362, **18**-0715
Guida, A.R., **10**-0727
Guida, W.C., **10**-0727, **19**-1091
Guihéneuf, G., **03**-0015

Guijarro, A., **12**-0618, **16**-0479
Guijarro, D., **15**-0753, **19**-1028
Guilhem, J., **03**-0207, **04**-0244
Guillamet, B., **13**-0312
Guillaumet, G., **10**-0911, **13**-0573
Guillemin, J., **12**-0724
Guillemin, J.-C., **18**-0771
Guillemonat, A., **15**-0108
Guin, C., **11**-0246, **11**-0247, **2**-0635, **15**-0255, **16**-0646
Guindon, Y., **05**-0242, **10**-0614, **10**-0798, **15**-1245, **15**-1281
Guingant, A., **15**-1045
Guinn, V.P., **18**-0064
Guinot, A., **10**-0084
Guir, C., **10**-1520
Guirado, A., **17**-0485
Guirado, G., **13**-0007
Guiry, P.J., **12**-0520
Guisnet, M., **10**-0778
Guiu, E., **10**-1459
Guixer, J., **15**-1814
Gujadhur, R., **13**-0102
Gujadhur, R.K., **13**-0201
Guk, Yu.V., **11**-0029, **11**-0138
Gula, M.J., **17**-0052
Gulea, M., **10**-1454
Gulevich, Yu.V., **10**-1846, **12**-0526, **13**-0602
Gulhane, R., **16**-1618
Gulino, F., **12**-0654
Gultneh, Y., **14**-0200
Gulyaev, N.D., **16**-1855
Gulyás, H., **15**-1491
Gulyukina, N.S., **12**-0670
Gum, A., **07**-0116
Gumaste, V.K., **10**-1027
Gumby, W.L., **05**-0128, **10**-0343
Gumienny, C., **11**-0629
Gunanathan, C., **12**-0355, **12**-0369, **16**-0233
Gunaratne, H.Q.N., **10**-0576
Gunasekar, D., **10**-1195
Gund, P., **04**-0425
Gund, T.M., **04**-0425, **05**-0083, **18**-0114
Gundersen, L.-L., **04**-0392
Gündogan, B., **16**-0973, **16**-1002
Gung, B.W., **08**-0196, **16**-0494
Gunn, D.M., **10**-1762
Gunning, H.E., **18**-0226
Gunnoe, T.B., **15**-0925
Gunsher, J., **15**-2326
Gunter, H.V., **14**-0304
Günthard, H., **19**-0386
Günthard, H.H., **02**-0183
Günther, B., **18**-0042
Günther, H., **02**-0102, **02**-0263, **02**-0277, **02**-0319, **02**-0321, **04**-0151, **05**-0148, **15**-2322, **18**-0468, **18**-0469, **18**-0470, **18**-0637, **18**-0642, **18**-0643, **18**-0645
Günther, W., **05**-0183
Günzl, W., **15**-2050
Guo, B., **02**-0402, **14**-0412, **16**-0645
Guo, C., **17**-0173
Guo, G., **15**-0657
Guo, H., **15**-0579, **16**-0957, **19**-1584
Guo, J., **16**-1061
Guo, J.X., **12**-0087
Guo, L., **11**-0257, **15**-1896
Guo, M., **10**-1640, **13**-0558, **19**-1028
Guo, M.-P., **19**-0802
Guo, Q., **15**-2380
Guo, Q.-X., **01**-0109, **13**-0138, **13**-0228, **01**-0111, **01**-0111
Guo, R., **15**-0413
Guo, S., **16**-0067, **16**-0152
Guo, W.-r., **15**-0303
Guo, X., **16**-1028
Guo, X.-X., **15**-0604
Guo, Y., **17**-0284
Guo, Z., **15**-0537, **16**-1828, **18**-0184, **19**-0645, **19**-0645
Guo, Z.-R., **13**-0171
Gupt, I., **15**-0093
Gupta, A., **15**-0564, **19**-0595
Gupta, A.K., **15**-0675
Gupta, B.D., **10**-0603
Gupta, B.G.B., **10**-1134, **10**-1176, **16**-0116, **19**-0691
Gupta, D., **19**-0348
Gupta, K.B., **15**-0254
Gupta, M., **10**-0593, **11**-0475, **11**-0554
Gupta, M.D., **19**-0974
Gupta, M.K., **15**-1606
Gupta, O.D., **12**-0136
Gupta, R., **11**-0429, **11**-0475, **12**-0121, **19**-0268, **19**-0625
Gupta, S., **19**-0203
Gupta, S.C., **19**-0203, **19**-0485
Gupta, S.K., **12**-0453, **15**-0406, **15**-0409, **15**-0574, **15**-0689, **18**-0423
Gupta, V., **12**-0121, **15**-0192, **15**-1261
Gupta, V.K., **13**-0017
Gupta, V.P., **04**-0296
Gupton, J.T., **13**-0157, **13**-0617, **19**-0389
Gur'yanova, E.N., **03**-0001
Gur'yanova, T.P., **12**-0506
Guram, A.S., **11**-0182, **13**-0177, **19**-0218
Gurien, H., **17**-0396
Gurjar, M.K., **18**-0309, **19**-1018
Gurka, D.F., **11**-0045
Gurr, P.A., **11**-0191
Gurskii, M.E., **10**-1762, **18**-0548
Gürtler, S., **15**-1096
Gurudutt, K.N., **10**-0851, **17**-0197
Gurumurthy, R., **10**-0101
Gurunath, S., **19**-0330
Gurwara, S.K., **15**-0195
Guse, I., **10**-0706
Guseinova, S.N., **11**-0407
Gusel'nikov, L.E., **01**-0009
Gushchin, A.V., **13**-0224
Gust, D., **01**-0087
Gustafson, D.H., **10**-0269, **18**-0098
Gustafson, G., **10**-0481, **15**-0046
Gustin, D.J., **04**-0124
Gut, I., **02**-0412
Gut, I.G., **02**-0381
Gutekunst, B., **01**-0011
Gutekunst, G., **01**-0011
Guth, O., **18**-0828
Guthi Konda, K., **15**-1903
Guthrie, J.P., **02**-0383, **08**-0054, **08**-0057, **08**-0140, **12**-0672, **12**-0676, **16**-0015, **16**-0018, **16**-0987, **16**-0993, **16**-1061, **16**-1512, **16**-1595, **16**-1596
Guthrie, R.D., **05**-0199, **05**-0231, 09-II-0004, **10**-0652, **12**-0104, **16**-1548, **18**-0004, **18**-0017
Gutierrez, E., **10**-0699
Gutiérrez, A., **04**-0504
Gutiérrez, I., **15**-2289
Gutiérrez, L.G., **15**-2150
Gutiérrez-Perez, R., **19**-0261
Gutman, A.L., **02**-0274, **16**-1793
Gutman, D., **05**-0271
Gutman, I., **02**-0119, **02**-0120
Gutmann, H., **15**-0435
Gutmann, R., **11**-0547
Gutnov, A.V., **16**-1444
Gutowski, F.D., **14**-0375
Gutowsky, H.S., **03**-0072, **05**-0233
Gutsche, C.D., **03**-0101, **03**-0123, **03**-0127, **03**-0131, **16**-1389, **17**-0510, **18**-0159, **18**-0174, **18**-0194, **18**-0217, **18**-0230, **18**-0237, **18**-0569
Guttenplan, J.B., **07**-0033

Guttieri, M.J., **15**-0436, **19**-1535
Gutzwiller, J., **04**-0203, **15**-0574
Guy, A., **10**-1019, **11**-0261, **12**-0340
Guy, R.G., **10**-0849
Guy, R.K., **13**-0143
Guyon, R., **10**-0060
Guyton, C.A., **15**-2222, **18**-0590
Guzei, I.A., **05**-0177
Guziec Jr., F.S., **10**-1182, **17**-0516, **17**-0526, **19**-0080, **19**-1520, **19**-1539
Guzik, H., **14**-0400, **19**-1579
Guzzi, U., **12**-0261, **13**-0471
Gwynn, D., **18**-0708
Gybin, A.S., **15**-2024
Gyoung, Y.S., **19**-0877
Gypser, A., **15**-1696

Ha, C., **14**-0078, **15**-1221
Ha, D., **16**-2098
Ha, D.-C., **16**-0687, **16**-1988
Ha, D.S., **19**-0732
Ha, H., **10**-0245
Ha, H.-J., **15**-1596, **15**-1695
Ha, J.D., **10**-1166
Ha, T., **02**-0373
Ha, Y.-H., **16**-0725
Haaf, W., **15**-1376
Haag, R., **13**-0486
Haag, W., **17**-0193
Haag, W.O., **17**-0140
Haak, E., **15**-0348, **15**-0355
Haak, J.R., **10**-0445
Haake, M., **16**-0101
Haaland, A., **02**-0167
Haas, A., **14**-0129
Haas, C.K., **15**-2269
Haas, J., **15**-1591
Haas, Y., **19**-0360, **19**-0363, **19**-0381
Haase, K., **16**-1889
Habashita, H., **10**-0234
Habata, Y., **07**-0058
Habaue, S., **16**-0657
Haberfield, P., **07**-0059, **07**-0060, **10**-0099, **10**-0418, **10**-0488, **10**-0489, **11**-0275, **16**-0015
Haberl, U., **15**-2093
Haberland, H., **11**-0350
Haberman, J.X., **16**-0587
Haberman, L.M., **10**-0969
Habib, M.J., **15**-1417
Habib, M.M., **15**-0417
Habibi, D., **10**-0642
Habibi, M.F., **04**-0242
Habibi, M.H., **14**-0422, **15**-1829
Habibzadeh, S., **16**-0145, **19**-0150
Habich, A., **18**-0705
Häbich, D., **10**-0688
Habu, H., **10**-0716
Haché, B., **15**-0301
Hachiya, I., **11**-0425, **11**-0548, **15**-2010, **16**-1007, **16**-1085
Hacker, N.P., **15**-2312
Hackett, P., **18**-0850
Hackfeld, L., **19**-1137, **19**-1138
Hackler, R.E., **18**-0396, **18**-0727
Hackler, U.E., **18**-0631
Hackman, B.M., **16**-0762
Hadad, C.M., **01**-0108, **02**-0024, **15**-2318, **18**-0220
Haddach, A.A., **19**-1626
Haddach, M., **13**-0527
Haddad, N., **15**-2219, **15**-2241, **15**-2249, **15**-2298
Haddon, H.A., **18**-0401
Haddon, R.C., **02**-0100, **02**-0113, **02**-0269, **02**-0272, **02**-0348, **02**-0366, **05**-0024, **05**-0332, **10**-0179
Haddon, V.R., **02**-0100, **02**-0272
Haddon, V.R., **10**-0171
Hadida, S., **12**-0263, **12**-0264
Hadj Ali Salem, M., **12**-0695
Hadjiarapoglou, L., **15**-1768
Hadjieva, B., **04**-0307
Hadjigeorgiou, P., **11**-0204
Hadju, E., **02**-0364, **15**-0139
Hadži, D., **03**-0008
Haelg, P., **15**-1489
Haese, W., **15**-1346, **15**-1368
Häfelinger, G., **02**-0092
Hafez, A.M., **12**-0124, **12**-0167, **15**-2180, **16**-2103, **16**-2105, **17**-0318
Haffner, C.D., **18**-0620
Häflinger, O., **08**-0018, **08**-0040
Hafner, A., **16**-0684
Hafner, H., **11**-0063
Hafner, K., **02**-0176, **02**-0178, **02**-0179, **02**-0180, **02**-0181, **02**-0320, **15**-1911
Haga, M.-a., **19**-0823
Haga, T., **16**-1016
Hagaman, E., **15**-0867
Hagan, S., **02**-0360
Hage, A., **19**-1022
Hagège, A., **03**-0136
Hagel, R., **04**-0175
Hageman, H.A., **10**-1190
Hageman, H.J., **04**-0333, **11**-0594
Hagemann, H., **19**-0028
Hagen, E.L., **05**-0020, **18**-0008, **18**-0022
Hager, L.P., **15**-1758
Hagihara, N., **13**-0536, **15**-2405
Hagihara, T., **15**-2304
Hagitani, A., **16**-1625
Hagiwara, E., **16**-0408
Hagiwara, H., **10**-0636, **10**-0676, **13**-0415, **13**-0481, **15**-0993, **16**-1017, **16**-1685, **18**-0359
Hagiwara, I., **10**-1634
Hagiwara, K., **16**-0545
Hagiwara, N., **13**-0439
Hagler, A.T., **04**-0302
Hagopian, R.A., **12**-0508
Hague, D.N., **06**-0052
Hahn, C.S., **18**-0886, **18**-0888, **19**-0137
Hahn, F.E., **12**-0614
Hahn, G., **19**-0900, **19**-1302
Hahn, J.-T., **19**-1213
Hahn, P., **19**-0055
Hahn, R.C., **11**-0107
Hahn, S., **03**-0030
Hahn, W., **11**-0350, **11**-0351
Hahn, Y.P., **18**-0034
Hahnfeld, J.L., **05**-0346
Hähnle, R., **10**-1075
Hai, A.K.M.A., **16**-2118
Haider, S.Z., **12**-0465, **12**-0467
Haidour, A., **17**-0155
Haiduc, I., **03**-0083, **12**-0001
Haidukewych, D., **17**-0356
Haight, A.R., **10**-0606
Haijun Jiao, H., **02**-0354
Hailes, H.C., **15**-2025
Haines, A.H., **11**-0533, **14**-0267, **15**-1655, **15**-1726, **16**-0105, **19**-0011, **19**-0012, **19**-0258, **19**-0311, **19**-0633, **19**-0638, **19**-0656, **19**-0672, **19**-0693, **19**-0694, **19**-0738
Haines, A.J., **19**-0045
Haines, A.M., **19**-0069
Haines, R.J., **18**-0756
Hair, C.M., **13**-0489, **13**-0495
Haire, D.L., **05**-0211
Hajdu, C., **12**-0322
Hájek, M., **15**-1355
Hajipour, A.R., **11**-0201, **11**-0292, **11**-0302, **16**-0057, **16**-0060, **16**-0063, **16**-0081, **16**-0083, **16**-0096, **16**-0313, **16**-1752, **19**-0072, **19**-0083, **19**-0086, **19**-0144, **19**-0152, **19**-0335, **19**-0803, **19**-0916
Hájiček, J., **16**-1858
Hajos, A., **19**-0913
Hajos, Z.G., **15**-1048, **16**-0972, **16**-1072
Hajós, A., **19**-0010, **19**-0874, **19**-0877, **19**-1291, **16**-0597, **17**-0374

Hajra, S., **15**-1217, **19**-0205
Hakamata, W., **16**-0151
Håkansson, M., **15**-1094
Håkansson, R., **04**-0268
Hakata, T., **10**-0900
Hakoda, K., **15**-0993
Hakushi, T., **15**-0158, **15**-2161
Haky, J.E., **15**-0022, **15**-0063
Halberstadt, M.L., **05**-0377, **12**-0379
Halbes, U., **12**-0293
Halcomb, R.L., **19**-0756
Halcour, K., **19**-1801
Halder, R., **15**-1310
Halek, G.W., **15**-2338
Hales J.L., **11**-0500
Hales, N.J., **15**-1440
Hales, R.H., **13**-0133
Halevi, E.A., **06**-0069, **06**-0075, **06**-0077, **06**-0078, **15**-2105, **18**-0630
Haley, M.M., **02**-0081, **02**-0289, **02**-0290, **02**-0302, **04**-0491, **05**-0064
Halgren, T.A., **04**-0401, **05**-0307
Hall Jr., H.K., **08**-0219, **15**-2100, **15**-2229
Hall, C., **15**-0352
Hall, C.D., **16**-1993, **17**-0056
Hall, D.G., **16**-0699, **16**-0705
Hall, D.M., **04**-0051
Hall, G.E., **04**-0256
Hall, G.G., **02**-0077, **02**-0010
Hall, J.A., **15**-1946, **18**-0895
Hall, J.B., **10**-0143
Hall, K.J., **16**-0424
Hall, L.H., **15**-2044
Hall, M.K., **13**-0023
Hall, N.D., **16**-1563
Hall, R.E., **06**-0080, **10**-0057, **10**-0079, **10**-0279
Hall, R.J., **18**-0709
Hall, S.S., **16**-0542, **16**-0952, **19**-1454
Hall, T.N., **13**-0008
Hall, W.L., **17**-0116, **17**-0127
Halland, N., **12**-0124, **15**-0996, **15**-1001, **16**-0941
Hallberg, A., **07**-0116, **07**-0117, **10**-0754, **10**-1275, **12**-0263, **12**-0264, **12**-0286, **12**-0305, **13**-0174, **13**-0361, **13**-0373, **13**-0374, **13**-0385, **13**-0392, **13**-0413, **13**-0415, **13**-0602
Hallé, J.-C., **13**-0005, **15**-2102
Haller, G.L., **06**-0037
Haller, I., **04**-0429, **15**-1320, **18**-0493
Haller, K.J., **01**-0011
Halley, F., **14**-0332
Hallissey, J., **19**-1011
Hallman, P.S., **15**-0416
Halloran, D.J., **17**-0240
Hallouis, S., **16**-1933
Halpern, B., **04**-0169, **04**-0209
Halpern, J., **04**-0146, **12**-0013, **15**-0515, **15**-0597, **15**-0598, **15**-2201, **18**-0837, **18**-0839
Halpern, M., **10**-0457, **17**-0307
Halpern, Y., **05**-0017, **10**-0596
Halsall, T.G., **19**-0074
Halstead, B.S.J., **07**-0108
Halstenberg, M., **10**-1099
Halterman, R.I., **10**-1759
Halterman, R.L., **15**-0430, **15**-1827, **16**-0493, **16**-0706
Haltiwanger, R.C., **04**-0090
Halton, B., **02**-0079, **02**-0082, **04**-0464, **04**-0466, **07**-0001
Halupka, M., **05**-0207
Halvorsen, A., **10**-0302
Ham, G.E., **10**-0494, **10**-0673, **10**-0872, **10**-0955, **15**-1883, **17**-0360, **18**-0580
Ham, J., **13**-0150
Hamachi, K., **19**-0520
Hamada, F., **03**-0059
Hamada, H., **15**-0626, **19**-0541, **19**-1022
Hamada, N., **15**-2063
Hamada, T., **12**-0476, **13**-0587, **15**-1829, **15**-1836, **16**-0416, **16**-0753, **16**-0918, **16**-0934, **16**-1117, **16**-1121, **19**-0520
Hamada, Y., **10**-1465, **10**-1798, **19**-0475
Hamaguchi, H., **03**-0109
Hamaguchi, S., **16**-1314
Hamai, K., **09**-0122
Hamamoto, H., **18**-0139
Hamamoto, I., **19**-1530
Hamamoto, K., **13**-0770
Hamamura, H., **18**-0836
Hamanaka, K., **11**-0101
Hamanaka, S., **11**-0013
Hamann, B.C., **13**-0175
Hamann, L.G., **13**-0187, **19**-0941
Hamaoka, S., **16**-1764
Hamaoka, T., **12**-0492, **12**-0494
Hamasaki, R., **16**-1095, **16**-2018
Hamashima, Y., **16**-1426, **16**-1438, **16**-1439
Hamatani, T., **16**-0645, **17**-0310
Hamblin, M.C., **11**-0379
Hambling, J.K., **14**-0113
Hambly, A.N., **08**-0078, **08**-0239
Hamdani, M., **13**-0077
Hamdouchi, C., **05**-0197, **12**-0426
Hamel, N., **10**-1859, **10**-1860, **15**-1383
Hamelin, J., **07**-0111, **15**-1964, **16**-0144, **16**-0294, **16**-0411, **16**-1832, **18**-0324
Hamelin, R., **05**-0158
Hamelink, E., **07**-0118
Hamer, J., **15**-1883, **15**-2122, **15**-2151, **16**-1395, **16**-2076, **16**-2083, **16**-2094
Hamereton, I., **15**-0981
Hamersma, J.W., **10**-0147
Hamill, H., **04**-0050
Hamilton Jr., E.J., **18**-0055
Hamilton, A.D., **03**-0150
Hamilton, G.A., **19**-0255
Hamilton, G.S., **16**-1538
Hamilton, J.A., **04**-0178, **15**-0417
Hamilton, R., **18**-0618
Hamilton, T.P., **15**-0011
Hamilton, W.C., **03**-0001
Hamlet, Z., **09**-0090
Hammadi, M., **19**-0639
Hammarström, L., **04**-0332
Hammer, J.D., **04**-0321
Hammerich, O., **05**-0318
Hammerschmidt, E., **10**-0808
Hammerton, D.A., **07**-0071
Hammerum, S., **16**-0047
Hammett, L.P., **05**-0062, **05**-0075, **06**-0043, **06**-0055, **08**-0111, **08**-0115, **08**-0124, **08**-0135, **11**-0007, **16**-1558
Hammitt, F.G., **07**-0066
Hammond, G.S., **04**-0230, **05**-0289, **05**-0333, **06**-0021, **07**-0011, **07**-0023, **07**-0024, **07**-0037, **07**-0044, **07**-0049, **11**-0062, **11**-0561, **15**-0005, **15**-0031, **15**-0032, **15**-2239, **15**-2242, **15**-2251, **17**-0140, **18**-0628, **18**-0743, **19**-1689
Hammond, M.E.W., **11**-0276
Hammond, R.C., **14**-0351
Hammond, W.B., **15**-2283, **16**-0043
Hammons, J.H., **05**-0099, **08**-0013, **08**-0058, **15**-0135, **18**-0100
Hamoir, C., **10**-0925
Hamon, L., **15**-1074
Hamor, T.A., **02**-0163
Hampel, F., **05**-0175, **08**-0110
Hampel, M., **15**-0024
Hampel, N., **10**-0009, **10**-1673, **11**-0354
Hampton, D.C., **13**-0783

Hamrick Jr., P.J., **10**-1581, **19**-1764
Hamsen, A., **16**-0565
Hamura, T., **13**-0050
Han, B., **01**-0011, **10**-0582, **15**-0422, **16**-0814, **16**-1155
Han, B.-H., **07**-0080, **15**-0175
Han, B.H., **07**-0086, **07**-0090, **10**-1226, **11**-0648, **16**-2003
Han, G.R., **19**-0576
Han, J., **13**-0413, **15**-0463
Han, J.-S., **10**-1194
Han, J.H., **19**-1549
Han, J.K., **19**-1449
Han, J.L., **19**-1213
Han, J.W., **07**-0118, **12**-0078, **15**-0835, **15**-1154, **15**-1719
Han, K.-J., **16**-1787
Han, L.-B., **15**-0376, **15**-0380, **15**-0381
Han, M., **15**-0820
Han, R., **16**-0872, **19**-1189
Han, S.-Y., **17**-0166
Han, W., **12**-0138, **19**-0823
Han, X., **10**-1472, **15**-0226, **15**-0233, **15**-0765, **15**-0890
Han, X.-W., **15**-0527
Han, Y., **10**-1858, **15**-1098, **15**-1157, **16**-0649
Han, Z., **16**-0992, **19**-0127
Hanack, H., **10**-0248, **10**-0249, **04**-0387
Hanack, M., **04**-0261, **04**-0350, **05**-0067, **05**-0068, **10**-0136, **10**-0150, **10**-0192, **10**-0248, **10**-0250, **10**-0252, **10**-0254, **10**-0256, **10**-0259, **10**-0381, **10**-1075, **11**-0471, **13**-0027, **15**-0035, **15**-0106, **16**-2057, **17**-0078
Hanafi, N., **15**-1001
Hanafusa, T., **06**-0067, **10**-0971, **10**-1149, **10**-1789, **15**-1545, **16**-0530, **16**-0535, **16**-0538, **16**-1294, **16**-2045, **19**-0974
Hanamoto, T., **13**-0448, **14**-0295
Hanamura, M., **10**-0202
Hanano, T., **12**-0179
Hanaoka, M., **15**-0239, **15**-1442, **16**-0069
Hanaoka, T.-a., **13**-0599
Hancock, J.E.H., appendixA-0001
Hancock, J.W., **10**-0239
Hancock, M.T., **12**-0757
Hancock, R.A., **11**-0216, **15**-2090
Hand, E.S., **16**-0020
Handa, S., **19**-1679
Handa, Y., **19**-1658
Handel, H., **16**-0539, **19**-1062
Handy, C.J., **13**-0632, **13**-0637
Handy, N.C., **04**-0168, **04**-0287
Handy, S.T., **09**-0114, **13**-0415, **13**-0416, **15**-2032, **16**-0950
Hane, J.T., **18**-0640
Haneda, A., **19**-1332
Hanesian, D., **07**-0080
Hanessian, S., **04**-0135, **10**-0614, **10**-0798, **10**-1089, **10**-1345, **16**-1316, **16**-1326, **16**-1655, **17**-0343, **19**-1680
Haney, W.A., **11**-0101
Hanfusa, T., **19**-0106
Hang, C., **15**-0967, **15**-2088
Hang, J.-F., **19**-1031
Haning, H., **10**-1613, **16**-0647
Hanissian, S.H., **09**-0078
Hanley, J.A., **04**-0035
Hanna, I., **10**-1540
Hanna, J., **19**-1713
Hanna, R., **17**-0309
Hanna, S.B., **19**-0836
Hanna, S.Y., **18**-0400
Hannan, J.J., **15**-0720
Hannan, W., **11**-0116
Hannedouche, J., **19**-1042
Hannick, S.M., **16**-0836
Hannon, F.J., **15**-1092, **15**-1173
Hanold, N., **04**-0471
Hanquet, G., **15**-1780
Hansch, C., **09**-0020, **09**-0063, **09**-0065, **09**-0068
Hansell, D.P., **10**-0367
Hansell, G., **10**-0110
Hansen, B., **16**-1262, **16**-1848
Hansen, D.E., **06**-0048
Hansen, E.C., **18**-0781
Hansen, H., **15**-2112, **18**-0526, **18**-0621, **18**-0654, **18**-0658, **18**-0686, **18**-0691, **18**-0704, **18**-0855
Hansen, H.-J., **05**-0319, **18**-0577, **18**-0578, **19**-0556, **18**-0073
Hansen, J., **13**-0682
Hansen, J.F., **14**-0335
Hansen, K.B., **10**-0677, **16**-0945
Hansen, K.C., **19**-0389
Hansen, M.C., **19**-1163, **19**-1472
Hansen, M.M., **16**-1025
Hansen, R.T., **15**-1150
Hansen, T., **11**-0387, **12**-0359, **15**-2302, **15**-2302
Hansen, T.M., **19**-0688
Hansford, K.A., **16**-1965
Hanson, A.W., **02**-0279
Hanson, B.E., **15**-1478
Hanson, G.C., **10**-0212
Hanson, J., **10**-0322
Hanson, J.R., **19**-1251
Hanson, K.R., **04**-0254
Hanson, M.P., **10**-0490
Hanson, M.V., **16**-1908
Hanson, P., **09**-0059, **14**-0351, **14**-0352, **19**-0823
Hanson, P.R., **16**-2072, **18**-0813
Hanson, R.M., **15**-1822
Hansske, F., **19**-1402
Hansson, C., **16**-1958
Hansson, L., **04**-0175
Hansson, S., **14**-0252
Hanus, V., **13**-0237
Hanyu, N., **16**-0687
Hanzawa, Y., **08**-0200, **10**-1819, **15**-1164, **15**-1341, **16**-0651
Hanzlik, R.P., **10**-1502, **15**-1732
Hao, C., **16**-1644
Hao, J., **16**-0571, **16**-0730
Hao, Q.-S., **10**-0879
Hao, X., **16**-0908
Hapala, J., **10**-0208, **17**-0030
Hapiot, P., **13**-0052
Happer, D.A.R., **02**-0372, **09**-0030, **15**-0564
Haque, M.S., **15**-1945, **16**-1991, **16**-1992, **18**-0229, **19**-0501
Haque, Sk.J., **16**-0149
Hara, H., **10**-1137
Hara, M., **14**-0365
Hara, N., **12**-0753
Hara, O., **10**-1465, **19**-0475
Hara, R., **10**-1779, **15**-0957, **15**-2380
Hara, S., **04**-0175, **10**-1044, **10**-1045, **12**-0538, **15**-1187, **15**-1191, **15**-1520, **15**-1548, **16**-0696, **17**-0410, **18**-0441, **18**-0447
Hara, T., **19**-0120
Hara, Y., **19**-1476
Harada, A., **03**-0186
Harada, K., **04**-0146, **15**-0597, **16**-0851, **16**-0931, **16**-1451, **19**-1136
Harada, M., **12**-0490, **15**-1586
Harada, R., **16**-1851
Harada, S., **02**-0070, **15**-0994, **16**-1272, **19**-1677
Harada, T., **02**-0070, **03**-0126, **11**-0507, **12**-0386, **12**-0433, **15**-0885, **15**-1014, **16**-0687, **16**-1116, **18**-0123, **19**-0848, **19**-1022, **19**-1023
Harada, Y., **04**-0390, **15**-0608, **17**-0161
Haraguchi, H., **18**-0904
Harano, K., **15**-0968, **18**-0613

Harano, Y., **15**-2037
Harayama, T., **11**-0328
Harbison, K.G., **13**-0028, **13**-0030, **13**-0719
Harbusch-Görnert, E., **10**-0446
Harch, P.G., **05**-0092
Harcken, C., **16**-1273
Harcourt, R.D., **15**-1945
Hardacre, J.M., **13**-0594
Hardcastle, I.R., **11**-0492
Harder, S., **10**-1538
Hardie, B.A., **11**-0025, **11**-0027
Hardies, D.E., **10**-0426
Hardin, J., **16**-0768
Hardin, J.D., **15**-1898
Harding, C.E., **10**-0256
Harding, D.R.K., **18**-0699, **19**-0842
Harding, K.E., **19**-0076
Harding, P.J.C., **19**-0934
Hardouin, C., **15**-0581, **19**-0905
Hardy Jr., R.A., **13**-0773
Hardy, W.B., **12**-0741
Hare, G.J., **06**-0064
Hare, P.E., **04**-0175
Hargett, J.L., **10**-0889
Hargis, J.H., **14**-0039, **14**-0046
Hargittai, I., **05**-0227
Hargreaves, M.K., **16**-1770
Hargreaves, R.T., **17**-0060
Hari, A., **19**-1198
Harich, K., **02**-0364
Harikishan, K., **10**-0682
Harirchian, B., **15**-1998
Hariri, R., **10**-0083, **10**-0279
Haritha, Y., **15**-1906, **19**-1316
Harjani, J.R., **11**-0555, **16**-1170
Harkema, S., **03**-0113
Harland, P.A., **10**-0992
Härle, H., **15**-2077
Harlow, K.J., **09**-0111
Harlow, R.L., **03**-0045, **05**-0382, **15**-0816, **19**-0848
Harman, W.D., **15**-0529, **15**-2074
Harmata, M., **15**-2434, **15**-0855
Harmata, M.A., **18**-0681
Harmon, C., **15**-2170
Harmon, C.A., **02**-0254
Harmon, K.H., **02**-0156
Harmon, R.E., **15**-0406, **15**-0409
Harmon, R.E., **15**-0574
Harmony, J.A.K., **05**-0295
Harmony, M.D., **01**-0052
Harms, K., **05**-0136, **05**-0143, **12**-0030, **15**-1368, **16**-0724, **16**-1437, **18**-0735
Harms, W.M., **19**-0557
Harmsen, D., **19**-0542
Harned, H.S., **08**-0052
Harnett, J.J., **16**-1381
Harney, D.W., **10**-1506
Harnying, W., **10**-1592
Harper, D.J., **19**-0202
Harper, J.J., **10**-0164, **18**-0018
Harper, R.W., **19**-0063
Harpold, M.A., **19**-0798
Harpp, D.N., **10**-0745, **10**-0776, **10**-0805, **12**-0174, **12**-0477, **19**-0792, **19**-0871, **19**-1425, **19**-1598
Harrack, Y., **10**-0923
Harre, M., **19**-0067
Harrelson Jr., J.A., **05**-0246, **08**-0192, **10**-1602
Harring, L.S., **15**-2347
Harrington, C.K., **10**-0294
Harris Jr., G.D., **10**-0899, **15**-0387
Harris Jr., J.F., **15**-0297, **16**-0207, **18**-0612
Harris, B.D., **16**-0362
Harris, B.R., **10**-0049
Harris, C.E., **16**-0057, **19**-0026, **19**-0416
Harris, C.J., **04**-0249
Harris, C.L., **10**-0981
Harris, C.M., **10**-0482
Harris, D.O., **02**-0035
Harris, E.E., **05**-0135
Harris, H.C., **16**-1512
Harris, H.P., **10**-0462
Harris, J.C., **10**-0079
Harris, J.M., **06**-0080, **10**-0038, **10**-0053, **10**-0057, **10**-0060, **10**-0162, **10**-0170, **10**-0279, **10**-0280, **10**-0308, **10**-0328, **10**-0429, **10**-0432, **10**-0448, **18**-0061
Harris, K.D.M., **03**-0069
Harris, M.C., **13**-0176, **13**-0182, **13**-0184
Harris, M.M., **10**-0719
Harris, N.J., **02**-0419
Harris, P.A., **02**-0415, **16**-0407
Harris, R.F., **16**-1185
Harris, S.H., **14**-0455, **14**-0458
Harris, T.M., **10**-0482, **16**-2036
Harris, W., **15**-0904
Harrison, A.T., **05**-0188, **08**-0205
Harrison, C.L., **15**-1117
Harrison, C.R., **17**-0459, **18**-0457
Harrison, D.J., **19**-1533, **19**-1609
Harrison, I.T., **03**-0194, **10**-1136, **15**-2330, **19**-0597
Harrison, J., **19**-0953
Harrison, J.M., **15**-2213, **15**-2215
Harrison, J.R., **10**-1211, **15**-0554, **19**-1242
Harrison, K.N., **15**-0699
Harrison, L.J., **05**-0252
Harrison, P.H.M., **04**-0454
Harrison, R.G., **10**-0520, **16**-0315, **16**-1293, **17**-0003, **17**-0037, **17**-0039, **17**-0057, **17**-0103, **19**-0252
Harrison, S., **03**-0194, **19**-0597
Harrison, S.T., **17**-0297
Harrison, T.J., **15**-0822
Harrity, J.P.A., **15**-1928, **15**-1973, **15**-2411, **18**-0770, **19**-1395
Harrod, J.F., **15**-1477, **19**-1703
Harrowfield, J.Mc B., **03**-0124
Harrowven, D.C., **11**-0548
Harrowven, D.C., **13**-0261
Hart, A.J., **05**-0130
Hart, C.R., **13**-0018
Hart, D.J., **14**-0020, **15**-0105, **15**-0768, **15**-1247, **16**-2098
Hart, E.J., **07**-0074
Hart, G., **10**-1725
Hart, H., **02**-0394, **07**-0052, **10**-0212, **11**-0367, **11**-0534, **11**-0592, **13**-0310, **15**-1787, **15**-2113, **19**-0722
Hart, L.S., **11**-0544, **11**-0552
Hart, P., **02**-0216
Hart, P.A., **19**-0075
Hart, P.W., **10**-1317
Hartan, H., **02**-0164
Hartemink, M.A., **16**-0198
Hartenstein, J.H., **18**-0640
Hartford, W.H., **19**-0620
Hartgerink, R.L., **13**-0622
Hartke, K., **02**-0178
Hartley, F.R., **03**-0083, **03**-0086, **04**-0146, **04**-0149, **05**-0145, **05**-0296, **10**-1250, **10**-1321, **10**-1445, **10**-1545, **10**-1841, **12**-0001, **12**-0002, **12**-0074, **12**-0311, **12**-0388, **12**-0424, **12**-0431, **12**-0432, **12**-0442, **12**-0474, **12**-0482, **12**-0504, **12**-0551, **12**-0564, **12**-0574, **12**-0582, **12**-0594, **13**-0263, **13**-0660, **15**-0401, **15**-0462, **15**-0597, **15**-0636, **15**-0760, **15**-0857, **15**-0947, **15**-0972, **15**-1375, **15**-1477, **15**-1478, **15**-1714, **15**-2362, **16**-0003, **16**-0460, **16**-1233, **18**-0420, **18**-0756, **19**-0956
Hartley, J.P., **11**-0200, **11**-0217, **11**-0423

Hartley, R.C., **18**-0602
Hartley, W.M., **10**-1630
Hartman, A., **15**-1534
Hartman, A.F., **10**-0724
Hartman, B., **15**-2302
Hartman, B.C., **10**-1542
Hartman, G.D., **17**-0345
Hartman, J.W., **15**-0242
Hartman, M.E., **18**-0239
Hartman, R.D., **17**-0345
Hartmann, J., **12**-0394, **12**-0395
Hartmann, M., **15**-2121
Hartmann-Schreier, J., **19**-0547
Hartmanns, J., **15**-0715
Hartner Jr., F.W., **16**-1367
Hartog, F.A., **12**-0583, **16**-0478
Hartshorn, M.P., **09**-0030, **11**-0057, **11**-0107, **15**-0562, **15**-2232
Hartshorn, S.R., **10**-0001, **10**-0070, **10**-0430, **11**-0042
Hartter, D.R., **08**-0118
Hartung, C.G., **15**-0314, **15**-0320, **15**-0331, **15**-0343, **15**-0348, **15**-0351
Hartung, J., **14**-0056, **15**-1283, **15**-1691, **15**-1693, **15**-1704
Hartung, W.H., **19**-1513
Hartwig, J., **16**-0885
Hartwig, J.F., **10**-1469, **12**-0333, **13**-0125, **13**-0173, **13**-0174, **13**-0175, **13**-0179, **13**-0318, **13**-0482, **13**-0583, **15**-0327, **15**-0329, **15**-0333, **15**-0389, **15**-0894
Hartwig, W., **19**-1409
Hartzell, G.E., **17**-0227
Hartzell, S.L., **16**-1235
Harusawa, S., **16**-1425
Harusawa, S., **16**-1459
Harutyanyan, S.R., **15**-1103
Harvery, J.N., **16**-1386
Harvey, D.F., **10**-0548
Harvey, G.R., **15**-0397, **15**-2190
Harvey, J.N., **17**-0289, **18**-0524
Harvey, K.A., **13**-0305
Harvey, M.C., **15**-1513
Harvey, R.G., **11**-0022, **15**-0533, **15**-0544, **19**-0012, **19**-0561
Harvey, S., **12**-0579
Harwood, H.J., **12**-0166
Has-Becker, S., **16**-1308
Hasan, S.K., **10**-0989, **19**-0408, **19**-1620
Hasan, T., **17**-0058
Hase, E., **16**-0921
Hase, T.A., **10**-0810, **10**-1666, **10**-1667, **10**-1693, **10**-1700
Hase, W.L., **10**-0002
Hasebe, M., **12**-0658, **14**-0435
Hasegawa, A., **15**-1561, **16**-0150
Hasegawa, E., **10**-0584, **14**-0100, **18**-0244
Hasegawa, H., **16**-1737
Hasegawa, J., **19**-1022
Hasegawa, K., **11**-0101, **15**-1679
Hasegawa, M., **10**-1829
Hasegawa, M., **14**-0143, **18**-0129, **18**-0158
Hasegawa, Y., **12**-0755, **16**-1454
Hasek, R.H., **15**-2185, **15**-2190
Haselbach, E., **05**-0320, **07**-0032
Hasenfratz, Ch., **08**-0084
Hasenfratz, H., **16**-2034
Hasha, D.L., **15**-0670, **15**-0671
Hashem, Md.A., **15**-1919
Hashemi, M.M., **02**-0358, **13**-0092, **16**-0074, **19**-0263
Hashemsadeh, M., **16**-0503, **16**-1352
Hashida, Y., **11**-0169
Hashidzume, H., **18**-0890
Hashiguchi, S., **15**-0607
Hashim, S.R., **19**-1031
Hashimoto, H., **10**-1703, **13**-0121, **13**-0362, **15**-2341, **16**-1282
Hashimoto, I., **15**-1343
Hashimoto, K., **19**-0637
Hashimoto, M., **12**-0656
Hashimoto, N., **16**-0402, **16**-0404
Hashimoto, S., **12**-0368, **16**-1039, **16**-1826, **16**-1830, **19**-0421
Hashimoto, Y., **02**-0390, **02**-0408, **13**-0424, **15**-1439, **16**-0650, **16**-0824, **16**-0828, **16**-0859, **18**-0129, **19**-1659
Hashish, Z.M., **19**-0023
Hashtroudi, H., **15**-0195
Hasiak, B., **18**-0382
Hasimoto, T., **12**-0535
Haskins, C.M., **15**-0389
Haslam, E., **16**-1630
Haslinger, U., **16**-0687
Hass, H.B., **12**-0204, **14**-0063, **16**-1150
Hassan, H.A., **16**-0512
Hassan, J., **13**-0301
Hassan, M., **12**-0060
Hassanali, A., **18**-0271
Hassdenteufel, J.R., **10**-0252
Hassel, O., **04**-0317, **04**-0332
Hassel, T., **19**-1281
Hasselmann, D., **15**-2096, **18**-0560
Hassenrück, K., **18**-0642, **18**-0647
Hassib, L., **16**-0867
Hassine, B.B., **15**-1862, **19**-1056
Hassner, A., **10**-0480, **10**-1022, **12**-0155, **12**-0199, **12**-0512, **15**-0020, **15**-0398, **15**-1624, **15**-1627, **15**-1629, **15**-1630, **15**-1631, **15**-1632, **15**-1633, **15**-2178, **15**-2210, **16**-1058, **16**-1665, **16**-2110, **17**-0455, **19**-0479
Hassouna, F., **13**-0627
Hasvold, L.A., **15**-0387, **15**-1363
Haswell, S.J., **07**-0106, **07**-0105
Haszeldine, R.N., **11**-0337, **18**-0169, **18**-0493
Hata, E., **15**-1838
Hata, G., **02**-0047
Hata, K., **18**-0517
Hata, N., **04**-0006
Hata, S., **14**-0204, **16**-0418
Hata, T., **14**-0080, **15**-0880, **16**-1716
Hatada, K., **04**-0087, **04**-0175, **04**-0177
Hatajima, T., **16**-0518
Hatakeda, K., **18**-0127, **18**-0316
Hatakeyama, S., **16**-0251, **16**-0636, **16**-0637
Hatamoto, Y., **15**-0763
Hatanaka, A., **10**-0060, **10**-0074
Hatanaka, K., **13**-0378, **16**-0855, **17**-0343
Hatanaka, N., **18**-0574
Hatanaka, T., **16**-0493
Hatanaka, Y., **10**-1194, **10**-1198, **10**-1207, **12**-0529, **13**-0619, **15**-0735
Hatano, B., **11**-0357, **19**-1461, **19**-1653, **19**-1695
Hatano, K., **05**-0348, **10**-1465
Hatano, M., **15**-0824, **16**-0571, **16**-0730
Hatayama, A., **15**-1829
Hatayama, Y., **19**-0060
Hatch, L.F., **10**-0291, **15**-2087
Hatch, M.J., **16**-1378, **18**-0258
Hatch, R.P., **16**-1729
Hatcher, B.G., **15**-2210
Hatem, J., **19**-1339, **19**-1341
Hatfield, G.L., **10**-1089
Hathaway, S.J., **15**-2158
Hatlevik, O., **11**-0233
Hatta, G., **15**-1757, **15**-1842
Hatta, T., **15**-1932

Hattori, A., **10**-1854
Hattori, H., **19**-1766, **19**-1773
Hattori, K., **05**-0287, **11**-0644, **15**-0411, **15**-1029, **18**-0340, **18**-0341
Hattori, R., **19**-1679
Hattori, T., **19**-1028
Hatz, E., **10**-0723
Hatzakis, N.S., **19**-0234
Hau, C.-S., **15**-0275
Haubenstock, H., **05**-0059, **19**-1014, **19**-1064
Haubrich, J.E., **18**-0463
Hauck, B.J., **15**-0586
Hauck, S.I., **15**-0386
Hauer, B., **18**-0155
Haufe, G., **04**-0070, **15**-0115, **15**-1545
Haumann, T., **02**-0055, **18**-0087
Haupt, F.C., **10**-0118
Hauptman, E., **13**-0231
Hauptmann, H., **14**-0398, **19**-1576
Hauri, R.J., **10**-0335
Hause, N.L., **17**-0011, **17**-0016
Hauser, C.R., **10**-0482, **10**-1284, **10**-1581, **10**-1605, **12**-0398, **13**-0760, **13**-0761, **13**-0764, **13**-0765, **16**-0102, **16**-1057, **16**-2014, **16**-2036, **16**-2037, **17**-0043, **17**-0444, **18**-0120, **18**-0412, **19**-0836, **19**-1764
Hauser, F.M., **15**-1712
Hauske, J.R., **04**-0170, **16**-1322
Hausman, M., **13**-0773
Hausser, J.W., **10**-0318, **18**-0507, **18**-0508
Haut, S.A., **19**-1468
Hautala, R., **07**-0044
Hautala, R.T., **07**-0040
Hautefaye, P., **10**-0952
Havel, J.J., **12**-0596
Havel, M., **17**-0389
Havelka, F., **16**-1720
Havenith, R.W.A., **02**-0083
Havinga, E., **04**-0333, **04**-0354, **04**-0365, **13**-0057, **19**-1219
Havlas, Z., **10**-0344
Havlin, R., **16**-1898
Havránek, M., **15**-0918
Haw, J.F., **05**-0095
Hawari, J.A., **14**-0146
Hawkins, C.M., **18**-0621
Hawkins, E.G.E., **14**-0290
Hawkins, J.M., **02**-0356, **15**-1042, **15**-2064, **15**-2066
Hawkinson, D.C., **10**-0439
Hawks III, G.H., **16**-2008
Hawley, D.M., **04**-0041
Hawryluk, N.A., **15**-2294
Hawthorne, M.F., **13**-0094, **11**-0062, **16**-0106
Hay, A S., **14**-0306
Hay, B.P., **16**-0009
Hay, D.R., **13**-0644
Hay, J.M., **05**-0202, **05**-0226
Hay, J.V., **13**-0589, **17**-0388
Hay, P.J., **05**-0332
Hayakawa, K., **15**-0048
Hayakawa, R., **16**-0819, **16**-1114, **16**-1384, **19**-0990, **19**-1021, **19**-1143, **19**-1610, **19**-1667
Hayakawa, S., **16**-1422, **16**-2015
Hayakawa, Y., **15**-1979, **19**-1322
Hayama, N., **10**-1039, **13**-0279, **13**-0466
Hayami, J., **06**-0081, **10**-0313, **13**-0019, **17**-0069
Hayami, K., **10**-0790
Hayasaka, S., **19**-0825
Hayasaka, T., **16**-0686
Hayase, S., **18**-0543
Hayashi, C., **19**-1041
Hayashi, E., **15**-0993
Hayashi, H., **07**-0033, **19**-1021
Hayashi, J., **15**-1175
Hayashi, K., **16**-0782, **16**-0995
Hayashi, M., **04**-0193, **10**-0552, **10**-1706, **10**-1771, **10**-1797, **13**-0424, **15**-0374, **15**-0625, **15**-0627, **15**-1439 **19**-1434
Hayashi, N., **04**-0121, **04**-0123, **15**-2198, **16**-0661, **18**-0222, **19**-1308
Hayashi, R., **12**-0469, **16**-2028
Hayashi, S., **10**-1464, **15**-0849, **16**-0373
Hayashi, T., **10**-0691, **10**-1298, **10**-1302, **10**-1304, **10**-1323, **10**-1460, **10**-1533, **10**-1549, **10**-1698, **11**-0418, **11**-0506, **12**-0035, **12**-0078, **15**-0201, **15**-0209, **15**-0353, **15**-0598, **15**-0657, **15**-0700, **15**-0932, **15**-1024, **15**-1121, **15**-1125, **15**-1130, **15**-1140, **15**-1154, **15**-1190, **15**-1217, **15**-1719, **16**-0893, **16**-1049, **16**-1190, **16**-1491, **16**-2010, **18**-0692, **19**-1041, **19**-1161
Hayashi, Y., **10**-0221, **11**-0518, **12**-0340, **15**-2139, **16**-0878, **19**-0505, **19**-0507
Hayashida, M., **10**-1137
Hayasi, Y., **12**-0245
Hayat, S., **10**-0860, **10**-1081
Hayday, K., **14**-0097
Hayden, W., **16**-2015
Hayen, A., **15**-1194
Hayer, M.F., **15**-1898
Hayes, B.L., **07**-0106, **07**-0116
Hayes, C.J., **15**-0900, **19**-1335
Hayes, D., **16**-1107
Hayes, J.-F., **10**-0246
Hayes, J.C., **14**-0200
Hayes, J.M., **12**-0609, **18**-0303
Hayes, P.D., **16**-0071, **16**-0174
Hayes, R., **18**-0482
Hayes, R.A., **18**-0227
Hayes, R.L., **18**-0091
Hayes, S., **05**-0158
Hayes, W., **03**-0191
Hayes, W., **19**-0192
Haymore, B.L., **03**-0108
Haynes, L.W., **03**-0083, **16**-0287, **19**-0047
Haynes, P., **18**-0539
Häyri, L., **10**-0810
Hays, D.S., **15**-1274, **16**-1502, **19**-1261, **19**-1407, **19**-1681, **19**-1682
Hayshi, T., **16**-1089
Hayter, B.R., **15**-1773
Hayward, R.C., **12**-0161, **14**-0431, **15**-1626, **15**-1686
Haywood-Farmer, J., **10**-0145, **10**-0146, **10**-0148, **10**-0149, **10**-0150, **10**-0151, **10**-0420
Hazarkhami, H., **10**-0812, **10**-1113, **17**-0156
Hazato, A., **18**-0601
Hazell, R.G., **15**-1001, **15**-1097, **15**-2146, **16**-0912, **16**-0948, **16**-1160
Hazen, G.G., **12**-0216
Hazra, B.G., **15**-1535
Hazzard, G., **16**-0192
He, B., **16**-1427, **16**-1433, **16**-1438
He, C., **15**-1904
He, G., **13**-0362
He, H., **07**-0120, **13**-0138, **13**-0213, **13**-0345
He, H.-Y., **10**-1199
He, L., **19**-0082, **19**-0342
He, M., **15**-0820, **15**-0821, **19**-1028
He, M.-Y., **16**-0150
He, S.-L., **05**-0310, **14**-0067, **14**-0074
He, W., **07**-0118, **07**-0119, **15**-0850
He, X., **12**-0581, **14**-0083, **18**-0058
He, Y., **10**-0608, **19**-1206, **19**-1374
He, Y.-P., **19**-1627

He, Z., **15**-2029, **19**-1265
Head, A.J., **17**-0124, **17**-0144
Head, N.J., **05**-0082
Headley, A., **15**-0354, **16**-0768
Headley, A.D., **08**-0165, **08**-0223, **08**-0235, **15**-1614
Healy, E.F., **02**-0018, **06**-0079, **19**-0892
Heaney, H., **03**-0137, **12**-0582, **13**-0037, **13**-0160, **15**-1730, **16**-0407, **18**-0381
Heard, G.L., **18**-0383
Hearn, M.J., **18**-0347
Hearn, R.A., **10**-0920
Heasley, G.E., **15**-0004, **15**-0033
Heasley, V.L., **15**-0004, **15**-0016, **15**-0033
Heath, J.R., **02**-0355
Heath, M.J., **17**-0269
Heath, N.S., **17**-0225
Heath, R.R., **16**-1144
Heathcock, C.H., **04**-0153, **04**-0422, **10**-1118, **10**-1522, **15**-0399, **15**-0465, **15**-1010, **15**-1013, **15**-1031, **15**-1032, **15**-1060, **16**-1013, **16**-1014, **16**-1018, **16**-1025, **16**-1033, **16**-1034, **16**-1065, **18**-0695
Heatom, N.J., **03**-0161
Hebbe, V., **16**-0389
Hebel, A., **13**-0486
Hebel, D., **11**-0312, **11**-0537, **15**-1582
Héberger, K., **15**-0051
Hebert, E., **18**-0413, **18**-0416
Hebrard, P., **10**-0991
Hecht, R., **18**-0074
Hecht, S.S., **16**-1694, **19**-0634
Heck, H. d'A., **16**-0024
Heck, M.-P., **10**-1208, **17**-0470
Heck, R., **10**-0055, **10**-0066, **10**-0171
Heck, R.F., **02**-0047, **10**-1399, **10**-1447, **10**-1841, **10**-1846, **10**-1849, **10**-1852, **12**-0074, **12**-0304, **13**-0360, **13**-0361, **13**-0363, **13**-0381, **13**-0387, **13**-0388, **13**-0389, **13**-0394, **13**-0417, **13**-0418, **13**-0420, **13**-0423, **13**-0603, **14**-0259, **15**-0406, **15**-0792, **15**-1378, **15**-1477, **15**-1494, **15**-2292, **15**-2429, **17**-0232, **19**-0056, **19**-0718, **19**-0957, **19**-1200
Heckrodt, T., **19**-0067
Heckroth, H., **12**-0101
Hedaya, E., **11**-0560
Hedayatullah, M., **19**-0748
Hedberg, C., **15**-2119
Hedberg, K., **04**-0282, **02**-0240, **03**-0050, **04**-0283, **04**-0441
Hedberg, L., **02**-0240, **04**-0441
Hedegaard, B., **18**-0696
Hederich, V., **10**-0739
Hedgecock Jr., H.C., **12**-0446
Hedhli, A., **10**-0920
Hedley, S.J., **15**-1973
Heemstra Jr., J.R., **16**-1046, **16**-1110
Heemstra, J.M., **08**-0217
Heep, U., **15**-2322, **18**-0469, **18**-0470
Heeren, J.K., **16**-1282
Heermann, D., **16**-1652
Heesing, A., **18**-0750, **19**-0023
Hegarty, A.F., **02**-0397, **05**-0238, **10**-0390, **10**-0492, **11**-0165, **12**-0089, **12**-0417, **13**-0687, **16**-0030, **16**-1570
Hegbom, I., **11**-0145
Hegde, S.G., **12**-0164
Hegde, V., **12**-0087
Hegde, V.R., **15**-0298
Hegedus, L., **10**-1251
Hegedus, L.S., **03**-0083, **10**-1254, **10**-1255, **10**-1332, **10**-1439, **10**-1447, **10**-1841, **10**-1842, **13**-0394, **14**-0443, **15**-0328, **15**-0406, **15**-1342, **15**-1477, **15**-1479, **15**-2292, **15**-2403, **16**-2010, **16**-2099, **16**-2100, **18**-0835
Hegedüs, C., **15**-1491
Hegeman, A.D., **18**-0685
Hegenberg, P., **02**-0347
Hehre, W.J., **01**-0052, **02**-0014, **02**-0028, **04**-0285, **04**-0396, **05**-0076, **05**-0092, **06**-0069, **06**-0072, **06**-0076, **08**-0235, **10**-0200, **15**-2044, **15**-2061, **02**-0371
Hei, S., **12**-0072
Heiba, E.I., **15**-1921, **19**-0436
Heibel, G.E., **15**-2254
Heiber, M., **18**-0631
Heicklen, J., **19**-0361
Heider, L., **11**-0508
Heidke, R.L., **18**-0035
Heiermann, J., **13**-0338
Heigl, U.W., **15**-2282
Heikens, D., **16**-1698
Heil, B., **15**-0598
Heilbron I.M., **19**-0074
Heilbronner, E., **02**-0216, **02**-0335, **04**-0240, **04**-0241, **04**-0416
Heiliger, L., **05**-0058
Heilmann, S.M., **10**-1662, **16**-1425
Heim, P., **19**-0882, **19**-0885, **19**-0889
Heimbach, H., **16**-1204
Heimbach, P., **10**-1251, **15**-2429, **15**-2431
Heimgartner, H., **04**-0460, **15**-2112, **18**-0691
Hein, G.E., **12**-0701
Hein, J.E., **16**-1040
Heine, H.W., **17**-0363
Heine, H.W., **18**-0580
Heinecke, U., **18**-0571
Heinich, A.M., **10**-0786
Heinisch, G., **14**-0337, **14**-0347
Heinrich, N., **18**-0077
Heinrich, P., **05**-0052
Heinsohn, G., **15**-1146
Heintz, M., **13**-0614
Heinz, K.J., **14**-0372
Heinz, W., **02**-0254
Heinzman, S.W., **15**-0571, **19**-1168
Heiser, B., **15**-0598
Heiss, C., **19**-1022
Heiszwolf, G.J., **10**-0488
Heitmann, P., **13**-0165
Heitz, M., **10**-1100
Hekmatshoar, R., **19**-1656
Helbert, M., **01**-0051, **03**-0015, **08**-0090, **08**-0092
Held, G., **12**-0419
Helder, R., **15**-1806
Heldrich, F.J., **13**-0463
Heldt, W.Z., **18**-0335
Helgason, A.L., **18**-0488
Helgeson, R., **15**-2112
Helgeson, R.C., **04**-0163, **04**-0164
Helgren, P.F., **16**-1851
Helgstrand, E., **11**-0010
Hélion, F., **16**-0608, **16**-1987, **19**-1648
Helland, I., **14**-0441, **16**-0372
Heller, B., **15**-0608, **15**-2422
Heller, D., **15**-0608, **15**-0609
Hellgardt, K., **13**-0411
Hellin, M., **15**-0024, **16**-1464, **16**-1467, **16**-1469, **16**-1470
Helliwell, M., **15**-0536, **15**-1680
Helliwell, S., **19**-0403
Hellmann, H., **15**-2256, **15**-2260, **16**-0394
Hellou, J., **16**-2032
Hellrung, B., **02**-0381, **12**-0101
Hellwinkel, D., **05**-0234
Helmchen, G., **04**-0098, **04**-0170, **04**-0225, **10**-1463, **10**-1640, **15**-1022, **15**-2058
Helmick, L.S., **13**-0677

Helmkamp, G.K., **17**-0225, **17**-0361
Helms, A.M., **05**-0289
Helquist, P., **10**-1252, **15**-0949, **15**-2287
Helquist, P.M., **13**-0462
Helsby, P., **11**-0148
Hembre, R.T., **19**-0460
Hembury, G.A., **03**-0069
Hemesley, P., **16**-1246
Hemgartner, H., **16**-1399
Hemingway, A., **04**-0253
Hemmer, H., **12**-0074
Hemmerling, M., **15**-0323, **15**-1280
Hemminger, J.C., **19**-0016
Hems, W., **19**-1028, **19**-1042
Hems, W.P., **09**-0101
Henbest, H.B., **15**-0113, **19**-0597, **19**-0833
Henchman, M., **10**-0345
Henderson Jr., W.A., **15**-2311
Henderson, D.A., **11**-0423
Henderson, G.N., **11**-0054, **18**-0034
Henderson, J.C., **19**-0753
Henderson, J.L., **16**-0584
Henderson, J.W., **05**-0076
Henderson, K.W., **16**-1107
Henderson, M.A., **18**-0695
Henderson, R.M., **11**-0616
Henderson, S., **16**-1021
Henderson, W.G., **08**-0219
Henderson, W.W., **10**-0617
Hendley, E.C., **18**-0885, **18**-0888
Hendrick, M.E., **05**-0338, **15**-2313
Hendricks, R.T., **15**-0988
Hendrickson, J.B., **06**-0001, **10**-0653, **10**-0715, **10**-0907, **10**-0992, **10**-1712, **15**-0133, **15**-0136, **15**-0785, **15**-1562, **16**-2164, **17**-0204, **17**-0350, **19**-1566
Hendriks, A.H.M., **19**-1397
Hendrix, J.P., **12**-0400
Hendry, D.G., **14**-0058, **14**-0121
Hendry, J., **19**-0671, **19**-0851
Hendry, J.B., **11**-0110
Hendy, B.N., **10**-0516
Henglein, A., **07**-0074
Hénin, F., **19**-0218
Henis, J.M.S., **12**-0051
Henke, B.R., **16**-1022
Henke, H., **19**-0366
Henkel, J.G., **18**-0640
Henkelmann, J., **16**-1918
Henley, R.L., **15**-0483, **15**-1657
Henne, A.L., **15**-0505
Hennessy, A.J., **13**-0424
Hennessy, E.J., **13**-0575
Hennessy, M.J., **12**-0217
Henning, R., **10**-0688
Henning, W., **18**-0630
Hennings, D.D., **13**-0332
Hennion, G.F., **10**-1290, **10**-1291, **18**-0390
Hennis, R.P., **18**-0480
Henri-Rousseau, O., **10**-0265, **15**-1992
Henrichs, M., **05**-0150
Henrichs, P.M., **10**-0116
Henrick, C.A., **15**-1080, **16**-1980
Henriksson, U., **19**-1064, **19**-1065
Henry, B.R., **01**-0053
Henry, D.J., **12**-0614
Henry, J.P., **18**-0628
Henry, J.R., **10**-0899, **19**-0395
Henry, L., **16**-1150
Henry, P.M., **15**-1534, **16**-1699, **19**-0387, **19**-0718, **19**-0721
Henshilwood, J.A., **15**-2438
Hensley, M., **15**-1723
Hentchoya Hémo, J., **16**-0356
Hentges, S.G., **15**-1866
Henze, D.K., **18**-0639
Henzel, R.P., **18**-0840, **18**-0845
Heo, C.K.M., **17**-0053
Heo, G.S., **03**-0107
Heo, J., **03**-0185
Hepler, L.G., **08**-0160, **08**-0238, **08**-0239, **09**-0026
Hepp, H.J., **15**-0714, **15**-1358
Heppenstall, T.J., **15**-2036
Heras, Md.R.C., **10**-1400
Heravi, M.M., **16**-0059, **16**-0063, **16**-0145, **19**-0088, **19**-0101, **19**-0102, **19**-0147, **19**-0150, **19**-0153, **19**-0154, **19**-1656
Herbert, J.M., **10**-1403
Herbert, M., **19**-0529
Herbert, W., **19**-1130
Herbich, J., **12**-0087
Herbst, G., **19**-0408
Herbst, M.D., **10**-0727
Herbstein, F.H., **03**-0166
Hercourt, A., **19**-1490
Hercules D.M., **11**-0564
Herd, A.K., **16**-1809
Herd, O., **13**-0237
Herderich, M., **15**-1828, **19**-0205
Herdle, W.B., **02**-0329
Herges, R., **02**-0340, **15**-1524
Heribanová, A., **19**-0567
Hering, N., **10**-0355
Hérion, H., **17**-0265
Herlem, M., **05**-0017
Herlihy, K.P., **18**-0149
Herling, J., **18**-0462
Herman, F., **19**-0601
Hermann, W.A., **10**-1303
Hermanns, N., **16**-0687
Hermans, B., **15**-1856
Hermawan, I., **12**-0132
Hermeling, D., **15**-1998
Hermsen, P.J., **16**-0687
Hernán, A.G., **15**-1231
Hernandez Jr., L., **16**-2108
Hernández, A., **17**-0145
Hernández, J.E., **19**-0317
Hernández, R., **14**-0208
Herndon, J.W., **15**-0356 **15**-2410, **15**-2414
Herndon, W.C., **02**-0004, **02**-0011, **02**-0108, **02**-0120, **02**-0128, **02**-0130, **10**-0212, **15**-2044, **15**-2103, **15**-2105, **15**-2108, **15**-2235, **18**-0477
Herod, A.A., **14**-0110
Herold, B.J., **05**-0327
Herold, L.R., **10**-0534
Heron N.M., **15**-0870, **18**-0814, **15**-1928
Herr, M.L., **02**-0226
Herr, R.J., **13**-0522, **15**-0387, **16**-0423
Herr, R.W., **10**-1542, **10**-1557
Herradua, P.S., **13**-0143
Herranz, E., **15**-1861, **15**-1866
Herrera, R.P., **12**-0618
Herrerías, C.I., **15**-2305
Herrero, L.A., **08**-0118
Herrick, E.C., **15**-2281, **19**-1733
Herring, A.P., **13**-0480
Herring, L.E., **15**-1994
Herrinton, P.M., **10**-1630
Herrlich, M., **11**-0354
Herrmann, A.W., **13**-0394
Herrmann, J.L., **10**-1614, **10**-1698, **15**-1348
Herrmann, P., **16**-0757, **10**-0121
Herrmann, R., **17**-0480
Herrmann, W.A., **05**-0348, **13**-0538, **15**-1738
Herron D.K., **18**-0551
Herron J.T., **19**-0010, **19**-0386
Herscheid, J.D.M., **11**-0312
Herschlag, D., **10**-0367
Hershberger, J., **15**-1171
Hershberger, S.S., **12**-0530, **14**-0389
Hershenson, F.M., **04**-0170, **15**-2045
Hershey, B., **16**-1021

Hershkowitz, R.L., **10**-1096, **13**-0252
Hertas, I., **13**-0158
Hertel, L.W., **14**-0244
Herterich, I., **10**-0136
Hertwig, R.H., **02**-0318
Hervas', M., **05**-0216
Hervé, G., **15**-0834
Herweh, J.E., **16**-2170
Herz, A.H., **11**-0039
Herzberg, D., **19**-1028
Herzberg, G., **05**-0275, **05**-0343
Herzig, D., **19**-0277
Herzog, K.J., **15**-1988
Hess Jr., B.A., **02**-0095, **02**-0107, **02**-0223, **05**-0047, **10**-0192, **10**-0197, **13**-0039, **18**-0539, **18**-0547
Hess, G.P., **16**-1796
Hess, H., **04**-0174
Hess, H.M., **15**-0560
Hess, R.E., **15**-2172, **16**-2080
Hess, T.C., **18**-0227
Hess, W.W., **19**-0079
Hesse, D.G., **04**-0462
Hesse, G., **04**-0175
Hesse, M., **12**-0669, **15**-0152, **16**-1858, **16**-1859, **18**-0159
Hesse, R.H., **12**-0729, **14**-0133, **14**-0134, **15**-1519, **18**-0869, **18**-0872
Hesse, S., **13**-0497
Heßler, A., **13**-0237
Hessler, D.P., **14**-0161
Hester, N.B., **19**-0714
Heublein, G., **15**-0014
Heuft, M.A., **10**-1062, **14**-0324
Heuman, P., **19**-1522
Heumann, A., **14**-0252
Heumann, K.G., **03**-0111
Heuring, D.L., **18**-0381
Heus, M., **15**-0502
Heus-Kloos, Y.A., **16**-1898
Heuschmann, M., **18**-0582
Heusler, K., **14**-0207, **18**-0085, **19**-1067
Heutling, A., **15**-0355
Heuzé, K., **13**-0556
Hevesi, L., **05**-0052, **10**-0771, **15**-1856, **19**-0010, **19**-0553
Hewitt, C.D., **11**-0310
Hewitt, G.W., **15**-0758
Hewitt, M., **05**-0150
Hext, N.M., **08**-0186
Hexter, R.M., **15**-2419
Hey, D.H., **10**-1320, **13**-0736, **14**-0031, **14**-0106, **14**-0108, **14**-0325, **14**-0329, **15**-1355, **15**-1357
Hey, J.P., **04**-0235, **04**-0246
Heyd, W.E., **10**-0250
Heydar, A., **10**-0928
Heydari, R., **11**-0128
Heydkamp, W.R., **12**-0515
Heyer, D., **19**-0603
Heymer, B., **13**-0322
Heyn, A.S., **15**-0860
Heyn, H., **17**-0507, **17**-0509
Hiatt, R., **10**-0740, **10**-0746, **15**-1726, **15**-1742
Hiatt, R.R., **15**-1795, **19**-0769
Hibbert, F., **03**-0043, **08**-0061, **08**-0096, **08**-0102, **08**-0180, **16**-0456, **16**-1587, **16**-1886
Hibbs, D.E., **15**-0323, **16**-1436
Hibert, M., **15**-2145
Hiberty, P.C., **01**-0048, **02**-0006, **02**-0041, **10**-0200
Hibino, H., **10**-1490
Hibino, K., **19**-0505, **19**-0507
Hibino, S., **15**-2122, **19**-1283
Hickey, E.R., **15**-2052
Hickey, M.J., **04**-0296
Hickinbottom, W.J., **11**-0367, **11**-0589, **19**-0423, **19**-1350
Hickmott, P.W., **10**-1674, **10**-1677
Hicks, F.A., **15**-1424, **15**-1465
Hicks, L.D., **19**-1449
Hicks, R., **07**-0105, **11**-0240, **15**-1744
Hida, K., **15**-0625
Hida, M., **13**-0216
Hida, T., **10**-1129
Hidai, M., **10**-0793, **11**-0333, **15**-0808, **19**-1241
Hidaka, T., **10**-1306
Hideura, D., **15**-0801, **15**-1437
Hiebert, J.D., **19**-0022
Hiebert, S., **10**-1534, **15**-0943
Hiegel, G.A., **10**-1069, **19**-0686
Hiel, G.P., **15**-2436
Hiemstra, H., **12**-0273, **13**-0237, **15**-0395, **15**-0913, **16**-1734, **18**-0813
Hienuki, Y., **04**-0422
Hierl, P.M., **10**-0345
Hiersemann, M., **18**-0405, **18**-0666, **18**-0702
Hierso, J.-C., **13**-0541
Higa, S., **16**-2023
Higashi, F., **16**-0436
Higashijima, M., **15**-0530
Higashimae, Y., **10**-1849
Higashino, T., **19**-0580
Higashizima, T., **15**-1480
Higasi, K., **02**-0026
Higginbotham, H.K., **01**-0056
Higgins, D., **10**-1431
Higgins, J., **13**-0252
Higgins, R., **14**-0153, **14**-0204, **14**-0234
Higgins, R.J., **11**-0162, **11**-0163
Higgins, S.D., **19**-1797
Higgins, W., **17**-0291
High, K.G., **15**-0707
Highcock, R.M., **15**-0016
Highet, R.J., **02**-0413
Hightower, T.R., **15**-0276, **15**-0387, **15**-1363, **19**-0055
Higley, D.P., **18**-0590, **19**-0373, **19**-0379
Higuchi, H., **02**-0322
Higuchi, M., **14**-0071
Higuchi, T., **10**-1302, **12**-0726, **16**-1809, **19**-0458
Hii, K.K., **13**-0364, **13**-0393, **13**-0401, **13**-0427, **15**-0339
Hiiragi, M., **10**-0804
Hilbert, J.M., **17**-0047
Hildebrand, J.P., **16**-0687, **19**-0184
Hildebrandt, B., **16**-0493
Hilderbrandt, R.L., **01**-0062
Hilgenkamp, R., **12**-0387
Hill, A.F., **02**-0042, **09**-0111
Hill, C.L., **12**-0341, **12**-0605, **12**-0606, **14**-0126, **14**-0282, **19**-0061, **19**-0453
Hill, D.G., **16**-2037
Hill, D.R., **16**-1634, **19**-0614
Hill, D.T., **15**-2326
Hill, E.A., **12**-0553, **15**-0867
Hill, H.A.O., **13**-0256
Hill, H.D.W., **14**-0327
Hill, H.W., **04**-0212
Hill, J.A., **12**-0023
Hill, K.A., **12**-0154
Hill, M.E., **11**-0139
Hill, R., **02**-0236
Hill, R.H., **19**-1519
Hill, R.K., **02**-0270, **04**-0014, **10**-1112, **15**-0969, **17**-0147, **17**-0454, **18**-0337, **18**-0394, **18**-0621, **18**-0625, **18**-0687, **18**-0688
Hill, R.L., **16**-1816
Hill, T., **16**-1172
Hiller, G., **16**-0204, **19**-1456
Hillhouse, G.L., **19**-1572
Hillier, A.C., **13**-0480
Hillier, I.H., **02**-0418, **15**-0985, **18**-0667, **18**-0709
Hillier, M.C., **09**-0105
Hillman, M.E.D., **16**-0771, **18**-0422
Hillmyer, M., **10**-0807
Hills, I.D., **13**-0350
Hilmersson, G., **08**-0208, **08**-0209, **10**-1123, **15**-0478,

15-0924, **15**-2025, **16**-0470, **16**-0490, **19**-0985, **19**-0985, **19**-1704
Hilpert, H., **04**-0040
Hilt, G., **15**-0796, **15**-2079, **16**-0879
Hilty, T.K., **16**-1076
Himabindu, K., **16**-1608
Himeshima, Y., **13**-0022
Himoe, A., **11**-0045, **11**-0047
Hin, Q.-H., **19**-1325
Hinakubo, Y., **19**-1674
Hinde, A.L., **15**-0538
Hindley, N.J., **16**-0799
Hine, J., **02**-0383, **03**-0030, **08**-0049, **08**-0160, **09**-0016, **09**-0022, **09**-0024, **09**-0025, **10**-0515, **11**-0484, **12**-0058, **15**-0547, **17**-0042
Hines, J.N., **17**-0343
Hines, W.G., **14**-0039
Hinkley, J.M., **10**-0481
Hinman, M.M., **15**-2297
Hinman, R.L., **16**-2085
Hino, F., **18**-0342
Hino, H., **16**-1759
Hino, T., **19**-1154
Hinsley, J., **15**-0806
Hinterding, K., **10**-0738
Hinton, J., **06**-0040
Hintze, H., **19**-0023
Hinze, J., **01**-0025, **01**-0028
Hinzen, B., **19**-0124
Hioki, H., **10**-0704
Hioki, K., **16**-0608, **18**-0732, **18**-0732
Hipperson, W.C.P., **19**-0327
Hirab, T., **10**-0220
Hirabayashi, K., **10**-1198, **13**-0398, **13**-0449, **13**-0519, **14**-0323, **15**-1935, **16**-0914, **10**-0606, **16**-2060
Hirabayashi, Y., **16**-1726
Hirabe, T., **19**-1339
Hiraga, Y., **16**-1228
Hirai, A., **10**-1803
Hirai, C., **03**-0138, **10**-1655
Hirai, H., **11**-0052
Hirai, K., **05**-0337, **15**-1491
Hirai, T., **14**-0174
Hiraike, H., **12**-0754
Hiraiwa, N., **02**-0322
Hiraiwa, Y., **10**-1120, **16**-1096
Hirakawa, A.Y., **07**-0012
Hirakawa, T., **12**-0144
Hirama, M., **15**-0612, **15**-1037, **15**-1697, **15**-1700, **16**-1026, **16**-1332
Hiramatsu, H., **16**-1167
Hiramoto, K., **16**-1661
Hirano, J., **16**-1710
Hirano, K., **10**-1625, **16**-0829, **16**-0909
Hirano, M., **12**-0113, **15**-0146, **15**-0496, **15**-1528, **19**-0688, **19**-0919
Hirano, S., **15**-0946
Hirano, T., **15**-0241, **15**-0608, **19**-0400
Hirano, Y., **19**-0383
Hirao, H., **15**-2049
Hirao, I., **11**-0501
Hirao, I., **16**-1968
Hirao, K., **15**-1461
Hirao, T., **10**-1214, **10**-1826, **13**-0294, **13**-0481, **15**-0921, **15**-1139, **15**-1464, **15**-1477, **19**-1302, **19**-1304, **19**-1591, **19**-1650, **19**-1653, **19**-1695
Hirao, Y., **14**-0191
Hiraoka, K., **10**-0178
Hiraoka, M., **03**-0101, **12**-0319
Hiraoka, N., **11**-0013
Hiraoka, S., **16**-0380
Hiraoka, Y., **16**-0687
Hirasawa, M., **16**-0553
Hirasawa, S., **15**-0595
Hirase, K., **15**-1210
Hirase, M., **15**-1445
Hirashima, T., **15**-1921
Hirashita, T., **10**-0221, **10**-1549, **16**-0600, **16**-0606, **16**-0878
Hirata, F., **15**-2037
Hirata, K., **16**-0620, **16**-1655
Hirata, R., **16**-2139
Hirata, T., **12**-0179, **15**-0626, **16**-1545, **19**-1022
Hirata, Y., **19**-0745, **19**-1434
Hirayama, F., **07**-0021
Hirayama, K., **15**-1391, **15**-2171
Hird, A.W., **15**-1136
Hird, M., **10**-1296
Hirobe, M., **19**-0458
Hiroi, K., **12**-0253, **17**-0294, **19**-0156, **19**-0688
Hirooka, S., **02**-0296, **02**-0303, **02**-0304, **02**-0306
Hirosawa, C., **10**-1565, **15**-1415, **15**-1416, **15**-1430
Hirose, Y., **10**-0657, **16**-0830
Hirota, E., **04**-0276, **05**-0275
Hirota, H., **10**-0404
Hirota, K., **10**-0596, **10**-0919, **10**-1360, **11**-0644, **12**-0731, **15**-0411, **15**-0576
Hirota, M., **09**-0076
Hirota, N., **05**-0208
Hirota, T., **13**-0782, **16**-0086
Hirotsu, K., **01**-0068, **03**-0163, **10**-1302, **15**-0354
Hirsch, J.A., **04**-0339
Hirsch, R., **05**-0138
Hirschmann, H., **04**-0253, **04**-0254
Hirshfeld, F.L., **02**-0292
Hirsl-Star(O(s;)ević, S., **10**-0208
Hirst, D.M., **02**-0002
Hirt, U.S., **19**-0197
His, S., **18**-0318
Hisano, T., **15**-1932
Hisatsune, I.C., **19**-0361
Hiscocks, S.P., **02**-0426
Hiskey, R.G., **19**-0798
Hitchcock, P.B., **13**-0480
Hitchcock, S.R., **12**-0469
Hite, G., **18**-0206
Hites, R.A., **16**-2052
Hiti, J., **05**-0279
Hitzler, M.G., **09**-0106
Hixson, S.S., **18**-0849, **18**-0855
Hiyama, R., **15**-0585
Hiyama, T., **10**-1194, **10**-1198, **10**-1207, **10**-1341, **10**-1438, **10**-1781, **10**-1782, **11**-0511, **12**-0287, **12**-0529, **13**-0398, **13**-0430, **13**-0449, **13**-0519, **13**-0619, **14**-0323, **15**-0589, **15**-0735, **15**-1492, **15**-1543, **16**-0565, **16**-1413, **16**-1546, **17**-0343, **19**-1038
Hiyama, Y., **16**-1521
Hiyashi, M., **19**-0019
Hlasta, D.J., **16**-1967
Ho, C., **06**-0082
Ho, C.-J., **18**-0090
Ho, C.-Y., **15**-1779
Ho, D.M., **02**-0074, **02**-0126, **03**-0200, **15**-1958
Ho, G., **05**-0386
Ho, H.C., **16**-0250
Ho, I., **17**-0082
Ho, J.J., **12**-0087
Ho, K.M., **14**-0402, **19**-1581
Ho, L.-M., **15**-1779
Ho, L.L., **17**-0344
Ho, M.M., **19**-1217
Ho, P.-S., **10**-1772
Ho, P.T., **15**-1696
Ho, S., **10**-0364
Ho, S.P., **03**-0121
Ho, T., **08**-0149, **10**-1227, **10**-1685, **16**-0064, **19**-0980
Ho, T.-I., **13**-0544, **14**-0334
Ho, T.-L., **16**-0250
Ho, T.L., **19**-0010, **19**-1364, **19**-1365
Hoa, K., **11**-0116
Hoang, H., **16**-1351
Hoang, L., **16**-1063

Hoang, T.H., **15**-0820
Hoard, J.A., **18**-0613
Hoashi, Y., **15**-1004
Hobbs, D., **15**-1269
Hobson, J.D., **10**-1186
Hobza, P., **03**-0072
Hoch, H., **10**-1677
Hochstrasser, R., **12**-0150
Hocker, J., **16**-2165
Hocking, M.B., **19**-0427, **19**-0429, **19**-0430
Hocks, L., **18**-0756
Hocquemiller, R., **13**-0308
Hodder, A.S., **18**-0797
Hodek, W., **17**-0476
Hodge, C.N., **03**-0061, **04**-0246
Hodge, J.D., **05**-0035, **05**-0048, **05**-0050
Hodge, P., **10**-0992, **12**-0681, **16**-0690, **16**-1817, **16**-1822, **17**-0459
Hodges, F.W., **11**-0588
Hodgson, B., **05**-0279
Hodgson, D.M., **10**-0934, **10**-1210, **10**-1538, **10**-1538, **16**-0472, **17**-0179, **17**-0210, **18**-0135
Hodgson, P.B., **12**-0370
Hodgson, P.K.G., **16**-1586, **18**-0032
Hodnett, E.M., **14**-0045, **17**-0062
Hodous, B.L., **15**-0368, **16**-2104
Hodson, D., **16**-2048
Hoefnagel, A.J., **09**-0064
Hoefnagel, M.A., **11**-0159
Hoefs, C.A.M., **17**-0229
Hoeg, D.F., **12**-0621, **19**-0836
Hoegerle, R.M., **17**-0407
Hoegy, S.E., **15**-1295
Hoekstra, A., **11**-0312
Hoekstra, M.S., **16**-2012
Hoem, A.B., **18**-0685
Hoen, R., **15**-0604
Hoesch, L., **04**-0040
Hoet, P., **18**-0509
Hofelich, T.C., **05**-0002, **05**-0072, **10**-0177
Hofer, E., **04**-0215
Hoff, C.D., **02**-0417
Hoff, D.J., **16**-1318
Hoff, E.F., **15**-0265, **15**-2213
Hoff, W.S., **19**-0411
Hoffman Jr., J.M., **02**-0235
Hoffman Jr., L., **16**-1378
Hoffman, B.C., **05**-0385
Hoffman, C., **15**-0105
Hoffman, D.H., **04**-0164, **12**-0031
Hoffman, D.K., **18**-0534
Hoffman, D.M., **15**-1732
Hoffman, N.W., **10**-1814
Hoffman, R.V., **13**-0782, **18**-0344, **18**-0346
Hoffman, T.D., **12**-0028, **12**-0682
Hoffmann, D., **05**-0182
Hoffmann, E., appendixA-0024
Hoffmann, F., **19**-0503
Hoffmann, H., **16**-1305
Hoffmann, H.M.R., **10**-1168, **12**-0081, **15**-0961, **15**-1979, **15**-2432, **16**-1889
Hoffmann, K.J., **11**-0280
Hoffmann, M.R., **07**-0069, **07**-0073, **07**-0074
Hoffmann, N., **15**-1049
Hoffmann, P., **16**-2124, **16**-2128, **16**-2133, **17**-0479
Hoffmann, R., **02**-0012, **02**-0052, **02**-0195, **04**-0074, **04**-0419, **05**-0330, **12**-0278, **15**-1659, **15**-1826, **15**-2053, **15**-2103, **15**-2106, **15**-2114, **15**-2258, **17**-0355, **18**-0474, **18**-0476, **18**-0525, **18**-0526, **18**-0531, **18**-0540, **18**-0620, **18**-0622, **18**-0639
Hoffmann, R.T., **18**-0393
Hoffmann, R.W., **05**-0138, **05**-0139, **10**-1324, **12**-0608, **12**-0614, **12**-0623, **13**-0037, **13**-0049, **13**-0079, **13**-0094, **13**-0164, **13**-0574, **14**-0361, **15**-1996, **16**-0443, **16**-0491, **16**-0493, **16**-0494, **16**-0697, **16**-0706, **16**-1019, **16**-1022, **18**-0728, **18**-0737, **16**-0537
Hoffmann, S., **08**-0106
Hoffmann, V.T., **04**-0446
Hoffmann-Röder, A., **15**-1026
Hofinger, A., **16**-0370
Höfle, G., **16**-1622, **18**-0233, **18**-0733
Höfle, G.A., **12**-0408, **16**-1203
Höfler, C., **19**-0023
Hofman, P.S., **11**-0596
Hofmann, A.W., **17**-0251
Hofmann, H.-J., **11**-0172
Hofmann, J.E., **11**-0384, **13**-0667, **17**-0286, **17**-0288
Hofmeyer, L.J.F., **07**-0120
Hofsløkken, N.U., **11**-0472
Hofstra, G., **16**-0209
Hofstraat, R., **16**-2081
Höft, E., **10**-0292
Höft, E., **11**-0488
Hogarth, M.J., **10**-1320
Högberg, H., **10**-1377
Högberg, H.-E., **15**-1931
Högberg, T., **16**-1827
Hoge, G., **15**-0603, **5**-0604
Hoge, G.S., **18**-0764, **18**-0831
Hogen-Esch, T.E., **05**-0127, **05**-0130
Höger, E., **19**-0326
Hogeveen, H., **05**-0031, **10**-0184, **12**-0048, **12**-0108, **12**-0343, **15**-0134, **15**-0218, **15**-1392, **15**-2234, **15**-2257, **16**-0490, **16**-1249, **18**-0007, **18**-0029, **18**-0096
Hogg, H.J., **16**-1596
Hogg, J.L., **16**-0102, **16**-1556
Hoggett, J.G., **11**-0029, **11**-0033, **11**-0041, **11**-0050, **11**-0083, **11**-0096
Hoggett, J.H., **11**-0119
Hogrefe, F., **02**-0175
Hohn, A., **15**-1381
Hohner, G., **02**-0061
Hoigné, J., **11**-0560
Hoiness, C.M., **15**-2327
Høj, B., **15**-1338
Hojatti, M., **02**-0386, **08**-0098, **08**-0105, **12**-0097, **15**-0218
Hojo, K., **02**-0250, **10**-1009
Hojo, M., **10**-0070, **15**-0876, **16**-1657, **19**-0934, **19**-1005, **19**-1392
Hoke, D., **19**-1295, **19**-1296, **19**-1344, **19**-1396
Holbrey, J.D., **09**-0111, **13**-0415
Holbrook, K.A., **18**-0169
Holcomb, A.G., **02**-0206, **10**-0141
Holcomb, H., **19**-0708
Holden, D.A., **14**-0045
Holder, R.W., **15**-2184, **15**-2210, **18**-0561
Holeman, D.S., **15**-1041
Hölemann, A., **16**-0671, **16**-0735, **16**-0736
Holland, G.W., **15**-1189
Holland, H.L., **19**-0795, **19**-0824
Hollander, F.J., **15**-2065
Holler, E.R., **19**-1356
Holliday, R.E., **13**-0033
Hollingsworth, C.A., **01**-0002
Hollinshead, D.M., **19**-1410
Hollis, R., **14**-0075
Hollis, T.K., **16**-1080
Hollis, W.M., **12**-0654
Hollist, G.O., **19**-0676
Hollister, K.R., **10**-1713
Holloway, F., **19**-0248
Holloway, R.L., **02**-0210
Hollowell, C.D., **01**-0074

Hollyhead W.B., **08**-0064, **08**-0059
Holm, A., **10**-0479, **10**-0615
Holm, T., **16**-0483, **16**-0523, **16**-0530, **16**-0532, **16**-0533, **16**-0540
Holman, R.W., **11**-0031
Holmberg, B., **16**-1553
Holme, D., **15**-0445
Holmes, A.B., **09**-0101, **13**-0177, **13**-0407, **13**-0492, **15**-1950
Holmes, D., **13**-0097
Holmes, I.P., **16**-1422
Holmes, J., **18**-0412
Holmes, J.L., **02**-0402, **05**-0074, **05**-0265, **10**-0184
Holmes, R.R., **19**-0749
Holmes, S.A., **04**-0382
Holmgren, A., **10**-0088
Holmquist, B., **16**-1571
Holmquist, C.R., **12**-0331
Holness, N.J., **17**-0069, **18**-0028
Holsboer, F., **02**-0224
Holt, G., **16**-2048
Holt, J., **08**-0112
Holt, R.J., **15**-2283
Holthausen, M.C., **02**-0318
Holton, J., **10**-1832, **12**-0074, **15**-0401
Holton, R.A., **15**-1047
Holtz, D., **08**-0219
Holtz, H.D., **08**-0233, **10**-0314
Holub, D.P., **19**-1697
Holubka, J.W., **12**-0209
Holy, A., **11**-0469
Holy, N., **16**-0405
Holy, N.L., **05**-0313, **10**-0285, **15**-0542
Holz, J., **15**-0609, **19**-1158
Hölzer, B., **12**-0614, **16**-0537
Homer, R.B., **08**-0024, **08**-0055, **16**-1570
Homma, K., **19**-1441, **19**-1471
Homma, M., **15**-2372
Hommeltoft, S.I., **05**-0222
Hommes, H., **10**-1726
Hommes, N.J.R.v.E., **02**-0104, **02**-0105
Homsi, F., **15**-1587
Hon, M., **04**-0410, **15**-0128, **18**-0161, **18**-0569, **18**-0580, **18**-0614
Hon, Y., **10**-0043, **10**-0322
Hon, Y.-S., **19**-0346
Honaker, M.T., **10**-0889
Honda, H., **15**-0665
Honda, K., **03**-0072, **17**-0216, **18**-0729
Honda, M., **16**-1104
Honda, T., **10**-0377, **12**-0326, **16**-0827, **18**-0348, **18**-0902, **19**-1670
Honda, Y., **15**-1260, **19**-0842
Hondo, T., **15**-0225, **15**-0392
Hondrogiannis, G., **15**-1550, **15**-2040
Höne, M., **08**-0089
Honegger, E., **04**-0241, **04**-0416
Hong, D.J., **10**-0501
Hong, J.-B., **15**-1364
Hong, J.-I., **13**-0136
Hong, M., **15**-1125
Hong, R.-K., **13**-0190, **14**-0388
Hong, S., **15**-0335, **15**-0338, **15**-1868, **15**-1871, **15**-1872
Hong, S.-p., **04**-0125, **18**-0680
Hong, W.S., **19**-1512
Hong, Y-T., **13**-0568
Hong, Y., **16**-1087, **16**-1972, **19**-1032
Hong, Y.-T., **10**-1624, **13**-0515, **16**-0739, **16**-0752
Hongo, H., **10**-1454
Hongoh, Y., **04**-0177
Hongwen, H., **10**-0992
Hongxun, D., **18**-0429
Honma, M., **15**-2304
Honma, S., **15**-1192
Honma, T., **15**-1791
Honma, Y., **15**-1158, **15**-1179
Hontschik, I., **11**-0406
Honwad, V.K., **16**-1898
Honzatko, R., **04**-0127, **04**-0146, **15**-0597
Hoobler, M.A., **10**-1742
Hood, F.P., **04**-0323
Hoodless, I.M., **19**-0023
Hoogzand, C., **04**-0502, **15**-2362, **15**-2407
Hoole, D., **11**-0236
Hoornaert, G., **15**-1652
Hoover, D.J., **04**-0207
Hoover, F.W., **15**-2198
Hooz, J., **10**-0585, **10**-0640, **10**-1645, **10**-1762, **10**-1763, **10**-1764, **12**-0153, **12**-0410, **12**-0411, **15**-1150, **15**-1151, **16**-0996, **18**-0458
Hope, E.G., **15**-1488
Hopf, H., **02**-0049, **02**-0050, **10**-0064, **15**-0106, **15**-1994, **15**-2183, **15**-2277
Hopff, H., **04**-0504, **09**-0089, **15**-2365, **16**-1698
Hopkins Jr., H.P., **08**-0191, **10**-0333
Hopkins, A., **16**-2146
Hopkins, P.B., **02**-0395, **17**-0341, **18**-0682
Hopkins, T.E., **12**-0719
Hopkinson, A.C., **03**-0047, **10**-0296, **10**-0301
Hoppe, D., **16**-1197, **16**-1206, **16**-1207
Hoppen, V., **04**-0330, **04**-0341
Hopper, C.R., **16**-1593
Hopperdietzel, S., **15**-1549
Horaguchi, T., **10**-0550, **12**-0117, **19**-0518
Horak, V., **19**-0659
Horan, C.J., **05**-0068, **13**-0027, **13**-0023
Hore, P.J., **05**-0220
Horeau, A., **04**-0144, **04**-0201, **04**-0209, **04**-0214
Horeis, G., **07**-0103
Horgan, A.G., **18**-0750
Horgan, A.J., **18**-0746
Horgan, S.W., **19**-0266
Hörhold, H., **11**-0321
Hori, H., **18**-0772
Hori, I., **10**-1698
Hori, K., **15**-1888, **15**-2428, **16**-1590
Hori, M., **15**-2428
Hori, R., **16**-0947
Hori, S., **15**-0928
Hori, T., **12**-0223, **12**-0224, **14**-0189
Hori, Y., **15**-0280, **15**-0281
Horibe, I., **04**-0206, **11**-0650
Horie, T., **13**-0155
Horie, Y., **13**-0424
Horiguchi, I., **15**-1236
Horiguchi, Y., **15**-1066, **19**-0479
Horikawa, M., **15**-2294
Horikawa, Y., **14**-0117
Horino, H., **19**-1769
Horino, Y., **10**-1498
Horita, K., **14**-0130
Horiuchi, C.A., **11**-0297, **12**-0126, **12**-0162, **12**-0175, **15**-1559, **15**-1576, **15**-1685, **19**-0342
Horiuchi, M., **16**-1368
Horiuti, I., **15**-0452
Horler, H., **18**-0077
Hormi, O., **15**-1823
Hormi, O.E.O., **15**-1694, **15**-1709
Horn, A.H.C., **14**-0076
Horn, U., **17**-0420
Hornaman, E.C., **17**-0273
Hornbuckle, S.F., **02**-0086
Horner, J.H., **05**-0306, **05**-0307, **05**-0310, **14**-0038, **14**-0070, **14**-0123, **15**-1221, **15**-1222, **15**-1272

Horner, L., **04**-0046, **04**-0193, **16**-1255, **16**-1305, **18**-0221, **19**-1424, **19**-1465
Hornfeld, H.L., **11**-0032
Hörnfeldt, A., **16**-1971
Horning, D.E., **13**-0702
Horning, E.C., **19**-0674
Horspool, W.M., **07**-0001, **15**-1932, **15**-2235, **15**-2238, **15**-2439, **16**-2083, **18**-0858
Horstmann, T.E., **15**-1318
Horton, D., **04**-0363
Horton, J.L., **09**-0078
Horvath, B., **19**-0470
Hosaka, K., **16**-2024
Hoshi, M., **12**-0497, **12**-0546
Hoshi, T., **10**-0676, **13**-0415, **15**-0993, **16**-1685, **18**-0359
Hoshino, E., **15**-1679
Hoshino, M., **12**-0263, **12**-0264, **12**-0276, **17**-0369, **19**-0842, **19**-0900
Hoshino, O., **10**-1137, **15**-1436
Hoshino, T., **03**-0186
Hoshino, Y., **15**-1741, **16**-1487
Hosie, L., **16**-0029
Hosmane, R.S., **02**-0146
Hosoi, K., **11**-0511
Hosokawa, H., **15**-1559, **15**-1576
Hosokawa, S., **16**-1127
Hosokawa, T., **19**-0721
Hosomi, A., **10**-1260, **15**-0225, **15**-0392, **15**-0587, **15**-0778, **15**-0876, **15**-1175, **16**-0183, **16**-0645, **16**-1017, **16**-1078, **16**-1079, **16**-1657, **16**-1940, **16**-1953, **19**-1005, **19**-1392
Hosoya, H., **02**-0133
Hosoya, N., **15**-1829, **15**-1909
Hossain, A.M.M., **19**-0408
Hossain, I., **15**-0618
Hossain, K.M., **10**-1406, **13**-0324
Hossain, M.A., **12**-0267
Hossain, M.M., **15**-1898
Hosseini, M., **15**-0472, **18**-0323
Hosseini, M.W., **03**-0153, **04**-0243
Hosseinnia, A., **15**-1296
Hosseinzadeh, R., **10**-1082, **13**-0227, **19**-0861
Hossenlopp, J.M., **07**-0046
Hostyn, S., **13**-0187
Hotta, Y., **16**-0500, **19**-0431
Hou, D., **19**-0996
Hou, D.-R., **15**-0425
Hou, G.-H., **15**-0604
Hou, I.-J., **10**-0288
Hou, K., **19**-0484
Hou, S.-J., **10**-0272, **10**-0958,
Hou, X.-L., **10**-0578, **10**-0674, **10**-0675, **10**-0924, **10**-1173, **10**-1454, **10**-1468, **10**-1571, **10**-1573, **16**-0851, **16**-0871, **16**-0911
Hou, Y., **12**-0370
Hou, Z., **15**-0734, **15**-0804, **19**-1649, **19**-1663
Houghton, T.J., **02**-0067
Houille, O., **16**-1543
Houk, J., **12**-0630
Houk, K.N., **02**-0040, **02**-0352, **03**-0001, **03**-0066, **04**-0295, **05**-0124, **05**-0273, **06**-0041, **07**-0001, **07**-0011, **08**-0193, **11**-0028, **12**-0092, **12**-0409, **14**-0057, **15**-0080, **15**-0103, **15**-0267, **15**-0963, **15**-0967, **15**-0970, **15**-0971, **15**-0990, **15**-0991, **15**-1213, **15**-1227, **15**-1696, **15**-1737, **15**-1781, **15**-1933, **15**-1939, **15**-1945, **15**-1946, **15**-1951, **15**-1955, **15**-1994, **15**-2004, **15**-2005, **15**-2017, **15**-2019, **15**-2057, **15**-2081, **15**-2088, **15**-2090, **15**-2098, **15**-2099, **15**-2103, **15**-2107, **15**-2116, **15**-2117, **15**-2118, **15**-2211, **15**-2433, **16**-1022, **16**-1029, **16**-1063, **18**-0461, **18**-0478, **18**-0482, **18**-0483, **18**-0484, **18**-0533, **18**-0551, **18**-0568, **18**-0605, **18**-0606, **18**-0639, **18**-0658, **18**-0669, **18**-0683, **18**-0707, **18**-0735, **18**-0852, **18**-0856, **19**-0952
Houle, F.A., **05**-0073
Houlihan, W.J., **16**-0972, **10**-0212
House, D., **15**-0534
House, H.O., **10**-1350, **10**-1575, **10**-1590, **10**-1646, **10**-1648, **10**-1649, **10**-1652, **10**-1674, **12**-0110, **12**-0328, **12**-0420, **12**-0560, **15**-0186, **15**-0401, **15**-0482, **15**-0533, **15**-0992, **15**-1063, **15**-1063, **15**-1071, **15**-1086, **15**-1088, **15**-1168, **15**-1171, **15**-1511, **15**-1585, **15**-1648, **15**-1726, **16**-0392, **16**-0527, **16**-0581, **16**-0969, **16**-0999, **16**-1255, **16**-1376, **16**-1697, **16**-1890, **16**-2011, **16**-2034, **17**-0388, **17**-0401, **18**-0196, **18**-0260, **18**-0352, **19**-0010, **19**-0012, **19**-0020, **19**-0070, **19**-0311, **19**-0876, **19**-0913, **19**-0961, **19**-0963, **19**-1218
Houser, H.J., **05**-0048
Houser, J.J., **05**-0035, **05**-0050, **17**-0041
Houser, R.W., **12**-0188
Houston, D., **18**-0100
Houston, T.A., **16**-1637
Hout, F.A.S., **07**-0120
Hovanes, B.A., **10**-0038
Höver, H., **02**-0198
Hoveyda, A.H., **10**-1474, **15**-0656, **15**-0696, **15**-0706, **15**-0710, **15**-0864, **15**-0868, **15**-0870, **15**-1136, **15**-1138, **16**-0417, **16**-0865, **16**-1439, **16**-1457, **17**-0187, **18**-0755, **18**-0770, **18**-0775, **18**-0780, **18**-0792, **18**-0800, **18**-0808, **18**-0814, **18**-0822, **18**-0823, **19**-0670
Howard, A.E., **04**-0357
Howard, J.A., **05**-0297, **14**-0045, **14**-0058, **14**-0218
Howard, J.A.K., **03**-0011, **03**-0070, **04**-0339, **15**-2431, **18**-0893
Howard, S.I., **19**-1014
Howard, S.T., **08**-0185
Howard, W.G., **14**-0214
Howarth, J., **13**-0491, **19**-1024
Howe, C.A., **13**-0734, **14**-0105
Howe, G.R., **19**-0769
Howe, R., **10**-0174
Howe, R.S., **10**-0995
Howell, A.R., **16**-0503, **16**-1352, **16**-1354, **16**-2091, **19**-0239, **19**-0535
Howell, B.A., **10**-0317
Howell, C.F., **17**-0259
Howell, H.G., **19**-1164
Howell, R., **18**-0370
Howell, R.G., **15**-1513
Howells, R.D., **10**-0381
Howk, B.W., **15**-0315
Howlett, K.E., **17**-0136
Howley, P.M., **15**-2313
Howlin, B.J., **15**-0981
Hoy, V.J., **03**-0011, **03**-0070
Hoye, R.C., **04**-0246
Hoye, T.R., **15**-1425, **17**-0309
Hoyle, C.E., **15**-2247
Hoyle, J., **05**-0144
Hoyt Jr., E.B., **17**-0348, **17**-0353
Hoyte, O.P.A., **10**-0713
Hoz, S., **04**-0435, **08**-0133, **10**-0023, **10**-0024, **10**-0025, **10**-0319, **10**-0321, **10**-0350, **10**-0362, **10**-0365, **10**-0366,

13-0750, **16**-0015, **17**-0055, **19**-0158
Hoz, T., **10**-0023, **10**-0319, **10**-1503, **17**-0402
Hrapchak, M.J., **16**-1431
Hrdlovič, P., **11**-0557
Hrovat, D.A., **04**-0521, **04**-0522, **05**-0239, **10**-0047, **18**-0543, **18**-0630
Hrubiec, R.T., **10**-0236, **10**-1103
Hruby, V.J., **15**-1098
Hrutfiord, B.F., **12**-0685, **13**-0164
Hsi, N., **18**-0025
Hsiao, C.-N., **16**-1634
Hsiao, Y., **15**-0615, **16**-0280
Hsieh, W., **18**-0101
Hsu, C.-Y., **16**-1641
Hsu, C.S., **10**-0038
Hsu, H.C., **12**-0492
Hsu, J.-L., **16**-0336
Hsu, J.N.C., **15**-2232
Hsu, S., **19**-0576
Hsu, S.K., **12**-0026
Hsung, R.P., **10**-0997
Hu, D.D., **06**-0026
Hu, A., **19**-1029
Hu, A.-G., **15**-0604
Hu, B., **10**-0737, **19**-0612, **19**-0680
Hu, C.-M., **16**-0451
Hu, H., **19**-0203, **19**-0485, **19**-0486, **19**-0823
Hu, J., **03**-0088, **15**-2148, **16**-0782, **16**-1001, **19**-0563
Hu, J.-b., **10**-1387, **19**-1035, **19**-1040
Hu, K.-N., **05**-0224
Hu, L., **10**-1010, **10**-1306, **16**-0770, **18**-0277, **19**-1191
Hu, L.-m., **19**-0858
Hu, Q., **10**-1549
Hu, Q.-S., **13**-0511
Hu, S., **15**-1758, **16**-2, **19**-0232
Hu, S.-R., **13**-0753
Hu, W., **15**-2065, **15**-2355
Hu, W.-X., **10**-1182
Hu, X., **10**-1453, **15**-0428, **15**-1137, **19**-0180, **19**-1230
Hu, X.-X., **13**-0112, **15**-1288, **15**-1309
Hu, X.E., **10**-0377
Hu, Y., **10**-0869, **10**-1475, **11**-0241, **12**-0298, **13**-0414, **15**-1137, **15**-1488, **15**-1955, **16**-1713, **16**-1714, **16**-1773, **16**-1913, **16**-1915, **16**-1919, **16**-1920
Hu, Y.-H., **16**-1357
Hu, Y.-Q., **10**-0879
Hu, Z., **14**-0082
Hua, I., **07**-0069
Hua, R., **15**-0278, **15**-1359, **15**-1654, **16**-1172
Hua, W.-T., **19**-1032
Hua, X.J., **16**-1346
Hua, Z., **12**-0288, **15**-0428, **15**-1138, **19**-0312
Hua-ming, Z., **15**-2105
Huang, B., **19**-0389
Huang, C., **08**-0108
Huang, C.-H., **15**-1218
Huang, C.-W., **13**-0432, **15**-2387
Huang, D., **06**-0066, **10**-0833, **16**-1919
Huang, F., **17**-0328
Huang, H., **04**-0292, **10**-0582, **11**-0314, **14**-0130, **15**-0428, **15**-0604
Huang, H.-L., **17**-0185
Huang, H.H., **11**-0613
Huang, I.-w., **15**-2381
Huang, J., **04**-0282, **08**-0202, **10**-0997, **13**-0, **15**-0422, **16**-1452
Huang, J.-M., **16**-0590
Huang, J.-S., **15**-2295, **19**-0549, **19**-0550
Huang, K.-H., **15**-1903
Huang, L., **16**-1371
Huang, L.-c., **19**-0393
Huang, L.-F., **10**-1282
Huang, L.W., **07**-0051
Huang, M., **02**-0218, **19**-1186
Huang, N.-P., **19**-0802
Huang, N.Z., **02**-0243
Huang, P.-Q., **16**-1852
Huang, P.C., **16**-1359, **19**-1572, **19**-1573
Huang, Q., **15**-0358, **15**-0919, **15**-2395
Huang, R., **19**-0715
Huang, S.D., **13**-0202
Huang, S.K., **10**-0060
Huang, S.L., **19**-0165
Huang, T.-B., **10**-0897
Huang, T.-H., **15**-0933
Huang, T.-S., **15**-1180
Huang, T.-Y., **16**-1029
Huang, T.T., **10**-1099
Huang, W., **16**-1433
Huang, W.-l., **05**-0258
Huang, W.-S., **15**-0941, **16**-0687, **16**-0712
Huang, X., **10**-1327, **10**-1852, **13**-0123, 13-, **13**-0177, **13**-0189, **13**-0201, **13**-0228, **13**-0583, **13**-0610, **15**-0303, **15**-0441, **15**-1030, **15**-1241, **15**-1284, **16**-1266, **16**-1273, **18**-0269, **18**-0275, **19**-1644
Huang, Y., **15**-1671, **15**-2003, **15**-2127, **15**-2132, **16**-0147, **16**-0645, **16**-0811, **16**-0834, **16**-1266, **19**-1269
Huang, Y.-P., **19**-0804
Huang, Y.-Z., **15**-1157, **16**-0649, **16**-1266
Huang, Y.C.J., **15**-2090
Huang, Z., **10**-0582, **10**-1675
Huang, Z.-Z., **16**-0835, **16**-1267
Huang-Minlon, **19**-1430
Huard, K., **16**-1372
Huba, F., **13**-0080
Hubbard, J.L., **08**-0179, **18**-0436, **18**-0437
Hubbard, R., **18**-0493
Hübel, W., **04**-0502, **15**-2362
Huber Jr., F.E., **12**-0691
Huber, E.W., **16**-0361
Huber, F.A.M., **16**-1959
Huber, G., **16**-1378, **19**-0326
Huber, H., **04**-0240, **18**-0497
Huber, J.E., **10**-0133
Huber, M.B., **15**-1166
Huber, R.S., **18**-0487
Huber, W., **02**-0282, **02**-0305, **02**-0307, **05**-0313
Huber-Buser, E., **04**-0452
Huber-Emden, H., **10**-0918
Hubert, A.J., **10**-0638, **12**-0057, **17**-0322
Hubig, S.M., **11**-0018, **15**-2028, **16**-2083
Hübner, G., **03**-0202
Hübner, T., **04**-0467
Hückel, W., **15**-0533, **17**-0078, **19**-0010
Huckin, S.N., **16**-1168
Huddleston, R.R., **16**-0701
Hudec, J., **04**-0268, **15**-1393, **15**-2116, **17**-0015, **18**-0564
Hudlický, M., **10**-0511, **10**-1036, **10**-1041, **10**-1042, **10**-1076, **12**-0675, **14**-0129, **15**-0166, **15**-0414, **15**-1655, **15**-1726, **17**-0497, **18**-0352, **19**-0009, **19**-0011, **19**-0069, **19**-0305, **19**-0387, **19**-0417, **19**-0633, **19**-0657, **19**-0672, **19**-0694, **19**-0739, **19**-0795, **19**-0873, **19**-0877, **19**-0878, **19**-0912, **19**-1290, **19**-1301,
Hudlicky, T., **04**-0410, **10**-1036, **10**-1124, **13**-0589, **15**-0128, **15**-1721, **15**-1722, **15**-1724, **15**-2231, **15**-2282, **18**-0161, **18**-0569, **18**-0580, **18**-0614

Hudrlik, A.M., **15**-0687, **15**-0711, **15**-0947, **16**-1234
Hudrlik, P.F., **05**-0188, **10**-1542, **10**-1650, **12**-0420, **15**-0687, **15**-0711, **15**-0947, **16**-1234
Hudson, A., **14**-0044
Hudson, C.E., **18**-0536, **19**-0377
Hudson, G.V., **04**-0422
Hudson, H.R., **10**-0203, **18**-0048
Hudson, R.F., **02**-0086, **10**-0328, **10**-0357, **10**-03, **16**-1513
Hudspeth, J.P., **18**-0613
Huerta, F.F., **10**-1437, **16**-1132
Huerta, M., **17**-0167
Huertas, I., **11**-0192
Huertas, R.E., **19**-1031
Huet, F., **10**-0540, **16**-1938
Huet, J., **16**-0852
Huffman, J.C., **10**-0189
Huffman, J.W., **13**-0714, **19**-0962
Huffman, M.A., **10**-1086, **16**-1883
Huffman, R.W., **16**-1845
Hufton, R., **15**-0887
Hug, G.L., **07**-0033, **07**-0034
Hug, M., **15**-1839
Huggins, M.T., **03**-0064
Huggins, M.L., **03**-0001
Hughes, C.M., **15**-1939
Hughes, D., **19**-1148
Hughes, D.D., **15**-2426
Hughes, D.E.P., **15**-0170
Hughes, D.L., **04**-0197, **09**-0105, **10**-0331, **10**-0333, **10**-0703, **13**-0237, **13**-0541, **16**-0280, **18**-0720
Hughes, D.O., **02**-0035
Hughes, E.D., **10**-0003, **10**-0014, **10**-0035, **10**-0036, **10**-0039, **10**-0330, **11**-0151, **11**-0153, **11**-0571, **11**-0572, **11**-0575, **12**-0010, **12**-0017, **12**-0088, **13**-0697, **16**-1562, **17**-0012, **17**-0034, **17**-0084, **17**-0085, **17**-0089, **17**-0105, **17**-0106, **17**-0108, **17**-0118, **17**-0121, **18**-0005, **18**-0742, **18**-0745
Hughes, G., **15**-0593
Hughes, L., **05**-0282, **14**-0075
Hughes, M.L., **17**-0107
Hughes, N., **12**-0580, **12**-0597, **13**-0075
Hughes, R., **14**-0396
Hughes, R.L., **18**-0121
Hughes, W.B., **16**-1282, **18**-0756, **18**-0758, **18**-0762
Hughmark, P.B., **18**-0329
Huh, C., **05**-0314
Huh, H., **10**-1657, **15**-1302
Huh, K., **10**-0900
Huh, S.C., **15**-1015
Huheey, J.E., **01**-0024, **08**-0234
Hühnerfuss, H., **04**-0225
Hui, R.A.H.F., **19**-0058
Hui, R.C., **15**-1344, **15**-1345, **16**-0510, **16**-0511
Huie, E.M., **15**-1932
Huisgen, R., **13**-0088, **13**-0164, **13**-0251, **15**-1932, **15**-1932, **15**-1945, **15**-1952, **15**-1967, **15**-1980, **15**-2166, **15**-2185, **15**-2186, **15**-2212, **15**-2216, **15**-2223, **15**-2225, **15**-2227, **15**-2228, **15**-2261, **18**-0285, **18**-0497, **18**-0506, **18**-0590, **19**-1280
Huisman, H.O., **12**-0189
Hulce, M., **02**-0051, **15**-1090
Hulkenberg, A., **17**-0474
Hull, K., **13**-0543
Hull, K.L., **19**-0513, **19**-0527
Hull, L.A., **19**-0488
Hull, W., **04**-0290
Hulliger, J., **19**-0386
Hüllmann, M., **16**-0519
Hulshof, L.A., **19**-0216
Hultin, P.G., **16**-1040
Hultzsch, K.C., **18**-0775
Hum, G.P., **19**-0253
Humbel, S., **16**-1062
Hummel, K., **10**-0256, **15**-2209, **15**-2221
Hummel, K.F., **15**-2313
Hummel, W., **19**-1022
Hummelen, J.C., **15**-1806
Humpf, H.-U., **19**-0547
Humphrey, G.R., **18**-0302
Humphrey, L.B., **05**-0279
Humphries, M.E., **10**-1463
Humphries, R.E., **02**-0075, **12**-0573
Humski, K., **10**-0060, **10**-0134, **10**-0217, **17**-0035
Hundertmark, T., **13**-0539, **16**-0091
Hung, C.-C., **15**-2120
Hung, C.-W., **04**-0081
Hung, J.C., **10**-1685
Hunger, J., **19**-0065
Hunger, M., **17**-0176, **17**-0314
Hünig, S., **05**-0396, **10**-0917, **10**-1662, **10**-1664, **10**-1677, **12**-0062, **12**-0214, **15**-0482, **16**-1205, **16**-1873, **16**-2041, **17**-0256, **19**-0004
Hunkler, D., **04**-0447
Hunt, D.A., **15**-1108
Hunt, D.F., **19**-0728
Hunt, I.R., **08**-0144
Hunt, J.C., **16**-1766
Hunt, J.D., **14**-0371
Hunt, K., **18**-0559
Hunt, KW., **18**-0364
Hunt, W.J., **05**-0332
Hunter, A.D., **16**-0886
Hunter, C.A., **03**-0069
Hunter, D.H., **05**-0125, **12**-0640, **17**-0037, **17**-0056, **18**-0194
Hunter, J.A., **15**-0358, **15**-2395
Hunter, J.E., **12**-0409
Hunter, W.E., **19**-1639
Huntress, E.H., appendixA-0024
Huntsman, W.D., **12**-0066, **18**-0617
Huo, M., **16**-0342, **18**-0798
Huo, S., **15**-0799, **15**-2404
Hupperts, A., **19**-1722, **19**-1723
Hurd, C.D., **16**-0155
Hurley, P.B., **18**-0134
Hurst, J.J., **04**-0232
Hursthouse, M.B., **03**-0028, **15**-1092, **15**-1269, **16**-1436, **19**-1129
Hurtado, G.R., **15**-0313
Hurwitz, M.J., **18**-0056
Hurwitz, S., **18**-0778
Husain, A., **10**-1089, **15**-0253, **16**-1523, **19**-1605
Huser, D.L., **15**-0544, **15**-0546
Husfeld, C.O., **15**-2435, **18**-0575
Hush, N.S., **02**-0409
Husk, G.R., **15**-2288
Hüsken, H., **19**-1022
Huskey, W.P., **16**-1556
Hussain, A., **12**-0726
Hussain, K.A., **18**-0797
Hussain, N., **19**-0634
Hussain, R.K., **15**-0806
Hussénius, A., **12**-0064
Hussey, A.S., **15**-0465
Hussey, R.E., **10**-0303
Hussoin, M.S., **10**-0653
Hussoin, Md.S., **17**-0204
Huston, S.E., **10**-0071
Huszthy, P., **04**-0177
Hutchings, M.G., **18**-0427, **18**-0432, **19**-1077, **17**-0309
Hutchins, M.G.K., **15**-0435
Hutchins, R.O., **04**-0359, **10**-0500, **10**-0803, **15**-0435, **15**-0638, **16**-0361, **17**-0309, **19**-0104, **19**-0934, **19**-1151, **19**-1154, **19**-1295, **19**-1296,

19-1331, **19**-1344, **19**-1383, **19**-1396, **19**-1417, **19**-1462, **19**-1494, **19**-1522, **19**-1750
Hutchins, R.R., **14**-0413
Hutchinson, E.G., **12**-0691
Hutchinson, J., **12**-0135, **17**-0349
Hutchinson, J.H., **19**-1729
Hutchinson, J.P., **14**-0200
Hutchinson, L.L., **12**-0578
Hutchinson, P.H., **04**-0309
Hutchinson, R.J., **04**-0512
Hutchison, C.A., **05**-0328
Hutchison, J.D., **10**-0333
Hutchison, R.J., **12**-0706
Huthmacher, K., **11**-0216
Hutta, D.A., **18**-0298
Hüttel, R., **19**-0718
Hüttmann, G., **15**-1485
Hutton, J., **19**-0967, **19**-1748
Hutton, R.S., **02**-0235, **05**-0289, **05**-0342
Huuskonen, J., **03**-0170
Huybrechts, G., **15**-2091
Huyffer, P.S., **18**-0862
Huynh, C., **10**-1536, **18**-0736
Huynh, T., **10**-0893
Huyser, E.S., **05**-0202, **14**-0001, **14**-0017, **14**-0040, **14**-0111, **14**-0114, **14**-0125, **14**-0147, **14**-0214, **15**-0050, **15**-0126, **15**-1353, **18**-0054, **19**-1689
Hwang, C.-D., **16**-1438
Hwang, D.-R., **16**-1438
Hwang, H., **10**-0179
Hwang, H.-J., **19**-1324
Hwang, H.H., **19**-0354
Hwang, J.-T., **15**-1249
Hwang, J.-W., **15**-1472
Hwang, J.P., **11**-0420
Hwang, L.K., **15**-1374
Hwang, S.H., **15**-1410
Hwang, Y.C., **16**-0543
Hwang-Lee, S., **15**-0675
Hwu, J.R., **07**-0051, **10**-1192, **16**-1641
Hyatt, J.A., **11**-0222, **19**-0293
Hyeon, T., **07**-0070, **15**-1431, **15**-1432, **15**-1432
Hylarides, M.D., **12**-0496
Hylton, T., **10**-1697, **10**-1702
Hyma, R.S., **16**-0771
Hyman, H.H., **11**-0313
Hymel, E., **16**-1021
Hynd, G., **15**-2301, **16**-0949, **16**-1230, **16**-1383, **18**-0487, **18**-0800
Hynes, M.J., **02**-0390
Hyoda, S., **03**-0163
Hyodo, M., **19**-0706, **19**-0816
Hyuga, S., **12**-0538, **15**-1187, **18**-0447
Hyun, M.H., **04**-0175

Iacazio, F., **19**-1021
Iacono, S.T., **15**-1444
Iannece, P., **15**-1741
Ianskanen-Lehti, K., **10**-0632
Ibarbia, P.A., **15**-0108
Ibatullin, U.G., **16**-1463
Ibazizene, M., **16**-0436
Ibbitson, D.A., **01**-0036
Ibers, J.A., **03**-0001, **03**-0086
Ibne-Rasa, K.M., **10**-0350, **11**-0617, **13**-0757, **15**-1786
Ibrahem, I., **16**-0414
Ibrahim, I.T., **16**-2067, **17**-0486
Ibrahim, S., **12**-0664
Ibrahim-Ouali, M., **10**-1617, **15**-2169
Ibuka, T., **10**-0234, **15**-0394, **15**-1092, **16**-1332
Ibuki, I., **10**-1796
Ibukuro, F., **03**-0193, **03**-0197
Ibusuki, Y., **13**-0050
Ichige, T., **10**-0678
Ichihara, A., **15**-2086
Ichihara, J., **10**-1149, **10**-1789, **15**-1545
Ichihashi, Y., **11**-0052
Ichikawa, H., **10**-0643, **19**-0155
Ichikawa, K., **11**-0376, **12**-0619, **13**-0285, **14**-0105, **15**-1536, **17**-0026, **18**-0761
Ichikawa, Y., **15**-1092
Ichimura, K., **10**-0906
Ichimura, Y., **10**-0627
Ichinari, D., **15**-0535
Ichinohe, M., **05**-0317
Ichiyanagi, T., **15**-2298
Iczkowski, R.P., **01**-0025
Ida, H., **02**-0069
Idacavage, M.J., **10**-1749, **18**-0420
Iddon, B., **16**-0434
Ide, N.D., **16**-1852
Ide, W.S., **16**-1493
Ideda, S., **12**-0319
Idemoto, T., **14**-0364
Iding, H., **16**-1500
Idoux, J.P., **09**-0071, **13**-0157, **19**-0389
Ie, Y., **11**-0463, **19**-1508
Ielmini, A., **13**-0471
Iesato, A., **15**-1877
Iesce, M.R., **15**-1941
Iffland, D.C., **10**-0486, **13**-0692
Igami, M., **19**-1119
Igarashi, K., **16**-0820, **19**-1661, **19**-1668
Igarashi, M., **19**-1493
Igdir, A.C., **16**-0986, **19**-0494
Igi, K., **11**-0414
Iglesias, B., **13**-0518
Iglesias, C., **04**-0369
Iglesias, E., **02**-0382, **02**-0385, **12**-0083, **12**-0198, **12**-0700
Ignatenko, A.V., **16**-1969, **18**-0548
Ignatonska, J., **18**-0828
Ignatov, S.M., **04**-0042
Ignatov, V.N., **15**-2238
Igonin, V., **05**-0263
Iguchi, H., **14**-0071
Iguchi, M., **15**-1297, **16**-0418
Iguchi, T., **16**-0436
Iguchi, Y., **15**-1022, **15**-1125
Ihara, M., **10**-0730, **15**-0769, **15**-0933, **15**-1292, **15**-2167, **17**-0381
Ihara, M., **19**-0279, **19**-0667
Ihara, Y., **16**-1590
Ihrig, A.M., **19**-0018
Ii-hsein, U., **18**-0616
Iida, A., **10**-1304, **12**-0318
Iida, D., **19**-0243, **19**-0244
Iida, H., **12**-0182
Iida, K., **15**-1700
Iida, S., **10**-1511
Iida, T., **10**-0672, **15**-1568
Iijima, T., **01**-0058, **01**-0083, **02**-0030, **17**-0158
Iimura, S., **16**-1676, **17**-0364
Iitaka, Y., **04**-0390, **17**-0289
Ikado, S., **18**-0686
Ikagawa, A., **15**-1004
Ikai, K., **10**-0060, **10**-0074
Ikai, K., **10**-0439
Ikariya, T., **12**-0265, **13**-0348, **13**-0407, **15**-1004, **15**-1024, **15**-1396, **16**-1653, **19**-1042, **19**-1048, **19**-1479, **15**-0576
Ikebe, M., **16**-1892
Ikeda, A., **15**-1559
Ikeda, H., **18**-0542
Ikeda, K., **15**-0598
Ikeda, M., **04**-0193, **10**-1852, **14**-0071, **15**-1220, **15**-1238, **15**-1254, **18**-0360
Ikeda, N., **16**-0645
Ikeda, S., **07**-0083, **10**-1009, **15**-0337, **15**-2374
Ikeda, S.-i., **15**-0604, **15**-0822, **15**-1135, **15**-2367, **15**-2375
Ikeda, T., **11**-0332, **12**-0735, **16**-0669
Ikeda, Y., **13**-0285, **13**-0438, **15**-1540, **16**-0645, **16**-1422
Ikegami, S., **10**-0179, **11**-0522, **12**-0368, **19**-0761, **19**-0897

Ikegashira, K., **10**-1781, **10**-1782, **12**-0287, **14**-0323
Ikekawa, N., **04**-0119
Ikemoto, Y., **16**-0645
Ikeno, T., **15**-0569, **15**-1886, **15**-2130, **16**-0731, **19**-0029, **19**-0923
Ikeshoji, T., **18**-0316
Ikonnikov, N., **16**-1426
Ikonnikov, N.S., **16**-1436, **16**-1438, **16**-1444
Ikorskii, V.N., **05**-0262
Ikumi, A., **10**-1294, **10**-1303, **10**-1384
Ikushima, Y., **09**-0095, **13**-0407, **13**-0408, **18**-0127, **18**-0316
Ikuta, S., **03**-0052, **08**-0225, **10**-0416
Il'ichev, Y.V., **18**-0548
Il'ina, G.P., **14**-0012
Ila, H., **11**-0336, **17**-0434, **18**-0248
Ilangovan, A., **16**-1684, **18**-0702
Ilangovan, P., **16**-1671
Ilankumaran, P., **16**-1690, **16**-1694
Ilao, M.C., **18**-0088
Iley, J., **12**-0709
Ilias, Md., **19**-1554
Ilieva, S., **04**-0307, **16**-1844
Illi, V.O., **16**-1607
Illuminati, G., **06**-0012, **10**-0378, **11**-0010, **11**-0107, **11**-0228, **13**-0008, **13**-0071
Illy-Cherry, S., **19**-1312
Ilyashenko, G., **10**-0955
Ilyushin, M.A., **11**-0138, **12**-0711
Imada, Y., **10**-1009, **10**-1012, **12**-0733, **12**-0749, **15**-1665, **16**-0931, **18**-0363
Imade, M., **15**-2049
Imagawa, H., **11**-0332, **15**-0829, **15**-1458, **15**-2371, **16**-1530
Imagire, J.S., **16**-0192
Imai, E., **19**-0591
Imai, H., **10**-1806
Imai, H., **15**-1506
Imai, N., **15**-2064, **15**-2337
Imai, T., **10**-1260, **15**-0680, **18**-0441, **18**-0442, **18**-0443
Imai, Z., **19**-1487
Imaizumi, J., **12**-0182
Imaizumi, M., **17**-0427
Imaizumi, S., **19**-1368, **19**-1369
Imamoto, T., **05**-0160, **10**-1089, **15**-0596, **15**-0610, **15**-2347, **16**-0433, **16**-0507, **16**-0509, **16**-0518, **16**-0522, **16**-1109, **16**-1250, **16**-1728, **17**-0362, **17**-0472, **18**-0270, **19**-1559, **19**-1697
Imamoto, Y., **19**-1653
Imamura, A., **02**-0052
Imamura, K.-i., **15**-0771
Imamura, P.M., **04**-0206, **19**-0367
Imamura, S., **10**-1849
Imamura, T., **16**-1128
Imanari, M., **03**-0193
Imanishi, T., **19**-0480
Imanzadeh, G., **16**-0313, **19**-0072
Imanzadeh, G.H., **16**-0057, **18**-0321
Imaoka, K., **10**-0464
Imaoka, M., **10**-1511
Imashev, U.B., **10**-0528
Imbeaux, M., **10**-1865
Imboden, C., **17**-0299
Imbos, R., **15**-1125, **16**-0787
Imbriglio, J.E., **15**-1368, **16**-0724, **16**-0800
Imhof, W., **15**-1462
Imhoff, M.A., **10**-0208, **18**-0018
Imi, K., **15**-0755
Imoto, T., **02**-0295
Impastato, F.J., **12**-0614, **12**-0684
Imper, V., **10**-0134
Imperiali, B., **16**-1018
Imwinkelried, R., **04**-0136, **16**-1681, **16**-2100
Inaba, S., **10**-1227, **13**-0465, **16**-1033, **19**-0847
Inaba, Y., **15**-0627, **15**-0624
Inada, K., **13**-0487
Inada, S., **18**-0686
Inada, Y., **10**-0793, **11**-0333
Inagaki, M., **12**-0233
Inagaki, S., **05**-0287, **18**-0466, **18**-0542, **19**-0655
Inagaki, T., **10**-1148
Inaki, K., **19**-0591
Inamoto, N., **01**-0029, **16**-0209, **16**-0218
Inamoto, Y., **11**-0368, **19**-0461
Inanaga, J., **14**-0295, **15**-1300, **16**-0630, **16**-1488, **16**-1489, **16**-1655, **17**-0202, **19**-0900, **19**-1302, **19**-1358, **19**-1418, **19**-1658
Inanaga, K., **15**-2167
Inazu, T., **03**-0129, **08**-0187, **10**-1243
Inbar, S., **07**-0032, **07**-0033
Inbasekaran, M., **12**-0190
Inch, T.D., **04**-0136
Incremona, J.H., **14**-0184, **15**-0142, **15**-0143
Indolese, A., **15**-0800
Indolese, A.F., **11**-0512, **13**-0611, **15**-0910
Inesi, A., **10**-0785, **12**-0745
Inesi, A., **12**-0752
Ing, H.R., **10**-0985
Ingalls, C.L., **15**-0583
Ingate, S.T., **15**-1437
Ingberman, A.K., **14**-0352
Ingham, R.K., **14**-0425
Ingham, S., **18**-0482
Inglis, G.G.A., **10**-0732
Ingold, C.F., **15**-1674
Ingold, C.K., **04**-0098, **07**-0013, **09**-0042, **10**-0003, **10**-0035, **10**-0036, **10**-0039, **10**-0330, **10**-0405, **11**-0151, **11**-0152, **11**-0153, **12**-0011, **12**-0017, **12**-0026, **12**-0095, **13**-0697, **15**-0027, **16**-1547, **16**-1554, **16**-1560, **16**-1562, **17**-0012, **17**-0034, **17**-0085, **17**-0089, **17**-0105, **17**-0106, **17**-0107, **17**-0108, **17**-0118, **17**-0121, **18**-0742, **18**-0744, **18**-0745
Ingold, E.H., **16**-1554
Ingold, K.U., **02**-0024, **04**-0291, **05**-0202, **05**-0208, **05**-0235, **05**-0282, **05**-0297, **05**-0308, **05**-0310, **14**-0049, **14**-0054, **14**-0067, **14**-0070, **14**-0074, **14**-0075, **14**-0077, **14**-0097, **14**-0116, **14**-0118, **14**-0119, **14**-0122, **14**-0163, **14**-0164, **14**-0214, **14**-0215, **14**-0216, **14**-0218, **15**-1212, **15**-1224, **18**-0054, **18**-0073, **18**-0078, **18**-0082, **18**-0089, **19**-1100
Ingrosso, G., **15**-0036
Inhoffen, E., **14**-0320
Inman, C.G., **15**-2244
Inners, R.R., **16**-1303
Innes, K.K., **07**-0012
Inoguchi, K., **15**-0607
Inoh, J.-I., **13**-0338
Inokawa, S., **10**-1039, **10**-1244
Inoki, S., **15**-0185, **15**-0197
Inokuchi, T., **10**-1805, **15**-1276, **16**-0161, **19**-0401, **19**-0745
Inokuma, S., **02**-0069
Inomata, K., **10**-1440, **16**-1655, **19**-0169, **19**-0592
Inomoto, Y., **10**-0208
Inoue, A., **13**-0317, **13**-0429, **15**-2276, **16**-0466, **16**-0865
Inoue, H., **11**-0332, **15**-0608, **15**-0777, **15**-0830, **15**-0831,

15-0920, **15**-1786, **15**-1853, **19**-1478
Inoue, I., **16**-0858
Inoue, K., **03**-0045, **05**-0291, **15**-0932, **16**-0218, **16**-1904, **19**-1101, **19**-1298, **19**-1308
Inoue, M., **11**-0341, **16**-0560, **16**-0668, **16**-1922
Inoue, R., **10**-1396, **10**-1550, **15**-0935
Inoue, S., **10**-1801, **11**-0517, **12**-0731, **15**-0906, **15**-1837, **16**-1422, **16**-1497, **17**-0216, **18**-0729, **19**-1027
Inoue, T., **10**-1098, **12**-0179, **15**-1590, **15**-2139, **16**-0985, **16**-0996, **19**-1028
Inoue, T.C., **16**-1571
Inoue, Y., **03**-0104, **04**-0196, **11**-0101, **12**-0300, **15**-0154, **15**-0155, **15**-0158, **15**-0160, **15**-0288, **15**-0929, **15**-1158, **15**-1179, **15**-2116, **15**-2161, **15**-2379, **16**-0892, **19**-1022
Inouye, Y., **18**-0733
Inubushi, T., **07**-0094
Inuidiata, F.P., **16**-1260
Inukai, T., **09**-0020, **15**-2044
Invergo, B.J., **19**-0662, **19**-0934, **19**-1013
Ioffe, A., **10**-0854
Ioffe, B.V., **05**-0396, **17**-0446, **19**-1279
Ioffe, S.L., **19**-1185
Iogansen, A.V., **08**-0217
Ionin, B.I., **15**-1315, **16**-1309
Ionita, L., **16**-0419
Ipaktschi, J., **16**-0913, **18**-0856, **19**-1417
Ippen, J., **02**-0175
Iqbal, J., **10**-1168, **12**-0316, **14**-0100, **15**-0254, **16**-1614, **16**-1725
Iqbal, M., **15**-1435
Irandoost, M., **10**-0655, **10**-0668
Iranpoor, N., **10**-0663, **10**-0665, **10**-0667, **10**-0681, **10**-0708, **10**-0812, **10**-0820, **10**-0848, **10**-0941, **10**-1090, **10**-1106, **10**-1113, **10**-1799, **10**-1807, **11**-0128, **11**-0138, **11**-0299, **15**-1577, **15**-1848, **15**-2420, **16**-0160, **16**-0234, **16**-0238, **16**-1396, **16**-1684, **17**-0156, **17**-0431, **17**-0466, **19**-0145, **19**-0762, **19**-0819, **19**-0856
Irelan, J.R.S., **19**-1733
Ireland, D.T., **02**-0344
Ireland, J.F., **07**-0016
Ireland, R.E., **10**-0912, **10**-1289, **18**-0677, **18**-0679, **18**-0687, **19**-0202
Iretskii, A.V., **11**-0629
Iri, K., **12**-0693
Irie, M., **07**-0058, **11**-0331, **15**-2300, **19**-0221, **19**-0520
Irie, T., **10**-0146, **10**-0161, **10**-0170
Iriuchijima, S., **12**-0181, **12**-0186
Irngartinger, H., **04**-0427, **04**-0437, **18**-0495
Irrgang, B., **10**-0355
Irsa, P., **15**-0448
Irvine, D., **15**-1243
Irvine, J.L., **10**-0060, **18**-0706
Irwin, K.C., **15**-1795
Irwin, R.S., **15**-2247
Isa, M., **19**-1796
Isaac, M.B., **16**-0591
Isaacs, E.S., **06**-0059
Isaacs, N.S., **05**-0002, **05**-0001, **05**-0099, **05**-0202, **05**-0327, **06**-0059, **09**-0087, **10**-0476, **10**-1159, **12**-0039, **14**-0437, **15**-2027, **15**-2180, **15**-2210, **15**-2213, **15**-2217, **16**-0612, **16**-1281, **16**-1571, **16**-2094
Isaev, I.S., **11**-0605, **11**-0637
Isaev, S.D., **18**-0325
Isaeva, Z.G., **18**-0096
Isagulyants, G.V., **16**-1470
Isagulyants, V.I., **16**-1462, **16**-1466, **16**-1470
Isaji, H., **17**-0289
Isaka, M., **16**-0581
Isakov, V.E., **10**-1496
Isakova, A.P., **11**-0496
Isaksson, R., **04**-0175
Isayama, S., **15**-0184, **15**-0185, **15**-0197
Isbister, R.J., **15**-1632
Isborn, C.M., **02**-0339
Iseki, K., **16**-0761
Isenberg, N., **15**-0095
Isenberger, K.M., **12**-0419
Isenberger, K.M., **16**-0977
Ishar, M.P.S., **15**-2133
Ishi-i, K., **15**-1520
Ishiba, A., **16**-0618, **16**-0640
Ishibashi, H., **11**-0521, **14**-0071, **15**-1220, **15**-1237, **15**-1238, **15**-1254, **16**-1261
Ishibashi, N., **16**-1657
Ishibashi, T., **11**-0140
Ishibashi, Y., **10**-1123
Ishibe, N., **03**-0060
Ishida, A., **19**-1441, **19**-1471
Ishida, H., **15**-1457
Ishida, K., **19**-0061
Ishida, M., **16**-0189, **16**-0226
Ishida, N., **16**-0509
Ishida, S., **05**-0317
Ishida, T., **15**-1705, **15**-1807, **16**-1221, **16**-1229
Ishida, Y., **05**-0250
Ishifune, M., **16**-0645
Ishigami, T., **15**-2198
Ishigedani, M., **16**-0893, **19**-1161
Ishiguro, K., **19**-0383
Ishihara, H., **15**-1888, **16**-0189, **19**-0881
Ishihara, K., **10**-1120, **10**-1522, **15**-0223, **15**-0786, **15**-2009, **16**-0150, **16**-1046, **16**-1047, **16**-1094, **16**-1096, **16**-1418, **16**-1671, **16**-1785, **16**-1801, **19**-1021
Ishii, A., **15**-1847, **16**-0209
Ishii, D., **19**-1028
Ishii, H., **14**-0143, **18**-0714
Ishii, J.-i., **15**-2370
Ishii, K., **10**-0965
Ishii, S., **10**-0729
Ishii, T., **10**-0730, **15**-1004, **16**-2024
Ishii, Y., **05**-0277, **10**-0606, **12**-0210, **12**-0211, **13**-0371, **13**-0401, **15**-0174, **15**-0377, **15**-0598, **15**-0621, **15**-0756, **15**-0763, **15**-0937, **15**-1210, **15**-1404, **15**-1561, **15**-1567, **15**-1757, **15**-1792, **15**-1842, **16**-1444, **16**-2060, **19**-0095, **19**-0130, **19**-0139, **19**-0315, **19**-0552, **19**-0580, **19**-0593, **19**-1241, **19**-1479
Ishikawa, A., **16**-0579
Ishikawa, F., **18**-0348
Ishikawa, H., **10**-1535, **16**-0364, **16**-1771
Ishikawa, M., **10**-1416, **15**-2404, **19**-1302
Ishikawa, N., **04**-0169, **07**-0080, **10**-1306, **13**-0263, **13**-0279, **16**-1203, **16**-1880
Ishikawa, R., **19**-1718
Ishikawa, S., **16**-1117, **16**-1121
Ishikawa, T., **10**-0950, **10**-1111, **11**-0332, **15**-2084, **16**-0545, **16**-1060, **16**-1645, **19**-0014, **19**-1035
Ishikura, M., **10**-1426, **13**-0633, **17**-0382
Ishimaru, K., **16**-0922
Ishimori, T., **03**-0109
Ishimoto, K., **19**-1447
Ishimoto, M., **12**-0755

Ishino, Y., **10**-0628, **13**-0533, **15**-1336, **16**-0579
Ishino, Y., **16**-1364
Ishitani, H., **08**-0188, **15**-1935, **15**-2010, **15**-2128, **16**-0381, **16**-0412, **16**-0871, **16**-0876, **16**-1121, **16**-1124, **16**-1454
Ishitobi, H., **10**-0161, **10**-0170
Ishiwata, F., **16**-0978
Ishiyama, T., **10**-1416, **10**-1417, **12**-0451, **13**-0625, **16**-0698, **16**-0885
Ishizaki, K., **10**-1322
Ishizaki, M., **10**-1137, **15**-1436
Ishizuka, T., **15**-0587, **15**-0749, **16**-1039
Iskander, Z., **12**-0088
Iskra, J., **11**-0287, **15**-1753
Islam, I., **19**-0735
Islam, Md.N., **15**-1994
Isler, M.P., **16**-1439
Ismagilova, G.S., **16**-2047
Ismailov, S.A., **15**-1980
Isobe, H., **17**-0205
Isobe, K., **13**-0415, **16**-1685
Isobe, M., **15**-1092
Isobe, T., **10**-1111, **16**-1645
Isobe, Y., **10**-1360
Isoe, S., **19**-0340
Isola, M., **16**-2144
Isolani, P.C., **08**-0231
Isotani, S., **15**-0611
Isozaki, S., **12**-0210
Israel, G., **13**-0719
Issacs, N.S., **02**-0312, **16**-0612
Isse, A.A., **10**-1854
Isukada, N., **15**-0929
Itabashi, K., **10**-0819
Itagaki, Y., **10**-0643, **19**-0155
Itai, A., **04**-0301
Itami, K., **10**-1200, **10**-1278, **13**-0448, **15**-0730, **15**-1409, **15**-1420
Itano, H.A., **19**-0295
Ito, A., **16**-0620
Ito, H., **08**-0200, **12**-0035, **15**-0587, **15**-0778, **15**-1158, **16**-0678, **16**-0975, **16**-1042, **16**-1044, **16**-1078, **16**-2135, **18**-0701
Ito, K., **10**-1464, **15**-2297, **15**-2337, **16**-1361, **16**-1604, **18**-0363
Ito, M., **02**-0342, **04**-0422
Ito, O., **14**-0120, **14**-0121
Ito, S., **02**-0200, **05**-0045, **05**-0046, **12**-0319 **13**-0781, **14**-0200, **14**-0204, **19**-0635, **19**-1666
Itô, S., **10**-0704, **15**-1697, **15**-2116, **16**-1026, **16**-1274, **18**-0685
Ito, T., **10**-1427, **12**-0278, **12**-0278, **12**-0470, **13**-0533, **15**-0528, **16**-0579, **16**-0620, **19**-1769
Ito, T.I., **19**-1616
Ito, Y., **10**-0689, **10**-0691, **10**-0919, **10**-1771, **10**-1806, **12**-0035, **12**-0731, **15**-0528, **15**-0598, **15**-0657, **15**-0700, **15**-0816, **15**-1409, **15**-1506, **15**-1827, **15**-1909, **15**-2351, **16**-0713, **16**-1190, **16**-1442, **16**-2127, **16**-2134, **16**-2135, **18**-0828, **19**-0843, **19**-0848
Ito, Y.N., **15**-1831, **15**-1888, **15**-1888
Itoh, A., **10**-0657, **10**-1438, **19**-0227, **19**-0421, **19**-0655
Itoh, H., **07**-0022, **15**-0122
Itoh, I., **11**-0216
Itoh, K., **10**-0815, **10**-1468, **10**-1469, **10**-1539, **12**-0501, **13**-0362, **15**-0766, **15**-0821, **15**-0823, **15**-1064, **15**-1459, **15**-1474, **15**-2370, **15**-2379, **15**-2384, **15**-2389, **15**-2393, **16**-0329, **19**-1254, **19**-1679
Itoh, M., **12**-0490, **12**-0518, **15**-1183, **15**-1184, **15**-1189, **15**-1192, **16**-1220, **18**-0453, **18**-0457, **19**-0340
Itoh, O., **19**-1783, **19**-1785
Itoh, S., **15**-0354
Itoh, T., **11**-0410, **13**-0137, **16**-0364, **16**-0364, **16**-1521, **19**-1518
Itohara, S., **16**-0921
Itoi, Y., **15**-1492
Itonaga, M., **11**-0436
Itooka, R., **15**-1022, **15**-1125
Ittah, Y., **10**-1017
Ittel, S.D., **03**-0086, **15**-1381
Iura, T., **19**-1094
Ivakhnenko, E.P., **16**-1607
Ivanov, D., **12**-0401
Ivanov, S.N., **16**-2143
Ivanov, V.B., **14**-0228, **15**-2156
Ivanov, V.V., **13**-0541
Ivanova, T.M., **04**-0264
Ivanyk, G.D., **10**-1075
Ives, D.A.J., **19**-1439
Ives, J.L., **12**-0693, **14**-0227, **15**-2151, **19**-0554
Ivey, R.C., **05**-0344
Ivin, K.J., **18**-0756, **18**-0836
Iwabuchi, Y., **16**-0636, **16**-0637
Iwadare, T., **18**-0872, **18**-0873
Iwahama, T., **15**-0377, **15**-0756, **15**-0937, **15**-1210, **15**-1757, **15**-1842 **19**-0095
Iwahara, K., **15**-1436
Iwahara, T., **10**-0688
Iwai, H., **16**-1116
Iwai, I., **12**-0065, **18**-0380
Iwai, J., **16**-0644, **16**-0873
Iwai, T., **04**-0075, **12**-0656, **13**-0533
Iwaki, S., **04**-0334
Iwakura, C., **15**-0608
Iwakura, Y., **16**-1758
Iwama, H., **16**-0871
Iwama, T., **13**-0332, **15**-2003, **17**-0519
Iwamoto, C., **16**-1245
Iwamoto, H., **04**-0270, **10**-0465
Iwamoto, S., **16**-0871
Iwamoto, T., **05**-0317
Iwamura, H., **04**-0505, **05**-0290, **05**-0291
Iwamura, H.I., **18**-0396
Iwamura, M., **18**-0396
Iwanaga, K., **10**-1637, **15**-2063
Iwanami, T., **16**-0713
Iwanek, W., **04**-0091
Iwao, M., **10**-1454, **13**-0648
Iwaoka, M., **11**-0038
Iwasa, S., **15**-2300, **16**-1653
Iwasaki, F., **19**-1009, **19**-1144
Iwasaki, M., **16**-1860
Iwasaki, N., **16**-1358
Iwasaki, Y., **13**-0128
Iwasawa, H., **10**-1589, **16**-1168, **15**-0903, **15**-1043, **15**-1660, **16**-0161, **16**-1016, **16**-1422
Iwasawa, T., **16**-0418
Iwasawa, Y., **18**-0836
Iwashima, K., **03**-0109
Iwata, A., **10**-1126, **10**-1443
Iwata, C., **19**-0480
Iwata, N., **14**-0373
Iwatani, K., **19**-1176
Iwaya, K., **10**-0584
Iwaya, M., **13**-0683
Iwazaki, Y., **15**-0576
Iwebuchi, Y., **15**-1826
Iyanar, K., **15**-1744, **19**-0767
Iyengar, D.S., **10**-0909, **10**-1139, **10**-1140, **16**-2154, **19**-0893, **19**-1208, **19**-1257, **19**-1259, **19**-1270, **19**-1382, **19**-1384, **19**-1547, **19**-1637, **19**-1640
Iyengar, N.R., **11**-0106, **11**-0272
Iyer, P.S., **10**-0119, **11**-0346, **18**-0073
Iyer, R., **17**-0349
Iyer, S., **13**-0399

Iyer, V.S., **16**-1957
Iyigün, Ç., **19**-0495
Iyoda, M., **02**-0301, **02**-0304, **10**-1227, **13**-0462, **15**-2322, **18**-0469, **18**-0470
Izatt, R.M., **03**-0101, **03**-0105, **03**-0108, **03**-0148, **04**-0163, **04**-0177
Izawa, H., **18**-0338
Izawa, K., **15**-0107, **15**-1600
Izawa, M., **15**-2084
Izawa, T., **10**-1511, **19**-1128
Izawa, Y., **05**-0371, **05**-0380, **18**-0222, **18**-0228
Izmailov, F.F., **01**-0029
Izquierdo, M.A., **14**-0069, **16**-2081
Izsak, D., **04**-0280
Izumi, J., **16**-1656
Izumi, K., **19**-1697
Izumi, M., **15**-1115
Izumi, T., **10**-1822, **13**-0362
Izumi, Y., **04**-0001, **04**-0136, **11**-0226, **15**-0602, **16**-1017, **16**-1282
Izutsu, M., **18**-0342

Jaber, J.J., **16**-1478, **18**-0607
Jaber, N., **15**-2119
Jablonski, R.J., **10**-0160
Jabri, N., **10**-1339, **15**-1062
Jachiet, D., **10**-1543
Jachmann, M., **16**-0687
Jackman, L.M., **02**-0100
Jackman, L.M., **02**-0272, **02**-0291, **05**-0127, **05**-0189, **05**-0190, **08**-0213, **08**-0214, **10**-0171, **10**-0341, **10**-0484, **12**-0420, **12**-0420, **15**-0417, **18**-0642, **19**-0023
Jackson, A.C., **16**-1483, **16**-1484
Jackson, A.E., **19**-1200
Jackson, C.L., **13**-0006
Jackson, F.L., **16**-1881
Jackson, H.L., **10**-1791
Jackson, J.E., **05**-0386
Jackson, L.L., **10**-0866
Jackson, L.L., **10**-0866
Jackson, P.M., **11**-0085
Jackson, R.A., **14**-0044, **14**-0049, **14**-0053, **14**-0089, **14**-0453, **19**-1414
Jackson, R.F.W., **10**-0630, **15**-1791
Jackson, R.W., **16**-1539
Jackson, T.C., **19**-0939
Jackson, T.J., **15**-2410
Jackson, W.F., **05**-0305
Jackson, W.M., **07**-0043
Jackson, W.R., **15**-1478, **15**-1486, **15**-1493, **15**-1500, **15**-1501, **15**-1504, **15**-1685, **16**-1422
Jackstell, R., **15**-0333, **15**-0342, **15**-1481, **16**-0306
Jacob III, P., **15**-1187, **16**-0544
Jacob, J., **17**-0226
Jacob, L., **10**-0825
Jacob, M., **05**-0309
Jacob, P., **01**-0094
Jacob, R.G., **16**-0583
Jacobi, P.A., **15**-0386
Jacobs, H.K., **09**-0098
Jacobs, P.A., **19**-0120
Jacobs, T.L., **10**-0291, **15**-0106, **15**-0109, **15**-1553, **15**-1802
Jacobs, T.L., **15**-2219
Jacobsen, E.N., **07**-0123, **10**-0583, **10**-0677, **10**-0738, **10**-1553, **10**-1572, **10**-1804, **11**-0402, **15**-0987, **15**-1003, **15**-1335, **15**-1691, **15**-1701, **15**-1702, **15**-1782, **15**-1827, **15**-1829, **15**-2149, **16**-0945, **19**-0823
Jacobsen, H., **15**-1832, **15**-1833
Jacobsen, M.F., **16**-0419
Jacobsen, W.N., **13**-0581
Jacobson, A.E., **16**-0148
Jacobson, B.M., **10**-0103, **15**-2117
Jacobson, G.B., **09**-0097, **09**-0108
Jacobson, M.A., **08**-0211
Jacobson, N., **14**-0352
Jacobson, R.A., **04**-0127, **04**-0146, **15**-0597
Jacobson, R.R., **18**-0708
Jacobus, J., **04**-0202, **04**-0212, **14**-0029, **15**-0491, **15**-0651, **18**-0737, **19**-1344
Jacox, M.E., **05**-0203, **05**-0276, **05**-0328
Jacquault, P., **07**-0111, **16**-0144, **18**-0324
Jacques, J., **04**-0009, **04**-0096, **04**-0156, **04**-0156, **04**-0182
Jacquesy, J., **11**-0264, **11**-0533, **11**-0536, **11**-0637
Jacquesy, J.-C., **15**-0718
Jacquier, R., **11**-0464, **16**-1816
Jacquier, Y., **15**-1901
Jacquot, L., **10**-0976
Jacquot, R., **10**-0884, **11**-0391
Jaculi, D., **19**-0271
Jadhav, P.K., **15**-0674, **15**-0675, **15**-0676, **15**-0679, **19**-1053
Jadhav, V., **04**-0181
Jadhav, V.K., **16**-0058
Jaegar, D.A., **09**-0112, **15**-2041
Jaeger, C.D., **14**-0416
Jaeger, D.A., **15**-2031
Jaenicke, S., **19**-0971
Jafarpour, M., **10**-1090
Jaffe, A., **02**-0235
Jaffe, M.H., **18**-0027
Jaffe, R.L., **04**-0293
Jaffé, H.H., **01**-0025, **02**-0013, **07**-0010, **09**-0017, **09**-0020, **11**-0070, **18**-0886, **18**-0888, **18**-0891
Jafri, J.A., **02**-0216
Jagadeshwar, N.V., **16**-1404
Jager, W.F., **07**-0061
Jager, W.W., **15**-1381
Jagner, S., **15**-1094
Jagodziński, T., **11**-0509
Jagodziński, T.S., **15**-1299
Jagoe, C.T., **18**-0565
Jagow, R.H., **06**-0083
Jagtap, H.S., **19**-0752
Jagtap, S.B., **15**-1033
Jahagirdar, D.V., **08**-0191
Jähme, J., **10**-0083, **15**-0265
Jahn, R., **04**-0437
Jahngen Jr., E.G.E., **16**-2040, **17**-0415
Jain, A., **04**-0454
Jain, A.K., **13**-0017
Jain, A.L., **19**-0713
Jain, M.L., **16**-1641
Jain, N., **13**-0105, **19**-0072
Jain, R.P., **10**-0633
Jain, S.L., **15**-1899, **16**-0390, **19**-0114, **19**-0782, **19**-0783, **19**-0785
Jaisankar, P., **19**-1431
Jaisinghani, H.G., **10**-0861
Jalali-Araghi, K., **19**-0350
Jalil, A.A., **13**-0436
James, B., **10**-1367, **15**-1067
James, B.G., **10**-0718
James, B.R., **15**-0406, **15**-0526
James, D.E., **15**-1477
James, D.R., **18**-0638
James, K.B., **15**-1046
James, L.L., **11**-0010
James, P., **13**-0491, **19**-1024
James, R.A., **10**-0717, **10**-0994
Jamieson, J.Y., **18**-0822
Jamil, Z., **19**-0219
Jamison, J.A., **18**-0576
Jamison, T.F., **16**-0712, **16**-0718
Jammot, J., **16**-0123
Jan, D., **15**-1959
Jan, G., **17**-0024
Jan, S., **15**-1827
Jana, S., **16**-0646
Jana, S.K., **11**-0423

Jana, U., **11**-0418, **18**-0138
Janda, K.D., **12**-0327, **13**-0128, **15**-1955, **16**-1045, **16**-1687, **16**-1823
Jandu, K.S., **14**-0033, **14**-0328
Janes, M.K., **10**-0705
Jang, D.O., **15**-1203, **16**-1717, **16**-1749, **16**-1784, **19**-1403, **19**-1404, **19**-1405, **19**-1406, **19**-1415, **19**-1470, **19**-1474
Jang, E.G., **15**-2268
Jang, H.-Y., **15**-0817
Jang, T.-S., **16**-0634
Jang, W.H., **15**-0835
Jang, Y.-J., **13**-0753, **15**-1149
Jani, A., **16**-1894
Janik, D.S., **15**-1785
Janke, N., **12**-0578
Janke, R.H., **04**-0070
Janker, B., **10**-0355
Jankowska, R., **19**-0904
Jankowski, B.C., **13**-0782
Jankowski, C.K., **15**-2022
Jannini, M.J.D.M., **19**-0611
Janosi, A., **17**-0265
Janoski, E.J., **18**-0116
Janousek, Z., **05**-0243
Janousek, Z., **05**-0245, **15**-2182, **15**-2222, **19**-0840
Janowski, W.K., **05**-0082
Jansat, S., **10**-1454, **10**-1459
Jänsch, H., **16**-1413
Jansen, A., **15**-0343
Jansen, B.J.M., **17**-0296
Jansen, M.P., **10**-0294, **17**-0035
Janssen, C.G.M., **19**-1397
Janssen, E., **15**-0866, **19**-1723
Janssen, M.J., **15**-0300, **16**-0002, **16**-0103, **17**-0344, **19**-1802
Janssen, S.J., **15**-1603
Janssens, F., **15**-1652
Janura, M., **13**-0237
Januszkiewicz, K., **19**-0726
Januszkiewicz, K.R., **15**-0524
Janzen, E.G., **05**-0211, **05**-0214, **05**-0260
Jaouen, G., **16**-0469, **16**-2058, **19**-0951, **19**-1060
Jaques, D., **10**-0521
Jarczewski, A., **17**-0052
Jardine, F.H., **02**-0043, **04**-0146, **14**-0446, **15**-0407, **15**-0408, **15**-0410, **15**-0416, **15**-0462, **15**-0597, **15**-1478
Jardine, F.R., **12**-0074
Jardine, I., **19**-1368
Jardine, P.D., **15**-1693
Jarikote, D.V., **11**-0237, **13**-0491
Jarowski, P.D., **02**-0040
Jarrahpour, A.A., **19**-0148
Jarret, R.M., **04**-0321
Jarvis, B.B., **10**-0305, **15**-0142, **17**-0348, **17**-0353
Jasat, A., **03**-0172
Jasinski, J.P., **16**-1138
Jaskot, K., **10**-0590
Jasne, S.J., **10**-0224
Jason, M.E., **04**-0519
Jasoni, R.L., **16**-0782, **16**-1001, **19**-0563
Jasor, Y., **16**-0403
Jaspars, M., **15**-0199, **16**-0746
Jasperse, C.P., **15**-1050, **15**-1197
Jasperse, C.P., **15**-1962, **15**-2066
Jasra, R.V., **15**-1830
Jasserand, D., **15**-1685
Jászay, Z.M., **16**-1808, **17**-0488
Jaszberenyi, J.C., **19**-1415
Jaszberenyi, J.Cs., **19**-1401, **19**-1405, **19**-1406
Jatczak, M., **10**-1134, **10**-1707, **16**-1378
Javaid, K., **12**-0039
Jawdosiuk, M., **04**-0497, **04**-0498
Jayaasree, S., **15**-1378
Jayachitra, G., **16**-0125
Jayakumar, K.N., **13**-0585, **13**-0664
Jayakumar, S., **15**-2133
Jayalakshmi, B., **17**-0465, **17**-0467
Jayanthi, A., **13**-0399
Jayaprakash, K., **13**-0750
Jayaraman, H., **16**-0020, **16**-1594
Jayaraman, M., **07**-0116
Jayasree, J., **10**-0601
Jayatilake, G.S., **16**-1422
Jean, A., **15**-0797
Jean, H.-J., **15**-1908
Jean, T.-S., **15**-1246
Jebaratnam, D.J., **16**-1189
Jedrzejczak, M., **16**-1745
Jedziniak, E.J., **14**-0151, **19**-0462
Jeevanandam, A., **16**-0163
Jeevnandam, A., **15**-2381
Jefcoate, C.R.E., **14**-0204
Jefferson, A., **18**-0654
Jefferson, E.A., **02**-0391, **15**-2268
Jeffery, E.A., **11**-0527, **16**-0676, **19**-1373
Jeffery, T., **10**-1766, **13**-0382, **13**-0384, **13**-0389, **13**-0403, **13**-0728
Jeffery-Luong, T., **10**-1290
Jefford, C.W., **04**-0424, **10**-0226, **10**-0318, **14**-0244, **14**-0245, **15**-2108, **15**-2282, **15**-2326, **18**-0477, **18**-0509, **19**-0688, **19**-1292
Jeffrey, G.A., **03**-0025, **03**-0029, **03**-0164, **18**-0637
Jeffs, P.W., **14**-0335
Jeganathan, A., **19**-0511
Jeganathan, S., **16**-1324
Jeganmohan, M., **13**-0553, **15**-2387
Jeger, O., **15**-0781, **17**-0504, **18**-0111
Jekő, J., **12**-0322
Jellal, A., **15**-1175
Jellison, K.M., **17**-0170
Jemison, R.W., **18**-0386, **18**-0387, **18**-0729
Jen, M., **01**-0060
Jenck, J., **15**-1477
Jencks, W.P., **02**-0383, **03**-0019, **06**-0037, **06**-0043, **06**-0059, **08**-0057, **08**-0104, **08**-0135, **08**-0140, **08**-0141, 09-II-0004, **10**-0075, **10**-0083, **10**-0084, **10**-0088, **10**-0279, **10**-0356, **10**-0357, **10**-0363, **10**-0367, **10**-0527, **10**-0533, **12**-0147, **12**-0642, **13**-0013, **16**-0001, **16**-0010, **16**-0014, **16**-0017, **16**-0019, **16**-0020, **16**-0031, **16**-0044, **16**-0045, **16**-0100, **16**-0259, **16**-0314, **16**-0316, **16**-0424, **16**-1511, **16**-1517, **16**-1763, **16**-1846, **16**-1847, **16**-1848, **16**-1849, **16**-1936, **17**-0044, **17**-0049
Jendza, K., **16**-0598
Jenkins Jr., R.H., **04**-0028
Jenkins, I.D., **04**-0044, **10**-0652, **10**-0702, **10**-0705
Jenkins, I.L., **13**-0216
Jenkins, J.A., **15**-2096, **18**-0589
Jenkins, P.R., **05**-0142, **12**-0035
Jenkins, S.I., **04**-0454
Jenkins, S.R., **19**-1313
Jenks, W.S., **17**-0284
Jenner, E.L., **15**-0796
Jenner, G., **09**-0085, **10**-0644, **12**-0731, **15**-0970, **15**-1291, **15**-2091, **15**-2096, **15**-2098, **16**-1179, **16**-1430, **16**-1450, **16**-1481, **16**-1482, **16**-1636, **16**-2130, **18**-0461
Jenner, P.J., **18**-0022, **18**-0102

Jenneskens, L.W., **02**-0062, **02**-0063, **02**-0083, **17**-0229, **18**-0519
Jennings, C.A., **13**-0640
Jennings, H.J., **12**-0697
Jennings, W.B., **04**-0250, **19**-0830
Jenny, E.F., **18**-0392
Jensen, A.E., **10**-1384, **10**-1388, **10**-1406
Jensen, D.R., **16**-0865, **19**-0120, **19**-0218
Jensen, F., **15**-2098, **17**-0005, **18**-0669
Jensen, F.R., **04**-0127, **04**-0146, **04**-0316, **04**-0323, **04**-0325, **04**-0328, **04**-0330, **04**-0331, **04**-0351, **11**-0214, **11**-0416, **12**-0002, **12**-0007, **12**-0011, **12**-0012, **12**-0013, **12**-0014, **12**-0017, **12**-0019, **12**-0022, **12**-0041, **12**-0424, **12**-0504, **12**-0505, **12**-0551, **15**-0134, **15**-0597, **17**-0139, **17**-0475, **18**-0094
Jensen, H.B., **15**-0466
Jensen, H.P., **19**-0470, **19**-0734
Jensen, J.F., **15**-0751
Jensen, J.L., **02**-0025, **10**-0530, **10**-0534, **15**-0195
Jensen, K.A., **10**-0615
Jensen, K.B., **15**-1097
Jensen, L., **16**-1252
Jensen, R.M., **05**-0150
Jensen, S.D., **16**-0188
Jensen, T.A., **13**-0187
Jensen, W.B., **08**-0143
Jenson, T.M., **10**-0151
Jentzsch, J., **14**-0292, **16**-0204, **19**-1456
Jeon, D.J., **10**-0625
Jeon, M., **16**-0637
Jeon, S., **19**-0609
Jeong, B.-s., **10**-1657
Jeong, B.S., **15**-1302
Jeong, H.J., **16**-1536
Jeong, K.-S., **15**-1658, **15**-1693, **15**-1704
Jeong, N., **12**-0599, **15**-1410, **15**-1439
Jeoung, M.K., **19**-1109, **19**-1113, **19**-1183
Jereb, M., **12**-0127
Jeremić, D., **14**-0210, **14**-0211, **14**-0212
Jerina, D.M., **04**-0038
Jerkunica, J.M., **10**-0176
Jernberg, N., **16**-1819
Jernelius, J.A., **18**-0775
Jeromin, G.E., **05**-0251
Jerphagnon, T., **15**-0428
Jerussi, R.A., **19**-0048, **19**-0468
Jesberger, M., **16**-0213
Jeske, M., **16**-0576, **19**-1654
Jesson, J.P., **15**-0464
Jessop, C.M., **15**-1243
Jessop, P.G., **12**-0265, **15**-0526, **15**-0614
Jeuell, C.L., **05**-0041
Jew, S., **16**-1148, **18**-0274
Jew, S.-s., **10**-1657, **15**-1302
Jewett, R., **10**-0916
Jewett, J.G., **06**-0072, **06**-0076, **10**-0208, **10**-0317
Jeyaraj, D.A., **16**-0008
Jeyaraman, R., **05**-0411, **10**-0853, **16**-0261, **19**-0488, **19**-1282
Jézéquel, M., **10**-1343
Jha, S., **13**-0196, **13**-0489
Jha, S.C., **10**-0595, **15**-1036
Jhurry, D., **13**-0077
Ji, G.Z., **08**-0084
Ji, J., **15**-1004, **15**-1050, **15**-1096
Ji, M., **19**-0800
Ji, R.Y., **15**-1826
Ji, S.-J., **16**-0631, **16**-1111
Ji, X., **19**-0174
Jia, C., **11**-0331, **13**-0447, **15**-1165
Jia, J.H., **02**-0243
Jia, L., **15**-1397, **15**-1403
Jia, X., **11**-0309, **15**-0413, **15**-1147, **16**-0549
Jia, Y., **16**-0558, **16**-0662
Jia, Y.-X., **19**-0082
Jia, Z.S., **10**-0061, **17**-0045
Jiaang, W.-T., **15**-1270
Jian, S., **19**-1370
Jiang, B., **13**-0276, **16**-0550, **16**-0552, **16**-0869, **19**-1031, **19**-1039
Jiang, D.O., **19**-1470
Jiang, F., **16**-1037
Jiang, G.J., **04**-0385
Jiang, H., **10**-1857, **14**-0307, **15**-1397, **15**-1403, **15**-2409
Jiang, H.L., **15**-1826
Jiang, J., **05**-0293
Jiang, J.-K., **16**-0687, **16**-0773, **16**-0785, **16**-0800, **16**-0802
Jiang, L., **12**-0523, **13**-0177, **16**-1311
Jiang, L.H., **16**-2120
Jiang, M.X.-W., **15**-2412
Jiang, N., **10**-1549
Jiang, R., **15**-1690
Jiang, S.A., **12**-0285
Jiang, T., **15**-0422, **16**-1155
Jiang, W., **10**-1773, **19**-0584
Jiang, W.-T., **15**-1218, **15**-1270
Jiang, X., **05**-0248, **14**-0188
Jiang, Y., **10**-1453, **10**-1454, **13**-0482, **15**-2127, **16**-0831, **16**-1428, **16**-1438, **18**-0277, **18**-0487, **18**-0689
Jiang, Y.-L., **10**-0879
Jiang, Y.-Z., **15**-0575, **15**-1128, **16**-0865, **16**-1037, **19**-1042
Jiang, Z., **13**-0064, **14**-0261
Jiao, H., **02**-0099, **02**-0104, **02**-0105, **02**-0251, **02**-0261, **02**-0309, **02**-0311, **02**-0338, **15**-0647, **15**-1947, **18**-0624
Jiao, X., **10**-1778
Jiao, X.H., **13**-0295
Jie, C., **18**-0630, **18**-0669
Jie, Z., **19**-1614
Jigajinni, V.B., **12**-0489
Jiménez, C., **13**-0576
Jiménez, J.L., **04**-0004, **04**-0300, **04**-0303, **15**-2004, **15**-2097
Jiménez-Estrada, M., **12**-0213
Jiménez-Tenorio, M., **15**-0284
Jiménez-Vázquez, H.A., **05**-0002
Jimeno, C., **16**-0687
Jiminez, J.L., **18**-0623
Jin, C.K., **16**-1536
Jin, F., **13**-0272
Jin, J., **15**-0762, **15**-0798
Jin, L., **10**-1486, **17**-0287
Jin, M., **16**-0939
Jin, M.-J., **10**-1454
Jin, Q., **12**-0359, **12**-0361
Jin, Q.-H., **16**-0655, **19**-1226
Jin, S.-J., **16**-0874
Jin, T., **12**-0634
Jin, T.-S., **16**-0233
Jin, W., **19**-1707
Jin, X., **15**-1456, **15**-2421
Jin, X.L., **15**-1300
Jin, Y., **19**-1265
Jin, Y.S., **12**-0128, **19**-0496, **16**-0630
Jin, Z., **10**-1629, **12**-0288, **15**-0177, **16**-1320, **19**-0312
Jindal, S.P., **18**-0018
Jindong, Z., **19**-1370
Jing, L., **12**-0581
Jinguji, M., **07**-0021
Jinnai, T., **17**-0161
Jinnouchi, K., **10**-0965
Jintoku, T., **11**-0505
Jira, R., **12**-0074, **14**-0259, **15**-0792, **19**-0718, **19**-0721
Jirgensons, A., **10**-0897

Jiricny, J., **10**-0995, **16**-0093, **16**-1459
Jirovetz, L., **16**-0195
Jitsukawa, K., **19**-0129
Jnaneshwara, G.K., **10**-0660, **16**-1153
Joannetaud, M., **11**-0536
Job, G.E., **12**-0523, **13**-0118, **13**-0205
Job, R.C., **04**-0252
Jochims, J.C., **16**-0434
Jochum, C., **15**-0547
Jockusch, S., **05**-0368
Jodhan, A., **05**-0358, **16**-1595, **16**-1596
Jödicke, K., **16**-2083, **16**-2088
Jödicke, T., **16**-0292
Jodry, J.J., **04**-0061
Joerg, S., **03**-0018
Joesten, M.D., **03**-0001
Joffee, I., **10**-0907
Jöge, T., **15**-0477
Joh, T., **15**-1461
Johannsen, M., **15**-0751, **15**-2146, **16**-0912
Johansen, J.E., **15**-0760
Johanson, R.G., **10**-0208
Johansson, A., **16**-0979
Johansson, F., **16**-0858
Johansson, K., **12**-0286
Johansson, M., **15**-1670
Johansson, R., **10**-1096
John, K.C., **16**-2042
John, L., **18**-0499
John, L.S., **19**-0203
Johns, J.W.C., **05**-0343
Johns, M.K., **19**-1021
Johnsen, U., **05**-0218
Johnson Jr., C.S., **04**-0264, **05**-0233, **06**-0056
Johnson Jr., H.W., **04**-0074, **04**-0167
Johnson, A.P., **04**-0101
Johnson, A.W., **02**-0086, **02**-0303, **16**-1255, **16**-1265
Johnson, B.F.G., **19**-1028
Johnson, C., **05**-0308
Johnson, C.A., **02**-0289
Johnson, C.C., **14**-0078
Johnson, C.D., **05**-0378
Johnson, C.D., **05**-0378, **06**-0017, **08**-0024, **08**-0055, **09**-0016, **09**-0038, **11**-0068
Johnson, C.N., **15**-2411
Johnson, C.R., **04**-0047, **10**-1344, **10**-1542, **10**-1557, **12**-0260, **15**-0120, **15**-1083, **15**-1712, **16**-1195, **16**-1218, **16**-1387, **16**-1388, **16**-1406, **16**-1895, **19**-0647, **19**-0648, **19**-0798
Johnson, D.E., **15**-2247
Johnson, D.R., **16**-0349
Johnson, E.S., **15**-0973
Johnson, F., **04**-0349, **10**-1130, **16**-1248, **16**-2053
Johnson, G., **15**-1565
Johnson, G.L., **14**-0167
Johnson, G.S., **17**-0457, **19**-1174
Johnson, H., **16**-1021
Johnson, J.E., **04**-0221
Johnson, J.R., **12**-0448, **15**-1482, **15**-2172, **16**-1209, **16**-2080
Johnson, J.S., **13**-0214, **15**-2064, **16**-1501
Johnson, K., **19**-1249
Johnson, L.A., **05**-0391
Johnson, L.K., **04**-0086
Johnson, M.D., **09**-0035, **14**-0053
Johnson, M.R., **15**-0187, **19**-0930
Johnson, M.W., **19**-0480
Johnson, N.A., **19**-0787
Johnson, N.B., **15**-0606
Johnson, P.L., **13**-0361
Johnson, R.A., **10**-0742
Johnson, R.D., **02**-0356
Johnson, R.E., **19**-1477
Johnson, R.G., **14**-0425
Johnson, R.L., **15**-1911
Johnson, R.P., **04**-0463, **04**-0481, **04**-0482, **04**-0486, **04**-0488, **07**-0054, **15**-2358
Johnson, S.A., **10**-0181, **10**-0206
Johnson, S.L., **16**-0014, **16**-0020, **16**-0031
Johnson, S.M., **02**-0325
Johnson, T.A., **18**-0705, **19**-1223
Johnson, T.J., **15**-2406
Johnson, T.R., **14**-0318
Johnson, W.S., **04**-0320, **10**-0635, **15**-0782, **15**-0783, **15**-0784, **15**-0785, **16**-1139, **18**-0676, **19**-0399
Johnsson, B., **03**-0057
Johnston, B.H., **16**-1635
Johnston, D.E., **18**-0117
Johnston, E.R., **03**-0077
Johnston, F., **15**-0030
Johnston, G.F., **12**-0020
Johnston, J.F., **11**-0101
Johnston, J.N., **13**-0181, **15**-1278, **16**-0919, **16**-0947, **18**-0128
Johnston, K P., **09**-0097
Johnston, K.M., **11**-0589, **14**-0288
Johnston, K.P., **09**-0097
Johnston, L.J., **05**-0285, **05**-0302, **05**-0310, **07**-0001
Johnston, R.D., **15**-0253
Johnstone, R.A.W., **10**-0589, **10**-1582, **15**-0518, **15**-1771, **15**-1989, **18**-0384, **18**-0398, **19**-0393, **19**-1102, **19**-1200, **19**-1223, **19**-1232
Johri, K.K., **14**-0436
Jokinen, S., **10**-0331
Jolicoeur, E., **15**-2339
Jolidon, S., **18**-0686
Jolley, K.W., **17**-0065
Jolly, P.W., **10**-1251, **15**-2431
Joly, D., **19**-0023
Joly-Goudket, M., **10**-1511
Jon, S.Y., **10**-1831, **16**-1507
Jona, H., **15**-0310
Jonas, K., **15**-0793
Jonas, L., **11**-0233
Jonas, M., **04**-0311
Jonassen, H.B., **15**-1498
Jonasson, C., **16**-0903
Jonathan, N., **02**-0127
Jones II, G., **05**-0285, **16**-2083
Jones III, F.M., **08**-0219, **08**-0220
Jones Jr., J., **15**-0997
Jones Jr., M., **05**-0327, **05**-0338, **05**-0349, **05**-0350, **05**-0359, **05**-0363, **05**-0373, **05**-0376, **05**-0380, **12**-0382, **15**-2272, **15**-2282, **15**-2312, **15**-2313, **15**-2316, **18**-0218, **18**-0640, **18**-0646
Jones, A., **14**-0110
Jones, A.D., **15**-0323
Jones, A.J., **02**-0095, **02**-0099
Jones, B.A., **04**-0163, **16**-0219
Jones, B.E., **10**-0063
Jones, C.W., **13**-0147, **13**-0256, **13**-0257
Jones, D., **15**-1562
Jones, D.A.K., **17**-0133
Jones, D.E., **15**-2434
Jones, D.M., **10**-0571
Jones, D.N., **17**-0126, **17**-0291
Jones, D.W., **02**-0211, **14**-0225, **15**-2050, **15**-2116
Jones, E., **16**-1383
Jones, E.R.H., **15**-0445, **19**-0074
Jones, F.N., **13**-0764
Jones, G., **16**-1165
Jones, G.A., **19**-1174

Jones, G.B., **18**-0487, **18**-0489, **18**-0491
Jones, G.C., **13**-0761
Jones, G.I.L., **04**-0295
Jones, G.T., **11**-0571
Jones, J., **10**-0570
Jones, J.B., **04**-0151, **10**-1701, **10**-1702, **19**-0688
Jones, J.H., **10**-0992
Jones, J.I., **11**-0500
Jones, J.K.N., **10**-1158
Jones, J.M., **06**-0071, **16**-1763
Jones, J.R., **05**-0104, **08**-0014, **11**-0113, **12**-0084, **14**-0352
Jones, J.W., **09**-0078
Jones, K., **15**-1232, **15**-1248, **15**-1253, **16**-1952
Jones, L.D., **13**-0462
Jones, M.B., **11**-0408
Jones, M.D., **19**-1028
Jones, M.E., **10**-0491, **17**-0120
Jones, M.F., **12**-0654
Jones, M.G., **10**-0162
Jones, M.R., **16**-2141
Jones, M.T., **15**-0543
Jones, N., **15**-1649
Jones, N.D., **12**-0224
Jones, N.R., **10**-1697
Jones, P.G., **01**-0063, **04**-0168, **04**-0287, **15**-2443
Jones, P.M., appendixA-0038
Jones, P.R., **10**-1698, **15**-0654, **16**-0562
Jones, R., **03**-0083, **10**-1063
Jones, R.A., **16**-2007
Jones, R.A.Y., **01**-0087, **02**-0189, **08**-0003, **08**-0024, **08**-0111, **08**-0135, **09**-0016, **09**-0024, 09-II-0002, **15**-2106, **18**-0477
Jones, R.J., **18**-0513
Jones, R.V.H., **15**-2301, **16**-1383
Jones, S., **16**-131, **19**-1031
Jones, S.R., **04**-0031, **14**-0266
Jones, W.A., **12**-0137, **12**-0648
Jones, W.D., **16**-2137
Jones, W.H., **16**-0310
Jones, W.J., **10**-0426, **19**-0639, **19**-0640, **19**-0642
Jones, W.M., **05**-0383, **05**-0390, **17**-0503
jones, M.L., **18**-0135
Jong, Y., **08**-0108
Jonsäll, G., **18**-0009
Jonsdottir, S., **04**-0371
Jonsson, S.Y., **15**-1664, **15**-1707
Jönsson, L., **13**-0115
Joos, R., **17**-0420
Jordan Jr., A.D., **16**-1325
Jordan, E.A., **17**-0133
Jordan, K.D., **15**-0086
Jordan, M.R., **02**-0364
Jordan, R.W., **15**-2173
Jorge, J.A.L., **10**-0312
Jorge, Z.D., **15**-1710
Jorge, Z.S., **14**-0177
Jorgensen, K.A., **12**-0124
Jorgensen, W.L., **10**-0017, **10**-0020, **10**-0021, **10**-0071, **13**-0002, **15**-0121, **15**-0145, **15**-2098
Jørgensen, C.K., **01**-0020, **01**-0022, **01**-0024, **01**-0028
Jørgensen, K.A., **10**-0949, **11**-0387, **12**-0146, **15**-0993, **15**-0996, **15**-1001, **15**-1097, **15**-1659, **15**-1696, **15**-1797, **15**-1826, **15**-1960, **15**-2132, **15**-2146, **16**-0384, **16**-0899, **16**-0912, **16**-0920, **16**-0941, **16**-0944, **16**-0948, **16**-1160, **16**-1160, **16**-1164, **19**-0287, **19**-0551
Jørgensen, M., **13**-0583
Jorgenson, M.J., **04**-0422, **08**-0118, **16**-0838, **16**-2085, **18**-0551, **19**-0921
Joris, L., **03**-0060
Josan, J.S., **17**-0343
José, S.M., **10**-0009, **16**-1566
Joseph, D., **13**-0470
Joseph, N., **15**-0404
Joseph, R., **10**-1068
Joseph, S.C., **19**-0857
Joseph, S.P., **15**-1257
Josephsohn, N.S., **16**-0417
Josey, A.D., **16**-1413
Josey, J.A., **15**-2121
Joshi, B.V., **19**-1541
Joshi, G.C., **15**-0510
Joshi, N.N., **10**-0595, **10**-1160, **10**-1417, **15**-1036, **19**-1672
Joshi, P.L., **16**-0058
Joshi, S.N., **16**-0687
Joshi, U.M., **16**-1692
Joshikawa, M., **11**-0333
Josien, H., **10**-0975
Joslin, C.G., **05**-0220
Jost, R., **08**-0015, **18**-0035
Jothilingam, S., **15**-1311, **16**-0162
Jouannetaud, M., **11**-0264, **11**-0533, **11**-0637
Joukhadar, L., **19**-1410
Joule, J.A., **10**-0726
Joung, M.J., **16**-0548
Jourdant, A., **15**-0415
Journaux, Y., **19**-0120
Journet, M., **15**-0440, **18**-0546
Jousseaume, B., **15**-0862, **16**-2004
Joussot-Dubien, J., **04**-0469
Jovanovic, M.V., **13**-0080
Jovanovich, A.P., **10**-0147
Jowtschinnikow, J.A., **03**-0203
Joya, T., **15**-0210
Joyasawal, S., **16**-1374
Joyner, B.L., **01**-0042
Jozefowicz, M., **19**-0748
Jozwiak, A., **16**-0288
Jończyk, A., **10**-0892, **16**-1225
Jroundi, R., **14**-0219
Ju, Y., **16**-0457, **16**-0459, **16**-0700
Juan, B., **02**-0234, **08**-0075
Juaristi, E., **04**-0285, **04**-0327, **04**-0354, **04**-0359, **04**-0361, **04**-0364, **04**-0372, **08**-0014, **08**-0215, **10**-0877, **16**-0688, **16**-1081
Jubault, P., **16**-1383
Juchnovski, I.N., **09**-0023
Judd, D.B., **19**-1171
Judd, K.R., **11**-0073
Judeh, Z.M.A., **11**-0396
Judy, W.A., **18**-0760, **18**-0824, **18**-0836
Juers, D.F., **18**-0850
Jug, K., **02**-0006, **02**-0092, **02**-0095, **02**-0111, **02**-0112
Juge, S., **19**-0789
Jugie, G., **11**-0469
Juhasz, M., **05**-0008, **08**-0106
Juhl, K., **16**-0384, **16**-0948, **16**-1160, **19**-0551
Juhlke, T., **10**-0079
Jukes, A.E., **16**-1893
Jula, T.F., **05**-0380
Julia, M., **10**-0400, **10**-0825, **10**-1486, **10**-1713, **13**-0315, **13**-0316, **15**-0050, **15**-0052, **17**-0287, **19**-0508, **19**-0841
Julia, S., **18**-0076, **18**-0736
Juliá, S., **15**-1814
Julienne, K., **16**-1384
Julin, S., **16**-1322
Julius, M., **15**-0728
Juliusburger, F., **10**-0014
Jullien, F.R., **04**-0127, **04**-0146, **15**-0597
Jumbam, D.N., **19**-1724
Jumonville, S., **14**-0027
Jun, C.-H., **15**-0930, **15**-1364
Jun, P., **10**-0592
Jun, S.I., **03**-0189
Jun, Y., **10**-1273, **12**-0409, **16**-0872, **19**-1189
Junchai, B., **18**-0429

Junckers, T.H.M., **13**-0196
Juneja, P.S., **14**-0045
Jung, A., **15**-1919, **16**-1033
Jung, C.W., **10**-0916
Jung, D.-S., **19**-0569
Jung, F., **16**-1195
Jung, G., **15**-1245
Jung, H.C., **19**-0809
Jung, H.H., **15**-0835
Jung, I.-H., **16**-1743
Jung, I.-S., **03**-0210
Jung, I.N., **10**-1194
Jung, J., **16**-0725, **16**-0734
Jung, J.-C., **11**-0269
Jung, K., **19**-0168
Jung, K.W., **10**-0610, **10**-0730, **10**-0859, **10**-0861, **10**-0973, **12**-0372, **13**-0439, **13**-0449, **13**-0477, **16**-0199, **16**-1867, **17**-0234
Jung, L.-j., **10**-0219
Jung, M.E., **10**-0547, **10**-1089, **10**-1133, **15**-1213, **15**-1227, **15**-1939, **16**-1064, **16**-1226, **18**-0613, **19**-0059, **19**-0129, **19**-0362
Jung, M.J., **15**-0465
Jung, S., **15**-1879
Jung, S.H., **13**-0569
Jung, Y.-J., **11**-0269, **15**-1436
Jung, Y.C., **13**-0439, **13**-0449, **13**-0477
Jung, Y.J., **16**-0352, **19**-0998, **19**-1324
Jung, Y.S., **15**-1298
jung, M.E., **15**-2081
Junga, H., **15**-1250, **18**-0804
Jungen, M., **04**-0181
Jungk, H., **11**-0318, **11**-0373, **11**-0600
Junjappa, H., **11**-0336, **17**-0434, **18**-0248
Junttila, M.H., **15**-1709
Jurayj, J., **18**-0669, **18**-0708
Jurczak, J., **03**-0101, **04**-0135
Jurewicz, A.T., **10**-0203
Jurečka, P., **03**-0072
Jurgeleit, W., **19**-1424
Jurion, M., **16**-0251
Jurić, S., **10**-0142
Jurka, J., **10**-1208
Jurkauskas, V., **12**-0370, **15**-0476, **15**-0594
Jurlina, J.L., **12**-0161, **14**-0431, **15**-1631
Jursic, B.S., **02**-0145, **16**-1782
Juršić, B., **10**-0611, **10**-1115, **17**-0425, **19**-0275
Jurss, C.D., **13**-0157
Just, G., **11**-0619, **15**-0024, **16**-2159, **19**-0708
Just, T., **18**-0338
Justicia, J., **16**-0646
Jutand, A., **10**-1850, **12**-0277, **13**-0302, **13**-0462
Juteau, H., **15**-2337
Jutz, C., **11**-0465
Jutz, J.C., **18**-0471
Jutzi, P., **01**-0009
Jutzi, P., **03**-0083
Juve Jr., H.D., **14**-0253, **19**-0479
Jyothi, K., **15**-1669, **16**-0383
Jyothirmai, B., **10**-0862, **10**-0958

Kaandorp, A.W., **11**-0205
Kaba, R.A., **05**-0235
Kabachnik, M.I., **08**-0223, **12**-0088
Kabakoff, D.S., **05**-0050
Kabalka, G.W., **08**-0147, **10**-0736, **10**-0807, **10**-1497, **10**-1746, **10**-1754, **10**-1761, **11**-0298, **12**-0443, **12**-0444, **12**-0446, **12**-0485, **12**-0491, **12**-0492, **12**-0495, **12**-0496, **12**-0514, **12**-0517, **13**-0221, **13**-0386, **13**-0489, **13**-0495, **13**-0545, **13**-0567, **13**-0714, **14**-0309, **15**-0491, **15**-0563, **15**-0651, **15**-0689, **15**-0695, **15**-1123, **15**-1183, **15**-1184, **15**-1189, **15**-1192, **15**-1550, **15**-1552, **15**-1552, **15**-2040, **16**-0130, **16**-0330, **16**-0444, **16**-0457, **16**-0459, **16**-0556, **16**-0700, **16**-0700, **16**-1149, **16**-1711, **16**-1876, **16**-1911, **18**-0431, **19**-0334, **19**-0922, **19**-1000, **19**-1017, **19**-1254, **19**-1462, **19**-1500, **19**-1598
Kabasakalian, P., **18**-0872
Kabbara, J., **15**-0616, **15**-1058
Kabbe, H., **17**-0303
Kabengele, T., **15**-2282
Kaberia, F., **19**-0440
Kablaoui, N.M., **15**-0973, **15**-1424, **15**-1465
Kaboudin, B., **10**-0821, **10**-0904, **16**-1309, **19**-0146
Kabus, S.S., **05**-0052
Kabuto, C., **04**-0503, **04**-0518, **15**-2171
Kabuto, K., **04**-0107, **19**-0934
Kachala, M.S., **19**-1679
Kacprzak, K., **16**-1772
Kacprzynski, M., **05**-0391
Kacprzynski, M.A., **10**-1474
Kad, G.-L., **10**-0474
Kad, G.L., **10**-1070, **10**-1071, **10**-1624, **16**-0993, **19**-0096, **19**-0469, **19**-0925
Kadaba, P.K., **15**-1948, **16**-1670
Kader, A.T., **10**-0263
Kaderli, S., **14**-0200
Kadib-Elban, A., **15**-0041
Kadoh, Y., **15**-0779
Kadokawa, J.-i., **10**-0716
Kadoma, Y., **10**-0365, **10**-0372
Kadorkina, G.K., **04**-0036
Kadota, I., **15**-0350, **15**-0354
Kadota, I., **15**-2363
Kadow, J.F., **11**-0436
Kadowaki, S., **15**-0983, **15**-1445
Kadoya, R., **15**-2084
Kadri, M., **15**-1945
Kadyrov, R., **16**-0344, **19**-1158
Kadzyauskas, P.P., **15**-1615
Kaeding, W.W., **11**-0052, **14**-0268, **19**-0426
Kaeseberg, C., **15**-0861
Kafafi, S.A., **08**-0223, **19**-0010
Kaftory, M., **02**-0396, **02**-0397
Kagan, H., **04**-0001
Kagan, H.B., **04**-0102, **04**-0136, **04**-0146, **04**-0149, **04**-0190, **04**-0268, **14**-0159, **15**-0597, **15**-2064, **16**-1189, **16**-2002, **18**-0143, **19**-0822, **19**-0823, **19**-0967, **19**-1670
Kagan, J., **12**-0636, **18**-0126
Kagan, J.F., **04**-0155
Kagarise, R.E., **04**-0288
Kagawa, M., **10**-0885
Kagayama, A., **02**-0158, **16**-0820, **19**-1661, **19**-1668
Kagel, J.R., **15**-2090
Kagen, B.S., **11**-0310, **14**-0129
Kageyama, H., **16**-0754, **16**-1121
Kageyama, T., **19**-0732
Kagoshima, H., **16**-0409, **16**-0650, **16**-0824, **16**-0828, **16**-0873, **16**-1103
Kagramanov, N.D., **05**-0227
Kahle, G.G., **16**-1922
Kahlert, E., **12**-0590
Kahn, B.E., **19**-1710
Kahn, M., **15**-1688
Kahn, S.D., **15**-2044, **15**-2061, **15**-2238
Kahne, D., **12**-0335, **16**-1575
Kahr, B., **02**-0072, **04**-0504, **05**-0230
Kahr, K., **19**-0750
Kahraman, M., **15**-2434
Kai, A., **16**-0859
Kai, H., **15**-1460
Kai, Y., **02**-0064, **02**-0070

Kaida, T., **03**-0201
Kaida, Y., **04**-0175
Kaiho, T., **04**-0133
Kaim, W., **02**-0239
Kainz, S., **19**-1155
Kaiser, R., **02**-0181
Kaiser, A., **01**-0042
Kaiser, C., **04**-0353
Kaiser, E.M., **05**-0099, **10**-0482, **12**-0398, **12**-0683, **15**-0533, **15**-0549, **16**-1603, **19**-0840
Kaiser, E.T., **05**-0313, **14**-0417, **15**-0543, **16**-1533, **16**-1816, **16**-2142
Kaiser, K.L., **15**-2257
Kaiser, S., **15**-0425, **19**-1615
Kaiwar, V., **19**-1018
Kajfež, F., **10**-0891
Kaji, A., **06**-0081, **10**-0313, **10**-0785, **15**-2045, **17**-0069, **19**-1530, **19**-1532, **19**-1536, **19**-1779
Kaji, K., **10**-0811
Kaji, M., **15**-0611, **19**-1022
Kajigaeshi, S., **10**-0796, **11**-0244, **11**-0292, **12**-0120, **12**-0132, **12**-0144, **12**-0721, **12**-0722
Kajimoto, T., **19**-0414
Kajioka, T., **15**-0849
Kajiro, H., **15**-0589, **16**-1546
Kajita, S., **10**-1206
Kakehi, A., **15**-1324
Kakeiu, H., **15**-1741
Kakikawa, T., **19**-1154
Kakimoto, H., **15**-0159
Kakinami, T., **11**-0244, **11**-0292, **12**-0120, **12**-0132, **12**-0144, **12**-0722
Kakiuchi, F., **10**-1196, **11**-0414, **11**-0463, **13**-0532, **15**-0726, **15**-0755, **16**-1977, **16**-1978, **19**-1508
Kakiuchi, K., **02**-0062, **02**-0064, **15**-1448
Kakiuchi, N., **19**-0120, **19**-0223, **19**-0719
Kakiya, H., **10**-1396, **10**-1550, **16**-0647
Kakkar, R., **04**-0304
Kaku, H., **10**-1704, **16**-1274
Kakui, T., **10**-0688
Kakumoto, K., **15**-0998, **15**-1025, **15**-1304
Kakusawa, N., **16**-1914
Kakushou, F., **11**-0317
Kakuuchi, A., **15**-1164, **15**-1341
Kalafer, M., **19**-1436
Kalani, M.Y.S., **18**-0683
Kalani, Y.S., **18**-0605
Kalatzis, E., **14**-0027
Kalchschmid, F., **11**-0366
Kalck, P., **15**-1381, **15**-1477
Kaldor, S.W., **15**-1688
Kale, R.R., **16**-1701
Kalechits, I.V., **18**-0756
Kalendra, D.M., **13**-0044
Kalesse, M., **16**-1112
Kaleya, R., **19**-0065
Kalinin, A.V., **12**-0368
Kalinkin, M.I., **15**-0401, **15**-0471, **19**-1360
Kalinovskii, I.O., **13**-0534, **14**-0384
Kalinowski, H., **04**-0437, **10**-1721, **18**-0652
Kalinowski, M.K., **08**-0229
Kalir, A., **10**-1021
Kalir, R., **11**-0552
Kalita, B., **10**-0946, **10**-1004, **19**-0697
Kalivretenos, A.G., **15**-2138
Kalkote, U.R., **19**-1212
Kallel, E.A., **18**-0461, **18**-0483
Kallen, R.G., **16**-1446
Kallenberg, H., **10**-1620
Kallfass, D., **18**-0495
Kallio, R.E., **15**-1721, **15**-1722
Kallmerten, J., **18**-0735
Kallury, R.K.M.R., **01**-0011
Kalman, J.R., **14**-0330
Kalmus, C.E., **11**-0564, **04**-0362, **16**-0026
Kaloustian, S.A., **04**-0250
Kalsey, S., **15**-1161, **15**-2033
Kalt, W., **11**-0642
Kalthod, V.G., **16**-1803
Kalvinsh, I., **10**-0897
Kalvoda, J., **14**-0207, **18**-0085
Kalyanakumar, R., **17**-0386
Kalyanam, N., **19**-1693
Kalz, W., **15**-1254
Kamada, T., **17**-0435
Kamai, G., **04**-0044
Kamakura, T., **17**-0382
Kamal, A., **10**-0560, **10**-1109, **10**-1138, **16**-0084, **16**-0088, **16**-0089, **16**-0233, **16**-0337, **16**-1781, **16**-2110, **19**-1195, **19**-1266, **19**-1267, **19**-1268
Kamal, F., **19**-1181
Kamal, M., **18**-0213
Kamal, V.P., **15**-0993
Kamat, R.J., **10**-0114
Kamat, S.K., **10**-0569
Kamat, V.P., **10**-0676
Kamata, K., **10**-1741, **19**-0571
Kamata, M., **19**-0367
Kamata, S., **16**-1655
Kamata, T., **10**-0896
Kambara, H., **02**-0030, **04**-0317
Kambe, N., **10**-1196, **10**-1294, **10**-1303, **10**-1384, **10**-1853, **12**-0246, **14**-0013, **15**-0309, **15**-0872, **16**-0437
Kambe, S., **16**-0606
Kamble, R.M., **11**-0341, **16**-0549, **16**-0614
Kamble, V.T., **16**-1602, **16**-1616
Kameda, K., **16**-0600
Kameda, Y., **15**-0595
Kamego, A.A., **10**-0329, **19**-0714
Kamei, T., **10**-1200, **10**-1278
Kamenka, J., **15**-0678
Kamer, P.C.J., **13**-0177, **13**-0369, **15**-1483, **19**-1022
Kametani T., **15**-0785
Kametani, H., **04**-0079
Kametani, T., **10**-0377, **10**-0804, **15**-2122, **19**-0279
Kameyama, A., **10**-1171
Kameyama, H., **10**-0612, **10**-1230
Kameyama, M., **11**-0260
Kameyama, T., **13**-0324
Kamigata, N., **11**-0260, **13**-0738, **14**-0170
Kamikawa, K., **10**-1635
Kamikawa, T., **10**-1323
Kamikawaji, Y., **15**-0048
Kamimura, A., **10**-1479, **15**-1228, **15**-1324, **15**-2045, **16**-1590, **17**-0139, **19**-1530, **19**-1532, **19**-1543
Kamimura, J., **19**-1445
Kamino, T., **19**-1035
Kaminoyama, M., **12**-0087
Kamiñski, R., **16**-0432
Kamitani, A., **15**-1473
Kamitori, Y., **19**-0934
Kamiura, K., **19**-1001
Kamiya, I., **15**-1402, **19**-1003
Kamiya, M., **19**-1093
Kamiya, N., **15**-0174
Kamiya, Y., **16**-0518
Kamiyama, M., **16**-1127
Kamińsa-Trela, K.K., **11**-0281
Kamkha, M.A., **10**-1314
Kamlet, J., **16**-1150
Kamlet, M.J., **03**-0015, **03**-0016, **10**-0429, **10**-0432, **10**-0443, **10**-0448
Kammann Jr., K.P., **16**-1937
Kammoun, M., **15**-1780
Kamo, O., **03**-0193
Kamochi, Y., **15**-0555, **15**-0556, **19**-1079, **19**-1080, **19**-1081
Kampar, E., **03**-0098
Kampar, V.E., **03**-0093

Kämper, F., **14**-0156
Kamphuis, J., **16**-0209, **19**-1484
Kampmeier, J.A., **14**-0448, **14**-0455, **14**-0458, **14**-0459, **17**-0139
Kamshii, L.P., **11**-0013
Kamyshova, A.A., **10**-1233
Kan, R.O., **11**-0510, **19**-1687
Kan, S., **11**-0414
Kan, Y., **13**-0276
Kan-Fan, C., **16**-0402
Kan-no, T., **13**-0481
Kanagasabapathy, S., **15**-0299, **16**-1674
Kanagasabapathy, V.M., **10**-0040, **10**-0083, **10**-0294, **16**-0157
Kanai, F., **15**-2064
Kanai, K., **16**-0827
Kanai, M., **15**-1095, **15**-1568, **15**-1874, **16**-0687, **16**-0698, **16**-1426, **16**-1438, **16**-1439
Kanamathareddy, S., **03**-0127
Kanamori, M., **15**-1559, **15**-1576
Kanamori, Y., **15**-0354
Kanatani, R., **10**-0688
Kanavarioti, A., **15**-0198
Kanaya, H., **10**-1863
Kanayama, T., **10**-1452
Kanazaki, S., **10**-1548
Kanazawa, S., **16**-1384
Kanbara, T., **03**-0129
Kanber, O., **12**-0501
Kanda, K., **16**-0687
Kanda, T., **15**-0523, **15**-0748
Kanda, Y., **10**-0788
Kandall, L.C., **10**-0715
Kandasamy, D., **04**-0362, **19**-0934, **19**-1295 **19**-1331
Kandetzki, P.E., **13**-0677
Kandpal, B.M., **19**-0228
Kane, V.V., **12**-0254
Kaneda, K., **15**-0528, **15**-1745, **15**-1791, **15**-1792, **16**-0149, **19**-0109, **19**-0120, **19**-0129
Kaneda, T., **02**-0062
Kaneko, C., **13**-0380, **15**-1427
Kaneko, H., **05**-0111
Kaneko, T., **15**-1407, **15**-1468, **15**-1469, **16**-0694
Kaneko, Y., **16**-0635, **16**-1051, **16**-1119
Kanellias, L., **10**-0208
Kanelo, K., **16**-0232
Kanemasa, S., **10**-1595, **15**-1932, **15**-1939, **15**-1956
Kanematsu, K., **15**-0048, **18**-0613
Kanematsu, T., **19**-1144
Kanemoto, K., **16**-1380
Kanemoto, S., **10**-1263
Kanerva, L.T., **16**-1557
Kanetaka, S., **16**-1070
Kanetani, F., **10**-1126
Kaneti, J., **09**-0023
Kang, B., **18**-0788, **18**-0789
Kang, C.H., **05**-0314, **14**-0026
Kang, H., **13**-0150
Kang, H.-Y., **14**-0011, **16**-0960, **19**-1512
Kang, H.J., **19**-0934
Kang, H.K., **10**-0072, **16**-2143
Kang, J., **10**-1453, **15**-0550, **15**-0861, **15**-2025
Kang, J.-L., **03**-0210
Kang, K.H., **19**-1222
Kang, L., **16**-1915
Kang, S., **17**-0166
Kang, S.-H., **10**-1194
Kang, S.-K., **10**-1197, **10**-1408, **10**-1624, **10**-1772, **10**-1778, **13**-0190, **13**-0191, **13**-0234, **13**-0295, **13**-0329, **13**-0330, **13**-0331, **13**-0340, **13**-0515, **13**-0517, **13**-0561, **13**-0568, **13**-0623, **14**-0388, **15**-0236, **15**-0833, **15**-1472, **16**-0725, **16**-0734, **16**-0752
Kang, S.-W., **16**-0687
Kang, S.B., **16**-0634, **17**-0166, **19**-1326, **19**-1655
Kang, S.H., **15**-0235, **15**-0262
Kang, S.I., **03**-0107
Kang, S.K., **10**-1166, **16**-0359
Kang, T., **16**-2093
Kang, Y., **12**-0288, **19**-0312, **19**-1188
Kang, Y.-F., **16**-0549
Kang, Y.-J., **16**-1866
Kanger, T., **19**-0476
Kanishchev, M.I., **18**-0002
Kankaanperä, A., **10**-0534, **10**-0574, **10**-0598, **10**-0658, **10**-0749, **10**-1061, **16**-1658
Kannan, M.A., **19**-1631
Kannan, V., **16**-0781, **16**-0795
Kanner, B., **08**-0190
Kanno, H., **16**-0264, **16**-0365, **19**-0685
Kanno, K.-i., **13**-0359
Kano, D., **15**-0390, **15**-1896
Kano, N., **16**-1346
Kano, S., **15**-1247, **19**-1283
Kano, T., **11**-0215
Kano, T., **11**-0412, **11**-0413
Kanofsky, J.R., **19**-0609
Kanoh, S., **04**-0177
Kantam, M.L., **10**-0752, **10**-0943, **11**-0214, **15**-1001, **15**-1669, **15**-1906, **16**-0383, **19**-0219, **19**-0781, **19**-1316
Kanter, J.P., **08**-0044, **17**-0053
Kanters, J.A., **03**-0025, **03**-0048
Kanth, J.V.B., **12**-0453, **13**-0168, **19**-1488
Kanth, S.R., **19**-1193
Kantlehner, W., **11**-0468
Kantner, S.S., **04**-0147, **10**-0217, **10**-1429, **10**-1430
Kantor, E.A., **05**-0053, **10**-0528
Kantor, S.W., **13**-0765, **18**-0412, **19**-0836
Kanyonyo, M.R., **19**-1791
Kao, J., **04**-0233, **15**-0239
Kapadia, S.R., **16**-0462
Kapdi, A.R., **13**-0480
Kapecki, J.A., **15**-2210, **15**-2217
Kaplan, E.D., **06**-0074
Kaplan, E.P., **16**-1943
Kaplan, F., **12**-0569, **18**-0228
Kaplan, J., **10**-0095
Kaplan, L., **04**-0164, **04**-0440, **05**-0202, **05**-0272, **10**-1096, **10**-1238, **14**-0041, **16**-0009, **16**-0184, **18**-0494
Kaplan, L.A., **19**-1211
Kaplan, M.L., **03**-0009, **10**-0422, **14**-0232, **18**-0549
Kapnang, H., **10**-1524
Kapon, M., **16**-0968
Kapoor, K.K., **15**-1791, **15**-1800
Kapoor, R., **10**-0626
Kapp, D.L., **15**-2162
Kappe, C.O., **07**-0103, **07**-0104, **07**-0106, **07**-0118, **07**-0119, **07**-0121, **10**-0703, **13**-0241, **13**-0326, **15**-2022, **18**-0773
Kappos, J.C., **15**-1679, **17**-0324
Kapps, M., **12**-0352, **18**-0727
Kaprinidis, N.A., **15**-2238
Kaptein, B., **15**-0913, **16**-0864, **19**-1484
Kaptein, R., **05**-0219, **14**-0327
Kapur, J.C., **16**-1893
Kapur, N., **15**-1929
Kapxhiu, E.A., **17**-0234
Kar, A., **15**-0161
Kara-Murza, C.G., **15**-1652
Karabatsos, G.J., **04**-0295, **06**-0076, **11**-0648, **18**-0021, **18**-0023, **18**-0025, **18**-0026, **18**-0045, **18**-0048
Karabelas, K., **13**-0361
Karadakov, P.B., **15**-1953, **15**-1954
Karade, N.N., **11**-0211
Karaev, S.F., **15**-0261
Karafiat, U., **16**-0329

Karakhanov, E.A., **14**-0198, **15**-0521
Karam, P.A., **10**-0203
Karaman, R., **10**-0432, **16**-2160, **19**-1742
Karamé, I., **18**-0145
Karami, B., **19**-0034
Karapinka, G.L., **15**-1494
Karasu, M., **10**-0716
Karatekin, E., **05**-0208
Karchaudhuri, N., **16**-0097, **16**-1174, **16**-1192
Kardile, G.B., **19**-0979
Kardon, F., **16**-0291
Kardos, N., **07**-0100
Karelson, M., **02**-0092, **02**-0112, **02**-0114, **02**-0117, **02**-0406, **02**-0415, **10**-0215, **12**-0083
Karen, W., **07**-0105
Karge, R., **15**-2058
Karger, B.L., **04**-0169, **04**-0171
Karger, M.H., **10**-0733, **10**-0761, **16**-1722
Karikomi, M., **10**-0676
Karim, A., **13**-0218
Karimi, A.-R., **19**-0149
Karimi, B., **10**-0568, **16**-0160, **116**-0166, **16**-0175, **16**-0234, **16**-0255, **16**-1439, **16**-1623, **17**-0156, **19**-0148, **19**-0151, **19**-0865, **19**-1608
Karimi, M.H., **16**-1646
Karimi, S., **15**-0634
Karimipour, M., **13**-0463
Kariv, E., **19**-1436
Karjalainen, J.K., **15**-1694, **15**-1823
Karkowski, F.M., **01**-0087
Karl, R., **14**-0292
Karliga, B., **16**-1609
Karlin, K.D., **14**-0200
Karlsson, S., **15**-1931
Karlström, A.S.E., **10**-1300, **10**-1437
Karmanova, I.B., **11**-0404
Karnes, J., **16**-1021
Karney, W.L., **02**-0339, **05**-0398
Karni, M., **15**-1790
Karo, W., **10**-0751
Karodia, N., **15**-2041, **17**-0265
Karoui, H., **05**-0214
Karpaty, M., **16**-1469
Karpeles, R., **19**-1598
Karpitskaya, L.G., **19**-0741
Karplus, M., **15**-2105
Karpov, A.S., **16**-1916
Karpyuk, A.D., **05**-0129, **05**-0130
Karrick, G.L., **15**-0538
Karstens, W.F.J., **15**-0395
Kartashov, A.V., **10**-0759, **14**-0135, **15**-1544
Kartashov, V.R., **15**-0280
Karthikeyan, G., **19**-0209
Karty, J.M., **05**-0033, **08**-0112
Karur, S., **15**-0354, **16**-0768
Kasahara, A., **10**-1822, **13**-0362, **15**-0400
Kasai, J., **19**-0571
Kasai, K., **15**-0958, **18**-0803
Kasai, N., **02**-0064, **02**-0070
Kasai, P.H., **01**-0081
Kasai, Y., **17**-0026
Kasaura, T., **16**-1307
Kascheres, C., **18**-0046
Kasei, A., **15**-1275
Kasei, N., **03**-0168
Kaselj, M., **19**-1019
Kashdan, D.S., **16**-2040
Kashefi-Naini, N., **16**-1571
Kashima, C., **16**-1940
Kashimura, K., **10**-0060, **10**-0074
Kashimura, S., **16**-0645, **16**-1491
Kashimura, T., **13**-0613
Kashin, A.N., **12**-0034, **12**-0037, **13**-0577, **14**-0376, **16**-0675
Kashinatham, A., **15**-0565
Kashino, S., **10**-1548, **13**-0782
Kashiwagi, H., **10**-0657
Kashiwagi, M., **15**-1184
Kashiwagi, R., **10**-1464
Kashiwagi, T., **14**-0438
Kashiwagi, Y., **19**-0689
Kashmiri, M.A., **10**-1607, **10**-1608
Kaska, W.C., **10**-1312, **15**-0501
Kaska, W.C., **15**-0712
Kasmai, H.S., **02**-0253
Kasner, M.L., **19**-0714
Kaspar, J., **19**-0960
Kasperczyk, J., **15**-0150
Kasperek, G.J., **16**-2150
Kaspr, L.T., **15**-0331
Kass, S.R., **05**-0135, **05**-0172, **08**-0134, **10**-0491, **15**-0131, **15**-0141, **19**-0531
Kassab, D.J., **10**-0624
Kasshinath, D., **13**-0474
Kassianidis, E., **15**-2020
Kasture, S.P., **11**-0221, **16**-1616
Kasturi, T.R., **19**-1467, **19**-1469
Kasu, P.V.N., **12**-0130
Kasuga, Y., **19**-1176
Kasukhin, L.F., **10**-1317, **10**-1318, **19**-1273
Kaszynski, P., **04**-0497, **04**-0498
Katagiri, N., **10**-1426
Katagiri, T., **16**-0531, **16**-0533
Katampe, I., **15**-0293
Katamura, M., **04**-0193
Kataoka, F., **19**-1725
Kataoka, M., **10**-0581, **19**-1022
Kataoka, N., **13**-0482
Kataoka, O., **16**-0069, **18**-0823
Kataoka, T., **17**-0519
Kataoka, Y., **16**-0683, **16**-1365, **19**-1051
Katayama, A., **14**-0364
Katayama, E., **15**-1457
Katayama, K., **12**-0068
Katayama, R., **19**-0635
Katayama, S., **19**-0650
Kate, S.S., **11**-0211
Kates, M.R., **10**-0181
Kather, K., **16**-2083
Kato, A., **02**-0390, **02**-0408, **18**-0732
Kato, H., **02**-0295, **02**-0341, **12**-0547, **15**-1506, **19**-1274
Kato, J., **16**-0161
Kato, K., **10**-0984, **15**-0185, **15**-0197, **17**-0490, **18**-0692
Kato, M., **01**-0069, **07**-0058, **10**-1512
Kato, N., **13**-0781, **15**-2069, **19**-1338
Kato, S., **10**-1280, **10**-1561, **15**-0748, **15**-1063, **16**-0226, **16**-1135, **16**-1245
Kato, T., **02**-0296, **02**-0303, **02**-0304, **02**-0306, **05**-0009, **12**-0319, **13**-0574, **15**-1586, **15**-1660
Kato, Y., **11**-0267, **15**-0914
Katoh, A., **19**-0732
Katoh, M., **19**-1670
Katoh, S., **04**-0177, **14**-0284
Katoh, Y., **15**-1061
Katohgi, M., **19**-1629
Katona, B.W., **12**-0470, **13**-0564
Katritzky, A.R., **01**-0087, **02**-0092, **02**-0095, **02**-0097, **02**-0112, **02**-0114, **02**-0117, **02**-0406, **02**-0415, **04**-0354, **08**-0024, **08**-0118, **08**-0123, **09**-0039, **10**-0001, **10**-0079, **10**-0081, **10**-0084, **10**-0215, **10**-0386, **10**-0387, **10**-0725, **10**-0768, **10**-0850, **10**-0897, **10**-1184, **10**-1199, **10**-1607, **10**-1608, **10**-1675, **10**-1675, **11**-0001, **11**-0065, **11**-0066, **11**-0068, **11**-0069, **12**-0083, **12**-0404, **13**-0072, **13**-0680, **15**-2122, **15**-2139, **16**-0277, **16**-0288, **16**-0407, **16**-0433,

Katritzky, A.R., (*Continued*) **16**-0847, **16**-1993, **17**-0257, **17**-0506, **19**-0777, **19**-1523, **19**-1544, appendixA-0038
Katsigras, G., **15**-1534
Katsoulos, G., **12**-0391
Katsuda, K., **11**-0331
Katsuki, T., **04**-0193, **10**-1464, **12**-0069, **12**-0226, **15**-1827, **15**-1829, **15**-1831, **15**-1836, **15**-1888, **15**-1909, **15**-1961, **15**-2297, **15**-2298, **15**-2300, **15**-2304, **15**-2337, **16**-1655, **18**-0363, **19**-0221, **19**-0512, **19**-0520, **19**-0521, **19**-0522, **19**-0535, **19**-0590, **19**-0823
Katsumura, N., **16**-0678
Katsumura, S., **18**-0465
Katsuro, Y., **10**-1533
Kattenberg, J., **12**-0189
Katz, A.H., **13**-0263, **13**-0283, **13**-0660, **19**-1798
Katz, C.E., **18**-0297
Katz, J., **10**-1751, **18**-0426, **18**-0448, **18**-0450
Katz, R.B., **14**-0340
Katz, S., **02**-0053
Katz, T.J., **02**-0184, **02**-0254, **02**-0255, **07**-0040, **15**-2098, **18**-0514, **18**-0756, **18**-0778, **18**-0836
Katzenellenbogen, J.A., **10**-1288, **15**-0282, **16**-1193
Katzenelson, O., **04**-0080
Katzin, M.I., **19**-0435
Katzka, C., **18**-0717
Kauer, J.C., **10**-0617
Kauffmann, T., **12**-0564, **12**-0625, **13**-0049, **13**-0682, **14**-0371, **14**-0377, **15**-1976, **15**-1977, **16**-0563, **16**-0565
Kaufman, D.H., **17**-0437
Kaufman, G., **17**-0269
Kaufman, M.J., **05**-0150
Kaufmann, D., **15**-2064, **18**-0630
Kaupp, G., **01**-0065, **07**-0053, **07**-0054, **10**-0452, **12**-0717, **15**-2112, **18**-0097
Kaur, D., **15**-0620
Kaur, G., **15**-0792, **16**-0324
Kaur, H., **10**-0848, **13**-0503
Kaur, I., **19**-0925
Kaur, J., **10**-1071, **11**-0418, **19**-0096, **19**-0925
Kaur, K.P., **10**-1070, **16**-0993
Kaur, P., **16**-0590
Kaushik, M.P., **10**-0835, **16**-0216
Kauss, V., **10**-0897
Kaval, N., **07**-0118, **07**-0119, **15**-2022
Kavarno, G.J., **07**-0029
Kavita, B., **15**-1001, **15**-1906
Kawa, H., **04**-0169
Kawa, S., **16**-1346
Kawaa, K., **13**-0439
Kawabata, A., **16**-1681
Kawabata, H., **13**-0040, **19**-0019
Kawabata, N., **15**-2327, **15**-2341, **16**-0562
Kawabata, T., **10**-1463, **16**-0149
Kawada, A., **11**-0423, **11**-0425
Kawada, K., **12**-0159
Kawada, M., **10**-0170
Kawafuchi, H., **15**-1276
Kawafuji, Y., **16**-0538
Kawaguchi, K., **05**-0275, **16**-1435
Kawaguchi, M., **16**-1764
Kawaguchi, Y., **03**-0186
Kawahama, R., **19**-1307
Kawahara, F., **15**-1324
Kawahara, Y., **03**-0123
Kawahito, A., **10**-1704
Kawai, K., **16**-1840
Kawai, M., **16**-0600
Kawai, T., **10**-0464, **13**-0082, **15**-0624, **15**-0625, **15**-0627, **19**-1021
Kawakami, J.-i., **15**-1402
Kawakami, J.H., **15**-0115, **15**-0116, **18**-0105, **19**-0897
Kawakami, T., **15**-1665, **16**-0931, **18**-0332
Kawakami, Y., **11**-0329, **12**-0284, **15**-0210
Kawaki, T., **13**-0121
Kawakita, T., **16**-0686
Kawamatsu, H., **13**-0630
Kawamura, M., **11**-0418, **11**-0442, **15**-1326, **16**-0790
Kawamura, N., **15**-0598
Kawamura, S., **15**-1594, **19**-1784
Kawamura, T., **10**-1206, **19**-0120
Kawamura, Y., **07**-0056, **10**-0704, **15**-0742, **15**-1691, **16**-0687, **19**-1032
Kawanishi, M., **13**-0101
Kawanishi, T., **16**-0892
Kawanishi, Y., **19**-0109, **19**-0129
Kawanisi, M., **17**-0175
Kawano, H., **15**-0598
Kawano, M., **15**-0160
Kawano, N., **19**-1781
Kawano, T., **16**-1545
Kawaragi, S., **11**-0342
Kawasaki, A., **11**-0485, **16**-1445
Kawasaki, H., **15**-1092, **16**-1032
Kawasaki, I., **19**-1670
Kawasaki, K., **12**-0226, **19**-0521
Kawasaki, M., **16**-0822
Kawasaki, N., **10**-1871
Kawasaki, S., **15**-2372
Kawasaki, T., **10**-0850, **15**-2388, **15**-2401
Kawasaki, Y., **16**-1444
Kawase, M., **19**-1150
Kawase, T., **01**-0011, **15**-2322, **18**-0469, **18**-0470
Kawashima, J., **13**-0449, **13**-0519
Kawashima, T., **03**-0135, **16**-1346
Kawasoe, S., **10**-1328
Kawasuji, T., **16**-1119
Kawata, I., **11**-0493
Kawate, T., **10**-1789, **16**-2045, **19**-1154
Kawathar, S.P., **15**-2378
Kawatsura, M., **10**-1460, **13**-0583, **15**-0327, **15**-0333
Kawauchi, T., **11**-0493
Kawazoe, Y., **10**-0350
Kay,K.-Y., **16**-1787
Kayagishi, S., **12**-0319
Kayaki, Y., **13**-0348, **13**-0407, **16**-1653
Kayaleh, N.E., **16**-1621
Kayama, M., **15**-1925
Kayano, A., **14**-0071, **15**-0056
Kaye, P.T., **16**-0805
Kaye, R.L., **15**-2096
Kayser, F., **10**-1333
Kayser, M.M., **16**-1340, **18**-0362, **18**-0362, **19**-1063, **19**-1476, **19**-1479
Kazahaaya, K., **16**-0237
Kazan, J., **10**-0748
Kazankov, M.V., **13**-0154
Kazankova, M.A., **12**-0524, **15**-0372, **15**-0373, **15**-0382
Kazanskii, B.A., **15**-2281
Kazantsev, A.V., **15**-0759
Kazemi, F., **10**-0809, **10**-0936, **10**-0941, **16**-1396, **19**-0246, **19**-0973
Kazimirchik, I.V., **04**-0372
Kazitsyna, L.A., **09**-0034
Kazlauskas, R.J., **04**-0196
Kazmaieer, U., **10**-1467
Kazmaier, P.M., **12**-0232, **19**-1788
Kazmaier, U., **18**-0701
Kazubski, A., **19**-1018

Kdota, I., **19**-1337
Keaffaber, J.J., **18**-0482
Kean, N.B., **12**-0645
Keana, J.F.W., **05**-0254
Kearley Jr., F.J., **13**-0043
Kearney, P.A., **06**-0064
Kearns, D.R., **14**-0228, **14**-0241, **15**-2156, **15**-2160
Keating, J.T., **10**-0393, **10**-0394
Keaveney, W.P., **19**-0349
Keay, B.A., **04**-0161, **08**-0144
Keay, J.G., **15**-0551
Kebarle, P., **03**-0052, **08**-0222, **08**-0223, **08**-0224, **08**-0225, **08**-0226, **08**-0227, **08**-0232, **10**-0178, **10**-0184, **10**-0271, **10**-0416
Keck, G.E., **10**-1262, **16**-0492, **16**-0640, **16**-0743, **16**-0794, **16**-0871, **16**-1662, **16**-1665, **19**-0983, **19**-0987
Keck, R., **10**-1179
Kee, K., **13**-0620
Kee, M., **19**-0800
Keefer, L.K., **19**-0010, **19**-1232
Keefer, R.M., **11**-0271
Keeffe, J.R., **02**-0384, **02**-0385, **02**-0386, **02**-0391, **06**-0037, **12**-0095, **12**-0097, **15**-0025, **17**-0044
Keegstra, K., **10**-0392
Keegstra, M.A., **13**-0064
Keehn, P.M., **02**-0061, **11**-0243, **19**-0674
Kees, F., **12**-0476
Kees, K.L., **19**-1709, **19**-1719, **19**-1725, **19**-1727
Keese, R., **04**-0491
Keese, R., **04**-0515
Kefalas, P., **16**-0982
Kegelaers, Y., **07**-0080
Keglevich, G., **15**-1001
Keh, C.C.K., **16**-0603
Keii, T., **15**-0794
Keijsper, J.J., **15**-1381
Keiko, V.V., **04**-0295
Keil, R., **15**-0708
Keillor, J.W., **18**-0269, **18**-0275
Keim, W., **09**-0109
Keinan, E., **10**-0907, **10**-1441, **15**-0572, **15**-0590, **16**-0110, **16**-1875, **19**-0454, **19**-0765, **19**-0920
Keirs, D., **19**-0283
Keith, A.J., **15**-0360
Keith, J.M., **12**-0751
Keith, T.A., **04**-0302
Keitoku, T., **19**-0095
Kel'in, A., **15**-0356
Kel'in, A.V., **10**-1670, **15**-0244
Kelkar, A.A., **13**-0203
Kelkar, S.V., **16**-0243
Kelleman, A., **19**-1626
Keller, C.E., **02**-0348
Keller, E., **15**-1019
Keller, M., **04**-0447
Keller, T.H., **04**-0390
Kelley, S., **16**-1911
Kellie, G.M., **04**-0319
Kellogg, M.S., **18**-0485
Kellogg, R.E., **07**-0028
Kellogg, R.M., **04**-0205, **04**-0478, **10**-0695, **10**-0709, **10**-1304, **14**-0242, **16**-0864, **17**-0002
Kellom, D.B., **17**-0127
Kelly III, R.A., **13**-0509
Kelly, B.G., **16**-0488
Kelly, B.J., **15**-1892
Kelly, C.A., **16**-0290
Kelly, C.F., **17**-0092
Kelly, D.P., **05**-0091, **10**-0182, **11**-0014, **18**-0727, **18**-0748
Kelly, D.R., **18**-0369
Kelly, E.G., **12**-0535
Kelly, F.W., **12**-0643, **17**-0122, **18**-0594, **18**-0654
Kelly, J.F., **16**-2113, **16**-2115
Kelly, J.W., **10**-0653, **10**-0900
Kelly, R.C., **15**-1660
Kelly, R.P., **11**-0168
Kelly, R.V., **12**-0379
Kelly, W.J., **10**-0159, **10**-0177, **10**-1480, **12**-0212, **12**-0338
Kelly, W.L., **10**-1622, **10**-0250
Kelsey, D.R., **10**-0255, **13**-0462
Kelso, M., **15**-1310
Kelso, P.A., **07**-0048
Kemernitskii, A.V., **15**-2238
Kemmer, R., **10**-0379
Kemnitz, C.R., **05**-0398
Kemp, M.I., **15**-0778, **15**-1475
Kemp, N.R., **01**-0016
Kemp, R.H., **04**-0283
Kemp, T., **05**-0068, **13**-0026, **13**-0027
Kemp-Jones, A.V., **02**-0248
Kempe, U.M., **15**-1927
Kempf, B., **10**-0009, **10**-0355, **10**-1673, **15**-0002
Kendall, J.T., **15**-1733
Kendall, P.E., **15**-1172
Kende, A.S., **19**-0814, **19**-1224
Kendrick Jr., L.W., **18**-0179
Kendrick, R.D., **05**-0077
Kenkre, S.L., **12**-0422, **16**-0977
Kennard, O., **01**-0052, **01**-0070, **02**-0031, **03**-0023, **03**-0025, **03**-0029, **03**-0045
Kennedy, A.R., **15**-1268
Kennedy, E.M., **11**-0118
Kennedy, G.J., **05**-0332
Kennedy, J.P., **10**-1376
Kennedy, J.W.J., **02**-0067, **02**-0068
Kennedy, K., **19**-0708
Kennedy, R.M., **15**-0231, **15**-1047
Kennedy, S.R., **18**-0611
Kennedy-Smith, J.J., **15**-0978, **18**-0688
Kennerly, R.E., **15**-0058
Kennewell, P.D., **16**-1405, **16**-1406
Kenny, C., **19**-1680
Kenny, D.H., **10**-0725
Kenny, J.A., **19**-1042
Kent, A.G., **15**-1478
Kent, B.A., **13**-0777
Kent, J.L., **15**-1450
Kenworthy, M.N., **13**-0289
Kenyon, J., **10**-0007, **18**-0010
Keogh, B.P., **15**-1069
Keogh, J., **15**-1627, **15**-1629, **19**-1295, **19**-1396
Kepler, K.D., **15**-0167
Keppens, M., **19**-0041
Keramane, E.-M., **10**-0646
Kerber, R.C., **10**-0089, **10**-0285, **10**-1602
Kercher, T., **16**-1420
Kerdesky, F.A.J., **16**-1018
Kerek, F., **16**-2071
Kerekes, A.D., **15**-1445
Kerekes, I., **10**-1079, **10**-1086, **10**-1178, **15**-0168, **15**-1545, **16**-0450, **16**-1880, **16**-1883
Kereselidze, R.V., **14**-0012
Keresztes, I., **16**-0977
Kergomard, A., **10**-0733, **15**-1578
Kerins, F., **13**-0446
Kerlinger, H.O., **14**-0268
Kernag, C.A., **19**-0196
Kerr, J.A., **01**-0089, **05**-0265, **14**-0062, **14**-0166, **16**-0009
Kerr, M.A., **12**-0364, **13**-0004, **16**-0305
Kerr, M.S., **15**-1368, **15**-1370, **16**-0723, **16**-0724, **16**-0726
Kerr, W.J., **15**-1429, **15**-1434, **15**-1475, **15**-1928, **16**-1107, **19**-0126
Kerrigan, N.J., **15**-1835
Kershner, L., **16**-1594
Kershner, L.D., **16**-0020
Kervennal, J., **12**-0742
Kerwin, S.M., **18**-0492
Kesanli, B., **19**-0959

Kesavan, V., **10**-0672, **10**-0929, **19**-0863
Kessar, S.V., **13**-0574
Kesseler, K., **16**-1033
Kesselgruber, M., **16**-0687
Kesselmayer, M.A., **15**-2078
Kessick, M.A., **10**-0430, **15**-0024
Kessler, H., **04**-0264, **04**-0271, **10**-0056, **15**-2292, **15**-2323, **18**-0234, **18**-0628
Kesten, S., **16**-2056
Kester, F.L., **01**-0092
Kester, J., **02**-0234
Kestner, M.M., **10**-0285, **10**-1480
Ketcham, R., **15**-2231
Ketley, A.D., **10**-0622, **16**-1731, **18**-0572
Kettle, S.F.A., **01**-0001
Keul, H., **19**-0352, **19**-0377
Keum, G., **16**-0634, **17**-0166, **19**-1326, **19**-1655
Keum, S., **18**-0887
Keum, S.R., **19**-1600
Keumi, T., **11**-0101, **11**-0434, **11**-0607, **16**-0321
Keung, E.C., **15**-0961
Keuper, R., **04**-0215
Keusenkothen, P.F., **10**-0472, **10**-0974, **15**-1255
Kevan, L., **15**-0543, **05**-0208
Kevan, L., **05**-0313
Kevill, D.N., **10**-0060, **10**-0077, **10**-0154, **10**-0196, **10**-0282, **10**-0350, **10**-0423, **10**-0425, **10**-0431, **10**-0432, **10**-0436, **10**-0439, **16**-0015, **16**-0020, **16**-1601
Keyerleber, M.A., **15**-0818
Keyes, M., **19**-1341
Keypour, H., **12**-0705
Keyton, D.J., **19**-1321
Keyvan, A., **16**-2054
Kézdy, F.J., **16**-1533
Kezuka, S., **15**-2130, **16**-0731
Khac, T.B., **16**-0403
Khachatrian, A.G., **19**-0255
Khadilkar, B., **19**-0112
Khadilkar, B.M., **10**-0861, **11**-0129, **11**-0432, **11**-0553, **13**-0104, **16**-0076, **16**-0128, **16**-0134, **18**-0716, **19**-0559
Khaimova, T.G., **16**-1462
Khairudinov, I.R., **16**-1470
Khakshoor, O., **19**-1147
Khalaf, A.A., **11**-0316, **11**-0362
Khalafi-Nezhad, A., **10**-1127, **16**-1789
Khaledy, M.M., **18**-0683
Khalfina, I.L., **19**-0741
Khalil, M.M., **15**-1735
Khamsi, J., **13**-0224
Khan, A.A., **16**-0388
Khan, A.M., **19**-1368
Khan, A.T., **10**-0561, **10**-0566, **16**-0255, **16**-0625
Khan, F., **19**-0143
Khan, F.A., **11**-0120, **16**-0007, **16**-0589
Khan, F.N., **15**-0898
Khan, I.U., **03**-0129
Khan, K.M., **10**-0786, **10**-0860, **10**-1081, **18**-0680
Khan, M.I., **05**-0374
Khan, M.A., **10**-1168, **12**-0316, **15**-0254
Khan, M.I., **15**-2324
Khan, M.M.T., **12**-0074 **15**-0206, **15**-0792, **15**-1477, **15**-2362, **15**-2429, **19**-0718
Khan, M.N., **10**-0986, **16**-0512, **16**-1591
Khan, N.A., **19**-0740
Khan, N.H., **15**-1830
Khan, S.A., **19**-0833
Khan, S.I., **15**-1213
Khan, T.A., **11**-0363, **17**-0434, **19**-0206
Khan, W.A., **10**-1716
Khananashvili, L.M., **15**-0705
Khanapure, S.P., **13**-0080, **13**-0574
Khanbabaee, K., **19**-0267
Khand, I.U., **15**-1417
Khandekar, A.C., **11**-0303
Khanna, I.K., **10**-1187
Khanna, P.L., **19**-0065
Khanna, R.K., **13**-0691, **14**-0357
Khanolkar, A.D., **15**-0878, **15**-0884
Kharasch, M.S., **10**-1227, **10**-1231, **10**-1321, **10**-1526, **10**-1536, **12**-0558, **12**-0574, **14**-0113, **14**-0262, **14**-0290, **14**-0291, **15**-0062, **15**-0285, **16**-0464, **16**-0842, **16**-0851, **16**-0951, **16**-1921, **16**-1931, **16**-1934, **17**-0523
Kharasch, N., **14**-0333, **14**-0335, **14**-0408, **15**-0297, **17**-0220, **17**-0516, **19**-0790, **19**-0868, **19**-1592
Khare, A., **19**-0112
Kharrat, A., **19**-1533
Khatri, H.N., **18**-0687
Khatri, J., **07**-0118
Khatri, N.A., **16**-0343
Khattak, J., **10**-0083, **10**-0279
Khau, V.V., **16**-2161
Khawaled, K., **10**-0699
Khazaei, A., **16**-0055, **19**-0860
Khazdooz, L., **11**-0201
Khedhair, K.A., **04**-0366
Khedkar, V., **15**-0314, **15**-0351
Kheifets, G.M., **02**-0379
Kheifets, V.I., **16**-1470
Khelevin, R.N., **11**-0197
Khenkin, A.M., **19**-0172
Khiar, N., **04**-0049
Khidekel', M.L., **18**-0500, **18**-0756, **15**-2199, **16**-0345
Khire, U.R., **15**-0672
Khlebnikov, A.F., **15**-2267
Khmel'nitskaya, E.A., **10**-1496
Khmel'nitskii, L.I., **13**-0687
Khodaei, M.M., **16**-1739, **16**-2054, **18**-0314, **19**-0084
Khodakov, Yu.S., **15**-0405
Khodykin, S.V., **12**-0143
Khoee, E., **16**-0060, **16**-0046, **16**-0063, **19**-0083
Khokhlov, P.S., **15**-1652
Kholodov, L.E., **02**-0341
Khong, A., **02**-0365
Khor, T., **09**-0060
Khorana, H.G., **16**-1659, **16**-1716
Khorlina, I.M., **19**-1115, **19**-1124, **19**-1391
Khosropour, A.R., **16**-1671
Khosrowshahi, J.S., **15**-1882
Khotinsky, E., **12**-0449
Khouri, F.F., **16**-0026
Khriachtchev, L., **04**-0297
Khristov, V.Kh., **15**-0060
Khrizolitova, M.A., **14**-0418
Khuddus, M.A., **19**-0648
Khudyakov, I.V., **05**-0304, **05**-0312, **14**-0023
Khundhar, M.H., **12**-0465, **12**-0467, **12**-0468
Khuong, K.S., **18**-0683
Khurana, A., **10**-1624
Khurana, J.M., **17**-0368, **19**-0228, **19**-0813, **19**-0839, **19**-0924, **19**-1169, **19**-1288, **19**-1339, **19**-1607
Khusid, A.Kh., **16**-0258
Khusnutdinov, R.I., **15**-2195
Khuthier, A., **18**-0400
Khutoryanskii, V.A., **12**-0034
Ki, S.H., **15**-1609
Kiakojoori, R., **19**-0088
Kiang, H., **15**-1403
Kiang, Y.-Z., **15**-0519
Kiany-Borazjani, M., **19**-0035, **19**-0038, **12**-0698

Kiasat, A.R., **10**-0809, **10**-0936, **16**-0079, **17**-0432, **19**-0246, **19**-0973
Kiattansakul, R., **15**-2444
Kiau, S., **18**-0487
Kice, J.L., **05**-0249, **10**-0212, **10**-0370, **10**-0837, **16**-2146, **16**-2150, **17**-0516
Kidawi, M., **07**-0111
Kiddle, J.J., **16**-1257, **18**-0773
Kido, F., **18**-0727
Kido, Y., **16**-1119
Kidwai, M., **09**-0119, **13**-0170
Kidwell, H., **04**-0079
Kidwell, R.L., **17**-0391
Kiedaisch, W., **15**-2323
Kiefer, E.F., **15**-2218, **15**-2219, **18**-0537
Kiefer, H.R., **16**-1571
Kielbania Jr., A.J., **18**-0842, **18**-0844
Kiely, A.F., **02**-0366, **18**-0822
Kiely, D.E., **19**-0105
Kienitz, H., **11**-0622
Kienzle, F., **09**-0098, **13**-0263, **13**-0660, **13**-0668, **14**-0336
Kierse, S., **15**-2293
Kiesewetter, M.K., **02**-0242
Kiesgen de Richter, R., **15**-0678
Kiesman, W.F., **15**-0606
Kiess, A.A., **19**-0351
Kiessling, A.J., **16**-1706
Kiessling, L.L., **15**-0292
Kiesten, E.I.S., **19**-1077
Kiewel, K., **12**-0301
Kiełbasiński, P., **10**-0841, **16**-2067, **9**-0795, **19**-0822, **19**-0826
Kiffer, D., **10**-0368
Kigasawa, T., **10**-0804
Kiggen, W., **03**-0119
Kiguchi, T., **15**-1275
Kihara, N., **03**-0182, **10**-0503
Kii, S., **16**-0621
Kiji, J., **10**-1849, **11**-0052, **15**-0611, **15**-2198, **19**-0967
Kiji, S., **12**-0126
Kijima, A., **16**-1593
Kikiya, H., **15**-2427
Kikuchi, H., **19**-0723
Kikuchi, K., **15**-0157, **19**-1035
Kikuchi, O., **10**-0020
Kikuchi, S.-i., **19**-1559
Kikuchi, T., **13**-0718
Kikuchi, W., **11**-0324
Kikugawa, Y., **11**-0194, **11**-0196, **14**-0405, **16**-0185, **16**-0257, **19**-1091, **19**-1150, **19**-1588
Kikukawa, K., **13**-0362, **13**-0724, **14**-0364, **14**-0366 **14**-0368
Kikukawa, T., **14**-0295
Kilbourn, M.R., **14**-0436
Kilburn, J.D., **15**-1231
Kilby, D.C., **11**-0305
Kilgore, M.W., **18**-0487
Kiliç, H., **02**-0247
Killion Jr., R.B., **10**-0240
Killough, J.M., **16**-1896
Killpack, M.O., **12**-0419
Kilpatrick, J.E., **04**-0382
Kilpatrick, M., **11**-0020
Kilway, K.V., **03**-0041, **02**-0359
Kim, A.I., **14**-0080
Kim, A.R., **16**-1508
Kim, B., **16**-0872
Kim, B.-K., **15**-0175
Kim, B.G., **18**-0789
Kim, B.H., **19**-1189, **19**-1213
Kim, B.M., **10**-0498, **10**-0858, **15**-0680, **15**-1436, **15**-1698, **16**-0708, **16**-1025, **18**-0777, **18**-0218
Kim, B.T., **10**-1500, **10**-1626, **17**-0528
Kim, C., **16**-0015, **16**-0838
Kim, C.-K., **16**-0044
Kim, C.-S., **18**-0487
Kim, C.-Y., **04**-0454
Kim, C.J., **10**-0157, **10**-0166
Kim, C.K., **10**-0019, **10**-0048
Kim, C.S., **15**-2138
Kim, C.U., **10**-1104, **15**-1080, **18**-0487, **19**-0650
Kim, D., **06**-0028
Kim, D.-H., **13**-0234, **13**-0515
Kim, D.-h., **18**-0789
Kim, D.-S., **18**-0903
Kim, D.-W., **19**-0231
Kim, D.J., **19**-1031
Kim, D.W., **10**-0411, **10**-0501, **10**-1117, **19**-0260, **19**-0809
Kim, D.Y., **10**-1584, **15**-1015, **16**-2167, **19**-1611
Kim, E.-H., **19**-0684
Kim, E.G., **16**-0360
Kim, E.J., **19**-1109, **19**-1113
Kim, H., **13**-0620, **15**-0820, **15**-1317
Kim, H.-C., **15**-1079
Kim, H.-J., **08**-0080, **10**-0311, **15**-1834, **19**-0523
Kim, H.-S., **16**-0381
Kim, H.-Y., **19**-0680
Kim, H.K., **10**-0501
Kim, H.R., **12**-0184
Kim, H.S., **10**-0501
Kim, H.Y., **09**-0021, **10**-0072, **15**-1136
Kim, I.-J., **15**-0930
Kim, I.C., **10**-0072
Kim, J., **03**-0210, **10**-1287, **12**-0040, **15**-1666, **16**-1717, **16**-1784, **18**-0688, **19**-1403, **19**-1470
Kim, J.-G., **19**-1470
Kim, J.-J., **16**-1866
Kim, J.-S., **10**-1408, **13**-0190
Kim, J.-W., **13**-0329
Kim, J.B., **11**-0073
Kim, J.C., **16**-1450
Kim, J.E., **03**-0123, **19**-1105, **19**-1107
Kim, J.G., **16**-0632
Kim, J.H., **15**-2028, **16**-1994, **19**-1549, **19**-1550, **19**-1600, **19**-1611, **19**-1612, **19**-1685
Kim, J.I., **13**-0389
Kim, J.K., **13**-0051, **15**-1853
Kim, J.M., **19**-1109, **19**-1113, **19**-1183
Kim, J.N., **16**-0387, **17**-0426
Kim, J.S., **15**-0835, **15**-1442
Kim, J.Y., **15**-1258, **16**-1536
Kim, K., **03**-0185, **03**-0189, **03**-0210, **12**-0200, **12**-0516, **12**-0696, **15**-0642, **16**-1582, **18**-0422
Kim, K.-C., **08**-0106
Kim, K.-i., **13**-0430
Kim, K.-J., **15**-1472
Kim, K.C., **19**-0030
Kim, K.H., **16**-0687
Kim, K.M., **10**-0625
Kim, K.S., **13**-0506, **19**-0137, **19**-1326
Kim, M., **04**-0493, **10**-1191, **15**-0235, **15**-0262, **15**-0820, **16**-1787, **18**-0327, **18**-0789, **18**-0800, **19**-1704
Kim, M.-J., **19**-1160
Kim, M.-S., **13**-0331
Kim, M.H., **10**-1584
Kim, M.J., **19**-1160
Kim, M.K., **16**-1536
Kim, N.D., **10**-0048
Kim, S., **02**-0403, **04**-0127, **04**-0146, **10**-0063, **10**-0163, **10**-0170, **10**-1031, **10**-1143, **10**-1593, **10**-1793, **10**-1831, **11**-0328, **13**-0620, **14**-0011, **15**-0597, **15**-0820, **15**-1152, **15**-1371, **16**-0596, **16**-1507, **16**-1980, **16**-1998, **17**-0487, **18**-0063, **18**-0270, **18**-0332, **18**-0819, **19**-0934, **19**-1301, **19**-1329

Kim, S.-G., **15**-0995
Kim, S.-H., **10**-1454, **16**-0564, **16**-1907, **18**-0820, **19**-1654
Kim, S.-I., **10**-0610, **10**-0730
Kim, S.-J., **05**-0331
Kim, S.-W., **15**-1431, **15**-1432, **15**-1432
Kim, S.-Y., **03**-0210, **12**-0263, **12**-0264
Kim, S.C., **15**-1834, **19**-0877, **19**-0888, **19**-1068, **19**-1496
Kim, S.H., **10**-0403, **10**-0440, **10**-0441, **10**-1516, **15**-1609, **15**-1613, **15**-1881, **16**-1994, **17**-0394, **19**-1600, **19**-1612
Kim, S.H., **19**-1685
Kim, S.i., **16**-0199
Kim, S.K., **15**-1258
Kim, S.P., **15**-2019
Kim, S.S., **10**-1166, **11**-0540, **14**-0026, **14**-0061, **16**-0706, **16**-1025, **16**-1051, **16**-1508, **19**-0188, **19**-0809
Kim, S.Y., **10**-1166, **14**-0061
Kim, T.-H., **14**-0388
Kim, T.-J., **10**-1626
Kim, T.H., **10**-1197
Kim, W.-Y., **10**-1772, **10**-1778
Kim, W.-Y., **16**-0752
Kim, Y., **12**-0087, **16**-0605, **16**-0634, **17**-0166, **19**-1188, **19**-1222, **19**-1326, **19**-1655
Kim, Y.-J., **03**-0034, **04**-0312, **08**-0215
Kim, Y.-M., **10**-1454, **13**-0561
Kim, Y.H., **10**-0735, **10**-1156, **12**-0184, **12**-0200, **12**-0696, **14**-0355, **16**-0192, **16**-0554, **16**-0823, **16**-1582, **17**-0394, **19**-0871, **19**-1165
Kim, Y.K., **15**-0336
Kim, Y.M., **13**-0299, **15**-1106
Kim, Y.S., **15**-1023, **19**-1105
Kim, H.S., **16**-2167
Kim, J.Y., **18**-0327
Kim, T.-J., **10**-1500
Kim., J.K., **15**-1914
Kimball, D.B., **02**-0289, **02**-0302
Kimbrough, D.R., **18**-0669
Kimel, W., **18**-0674
Kimling, H., **04**-0473, **04**-0474, **04**-0475, **10**-0350
Kimoto, K., **17**-0175
Kimura, A., **16**-1472
Kimura, F., **15**-0748
Kimura, J., **16**-1228
Kimura, K., **15**-0811, **16**-0218, **16**-0565, **16**-1006, **16**-1017, **19**-1021
Kimura, M., **01**-0083, **02**-0030, **10**-0881, **10**-1498, **15**-0593, **16**-0666, **16**-0711, **16**-0719, **16**-2024, **16**-2084, **18**-0549, **18**-0876
Kimura, O., **13**-0752
Kimura, S., **18**-0194
Kimura, T., **07**-0083, **07**-0098, **15**-0569, **17**-0241
Kimura, Y., **03**-0109, **10**-0676, **10**-0709, **10**-1820, **13**-0254, **15**-1536, **17**-0307
Kinal, A., **15**-2200
Kinart, W.J., **15**-0975
Kinbara, K., **15**-0154
Kinchin, E., **17**-0211
Kinderman, S.S., **18**-0813
Kindler, K., **19**-1285
Kindon, N.D., **10**-0934
Kindon, N.D., **12**-0035
King II, R.M., **11**-0233
King, A., **10**-1128
King, B.T., **18**-0528
King, F., **15**-1690, **19**-1042
King, G.S.D., **02**-0325
King, G.W., **07**-0013
King, H.F., **05**-0306, **14**-0084
King, J.A., **19**-1799
King, J.C., **15**-2350
King, J.F., **04**-0220, **10**-0015, **10**-0290, **16**-2146, **16**-2147, **17**-0320, **18**-0699, **19**-0842
King, J.L., **17**-0343
King, K., **02**-0085, **15**-2086, **16**-2049
King, R.A., **02**-0252
King, R.B., **03**-0083, **15**-1497
King, R.W., **13**-0677, **15**-0046, **17**-0141, **17**-0229, **17**-0235, **17**-0258
King, S.A., **15**-1004
King, S.M., **15**-0708
King, S.W., **19**-0350, **19**-0351
King, T.J., **04**-0240
Kingsbury, C.A., **04**-0279, **04**-0383, **10**-0161, **10**-0170
Kingsbury, C.L., **15**-1169
Kingsbury, J.S., **18**-0770, **18**-0800
Kingsland, M., **11**-0069
Kingston, H.M., **07**-0105, **07**-0106
Kingston, J.F., **16**-2032
Kinner, L., **10**-1312
Kinney, E.P., **13**-0401
Kinney, W.A., **15**-1997
Kinoshita, A., **15**-0800, **15**-2391, **18**-0814
Kinoshita, H., **10**-1440, **10**-1498, **13**-0333, **15**-0743, **15**-2385, **16**-1655, **19**-0592
Kinoshita, K., **16**-1422
Kinoshita, N., **10**-1463
Kinoshita, S., **11**-0498
Kinoshita, T., **03**-0130, **05**-0111, **05**-0117, **05**-0201, **10**-0060, **10**-0073, **10**-0074, **15**-0535, **15**-0994, **16**-1272, **19**-1677
Kinoshita, Y., **16**-1851
Kinstle, T.H., **17**-0015
Kinter, K.S., **15**-1051
Kintner, R.R., **11**-0609, **14**-0447, **19**-0428
Kinzelmann, H., **12**-0578
Kipke, J., **08**-0088
Kipphardt, H., **10**-1661, **15**-1347
Kiprianova, L.A., **10**-0573, **19**-1570
Kira, M., **05**-0245, **05**-0317, **16**-0761
Kirahara, M., **19**-0142
Kiran, B., **02**-0105
Kirby, A.J., **01**-0063, **04**-0168, **04**-0287, **04**-0342, **04**-0363, **04**-0454, **05**-0349, **10**-0533, **10**-0537, **10**-0538, **13**-0013, **16**-0030, **16**-0032, **16**-1549, **16**-1560, **16**-1571, **16**-1936
Kirby, G.W., **04**-0102, **04**-0136, **04**-0268, **08**-0160, **12**-0509, **15**-0401, **17**-0243, **19**-0012, **19**-0310, **19**-0873
Kirby, R.E., **01**-0016
Kirchhoefer, P.L., **15**-0855
Kirchhoff, J.H., **13**-0350
Kirchhoff, R.A., **16**-1195
Kirchner, J.J., **18**-0682
Kirin, V.N., **10**-0763, **15**-0010
Kirino, K., **13**-0281
Kiripolský, M., **07**-0092
Kiritani, R., **13**-0113, **16**-2142
Kirk, D.N., **04**-0268
Kirk, G.G., **15**-1434
Kirk, J.M., **10**-0630
Kirk, K.L., **18**-0494
Kirkland, T.A., **18**-0801
Kirkor, E., **03**-0165
Kirkpatrick, D., **10**-1159, **12**-0693, **19**-1292
Kirkpatrick, E., **19**-0708
Kirms, M.A., **02**-0319
Kirmse, W., **05**-0327, **05**-0336, **05**-0359, **05**-0360, **05**-0383, **05**-0386, **10**-0119, **10**-0121, **10**-0173, **10**-0178, **10**-0226, **10**-0317, **10**-0389, **10**-0514,

12-0345, **12**-0349, **12**-0352, **12**-0376, **15**-2261, **15**-2270, **18**-0002, **18**-0011, **18**-0019, **18**-0027, **18**-0028, **18**-0042, **18**-0046, **18**-0171, **18**-0211, **18**-0212, **18**-0221, **18**-0222, **18**-0482, **18**-0630, **18**-0727
Kirn, W.N., **16**-0441
Kirner, W.R., **10**-0303
Kirollos, K.S., **12**-0060
Kirpichenko, S.V., **15**-0308, **19**-1789
Kirpichenok, M.A., **01**-0029
Kirrmann, A., **05**-0158
Kirsanov, A.V., **16**-0446, **16**-1811
Kirsch, G., **02**-0324, **13**-0497
Kirsch, J.F., **16**-0022
Kirsch, S.F., **18**-0690
Kirschberg, T., **14**-0073
Kirschke, K., **19**-0056
Kirschleger, B., **12**-0621
Kirschner, S., **18**-0092
Kirschning, A., **15**-1919, **16**-0429
Kirss, R.U., **05**-0222
Kirst, H.A., **10**-1288, **19**-1236
Kirste, B., **05**-0208
Kirtane, J.G., **10**-0494
Kirwan, J.N., **19**-1301, **19**-1415
Kisanga, P., **15**-0764, **16**-0748
Kisanga, P.B., **16**-1154
Kise, M., **13**-0101, **10**-1204, **10**-1719, **19**-1699, **19**-1700
Kiselev, V.D., **15**-2004
Kiselyov, A.S., **14**-0346
Kishi, A., **19**-0580
Kishi, I., **19**-1767, **10**-1849
Kishi, K., **17**-0435
Kishi, Y., **04**-0121, **04**-0122, **04**-0123, **15**-1688, **16**-0721, **16**-0836
Kishikawa, K., **15**-1731, **18**-0229
Kishikawa, Y., **15**-2376
Kishimoto, S., **16**-0670
Kishimoto, Y., **15**-1396
Kishimura, K., **18**-0441
Kishioka, Y., **19**-1021
KishoreBabu N., **13**-0585
Kiso, S., **19**-1618
Kispert, L.D., **02**-0207, **05**-0280
Kiss, G., **15**-1382
Kiss, J., **09**-0013
Kissel, W.J., **19**-0448
Kissel, W.S., **15**-0604
Kissling, R.M., **13**-0177, **16**-1695
Kita, I., **16**-1940
Kita, T., **10**-0309
Kita, Y., **10**-0850, **12**-0252, **14**-0008, **18**-0139, **19**-1781, **19**-1783
Kitaev, Yu.P., **16**-0530
Kitagaki, S., **15**-0238
Kitagawa, A., **11**-0524
Kitagawa, H., **11**-0290, **19**-0244
Kitagawa, K., **13**-0317, **16**-0466
Kitagawa, O., **12**-0179, **15**-0839, **15**-1590
Kitagawa, S., **19**-1767
Kitagawa, T., **04**-0455, **05**-0064, **05**-0084, **05**-0117, **05**-0201, **10**-0125, **10**-0299, **10**-0301, **15**-2322, **18**-0469, **18**-0470, **18**-0590, **18**-0643
Kitagawa, Y., **10**-1257
Kitaguchi, H., **12**-0112, **14**-0144
Kitahara, N., **16**-0609
Kitahara, T., **15**-2126
Kitahara, Y., **15**-2222
Kitahonoki, K., **19**-1245
Kitajima, H., **11**-0101, **11**-0434, **11**-0607, **15**-2337
Kitamura, M., **04**-0149, **10**-1123, **12**-0297, **13**-0359, **15**-0596, **16**-0373,l **16**-0489, **16**-1013, **19**-1027
Kitamura, T., **10**-1169, **11**-0331, **11**-0370, **12**-0211, **12**-0441, **13**-0040, **13**-0447, **15**-1165, **16**-1572, **18**-0830, **19**-1707
Kitani, A., **15**-0371
Kitano, T., **18**-0360
Kitano, Y., **04**-0193, **11**-0328, **15**-0241, **15**-1508
Kitao, T., **09**-0064, **19**-1784
Kitaoka, Y., **19**-1784
Kitatani, K., **10**-1341
Kitatsuji, C., **15**-0558
Kitayama, K., **10**-0691
Kitayama, Y., **13**-0481
Kitazawa, E., **16**-1128
Kitazume, T., **07**-0080, **10**-0678, **10**-1558, **18**-0244
Kitching, W., **04**-0329, **04**-0340, **05**-0092, **05**-0103, **08**-0062, **12**-0002, **12**-0014, **12**-0035, **12**-0036, **12**-0037, **12**-0046, **12**-0479, **15**-0186
Kite, G.F., **14**-0427
Kitgawa, H., **17**-0295, **19**-0243
Kito, T., **11**-0501
Kitoh, K., **11**-0436
Kitschke, B., **02**-0180
Kittredge, K.W., **05**-0122
Kitugawa, Y., **16**-0353
Kityama, Y., **15**-0993
Kivelevich, D., **02**-0223
Kivinen, A., **16**-1510, **16**-1763
Kiwiet, N.J., **15**-2117
Kiyan, N.Z., **10**-0312, **16**-2139
Kiyobayashi, T., **02**-0331
Kiyooka, S., **16**-1051, **16**-1119, **16**-1435
Kiyosawa, Y., **10**-0552
Kiyoshige, K., **19**-0915
Kiyota, K., **15**-0903
Kiyota, M., **10**-1171
Kizaki, H., **13**-0625
Kizaki, N., **19**-1022
Kizil, M., **15**-1269
Kizilian, E., **08**-0172
Kizirian, M., **18**-0052
Kizner, T.A., **13**-0106
Klaassen, A.A.K., **02**-0254
Klaboe, P., **04**-0283
Klabunde, K.J., **12**-0596
Klabunovskii, E.I., **04**-0136, **04**-0146, **15**-0597, **15**-2077, **19**-1349
Klaeboe, P., **04**-0333
Klages, U., **04**-0369
Klahre, G., **16**-1305
Klamann, D., **10**-0760, **16**-2158
Klamer, J.C., **02**-0063
Klamt, A., **10**-0410
Klang, J.A., **14**-0421, **19**-0436, **19**-1718, **19**-1725
Klapars, A., **12**-0523, **13**-0201, **13**-0212, **13**-0228, **13**-0229, **13**-0232, **13**-0258, **13**-0275
Klappa, J.J., **16**-0284
Klaps, E., **15**-0939
Klärner, F., **17**-0303, **18**-0539, **18**-0559, **18**-0560, **18**-0567
Klärner, F.-G., **02**-0055
Klasinc, L., **05**-0152
Klauck, G., **02**-0243
Klaunzer, N., **12**-0062
Klausner, A.E., **08**-0038
Klausner, Y.S., **16**-1795
Klawonn, M., **15**-1764
Klebe, J., **15**-2316
Kleeman, A., **04**-0136
Kleeman, M., **15**-2190
Kleijn, H., **15**-0951
Kleimann, H., **16**-2133
Klein, D.J., **02**-0120
Klein, G., **10**-0152, **16**-1158
Klein, H., **15**-1481, **15**-1979, **16**-0306, **19**-0411
Klein, H.P., **19**-0470
Klein, H.S., **01**-0049
Klein, J., **10**-1338, **12**-0393, **15**-0187, **15**-0647, **15**-0650, **15**-1168, **15**-1585, **16**-1031
Klein, P., **07**-0080
Klein, R.F.X., **19**-0659
Klein, W.R., **12**-0561

Kleinfelter, D.C., **10**-0188, **18**-0100
Kleinman, M.H., **05**-0208
Kleinschmidt, R.F., **15**-0349
Kleinstück, R., **17**-0459, **17**-0484
Klem, R., **19**-0446
Klemmensen, P., **10**-0910
Klemperer, W., **03**-0072
Klender, G.J., **15**-0640
Klenke, K., **15**-0715
Klepacz, A., **10**-0898, **13**-0177
Kless, A., **18**-0533
Klessinger, M., **04**-0266, **11**-0078
Klester, A.M., **18**-0118
Klibanov, A.M., **04**-0151
Kliewer, M.A., **15**-0488
Kliimann, H., **16**-2124
Klimisch, R.L., **17**-0090
Klimkina, E.V., **16**-1970
Klimo, V., **14**-0004, **14**-0005
Klimov, E.M., **16**-1673
Klimova, E.I., **16**-1480
Kline, A.D., **04**-0130
Kline, M., **05**-0382
Kline, M.W., **18**-0385
Klinedinst Jr., P.E., **10**-0066
Klingberg, D., **18**-0488
Klingensmith, L.M., **13**-0482
Klinger, F., **18**-0480
Klingler, F.D., **19**-0708
Klingsberg, E., **18**-0198
Klingstedt, T., **10**-1381
Klink, J.R., **11**-0577, **11**-0578
Klivenyi, P., **05**-0212
Klobukowski, M., **15**-0012
Kloc, K., **19**-0707
Klochkov, V.V., **06**-0056
Kloetzel, M.C., **15**-1990
Kloetzing, R.J., **10**-1454
Kloosterziel, H., **10**-0488, **18**-0549, **18**-0566
Klopfenstein, C.E., **02**-0333
Klopman, G., **05**-0031, **10**-0328, **15**-2103
Klopper, W., **02**-0251
Klosa, J., **16**-1804
Klose, G., **18**-0855
Klose, T.R., **12**-0729
Kloster, R.A., **15**-2294
Klotz, H., **07**-0080
Klotz, K.L., **10**-1630
Klotz, P., **16**-0379
Klucik, J., **19**-0338
Klug, W., **02**-0330
Kluge, H., **17**-0476
Kluge, R., **19**-0503
Kluger, R., **06**-0076, **16**-0018, **16**-0034, **16**-1766
Klumpp, D.A., **11**-0327, **15**-2398
Klumpp, G.W., **06**-0006, **06**-0020, **08**-0136, **09**-0001, **10**-0079, **10**-0328, **10**-0399, **10**-0711, **12**-0584, **15**-0043, **15**-2106, **18**-0590, **18**-0640
Klunder, J.M., **13**-0759, **15**-1564, **15**-1822
Klusacek, H., **16**-2133, **18**-0640
Klusener, P.A.A., **12**-0421
Klutsch, G., **19**-0357
Klyashchitskii, B.A., **04**-0159
Klym, A., **08**-0057
Klyne, W., **04**-0096, **04**-0102, **04**-0268
Klyuev, M.V., **16**-0345
Knapp, F.F., **12**-0495
Knapp, R.T., **07**-0066
Knapp, S., **15**-1593, **19**-0050
Knauer, K.H., **02**-0180
Knaup, G.L., **02**-0176
Knaus, E.E., **10**-1523, **16**-1792
Knauss, D.C., **16**-1601
Knauss, E., **15**-2077
Knausz, D., **16**-0291
Knecht, M., **16**-1370
Kneen, G., **15**-2116
Kneib-Cordonier, N., **16**-1816
Kneipp, K.G., **06**-0064
Knettle, B.W., **19**-1145, **19**-1704
Kniel, P., **19**-1536
Knier, B.L., **10**-0088
Kniežo, L., **17**-0015
Knifton, J.F., **19**-1212
Knight, C., **19**-0614
Knight, D.W., **15**-0323, **15**-0389, **18**-0597, **18**-0677, **18**-0680
Knight, G.T., **12**-0715
Knight, J.C., **19**-1469
Knight, J.D., **18**-0035
Knight, J.G., **15**-1902
Knight, J.W., **15**-1776, **17**-0254
Knight, K.S., **15**-0778
Knights, E.F., **15**-0649, **18**-0438
Knipe, A.C., **03**-0101, **10**-0400, **10**-0622, **10**-1599, **16**-1635, **16**-1731, **17**-0054
Knist, J., **18**-0011, **18**-0046
Knobelsdorf, J., **16**-2056
Knobler, C.B., **03**-0121, **03**-0171
Knoche, H., **18**-0761
Knoche, W., **11**-0013
Knochel, P., **06**-0016, **10**-1329, **10**-1333, **10**-1354, **10**-1364, **10**-1373, **10**-1384, **10**-1385, **10**-1388, **10**-1406, **10**-1407, **10**-1454, **10**-1669, **10**-1828, **12**-0437, **12**-0572, **12**-0599, **13**-0225, **13**-0313, **13**-0319, **15**-0375, **15**-0682, **15**-0702, **15**-0901, **15**-0902, **15**-0953, **15**-0959, **15**-1143, **15**-1144, **15**-1749, **15**-1843, **16**-0480, **16**-0500, **16**-0546, **16**-0645, **16**-0889, **16**-1897, **19**-0182, **19**-0185, **19**-0720
Knoeber, M.C., **04**-0357
Knölker, H.-J., **15**-2443
Knoll, F., **01**-0009
Knoll, F.M., **18**-0618
Knopp, M., **18**-0703
Knorr, R., **05**-0351
Knossow, M., **04**-0164, **04**-0165
Knowles, J.R., **04**-0031, **18**-0658
Knowles, W.S., **04**-0146, **04**-0151, **15**-0426, **15**-0597, **19**-0347
Knox, B.E., **01**-0092
Knox, D.E., **10**-0108
Knox, G.R., **15**-1417, **17**-0261, **19**-1432
Knox, K.R., **15**-0840
Knox, L.H., **02**-0157, **05**-0380, **10**-0042, **10**-0049, **12**-0351, **15**-2319
Knox, S.A.R., **02**-0177
Knözinger, H., **17**-0174, **17**-0176
Knudsen Jr., G.A., **18**-0070
Knudsen, R.D., **13**-0751
Knudson, K.R., **16**-0920
Knunyants, I.L., **02**-0400, **15**-0072, **15**-1601, **15**-1622, **16**-0041, **16**-1255
Knupfer, H., **17**-0479
Knutov, V.I.S., **03**-0114
Knutson, D., **06**-0035
Knutson, F.J., **10**-0385
Knutson, P.L.A., **10**-0482
Knutson, R.S., **10**-0134
Knutsson, L., **18**-0202, **18**-0205, **18**-0209
Ko, B.-S., **15**-0833, **16**-0725
Ko, D.-H., **16**-0687
Ko, E.C.F., **10**-1188, **17**-0072, **18**-0024
Ko, H.C., **09**-0026
Ko, J.-y., **10**-0551
Ko, J.J., **19**-1685
Ko, J.S., **19**-1329
Ko, M., **19**-0430
Ko, S., **15**-1374, **15**-1406
Ko, S.-B., **10**-0975, **15**-0078
Ko, S.-L., **15**-1507
Ko, S.Y., **10**-0678, **15**-1822

Ko, Y.K., **19**-0231
Kobayashi, F., **16**-0819
Kobayashi, H., **10**-0465, **13**-0022, **18**-0368, **19**-0431
Kobayashi, J., **16**-1098
Kobayashi, K., **15**-0730, **15**-0816, **16**-1413, **18**-0828
Kobayashi, M., **10**-0504, **10**-0900, **10**-1818, **13**-0738, **13**-0748, **19**-0827, **19**-1369
Kobayashi, N., **16**-0859, **19**-1032
Kobayashi, S., **08**-0188, **08**-0230, **10**-0252, **10**-0273, **10**-0274, **10**-0282, **10**-0919, **10**-1009, **10**-1436, **10**-1498, **10**-1586, **10**-1618, **11**-0370, **11**-0423, **11**-0425, **11**-0456, **11**-0548, **12**-0731, **13**-0487, **15**-0420, **15**-0998, **15**-1025, **15**-1054, **15**-1060, **15**-1304, **15**-1326, **15**-1548, **15**-1668, **15**-1705, **15**-1935, **15**-2010, **15**-2128, **16**-0381, **16**-0412, **16**-0416, **16**-0609, **16**-0619, **16**-0686, **16**-0753, **16**-0755, **16**-0790, **16**-0823, **16**-0871, **16**-0871, **16**-0909, **16**-0914, **16**-0915, **16**-0918, **16**-0934, **16**-0935, **16**-0944, **16**-1007, **16**-1052, **16**-1081, **16**-1083, **16**-1085, **16**-1086, **16**-1092, **16**-1098, **16**-1117, **16**-1119, **16**-1121, **16**-1122, **16**-1124, **16**-1125, **16**-1127, **16**-1422, **16**-1426, **16**-1454, **16**-1676, **18**-0147, **19**-0901, **19**-1596
Kobayashi, Sh., **16**-0876
Kobayashi, T., **05**-0085, **10**-0811, **10**-1805, **10**-1868, **10**-1870, **10**-1872, **12**-0348, **12**-0694, **13**-0448, **13**-0575, **15**-1423, **16**-0436, **16**-1261, **19**-0068
Kobayashi, Y., **04**-0121, **04**-0122, **04**-0123, **04**-0193, **10**-0512, **10**-0819, **15**-0794, **15**-2260, **16**-0761, **18**-0649, **19**-0848
Kobayasshi, K., **11**-0330
Kober, H., **05**-0404, **15**-2322, **18**-0469, **18**-0470, **18**-0643
Kobierski, M.E., **10**-0857
Kobori, K., **19**-1038
Kobori, N., **13**-0748
Kobori, T., **15**-1607
Kobori, Y., **10**-1302
Koboyashi, K., **03**-0149
Köbrich, G., **04**-0491, **12**-0620, **12**-0623, **17**-0003, **17**-0311
Kobrina, L.S., **13**-0076, **13**-0085, **14**-0031, **18**-0250
Kobs, U., **15**-0596
Kobsa, H., **11**-0556, **11**-0559
Kobuke, Y., **15**-2117
Kobyashi, J.-i., **16**-0579
Koch Jr., F.W., **11**-0409
Koch Jr., S.D., **14**-0168
Koch, D., **18**-0772
Koch, E., **05**-0067, **10**-0200
Koch, G.K., **16**-2039
Koch, H., **05**-0241
Koch, H.F., **17**-0037, **17**-0056
Koch, J., **16**-2109
Koch, J.G., **17**-0064
Koch, J.R., **15**-1721, **15**-1722
Koch, K.R., **18**-0420
Koch, M., **13**-0083
Koch, R., **15**-1194
Koch, S., **16**-0292
Koch, V.R., **14**-0104
Koch, W., **02**-0318, **10**-0133, **10**-0185, **10**-0186, **10**-0201, **10**-0206, **10**-0208, **15**-0140, **15**-2335, **18**-0077
Kochetkov, A.N., **15**-0372
Kochetkov, K.A., **04**-0136
Kochetkov, N.K., **10**-0243, **15**-1652, **16**-1673
Kochetkova, N.S., **02**-0166
Kochi, J.K., **03**-0075, **03**-0095, **05**-0202, **05**-0208, **05**-0210, **05**-0219, **05**-0249, **05**-0272, **05**-0281, **05**-0288, **10**-1052, **10**-1251, **10**-1292, **10**-1294, **10**-1296, **10**-1320, **10**-1507, **11**-0018, **11**-0019, **11**-0101, **11**-0119, **11**-0156, **12**-0025, **12**-0042, **12**-0278, **13**-0462, **13**-0662, **14**-0024, **14**-0031, **14**-0041, **14**-0044, **14**-0062, **14**-0087, **14**-0088, **14**-0090, **14**-0114, **14**-0125, **14**-0196, **14**-0214, **14**-0262, **14**-0265, **14**-0271, **14**-0339, **14**-0352, **14**-0374, **14**-0432, **15**-0022, **15**-0050, **15**-0052, **15**-0285, **15**-0859, **15**-1655, **15**-1795, **15**-2028, **15**-2403, **16**-2083, **17**-0139, **18**-0054, **18**-0072, **18**-0081, **18**-0168, **18**-0380, **19**-0272, **19**-0273, **19**-0433, **19**-0435, **19**-0436, **19**-0438, **19**-0439, **19**-0718
Kocián, O., **17**-0026
Kocieński, P., **10**-1532
Kociolek, M.G., **15**-2358
Kock, I., **15**-0667
Kocovsky, P., **13**-0237
Kocsis K., **17**-0504
Koda, T., **13**-0348
Kodama, H., **10**-0886, **10**-1376, **10**-1453
Kodama, S., **19**-0161, **19**-0176
Kodama, T., **13**-0481, **15**-0993, **19**-0227, **19**-0421, **19**-0655
Kodanko, J.J., **13**-0378
Kodera, M., **16**-1728
Kodoi, K., **15**-1467
Kodomari, M., **11**-0260, **11**-0343
Kodukulla, K., **15**-1936
Koeberg-Telder, A., **08**-0028, **08**-0029, **11**-0207, **11**-0626, **11**-0627
Koehl Jr., W.J., **15**-1921
Koehler, K., **13**-0400
Koehn, W., **15**-2209
Koelliker, V., **15**-1585
Koelling, J.G., **06**-0074
Koelsch, C.F., **10**-1794
Koeng, F.R., **10**-0147
Koenig, K.E., **04**-0146, **15**-0597, **15**-0599, **15**-0601, **16**-2046
Koenig, M., **15**-1039
Koenig, R.J., **16**-1966
Koenig, T.M., **10**-1801
Koenigsberger, R.U., **12**-0040
Koening, P.E., **16**-1762
Koepp, E., **16**-1210
Koeppl, G.W., **06**-0089
Koerner, M., **12**-0571
Koga, G., **18**-0739
Koga, K., **04**-0145, **04**-0163, **10**-1618, **10**-1639, **12**-0108, **12**-0691, **13**-0694, **15**-1042, **15**-1092, **15**-1093, **15**-1095, **15**-1693, **15**-2063, **16**-0858, **16**-1032
Koga, N., **02**-0029, **07**-0022, **15**-0099, **15**-0115, **15**-0463, **18**-0739
Koga, T., **13**-0619
Koga, Y., **15**-1423
Kogami, K., **16**-0995
Kogan V., **13**-0481
Kogan, G.A., **02**-0032, **02**-0036
Kogan, L.M., **19**-1548
Kogure, K., **19**-0723
Kogure, T., **19**-0929
Koh, H.Y., **10**-1516, **10**-1549, **16**-0605, **19**-1188, **19**-1222, **19**-1512
Koh, Y., **15**-0922
Koharski, D., **19**-1295, **19**-1396
Kohaus, R.L., **16**-0071
Kohda, K., **10**-0350
Kohl, D.A., **01**-0061, **05**-0344, **15**-0058

Kohler, B., **07**-0015
Kohler, B.A.B., **16**-1077
Köhler, V., **16**-1105
Kohli, T.-P., **05**-0098
Kohll, C.F., **10**-0712
Kohlmiller, C.K., **19**-0361
Kohlpaintner, C.W., **15**-1381
Kohmarch, G., **16**-0238
Kohmoto, S., **15**-1731, **18**-0229
Kohmura, Y., **12**-0226, **19**-0535
Kohn, H., **15**-1879
Kohne, J., **19**-1321
Kohnke, F.H., **02**-0312
Kohno, M., **12**-0745
Kohno, S., **19**-1304
Kohno, Y., **15**-0624
Kohnstam, G., **10**-0079, **10**-0084, **10**-0424, **11**-0037, **13**-0770
Kohra, S., **16**-1953
Koide, K., **19**-0914
Koide, T., **19**-1354
Koike, N., **10**-0717
Koike, T., **13**-0450, **15**-1181, **16**-0751, **16**-1102, **19**-1042
Koiyama, Y., **10**-1454
Koizumi, M., **12**-0087, **15**-0608
Koizumi, T., **15**-1391
Kojima, A., **13**-0379
Kojima, M., **15**-2247
Kojima, R., **10**-0965, **15**-0319
Kojima, T., **11**-0341, **13**-0314, **15**-2044, **16**-0922, **19**-0288
Kok, D.M., **15**-2234
Kok, G.B., **01**-0042
Kokel, B., **11**-0175
Kokes, R.J., **15**-0405
Koketsu, M., **16**-0189, **19**-0881
Kokhlova, V.M., **13**-0107
Kokil, P.B., **15**-0018
Kokin, A.A., **14**-0142, **14**-0150
Kokin, K., **16**-1307
Kokko, B., **12**-0511
Kokko, B.J., **12**-0509, **12**-0510
Kokubo, K., **15**-0159, **15**-1360
Kokubo, T., **15**-1711
Kokumai, R., **15**-2276, **19**-0044
Kol, M., **15**-1582
Kolano, C., **05**-0207
Kolar, L.W., **10**-0724
Kolasa, T., **10**-0993
Kolb, H.C., **15**-1658, **15**-1692, **15**-1696
Kolb, M., **10**-1176, **10**-1666
Kolb, V.M., **17**-0344
Kolbah, D., **10**-0891
Kolbasenko, S.I., **15**-1850
Kolbeck, K.J., **07**-0070
Koldobskii, G.I., **18**-0291, **18**-0293, **18**-0305
Kolehmainen, E., **03**-0120
Kolesar, T.F., **15**-2210
Kolesnichenko, G.A., **14**-0203
Koley, D., **15**-0278
Kölle, U., **19**-0221
Köllhofer, A., **13**-0539
Kollman, P.A., **03**-0001, **04**-0357
Kollmar, H., **02**-0216
Kollonitsch, J., **10**-1078, **19**-1516
Kolomiets, A.F., **10**-0494, **10**-0817
Kolomitsyn, I.V., **14**-0150
Kolomnikov, I.S., **15**-0406, **16**-0842
Kolomnikova, G.D., **02**-0156, **15**-0401
Kolos, W., **01**-0003
Kolsaker, P., **02**-0431, **19**-0375
Kolshorn, H., **04**-0471, **04**-0472, **15**-2047
Kolthoff, I.M., **08**-0007, **08**-0039
Koltun, E.S., **19**-0531
Koltunov, K.Yu., **15**-0623, **15**-1148
Kolyaskina, Z.N., **15**-1638
Komarov, I.V., **04**-0454, **05**-0349
Komarov, N.V., **10**-1784
Komatsu, H., **15**-1387
Komatsu, K., **02**-0158, **02**-0199, **05**-0064, **05**-0117, **05**-0201, **10**-0060, **10**-0074, **15**-1034, **15**-2069
Komatsu, K.i., **19**-0367
Komatsu, M., **10**-0628, **10**-1827, **10**-1840, **10**-1853, **15**-0390, **15**-1066, **15**-1400, **15**-1782, **15**-1896, **15**-1904, **15**-1910, **16**-1892, **19**-0591, **19**-0607
Komatsu, N., **19**-1004
Komatsuzaki, T., **09**-0076
Komeyama, K., **15**-0371
Komin, J.B., **15**-1804
Komine, N., **15**-0146, **15**-0889
Komiya, N., **12**-0337, **19**-0516, **19**-0516, **19**-0569, **19**-0570
Komiya, S., **12**-0278, **15**-0146
Komiya, Y., **14**-0281
Komiyama, M., **03**-0174, **11**-0052, **16**-1520
Komiyama, S., **16**-1454
Kommandeur, J., **07**-0020
Komornicki, A., **10**-0179, **18**-0669
Komoto, I., **11**-0456, **16**-1083
Komoto, R.G., **10**-1843
Komoto, R.G., **10**-1844
Kompa, K., **11**-0181
Komura, K., **10**-1230
Komura, M., **16**-1051
Komuro, Y., **15**-2065
Konakahara, T., **13**-0541, **16**-0553
Konasewich, D.E., **08**-0137
Koncos, R., **11**-0316, **12**-0354
Kondaji, G., **11**-0435
Kondakov, D.Y., **15**-0906
Kondaskar, A., **10**-0923, **10**-0925, **10**-0926
Kondo, A., **13**-0256, **19**-0823
Kondo, H., **15**-0442, **15**-2374
Kondo, I., **14**-0373
Kondo, J.N., **05**-0069
Kondo, K., **10**-0900, **10**-1270, **12**-0735, **15**-2152, **16**-1854, **19**-0401
Kondo, M., **13**-0448
Kondo, S., **02**-0322, **10**-1328, **16**-1785
Kondo, T., **10**-0788, **10**-0880, **10**-1469, **13**-0538, **15**-0340, **15**-1467, **15**-1696, **16**-0268
Kondo, Y., **10**-1466, **13**-0348
Kondolff, I., **10**-1420
Kondrat'eva, L.A., **16**-1186
Kondrat'eva, L.V., **15**-0047, **15**-0348
Kondratenko, M., **15**-2446
Kondratenko, M.A., **15**-2438
Kondratov, S.A., **13**-0216
Konen, D.A., **14**-0151, **16**-1252
Kong, F., **10**-0801, **12**-0114
Kong, N., **15**-2296
Kong, S., **10**-1610, **15**-0148
König, C., **15**-1911
König, E., **19**-1571, **19**-1573
König, H., **13**-0164
König, J., **18**-0538, **18**-0551, **18**-0552
König, W.A., **04**-0173, **04**-0175, **13**-0485
Königshofen, H., **02**-0173, **02**-0274, **02**-0319
Konijn, M., **10**-0317
Konishi, H., **02**-0203, **11**-0052, **16**-0915, **19**-0967
Konishi, K., **15**-1837
Konishi, M., **10**-1302
Kono, D.H., **16**-1888
Kono, H., **10**-1762
Kono, K., **13**-0724
Kono, K., **14**-0364, **14**-0368, **16**-0608, **18**-0732
Konoike, T., **19**-0843, **19**-0848
Konopelski, J.P., **13**-0579, **13**-0580

Konovalov, A.I., **15**-1932, **15**-1981, **15**-2004
Konrad, G., **04**-0175
Konradi, A.W., **19**-1662, **19**-1663
Konshin, V.V., **10**-1784
Konstantinou, Z., **10**-1448
Konuma, M., **19**-0825
Konwar, D., **17**-0464, **19**-0230, **19**-1248
Konya, D., **15**-1437, **15**-1452
Koo, B.-S., **19**-0184, **19**-0684
Koo, I.S., **16**-0015, **16**-1511
Koo, S., **19**-0800
Koock, S.U., **10**-0137
Kooijman, H., **13**-0237, **19**-0216
Kooistra, D.A., **16**-0181, **19**-1450
Kool, E., **16**-1496
Koola, J.J., **14**-0239
Koolhaas, W.E., **02**-0062
Koosha, K., **15**-1170
Kooyman, E.C., **02**-0123, **11**-0277, **11**-0638, **14**-0103, **14**-0127, **14**-0127, **17**-0132, **17**-0137
Kop, J.M.M., **16**-2039
Kopach, M.E., **10**-0857
Kopecky, D.J., **19**-1483
Kopecky, J., **16**-1811
Kopecky, K.R., **05**-0333, **12**-0028, **15**-0012
Kopel, L.C., **13**-0543
Kopf, J., **04**-0517, **15**-2402
Kopinke, F., **14**-0064
Kopka, I.E., **04**-0512
Koplick, A.J., **18**-0048
Kopp, F., **10**-1329
Kopp, J.Z., **06**-0061
Kopp, R., **10**-0250
Koppel, I., **08**-0223
Koppel, I.A., **08**-0161, **10**-0443
Koppenhoefer, B., **04**-0175
Koppes, W.M., **16**-1888
Kopping, B., **15**-0752, **15**-1196
Koptyug, V.A., **11**-0012, **11**-0013, **11**-0029, **11**-0088, **11**-0605, **11**-0637, **18**-0006, **18**-0030, **18**-0035, **18**-0250
Koradin, C., **15**-0902, **16**-0889
Korber, H., **19**-0372
Korcek, S., **14**-0218
Korchagina, D.V., **18**-0035, **18**-0250
Kore, A.R., **19**-0324
Koreeda, M., **18**-0682, **18**-0731, **19**-0941
Koren, R., **10**-0078
Koreshkov, Yu.D., **02**-0203, **15**-2310
Korivi, R.P., **15**-2381
Kormos, B.L., **10**-0337
Korn, S., **15**-0806
Korn, T.J., **13**-0313
Kornblum, N., **10**-0089, **10**-0285, **10**-0426, **10**-0486, **10**-0488, **10**-0489, **10**-0781, **10**-1001, **10**-1479, **10**-1480, **10**-1481, **10**-1482, **10**-1483, **10**-1484, **10**-1602, **10**-1604, **12**-0212, **12**-0338, **13**-0692, **16**-0119, **19**-0639, **19**-0640, **19**-0642, **19**-1531, **19**-1570
Kornegay, R.L., **04**-0323, **10**-0131
Korneva, L.M., **02**-0144
Korobitsyna, I.K., **10**-0390, **18**-0211, **18**-0218
Korolev, B.A., **08**-0217
Korolev, D.N., **13**-0526
Koroniak, H., **18**-0461, **18**-0471, **18**-0482, **18**-0589
Koroniak, L., **10**-1124
Korostova, S.E., **10**-1517
Korostylev, A.P., **13**-0086
Korshak, V.V., **13**-0534
Korshunov, S.P., **19**-0010
Kort, C.W.F., **11**-0203, **11**-0206
Korte, S., **04**-0467
Korte, W.D., **10**-1312
Korth, H., **05**-0243, **05**-0245, **19**-1532
Korth, H.-G., **01**-0090, **01**-0104
Kortüm, G., **08**-0018
Korver, G.L., **18**-0656
Korytnyk, W., **19**-0993, **19**-1077
Korytsky, O.L., **10**-0890, **10**-1188
Korzeniowski, S.H., **03**-0101, **13**-0691, **13**-0737, **19**-1564
Korzhenevskaya, N.G., **09**-0048
Kos, A.J., **10**-0133
Kos, N.J., **01**-0087
Kosak, J.R., **11**-0592
Kosbahn, W., **18**-0708
Koseki, A., **16**-1685
Kosel, C., **13**-0682
Koser, G.F., **18**-0273
Köser, H.G., **02**-0234
Koshchii, V.A., **11**-0351
Koshiba, N., **11**-0328
Koshino, J., **18**-0435
Koshiro,Y., **19**-1769
Koshoji, G., **15**-0371, **15**-0732
Koshtaleva, T.M., **18**-0305
Koshy, K.M., **17**-0035
Kosinska, W., **12**-0085
Kosjek, B., **19**-1022
Koski, W.S., **05**-0205
Koskikallio, E.A., **16**-1693
Koskikallio, J., **10**-0331, **10**-0351
Koskimies, J.K., **04**-0141, **10**-1666, **10**-1700
Koskinen, A.M.P., **12**-0214
Kosma, P., **16**-0370
Kosower, E.M., **03**-0080, **04**-0422, **10**-0430, **10**-0444, **19**-1572, **19**-1573
Kosswig, K., **19**-0304
Kost, A.N., **11**-0496, **15**-0314
Kost, D., **01**-0010
Koster, D.F., **15**-0969
Koster, G.F., **10**-0115
Köster, A.M., **02**-0006, **02**-0095, **02**-0111
Köster, F., **16**-0850
Köster, H., **05**-0147
Köster, R., **12**-0445, **15**-0685
Köster, R., **15**-1183
Kostermans, G.B.M., **02**-0062
Kostikov, R.R., **02**-0196, **02**-0205, **15**-2267, **15**-2277
Kostova, K., **16**-0487, **04**-0042
Kostyk, M.D., **05**-0050
Kostyukov, I.N., **14**-0012
Kostyukovskii, Ya.L., **12**-0699
Kosuge, T., **19**-1569
Kosugi, M., **10**-1262, **10**-1634, **10**-1825
Kosugi, M., **13**-0439
Kosugi, Y., **14**-0045
Kosynkin, D., **03**-0075
Kosynkin, D.V., **11**-0293
Kotake, H., **10**-1440, **16**-1655
Kotani, Y., **10**-0313
Kotcher, P.G., **13**-0033
Koteel, C., **19**-0099
Kotelevskii, S.I., **02**-0152
Kotera, K., **19**-1245
Koth, H.F., **17**-0064
Kotha, S., **10**-1595, **13**-0474, **18**-0668
Kotian, K., **16**-1950
Kotian, K.D., **16**-0185
Koto, H., **16**-0507
Kotora, M., **10**-1326, **10**-1779, **12**-0689, **15**-0841, **15**-0958, **15**-2424, **18**-0803
Kotrusz, P., **15**-1017
Kotschy, A., **13**-0537
Kotsuki, H., **10**-0581, **10**-1157, **11**-0341, **13**-0314, **15**-1004, **15**-1019, **16**-1036, **16**-1860, **18**-0357, **18**-0363, **19**-1392
Kotsuma, T., **15**-0830
Kotti, S.R.S.S., **15**-0354, **15**-1614

Kou, Y., **08**-0114
Koubek, E., **13**-0757
Koudelka, J., **01**-0035
Kouge, K., **15**-2337
Kourouli, T., **16**-0982, **15**-0732
Koutecky, J., **05**-0285
Kouwenhoven, A.P., **12**-0053, **15**-2197
Kovac, B., **04**-0240
Kovac, F., **19**-0234
Kovacic, M.K., **10**-0878
Kovacic, P., **04**-0497, **04**-0498, **10**-0964, **11**-0177, **11**-0178, **11**-0186, **11**-0187, **11**-0408, **11**-0409, **12**-0719, **14**-0269, **17**-0445, **18**-0345
Kovacs, C.A., **18**-0402, **18**-0417
Kovacs, J., **10**-0212
Kovács, I., **15**-1496
Kovalenko, S.V., **13**-0267
Kovalensky, A.Yu., **12**-0359
Kovalev, B.G., **16**-0485
Kovaćević, M., **04**-0164
Kovač, B., **05**-0252
Kovačević, B., **08**-0085
Kovelesky, A.C., **10**-1733
Köver, A., **12**-0081
Kovrizhnykh, E.A., **05**-0148
Kovtonyuk, V.N., **18**-0250
Kovtunenko, V.A., **15**-2088
Kowal, J.J., **15**-0440
Kowalak, S., **15**-0433
Kowalski, C.J., **12**-0398, **16**-1991, **16**-1992, **18**-0229
Kowalski, M.H., **10**-1411
Kowalski, T., **10**-0209
Koyabu, M., **13**-0139
Koyama, I., **10**-0252
Koyama, K., **15**-1642, **19**-0605
Koyanagi, M., **16**-2044
Koyano, M., **16**-0565
Koyano, T., **15**-1536
Koyasu, K., **19**-0923
Koyunçu, D., **19**-0855
Koz'min, A.S., **04**-0437, **10**-0762, **15**-0010, **15**-1572, **15**-1580
Kozaki, T., **10**-0020
Kozhevnikov, I.V., **10**-0424, **11**-0418, **13**-0361
Kozhushko, B.N., **16**-1309
Kozhushkov, S.I., **04**-0339, **10**-1598, **12**-0744, **18**-0087, **18**-0528
Koziar, J.C., **07**-0005
Koziara, A., **10**-0907, **10**-1020, **19**-1275
Kozikowski, A.P., **10**-1089
Kozima, K., **03**-0051
Kozima, S., **11**-0357
Koziski, K.A., **13**-0098
Kozlikovskii, Ya.B., **11**-0351
Kozlov, V.A., **11**-0632
Kozlov, V.V., **13**-0246
Kozlowski, J., **10**-1540, **15**-1075
Kozlowski, J.A., **10**-1332, **10**-1353, **10**-1355, **12**-0560, **12**-05, **15**-1076
Kozlowski, M.C., **16**-0692
Kozmin, A.S., **10**-0763
Kozmin, S.A., **10**-0692, **15**-0826, **18**-0757
Kozuka, S., **14**-0045, **14**-0438, **19**-1604
Kočevar, M., **16**-1684, **16**-1708
Kočovský, P., **10**-1471, **16**-0756, **16**-0757, **16**-0760, **19**-1141
Kołsov, A.I., **02**-0379
Kraakman, P.A., **02**-0062, **15**-2282
Kraeutler, B., **12**-0658, **14**-0416
Krafczyk, R., **12**-0365
Krafft, M.E., **10**-1462, **15**-1415, **15**-1416, **15**-1428, **15**-1430, **15**-1439, **15**-1451, **15**-1464, **19**-0217, **19**-1360
Krafft, T.E., **14**-0423
Kraft, L., **19**-0325
Kraft, S., **18**-0800
Kraka, E., **04**-0402, **04**-0416, **04**-0420
Krakauer, H., **19**-0001
Krakowiak, K.E., **03**-0101
Kralj, P., **11**-0304
Kramař, J., **12**-0395
Kramer, B.D., **15**-2251
Kramer, G.M., **05**-0015, **10**-0182, **15**-0132
Kramer, G.W., **16**-1820
Kramer, K.E., **18**-0367
Kramer, P.A., **12**-0053
Krämer, T., **16**-1207
Kramps, L., **15**-1810
Krane, J., **03**-0106, **04**-0329
Kranich, R., **10**-1630
Krantz, A., **02**-0212
Krapcho, A.P., **10**-0208, **12**-0325, **12**-0654, **15**-2285, **16**-2040, **17**-0415, **18**-0020
Krasik, P., **16**-1684
Krasna, A.I., **15**-0455
Krasnaya, Zh.A., **10**-1476
Krass, N., **11**-0535
Kratzer, O., **16**-1265
Kraus, G.A., **10**-0043, **10**-0322, **10**-1287, **10**-1390, **15**-1000, **15**-1230, **15**-1372, **15**-1925, **15**-2045, **19**-0055, **19**-1468
Kraus, K.W., **16**-0956, **16**-1929
Kraus, M., **17**-0176
Kraus, M.A., **16**-1817
Kraus, W., **19**-1338
Krause, H., **10**-1330, **13**-0311
Krause, N., **10**-1429, **10**-1767, **15**-0365, **15**-1026, **15**-1170
Krause, P., **10**-0150
Krause, R.A., **04**-0434
Krause, V., **12**-0646
Krauss, H., **12**-0080
Krauss, H.J., **12**-0080
Krauss, I.J., **15**-1490
Krauss, S.R., **15**-1170
Krayushkin, M.M., **11**-0321
Krebs, A., **04**-0471, **04**-0473, **04**-0474, **04**-0475, **04**-0477, **04**-0501, **04**-0517, **15**-0086, **18**-0204, **18**-0701
Krebs, A.W., **02**-0196
Krebs, O., **15**-0991, **18**-0487
Krebs, P.J., **14**-0014
Kreevoy, M.M., **06**-0006, **06**-0022, **06**-0024, **06**-0026, **06**-0028, **08**-0102, **08**-0118, **08**-0137, **10**-0352, **10**-0524, **10**-0532, **10**-0534, **10**-0535, **10**-0571, **10**-0637, **19**-1487
Kreft III, A.F., **10**-0228
Kreh, R.P., **19**-0623
Kreider, E.M., **13**-0773, **13**-0775
Kreil, D.J., **18**-0574
Kreile, J., **02**-0215
Kreimerman, S., **10**-1840, **10**-1853, **15**-1400
Kreiser, W., **19**-0978
Kreiter, C.G., **02**-0348
Kremer, K.A.M., **04**-0143
Kremzow, D., **15**-0366
Krepski, L., **16**-1425
Krepski, L.R., **15**-2178, **19**-1709, **19**-1719, **19**-1725, **19**-1727
Kresge, A., **08**-0136, **08**-0137
Kresge, A., **12**-0083
Kresge, A.J., **12**-0101, **02**-0383, **02**-0385, **02**-0386, **02**-0388, **02**-0389, **02**-0391, **02**-0393, **02**-0394, **06**-0037, **06**-0062, **06**-0076, **06**-0087, **06**-0089, **08**-0057, **08**-0098, **08**-0104, **08**-0105, **08**-0118, **10**-0027, **10**-0530, **10**-0533, **10**-0536, **10**-0570, **10**-0571, **10**-0572, **10**-0574, **11**-0110, **12**-0084, **12**-0095, **12**-0097, **12**-0100, **12**-0150, **15**-0025, **15**-0079, **15**-0215, **15**-0218, **15**-0251, **16**-1936
Kresge, A.R., **02**-0384

Kresin, V.Z., **07**-0043
Krespan, C.G., **15**-2075
Kress, A., **02**-0207
Kress, J., **16**-1367, **18**-0836
Kress, R.B., **04**-0187
Kresze, G., **12**-0223, **15**-2122, **16**-1378, **18**-0708
Kretchmer, R.A., **14**-0384
Kretzschmar, G., **17**-0149
Kreuder, R., **16**-1308
Kreutz, O.C., **19**-1021
Krezeminski, M.P., **16**-0699
Krichevtsova, T.I., **16**-2170
Kricka, L.J., **15**-2195, **15**-2235
Krief, A., **10**-0771, **10**-0826, **10**-1089, **10**-1715, **12**-0620, **15**-1114, **15**-1708, **16**-0486, **17**-0199, **17**-0200, **17**-0222, **18**-0133, **18**-0235, **19**-0010, **19**-0553, **19**-0823, **19**-1620
Krieg, H., **02**-0282, **02**-0284
Krieger, C., **02**-0064, **02**-0308, **03**-0029, **04**-0073, **08**-0089, **08**-0182, **08**-0183, **08**-0186
Krieger, J.K., **11**-0073, **14**-0378
Krieger, K.A., **19**-0977
Krieger, P.E., **15**-0253
Krimen, L.I., **16**-2053
Krimer, M.Z., **15**-0021
Krimm, H., **11**-0386
Krimmer, H., **18**-0227
Krimmer, H.-P., **15**-0609
Krintel, S.L., **15**-1277
Krische, M.J., **15**-0817, **15**-1970, **15**-2175, **16**-0701, **16**-0704, **16**-0720, **16**-0722
Krishna, A.D., **11**-0219
Krishna, G.R., **15**-2007
Krishna, P.R., **10**-0862, **10**-1131, **16**-0781, **17**-0316
Krishnamurthy, D., **16**-0640
Krishnamurthy, R., **14**-0020
Krishnamurthy, S., **08**-0179, **19**-0874, **19**-0877, **19**-0882, **19**-0886, **19**-0888, **19**-0889, **19**-0903, **19**-0949, **19**-0994, **19**-1068, **19**-1292, **19**-1293, **19**-1379, **19**-1399, **19**-1490
Krishnamurthy, V., **12**-0259, **14**-0298
Krishnamurthy, V.V., **05**-0083, **11**-0133, **16**-1294, **18**-0073
Krishnamurti, R., **10**-1132
Krishnaswamy, D., **19**-1273
Krishnaveni, N., **10**-0671
Krishnaveni, N.S., **10**-0546, **19**-0200
Krishtalik, L.I., **15**-0540
Kristensen, J., **10**-1632
Kristián, P., **16**-1755
Kristiansen, P.O., **03**-0106
Kristol, D.S., **07**-0080
Kritchevsky, J., **15**-0062
Krivokapic, A., **04**-0392
Kriz Jr., G.S., **06**-0073
Krogh, E.T., **02**-0389
Krogh, J.A., **16**-0118
Krogh-Jespersen, K., **02**-0199, **02**-0207, **05**-0386, **05**-0372
Krohn, K., **19**-0267
Kröhnke, F., **12**-0414
Krois, D., **16**-0042
Krolikiewicz, K., **16**-1655
Kroll, W.R., **18**-0796
Kromhout, R.A., **03**-0009
Krompiec, M., **15**-0150
Krompiec, S., **15**-0150
Kron, T.E., **03**-0143
Kronenberg, W.J., **04**-0306
Kroner, J., **02**-0222
Krongauz, E.S., **19**-0553
Kronja, O., **05**-0097, **05**-0098, **10**-0134, **10**-0142
Kroon, J., **03**-0025, **03**-0048
Kropp, P.J., **07**-0054, **12**-0080, **15**-0167, **15**-1730, **18**-0535, **18**-0860, **18**-0863, **19**-0758
Kroto, H.W., **02**-0355
Krough-Jespersoen, K., **18**-0093
Kroutil, W., **19**-1022
Krow, G., **04**-0014, **04**-0100
Krow, G.R., **18**-0237, **18**-0294, **18**-0320, **18**-0353, **18**-0636
Krska, S.W., **15**-0615
Krstulović, A.M., **04**-0171
Krubiner, A., **19**-1615
Kruck, P., **19**-0326
Krueger, C.A., **16**-1457
Krueger, S.M., **18**-0480
Krüerke, U., **04**-0502
Krug, C., **12**-0333
Kruger, A.W., **04**-0383, **12**-0106
Kruger, J.E., **18**-0023, **18**-0026
Kruger, T.L., **08**-0059, **08**-0064, **18**-0654
Krüger, C., **02**-0326, **15**-2431
Krüger, C.M., **15**-1816
Krüger, H., **06**-0052
Krüger, L., **19**-0796
Kruizinga, W.H., **10**-0695, **10**-0709
Kruk, C., **08**-0028
Krull, K.L., **08**-0171
Krumpe, K.E., **12**-0349
Krumper, J.R., **16**-0947
Krupička, J., **17**-0026
Kruppa, G.H., **05**-0083
Kruse, C.G., **04**-0092, **07**-0120
Kruse, C.W., **15**-0349
Kruse, L.I., **06**-0015, **06**-0017, **11**-0060
Kruse, R.B., **15**-0048
Krusic, P.J., **05**-0281
Kryger, L., **10**-0005
Krygowski, T.M., **02**-0068, **02**-0092, **02**-0188, **02**-0092, **02**-0112, **02**-0137, **08**-0174
Krylov, E.N., **11**-0631
Kryshtal, G.V., **15**-0992, **15**-1011
Kryuchkova, L.V., **13**-0256
Krzhizhevskii, A.M., **18**-0046
Ku, A.T., **05**-0032
Ku, A.Y., **18**-0852
Ku, B., **16**-0236
Ku, C.-K., **14**-0334
Kuang, C., **14**-0439, **17**-0383
Kuang, K., **10**-0112
Kuang, Y., **15**-1690
Kuang, Y.-Q., **15**-1690, **15**-1706
Kuang, Y.-Y., **16**-0342, **18**-0798
Kuar, K.P., **10**-0474
Kubánek, V., **19**-0010
Kubler, D.G., **10**-0530
Kubo, A., **04**-0195
Kubo, M., **02**-0274, **02**-0326
Kubo, T., **11**-0630
Kubo, Y., **19**-0907
Kubota, A., **11**-0252
Kubota, H., **04**-0195, **11**-0531, **15**-2322, **18**-0469, **18**-0470
Kubota, K., **11**-0169, **16**-0303, **16**-0762
Kubota, N., **15**-0626, **19**-1022
Kubota, S., **05**-0284, **15**-0968
Kubota, T., **19**-1679
Kubota, Y., **13**-0599, **13**-0604, **13**-0605, **13**-0608
Kubu, M., **16**-1116
Kubuto, C., **10**-1454
Kucerovy, A., **12**-0568
Kuchar, E.J., **15**-1525
Kucher, R.V., **15**-1735
Kucherov, V.F., **10**-1476, **15**-0106, **15**-1011, **17**-0003
Kuchitsu, K., **01**-0074, **02**-0030
Kuchitsu, K., **04**-0317
Kuck, D., **04**-0434
Kuck, V.J., **02**-0235, **05**-0342
Kuczkowski, R.L., **01**-0052, **19**-0345, **19**-0359, **19**-0371, **19**-0376, **19**-0377, **19**-0378, **19**-0379, **19**-0382
Kudian, A.K., **01**-0039
Kudo, K., **13**-0613, **18**-0129
Kudo, T., **11**-0332, **15**-0555, **15**-0556, **16**-0545, **19**-1079, **19**-1080, **19**-1081
Kudo, Y., **19**-1369

Kudoh, M., **12**-0326
Kudryavtsev, R.V., **18**-0888
Kuebart, F., **02**-0277
Kuebrich, J.P., **16**-1494
Kuehne, M.E., **04**-0131, **10**-1674, **10**-1679, **14**-0257, **15**-2350, **19**-1487
Kuethe, J.T., **09**-0105
Kugatova-Shemyakina, G.P., **04**-0264
Kuhla, D.E., **15**-2116
Kühle, E., **14**-0273, **15**-1601
Kuhler, J.L., **16**-0423
Kuhlman, M.L., **19**-1302, **19**-1671
Kuhlmann, D., **14**-0377
Kuhlmann, H., **15**-1346, **15**-1368, **16**-0724, **16**-1497
Kuhlmann, K.F., **11**-0154
Kuhn, A., **05**-0407
Kuhn, C., **12**-0103
Kuhn, H.J., **14**-0227, **14**-0241
Kuhn, S.J., **11**-0138, **11**-0013, **11**-0025, **11**-0026, **11**-0027, **11**-0319, **11**-0347, **11**-0458, **11**-0490, **16**-1884, **16**-1885
Kühn, T., **18**-0361
Kühnau, D., **10**-0949
Kühne, H., **19**-0386
Kuhnen, F., **14**-0433
Kuhnert, N., **07**-0113, **15**-0962, **15**-1175
Kuipers, H.P.C.E., **15**-1798
Kuivila, H.G., **12**-0631, **19**-1001, **19**-1100, **19**-1307, **19**-1346
Kükenhöhner, T., **16**-0684
Kukes, S., **06**-0026
Kuki, A., **10**-1595
Kukolja, S., **10**-0987
Kukreja, G., **19**-1169
Kukuhara, T., **10**-1045
Kukui, Y., **10**-1849
Kukushkin, V.Yu., **19**-1602
Kul'bovskaya, N.K., **15**-0049, **15**-0295
Kulak, A.N., **15**-0236
Kulawiec, R.J., **12**-0081
Kulczycki Jr., A., **15**-2313
Kulenovic, S.T., **12**-0177
Kulganek, V.V., **15**-0992, **15**-1011
Kulicke, K.J., **05**-0177
Kulik, N.I., **10**-0033
Kulik, N.I., **10**-0406
Kulinkovich, O.G., **10**-1496, **10**-1670, **11**-0483
Kulkarni, M.G., **19**-0136
Kulkarni, S.J., **11**-0248, **11**-0256, **11**-0289, **16**-1672
Kulkarni, S.R., **16**-0178
Kulkarni, S.U., **10**-1114, **15**-0644, **15**-0658, **15**-0659, **15**-0666, **15**-06, **18**-0444, **18**-0448
Kulp, S.S., **19**-0450
Kumada, M., **10**-0688, **10**-1250, **10**-1302, **10**-1303, **10**-1304, **10**-1533, **12**-0035
Kumadaki, I., **10**-0512, **15**-2260, **18**-0649
Kumagai, N., **15**-0994, **16**-0898, **16**-1044, **19**-1677
Kumagai, T., **07**-0058
Kumai, S., **18**-0011
Kumamoto, T., **10**-0950
Kumar, .D.K., **12**-0732
Kumar, A., **13**-0017, **13**-0105, **15**-1763, **16**-0777, **18**-0344, **19**-0072
Kumar, B.A., **16**-2153
Kumar, C.V., **14**-0395, **15**-2254
Kumar, D., **14**-0079, **16**-0244, **18**-0492, **19**-0033
Kumar, G., **12**-0708
Kumar, G.A., **03**-0040
Kumar, G.D.K., **10**-0959
Kumar, G.M., **10**-0963, **10**-1574, **11**-0195, **16**-1476
Kumar, H.M.S., **18**-0608, **10**-0865, **15**-1004, **16**-0324, **16**-0930, **16**-1175, **16**-1374, **17**-0439, **18**-0301, **18**-0662
Kumar, J.S.D., **15**-1295, **19**-1217
Kumar, K.A., **16**-1768
Kumar, K.S.R., **15**-0193
Kumar, M.P., **10**-1537, **18**-0152, **16**-1747, **17**-0439, **19**-1117
Kumar, N.S., **04**-0160
Kumar, P., **15**-0298, **19**-0077
Kumar, R., **09**-0102, **13**-0713, **14**-0357
Kumar, R.K., **15**-1674
Kumar, S., **16**-0271, **16**-0590, **16**-0592
Kumar, S.P., **11**-0435
Kumar, V., **16**-0235, **16**-0592
Kumar, V.A., **16**-0007
Kumaragurubaran, N., **12**-0146, **16**-0384, **16**-0807
Kumaran, G., **17**-0150
Kumareswaran, R., **15**-2007, **16**-1617, **19**-0595
Kumarev, V.P., **11**-0583
Kumata, Y., **04**-0011
Kume, A., **11**-0644
Kümin, A., **12**-0035
Kumli, K.F., **16**-1304
Kümmerlin, M., **04**-0386
Kumobayashi, H., **14**-0246, **15**-0611, **19**-1027, **19**-1027
Kumps, L., **16**-1239
Kunai, A., **10**-1126, **10**-1418, **10**-1443, **14**-0200, **14**-0204, **19**-0635
Kunda, S.A., **12**-0496
Kündig, E.P., **15**-2446
Kundu, A., **16**-1369
Kundu, M.K., **16**-0775, **19**-1042
Kundu, N.G., **10**-1780, **13**-0387, **16**-1915, **18**-0040
Kunerth, D.C., **10**-0693, **13**-0103
Kunesch, E., **12**-0654
Kunesch, N., **10**-1521
Kung, D.W., **10**-1659
Kung, L.-R., **15**-1100
Küng, W., **18**-0051
Kunieda, T., **19**-1049
Kunii, H., **15**-0122
Kunin, A.J., **12**-0742
Kunisada, H., **10**-1328
Kunishima, M., **10**-0846, **16**-0608, **18**-0732, **19**-1578
Kunitake, K., **12**-0547
Kuniyasu, H., **10**-1294, **10**-1303, **12**-0754, **15**-0309, **15**-0312
Kunng, F., **19**-1374
Kunshenko, B.V., **16**-0448
Kuntz, K.W., **16**-1457
Kunwar, A.C., **15**-2252
Kunz, H., **15**-1146, **16**-2133
Kunz, K., **13**-0119
Kunzer, A., **12**-0308
Künzer, H., **15**-2078
Kuo, H., **12**-0498
Kuo, M., **10**-0294
Kuo, S.C., **16**-0289
Kuo, Y., **16**-2038
Kuok, M., **04**-0292
Kupchan, S.M., **14**-0335
Kupczyk-Subotkowska, L., **18**-0656, **18**-0658
Kurabayashi, K., **18**-0640
Kurabayashi, S., **10**-0313
Kurahashi, N., **10**-0886
Kuramitsu, T., **15**-2405
Kurashima, F., **19**-0689
Kurata, K., **19**-1543
Kurata, T., **15**-1217
Kurata, Y., **13**-0218
Kurchan, A.N., **10**-0813
Kurdistani, S.K., **03**-0172
Kurek, J.T., **15**-0187, **15**-0260, **16**-2059
Kuresky, R.I., **15**-1830
Kuribayashi, M., **16**-1102

Kurihara, A., **10**-1829, **16**-0364, **16**-0364
Kurihara, H., **15**-2009
Kurihara, K., **10**-1306
Kurihara, M., **12**-0318, **16**-0151, **16**-1089
Kurihara, T., **13**-0738, **16**-1425, **16**-1459, **16**-1655
Kurimoto, M., **10**-1815
Kurita, J., **16**-1914
Kurita, K., **16**-1758
Kurita, Y., **04**-0075, **16**-0923
Kuriyama, M., **15**-1125, **16**-0894, **16**-0908
Kuriyama, Y., **07**-0022
Kurland, R.J., **05**-0088
Kuroboshi, M., **10**-1198, **10**-1207, **13**-0297, **15**-1543, **16**-0670
Kuroda, K., **15**-2152
Kuroda, M., **13**-0328
Kuroda, S., **02**-0296, **02**-0303, **02**-0304, **02**-0306, **02**-0328, **15**-0849
Kuroda, T., **16**-0565, **16**-1121
Kuroda, Y., **03**-0078, **03**-0174, **11**-0630
Kurokawa, T., **15**-0528
Kuroki, T., **10**-0828
Kuroki, Y., **16**-0761
Kurono, N., **13**-0436
Kurosa, M., **16**-0623
Kurosawa, H., **11**-0323, **12**-0754, **15**-0802
Kurosawa, K., **11**-0487, **15**-2154
Kurosawa, S., **15**-0176
Kuroyanagi, M., **19**-0999
Kurozumi, S., **12**-0253, **14**-0359
Kurreck, H., **05**-0208, **07**-0004
Kursanov, D.N., **02**-0159, **02**-0203, **10**-1382, **15**-0401, **15**-0471, **15**-0514, **15**-0717, **15**-2310, **16**-0182, **19**-1360, **19**-1450, **19**-1454
Kürshner, U., **02**-0326
Kurt, R., **15**-2040
Kurth, M., **15**-2063
Kurth, M.J., **10**-1590, **14**-0312, **17**-0263, **19**-1033
Kurth, T.L., **02**-0219
Kurts, A.L., **10**-0478, **10**-0484, **10**-0488, **10**-0489, **10**-0490, **10**-0769, **10**-1087
Kurtz, K.C.M., **10**-0997
Kurukulasuriya, R., **16**-1634
Kurumizawa, S., **15**-1590
Kurushima, H., **15**-1130
Kurusu, T., **16**-2149
Kurusu, Y., **10**-0885, **16**-0495, **16**-0620, **16**-0635
Kurz, J.L., **05**-0378, **08**-0107, **10**-0499, **10**-0499
Kurz, L.C., **10**-0499
Kurzawa, J., **17**-0046
Kurzer, F., **16**-2067
Kusabayashi, S., **10**-0220, **10**-1313, **15**-1941, **19**-0371, **19**-1339
Kusaka, C., **19**-1578
Kusakabe, M., **04**-0193
Kusaki, I., **16**-1618
Kusakin, M.S., **16**-1855
Kusama, H., **15**-0903
Kusano, K., **13**-0615
Kusche, A., **18**-0735
Kushino, Y., **10**-1852
Kustanovich, Z., **04**-0170
Kusuda, K., **19**-1358, **19**-1418
Kusui, K., **19**-1093
Kusumoto, H., **03**-0060
Kusumoto, T., **10**-1089
Kutateladze, A.G., **10**-0813, **15**-1202, **15**-1850, **16**-2086
Kutchan, T.M., **18**-0569
Kutepow, N.V., **15**-1378, **15**-2362
Kutney, G.W., **01**-0009
Kutsuwa, E., **12**-0433
Kutyrev, A.A., **15**-0039
Kutyrev, G.A., **16**-0213
Kutzelnigg, W., **02**-0013
Kuwabara, S., **15**-0823
Kuwabara, T., **14**-0246, **19**-0570
Kuwabe, S.-i., **13**-0124
Kuwajima, I., **10**-1358, **10**-1589, **10**-1650, **15**-0971, **15**-0989, **15**-1066, **16**-0498, **16**-0581, **16**-1016, **16**-1168, **16**-1195, **19**-0479
Kuwamura, T., **10**-0274
Kuwano, R., **10**-1466, **13**-0179, **15**-0333, **15**-0528
Kuwata, K.T., **15**-0967
Kuwjima, I., **13**-0595
Kuyper, L.F., **05**-0130
Kuz'min, S.V., **19**-1548
Kuz'min, V.A., **05**-0304, **05**-0312, **07**-0007
Kuzmanova, R.B., **09**-0023
Kuznetsov, D.V., **14**-0128
Kuznetsov, L.L., **12**-0710
Kuznetsov, M.A., **05**-0396
Kuznetsova, T.S., **10**-1598
Kvaran, A., **04**-0371
Kveseth, K., **04**-0283
Kvíčala, J., **10**-1046
Kwa, T.L., **10**-1218
Kwak, J., **18**-0788
Kwak, K.H., **10**-1029
Kwan, T., **04**-0174
Kwart, H., **02**-0085, **06**-0059, **06**-0064, **08**-0233, **10**-0060, **12**-0168, **14**-0086, **15**-0549, **15**-1732, **15**-2086, **16**-1481, **16**-1485, **16**-2049, **17**-0014, **17**-0031, **17**-0064, **17**-0072, **17**-0074, **17**-0495, **18**-0696, **18**-0697, **18**-0746, **18**-0750, **19**-0249
Kwart, H.K., **06**-0043
Kwart, L.D., **14**-0086, **15**-1724
Kwast, A., **13**-0671, **16**-1225
Kwiatek, J., **15**-0417
Kwiatkowski, D., **16**-0632
Kwiatkowski, G.T., **10**-0133, **16**-1316, **16**-1317
Kwitowski, P.T., **15**-2197
Kwok, F.C., **02**-0402
Kwok, W.K., **17**-0056
Kwon, D.W., **10**-0735, **10**-1156, **16**-0554
Kwon, H.B., **10**-1411
Kwon, H.S., **13**-0331
Kwon, J.S., **16**-0605
Kwon, K.M., **03**-0123
Kwon, O.O., **19**-1109, **19**-1113, **19**-1183
Kwon, S., **10**-1659
Kwon, S.S., **19**-1114
Kwon, T.W., **15**-1106, **16**-1174, **16**-1272
Kwong, F.Y., **13**-0138, **13**-0202, **13**-0242
Kwong, H., **15**-1691
Kwong, H.-L., **15**-1693, **15**-1696, **15**-1704, **15**-1903, **19**-0534
Kyba, E.B., **04**-0163
Kyba, E.P., **05**-0406, **18**-0283
Kyler, K.S., **10**-1610, **14**-0385, **19**-1422
Kyoda, M., **15**-1337
Kyong, J.B., **10**-0060
Kyrtopoulos, S.A., **12**-0702
Kyte, B., **18**-0362
Kyung, S., **16**-0677, **16**-0679
Kyung, S.H., **16**-0519
Kyushin, S., **05**-0245

L'Abbé, G., **05**-0404
L'Ecuyer, P., **13**-0758
L'Hereux, A., **13**-0213
L'Hermine, G., **15**-0111
L'Hermite, N., **13**-0325
L'Heureux, A., **07**-0120
La Belle, B.E., **19**-0900
La Chapelle, E., **11**-0257
La Londe, R.T., **14**-0417

La Rochelle, L.K., **16**-0688
La Rosa, C., **10**-0992
la Cour, T.V., **15**-0751
la Zerda, J., **10**-0610
La, B., **19**-1017
La, D.S., **18**-0780, **18**-0792
Laali, K., **08**-0019, **10**-0391, **11**-0022, **11**-0487, **18**-0035
Laali, K.K., **11**-0022, **11**-0119, **11**-0147, **19**-0529
Laan, J.A.M., **11**-0351, **19**-0057, **19**-0352
Laane, J., **04**-0352
Laane, R.W.P.M., **15**-1806
Laarhoven, W.H., **04**-0067, **04**-0069, **18**-0471, **18**-0512, **18**-0515, **18**-0518
Laba, V.I., **15**-0049, **15**-0295
Labadie, J., **16**-0363, **16**-1746
Labadie, J.W., **12**-0279, **16**-1904
Labadie, S.S., **10**-1824, **16**-1016, **16**-2176
Labano, S., **15**-1136
Labar, D., **18**-0133
Labastida, V., **04**-0327
Labaudiniere, R., **10**-0789
Labeish, N.N., **15**-1611
Labelle, M., **16**-1834
Labertrande, J., **10**-0229
Labiad, B., **16**-1644, **16**-1718
Labinger, J.A., **15**-0706
Labo, A.M., **15**-1891
Laboureur, J.L., **18**-0133, **18**-0235
Labrouillère, M., **10**-1092
Labunskaya, V.I., **15**-2199, **18**-0500
Lacey, R.N., **16**-1598
Lachance, A., **12**-0653
Lachance, H., **16**-0699, **16**-0705
Lacher, B., **14**-0434
Lachhein, S., **15**-0091, **15**-1214
Lachkar, A., **08**-0090
Lack, R.E., **15**-0124
LaCount, R.B., **16**-1265
Lacourt, A., **15**-1578
Lacroix, T., **10**-0913
Ladenheim, H., **16**-1584
Ladjama, D., **12**-0315
Laemmle, J., **16**-0523, **16**-0524, **16**-0525, **16**-0526
Laemmle, J.T., **04**-0138, **16**-0005
Laera, S., **13**-0399
Laferriere, M., **05**-0113
Lafferty, W.J., **01**-0052
Laffitte, J., **17**-0349
Lafont, F., **13**-0525
Lafontaine, J.A., **10**-1640
Laganis, E.D., **02**-0151, **15**-1785
Lago, J.M., **16**-1664
Lagow, R., **12**-0585
Lagow, R.J., **14**-0130
Lagow, R.L., **05**-0152
Lagowski, J.M., **13**-0072, **19**-0777, **19**-1544
Lahav, M., **04**-0102, **04**-0188
Lahiri, K., **13**-0474
Lahmann, M., **10**-1123
Lahoti, R.J., **11**-0237
Lahousse, F., **15**-2182, **15**-2222, **17**-0358, **19**-0840
Lahrache, H., **15**-0930
Lahti, M., **10**-0534
Lahti, M.O., **10**-0536
Lahti, P.M., **05**-0293
Lahuerta, P., **15**-2304
Lai, C., **14**-0204
Lai, C.W., **13**-0242
Lai, G., **16**-0335, **18**-0693
Lai, H.-C., **10**-0881
Lai, J.-Y., **10**-0795
Lai, J.T., **16**-0269
Lai, S., **16**-1138
Lai, Y., **02**-0125, **10**-1501, **12**-0580, **12**-0602, **19**-1658, **19**-1710
Lai, Y.H., **02**-0280
Lai, Z., **06**-0085, **10**-0414
Laicher, F., **10**-1456
Laidig, K., **15**-0143
Laidig, K.E., **04**-0278, **08**-0193, **10**-0201
Laidlaw, G.M., **04**-0508
Laidler, D.A., **03**-0101
Laidler, K.J., **01**-0095, **06**-0005, **06**-0047
Lail, M., **15**-0925
Laila, A.H., **12**-0039
Laine, R.M., **15**-0436, **19**-0288
Laing, M., **01**-0086
Laishevtsev, I.P., **13**-0377, **13**-0391
Laity, J.L., **02**-0100
Lajis, N. Hj., **16**-0512
LaJohn, L.A., **05**-0120
Lajunen, M., **10**-0178, **10**-0574, **10**-0632
Lake, F., **16**-0687
Lake, J.F., **15**-1322
Lakhvich, F.A., **19**-1446
Lakminarayana, B., **19**-1268
Lakouraj, M., **16**-1615
Lakouraj, M.M., **16**-0053, **16**-0245, **16**-1629, **10**-0897
Lakritz, J., **18**-0284
Lakshimaiah, G., **10**-1216
Lakshmi, A.B., **15**-2252
Lakshminarayana, V., **16**-0077, **16**-1580
Lal, G.S., **12**-0440
Lal, J., **18**-0825
LaLancette, E.A., **02**-0255
Lalancette, J.M., **12**-0653
Lalić, G., **10**-1562
Lallemand, J.Y., **10**-1689
Lalloz, L., **13**-0080
Laloi, M., **10**-0368
Laloi-Diard, M., **10**-0366
LaLonde, R.T., **04**-0256, **15**-0134, **16**-1870
Lam, B., **10**-0191
Lam, C., **16**-0034
Lam, C.H., **14**-0402, **19**-1581
Lam, H., **10**-0690
Lam, H.W., **15**-1247, **16**-1161
Lam, J.N., **12**-0404
Lam, K.H., **15**-1844
Lam, L.K.M., **10**-0057, **10**-0279, **10**-0280
Lam, P.Y.S., **13**-0209, **13**-0231
LaMaire, S.J., **15**-0708
Lamarque, L., **15**-0999, **15**-1923
Lamartine, R., **03**-0125
LaMattina, J.L., **19**-1212
Lamaty, G., **06**-0080, **10**-0084, **10**-0148, **10**-0537, **12**-0095, **16**-0228, **19**-0247, **19**-0951, **19**-1060
Lamb, J.D., **03**-0105
Lamb, J.T., **10**-0138
Lambert, A., **18**-0359
Lambert, C., **08**-0110
Lambert, D., **19**-1796
Lambert, D.M., **19**-1791
Lambert, G.J., **14**-0378
Lambert, J.B., **01**-0087, **02**-0206, **02**-0374, **04**-0033, **04**-0349, **04**-0353, **04**-0354, **05**-0028, **05**-0057, **05**-0339, **10**-0112, **10**-0136, **10**-0141, **10**-0147, **10**-0179, **10**-0279, **15**-0139, **15**-2282, **15**-2316, **18**-0613
Lambert, J.L., **05**-0126
Lamberti,V., **16**-1650
Lambrechts, H.J.A., **08**-0029, **11**-0204
Lamidey, A.-M., **10**-0952
Lamm, B., **10**-1591
Lammer, O., **17**-0414
Lammert, S.R., **10**-0987
Lammertsma, K., **02**-0419, **02**-0422, **05**-0002, **11**-0208, **15**-2072
Lammiman, S.A., **16**-0192
Lamoreaux, M.J., **15**-1840

Lamothe, S., **10**-1600
Lamoureux, C., **19**-1220
Lampariello, L.R., **07**-0123
Lampe, J., **16**-1014
Lampman, G.M., **04**-0435, **10**-1235
Lamrani, M., **16**-0566
Lämsä, M., **03**-0170
Lamson, D.W., **10**-1315, **19**-1750
Lamy-Pitara, E., **15**-0424
Lan, J.-B., **13**-0206
Lana, J.C.A., **16**-1777
Lancaster, N.L., **11**-0130
Lancelot, C.J., **10**-0057, **10**-0158, **10**-0162, **10**-0164, **10**-0279, **10**-0280
Lancelot, L.A., **10**-0153
Land, D.P., **19**-0016
Landau, R.L., **05**-0218, **10**-1314, **12**-0627
Landau, R.N., **15**-0434
Landell, R.G.M., **13**-0034
Lander Jr., S.W., **15**-1932
Landers, J.P., **14**-0118
Landesberg, J.M., **03**-0092
Landesman, H., **10**-1674, **10**-1678
Landgrebe, J.A., **10**-0317, **12**-0017
Landgrebe, K., **15**-1925
Landini, D., **10**-0305, **10**-0347, **10**-0453, **10**-0456, **10**-0951, **10**-0983, **10**-1065, **10**-1116, **13**-0324, **15**-0173, **17**-0369, **19**-0104, **19**-1250
Landino, J.P., **15**-0022
Landis, C.A., **15**-2394, **18**-0490
Landis, M.E., **15**-2161, **15**-2257
Landis, P.S., **17**-0125, **18**-0874
Landis, P.S., **18**-0878
Landmesser, N.G., **18**-0239
Lando, V.R., **13**-0297, **13**-0444, **13**-0475
Landon, S.J., **16**-1309
Landor, P.D., **17**-0378
Landor, S.R., **04**-0064, **15**-0106, **15**-0109, **15**-1553, **15**-1802, **15**-1994, **15**-2183, **15**-2284, **15**-2284, **17**-0378
Landré, P.D., **15**-0957
Landry, S.R., **15**-1281
Lane, A.G., **19**-0354
Lane, B.S., **13**-0504, **15**-1741
Lane, C.A., **16**-1556
Lane, C.F., **12**-0013, **12**-0488, **15**-0635, **15**-0689, **16**-0361, **18**-0429, **19**-0882, **19**-0889, **19**-0994, **19**-1151
Lane, G.C., **04**-0124
Lane, J.F., **18**-0266
Laneman, S., **13**-0238
Lang, D., **15**-2001, **15**-2096
Lang, E.S., **19**-1425
Lang, F., **10**-0624
Lang, J., **15**-0609
Lang, K., **19**-0858
Lang, R.W., **12**-0134
Láng, K.L., **10**-0376
Lang-Anderson, M.M.S., **15**-0887
Langa, F., **07**-0112, **07**-0121, **15**-2022, **16**-1174, **18**-0322, **18**-0858
Lange, B.C., **05**-0127, **05**-0189, **05**-0190, **10**-0341, **10**-0484, **12**-0420
Lange, G., **05**-0151
Lange, G.L., **19**-0387
Lange, H., **04**-0249, **04**-0490, **18**-0631
Lange, J.H.M., **07**-0120
Lange, U.E.W., **19**-1133
Langemann, A., **12**-0028
Langemann, K., **18**-0772, **18**-0797
Langensee, P., **02**-0254
Langer Jr., A.W., **12**-0392
Langer, F., **15**-1143
Langer, P., **16**-1105
Langer, V., **04**-0054
Langford, M.M., **11**-0120
Langhals, E., **10**-1616, **15**-1952
Langhals, H., **10**-0428, **10**-1616
Langille, J.D., **16**-0305
Langille, N.F., **10**-0564
Langkopf, E., **15**-2435, **18**-0575
Langle, S., **10**-1419
Langler, R.F., **02**-0192, **19**-1609
Langlet, J., **15**-2105
Langlois, B.R., **11**-0484
Langlois, D.P., **10**-0397
Langlois, N., **19**-0479
Langlois, Y., **15**-2146, **19**-0479
Langshaw, J., **14**-0097
Langstrom, B., **09**-0108
Lankamp, H., **05**-0231
Lankin, D.C., **19**-0266
Lanneau, G.F., **19**-1099, **19**-1105
Lannonn, M.I., **15**-2119
Lannou, M.-I., **16**-1987, **19**-1648
Lansbury, P.T., **05**-0411, **18**-0328, **18**-0411, **18**-0414, **19**-0942
Lansinger, J.M., **16**-0443
Lansky, A., **16**-1823
Lanter, J.C., **18**-0128
Lanz, K., **02**-0164
Lanz, M., **19**-1498, **19**-1499
Lapachev, V.V., **02**-0420
Lapekas, S.P., **16**-1803
Lapenue, M., **10**-1794
Lapeva, T., **18**-0814
Lapidus, A.L., **10**-1851, **15**-1375, **16**-0842
Lapin, Yu.A., **15**-1850
Laportere, A., **07**-0114, **11**-0220, **15**-0964, **16**-1091, **16**-2029, **19**-1318
Lapouyade, R., **10**-1794
Lappert, M.F., **12**-0448, **12**-0466, **16**-1496, **18**-0837
Lapworth, A., **16**-1495
Laramay, S., **10**-0322
Larchar, A.W., **16**-0205
Larcheveque, M., **12**-0693, **19**-0478
Larchevêque, M., **10**-1542, **15**-0467, **15**-1092, **16**-2152, **17**-0448, **18**-0692
Lardelli, G., **16**-1650
Lardicci, L., **15**-0363, **16**-1925, **17**-0375, **17**-0376, **19**-1121
Large, J.M., **15**-1254
Large, R., **14**-0290
Large, S.E., **10**-1453
Larhed, M., **07**-0116, **07**-0117, **07**-0118, **10**-0754, **11**-0513, **12**-0263, **12**-0264, **12**-0286, **13**-0373, **13**-0375, **13**-0385, **13**-0392, **13**-0413, **13**-0415, **13**-0602
Larichev, V.S., **16**-1444
Larionov, O.V., **12**-0744
Larkin, D.R., **19**-0701
Larksarp, C., **16**-0187
Larkworthy, L.F., **13**-0696
Laroche, C., **15**-0881
Laroche, P., **18**-0509
LaRochelle, R., **18**-0727
Larock, R.C., **10**-0231, **10**-0586, **10**-0648, **10**-0693, **10**-0937, **10**-0947, **10**-1037, **10**-1056, **10**-1059, **10**-1219, **10**-1237, **10**-1266, **10**-1267, **10**-1297, **10**-1335, **10**-1377, **10**-1518, **10**-1545, **10**-1556, **10**-1579, **10**-1596, **10**-1599, **10**-1610, **10**-1611, **10**-1612, **10**-1623, **10**-1656, **10**-1666, **10**-1691, **10**-1695, **10**-1732, **10**-1832, **11**-0224, **11**-0409, **11**-0417, **11**-0441, **11**-0458, **11**-0532, **11**-0621, **12**-0056, **12**-0110, **12**-0172, **12**-0238, **12**-0312, **12**-0324, **12**-0475, **12**-0482, **12**-0483, **12**-0527, **12**-0530, **12**-0539, **12**-0559, **12**-0652,

Larock, R.C., (*Continued*) **12**-0690, **13**-0197, **13**-0250, **13**-0278, **13**-0361, **13**-0363, **13**-0368, **13**-0378, **13**-0389, **13**-0421, **13**-0422, **13**-0464, **13**-0612, **13**-0621, **13**-0624, **13**-0656, **14**-0124, **14**-0207, **14**-0248, **14**-0251, **14**-0369, **14**-0381, **14**-0382, **14**-0382, **14**-0384, **14**-0389, **14**-0389, **14**-0401, **14**-0429, **15**-0165, **15**-0186, **15**-0189, **15**-0206, **15**-0206, **15**-0228, **15**-0258, **15**-0263, **15**-0274, **15**-0276, **15**-0282, **15**-0358, **15**-0370, **15**-0387, **15**-0399, **15**-0442, **15**-0504, **15**-0560, **15**-0573, **15**-0602, **15**-0639, **15**-0919, **15**-0947, **15**-0960, **15**-1054, **15**-1063, **15**-1066, **15**-1078, **15**-1090, **15**-1193, **15**-1197, **15**-1363, **15**-1408, **15**-1510, **15**-1555, **15**-1571, **15**-1581, **15**-1584, **15**-1655, **15**-1725, **15**-1854, **15**-1980, **15**-2166, **15**-2261, **15**-2270, **15**-2271, **15**-2362, **15**-2363, **15**-2395, **15**-2396, **15**-2396, **15**-2396, **15**-2397, **16**-0121, **16**-0126, **16**-0158, **16**-0350, **16**-0438, **16**-0478, **16**-0496, **16**-0584, **16**-0870, **16**-0964, **16**-1064, **16**-1076, **16**-1187, **16**-1232, **16**-1255, **16**-1283, **16**-1288, **16**-1375, **16**-1462, **16**-1488, **16**-1519, **16**-1576, **16**-1619, **16**-1631, **16**-1648, **16**-1678, **16**-1702, **16**-1715, **16**-1800, **16**-1824, **16**-1853, **16**-1878, **16**-1882, **16**-1900, **16**-1939, **16**-2005, **16**-2094, **17**-0153, **17**-0196, **17**-0206, **17**-0238, **17**-0293, **17**-0302, **17**-0312, **17**-0330, **17**-0370, **17**-0393, **17**-0423, **17**-0469, **17**-0473, **18**-0142, **18**-0159, **18**-0214, **18**-0351, **18**-0445, **18**-0600, **18**-0730, **19**-0024, **19**-0045, **19**-0055, **19**-0069, **19**-0109, **19**-0313, **19**-0318, **19**-0387, **19**-0449, **19**-0575, **19**-0638, **19**-0657, **19**-0669, **19**-0672, **19**-0688, **19**-0694, **19**-0708, **19**-0891, **19**-0912, **19**-0947, **19**-1015, **19**-1071, **19**-1084, **19**-1099, **19**-1105, **19**-1123, **19**-1166, **19**-1179, **19**-1196, **19**-1234, **19**-1256, **19**-1290, **19**-1301, **19**-1352, **19**-1372, **19**-1381, **19**-1392, **19**-1394, **19**-1440, **19**-1482, **19**-1486, **19**-1562, **19**-1580, **19**-1647, **19**-1711, **19**-1728, **19**-1768
Larouche, D., **15**-0911
Larrahondo, J., **17**-0494
Larrosa, I., **16**-1015
Larsen, A.S., **09**-0111
Larsen, D.S., **15**-0073, **15**-1604
Larsen, D.T., **17**-0094
Larsen, D.W., **15**-0057
Larsen, J., **15**-0894, **19**-0287
Larsen, J.W., **05**-0092, **10**-0085, **10**-0430, **10**-0444, **11**-0111
Larsen, R.D., **15**-0440
Larsen, S., **19**-0475
Larson, C.A., **10**-0920
Larson, E.G., **05**-0339
Larson, G.L., **06**-0016, **10**-1643, **14**-0171
Larson, H.O., **10**-1001, **12**-0207, **19**-0640, **19**-0763
Larson, J.K., **10**-1590, **16**-2034
Larson, J.W., **08**-0146
Larson, K.D., **19**-0281
Larson, S., **11**-0298
Larsson, E.M., **14**-0252
LaRue, M., **17**-0343
Lasemi, Z., **10**-1082
Lash, T.D., **03**-0134
Lashley, J.C., **19**-0530
Lashley, L.K., **14**-0372
Laskar, D.D., **10**-0843, **16**-0149, **16**-0234, **16**-0882, **16**-0927, **16**-1253, **16**-1997, **19**-1264
Laskovics, F.M., **16**-0040
Lasne, M., **02**-0412, **15**-2086
Lasne, M.-C., **16**-0436, **16**-1765, **16**-1925
Lasne, M.C., **16**-0263
Laso, N.M., **15**-1334
Lasperas, M., **16**-0527
Lassaletta, J.-M., **19**-0300
Last, L.A., **18**-0506
Lastomirsky, R.R., **18**-0367
Laszlo, P., **01**-0033, **06**-0069, **08**-0146, **11**-0141, **11**-0142, **11**-0348, **15**-1795, **16**-1817, **18**-0183
Lathan, W.A., **01**-0052
Lathioor, E.C., **07**-0036
Latif, N., **17**-0224
Latimore, M.C., **06**-0064
Latouche, R., **16**-0411
Latourette, H.K., **11**-0443
Lattanzi, A., **15**-0232, **15**-1741, **19**-0823
Lattes, A., **10**-1006, **15**-0314, **15**-0327, **16**-1021
Latxague, L., **13**-0077
Latypov, S.K., **04**-0108, **04**-0110
Latypova, F.M., **10**-1382
Lau, C.D.H., **04**-0405, **04**-0407, **04**-0420
Lau, C.J., **04**-0189
Lau, C.P., **16**-0648
Lau, J.C., **16**-1234
Lau, K.-C., **19**-0746
Lau, K.S.Y., **17**-0328
Lau, P.W.K., **16**-1195
Lau, T.-C., **19**-0610, **19**-0618
Lau, W., **13**-0662
Lau, Y.K., **08**-0222, **08**-0223
Laube, T., **02**-0373, **05**-0008, **05**-0083, **05**-0127, **05**-0192, **10**-0132, **10**-0187, **16**-0006
Laue, P., **12**-0480
Lauens, M., **10**-1534
Lauenstein, O., **14**-0142, **14**-0150
Lauer, R.F., **12**-0248, **17**-0290, **17**-0293
Lauer, W., **12**-0646
Lauer, W.M., **18**-0705
Laufer, A.H., **05**-0334
Laugal, J.A., **15**-0550
Laughlin, R.G., **05**-0377
Laughton, P.M., **06**-0087
Launay, J., **04**-0136
Laungani, A.Ch., **15**-1137
Lauransan, J., **03**-0015
Laureillard, J., **10**-0083
Laurence, C., **01**-0051, **03**-0015, **08**-0090, **08**-0091, **08**-0092, **08**-0093, **08**-0094, **08**-0095, **09**-0016, **10**-0430
Laurent, A., **12**-0223, **12**-0508, **15**-0115, **15**-1545, **16**-0954, **18**-0033, **18**-0324, **19**-1245
Laurent, M., **10**-0897
Laurent, P., **10**-1820
Laurent, R., **07**-0114
Laurent-Robert, H., **16**-1091
Laurenti, D., **10**-0886
Laurenzo, K.S., **13**-0680
Lauria, E., **15**-0243
Laurie, V.W., **01**-0038, **01**-0052, **04**-0465, **08**-0233
Lauru, S., **11**-0218
Lautens, M., **10**-0666, **10**-1555, **13**-0441, **13**-0608, **15**-0858, **15**-0932, **15**-0943, **15**-2441, **17**-0233, **18**-0783, **19**-1386
Lauterbach, H., **15**-0014
Laval, G., **12**-0657
Lavallée, P., **10**-1089
Lavanish, J.M., **04**-0435
Lavarez-Toledano, C., **19**-0261
Lavastre, O., **18**-0773

Lavenot, L., **13**-0301
Lavie-Compin, G., **10**-0925
Lavieri, F.P., **18**-0860
Lavigne, A., **19**-0279
LaVilla, J.A., **05**-0386
Lavis, J.M., **12**-0258
Lavlinskaia, N., **07**-0116
Lavrov, V.I., **10**-0661, **15**-0250
Law, F.C.P., **18**-0076
Law, K.S., **03**-0072
Lawesson, S., **10**-0910, **12**-0438, **16**-0211, **16**-0212, **16**-0220, **16**-1252, **16**-1807, **18**-0696
Lawesson, S.-O., **16**-0220
Lawler, M.J., **10**-1468
Lawler, R.G., **05**-0218, **05**-0219, **05**-0221, **05**-0222, **10**-1314, **10**-1318, **10**-1320, **12**-0604, **12**-0627, **12**-0628
Lawlor, J.M., **15**-0417
Lawrence, J.P., **18**-0756
Lawrence, K.E., **12**-0611
Lawrence, L.M., **12**-0606
Lawrence, N.J., **10**-1431, **16**-1345
Lawrence, R.M., **04**-0196
Lawrie, C.J., **15**-2402
Lawrie, C.W., **16**-1571
Lawrynowicz, W., **15**-2275
Laws, A.P., **11**-0112
Lawson, A.J., **11**-0162
Lawson, D.D., **02**-0135
Lawson, E.C., **19**-0950
Lawson, J., **02**-0295
Lawson, R.C., **05**-0212
Lawton, B.T., **18**-0886
Lawton, R.G., **02**-0358, **10**-0122
Laxman, E., **10**-0560, **10**-1138, **16**-1781, **19**-1267
Laxman, N., **10**-1109, **16**-1781
Laxmi, Y.R.S., **19**-0893
Laye, P.G., **04**-0234
Layek, S., **14**-0440
Laynez, J., **08**-0125, **08**-0131
Layton, R.B., **15**-1150, **15**-1151
Lazar, L., **02**-0429
Lazár, M., **14**-0004
Lazár, M., **14**-0005
Lázár, L., **02**-0430
Lazareva, M.I., **14**-0162, **19**-0606
Lazaridis, N.V., **12**-0160
Lazaris, A.Ya., **16**-0139
Lazarus, M., **19**-0547
Lazdins, I., **10**-0062
Lazny, R., **16**-0091, **16**-1029
Lazzaroni, R., **11**-0355
Le Bars, J., **13**-0399
Le Berre, A., **15**-0346
Le Bideau, F., **16**-0469
Le Bigot, Y., **16**-1324
Le Blanc, R., **13**-0161
Le Blond, C., **19**-1028
Le Blond, C.R., **13**-0480
Le Borgne, J.F., **17**-0448
Le Bris, A., **16**-0346
Le Carpentier, J., **05**-0063, **05**-0075, **11**-0424, **11**-0454
Le Corre, M., **19**-1490, **19**-1509
Le Deit, H., **19**-1509
Le Drian, C., **13**-0521, **18**-0037
Le Fave, G.M., **10**-0510
Le Fevre, R.J.W., **03**-0099, **04**-0280
Le Gall, T., **16**-1381
Le Gras, J., **15**-2326
Le Guen, J., **11**-0049
Le Hénaff, P., **16**-0036
Le Maistre, J.W., **17**-0444
Le Marrec, N., **16**-0874
Le Maux, P., **15**-2307
Le Merrer, Y., **16**-1057
Le Moigne, F., **05**-0214
Le Ny, G., **10**-0208
Le Paih, J., **15**-0813
Le Perchec, P., **15**-0961, **18**-0671
Le Questel, J.-Y., **08**-0090
Le Roux, C., **11**-0423
Le Tadic-Biadatti, M.-H., **05**-0308
le Noble, W.J., **05**-0099, **06**-0051, **09**-0087, **10**-0063, **10**-0081, **10**-0178, **10**-0476, **10**-0, **10**-0515, **15**-0119, **15**-2027, **16**-0006, **17**-0067, **19**-1019, **19**-1339
Le, J.C.D., **15**-0604
Le, N.A., **15**-2282
Le, V.T., **10**-0557
Le, Z.-G., **10**-0869, **10**-1475, **16**-1773
Lea, L., **10**-1437
Leach, A.G., **15**-0967, **15**-0991, **15**-1213, **15**-2019, **16**-1738, **18**-0568, **18**-0605
Leach, D.R., **14**-0389
Leadbeater, N.E., **07**-0118, **07**-0119, **09**-0117, **13**-0260, **13**-0277, **13**-0298, **13**-0482, **13**-0493, **13**-0529, **13**-0541, **13**-0546, **15**-1741, **16**-0774, **13**-0271
Leader, H., **15**-0498, **16**-2160
Leahy, D.K., **10**-0607, **10**-1468, **10**-1469, **10**-1640
Leahy, J.W., **16**-0772, **16**-0777 **16**-0797
Leake, W.W., **13**-0572
Leal, J.M., **08**-0118
Leal, S., **13**-0401
Leandri, E., **11**-0242
Leanna, M.R., **19**-0195
Leardini, R., **05**-0310, **18**-0073
Learn, K., **19**-1383, **19**-1417, **19**-1494
Learn, K.S., **16**-0493
Lease, M.F., **15**-0485
Leathers, T., **19**-0708
Leavell, K.H., **02**-0080, **18**-0589
Leaver, D., **02**-0317
Leavey, T., **13**-0606
Lebedev, B.L., **15**-0713
Lebedev, M.Y., **16**-2055
Lebedev, S.A., **15**-1199
LeBel, N.A., **10**-0133, **15**-0054, **15**-0126, **16**-0966, **16**-1469, **17**-0003, **17**-0249, **17**-0259
Lebel, H., **15**-2337, **16**-1372, **16**-1373
Leber, P.A., **18**-0473, **18**-0582
Leber, W., **18**-0642
LeBerre, N., **16**-2157
LeBlanc, B.F., **17**-0422
LeBlanc, R., **18**-0609
Leblanc, J.C., **19**-1099
Leblanc, Y., **10**-1089, **15**-0384, **16**-1326
LeBlond, C., **15**-0434
LeBras, J., **19**-0533
Lebreton, C., **16**-0878
Lebreton, J., **16**-0578
Lebrilla, C.B., **15**-0450
Leca, D., **15**-2400
Lecadet, D., **16**-1398
Lecce, L., **15**-0125
Lecea, B., **15**-1944, **15**-1947, **15**-2055, **16**-0832
Lechevallier, A., **10**-0540
Lechtken, P., **07**-0040, **18**-0495
LeClair, G., **15**-2022
Leclerc, E., **10**-0848
Lécolier, S., **16**-0436
Lecomte, F., **13**-0334
Lecomte, J.-P., **07**-0076
Lecomte, L., **10**-0587, **16**-0469
Leconte, M., **18**-0756, **18**-0821
Lectka, T., **03**-0061, **03**-0062, **12**-0049, **12**-0124, **12**-0167, **15**-2064, **15**-2180, **16**-2103, **16**-2105, **16**-2106, **17**-0318, **19**-1273, **19**-1709
Led, J.J., **03**-0077
Ledaal, T., **17**-0523
Lededev, B.A., **12**-0711
Lederer, M., **15**-1579
Ledlie, D.B., **15**-1074, **18**-0052

Lednicer, D., **04**-0068, **16**-0102
Ledon, H., **12**-0215
Ledon, H.J., **15**-1795
Ledoux, M.J., **15**-0454
Ledwith, A., **05**-0318, **05**-0380, **15**-2195, **15**-2235, **17**-0496
Lee Jr., C.T., **09**-0097
Lee, A., **16**-1735
Lee, A.-L., **15**-0147, **15**-1667
Lee, A.F., **13**-0480
Lee, A.S.-Y., **16**-0959, **16**-1640
Lee, A.W.M., **17**-0234
Lee, B., **17**-0524
Lee, B.-S., **10**-0019, **10**-0052
Lee, B.C., **10**-0313
Lee, B.M., **19**-1189
Lee, C., **13**-0645, **19**-0099, **19**-0120
Lee, C.-H., **16**-1966
Lee, C.-L.K., **16**-0862
Lee, C.-S., **15**-1903, **19**-0569
Lee, C.-W., **13**-0506
Lee, C.B., **16**-0168, **16**-0179
Lee, C.C., **02**-0142, **10**-0156, **10**-0210, **10**-0210, **11**-0379, **15**-0137, **18**-0002, **18**-0022, **18**-0023, **18**-0024, **18**-0026
Lee, C.G., **16**-0387
Lee, C.K., **19**-0184
Lee, C.K.Y., **15**-1950
Lee, C.S., **10**-1614, **14**-0061
Lee, C.W., **15**-2041, **18**-0767, **18**-0795, **18**-0805
Lee, D., **13**-0191, **15**-0005, **16**-0373, **18**-0684, **18**-0781, **18**-0789
Lee, D.-H., **15**-2058
Lee, D.-M., **15**-0833
Lee, D.-S., **15**-1139, **19**-1052
Lee, D.C., **15**-0816
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Lee, D.G., **08**-0027, **08**-0036, **15**-1679, **19**-0010, **19**-0047, **19**-0070, **19**-0073, **19**-0099, **19**-0103, **19**-0110, **19**-0249, **19**-0250, **19**-0388, **19**-0391, **19**-0403, **19**-0409, **19**-0417, **19**-0426, **19**-0453, **19**-0565, **19**-0566, **19**-0590, **19**-0671, **19**-0693, **19**-0731, **19**-0740, **19**-0831, **19**-0851
Lee, D.R., **15**-0855
Lee, E., **03**-0210, **15**-1258, **15**-1371
Lee, E.J., **19**-0740
Lee, E.K.C., **07**-0044
Lee, F.-C., **15**-0908
Lee, F.L., **04**-0502
Lee, G., **04**-0491
Lee, G.A., **19**-0660
Lee, G.H., **15**-2302
Lee, G.H., **17**-0528
Lee, G.K., **19**-0773
Lee, G.M., **15**-1641
Lee, H., **08**-0155, **15**-1364, **16**-1743, **16**-1787, **19**-0561
Lee, H.-C., **16**-1029, **16**-1030
Lee, H.-W., **13**-0190
Lee, H.-Y., **15**-0479, **18**-0789
Lee, H.D., **18**-0448
Lee, H.J., **19**-1299
Lee, H.K., **17**-0528
Lee, H.M., **13**-0341, **13**-0401
Lee, H.S., **19**-1183
Lee, H.T., **19**-1077
Lee, H.W., **05**-0314, **09**-0021, **10**-0052, **10**-0072, **10**-0304, **16**-2143
Lee, I., **06**-0025, **06**-0026, **09**-0021, **10**-0019, **10**-0048, **10**-0052, **10**-0072, **10**-0304, **10**-0313, **15**-0164, **16**-1512, **16**-2143
Lee, I.H., **06**-0028
Lee, I.S., **16**-0823, **19**-1165
Lee, J., **02**-0416, **07**-0032, **10**-0499, **10**-1089, **18**-0243, **19**-1361
Lee, J.-H., **12**-0295, **16**-0752
Lee, J.-y., **13**-0635
Lee, J.B., **16**-1879, **18**-0352, **18**-0376, **18**-0836, **19**-1305
Lee, J.C., **10**-0588, **10**-0694, **10**-1031, **10**-1083, **12**-0122, **12**-0128, **12**-0129, **19**-0208, **19**-0332, **19**-0459, **19**-0496, **19**-0524, **19**-0555, **19**-1183
Lee, J.G., **10**-1029, **14**-0356, **17**-0015, **19**-0030, **19**-0732, **19**-1188
Lee, J.H., **10**-1453, **15**-1136
Lee, J.I., **10**-0694, **16**-1963, **16**-1980
Lee, J.K., **03**-0001, **16**-0136
Lee, J.K., **18**-0601
Lee, J.M., **18**-0788
Lee, J.T., **10**-1551
Lee, J.W., **03**-0189
Lee, J.Y., **03**-0184, **19**-0208
Lee, K., **10**-0735, **10**-1401, **10**-1471, **13**-0620, **15**-0820, **15**-0903, **15**-0918, **15**-1079, **15**-1177, **16**-0599, **16**-2167
Lee, K.-J., **16**-1742, **19**-0184, **19**-0684
Lee, K.-S., **11**-0171
Lee, K.C., **19**-1213
Lee, K.J., **15**-1834
Lee, K.M., **19**-0231
Lee, K.W., **18**-0886, **18**-0888, **19**-1107
Lee, K.Y., **16**-0387, **19**-0260
Lee, L., **15**-0069
Lee, L.C., **15**-1550
Lee, L.F., **16**-0581
Lee, L.Y., **19**-0416
Lee, M., **13**-0620, **19**-0120
Lee, M.J., **10**-1626
Lee, M.K.T., **03**-0051
Lee, M.W., **06**-0059
Lee, N.E., **15**-0430
Lee, N.H., **19**-0137, **19**-0569, **19**-1213
Lee, N.R., **16**-1963
Lee, P.G., **15**-2331
Lee, P.H., **10**-1401, **10**-1402, **10**-1471, **13**-0567, **13**-0620, **15**-0820, **15**-0903, **15**-0918, **15**-1079, **15**-1177, **16**-0596, **16**-0599, **18**-0243
Lee, P.S., **15**-0145
Lee, R.E., **05**-0126
Lee, S., **10**-1279, **13**-0583, **13**-0620, **15**-0820, **16**-0739, **18**-0719
Lee, S.-G., **15**-1411, **15**-1436, **15**-1439, **16**-1536
Lee, S.-g., **15**-0604
Lee, S.-H., **13**-0191, **13**-0515
Lee, S.-J., **16**-0637
Lee, S.-W., **13**-0330, **13**-0331, **13**-0517, **16**-0734
Lee, S.-Y., **15**-0820, **15**-1596
Lee, S.B., **13**-0136, **15**-0235, **15**-0262
Lee, S.E., **19**-1183
Lee, S.H., **15**-0494, **16**-0351, **19**-0998, **19**-1324, **19**-1751
Lee, S.I., **15**-1411, **15**-1431, **15**-1432, **15**-1438, **15**-1439
Lee, S.J., **10**-1166, **12**-0122, **15**-1312, **16**-1994, **19**-0208, **19**-1612, **19**-1685
Lee, S.K., **18**-0722
Lee, S.L., **19**-1480
Lee, S.P., **16**-1811
Lee, S.S., **15**-1432
Lee, S.W., **10**-1402, **13**-0378, **13**-0620, **13**-0620, **16**-0221
Lee, S.Y., **02**-0403, **17**-0361
Lee, T.J., **02**-0062
Lee, T.S., **19**-0078
Lee, T.V., **19**-1022
Lee, T.W., **15**-2012
Lee, T.W.S., **08**-0049, **16**-2146
Lee, W., **10**-1723, **15**-2314, **16**-1080, **19**-0337
Lee, W.-D., **16**-0777, **16**-0788
Lee, W.-M., **10**-0600

Lee, W.-S., **19**-0534
Lee, W.G., **05**-0135, **17**-0056
Lee, W.K., **10**-1272, **12**-0630, **16**-0946
Lee, W.S., **16**-1751
Lee, W.Y., **03**-0147
Lee, Y., **16**-1988, **19**-1277
Lee, Y.-M., **16**-1174
Lee, Y.-T., **13**-0295
Lee, Y.B., **16**-0136
Lee, Y.C., **19**-0332
Lee, Y.R., **18**-0218
Lee, Y.S., **10**-0052, **18**-0788
Lee, Y.T., **12**-0052
Lee,Y.Y., **16**-0136
Lee-Ruff, E., **08**-0077, **10**-0296, **10**-0301, **17**-0511
Lee, I., **16**-0752
Lee, K., **16**-0596
Lee, S.-J., **10**-1454
Leebrick, J.R., **12**-0457
Leeds, J.P., **19**-1236
Leeke, G.A., **15**-1950
Leeming, S.W., **13**-0269
Leenson, I.A., **15**-0181
Leermakers, P.A., **05**-0333, **17**-0527
Lees, W.A., **03**-0039
Leese, M.P., **13**-0400
Lefebvre, C., **10**-0400
Lefebvre, D., **08**-0191
Lefebvre, F., **18**-0821
Lefebvre, G., **16**-0346
Lefeuvre, M., **16**-1713
Lefeuvre, S., **07**-0114, **15**-2022
Leffek, K.T., **06**-0070, **06**-0074, **06**-0086, **08**-0102, **10**-1188, 13, **17**-0046, **17**-0052
Leffingwell, J.C., **14**-0290, **19**-0025
Leffler, J.E., **06**-0043
LeFlohic, A., **18**-0812
Lefort, L., **15**-1131
Lefour, J., **02**-0006, **02**-0041
Lefrançois, J.-M., **10**-0625
LeGall, T., **15**-0701
Legan, E., **10**-0370, **16**-2150
Legars, P., **10**-0587
Legault, R., **18**-0143
Leggett, T.L., **05**-0344
Leggett, T.L., **15**-0058
Leginus, J.M., **15**-1932
LeGoff, E., **02**-0178
LeGoff, E., **15**-2329
Legon, A.C., **03**-0026, **03**-0037, **04**-0377, **04**-0380
Legrand, M., **04**-0268
Legrand, O., **10**-1155, **19**-1032
Legros, J., **10**-1439, **15**-1770, **16**-0863
LeGuyader, F., **15**-0865
Lehd, M., **15**-2098
Lehmann, C.W., **18**-0828, **19**-1129
Lehmann, U., **13**-0434
Lehmkuhl, H., **05**-0163, **15**-0866
Lehn, J., **04**-0243
Lehn, J.M., **03**-0101, **03**-0116, **03**-0118, **03**-0119, **03**-0153, **04**-0033, **04**-0036, **04**-0163, **04**-0242, **04**-0244, **05**-0121, **18**-0842
Lehner, H., **16**-0042
Lehnert, E.K., **15**-2353
Lehnert, W., **16**-1191, **19**-0446
Lehnig, M., **05**-0246
Lehr, G.F., **10**-1320
Lehr, R.E., **15**-2103, **15**-2107, **15**-2108, **15**-2110, **15**-2111, **15**-2183, **15**-2184, **17**-0354, **18**-0166, **18**-0477, **18**-0478
Lei, A., **13**-0477, **15**-0820, **15**-0821, **19**-1028
Lei, C.-J., **10**-1776
Lei, X., **10**-1370
Lei, X., **16**-1280
Lei, Z.-G., **11**-0241
Leibfritz, D., **19**-1573
Leigh, D.A., **03**-0196, **10**-0854
Leigh, G., **18**-0756
Leigh, S.J., **04**-0163
Leigh, W.J., **07**-0036, **07**-0054, **18**-0475, **18**-0481
Leighton, J.L., **15**-1136, **15**-1490, **16**-0762, **16**-0916
Leighton, T.G., **07**-0069
Leijonmarck, H., **11**-0335
Leimer, K.E., **17**-0092
Lein, G.M., **03**-0142
Leinhard, G.E., **16**-0020
Leino, R., **19**-0867
Leis, J.R., **11**-0125, **12**-0197, **12**-0700
Leiserowitz, L., **04**-0102, **04**-0188
Leisten, J.A., **10**-0521, **16**-1600
Leister, M.C., **04**-0389
Leitch, L.C., **11**-0116
Leite, S.L.S., **19**-0862
Leitereg, T.J., **04**-0137
Leitich, J., **04**-0212
Leitner, A., **10**-1299, **13**-0311, **15**-0894
Leitner, W., **09**-0099, **18**-0772, **19**-1155
Leivers, M., **18**-0503
Lejon, T., **16**-0372
Lekhok, K.C., **16**-1176
LeLagadec, R., **10**-1247
Leleu, G., **19**-0674
Lem, G., **15**-0154, **15**-2238
LeMahieu, R., **19**-1457
LeMaire, M., **10**-0605, **18**-0145
LeMaire, S.J., **15**-1505
Lemaire, J., **19**-0701
Lemaire, M., **10**-0976, **10**-1019, **11**-0261, **12**-0340, **13**-0301, **15**-0865, **16**-1778, **19**-1028
Lemaire-Audoire, S., **19**-1622
Lemal, D.M., **02**-0151, **04**-0435, **15**-1785, **15**-2255, **17**-0351, **18**-0493, **18**-0494
Lemay, G., **16**-0517, **16**-0953
Lemek, T., **13**-0671
LeMénez, P., **10**-1521
Lemenovskii, D.A., **02**-0166
Lemière, G.L., **04**-0017
Lemière, G.L.F., **13**-0174, **13**-0178, **13**-0196
Lemieux, R.U., **04**-0363, **04**-0366, **15**-1674, **19**-0390, **19**-0399
Lemin, A.J., **19**-0074
Lemini, C., **18**-0232
Lemor, A., **10**-1019
Lemoucheux, L., **16**-0436, **16**-1765, **16**-1925
Lemoult, S.C., **18**-0362
Lempert, K., **16**-1660
Lena, J.I.C., **19**-0320
Lenardão, E.J., **15**-0313
Lendzian, F., **07**-0018
Lengel, R.K., **05**-0332
Lengyel, I., **10**-1000, **11**-0253
Lenmartz, H.-W., **05**-0290
Lennartz, H., **10**-0175, **15**-2232, **18**-0590
Lenoir, D., **01**-0043, **10**-0177, **10**-0178, **10**-0181, **15**-1515, **15**-1524, **19**-1710, **19**-1713
Lensen, N., **16**-1999
Lentz, C.M., **10**-1370, **15**-1091
LeNy, G., **10**-0134
Lenz, F., **15**-0087
Lenz, G., **15**-2235, **16**-2083
Lenz, G.R., **15**-2238
Lenz, P.A., **10**-0530, **10**-0534
Lenz, R., **19**-0124, **19**-0125
Leo, A., **09**-0020, **09**-0063, **19**-0250
Léon, H., **16**-0878
Leonard, J.E., **04**-0230, **10**-0341
Leonard, N.J., **04**-0458, **16**-0295, **19**-0046, **19**-0798
Leonard, N.M., **16**-0160, **16**-0764, **18**-0140
Leonarduzzi, G.D., **15**-0195
Leone, R.E., **18**-0009

Leone-Bay, A., **13**-0253, **19**-1363
Léonel, É., **13**-0304, **15**-2273
Leong, A.Y.W., **10**-1668
Leonov, A.A., **16**-1309
Leonov, A.P., **15**-0810
Leonova, E.V., **02**-0166
Leonova, T.V., **16**-1855
Leopold, A., **13**-0691
Leopold, D.G., **05**-0332
Leou, S.-P., **15**-0481, **15**-0918
LePage, T.J., **02**-0041, **05**-0278
Lepeska, B., **15**-0031, **15**-0654, **15**-0654
Lepifre, F., **07**-0118
Lepley, A.R., **05**-0218, **10**-1314, **10**-1314, **10**-1716, **12**-0627, **13**-0164, **13**-0759, **18**-0380, **18**-0387, **18**-0388, **05**-0219
Lepoint, T., **07**-0082
LePoire, D.M., **10**-0756
Lepore, S.D., **10**-0608
LeQuestel, J.-Y., **08**-0092
Leray, E., **05**-0273
Lerebours, R., **13**-0544, **13**-0504
Leriverend, C., **16**-1384
Leriverend, P., **18**-0553
Lerman, O., **11**-0266, **11**-0312, **12**-0137, **15**-1582
Lerner, L.R., **19**-0722
Leroi, G.E., **04**-0276, **13**-0047
LeRoux, C., **10**-1092, **16**-1091
Leroux, Y., **16**-0497
Leroy, B., **10**-0549
Leroy, M., **03**-0136
Lerum, R.V., **15**-1154
Lesage, D., **15**-1452
Lesar, A.M., **11**-0078
Leseul, J., **16**-1847
Lesheski, L., **10**-1437
Leshina, T.V., **10**-1314
Lesieur, D., **19**-1791
Lesko, P.M., **04**-0495
Lesma, G., **16**-0687
Lesovoy, D.E., **16**-1444
Lessard, J., **15**-1611
Lessène, G., **12**-0320
Lester Jr., W.A., **07**-0015, **07**-0043
Leszczynski, J., **12**-0087, **17**-0206
LeTadic-Biadatti, M.-H., **05**-0306
Lete, E., **16**-1964
Letendre, L.J., **10**-1560
Lethbridge, A., **19**-0724
Letort, M., **19**-0701
LeTourneau, M.E., **12**-0190
Letsinger, R.L., **17**-0184, **19**-1219, **19**-1689, **13**-0286
Leuck, D.J., **16**-0361
Leung, C., **01**-0042
Leung, C.W., **16**-0681
Leung, D., **18**-0503
Leung, K.P., **16**-1468
Leung, M.-K., **12**-0459
Leung, M.-k., **04**-0081
Leung, S.-W., **15**-2088
Leung, S.S.-W., **16**-0463
Leung, T., **04**-0422
Leung, W., **13**-0422
Leuschner, G., **14**-0289
Leusink, A.J., **18**-0329
Leusink, J., **03**-0083
Leussing, D.L., **16**-0157
Lev, D.A., **15**-0213
Levai, A., **15**-1807, **12**-0322
Levand, O., **19**-0640
Levanda, O.G., **19**-0721
Levart, M., **15**-1795
Levchenko, T.S., **10**-1476
Levek, T.J., **15**-2219
Levene, R., **10**-1338, **15**-0187
Leveque, J.-M., **07**-0083
Lever Jr., O.W., **10**-1666, **12**-0408, **15**-1349, **16**-1203
Leveson, L.L., **10**-0519
Levi, G.I., **01**-0095
Levi, N., **07**-0050
Levillain, J., **10**-1454
Levin, C., **10**-0171
Levin, C.C., **04**-0074
Levin, D., **16**-0624, **16**-0871
Levin, J.I., **12**-0270, **15**-2122, **16**-1835
Levin, P.P., **05**-0304
Levin, R.D., **08**-0223
Levin, R.H., **13**-0037
Levina, A., **19**-0537
Levina, I.S., **15**-2238
Levina, I.Yu., **18**-0035, **18**-0046
Levina, R.Ya., **18**-0616
Levine, R., **12**-0674, **13**-0572
Levine, R.A., **04**-0389
Levine, S.G., **19**-1067
Levinson, M.I., **16**-0213
Levisalles, J., **12**-0074, **15**-1074, **18**-0836
Levisky, J.A., **11**-0187
Levit, A.F., **13**-0746, **19**-0755, **19**-1570
Levitin, I., **19**-1295
Levitin, I.Ya., **12**-0013
Levitina, E.S., **04**-0136
Levitt, B.W., **13**-0679
Levitt, L.S., **01**-0046, **09**-0059, **13**-0679
Levitt, T.E., **16**-1812, **19**-1077
Levitz, M., **10**-0012
Levkovskaya, G.G., **15**-1608
Levy, A.B., **10**-1764, **12**-0500, **12**-0518, **15**-0020, **15**-1634, **18**-0429, **18**-0435
Levy, A.J., **15**-0044, **15**-0045
Levy, G.C., **08**-0023
Levy, H., **18**-0596
Levy, J.F., **10**-0069
Levy, M., **15**-1536
Lew, G., **18**-0449
Lewarchik, R.J., **13**-0749
Lewars, E.G., **15**-1784
Lewars, Y., **18**-0223
Lewellyn, M.E., **17**-0343
Lewin, A.H., **03**-0012, **10**-0711, **11**-0488, **13**-0459
Lewis, D.C., **14**-0045, **18**-0081
Lewis, D.E., **06**-0063, **06**-0069
Lewis, D.L., **16**-1382
Lewis, E.S., **02**-0080
Lewis, E.J., **15**-2332
Lewis, E.S., **06**-0026, **06**-0059, **06**-0062, **08**-0142, **08**-0162, **09**-0016, **09**-0035, **10**-0089, **10**-0103, **10**-0211, **10**-0212, **10**-0229, **10**-0304, **13**-0029, **13**-0033, **14**-0045, **18**-0589, **19**-1569
Lewis, F.D., **15**-2235, **15**-2247, **18**-0282
Lewis, G.N., **10**-0003
Lewis, G.R., **03**-0209
Lewis, H.B., **14**-0335
Lewis, H.L., **05**-0149
Lewis, I.C., **09**-0047, **09**-0050, **09**-0052, **09**-0054
Lewis, J.D., **19**-0892
Lewis, J.W., **19**-1526
Lewis, M., **05**-0068, **13**-0027
Lewis, M.D., **15**-1728
Lewis, N., **15**-1791
Lewis, N.G., **16**-2159
Lewis, N.J., **13**-0094
Lewis, R.G., **10**-0269, **18**-0098
Lewis, R.J., **11**-0144
Lewis, R.S., **07**-0044
Lewis, S.N., **18**-0076, **18**-0352
Lewis, T., **18**-0815
Lewis, T.A., **15**-1042
Lex, J., **02**-0282, **02**-0284, **02**-0295, **02**-0326, **02**-0330
Ley, S.V., **02**-0255, **10**-0558, **10**-0604, **12**-0163, **12**-0247, **15**-0147, **15**-0420, **15**-1007, **15**-1667, **15**-1724, **16**-0341, **16**-1236, **16**-1428, **16**-1540, **16**-1738, **19**-0010, **19**-0058, **19**-0072, **19**-0123, **19**-0124,

19-0125, **19**-0128, **19**-0264, **19**-0267, **19**-0677, **19**-0894
Leybach, H., **10**-1000
Leydet, A., **18**-0213
Leyrer, U., **04**-0037
Leyva, E., **05**-0408
Leznoff, C.C., **16**-1822, **16**-1823
Lhermitte, F., **15**-1749, **19**-0720
Lhoste, P., **10**-0802
Li, A., **18**-0487
Li, A.-H., **16**-1326
Li, C., **03**-0045, **10**-0010, **15**-1254, **19**-0174
Li, C.-J., **03**-0005, **03**-0006, **10**-1596, **10**-1774, **10**-1775, **13**-0297, **13**-0324, **15**-0721, **15**-0744, **15**-0895, **15**-1153, **15**-1155, **15**-1158, **15**-1180, **15**-1373, **16**-0296, **16**-0297, **16**-0299, **16**-0461, **16**-0481, **16**-0482, **16**-0587, **16**-0603, **16**-0649, **16**-0887, **16**-0890, **16**-0900, **16**-1092, **16**-1477, **19**-1664
Li, C.-Q., **16**-0773, **16**-0800
Li, C.J., **10**-1549, **16**-0639, **16**-0875
Li, C.S., **13**-0259
Li, D-R., **19**-0082
Li, D., **16**-0067, **16**-0152
Li, D.-P., **10**-0879
Li, F., **10**-0737, **13**-0108
Li, G., **10**-0978, **13**-0221, **15**-0354, **15**-1609, **15**-1613, **15**-1614, **15**-1864, **15**-1881, **15**-1896, **16**-0768, **16**-0769, **16**-0782, **16**-0785, **16**-0786, **16**-0798, **16**-0980
Li, G.-Y., **13**-0480
Li, G.S., **19**-1492, **19**-1504
Li, G.Y., **15**-1868
Li, H., **12**-0250, **13**-0482, **15**-1004, **15**-2354, **16**-0717
Li, J., **10**-0508, **10**-1857, **13**-0413, **14**-0307, **15**-1397, **15**-1403, **15**-2409, **16**-0884, **19**-0673, **19**-0678
Li, J.-H., **13**-0501, **13**-0542, **15**-0891, **15**-2372
Li, J.-P., **19**-0291
Li, J.-T., **16**-1173, **19**-1645, **19**-1646, **19**-1652
Li, J.-W., **13**-0112, **15**-1309, **15**-1319
Li, J.C., **04**-0465
Li, J.D., **12**-0406
Li, J.P., **17**-0125
Li, K., **15**-1122, **19**-0941
Li, L., **10**-1163, **13**-0401, **13**-0481, **15**-0287, **15**-1309, **19**-1116
Li, L.-H., **16**-0655
Li, L.-J., **16**-1173
Li, L.-S., **16**-1055
Li, M., **16**-0168
Li, M.-J., **19**-1675
Li, N., **16**-1644
Li, N.-S., **15**-0695, **19**-0334
Li, P., **10**-0509, **13**-0539, **13**-0549, **15**-1133, **16**-1289, **19**-0583, **19**-1199, **19**-1601
Li, P.T., **12**-0599
Li, R., **07**-0022, **10**-0584, **15**-1982
Li, S., **10**-0538, **10**-1717, **15**-1761, **16**-0834, **16**-1714
Li, S.-H., **10**-0542
Li, S.J., **10**-1273
Li, T., **15**-0435, **18**-0676
Li, T., **19**-1660
Li, T.-S., **10**-0542, **10**-0553, **16**-0233, **16**-1173, **19**-1645, **19**-1652
Li, T.-s., **19**-1646
Li, W., **10**-0508, **13**-0171, **19**-0037
Li, W.-K., **19**-0746
Li, W.-S., **16**-1828
Li, W.R., **11**-0397
Li, X., **05**-0248, **10**-1080, **10**-1454, **11**-0119, **15**-0168, **15**-0413, **15**-1125, **15**-1139, **15**-1147, **15**-1628, **15**-2129, **15**-2148, **16**-0549, **19**-0082, **19**-1031, **19**-1042
Li, X.-G., **16**-0687
Li, X.-R., **16**-0591, **16**-1093
Li, Y., **01**-0042, **12**-0409, **15**-0352, **15**-1868, **15**-1870, **15**-2088, **15**-2100, **15**-2295, **16**-1022, **16**-1427, **16**-1428, **16**-1433, **16**-1438
Li, Y.-G., **19**-1675
Li, Y.-L., **15**-2333
Li, Y.-M., **15**-0604, **15**-1136
Li, Y.-Q., **16**-0168, **16**-0655
Li, Z., **10**-0882, **10**-1105, **10**-1572, **10**-1774, **10**-1775, **11**-0276, **13**-0359, **14**-0060, **15**-1456, **15**-1765, **15**-1885, **15**-2421, **16**-0296, **16**-0297, **16**-0435, **16**-0558, **16**-1036, **16**-1969, **19**-0543, **19**-0544, **19**-0545, **19**-0546, **19**-0617
Li, Z.-B., **16**-0549
Li, Z.-Y., **19**-1021, **19**-1022
Li, W., **15**-0610
Liagre, M., **10**-0468
Lian, H., **15**-0578
Liang, B., **13**-0365, **15**-1405
Liang, C.D., **04**-0170
Liang, G., **02**-0172, **05**-0052, **05**-0083, **05**-0090, **10**-0044, **10**-0116, **10**-0168, **10**-0181, **10**-0191, **11**-0015, **15**-0850
Liang, J., **15**-1136
Liang, K.S.Y., **14**-0329
Liang, L., **15**-1133, **15**-1136
Liang, P.H., **19**-0451
Liang, S., **16**-1438
Liang, X., **13**-0187, **15**-1137, **19**-0180
Liang, Y., **12**-0517, **15**-1137
Liang, Z., **18**-0809
Liao, H.-Y., **15**-0283
Liao, Q., **16**-1950
Liao, W., **16**-1028, **19**-0962
Liao, W.-W., **15**-1122, **16**-1394
Liao, Y., **05**-0293, **13**-0548, **16**-0147
Liao, Y.-L., **12**-0459
Lias, S.G., **08**-0223
Libbey, W.J., **18**-0039
Liberek, B., **10**-1174
Liberles, A., **01**-0001
Libertini, E., **12**-0152, **19**-1714
Liblikas, I., **10**-0999
Libman, J., **16**-0180
Lichtenberger, F., **18**-0487
Lichtenthaler, F.W., **16**-1150, **19**-0708
Lichtin, N.N., **10**-0333
Licini, G., **19**-0308
Lick, C., **10**-0746
Lide Jr., D.R., **01**-0037, **01**-0060, **01**-0076, **01**-0084, **01**-0085, **04**-0276
Lidert, Z., **02**-0267
Lidström, P., **07**-0106, **07**-0116, **07**-0117
Liebe, J., **02**-0064
Liebeskind, L.S., **12**-0256, **12**-0276, **13**-0144, **13**-0480, **13**-0504, **13**-0566, **16**-1976, **16**-1979, **19**-1229
Liebl, M., **18**-0772
Liebman, J.F., **01**-0080, **02**-0051, **02**-0039, **02**-0146, **02**-0204, **02**-0331, **02**-0352, **04**-0402, **04**-0409, **04**-0424, **04**-0462, **05**-0327, **08**-0223, **18**-0646
Liebman, J.F.S., **18**-0113
Liebscher, J., **15**-1299
Liedhegener, A., **16**-2165
Liedholm, B., **13**-0256
Lien, A.P., **11**-0598
Lienard, P., **16**-1030

Lienert, J., **17**-0489
Lienhard, G., **10**-0571
Lienhard, G.E., **12**-0084, **12**-0099
Liesemer, R.N., **16**-1469
Liesen, P.J., **13**-0389, **19**-1758
Liesenfelt, H., **15**-0466
Lieske, C.N., **16**-1466
Liew, C.C., **18**-0316
Lifson, S., **04**-0177
Liggero, S.H., **18**-0119
Light, J., **19**-1309
Lightfoot, A.P., **12**-0456
Lightner, D.A., **03**-0064, **04**-0088, **17**-0224
Lightner, S.A., **04**-0058
Ligthart, G.B.W.L., **19**-0216
Liguori, L., **14**-0138, **19**-0331, **19**-0336
Lii, J.-H., **04**-0399, **04**-0400
Liiu, Y., **16**-0631
Likhar, P.R., **10**-1537
Likhomanova, T.I., **15**-1541
Likhotvorik, I.R., **05**-0365, **05**-0363
Lilburn, J., **13**-0122
Liler, M., **08**-0010, **08**-0024, **08**-0116, **08**-0123, **08**-0160, **15**-0183
Liljefors, T., **04**-0332, **04**-0505
Lill, S.O.N., **17**-0216
Lilla, G., **17**-0095
Lillford, P.J., **15**-0290
Lillocci, C., **10**-0378
Lim, C.J., **10**-1593, **14**-0011, **16**-1998, **18**-0819
Lim, D., **16**-1814
Lim, D.S., **15**-1136
Lim, E.C., **07**-0022
Lim, G., **17**-0074
Lim, H.J., **19**-1655
Lim, J., **15**-1258
Lim, K.-H., **10**-1772
Lim, L.N., **18**-0463
Lim, S., **15**-0907
Lim, S.C., **12**-0184
Lim, W.Y., **15**-0136
Lim, Y., **16**-0725, **16**-0734
Lim, Y.-K., **11**-0171
Lim, Y.M., **13**-0480
Lim, Y.Y., **16**-2125
Lím, D., **16**-2019
Lima, C.F., **12**-0672
Limburg, D.C., **16**-1538
Limmert, M.E., **13**-0339
Lin'kova, M.G., **15**-1601
Lin, C., **10**-1767
Lin, C.-A., **13**-0400, **13**-0487, **13**-0551
Lin, C.-C., **12**-0459, **15**-0613, **19**-1670
Lin, C.-F., **15**-0918
Lin, C.H., **15**-2436
Lin, C.Y., **02**-0212
Lin, D.K., **19**-0713
Lin, G.-Q., **19**-1021, **19**-1022, **19**-1697
Lin, H., **04**-0088, **10**-1600, **16**-0493
Lin, H.-C., **15**-1270
Lin, H.-H., **15**-0908
Lin, H.C., **10**-0596, **11**-0029, **11**-0093, **11**-0149, **11**-0455, **12**-0209
Lin, J., **03**-0022, **10**-1548, **15**-0707
Lin, J.-M., **12**-0321
Lin, J.J., **15**-0571
Lin, K.-W., **16**-1360
Lin, L.-S., **16**-0959
Lin, L.K., **15**-0598
Lin, L.W., **07**-0052
Lin, M., **15**-2006, **16**-0006, **16**-1021
Lin, M.-J., **16**-0559, **16**-0593
Lin, M.-Y., **15**-2399
Lin, N., **05**-0368
Lin, P.-S., **15**-0761, **15**-1145
Lin, R., **05**-0253
Lin, S., **11**-0650, **12**-0469, **19**-1116, **19**-1503
Lin, S.-I., **10**-1286, **16**-0124
Lin, S.-W., **19**-0346
Lin, S.H., **07**-0020
Lin, W., **19**-0959, **19**-1029, **19**-1265
Lin, W.-Q., **16**-0865
Lin, W.-W., **15**-1149
Lin, X., **15**-0344, **15**-1282
Lin, Y., **10**-0189, **15**-2090
Lin, Y.-L., **18**-0527
Lin, Y.-S., **10**-0440, **13**-0602, **15**-0341
Lin, Z.-P., **19**-1652
Linck, C.F., **19**-0241
Linclau, B., **10**-1105, **16**-1642, **16**-1643
Lincoln, D.N., **05**-0049
Lincoln, S.F., **03**-0186
Linda, P., **02**-0415, **11**-0470
Lindbeck, A.C., **12**-0565
Lindberg, T., **15**-2122, **19**-0068
Lindeman, S.V., **03**-0075, **15**-2028
Linden, A., **15**-1944
Linden, S., **12**-0058
Lindén, A.A., **19**-0796
Linder, L., **18**-0534
Linder, M.R., **16**-2117
Linder, S.M., **12**-0662
Linderman, J.J., **18**-0900
Linderman, R.J., **15**-1066
Lindert, A., **10**-1614, **12**-0176, **16**-2020, **19**-0841
Lindlar, H., **15**-0435, **15**-0436
Lindley, J., **13**-0117
Lindner, D.L., **15**-0464
Lindner, E., **05**-0060, **18**-0835
Lindner, H.J., **02**-0174, **02**-0176, **02**-0180, **02**-0225, **05**-0143
Lindow, D.F., **15**-0544
Lindsay Smith, J.R., **04**-0512, **11**-0262, **14**-0153, **14**-0204, **15**-2050
Lindsay, C.I., **10**-1225, **15**-1254
Lindsay, C.M., **12**-0402
Lindsay, D.A., **18**-0082
Lindsay, D.G., **12**-0354
Lindsay, D.M., **15**-1429, **15**-1434, **19**-0126
Lindsay, H.A., **18**-0680
Lindsay, L.M., **10**-1852
Lindsey Jr., R.V., **14**-0418, **15**-0796, **15**-2198
Lindsey, A.S., **11**-0500
Lindsley, C., **15**-0509
Lindsley, C.W., **12**-0313
Lindstrom, M.J., **14**-0185
Lindström, U.M., **09**-0092, **10**-0922
Lindy, L.B., **10**-1713
Lineberger, W.C., **05**-0132, **05**-0273, **05**-0332
Linehan, J.C., **19**-0608
Linevsky, M.J., **01**-0092
Ling, H.-Y., **16**-0862
Ling, R., **10**-0735
Ling, Y.-C., **16**-0163
Lingaiah, N., **17**-0440
Linke, S., **18**-0281
Linker, T., **15**-1832
Linn, W.J., **15**-1986
Linnett, J.W., **02**-0002
Linsay, E.C., **10**-0217
Linschitz, H., **07**-0032, **07**-0033
Linss, J., **04**-0038
Linstead, R.P., **16**-0426, **19**-0023
Linstrumelle, G., **10**-1269, **10**-1290, **10**-1294, **10**-1297, **10**-1536, **13**-0693, **15**-0838
Lintanf, V., **10**-1688
Linti, G., **05**-0180
Lintner, W., **07**-0080
Lion, C., **10**-0208, **10**-1368, **10**-1370, **10**-1751, **12**-0303, **14**-0434, **16**-1926, **16**-2040
Lions, F., **15**-1046

Liotta, C., **01**-0042, **03**-0102, **10**-0227, **10**-0333, **10**-0453, **10**-0454, **10**-0461, **10**-0462, **10**-0610, **10**-0696, **10**-1047, **10**-1619, **10**-1787, **15**-2274, **16**-1225, **16**-1255
Liotta, C.L., **10**-0411, **10**-1649, **15**-0614, **16**-0028
Liotta, D., **05**-0119, **10**-0771, **10**-0801, **10**-0826, **12**-0244, **12**-0245, **12**-0251, **16**-0530, **16**-1024, **17**-0290, **18**-0733, **19**-0010
Liotta, D.C., 09-II-0006
Liotta, L.F., **15**-0439
Liotta, R., **19**-0411
Lipinski, C.A., **10**-1289
Lipinsky, E.S., **15**-2244
Lipińska, T., **18**-0715
Lipkowitz, K.B., **08**-0174
Lipnick, R.L., **04**-0381, **04**-0382
Lipp, H.I., **10**-0866
Lippard, S.J., **15**-1825
Lippens, G., **12**-0103
Lipshutz, B.H., **10**-0548, **10**-1332, **10**-1333, **10**-1335, **10**-1337, **10**-1348, **10**-1353, **10**-1355, **10**-1356, **10**-1367, **10**-1375, **10**-1410, **10**-1540, **10**-1694, **11**-0651, **12**-0313, **12**-0560, **12**-0570, **12**-0571, **12**-0751, **13**-0163, **13**-0198, **13**-0237, **13**-0530, **13**-0555, **14**-0390, **15**-0509, **15**-0594, **15**-0708, **15**-1067, **15**-1067, **15**-1071, **15**-1075, **15**-1076, **15**-1082, **15**-1344, **15**-2155, **16**-0690, **19**-0120, **19**-0440, **19**-0477, **19**-1045, **19**-1162
Lipsky, S., **07**-0021
Lipsky, S.D., **16**-0542
Liptak, M.D., **08**-0170, **08**-0175
Lipton, M., **16**-1835
Lipton, M.F., **17**-0274
Liras, L., **15**-2302
Liras, S., **10**-0322, **15**-2045
Lis, T., **03**-0013
Lisle, J.B., **01**-0052
Lissel, M., **10**-0455, **10**-0716, **10**-1644, **10**-1703, **19**-0337
Lissi, E.A., **07**-0047
List, B., **10**-1687, **15**-0993, **15**-1004, **16**-0384, **16**-0414, **16**-1036, **16**-1063
Listemann, M.L., **18**-0829
Lister, M.A., **16**-1018
Lister-James, J., **14**-0133, **14**-0134, **15**-1519
Liston, T.V., **12**-0411
Littell, R., **19**-0049
Litterer, W.E., **15**-1171
Littke, A.F., **12**-0270, **13**-0299, **13**-0364, **13**-0367, **13**-0480, **13**-0539
Little, D.M., **14**-0082
Little, D.A., **02**-0254
Little, E.L., **15**-0315
Little, J., **12**-0706
Little, R.D., **10**-1337, **16**-0821, **18**-0853
Little, W.T., **16**-1211
Littler, J.S., 09-II-0005, **11**-0544, **11**-0552, **19**-0005, **19**-0253, **19**-0256, **19**-0257
Litvinenko, L.M., **13**-0086, **16**-2170
Litvinenko, M., **16**-2155
Litvinov, V.P., **16**-1409
Liu, M.T.H., **05**-0366
Liu, B., **10**-0185, **10**-0186, **10**-0201, **10**-1010, **13**-0305, **15**-0140, **15**-0239, **17**-0185, **18**-0277, **19**-1090, **19**-1191
Liu, B.-S., **12**-0321
Liu, B.Y., **10**-0594
Liu, C., **15**-0765, **15**-0820
Liu, C.Z., **02**-0359
Liu, D., **10**-0692, **15**-0412, **15**-1903
Liu, D.-x., **16**-0687
Liu, F., **19**-0858
Liu, G., **15**-0897
Liu, G.-B., **10**-0507, **15**-0523
Liu, G.-H., **16**-0691
Liu, H-J., **16**-1136
Liu, H., **04**-0268, **05**-0185, **10**-0975, **11**-0358, **15**-0519, **15**-1249, **15**-1602, **15**-2127, **16**-1728, **16**-1811, **18**-0576, **19**-1042
Liu, H.-J., **10**-1494, **15**-1100, **16**-1067, **19**-0904
Liu, H.J., **18**-0240
Liu, J., **13**-0237, **13**-0401, **13**-0481, **15**-1614, **15**-1737, **16**-0627, **16**-1649, **17**-0415, **19**-1028, **19**-1660
Liu, J.-M., **10**-0879
Liu, J.-P., **16**-0095
Liu, J.-T., **10**-1379, **13**-0753, **15**-1149
Liu, J.-X., **19**-1451
Liu, J.-Y., **10**-1379, **15**-1149
Liu, J.S., **05**-0048, **05**-0049
Liu, K., **06**-0077, **10**-0179, **10**-0294, **10**-0437, **15**-0115, **15**-0116, **15**-0117, **17**-0015, **18**-0861
Liu, K.-T., **10**-0272, **10**-0288, **10**-0440
Liu, K.T., **10**-0275
Liu, L., **01**-0109, **01**-0111, **13**-0138, **13**-0228, **15**-1254, **16**-0549, **18**-0514, **19**-0174, **19**-0202
Liu, L.F., **03**-0208
Liu, L.H., **04**-0472
Liu, L.K., **16**-2147, **17**-0320
Liu, M., **04**-0355, **15**-2066
Liu, M.M., **15**-2201
Liu, M.T.H., **05**-0297, **05**-0366, **05**-0384, **05**-0386, **12**-0353, **15**-2098, **18**-0089
Liu, P., **15**-1372, **15**-1665, **15**-1746, **16**-1414
Liu, P.C., **08**-0133
Liu, P.N., **19**-1042, **19**-1043
Liu, Q., **10**-1024, **14**-0313, **19**-0671
Liu, Q.Y., **05**-0188
Liu, R., **19**-0180
Liu, R.-S., **15**-1783, **15**-2399, **17**-0185, **18**-0152
Liu, R.S.H., **14**-0334, **15**-2075, **15**-2239, **15**-2251
Liu, S., **10**-0029, **10**-0032, **10**-0981, **11**-0371, **11**-0372, **19**-0338
Liu, S.-M., **19**-1645
Liu, S.-Y., **13**-0480, **19**-1776
Liu, T., **14**-0459
Liu, W., **18**-0090
Liu, W.-J., **13**-0501
Liu, W.-y., **19**-0919
Liu, W.-Z., **01**-0103
Liu, X., **13**-0583, **15**-0214, **15**-0604
Liu, X.-x., **10**-1419
Liu, Y., **10**-1779, **13**-0272, **13**-0504, **13**-0571, **14**-0403, **15**-2297, **16**-0939, **16**-1362, **16**-1613, **19**-0161
Liu, Y.-i., **03**-0133
Liu, Y.-S., **13**-0399
Liu, Z., **10**-0584, **10**-0701, **10**-1089, **13**-0197, **13**-0414, **15**-1245, **16**-0435, **16**-0939, **16**-1913, **16**-1920, **19**-0209
Liu, X., **13**-0700
Liua, Z., **16**-1915
Livant, P., **12**-0604, **15**-2354
Livett, M.K., **02**-0409
Livinghouse, T., **10**-1542, **15**-0336, **15**-0768, **15**-0820, **15**-1426, **16**-1420, **18**-0814
Livingston, A.G., **13**-0402
Livingston, R.C., **14**-0300
Livingstone, D., **03**-0069
Liz, R., **19**-1022
Lizarzaburu, M.E., **10**-0647

Lizzani-Cuvelier, L., **16**-0225
Ljunggren, S.O., **19**-0721
Lkauber, D.J., **13**-0236
Llama, E.F., **18**-0141
Llamas, T., **10**-1454
Llebaria, A., **15**-0916, **16**-0672, **16**-1759, **18**-0804
Lledós, A., **12**-0087
Llera, J.-M., **19**-0300
Llewellyn, G., **10**-0282, **10**-0379, **10**-0404, **10**-0430, **10**-0435, **16**-1601
Llewellyn, J.A., **06**-0070, **06**-0086
Llopis-Mestre, V., **11**-0130
Llorca-Baragaño, M.A., **15**-2289
Lloyd, D., **02**-0090, **02**-0093, **02**-0133
Lloyd, D.J., **17**-0072, **17**-0077, **17**-0098
Lloyd, G.J., **16**-1571
Lloyd, J.R., **05**-0020
Lloyd, R.V., **14**-0040
Lloyd, W.G., **14**-0214
Lloyd-Jones, G.C., **15**-0700, **16**-0587
Lloyd-Williams, P., **13**-0504
Lo, C.-Y., **15**-1783, **17**-0185
Lo, D.H., **02**-0018
Lo, H.-C., **16**-1029
Lo, M.M.-C., **10**-1155, **12**-0363
Loader, C.E., **11**-0068
Loan, L.D., **19**-0369
Loar, M.K., **12**-0278
Löber, O., **15**-0327
Lobkovsky, E.B., **10**-1552
Lobo, A.M., **04**-0101, **15**-1907, **16**-0027
Locatelli, F., **05**-0383, **19**-0042
Locatelli, M., **10**-0931
Locati, L., **15**-1818
Locher, C., **11**-0403, **16**-0728
Lochmann, L., **16**-2019
Lock, C.J.L., **05**-0050
Lock, S., **16**-0661
Locke, A.W., **16**-0119
Lockley, W.J.S., **11**-0115
Lockyer Jr., G.D., **14**-0007
Lodder, G., **05**-0065, **12**-0484, **18**-0856
Loe, Ø., **12**-0359
Loening, K., **04**-0098
Loening, K.L., **05**-0006, **06**-0047
Loeppky, R.N., **10**-0305, **12**-0706, **12**-0706, **13**-0180
Loeschorn, C.A., **18**-0238
Löffler, F., **15**-2293
Löfstedt, J., **15**-0832
Loft, M.S., **10**-1463
Loftfield, R.B., **18**-0199
Logan, T.J., **12**-0400, **18**-0253
Logue, M.W., **16**-2015
Loh, T.-P., **15**-1056, **15**-1286, **15**-2006, **16**-0410, **16**-0559, **16**-0590, **16**-0591, **16**-0593, **16**-0610, **16**-0628, **16**-0631, **16**-0658, **16**-0738, **16**-0862, **16**-1005, **16**-1081, **16**-1093, **16**-1108, **16**-1111
Lohmer, G., **13**-0397
Lohmer, R., **13**-0397
Lohray, B.B., **04**-0194, **10**-1018, **15**-1656, **15**-1674, **15**-1689, **15**-1694
Lohri, B., **04**-0141
Lohse, O., **13**-0503
Loim, L.M., **16**-0182
Loim, N.M., **15**-0471, **19**-1450, **19**-1454
Loiseau, A.-M., **16**-0225
Loken, H.Y., **12**-0628
Lokensgard, J.P., **15**-2255, **18**-0494
Lokot, I.P., **19**-1446
Lokshin, B.V., **02**-0254
Loktev, A.S., **15**-0521
Loktev, V.F., **18**-0250
Lomas, D., **15**-2170
Lomas, J.S., **05**-0279, **12**-0661, **12**-0666, **16**-0514, **17**-0157
Lombardi, P.J., **16**-0762
Lombardo, D.A., **12**-0080
Lombardo, L., **16**-0500
Lombardo, M., **16**-0601
Lommes, P., **05**-0245
Lomölder, R., **17**-0514
Loncar, M., **11**-0160
Loncharich, R.J., **15**-0970, **15**-2098, **16**-1323, **18**-0551
London, G., **19**-1460
Lonez, F., **19**-0823
Long, D.A., **11**-0405
Long, F.A., **03**-0067, **11**-0110, **11**-0613, **12**-0098, **16**-1562
Long, J., **15**-2148, **15**-2343
Long, J.A., **02**-0419
Long, M.A., **11**-0116, **11**-0117, **11**-0118
Long, Q., **10**-0768, **16**-0288
Long, R.A.J., **14**-0033, **14**-0328
Longas, M.O., **10**-0209
Longenecker, H.E., **16**-1881
Longford, D., **10**-1411
Longmire, J.M., **18**-0689, **19**-0054
Longo Jr., L.S., **19**-0581, **19**-0594
Longone, D.T., **12**-0439
Longoria, M.A., **15**-2298
Longstaff, P.A., **02**-0043
Longstaff, S.C., **15**-1245
Longuet-Higgins, H.C., **02**-0103, **18**-0476
Lönnqvist, J.-E., **19**-0867
Lonsdale, K., **01**-0055
Loo, D., **12**-0511
Look, G.C., **16**-0148
Loomis, G.L., **16**-1289
Loones, K.T.J., **13**-0174, **13**-0178, **13**-0187
Loop, C.K., **12**-0402
Loos, R., **10**-0355
Loosen, K., **18**-0027
Lop Galbo, F., **16**-0687
Lopata, A., **15**-0051
Lopatin, B.V., **15**-0047
Lopatina, V.S., **15**-1199
Lopes, C.C., **15**-1120
Lopes, E.C.S., **16**-0776
Lopes, R.S.C., **15**-1120
Lopez, L., **10**-0819, **10**-1530, **13**-0399, **13**-0415, **15**-2164, **18**-0123
Lopez, M., **19**-1037
Lopez, R.C.G., **16**-0210
Lopez, R.M., **19**-1407
Lopez, V.O., **09**-0047, **09**-0055
Lopez, X., **16**-0832
López, C.J., **15**-1665
López, F., **10**-1469, **15**-1103, **18**-0791
López, J.C., **15**-1224, **15**-1718
López, L.A., **15**-2415
López, M.C., **16**-0810
López, P., **15**-2063
López, R., **13**-0131
López-Alvarado, P., **10**-0990
López-Calahorra, F., **16**-1496
López-Cortés, J.G., **19**-0261
López-González, D., **12**-0213
Lopez-Rodriguez, G., **19**-1523
Lopp, M., **19**-0476
Łopusiński, A., **19**-0788
Lor, M.H., **15**-2072
Lorand, J.P., **03**-0095, **04**-0010, **05**-0279, **13**-0025, **18**-0397
Lorca, M., **16**-0623
Lord, E., **17**-0056
Lord, R.C., **04**-0378
Loren, S., **15**-2064, **15**-2066
Lorenc, Lj., **14**-0210
Lorenz, O., **19**-0369
Lorenz, R., **16**-0405
Lorenzi, P., **15**-1534
Lorenzo, A., **10**-1181
Lorenzo, E., **16**-0839
Lorenzo, F.M., **12**-0703
Lorenzo, S., **03**-0209

Loreta, M.A., **15**-1889
Lorette, N.B., **18**-0676
Lorimer, J.P., **07**-0079, **07**-0082
Lorne, R., **10**-1269, **18**-0736
Lorne, R.C.R., **18**-0076
Lorte, A., **10**-1422
Los, J.M., **11**-0613
Losensky, H., **03**-0152
Loska, R., **15**-1242
Lossing, F.P., **02**-0237, **02**-0402, **05**-0265, **10**-0184, **05**-0074
Lothrop, W.C., **13**-0461
Lotoski, J.A., **10**-1276
Lotsch, W., **05**-0231
Lötsch, G., **14**-0347
Lotter, H., **16**-1190
Lotto, G.I., **15**-1693
Lotz, M., **10**-1454
Lou, B., **15**-0657
Lou, J., **19**-0110
Lou, J.-D., **19**-0093, **19**-0111
Lou, J.D., **19**-0094
Lou, S., **16**-1188
Lou, Y., **15**-2294
Loubinoux, B., **10**-0911
Loudon, A.G., **17**-0248
Loudon, G.M., **12**-0227, **15**-0025, **18**-0272
Loudon, J.D., **13**-0084, **14**-0195
Lough, A.J., **05**-0348, **10**-1423, **15**-0858, **15**-2441, **16**-0742
Lough, W.J., **04**-0171
Loughlin, W.A., **10**-0705
Louie, J., **13**-0175, **15**-0249, **15**-2441, **18**-0769, **18**-0794
Loupy, A., **07**-0106, **07**-0111, **10**-0468, **10**-0589, **10**-0699, **10**-0973, **10**-1047, **10**-1049, **10**-1787, **11**-0429, **12**-0121, **13**-0109, **15**-0930, **15**-1039, **16**-0372, **16**-0779, **16**-1174, **16**-1174, **16**-1542, **16**-1644, **16**-1718, **16**-1789, **17**-0073, **17**-0112, **17**-0307, **18**-0308, **18**-0322, **18**-0715, **18**-0773, **19**-0564, **19**-1062
Lourak, M., **13**-0462
Louvet, A., **10**-1216
Louw, R., **11**-0638, **17**-0132, **17**-0137
Lovas, F.J., **01**-0052, **19**-0361, **19**-0383
Lovato, G., **16**-1576
Love, B.E., **16**-0270, **16**-0386
Love, J.A., **15**-2435, **18**-0575, **18**-0833
Love, M.E., **10**-0499
Lovel, C.G., **15**-1500, **15**-1504
Lovell, H., **19**-1022
Lovely, C.J., **12**-0367, **13**-0228
Lovely, J.-C., **15**-1436
Lovering, E.G., **01**-0095
Lovey, A.J., **16**-2040
Lovtsova, A.N., **18**-0026
Low, K.-H., **13**-0478
Lowe, G., **04**-0030, **04**-0031, **19**-0023
Lowe, J.P., **04**-0277, **17**-0090
Lowe, K.L., **05**-0292
Lowe, P.A., **02**-0086, **10**-0824, **16**-1255
Lowe, S.R., **19**-1679
Lowell, S., **10**-0303
Lowenthal, R.E., **15**-2297
Lower, A., **19**-1045
Lower, S.K., **07**-0024
Lowery, M.K., **18**-0345
Lown, J.W., **15**-1965, **15**-1966
Lowry, N., **10**-0148
Lowry, T.H., **02**-0008, **05**-0025, **05**-0138, **16**-0044
Loy, R.N., **15**-0367
Loza, R., **18**-0574
Lozanova, A.V., **15**-2024
Lozinskii, M.O., **10**-1034, **10**-1578, **12**-0194
Lu, C.V., **11**-0233
Lu, G., **16**-0549
Lu, J., **13**-0413, **16**-0631, **19**-0037
Lu, J.-F., **16**-0674
Lu, K., **15**-1084
Lu, L., **16**-0342, **16**-0875, **18**-0798
Lu, L.-H., **19**-0111
Lu, L.D., **04**-0193
Lu, M.D., **04**-0187
Lu, P., **17**-0385, **18**-0122
Lu, S., **08**-0099, **12**-0739, **16**-0687, **16**-1148, **16**-1856, **18**-0643
Lu, S.-M., **15**-0527, **16**-2123
Lu, S.-P., **16**-1353
Lu, T., **15**-2283
Lu, W., **11**-0331, **13**-0447, **15**-1165, **16**-0594, **16**-0602, **16**-0874, **16**-0880, **16**-0881
Lu, X., **10**-1472, **15**-0772, **15**-0897, **15**-0991, **15**-1944, **16**-0699, **16**-0705, **17**-0173, **19**-0784
Lu, X.-R., **03**-0123
Lu, Y., **04**-0191, **13**-0171, **13**-0475, **19**-0680
Lu, Y.-F., **18**-0484
Lu, Y.-Q., **10**-1596, **16**-0587
Lu, Y.-Y., **16**-1784
Lu, Z., **13**-0202
Lü, S., **19**-1035
Lü, S.-F., **19**-1032
Lü, W., **15**-2301
Lü, Y.-X., **16**-0323
Luanay, D., **10**-1790
Luanphaisarnnont, T., **16**-0712
Luart, D., **13**-0334
Lübben, D., **15**-1691
Lubell, W.D., **16**-1965
Lubin, C.E., **15**-1939
Lubin, N., **15**-2143, **16**-0777
Lubin-Germain, N., **15**-2033, **16**-0555, **16**-0595, **16**-1917
Lubineau, A., **15**-1028, **15**-2143, **16**-0777, **16**-1078
Lubitz, W., **05**-0208, **07**-0018
Luborsky, F.E., **11**-0020
Lucarini, M., **01**-0104, **05**-0310, **14**-0018, **14**-0019
Lucas, G.B., **18**-0365
Lucas, H., **19**-1615
Lucas, H.J., **10**-0105
Lucchese, R.R., **05**-0332
Lucchetti, J., **15**-1114
Lucchini, V., **08**-0009, **15**-0021, **15**-1841, **15**-1998
Lucero, C.G., **10**-1433
Luchaco, C.A., **15**-0870
Luchaco-Cullis, C.A., **19**-0670
Luche, J., **10**-0473, **10**-1150, **10**-1434, **12**-0609, **13**-0098, **15**-1142, **16**-0479, **16**-0580, **19**-0922, **19**-0941, **19**-1663
Luche, J.-L., **07**-0080, **07**-0084, **07**-0091, **07**-0100, **10**-0468, **11**-0230, **15**-1141
Luche, J.L., **14**-0159, **15**-0190, **15**-1199, **16**-0645, **16**-0840, **16**-0966
Luche, M., **16**-0403
Lucherini, A., **18**-0825
Luchinat, C., **04**-0205
Lucht, B.L., **05**-0195, **08**-0204, **08**-0205, **08**-0206, **16**-0977
Lucien, J., **10**-0778
Lucken, E.A.C., **05**-0153
Luckenbach, R., appendixA-0023, appendixA-0024
Lucon, M., **01**-0051, **10**-0430
Luçon, M., **03**-0015
Lüdke, G., **16**-2128
Lüdke, G., **16**-2133
Ludley, P., **15**-2041
Ludwieg, A., **10**-1606
Ludwig, M., **13**-0393
Ludwig, U., **18**-0385, **18**-0387, **18**-0389, **18**-0390
Lue, P., **16**-0288
Luef, W., **04**-0515
Luengo, J.I., **18**-0682
Lüers, S., **15**-0796

Luft, R., **09**-0075
Luftmann, H., **14**-0156
Lugad, A.G., **19**-1212
Luger, P., **04**-0379, **18**-0637
Lugo-Mas, P., **19**-0688
Luh, T., **02**-0343, **14**-0401, **14**-0402, **19**-1580, **19**-1581
Luh, T.-Y., **10**-1282
Lührs, K., **19**-1285
Lui, B., **12**-0145
Lui, C.Y., **10**-0187, **18**-0108
Luibrand, R.T., **18**-0040, **19**-0933
Luidhart, T., **11**-0298
Luis, A.L., **15**-2175, **16**-0722
Luis, S.V., **13**-0046, **16**-1289
Luk'yanenko, N.G., **10**-0470
Luk'yanets, E.A., **19**-0837
Luka, G.Ya., **13**-0731
Lukacs, G., **04**-0206
Lukacs, Z., **19**-0540, **19**-0542
Lukanich, J.M., **13**-0594
Lukas, J., **05**-0018, **05**-0030, **05**-0032, **12**-0053
Lukas, J.H., **15**-2197
Lukashev, N.V., **15**-0759
Lukashevich, V.O., **18**-0739
Łukasiewicz, M., **19**-0675
Luke, G.P., **14**-0385
Luke, M.O., **12**-0055, **15**-0465, **15**-0466
Lukehart, C.M., **02**-0166
Lukevics, E., **10**-0767, **13**-0570
Lukin, K., **11**-0155
Lukin, O., **03**-0198
Lukins, P.B., **02**-0140
Luknitskii, F.I., **15**-2184, **16**-0039, **17**-0319
Luliński, P., **11**-0284, **11**-0286
Lum, R.C., **17**-0120
Lumb, J.T., **12**-0679
Luna, D., **15**-0454, **15**-0574
Luna, H., **15**-1724
Lunazzi, L., **04**-0059, **04**-0060, **04**-0087m **04**-0291, **04**-0315, **04**-0416
Lund, H., **10**-0091, **10**-0092, **14**-0130, **14**-0415, **19**-0955, **19**-1228, **19**-1317, **19**-1691
Lund, T., **10**-0091, **10**-0092, **14**-0441
Lundberg, S., **16**-1709
Lundeen, A.J., **17**-0158
Lundquist, J.T., **19**-0623
Lundstedt, T., **19**-1791
Luneau, D., **05**-0291
Lunetta, S.E., **15**-2332
Lüning, U., **05**-0010, **14**-0188, **15**-2293
Lunn, G., **19**-0010, **19**-1232
Luo, F., **14**-0372
Luo, F.-T., **13**-0400, **13**-0487, **13**-0551, **15**-0388, **15**-0941, **15**-1507, **16**-0127
Luo, G., **07**-0118
Luo, H., **15**-0428
Luo, J., **15**-1405
Luo, M., **16**-0636, **16**-0637
Luo, S., **16**-0767, **16**-0774, **16**-0777
Luo, X.-L., **15**-0418
Luo, X.M., **15**-1826
Luo, Y., **13**-0126, **16**-0900
Luong-Thi, N., **13**-0389, **16**-1893
Lupes, M.E., **16**-1494
Luque, F.J., **03**-0075, **03**-0076, **03**-0079
Lusch, M.J., **06**-0015, **06**-0019, **15**-1089
Lush, R.K., **15**-1247
Lusinchi, X., **15**-1780, **18**-0156
Lusk, D.I., **12**-0621, **19**-0836
Luskus, L.J., **15**-2117
Lustgarten, R.K., **10**-0131, **10**-0132
Lustyk, J., **05**-0310
Lusztyk, E., **19**-1100
Lusztyk, J., **05**-0282, **05**-0297, **05**-0310, **05**-0384, **14**-0067, **14**-0074, **14**-0116, **14**-0118, **14**-0119, **14**-0122, **14**-0163, **15**-1212, **15**-1221, **18**-0078, **19**-1100
Lusztyk, J.L., **18**-0082
Lutete, L.M., **15**-0350, **15**-0354
Luthe, H., **15**-0101
Lüthi, H.P., **02**-0251, **03**-0072
Luthra, N.P., **06**-0010
Lutomski, K.A., **10**-1743
Luts, S., **08**-0113
Lutsenko, S., **19**-1049
Lutskii, A.E., **03**-0043
Lutter, H., **16**-1496
Lüttke, W., **01**-0079
Lutz, B., **03**-0036
Lutz, C., **15**-1143
Lutz, F., **16**-0747
Lutz, G., **15**-2029
Lutz, M., **15**-2072
Lutz, R.P., **18**-0618, **18**-0712
Lutz, S., **04**-0175
Lutz, W., **16**-1032
Luu, B., **12**-0454
Luukkonen, E., **10**-0331
Lux, R., **19**-1280
Luz, Z., **04**-0382, **18**-0619, **18**-0637
Luzikov, Y.N., **13**-0377, **13**-0391
Luzikova, E.V., **10**-1782
Luzung, M.R., **15**-0825
Luzzio, F.A., **16**-1150, **19**-0080, **19**-0562, **19**-0775, **19**-1194
Luçon, M., **08**-0094, **08**-0095
Lwazaki, K., **15**-0885
Lwowski, W., **05**-0396, **05**-0403, **05**-0405, **05**-0411, **10**-1025, **12**-0231, **12**-0233, **12**-0235, **15**-1911, **18**-0265, **18**-0281, **18**-0282
Ly, T.W., **16**-1067
Lyerla, J.R., **11**-0016
Lyford, L., **16**-0487
Lyga, J.W., **13**-0708
Lygo, B., **10**-1567, **15**-1807, **15**-1809, **15**-1811, **15**-1815
Lyle, G.G., **04**-0012
Lyle, R.E., **04**-0012, **19**-1212
Lynch, G.J., **15**-0187
Lynch, J., **15**-1972
Lynch, K.M., **04**-0431
Lynch, P.P., **19**-1526
Lynch, S.M., **15**-2000
Lynch, T., **05**-0245
Lynch, T.-Y., **05**-0246
Lynch, T.J., **19**-1765
Lynch, V., **15**-0202
Lynd, R.A., **10**-1377
Lynn, D.M., **18**-0801
Lyons, A., **07**-0040
Lyons, J.E., **15**-0406, **19**-1476
Lysenko, V.P., **16**-1403
Lyster, M.A., **10**-1133
Lythgoe, D.J., **19**-1129
Lyushin, M.M., **11**-0407

Ma'Mani, L., **16**-1439
Ma, D., **10**-0979, **13**-0117, **13**-0202, **13**-0481, **16**-1962, **19**-0573
Ma, H.-r., **13**-0500
Ma, J., **05**-0287, **10**-1225, **16**-0594, **18**-0475
Ma, J.C., **03**-0075
Ma, J.-A., **12**-0133, **15**-1885
Ma, S., **10**-1271, **12**-0292, **15**-0237, **15**-0286, **15**-0287, **15**-1471, **18**-0809, **19**-1386
Ma, V., **16**-1719
Ma, Y., **05**-0393, **13**-0581
Ma, Y.-R., **16**-0233
Ma, Y.-x., **19**-0919
Ma, Z., **15**-1962
Ma, S., **15**-0395
Maadhuri, Ch., **16**-0763
Maag, H., **16**-0402, **16**-0404
Maahs, G., **02**-0347
Maas, G., **04**-0479, **05**-0364, **10**-0390, **12**-0214, **13**-0693,

15-0757, **15**-2063, **15**-2292, **17**-0281, **17**-0496, **18**-0215, **18**-0496, **18**-0643, **19**-0297
Maas, L.W., **19**-0418
Maas, M., **13**-0653, **14**-0337
Maas, W., **16**-0103
Maass, G., **03**-0144
Mabille, C., **14**-0233
Mabrouk, P.A., **09**-0100
Mabry, T.J., **15**-1723
Mabuchi, T., **10**-1719
MacAlpine, G.A., **17**-0417
Macaulay, J.B., **15**-2058
Macaulay, S.R., **12**-0067
Maccarone, E., **16**-2143
Macchia, B., **10**-0580
Macchia, F., **10**-0580, **10**-0663, **10**-0814, **10**-0953, **10**-0954, **10**-1150, **10**-1564
Macchitella, D., **19**-0187
Macciantelli, D., **04**-0059, **04**-0291, **10**-1209
MacClellan, A.L., **01**-0036
Maccoll, A., **05**-0265, **17**-0003, **17**-0122, **17**-0122, **17**-0129, **17**-0130
Maccoll, A.B., **17**-0144
MacDonald, D.J., **02**-0344
MacDonald, I.D., **02**-0387
Macdonald, D., **18**-0608, **18**-0609
Macdonald, G., **15**-1791
Macdonald, G.J., **12**-0323
Macdonald, T.L., **10**-1726, **12**-0568, **15**-2353
MacDougall, K.N., **19**-1141
MacGarvey, U., **05**-0212
MacGee, D.I., **17**-0359
MacGibbon, A.K.H., **17**-0065
MacGillavry, C.H., **05**-0088
Mach, G.W., **08**-0118
Mach, M.H., **11**-0278, **11**-0642
Machajewski, T.D., **10**-1642
Macheleid, J., **10**-0391, **10**-0396
Macheño, O.G., **15**-2148
Machida, H., **17**-0369
Machida, Y., **10**-0743
Machigashira, N., **15**-1254
Machiguchi, T., **02**-0214
Machii, D., **07**-0094
Machleder, W.H., **15**-1804, **15**-1805, **18**-0205
Machnitzki, P., **13**-0237
Macho, V., **10**-0183
Machrouhi, F., **12**-0470, **13**-0564
Machuqueiro, M., **16**-1036
Maciejewski, G., **19**-1552, **19**-1553
Macielag, M., **18**-0860
MacIntyre, D.W., **09**-0052
Mack, A.G., **13**-0460
Mack, H.-G., **04**-0293
Mack, J.P.G., **12**-0060
MacKay, D.B., **10**-1423
Mackay, G.I., **08**-0051, **08**-0237, **10**-0336
Mackenzie, D.R., **11**-0313
Mackenzie, K., **10**-0213, **12**-0057, **17**-0502, **18**-0893, **18**-0896
Mackenzie, P.B., **16**-1032
Mackie, R.K., **10**-1097, **17**-0337
Mackiernan, J., **15**-0134
Mackintosh, N., **12**-0370
Macklen, E.D., **08**-0078, **08**-0238
Mackor, E.L., **05**-0015, **11**-0004
MacLachlan, M.J., **03**-0190
Maclaren, J.A., **19**-0790
MacLean, C., **02**-0062, **04**-0283, **05**-0231, **11**-0004
Macleod, L.C., **19**-1458
Maclin, K.M., **16**-0468, **16**-0574
MacMillan, D.W.C., **11**-0353, **12**-0124, **13**-0512, **15**-1008, **15**-2051, **16**-1036
MacNeil, S.L., **10**-1283
MacNicol, D.D., **03**-0101, **03**-0105, **03**-0119, **03**-0141, **03**-0155, **03**-0156, **03**-0157, **03**-0162, **03**-0164, **03**-0166, **03**-0167, **03**-0174, **03**-0175, **03**-0177, **03**-0210
MacNulty, B.J., **17**-0034, **17**-0118, **17**-0121
Macoas, E.M.S., **04**-0297
Macomber, D.W., **02**-0166
Macomber, R., **10**-0137
Macomber, R.S., **19**-0173
Macor, J.E., **11**-0245
MacPeek, D.L., **15**-1801
MacPhee, J.A., **09**-0059, **09**-0074, **09**-0074, **16**-1929, **16**-1930
MacQuarrie, R.A., **08**-0059
Macquarrie, D.J., **10**-1047, **15**-1012, **18**-0359
MacWeeny, R.M., **01**-0001
Madalengoitia, J.S., **16**-1402
Madan, C., **11**-0195
Madan, Ch., **16**-0332
Madan, K., **04**-0164
Madan, P., **04**-0196
Madan, V., **12**-0013
Madaule-Aubry, F., **10**-0415
Maddaford, S.P., **13**-0272, **15**-1125
Maddaluno, J., **05**-0178, **08**-0198, **16**-0470
Madder, R.D., **04**-0454
Maddess, M.L., **10**-1555, **18**-0783
Maddocks, P.J., **18**-0428
Maddox, M.L., **02**-0261
Madec, J., **19**-1028
Mader, M.M., **19**-1289
Madesclaire, M., **19**-0795, **19**-1602
Madhavan, D., **19**-0806
Madhavan, S., **19**-1071
Madhi, S., **16**-0383
Madhsudhan, P., **16**-1638
Madhusaw, R.J., **15**-2399
Madhusudhan, P., **15**-0565, **16**-0322, **17**-0442
Madine, J.W., **15**-0818
Madjdabadi, F.A., **11**-0405
Madler, M.M., **19**-0338
Madni, M., **05**-0393
Mador, I.L., **15**-0417
Madrakian, E., **11**-0127, **11**-0134
Madras, G., **09**-0102
Madrász, J., **15**-1491
Madrigal, D., **10**-0877
Madrikian, E., **12**-0698
Madroñero, R., **16**-2053
Madsen, J.Ø., **19**-1022
Madsen, R., **18**-0789
Madura, J.D., **08**-0210
Madurro, J.M., **19**-0579
Madyar, V.R., **11**-0129, **11**-0553, **16**-0134
Maeda, H., **03**-0027, **14**-0013
Maeda, H., **16**-1923, **19**-1354
Maeda, K., **10**-1202
Maeda, M., **15**-2337
Maeda, T., **11**-0329
Maeda, Y., **12**-0289, **13**-0139, **13**-0509, **19**-0120, **19**-0223
Maekawa, H., **10**-0612, **11**-0542, **12**-0501, **15**-1336, **15**-1337, **19**-1678
Maekawa, N., **02**-0158, **15**-1238
Mäeorg, U., **15**-0545
Maercker, A., **05**-0171, **12**-0397, **12**-0567, **16**-1255, **17**-0180
Maerker, C., **02**-0104, **05**-0078
Maerschalk, C., **07**-0082
Maerten, E., **13**-0627
Maes, B.U.W., **13**-0174, **13**-0178, **13**-0187, **13**-0196
Maesano, M.G., **15**-0293
Maestro, M.A., **10**-1454, **15**-1437
Maezaki, N., **15**-1115
Maffei, M., **19**-1021

Maftouh, M., **19**-1243
Magano, J., **19**-1077
Magdassi, S., **10**-0458
Magdesieva, T.V., **12**-0043
Magdolen, P., **07**-0093, **13**-0169
MaGee, D.I., **15**-0318
Magee, M.P., **19**-1157
Magennis, S.A., **13**-0423
Mager, S., **02**-0428, **04**-0076, **04**-0362
Mägerlein, W., **10**-1630, **13**-0611
Mageswaran, R., **03**-0151
Mageswaran, S., **03**-0151, **17**-0415, **18**-0386, **18**-0729
Maggi, R., **11**-0409, **15**-1770, **16**-0233, **16**-0255, **16**-1151, **19**-0532, **19**-0823
Maggini, M., **04**-0520
Magid, R.M., **10**-0218
Magid, R.M., **10**-0226, **10**-1101, **10**-1248
Magin, A., **15**-2362
Magna, L., **08**-0113
Magnaane, R., **17**-0200
Magnane, R., **17**-0199
Magnera, T.F., **10**-0271, **10**-0416
Magnier, E., **08**-0172
Magnin, D.R., **13**-0187
Magnotta, F.A., **16**-2170
Magnus, A.S., **19**-0184
Magnus, P., **15**-0197, **15**-0202,. **15**-0588, **15**-1419, **15**-1449, **16**-1232, **16**-1241
Magnus, P.D., **10**-1712, **15**-1998, **16**-2058
Magnuso, R.H., **12**-0013
Magomedev, N.A., **15**-0856
Magoon, E.F., **18**-0064
Magrath, J., **10**-0543
Maguire, A.R., **15**-1529
Maguire, J.A., **19**-0061
Magyar, E.S., **10**-0141
Mah, Y.J., **16**-1508
Mahadevan V., **10**-1552
Mahadevan, R., **02**-0280
Mahadevan, V., **10**-1552
Mahaffy, P.G., **19**-0241
Mahajan, A.N., **19**-1186
Mahajan, M.P., **15**-2133
Mahajan, S.W., **10**-1107
Mahale, G.D., **17**-0429
Mahalingam, A.K., **16**-1671, **18**-0702
Mahanty, J.S., **13**-0387
Maharvi, G.M., **10**-1081
Mahata, P.K., **18**-0248
Mahboubghah, N., **16**-0081
Mahdavi, H., **10**-0936, **10**-1164, **19**-0917
Mahé, R., **15**-0281
Mahender, G., **15**-1141, **16**-1526, **16**-1532
Mahender, I., **16**-1647
Mahendran, K., **10**-0333
Mahendran, M., **05**-0050
Maher, D.J., **16**-0778
Maher, J.P., **18**-0893
Mahesh, B., **19**-1205
Mahía, J., **10**-1454, **15**-1437
Mahindroo, V.K., **18**-0456
Mahiou, B., **15**-0101
Mahjoor, P., **13**-0503
Mahler, G.S., **04**-0175
Mahler, J.E., **02**-0348
Mahler, U., **16**-1189
Mahmud, H., **13**-0228
Mahmud, K.A.M., **11**-0029
Mahon, M.F., **10**-1463
Mahoney, W.S., **16**-1073
Mahrwald, R., **10**-0886, **16**-0973, **16**-1002, **16**-1009, **16**-1038, **16**-1684
Mahrwald, R., **19**-1771
Mahuteau, J., **15**-1301
Mahy, J., **15**-1892
Mahy, J.P., **12**-0224
Mai, K., **16**-1449
Mai, W.P., **15**-0272
Maia, A., **10**-0347, **10**-0456, **10**-1608
Maia, A.M., **10**-0305
Maia, M.P., **16**-0831
Maier, A., **15**-0757
Maier, A.H., **11**-0448
Maier, A.J., **11**-0046
Maier, G., **02**-0164, **02**-0204, **02**-0208, **02**-0213, **02**-0220, **04**-0437, **04**-0501, **15**-2322, **17**-0512, **18**-0468, **18**-0469, **18**-0470, **18**-0496, **18**-0645, **18**-0646, **18**-0652
Maier, M.E., **18**-0764, **18**-0814
Maier, W.F., **04**-0492, **12**-0655, **15**-0436, **15**-0450, **15**-0458, **15**-0460, **15**-0461, **15**-0501, **19**-1097, **19**-1286, **9**-1535
Maietti, S., **15**-1791
Maifeld, S.V., **18**-0789
Maigrot, N., **16**-1190
Maikap, G.C., **19**-0652, **19**-0839
Maillard, B., **10**-0741, **14**-0070, **19**-1100
Maillard, D., **19**-1050, **19**-1776
Mailleux, I., **10**-0610
Maimind, V.I., **02**-0159, **12**-0718, **18**-0885, **18**-0888
Mains, H.E., **14**-0262
Maio, W.A., **10**-1792
Maiolo, F., **13**-0135
Maione, A.M., **19**-0134
Maiti, G., **11**-0246, **12**-0635, **15**-0255
Maiti, S., **16**-1606, **16**-1750
Maiti, S.N., **15**-0162, **19**-1262, **19**-1643
Maitland Jones, J., **05**-0409
Maitlis, P.M., **02**-0227
Maitlis, P.M., **02**-0227
Maitlis, P.M., **15**-2257, **15**-2362, **15**-2405, **19**-0721
Maitra, K., **02**-0364
Maitra, U., **11**-0643
Maitraie, P., **19**-1193
Maiuolo, L., **10**-0545, **10**-1123, **16**-1618
Maiz, J., **16**-0832
Maizell, R.E., appendixA-0001
Majchrzak, M.W., **15**-1945
Majdoub, M., **10**-0699, **16**-1644
Majee, A., **16**-0369, **16**-0578, **19**-1133
Majerski, Z., **02**-0414, **10**-0199, **10**-0208, **18**-0029, **18**-0119, **18**-0224
Majetich, G., **07**-0102, **07**-0105, **11**-0240, **11**-0371, **11**-0372, **15**-1176, **15**-1744, **15**-2022, **19**-1385
Majewski, M., **08**-0194, **12**-0423, **16**-1026, **16**-1029
Majhi, A., **15**-1141
Majo, V.J., **15**-0769
Majo, V.J., **18**-0312
Majumdar, K.C., **15**-1277, **18**-0690, **18**-0698
Majumdar, K.K., **16**-0577
Majumdar, S.P., **18**-0240
Mak, A.N.S., **11**-0615
Mak, C.-K., **19**-0610, **19**-0618
Mak, K.T., **17**-0343
Mak, T.C.W., **02**-0243, **03**-0155
Mak, X.Y.;Lium Y., **13**-0179
Makabe, M., **16**-0905
Makani, S., **11**-0264
Makarova, L.G., **12**-0429, **12**-0482, **12**-0559, **13**-0720, **12**-0549
Makhija, R.C., **19**-0628
Makhon'kov, D.I., **11**-0287, **11**-0297
Makhova, I.V., **12**-0677
Maki, A.G., **01**-0052
Maki, S., **15**-0608, **19**-0400
Maki, T., **05**-0250, **18**-0276, **19**-1009, **19**-1094, **19**-1144

Maki, T., **19**-1354
Maki, Y., **10**-1360
Makido, T., **18**-0678
Makin, S.M., **15**-1109
Makino, K., **07**-0067, **19**-0475
Makino, T., **15**-0821
Makinouchi, S., **13**-0619
Makioka, Y., **19**-1707
Makisumi, Y., **18**-0697, **18**-0730
Makone, S.S., **16**-0050, **16**-0178
Makosza, M., **10**-0453, **10**-0458, **10**-0892, **10**-1580, **10**-1619, **15**-10, **16**-1225, **19**-0817, **19**-1740
Mąkosza, M., **10**-1043, **13**-0670, **13**-0671, **13**-0672, **13**-0673, **13**-0674, **16**-1391
Makovetskii, K.L., **15**-2362
Maksić, Z., **04**-0417
Maksić, Z.B., **02**-0082, **02**-0318, **02**-0348, **08**-0085, **08**-0120, **11**-0078
Maksimovic, L., **16**-0612
Maksimović, Z., **14**-0210
Maksyutin, Yu.K., **03**-0080
Makwana, V.D., **19**-0239
Mal, D., **10**-0842
Malacria, M., **10**-1277, **15**-0834, **15**-1224, **15**-1273, **15**-1975, **15**-2386, **15**-2400, **15**-2442, **18**-0546
Malagutti, C., **16**-1260
Malament, D.S., **15**-2313
Malan, C., **10**-1437, **15**-0615, **19**-1028
Malana, M.A., **16**-1587
Malanga, C., **16**-1925, **17**-0375, **17**-0376, **19**-1121
Malarski, Z., **03**-0013
Malasare, M.G., **16**-0656
Malashock, D.S., **10**-0582
Malatesta, V., **14**-0097
Malcolm, S.C., **12**-0358
Malda, H., **10**-1374
Maldonado, L., **10**-1662, **15**-1351
Malecki, A., **10**-0928
Maleczka Jr., R.E., **11**-0657, **12**-0258, **12**-0266, **13**-0097, **13**-0563, **16**-1904, **18**-0407, **18**-0409
Malek, F., **14**-0453, **19**-1414
Málek, J., **15**-1355, **19**-0010, **19**-0880, **19**-1066, **19**-1182, **19**-1507
Maleki, M., **10**-0301
Malerich, J.P., **04**-0311
Malfroot, T., **10**-1187
Malherbe, R., **15**-2096, **18**-0589
Malhotra, N., **02**-0117
Malhotra, R., **10**-0649, **10**-1134, **10**-1176, **11**-0119, **11**-0125, **11**-0154, **12**-0203, **19**-0253
Malhotra, S.V., **09**-0113, **15**-2041, **16**-0687
Mali, R.S., **12**-0388, **12**-0405
Mali, S.I., **11**-0273
Malik, K.M.A., **16**-1436
Malik, S.S., **11**-0120
Malinowski, M., **19**-1714, **19**-1718, **19**-1727
Malkin, Yu.N., **07**-0007
Malkov, A.V., **10**-1471, **16**-0756, **16**-0757, **16**-0760, **19**-1141
Malkus, H., **10**-0148
Malladi, R.R., **10**-0736, **16**-1911, **19**-0334, **19**-1000
Mallakpour, B., **16**-0096
Mallakpour, S.E., **16**-0057, **16**-0060, **16**-0063, **16**-0096, **19**-0072, **19**-0083, **19**-0086, **19**-0144, **19**-0152, **19**-0803, **19**-0916
Mallan, J.M., **12**-0388, **15**-0549
Mallart, S., **12**-0508
Mallat, T., **19**-0120
Mallet, J.J., **15**-2091
Mallion, R.B., **02**-0008, **02**-0099
Mallison, P.R., **18**-0432
Mallory, C.W., **02**-0310, **18**-0512
Mallory, F.B., **02**-0310, **18**-0512
Malmberg, H., **10**-1353
Malmvik, A., **19**-1064, **19**-1065
Malnar, I., **10**-0142
Malnick, L.M., **15**-1204
Malone, G.R., **10**-1733, **10**-1735
Malone, Y.M., **13**-0424
Maloney, J.R., **13**-0669
Malpass, D.B., **16**-0500
Malpass, J.R., **16**-2114, **18**-0344, **18**-0636
Malpezzi, L., **04**-0038
Malrieu, J., **15**-2105
Malsch, K., **04**-0437
Malsch, K.D., **02**-0218
Malte, A., **16**-1898
Maltese, F., **15**-1365, **16**-1842, **19**-1726
Maltsev, A., **05**-0407
Maltsev, A.K., **05**-0227, **05**-0328, **15**-2315
Malvestiti, I., **16**-0826
Malykhin, E.V., **14**-0203
Mamaev, V.P., **02**-0420, **09**-0020
Mamai, A., **16**-1402
Mamalis, P., **18**-0686
Mamdani, H.T., **18**-0602
Mamedova, Yu.G., **05**-0255
Mamposo, T., **16**-1192
Mampreian, D.M., **15**-1138
Mamuzić, R.I., **14**-0210
Man, T.-O., **04**-0081
Manabe, K., **10**-1498, **15**-0998, **15**-1025, **16**-0416, **16**-0619, **16**-0753, **16**-0918, **16**-0934, **16**-1092, **16**-1098, **16**-1117, **16**-1121, **16**-1676
Manabe, O., **07**-0058, **13**-0770, **19**-1574
Manabe, S., **11**-0332
Manage, A.C., **10**-1487
Manas, A.R.B., **11**-0487
Manatt, S.L., **02**-0127, **02**-0223
Manchand, P.S., **10**-1451
Mancheño, O.G., **10**-1454, **16**-0687, **16**-0688
Mancini, G., **04**-0052, **15**-0194
Mancini, G.J., **18**-0628
Mancuso, A.J., **19**-0162
Mancuso, N.R., **18**-0328
Mancuso, R., **12**-0734
Mandai, T., **16**-1004
Mandal, A.K., **10**-1107, **10**-1131, **15**-0675, **19**-1053
Mandal, B., **11**-0322
Mandal, G.C., **14**-0440
Mandal, K., **18**-0668
Mandal, S.B., **19**-1487
Mandal, S.K., **19**-0218
Mandal, T., **10**-0829, **10**-0829, **15**-1332
Mandel, F., **06**-0059
Mandel, S.M., **05**-0402
Mandelbaum, A., **16**-1891
Mander, L.N., **03**-0203, **04**-0001, **04**-0098, **04**-0100, **04**-0115, **04**-0116, **04**-0117, **04**-0126, **04**-0156, **04**-0157, **04**-0259, **04**-0274, **04**-0316, **04**-0351, **04**-0376, **04**-0424, **16**-2031, **18**-0729
Mandoli, A., **15**-1136, **16**-0787
Mandolini, L., **06**-0010, **06**-0011, **06**-0012, **10**-0343, **10**-0709, **11**-0101
Mane, R.B., **11**-0249, **16**-1157
Manek, M.B., **05**-0308, **14**-0078
Manenschijn, A., **05**-0223
Manescalchi, F., **15**-1667, **19**-0391
Mang, J.Y., **16**-2167

Mangeney, P., **04**-0111, **10**-1520, **10**-1531, **10**-1538, **15**-1062, **15**-1092, **15**-1133, **15**-1136, **16**-0868, **17**-0217, **19**-1692
Mangini, A., **02**-0089, **04**-0047, **05**-0119, **05**-0120, **05**-0121, **05**-0122, **10**-0771, **15**-0021, **16**-1402
Manglik, A.K., **11**-0096
Mango, F.D., **15**-2199, **18**-0083, **18**-0500, **18**-0825, **18**-0836
Mangoni, L., **15**-1685, **17**-0199
Mangroo, D., **16**-1669
Mangru, N.N., **17**-0035
Manhas, M.S., **07**-0116, **07**-0105, **10**-1599
Manimaran, T., **10**-1032
Manju, K., **15**-0792, **16**-1426
Manjuvani, A., **16**-0781
Mankand, N.P., **13**-0306
Manley, J.M., **16**-1803
Mann, A., **13**-0608, **15**-2145, **16**-0379
Mann, D.E., **01**-0037, **01**-0085, **05**-0328
Mann, G., **13**-0125
Mann, J., **10**-1041, **15**-2432
Mann, K., **02**-0206
Mann, L.W., **15**-2438
Mann, M., **02**-0274
Manna, S., **10**-1798
Mannarini, N., **13**-0399
Mannen, S., **19**-0295
Manner, J.A., **10**-0165, **10**-0166
Mannhardt, H., **07**-0008
Männig, D., **15**-0697
Mannina, L., **03**-0079
Mannion, M.R., **02**-0067, **02**-0068, **13**-0370
Mannschreck, A., **04**-0038, **04**-0039, **04**-0225, **04**-0508
Mannucci, S., **17**-0376, **19**-1121
Mano, E., **19**-0678
Mano, H., **17**-0031
Manoharan, M., **02**-0105, **02**-0311, **04**-0337, **04**-0343, **05**-0029
Manor, P.C., **03**-0176
Manor, S., **10**-1146
Manoso, A.S., **13**-0631, **13**-0637
Manoury, E., **15**-1691
Mansfield, K.T., **15**-2203, **15**-2206
Manske, R.H.F., **10**-0985
Mansoor, U.F., **12**-0327
Mansuy, D., **12**-0224, **15**-1892
Manta, N., **16**-1134
Mantano, Y., **19**-0245
Manthey, J.W., **10**-0285
Manuel, G., **19**-1403
Manuilov, A.V., **10**-0393
Manyem, S., **14**-0030
Manyik, R.M., **10**-0902
Manzano, F.L., **14**-0177
Manzer, L.E., **13**-0599
Manzo, P.G., **07**-0096, **13**-0062
Manzocchi, A., **19**-0098, **19**-0440
Mao, C., **18**-0499
Mao, J., **16**-0687, **19**-1159
Maple, S.R., **16**-0988
Maquestiau, A., **04**-0486
Mar, E.K., **10**-1542
Maradyn, D.J., **15**-2248
Maragni, P., **11**-0218
Marais, D.J., **02**-0034, **02**-0037
Maran, U., **02**-0406, **12**-0083
Marans, N.S., **12**-0431
Marao, I., **15**-1947
Marbet, R., **18**-0676
Marcaccioli, S., **02**-0058
Marcantoni, E., **10**-0845, **10**-1064, **10**-1123, **11**-0457, **15**-1018, **15**-1105, **15**-1289, **16**-0487, **16**-0521, **16**-0615, **16**-1618, **16**-1666, **17**-0160, **19**-0997
Marcantonio, K.M., **13**-0272
Marcelli, T., **15**-0225
March, J., **11**-0191, **12**-0633, **12**-0660, **12**-0680, **16**-0514
March, S., **15**-1136
Marchalin, S., **16**-1189
Marchand, A.P., **03**-0101, **04**-0441, **05**-0347, **15**-2103, **15**-2107, **15**-2108, **15**-2110, **15**-2110, **15**-2111, **15**-2183, **15**-2184, **15**-2261, **17**-0168, **17**-0170, **17**-0354, **17**-0478, **18**-0166, **18**-0477, **18**-0841
Marchand, C., **15**-2022
Marchand-Brynaert, J., **10**-0897, **15**-2003, **15**-2048, **15**-2212
Marchelli, R., **12**-0118
Marchese, G., **10**-1265, **10**-1770, **16**-1924, **16**-1929, **16**-1929, **17**-0013, **17**-0031, **17**-0056
Marchese, L., **10**-0819
Marchesini, A., **02**-0143
Marchot, E.C., **05**-0200
Marchueta, I., **15**-2364
Marcin, L.R., **10**-0899
Marciniak, B., **07**-0033, **07**-0034
Marcinkiewicz, S., **18**-0686
Marcinow, Z., **02**-0360, **02**-0362, **02**-0363
Marco, J.A., **02**-0277, **16**-0996, **16**-1289
Marco, M., **07**-0118, **07**-0119, **13**-0493, **13**-0546
Marco-Contelles, J., **15**-0834, **15**-1225, **15**-1437
Marcotullio, M.C., **10**-0563, **10**-0925, **12**-0723, **15**-1625, **16**-0149, **19**-0668, **19**-1726
Marcoux, J.-F., **13**-0117, **13**-0174, **13**-0385, **15**-2340, **19**-1148
Marcum, J.D., **05**-0313
Marcus, J., **16**-1423
Marcus, N.L., **18**-0868
Marcus, R., **16**-1289
Marcus, R.A., **06**-0027, **08**-0137
Marcuzzi, F., **15**-0034
Marder, T.B., **15**-0696
Marecot, P., **15**-0424
Mareda, J., **10**-0011, **10**-0326, **15**-2282
Marek, I., **10**-0625, **10**-1385, **10**-1520, **10**-1531, **12**-0347, **15**-0500, **15**-0874
Marets, J., **15**-1168
Marfat, A., **15**-0949
Margaretha, P., **07**-0001, **15**-2238
Margarita, R., **19**-0204, **19**-1770
Margerison, D., **06**-0053, **06**-0054
Margolin, Z., **06**-0077, **06**-0078, **08**-0051
Margot, C., **17**-0209
Margrave, J.L., **01**-0025, **02**-0080, **04**-0320, **05**-0346, **14**-0130
Margues, A., **19**-0815
Margulis, M.A., **07**-0067, **07**-0070, **07**-0079
Margulis, T.N., **04**-0378
Maria, P., **03**-0016, **08**-0076, **08**-0146
Maria, P.-C., **08**-0087
Marianelli, R.S., **16**-1469
Mariani, A., **19**-1141
Mariano, P.S., **07**-0029, **07**-0044, **15**-1295, **15**-1298, **18**-0849
Marianucci, E., **16**-0272
Marié, J.-C., **10**-1277
Mariet, N., **15**-2169
Marigo, M., **12**-0124, **12**-0146
Marin, M., **19**-0815
Marinas, J.M., **13**-0576, **15**-0191, **15**-0454, **15**-0574, **19**-1762

Marinelli, F., **13**-0504, **15**-0245, **15**-0848, **15**-2423, **16**-0163, **16**-0279
Marinelli, G.P., **13**-0281
Marinescu, L., **16**-1873
Marinescu, L.G., **16**-1873
Marinez, E.R., **11**-0212
Marini, F., **15**-0273
Marino, G., **02**-0149, **10**-0038, **11**-0067, **11**-0081, **11**-0082, **11**-0470
Marino, J.P., **11**-0516, **14**-0315, **19**-1786
Marino-González, A., **19**-0181
Marioni, F., **15**-0014, **15**-0022
Marisco, W.E., **15**-0492
Mark, H.W., **10**-0136, **10**-0141, **10**-0179
Mark, V., **10**-0229
Markby, R., **15**-1377
Markgraf, J.H., **19**-0574, **19**-0585, **19**-0586
Markham, J., **15**-0815
Markham, J.P., **15**-0825
Markides, K.E., **09**-0108
Markiewicz, M.K., **03**-0113
Markiewicz, W., **10**-0801
Märkl, R., **10**-0254
Marko, D.E., **04**-0349
Marko, I., **15**-1691, **15**-1701, **15**-1702, **10**-0549, **14**-0194, **14**-0274, **15**-1285, **15**-1529, **15**-1530, **15**-2102, **16**-0681, **16**-0799, **16**-1618, **16**-1909, **19**-0122, **19**-0123
Markò, I.E., **16**-1239
Markó, L., **15**-1495, **15**-1496, **15**-1497
Markov, J., **15**-0843
Markov, P., **10**-0833
Marković, D., **08**-0123
Markovski, L.N., **01**-0009, **16**-1887
Marks, M.J., **16**-2135
Marks, T.J., **15**-0335, **15**-0338, **15**-0699, **15**-1868, **15**-1869, **15**-1870, **15**-1871, **15**-1872
Marktscheffel, F., **19**-0326, **19**-1378
Markwell, R.E., **14**-0133, **14**-0134
Markworth, C.J., **13**-0543
Marle, I., **04**-0175
Marlier, J.F., **16**-0018
Marmsäter, F.P., **12**-0368
Maroni, R., **10**-0258, **15**-1639
Marotta, E., **15**-0225
Marples, B.A., **15**-1782
Marquais, S., **10**-1373, **10**-1395, **10**-1413
Marquarding, D., **16**-2124, **16**-2128, **16**-2133, **17**-0479
Marque, S., **13**-0109
Marques, C.A., **19**-0339
Marques, F.de.A., **16**-0583
Marques, M.M., **16**-0027
Marquet, A., **04**-0144, **05**-0138, **16**-0403
Marquet, J., **11**-0192, **13**-0007, **13**-0064, **13**-0066, **13**-0158
Marquez, A., **16**-0470
Marquez, R., **15**-1227
Marquez, V.E., **19**-1485
Márquez, F., **16**-0672
Marquié, J., **11**-0220, **16**-2029, **19**-1318
Marquis, E.T., **04**-0483
Marradi, M., **19**-0774
Marren, T.J., **15**-1083
Marriott, P.R., **14**-0097
Marriott, S., **01**-0042, **09**-0049, **09**-0052, **09**-0055
Marrocco, M., **19**-0623
Marsaioli, A.J., **18**-0655
Marsch, M., **05**-0136, **05**-0143
Marschner, C., **10**-1662
Marsella, J.A., **10**-0906
Marsh, F.D., **12**-0235
Marshall, C., **04**-0101
Marshall, D.R., **11**-0463, **17**-0049
Marshall, J.A., **04**-0468, **04**-0470, **04**-0493, **10**-1557, **10**-1559, **15**-0257, **15**-0984, **16**-0557, **16**-0609, **17**-0343, **18**-0735, **19**-1184
Marshall, J.L., **04**-0264, **16**-1670, **19**-0018, **19**-1320
Marshall, P.A., **15**-0647
Marshall, P.J., **16**-0029
Marshall, R.L., **16**-0612
Marshall, T.B., **15**-2172, **16**-2080
Marshall, W.J., **12**-0365
Marshall, W.S., **18**-0329
Marsi, M., **17**-0190
Marsman, B., **15**-1806
Marson, C.M., **10**-0386, **10**-1608, **15**-0383, **16**-0433, **16**-0433
Marstokk, K., **03**-0054
Marston, C.R., **15**-0253
Martel, J.P., **16**-1381
Martell, A.E., **12**-0074, **15**-0206, **15**-0792, **15**-1477, **15**-2362, **15**-2429, **19**-0718
Martelli, G., **15**-2174
Marten, D.F., **10**-1436
Martens, D., **02**-0257, **18**-0506
Martens, H., **15**-1652
Martens, J., **04**-0136
Marth, C.F., **16**-1293, **16**-1296
Marti, M.J., **10**-1006
Martin, A., **12**-0254, **14**-0216, **16**-1907
Martin, B., **12**-0637
Martin, B., **16**-1774
Martin, C.G., **11**-0363, **19**-0206
Martin, D., **10**-0408, **10**-0616, **16**-2066
Martin, E., **10**-1454
Martin, G.J., **11**-0469
Martin, H., **15**-2196, **18**-0647
Martin, H.-D., **18**-0642
Martin, H.J., **15**-1004, **16**-0414
Martin, I., **17**-0131
Martin, J., **04**-0363, **16**-1248
Martin, J.C., **05**-0050, **05**-0233, **10**-0198, **12**-0402, **14**-0026, **14**-0049, **14**-0114, **14**-0183, **14**-0184, **15**-2185, **15**-2190, **15**-2212, **16**-2113, **19**-0198, **19**-0198
Martin, J.S., **03**-0052
Martin, K., **05**-0187
Martin, K.J., **19**-1517
Martin, M.G., **10**-0988
Martin, M.M., **04**-0457, **18**-0050, **18**-0074, **18**-0085
Martin, M.T., **16**-1780
Martin, P., **15**-1642, **15**-2178
Martin, P.L., **10**-0079
Martin, P.S., **15**-1298
Martin, R., **10**-1299, **11**-0550
Martin, R.A., **19**-1738
Martin, R.B., **19**-1689
Martin, R.H., **19**-1056
Martin, S.F., **18**-0802
Martin, V.S., **19**-0590
Martín, J.D., **18**-0820
Martin, R.B., **06**-0031, **16**-0103, **16**-0315, **16**-1556
Martin, R.H., **04**-0186, **04**-0067, **04**-0068, **04**-0069, **15**-1862
Martin, S.F., **10**-0504, **10**-1665, **10**-1728, **15**-2121, **15**-2302, **16**-0399, **16**-1195, **16**-1273
Martin, S.J., **15**-1915
Martin, V.S., **04**-0193
Martin, W.P., **12**-0323
Martin, W.B., **16**-0385
Martín, M., **19**-1272
Martín, R., **16**-1940
Martín, S.E., **19**-0116, **19**-0805
Martín, V.S., **19**-0408
Martín, Y., **16**-0831
Martín-Matute, B., **13**-0441
Martín-Ruiz, B., **13**-0366
Martinek, T.A., **02**-0429
Martinelli, G., **16**-1322

Martinelli, M.J., **16**-2161
Martinengo, T., **04**-0196
Martinez, A.G., **10**-0254, **16**-2057
Martinez, C.A., **18**-0362
Martinez, F.N., **05**-0307, **14**-0068, **14**-0123
Martinez, G., **17**-0415
Martinez, J., **15**-0667
Martinez, L.A., **19**-0089
Martínez, P., **15**-0753
Martinez, R.I., **19**-0010, **19**-0386
Martínez, A.G., **10**-0791, **10**-1362, **10**-1400, **11**-0471
Martínez, F., **18**-0141
Martínez, I., **16**-1352, **16**-1354
Martínez, K., **16**-1352
Martínez, R., **10**-0720, **15**-1244
Martínez, S., **15**-2415
Martinez-Davila, C., **18**-0586
Martinez-Gallo, J.M., **12**-0125
Martinon, S., **15**-2234
Martinović, S., **16**-1479
Martins, T.L.C., **12**-0294, **15**-0216, **15**-0291
Martinu, T., **05**-0365
Marto, S.J.L., **15**-1907
Marton, D., **16**-0645
Márton, J., **11**-0010
Martorell, A., **15**-1136
Martorell, G., **12**-0389, **13**-0237, **13**-0299
Marty, R.A., **02**-0181
Marty, W., **04**-0205
Martynov, A.V., **15**-0297
Martynov, V.F., **16**-1215
Martynow, J., **19**-0371
Martz, J.T., **10**-1187
Marumoto, S., **18**-0607
Maruo, M., **15**-1330
Maruoka, H., **16**-0676
Maruoka, K., **10**-0643, **12**-0368, **12**-0521, **15**-0704, **15**-0707, **15**-0971, **15**-1001, **15**-2344, **16**-0621, **16**-1101, **16**-1487, **16**-1503, **16**-1691, **16**-1839, **17**-0277, **18**-0143, **18**-0158, **18**-0339, **18**-0340, **18**-0341, **18**-0702, **19**-0155, **19**-0946, **19**-0965, **19**-1004, **19**-1244, **19**-1774
Marusawa, H., **14**-0105
Marutani, Y., **16**-0687
Maruyama, K., **10**-1261, **10**-1375, **10**-1509, **11**-0444, **14**-0395, **15**-1991, **15**-2257, **16**-0491, **16**-0531, **16**-0533, **16**-0613, **16**-1017, **17**-0031, **19**-0258, **19**-0633
Maruyama, T., **16**-1047, **16**-1051, **16**-1418
Maruyama, Y., **11**-0342, **18**-0189
Marvel, C.S., **04**-0001, **04**-0013
Marvell, E.N., **10**-0134, **11**-0628, **15**-0435, **17**-0491, **18**-0166, **18**-0471, **18**-0497, **18**-0599, **18**-0613, **18**-0704, **18**-0705
Marx, A., **16**-0626
Marx, J.N., **15**-0180, **18**-0034
Marx, K.H., **10**-1463
Marx, M., **19**-0161
Marx, R., **05**-0236
Maryanoff, B., **19**-1750
Maryanoff, B.E., **04**-0026, **15**-2390, **15**-2425, **16**-1255, **16**-1298, **16**-1303, **16**-1323, **16**-1324, **16**-1325, **19**-0950, **19**-1331
Maryanoff, C.A., **04**-0026, **16**-0362, **16**-1024, **19**-1295, **19**-1331
Maryott, A.A., **01**-0037
Marzabadi, C.H., **04**-0348
Marzi, M., **16**-1733
Marziano, N.C., **08**-0129
Marzilli, T.A., **10**-1318
Marzin, C., **02**-0415
Marzinzik, A., **18**-0717
Marzorati, L., **19**-1782
Mas, J.-M., **10**-1062
Mas, R.H., **04**-0422
Masada, H., **10**-0596, **10**-0597, **10**-0602, **10**-1844
Masaki, M., **02**-0421
Masaki, Y., **10**-0657, **10**-0811, **10**-0846, **19**-0227, **19**-0421, **19**-0655
Masala, S., **19**-0677
Masamichi, T., **07**-0012
Masamune, H., **15**-1822
Masamune, S., **01**-0011, **02**-0208, **02**-0214, **02**-0220, **02**-0248, **02**-0250, **04**-0133, **04**-0148, **15**-0680, **15**-2297, **16**-0708, **16**-0985, **16**-1014, **16**-1018, **16**-1025, **16**-1034, **16**-1050, **16**-1315, **16**-1651, **16**-1655, **18**-0487, **18**-0840, **18**-0843, **19**-0445, **19**-1294
Masaracchia, J., **15**-2209
Masaya, K., **15**-0971
Mascal, M., **03**-0132
Mascareñas, J.L., **15**-0827, **18**-0791
Mascarenhas, C.M., **19**-1776
Masci, B., **03**-0130, **11**-0138
Masdeu, A.M., **12**-0748
Masdeu-Bultó, A.M., **10**-1454
Mase, N., **15**-1004
Mase, T., **11**-0267, **13**-0137
Maseras, F., **04**-0049
Mashima, K., **19**-1051
Mashima, M., **07**-0079
Mashiro, R., **16**-1121
Mashyanov, M.N., **15**-0181
Masias, A., **10**-0488, **10**-0489
Masilamani, D., **19**-1331
Maskell, R.K., **16**-1496
Maskill, H., **08**-0081, **08**-0156, **10**-0060, **10**-0083, **10**-0395, **16**-2140
Maslak, P., **12**-0232
Masler, W.F., **04**-0146, **15**-0597
Maslin, D.N., **19**-1115
Masllorens, J., **13**-0365, **13**-0420
Maslov, S.A., **19**-0701
Maslowsky Jr., E., **12**-0001
Mason, D., **10**-0458
Mason, H.J., **11**-0245
Mason, R., **02**-0259, **02**-0265, **03**-0083
Mason, S.F., **04**-0126
Mason, T.J., **07**-0079, **07**-0082, **07**-0095, **07**-0066
Masour, T.S., **10**-0508
Massa, A., **15**-1822, **16**-0756, **16**-0757, **19**-0823
Massa, W., **12**-0030, **15**-0094
Massaccesi, M., **11**-0457, **16**-0521, **16**-1618
Massanet, G.M., **14**-0177, **15**-0284, **15**-1710
Massat, A., **04**-0295
Masse, J.P., **10**-1303
Massey, A.G., **12**-0573
Massey, W.D., **10**-0895
Massicot, F., **19**-1312
Masson, G., **15**-1009
Masson, S., **10**-1454
Massoui, M., **19**-0708
Massy, D.J.R., **16**-0398
Massy-Westropp, R.A., **10**-1518, **16**-1340, **19**-1395
Mastantuono, A., **16**-0831
Masterman, S., **10**-0003, **10**-0014, **16**-1562, **17**-0105
Masters, A.P., **17**-0392
Mastracchio, A., **13**-0193
Mastrorilli, E., **15**-0036, **16**-0442
Masuda, H., **15**-1561, **19**-1745
Masuda, M., **13**-0583
Masuda, R., **19**-0934
Masuda, S., **01**-0029, **11**-0375, **18**-0352

Masuda, Y., **10**-1217, **12**-0452, **12**-0546, **13**-0293, **13**-0633, **15**-1192
Masui, A., **03**-0168
Masui, M., **19**-0487
Masumi, N., **13**-0615
Masuno, M.N., **15**-0474
Masure, D., **11**-0226, **15**-2102
Masuyama, Y., **10**-0885, **16**-0495, **16**-0620, **16**-0635, **19**-0130, **19**-0450
Mata, J., **19**-0970
Mata, P., **04**-0101
Matacz, Z., **10**-1580, **12**-0212, **12**-0338
Mataka, S., **10**-0507
Matallana, A., **04**-0383
Matano, Y., **10**-1201, **19**-0119
Matasa, C., **12**-0204
Matassa, V.G., **12**-0035
Mateescu, G.D., **05**-0083, **10**-0181, **11**-0014, **11**-0015
Mateo, C., **12**-0276, **15**-2392
Mateo, S., **06**-0062
Mateus, C.R., **16**-0776
Mathé, D., **07**-0111
Matheny, N.P., **14**-0207
Mathes, C., **18**-0828
Matheson, A.F., **06**-0074
Mathew T.S., **19**-0136
Mathew, J., **19**-0491
Mathew, L., **10**-0565, **14**-0074
Mathew, T., **04**-0447, **11**-0157, **11**-0223, **11**-0236
Mathey, F., **10**-1454
Mathias, J.P., **02**-0312
Mathias, L.J., **10**-0467
Mathieu, B., **08**-0189, **15**-2004, **15**-2011
Mathieu, J., **04**-0136, **15**-2105
Mathre, D.J., **18**-0302
Mathur, N.K., **16**-1817
Mathur, S.N., **10**-0459
Mathvink, R.J., **15**-1352
Mathy, A., **18**-0183
Matias, P., **18**-0637
Matice, J.J., **11**-0556
Matier, W.L., **13**-0773
Matin, S.B., **19**-1131
Matínez, R., **04**-0361
Matinopoulos-Scordou, A.E., **13**-0571
Matić, R., **14**-0212
Matlack, G.M., **19**-0838
Matos, C.R., **15**-2177
Matos, M.R.P.N., **10**-1213
Matović, R., **10**-1562
Mátrai, J., **18**-0593
Matshshita, Y., **15**-0204
Matsson, O., **10**-0854, **12**-0064, **17**-0038
Matsu, J.-i., **11**-0423
Matsuba, N., **05**-0258, **05**-0259
Matsubara, K., **19**-1094
Matsubara, S., **13**-0433, **15**-0945, **15**-1206, **15**-1265, **15**-1290, **16**-0669, **16**-0823, **16**-1368, **17**-0310, **19**-0215, **19**-1659
Matsubara, Y., **11**-0542, **15**-1921
Matsubra, S., **16**-1365
Matsuda, A., **16**-1277, **18**-0488
Matsuda, H., **12**-0317, **12**-0755, **16**-1727, **17**-0310, **19**-1001, **19**-1139
Matsuda, I., **10**-1468, **10**-1469, **15**-1055, **15**-1459, **15**-1474, **16**-1017
Matsuda, K., **05**-0290, **10**-0170, **19**-0066
Matsuda, M., **14**-0120
Matsuda, S., **14**-0373
Matsuda, T., **11**-0507, **13**-0362, **13**-0366, **13**-0724, **14**-0364, **14**-0368, **19**-1022 **19**-1023
Matsuda, Y., **02**-0317, **16**-0694
Matsugi, M., **12**-0252, **14**-0008
Matsuhashi, H., **10**-1198, **10**-1207, **15**-1773
Matsui, H., **16**-0022
Matsui, R., **15**-0608
Matsui, T., **09**-0026, **15**-0203, **15**-0204, **16**-0823
Matsukawa, M., **17**-0202
Matsukawa, S., **16**-0522, **16**-1109, **16**-1119, **19**-1674
Matsukawa, Y., **15**-0940
Matsuki, K., **19**-1478
Matsukida, H., **15**-1237
Matsumasa, K., **15**-1360
Matsumoto, A., **05**-0277
Matsumoto, H., **03**-0126, **10**-0513, **10**-1227, **13**-0465, **15**-1183, **15**-1641
Matsumoto, K., **06**-0051, **09**-0085, **09**-0086, **10**-0475, **12**-0252, **15**-1773, **15**-1843, **15**-2136, **16**-1017, **16**-1149, **16**-1163, **16**-1450, **16**-1826, **16**-1830, **18**-0148, **19**-1781
Matsumoto, M., **02**-0304, **02**-0306, **04**-0212, **10**-1196, **15**-0417, **15**-2152, **19**-0431
Matsumoto, N., **16**-1095, **16**-1134
Matsumoto, S., **15**-0354, **16**-0711
Matsumoto, T., **04**-0193, **10**-0504, **10**-1089, **13**-0050, **16**-1497
Matsumoto, Y., **10**-0691, **12**-0035, **15**-0657, **15**-0700, **16**-0754
Matsumura, A., **15**-0922
Matsumura, H., **15**-0841
Matsumura, K., **15**-0611
Matsumura, R., **10**-0676
Matsumura, S., **19**-0120, **19**-0223, **19**-1343
Matsumura, T., **15**-2304
Matsumura, Y., **05**-0250, **14**-0284, **17**-0435, **18**-0276, **18**-0340, **19**-1009, **19**-1144, **19**-1563
Matsunaga, H., **19**-1049
Matsunaga, N., **01**-0091, **02**-0039, **02**-0039
Matsunaga, S., **10**-0689, **15**-0994, **15**-1023, **15**-1303, **16**-0898, **16**-1044, **16**-1272, **19**-0340, **19**-1677
Matsunaka, K., **19**-0552
Matsuno, T., **19**-1670
Matsuo, G., **15**-0749
Matsuo, H., **16**-1051
Matsuo, J-i., **11**-0423, **10**-1618, **11**-0290, **11**-0324, **17**-0295, **19**-0243, **19**-0244
Matsuo, K., **12**-0720
Matsuo, T., **16**-1119
Matsuo, Y., **16**-1041, **19**-0688
Matsuoka, H., **19**-1659
Matsuoka, K., **16**-0493, **19**-1006, **19**-1058
Matsuoka, M., **19**-0967
Matsuoka, T., **13**-0314, **15**-0968
Matsushima, Y., **10**-1469
Matsushita, H., **10**-1377, **15**-1236, **19**-1287
Matsushita, M., **05**-0284, **16**-0133
Matsushita, N., **10**-1704
Matsushita, T., **10**-0273
Matsushita, Y., **15**-0203
Matsuura, H., **16**-0633
Matsuura, T., **15**-2155, **18**-0880, **19**-0281
Matsuura, Y., **04**-0334, **15**-0374
Matsuya, T., **14**-0013
Matsuya, Y., **16**-0782
Matsuya, Y., **19**-1518
Matsuyama, H., **11**-0260
Matsuyama, K., **05**-0297, **10**-1654
Matsuyama, T., **16**-0535
Matsuyama, Y., **10**-1466
Matsuza, S., **15**-1066

Matsuzaki, S., **10**-0734
Matsuzawa, H., **19**-0985
Matsuzawa, S., **16**-0581
Matsuzono, M., **13**-0648
Matt, C., **10**-1830, **15**-1939, **16**-0115
Matt, D., **03**-0179
Matt, J.W., **18**-0077
Matta, C.F., **04**-0454
Mattay, J., **04**-0091, **14**-0073, **15**-2063
Matte, D., **12**-0725
Matter, Y.M., **15**-0101
Mattern, D.L., **15**-0969
Mattern, R.-H., **17**-0151
Mattes, H., **10**-1142
Mattes, K., **13**-0047
Mattes, S.L., **07**-0054, **15**-2252
Matteson, D.S., **12**-0471, **10**-1415, **10**-1417, **12**-0002, **12**-0442, **12**-0458, **15**-0636, **15**-0661, **15**-0674, **15**-1660, **16**-1393, **18**-0420, **18**-0434
Matteucci, M., **19**-0797
Matthews, B.R., **16**-1422
Matthews, C.N., **16**-1302
Matthews, G.J., **15**-1633
Matthews, I.R., **10**-1538
Matthews, P.S.C., **01**-0001
Matthews, R.T., **05**-0212
Matthews, W.S., **05**-0105, **17**-0344
Matthey, G., **11**-0489
Matts, T.C., **10**-0079
Mattson, A.E., **15**-1339, **15**-1368, **16**-0724
Mattson, R.J., **16**-0361
Matturo, M.G., **04**-0519
Matturro, M., **18**-0623
Matty, L., **19**-1148
Matui, C., **10**-1126, **10**-1443
Matula, T.J., **07**-0075
Matusamy, S., **12**-0355, **15**-0807
Matusch, R., **02**-0178, **04**-0437, **17**-0512
Matuszewski, B., **17**-0515
Matveev, A.A., **10**-0202, **10**-0425
Matveeva, E.D., **10**-1087
Matveeva, M.K., **13**-0720
Matvienko, V.N., **10**-0263
Matyusha, A.A., **11**-0351
Matz, J.R., **14**-0413, **14**-0414
Matzger, A.J., **02**-0289
Matzner, E., **15**-2116
Mau, A.W.-H., **13**-0413
Mauder, H., **16**-2087
Mauduit, M., **18**-0771
Mauger, E., **15**-0087
Maughan, P.J., **11**-0567
Maughan, W., **10**-0992
Mauksch, M., **02**-0338, **02**-0339
Mauleón, P., **15**-1129
Maulitz, A.H., **02**-0081
Maumy, M., **11**-0539, **19**-0279, **19**-0436
Maurel, R., **10**-0778
Mauret, P., **15**-2407
Mauriello, G., **11**-0285
Maurin, J., **08**-0174
Maus, S., **16**-0564
Mauzé, B., **10**-1524, **16**-1223
Maverick, A., **10**-0392
Maverick, E., **02**-0271
Mävers, U., **16**-1270
Mavropoulos, I., **15**-0264
Mavrov, M.V., **15**-0106
Maw, G., **12**-0456
Maw, G.A., **17**-0107, **17**-0108, **17**-0121
Mawson, S.D., **12**-0197
Maxton, P.M., **03**-0072
Maxwel, J.I., **08**-0049
Maxwell, B.E., **18**-0746
Maxwell, B.J., **15**-1279
Maxwell, C.R., **10**-1538
Maxwell, R.J., **14**-0151, **18**-0047
May, E.J., **15**-2306
May, E.L., **11**-0401
May, G.L., **14**-0330
May, H., **10**-0639
May, J.A., **17**-0279
May, L.M., **19**-0076
May, P.J., **09**-0015
May, S.A., **11**-0335
Mayadunne, R.T.A., **15**-1257
Mayahi, M.F., **14**-0103, **16**-1846
Mayants, A.G., **12**-0709
Mayasundari, A., **13**-0428
Maye, J.P., **15**-0778
Mayeda, E.A., **19**-0691
Mayer, A., **19**-1800
Mayer, E., **11**-0366
Mayer, J., **02**-0272, **09**-0100
Mayer, R., **16**-0002, **16**-0204, **16**-1724, **19**-1456, **19**-1791, **19**-1802
Mayer, R.P., **18**-0035
Mayer, S., **07**-0118
Mayer, S.F., **10**-0703
Mayer, U., **04**-0478, **14**-0263
Mayers, D.A., **18**-0126
Maynard, G.D., **12**-0665, **18**-0601
Maynes, G.G., **15**-0142
Mayo, **18**-0161
Mayo, F.R., **15**-0172, **14**-0022, **14**-0214, **15**-0062
Mayo, J.D., **10**-0294
Mayo, K.G., **18**-0773
Mayon, P., **15**-1225
Mayoral, E.P., **18**-0570
Mayoral, J.A., **15**-2038, **15**-2054, **15**-2059, **15**-2063, **15**-2305, **16**-0689
Mayr, H., **05**-0072, **05**-0098, **10**-0009, **10**-0028, **10**-0282, **10**-0355, **10**-0407, **10**-1673, **11**-0354, **15**-0002, **15**-0029, **15**-0716, **15**-1636, **15**-1637, **15**-1927, **15**-1963, **15**-1979, **15**-2212, **15**-2282, **16**-1020, **16**-1419
Mayuoka, K., **10**-0713
Mazaleyrat, J., **16**-0490, **16**-1190
Mazhar-Ul-Haque, **16**-1302
Mazid, M., **15**-1092
Mazidi, M.R., **16**-0063
Mazik, M., **03**-0065
Mazloumi, Gh., **16**-1752
Mazume, T., **16**-1726
Mazur, R.H., **10**-0193
Mazur, S., **02**-0237
Mazur, U., **19**-0379
Mazur, Y., **10**-0733, **10**-0761, **16**-0110, **16**-0180, **16**-1722, **19**-0454, **19**-0765
Mazzacani, A., **15**-1770, **16**-0255, **16**-1151, **19**-0532
Mazzali, A., **16**-1260
Mazzanti, A., **04**-0060, **04**-0087, **04**-0315, **04**-0416
Mazzeo, C., **18**-0123
Mazzocchi, P.H., **15**-2235, **18**-0471, **18**-0590
Mazzola Jr., R.D., **15**-1412
Mazzone, L., **10**-1325
Mbiya, K., **15**-2146
McAdams, L.V., **17**-0357
McAdoo, D.J., **18**-0536
McAlister, D.R., **15**-2405
McAlister, J.A., **16**-1601
McAllister, G.D., **16**-0341
McAllister, M.A., **03**-0001, **03**-0040, **04**-0221, **16**-2112
McAllister, T.L., **12**-0285
McAnda, A.F., **15**-0624
McBay, H.C., **14**-0288, **14**-0290
McBee, E.T., **11**-0224, **14**-0063
McBride, C.M., **19**-0026
McBride, J., **05**-0231
McBride, J.M., **02**-0235, **04**-0186, **18**-0056
McCabe, J.F., **03**-0069
McCabe, J.R., **15**-2096
McCague, R., **02**-0267, **02**-0270
McCall, J.M., **18**-0850

McCall, M.J., **18**-0032
McCallum, J.S., **19**-1374
McCann, S., **18**-0667
McCapra, F., **09**-0015
McCarney, C.C., **17**-0392
McCarrick, M.A., **15**-2118
McCarroll, A.J., **15**-1218
McCarron, M., **19**-0393
McCarry, B.E., **15**-0784
McCarthy Jr., J.R., **18**-0044
McCarthy, D.G., **06**-0045, **17**-0478
McCarthy, J.R., **10**-0899, **12**-0190, **13**-0430, **13**-0527, **16**-0361
McCarthy, K.E., **10**-1353
McCarty, C.G., **04**-0219, **17**-0450, **18**-0306, **18**-0874, **18**-0874
McCasland, G.E., **04**-0018
McCaulay, D.A., **11**-0598
McCauley, M.D., **19**-1459
McCay, P.B., **05**-0260
McCleland, C.W., **15**-1537
McClellan, A.L., **01**-0034, **03**-0001, **03**-0032
McClelland, R.A., **05**-0011, **05**-0397, **08**-0117, **09**-0067, **10**-0040, **10**-0329, **10**-0527, **10**-0530, **10**-0536, **13**-0771, **16**-0023, **16**-0027, **16**-0157, **16**-1595, **16**-1596
McCloskey, C.J., **10**-1505, **19**-1720
McCloskey, C.M., **10**-1119
McCloskey, P.J., **11**-0653
McClung, R.E.D., **15**-0012
McClure, C.K., **15**-1688, **15**-1988, **16**-1018, **16**-1706
McClure, J.D., **18**-0366
McClure, M., **18**-0160
McClure, M.S., **13**-0649
McCluskey, A., **11**-0396, **16**-0629, **16**-1172
McCluskey, J.G., **10**-1186
McCollum, G.J., **09**-0060
McCombie, S.W., **10**-1286, **13**-0442, **16**-2178
McCombie, S.W., **19**-1402
McCombs, D.A., **15**-0548
McConaghy Jr., J.S., **05**-0403
McConnell, H.M., **05**-0273
McConvey, I.F., **13**-0407, **13**-0492
McCormac, P.B., **13**-0415
McCormick, J.P., **19**-0480, **19**-0650
McCormick, J.R.D., **16**-1285
McCortney, B.A., **10**-0103
McCown, J.D., **10**-0381
McCoy, L.L., **03**-0041, **14**-0178, **14**-0181
McCrary Jr., T.J., **10**-0279
McCrindle, R., **19**-1338
McCubbin, Q.J., **15**-1493
McCulla, R.D., **17**-0284
McCullagh, J.V., **15**-0820, **15**-2391
McCullough, J.J., **15**-0113, **15**-2439
McCullough, K.J., **04**-0086
McCullough, L.G., **18**-0828, **18**-0829
McDaid, P., **15**-1331, **16**-1627
McDaniel, A.L., **10**-0889
McDaniel, C.W., **03**-0101, **04**-0177
McDaniel, D.H., **03**-0052, **03**-0055, **08**-0018, **08**-0040, **09**-0033
McDermott, J.X., **19**-0727
McDermott, M., **10**-0462, **19**-0854
McDermott, P.J., **14**-0423
McDonagh, P.M., **04**-0369
McDonald, C., **19**-0708
McDonald, D.Q., **15**-0123
McDonald, F.E., **15**-0231, **15**-0246, **15**-0335
McDonald, G.J., **06**-0074
McDonald, J.H., **04**-0141
McDonald, K., **12**-0385
McDonald, R., **04**-0072
McDonald, R.L., **08**-0127
McDonald, R.N., **15**-1786, **18**-0251
McDonald, S., **14**-0089
McDonald, S.R., **10**-0436
McDonald, W.S., **15**-2187
McDonough, C.S., **18**-0685
McDougal, N.T., **16**-0801
McDougal, P.G., **04**-0206, **15**-1850
McDougall, A.O., **16**-0037
McDougall, P.J., **16**-1146
McElvain, S.M., **10**-0659
McElvany, S.W., **02**-0356
McEnroe, F.J., **16**-0542
McEwen, A.B., **04**-0241, **15**-0436
McEwen, I., **03**-0057, **17**-0050, **17**-0133, **17**-0191
McEwen, W.E., **16**-1294, **16**-1304, **18**-0557
McFarland, C., **18**-0680
McFarland, P.E., **16**-1893
McFarlane, F.E., **10**-0162
McGaffin, G., **18**-0571, **18**-0590
McGahan, T.J., **10**-0698
McGahey, L.F., **12**-0014
McGarraghy, M., **12**-0089, **12**-0417
McGarrigle, E.M., **15**-1835
McGarrity, J.F., **02**-0402, **05**-0151, **10**-0391, **10**-0637, **19**-0361
McGarrity, M.J., **10**-0015
McGarry, D.G., **16**-0849
McGarvey, B.R., **15**-0416
McGarvey, G., **12**-0619
McGarvey, G.J., **12**-0568
McGee Jr., H.A., **15**-2283
McGee Jr., K.F., **15**-2436
McGee, L.R., **16**-1003
McGee, M.J., **19**-0450
McGee, T.W., **15**-1539
McGhie, J.F., **19**-1410, **19**-1411
McGill, C.K., **13**-0676
McGill, P., **15**-1744
McGillivray, G., **13**-0099
McGinnis, J., **18**-0778
McGirk, R.H., **10**-0049
McGlinchey, M.J., **02**-0351, **12**-0596
McGoff, D., **08**-0079
McGrail, P.T., **10**-1225, **15**-1254
McGrath, B.P., **14**-0186
McGrath, D.V., **15**-1696, **19**-0196
McGreer, D.E., **17**-0504
McGregor, S.D., **17**-0351
McGuchan, D.C., **13**-0658
McGuiness, J.A., **14**-0164
McGuire, M.A., **16**-2010, **16**-2099
McGuirk, P.R., **15**-0949
McHenry, B.M., **14**-0413
McInnis, E.L., **18**-0464
McIntosh, C.L., **02**-0213, **13**-0047
McIntosh, M.C., **04**-0125, **10**-0899, **18**-0680
McIntyre, J.S., **05**-0015
McIsaac Jr., J.E., **10**-0372, **15**-1776
McIver Jr., R.T., **02**-0371, **08**-0223, **08**-0231, **08**-0235, **08**-0236, **12**-0661, **16**-1568, **19**-0016
McIver, E.G., **10**-0600
McKean, D.R., **10**-1048, **12**-0316, **17**-0190
McKee, B.H., **10**-1411
McKee, D.W., **15**-0454
McKee, R., **15**-2126
McKeer, L.C., **11**-0262
McKellin, W.H., **19**-1616
McKelvey Jr., J.M., **11**-0305
McKelvey, D.R., **01**-0002, **06**-0087

McKelvey, R.D., **14**-0097, **18**-0854
McKelvie, N., **16**-1262, **16**-1289
McKendrick, J.J., **03**-0156
McKendry, S., **15**-1928
McKenna, C.E., **19**-1571, **19**-1573
McKenna, J., **17**-0084
McKennis, J.S., **18**-0502, **18**-0638
McKennon, M.J., **13**-0780, **19**-1082
McKenzie, A., **15**-0006
McKenzie, C.J., **16**-0132
McKenzie, J.R., **15**-1066
McKeon, J.E., **19**-0588
McKeown, E., **14**-0234
McKervey, M.A., **04**-0050, **04**-0136, **04**-0457, **10**-0576, **12**-0352, **12**-0357, **12**-0687, **15**-2286, **15**-2298, **18**-0050, **18**-0113, **18**-0117, **19**-1780
McKie, J.A., **16**-0498
McKillop, A., **10**-0542, **11**-0229, **11**-0405, **13**-0099, **13**-0100, **13**-0263, **13**-0283, **13**-0284, **13**-0575, **13**-0660, **14**-0336, **14**-0370, **14**-0371, **14**-0431, **16**-1412, **16**-1605, **16**-1817, **16**-2008, **16**-2042, **18**-0231, **19**-0010, **19**-0097, **19**-0405, **19**-0454, **19**-0770, **19**-0855, **19**-1798
McKinley, N.F., **10**-1514
McKinnell, R.M., **11**-0137, **19**-0115
McKinney, M.A., **19**-1341
McKinney, R.J., **15**-1504
McKinnis, B.R., **16**-0449
McKinnon, D.M., **03**-0054
McKittrick, B.A., **10**-0497
McKnight, C., **18**-0070
McKoon, E., **15**-0614
McKown, J.W., **14**-0200
McKusick, B.C., **10**-1791, **15**-0073, **15**-2192, **15**-2279, **16**-0205
McLafferty, F.J., **02**-0039
McLafferty, F.W., **14**-0168
McLain, S.J., **18**-0836
McLane, R.C., **16**-0925
McLauchlan, K.A., **05**-0220
McLaughlin, M., **15**-1429
McLaughlin, M.L., **06**-0026
McLaughlin, T.G., **19**-0714
McLay, G.W., **15**-1046, **16**-1605
McLean, S., **18**-0539
McLeish, M.J., **19**-1573
McLennan, D.J., **06**-0062, **06**-0069, **10**-0060, **10**-0079, **10**-0083, **10**-0304, **17**-0036, **17**-0037, **17**-0061, **17**-0064, **17**-0068, **17**-0069, **17**-0073, **17**-0074
McLeod Jr., W.D., **16**-0956
McLeod, M.D., **15**-1863
McMahon, R.J., **05**-0388, **18**-0227
McMahon, T.B., **08**-0146, **08**-0223, **10**-0010
McManus, S., **10**-0102, **10**-0420
McManus, S.P., **05**-0001, **05**-0002, **05**-0099, **05**-0202, **05**-0313, **05**-0327, **05**-0396, **10**-0060, **10**-0119, **10**-0308, **10**-0328, **10**-0432, **10**-0920, **12**-0345, **13**-0037, **14**-0001, **15**-0016, **15**-2261, **16**-0193
McMasters, D., **02**-0331
McMeeking, J., **15**-2201
McMichael, K.D., **18**-0656
McMillan, F.H., **19**-1799
McMillan, W.D., **02**-0071
McMillen, D.F., **05**-0265
McMillen, D.W., **15**-1512
McMillen, H.A., **18**-0487, **18**-0488
McMorran, D.A., **15**-1366
McMullan, R.K., **18**-0637
McMurdie, N., **10**-0324
McMurry, J., **10**-1174
McMurry, J.E., **03**-0061, **03**-0062, **04**-0246, **10**-0401, **10**-1346, **10**-1347, **10**-1359, **10**-1503, **10**-1816, **12**-0049, **12**-0257, **16**-1065, **17**-0331, **17**-0402, **19**-1680, **19**-1709, **19**-1710, **19**-1714, **19**-1716, **19**-1719, **19**-1721, **19**-1725, **19**-1727
McMurry, M.E., **08**-0165
McNabb, S.B., **16**-0940
McNally, S.J., **15**-0993
McNamara III, W.B., **07**-0070, **07**-0072
McNamara, C., **15**-1690
McNamara, J.P., **15**-0985
McNaught, A.D., **05**-0006, **06**-0047
McNees, R.S., **12**-0400
McNeill, K., **16**-0284
McNelis, E., **11**-0622
McNesby, J.R., **05**-0377, **12**-0379, **12**-0379
McNulty, J., **07**-0097, **13**-0491, **16**-1173
McOsker, C.C., **15**-0471, **19**-1303
McParland, M., **18**-0272
McPhee, D.J., **19**-1533
McPhee, W.D., **18**-0198
McPherson, C.A., **15**-0030
McQuilkin, R.M., **02**-0300, **02**-0301, **02**-0305
McQuillin, F.J., **15**-0416, **19**-1368
McRiner, A.J., **15**-0536
McRowe, A.W., **18**-0100
McShane Jr., H.F., **16**-2069
McSorley, E., **13**-0649
McSweeney, J.V., **13**-0665
McTigue, P., **08**-0038
McTigue.P.T., **08**-0034
Mdleleni, M.M., **07**-0070
Meagley, R.P., **12**-0356
Meah, M.Y., **10**-0662
Meakin, P.Z., **15**-0464
Mealy, M.J., **15**-0878, **18**-0406
Meanwell, N.A., **11**-0436
Mebane, R.C., **15**-1588, **19**-1313
Mecca, T.G., **10**-0077, **10**-0222
Mechiorre, P., **10**-0931
Mechoulam, H., **18**-0738
Meckel, M., **02**-0259
Meckler, H., **16**-0423
Medary, R., **18**-0509
Médebielle, M., **13**-0052, **16**-0572
Medel, R., **15**-0302, **18**-0781
Medici, A., **15**-1791, **19**-0232, **19**-0872
Medina, J.R., **15**-0652
Medina, M.A., **05**-0141, **05**-0181
Medina, R., **13**-0033
Medson, C., **19**-1022
Meehan, G.V., **04**-0325, **18**-0551
Meek, A.G., **10**-0203
Meek, J.S., **10**-0841, **17**-0011
Meekel, A.A.P., **15**-2017
Meerbeek, T.G., **18**-0329
Meerdink, J.E., **10**-0980
Meerwein, H., **10**-0739, **12**-0345, **18**-0014
Megarity, E.D., **07**-0054
Meghani, P., **16**-0757
Meguriya, N., **16**-0645
Meguro, M., **10**-0958, **10**-1544, **15**-0362
Mehdi, A., **13**-0481
Mehdinejad, H., **13**-0227
Mehler, G., **15**-0413, **15**-0600
Mehler, K., **05**-0163
Mehltretter, G., **11**-0512
Mehltretter, G.M., **19**-0238
Mehmandoust, M., **18**-0692

Mehmedbasich, E., **16**-1469
Mehrdad, M., **10**-0928
Mehrotra, **19**-1605
Mehrotra, A., **10**-0808
Mehrotra, A.K., **10**-1089, **15**-2185, **16**-0164, **16**-1523, **18**-0733
Mehrsheikh-Mohammadi, M.E., **05**-0245, **10**-0306, **14**-0089
Mehta, A.S., **17**-0248
Mehta, G., **02**-0197, **02**-0360, **10**-0188, **10**-0693, **16**-0007, **16**-0008
Mehta, S., **10**-1199, **19**-0839
Mei, Y., **19**-0312
Meidar, D., **10**-1147, **11**-0636, **15**-0207
Meidine, M.F., **10**-0995
Meienhofer, J., **16**-1797, **16**-1816, **16**-2133
Meier, G.B., **19**-1538
Meier, G.P., **16**-1301
Meier, H., **02**-0066, **04**-0471, **04**-0472, **12**-0646, **15**-2047, **17**-0502, **18**-0211
Meier, M., **18**-0404
Meier, M.S., **02**-0366
Meier, T., **10**-1456
Meiere, S.H., **15**-2074
Meignein, C., **16**-0716
Meijer, A., **15**-2030
Meijer, E.W., **07**-0061, **11**-0480, **12**-0743
Meijer, J., **10**-0230, **12**-0500, **15**-0951
Meijer, R.H., **19**-0216
Meijide, F., **12**-0703
Meinecke, A., **10**-1536
Meinema, H.A., **15**-0522
Meintzer, C.P., **14**-0158, **14**-0188
Meinwald, J., **04**-0232, **04**-0435, **12**-0237, **15**-1618, **17**-0269, **18**-0641, **18**-0642
Meinwald, Y.C., **04**-0078, **04**-0435, **15**-1618
Meisenheimer, J., **13**-0006
Meisinger, R.H., **02**-0255
Meislich, H., **10**-0224
Meister, A., **16**-2136
Meister, H., **17**-0252, **17**-0311
Meisters, A., **10**-1506, **15**-1146, **16**-0676, **16**-1974
Meiswinkel, A., **15**-0413
Meixner, J., **15**-1214
Mekhalfia, A., **14**-0194, **14**-0274
Mekhtiev, S.D., **11**-0407
Mekhtieva, V.Z., **15**-0261
Mekley, N., **05**-0394
Melamed, D.B., **12**-0699
Melamed, M., **12**-0449
Melamed, U., **05**-0135
Melander, L., **06**-0059, **11**-0006
Melby, L.R., **03**-0097
Melchiorre, P., **15**-0993, **16**-1434
Mele, G., **18**-0123
Melega, W.P., **02**-0172
Melera, A., **02**-0273
Meli, A., **15**-0279, **15**-2406
Melikyan, G.G., **15**-1650
Melikyan, V.R., **16**-1462
Mello, R., **19**-0515, **19**-0615, **19**-0799
Mellon, M.G., appendixA-0001
Melloni, A., **10**-1469
Melloni, G., **10**-0258, **11**-0376, **15**-0034, **15**-0079, **15**-0082, **15**-1639, **19**-1537
Mellor, D.P., **04**-0007
Mellor, J.H., **14**-0266
Mellor, J.M., **04**-0240, **15**-1851, **15**-1917, **15**-2117, **19**-0438
Melman, A., **16**-1663
Melnyk, O., **12**-0103
Melpolder, J.B., **02**-0047
Melpolder, J.P., **13**-0423
Melville, M.G., **11**-0481
Melvin Jr., L.S., **02**-0089, **16**-1376, **16**-1402
Memarian, H.R., **19**-0035, **19**-0036, **19**-0038, **19**-0039, **19**-0040
Menapace, H.R., **18**-0758
Menapace, L.W., **19**-1346
Menashe, N., **15**-0220
Mencarelli, P., **04**-0052, **05**-0241
Menche, D., **16**-0647
Mende, U., **02**-0213
Mendenhall, G.D., **14**-0232, **19**-0281
Mendez, R., **04**-0372
Méndez, F., **08**-0158
Méndez, M., **10**-1472, **13**-0311, **15**-0776, **15**-0818, **15**-0820
Méndez-Andino, J., **18**-0806
Mendonça, G.F., **15**-0178
Mendonça, J.de S., **19**-1088
Mendonça, P., **13**-0194
Mendoza, J.S., **19**-1224
Menegheli, P., **11**-0495
Menendez, M., **16**-0135
Menéndez, J.C., **10**-0990, **15**-2144
Menes-Arzate, M., **15**-1244
Meneses, R., **15**-0578, **16**-1618, **19**-0940
Meneyrol, J., **19**-1243
Menezes, P.H., **10**-0828, **15**-0944, **15**-1325
Menezes, R.F., **15**-2061
Meng, G., **16**-0323, **19**-1627
Meng, Q., **12**-0100, **12**-0101, **16**-0762
Meng, W.-D., **15**-1671
Meng, X.-J., **19**-1017
Meng, Y., **15**-1158
Meng, Z., **13**-0040
Menge, W.M.P.B., **16**-1249
Mengel, W., **16**-1226
Mengenhauser, J.V., **16**-2070
Menger, F.M., **03**-0143, **04**-0310, **04**-0435, **06**-0010, **10**-0176, **16**-0028, **16**-1570, **16**-1593, **19**-0099
Menges, F., **15**-0425, **15**-0605
Mengler, H., **16**-2047
Menichetti, S., **15**-1607, **15**-1845
Mennen, S., **15**-1368, **16**-0724
Menon, B., **05**-0110, **05**-0130, **08**-0065, **08**-0066
Menon, B.C., **12**-0639
Menoret, G., **18**-0143
Menyailo, A.T., **19**-0345
Menzel, K., **12**-0299
Menzer, S., **03**-0184
Meot-Ner, M., **03**-0001, **05**-0026, **08**-0191, **08**-0223
Méou, A., **15**-0999, **15**-1923
Meracz, I., **15**-2042
Merbouh, N., **19**-0196
Mercier, F., **10**-1454
Mereddy, A.R., **12**-0485
Meredith, C.C., **02**-0134
Mereiter, K., **16**-0687
Merényi, R., **04**-0440, **05**-0243, **05**-0245, **15**-2182, **15**-2222, **15**-2359, **17**-0358, **18**-0634, **18**-0635, **18**-0729, **19**-0840, **19**-1795
Merer, A.J., **07**-0014
Meresz, O., **16**-1468
Mereu, A., **16**-0777, **16**-0803
Mergelsberg, I., **14**-0455
Merger, F., **16**-1649
Merinero, J.A.V., **19**-0336
Merino, P., **16**-0929
Merk, W., **18**-0500, **18**-0501
Merkel, A., **10**-0344
Merkert, J., **15**-1298
Merkley, J.H., **15**-0861, **15**-0862
Merkushev, E.B., **11**-0282, **12**-0522, **13**-0262, **19**-0741
Merle, D., **16**-2132
Merlic, C.A., **10**-1485, **13**-0361, **15**-2266

Merlin, A., **12**-0725
Mermoud, F., **19**-0023
Mero, C.L., **15**-1207
Merola, J.S., **04**-0422
Mérour, J.-Y., **19**-1627
Merrer, D.C., **18**-0089
Merrifield, E., **15**-1782
Merrifield, J.H., **10**-1824
Merrifield, R.B., **16**-1815, **16**-1816, **16**-1818, **16**-1819
Merrigan, S.R., **15**-2004, **15**-2088
Merrill, R.E., **10**-1275
Merritt, A., **10**-1790
Merritt, E.A., **16**-0138
Merritt, J.E., **15**-0936
Merritt, M.V., **10**-0742
Merritt, R.F., **15**-1519
Merstetter, P., **05**-0315, **05**-0320
Mertes, J., **15**-2063
Mertes, K.B., **03**-0153
Mertes, M.P., **03**-0153
Méry, D., **13**-0556
Merz Jr., K.M., **02**-0218
Merz, E., **13**-0744
Mesaros, E., **04**-0076
Meshcheryakov, A.P., **14**-0287
Meshram, H.M., **11**-0394
Meshram, H.M., **16**-0080, **16**-0252, **16**-1611, **16**-1748, **17**-0433, **19**-0798, **19**-0864, **19**-1214, **19**-1599
Mesić, M., **10**-0120
Meske-Schüller, J., **04**-0475, **04**-0484
Meskens, F.A.J., **16**-0140, **16**-0146
Meskin, A.J., **17**-0139
Meslem, J.M., **19**-1339
Mesnard, D., **10**-1524, **10**-1765, **17**-0148
Messeguer, A., **19**-0384
Messer, L.A., **19**-0411, **19**-0462
Messina, G., **11**-0013
Messinger, J., **16**-0429
Messmer, G.G., **13**-0010
Mestdagh, H., **10**-1865
Mestres, R., **15**-1119, **18**-0308, **19**-0840
Mészáros, L., **16**-2001
Meta, C.T., **19**-0914
Metcalf, B.W., **02**-0300, **02**-0304, **02**-0327
Metelitsa, D.I., **14**-0195, **15**-1726
Metesich, M.A., **12**-0649
Meth-Cohn, O., **05**-0396, **11**-0466, **15**-1791, **15**-1940, **19**-0010
Metivier, P., **10**-1062
Metoki, K., **15**-2036
Metsger, L., **19**-0596
Metts, L., **07**-0054
Metz, M.V., **15**-0335, **15**-1871, **15**-1872
Metz, P., **18**-0688
Metz, T.E., **15**-2078
Metz, W.A., **15**-2290
Metzger, J., **13**-0736, **13**-0743, **14**-0326
Metzger, J.O., **15**-0715, **15**-0909, **15**-1194
Metzner, P., **16**-0004, **16**-0227, **16**-1384, **16**-1385
Meul, T., **02**-0282, **02**-0320
Meuldijk, J., **19**-0216
Meunier, B., **18**-0350, **19**-0456
Meunier, P., **13**-0541
Meurer, E.C., **16**-1350
Meurer, K.P., **04**-0067
Meurling, P., **16**-0201
Meybodi, F.A., **18**-0314
Meyer, A.Y., **09**-0068, **09**-0072
Meyer, C., **16**-0747, **16**-1961, **18**-0318, **18**-0812
Meyer, C.J., **14**-0200
Meyer, D.T., **02**-0358
Meyer, E., **16**-1078, **16**-1793
Meyer, E.A., **03**-0071
Meyer, F., **16**-0863
Meyer, F.E., **12**-0274, **13**-0418
Meyer, F.J., **05**-0151
Meyer, G., **13**-0142, **13**-0468, **13**-0713
Meyer, G.R., **15**-0031, **15**-0559
Meyer, J., **19**-1273
Meyer, J.W., **11**-0561
Meyer, K.H., **02**-0408, **19**-1458
Meyer, M.P., **15**-0967
Meyer, M.D., **19**-0411, **19**-0462
Meyer, M.W., **11**-0604, **11**-0606
Meyer, N., **10**-1731
Meyer, O., **12**-0352, **15**-1022
Meyer, R.G., **18**-0846
Meyer, S.D., **19**-0200
Meyer, T.J., **06**-0062
Meyer, W.C., **16**-2114
Meyer, W.L., **04**-0389
Meyers, A.I., **04**-0145, **04**-0170, **10**-1307, **10**-1661, **10**-1724, **10**-1725, **10**-1733, **10**-1735, **10**-1736, **10**-1738, **10**-1739, **10**-1740, **10**-1741, **10**-1743, **10**-1744, **12**-0336, **12**-0405, **12**-0534, **13**-0456, **13**-0469, **13**-0640, **14**-0428, **16**-1032, **19**-0052, **19**-1082
Meyers, C., **13**-0178
Meyers, C.Y., **14**-0408, **15**-0297, **17**-0220, **17**-0344, **17**-0516, **18**-0697, **19**-0790, **19**-1592
Meyers, M., **15**-0016, **18**-0164
Meyers, M.B., **18**-0011
Meyerson, S., **13**-0037, **13**-0744, **15**-2075, **8**-0021, **18**-0023, **18**-0025, **18**-0026
Meynhardt, B., **15**-2293
Meystre, C., **19**-1067
Mez, H.C., **02**-0228
Mečiarova, M., **19**-0567, **07**-0092, **07**-0093, **13**-0169
Mhehe, G.L., **19**-0904
Mi, A., **10**-1453, **10**-1454, **13**-0482, **16**-0831, **19**-1265
Mi, A.-Q., **15**-1128, **16**-0865, **16**-1037
Mi, X., **16**-0767, **16**-0774
Miani, F., **17**-0267
Miano, J.D., **07**-0026
Miao, G., **10**-1334, **10**-1365, **15**-1169
Miao, H., **15**-0245
Miao, M., **16**-0552
Miao, Q., **16**-0661
Miao, W., **16**-0602
Mibae, J., **19**-1746
Micalizio, G.C., **16**-0699
Micetich, R.G., **19**-1643
Micha-Screttas, M., **14**-0411, **14**-0413, **18**-0192
Michael, A., **15**-0007, **17**-0013
Michael, F.E., **15**-0604
Michael, P., **16**-1290
Michael, U., **16**-1971
Michaelis, W., **15**-0101
Michaels, R.J., **10**-1582
Michaelsen, H., **18**-0571
Michaelson, R.C., **15**-1795
Michaely, W.J., **10**-1842
Michailenko, I.E., **17**-0149
Michalczyk, M.J., **01**-0011, **01**-0012
Michaud, G., **10**-1424, **13**-0729
Michaut, M., **15**-0766
Michejda, C.J., **15**-1514, **15**-1879
Michel, P., **16**-1290
Michel, R.E., **10**-0089, **10**-1602
Michelet, V., **15**-0932, **15**-0977, **15**-1125
Michelot, D., **18**-0736
Michelotti, E.L., **10**-1532
Michels, H.P., **02**-0299
Michibata, T., **19**-1093
Michie, J.K., **16**-0165
Michl, J., **01**-0009, **01**-0011, **01**-0012, **02**-0037, **02**-0218, **03**-0165, **04**-0432, **04**-0469,

04-0497, **04**-0498, **07**-0001, **15**-2103, **18**-0462, **18**-0528
Michno, D.M., **18**-0464
Michos, D., **15**-0418
Michrowska, A., **18**-0811
Mickelson, E.T., **19**-0753
Micskei, K., **12**-0322
Middlemiss, D., **15**-1434, **15**-1928
Middleton, W.J., **10**-1077
Midgley, G., **15**-1921
Midland, M.M., **10**-1759, **10**-1764, **12**-0434, **12**-0443, **12**-0447, **12**-0490, **12**-0518, **15**-1183, **16**-1184, **18**-0429, **18**-0435, **18**-0453, **18**-0455, **19**-1014, **19**-1018, **19**-1053
Midorikawa, H., **10**-1698
Miekka, R.G., **17**-0041
Mielert, A., **15**-2001
Mielniczak, G., **19**-0788
Mierop, A.J.C., **15**-0043
Miesch, M., **16**-1137
Miftakhov, M.S., **14**-0383
Migdal, C.A., **17**-0073
Miginiac, L., **10**-1524, **10**-1765, **12**-0033, **15**-1081, **17**-0148
Miginiac, P., **12**-0660, **15**-0041, **15**-1086
Migita, T., **10**-1262, **10**-1634, **10**-1825
Migliorese, K.G., **15**-1570
Mignani, G., **12**-0670
Mignani, G., **15**-0733
Mignani, S., **15**-1969, **19**-0840
Mignard, M., **15**-1795
Mignini, E., **16**-0808
Mihailović, M.Lj., **14**-0206, **14**-0210, **14**-0211, **14**-0212, **19**-0006, **19**-0274
Mihalič, Z., **10**-0142
Mihara, J., **15**-1836, **19**-0520
Mihara, M., **10**-0628, **15**-1402, **16**-1364
Mihelich, E.D., **04**-0170, **10**-1740, **10**-1741
Mihovilovic, M.D., **10**-1268, **18**-0362
Miiller, D.E., **19**-0018
Mijlhoff, F.C., **04**-0283, **04**-0317
Mijs, W.J., **19**-0010
Mikaelyan, R.G., **05**-0328
Mikami, K., **04**-0061, **13**-0237, **15**-0824, **15**-0985, **15**-2064, **16**-0571, **16**-0730, **16**-1119, **16**-1487, **18**-0730, **18**-0735, **19**-1387
Mikami, M., **03**-0072
Mikami, S., **15**-1265
Mikawa, H., **15**-2194
Mikhail, G., **15**-2235
Mikhail, G.K., **18**-0235
Mikhailov, B.M., **01**-0075, **02**-0036, **10**-1762
Mikhailov, I.E., **18**-0540
Mikhaleshvili, I.L., **15**-0049
Miki, K., **03**-0168, **15**-0227, **16**-1854
Miki, M., **16**-0687
Miki, T., **16**-1013
Miki, T., **16**-1809
Mikol, G.J., **19**-1788
Mikoluk, M.D., **15**-0421
Mikołajczyk, M., **04**-0047, **10**-0841, **15**-1205, **16**-2067, **19**-0795, **19**-0795, **19**-0822, **19**-0826, **19**-0853, **19**-1602
Mil'tsov, S.A., **14**-0065, **14**-0158
Mil'vitskaya, E.M., **18**-0614
Milakofsky, L., **10**-0430
Milan, A., **10**-0582
Milan, D.S., **16**-2166
Milani, P., **16**-0687
Milano, D., **15**-1851
Milaszewski, R.F., **10**-0223
Milburn, R.M., **15**-0083
Milcoveanu, A.B., **07**-0095
Mile, B., **05**-0203, **19**-0361, **19**-0380
Milenkov, B., **12**-0669
Miles J.H., **11**-0611
Miles, B., **16**-1021
Miles, D.E., **03**-0030
Miles, M.L., **16**-2036
Miles, T.J., **10**-1538
Miles, W., **14**-0086
Milesi, L., **17**-0369
Milet, A., **15**-1418, **15**-1452, **15**-1453
Milewski, C., **19**-1750
Milewski, C.A., **17**-0309
Milgram, B.C., **16**-1944
Milhailović, M.Lj., **14**-0206
Militzer, H., **10**-1605, **10**-1606
Militzer, H.-C., **15**-1816, **19**-0238
Miljanić, O.Š., **07**-0119
Mill, T., **14**-0058
Millar, A., **13**-0649
Millar, I.T., **13**-0712
Millar, R.W., **03**-0160, **10**-0764, **11**-0123
Millard, A.A., **10**-1633
Millbanks, C., **15**-1232
Millen, D., **03**-0026
Millen, D.J., **11**-0152
Miller Jr., W.T., **14**-0168, **15**-0074
Miller, A.E.G., **19**-1184
Miller, A.H., **12**-0439
Miller, A.R., **12**-0093
Miller, A.W., **12**-0756
Miller, B., **05**-0126, **18**-0185
Miller, B.L., **19**-1198
Miller, B.W., **04**-0240
Miller, C.E., **15**-0482
Miller, C.P., **17**-0437
Miller, D., **16**-0540
Miller, D.O., **02**-0068
Miller, D.A., **04**-0309
Miller, D.B., **10**-1376, **10**-1725
Miller, D.D., **19**-1721
Miller, D.J., **17**-0064, **17**-0073
Miller, D.O., **02**-0281
Miller, E.B., **13**-0029
Miller, E.G., **18**-0737
Miller, E.H., **12**-0457
Miller, F.A., **04**-0378
Miller, G., **15**-1074
Miller, G.I., **15**-1215
Miller, I.J., **05**-0051
Miller, J., **08**-0232, **10**-0312, **10**-1005, **13**-0003, **13**-0028, **13**-0068, **13**-0069, **13**-0081, **13**-0087, **15**-0397, **15**-1624, **16**-2139
Miller, J.A., **10**-1020, **10**-1038, **13**-0535, **15**-1534, **16**-0165, **17**-0228, **18**-0452
Miller, J.J., **18**-0076
Miller, J.L., **15**-0014
Miller, J.M., **10**-0697, **13**-0147, **13**-0256
Miller, J.S., **08**-0231, **12**-0661
Miller, K.D., **11**-0028
Miller, K.M., **16**-0712, **16**-0718
Miller, L.L., **18**-0557, **19**-0691, **19**-1334
Miller, L.S., **18**-0642
Miller, M., **10**-0582, **10**-1448
Miller, M.J., **10**-0993, **10**-1478, **12**-0227
Miller, M.W., **13**-0442
Miller, N.A., **15**-1160
Miller, N.C., **12**-0647
Miller, R.B., **12**-0619, **15**-0862
Miller, R.D., **12**-0316, **17**-0190
Miller, R.E., **19**-0351
Miller, R.F., **12**-0220
Miller, R.G., **15**-2075
Miller, R.J., **05**-0219
Miller, R.L., **14**-0380
Miller, R.S., **19**-1671
Miller, S.I., **01**-0113, **05**-0135, **10**-0265, **10**-0286, **15**-0079, **15**-21, **17**-0056

Miller, S.J., **10**-0847, **15**-1318, **15**-1368, **15**-2064, **16**-0724, **16**-0800, **18**-0796, **18**-0820, **19**-1617
Miller, S.P., **07**-0118, **18**-0702, **19**-1760
Miller, W.H., **12**-0465, **12**-0467
Milliet, P., **15**-1780
Milligan, B., **10**-0832, **10**-0838
Milligan, D.E., **05**-0276, **05**-0328
Milligan, G.L., **18**-0297
Millon, J., **10**-1269
Mills, A.M., **19**-0216
Mills, I.M., **04**-0378
Mills, O.S., **02**-0163, **02**-0228
Mills, S.G., **02**-0406
Mills, W.H., **02**-0078, **11**-0076
Milne, D.J., **17**-0216
Milne, G.M., **10**-1102, **10**-1263
Milowiz, L., **11**-0406
Milstein, D., **10**-1822, **13**-0366, **13**-0431, **13**-0607, **15**-1381, **18**-0143
Milstein, S.R., **18**-0349
Mimero, P., **10**-1125
Mimoun, H., **15**-1795, **19**-0725
Mimun, A., **02**-0285
Mimura, H., **10**-1244
Minachev, Kh.M., **15**-0405
Minakata, S., **10**-0628, **10**-1840, **15**-0390, **15**-1400, **15**-1782, **15**-1896, **15**-1904, **15**-1910, **19**-0591
Minami, I., **10**-1447, **10**-1630, **17**-0327, **19**-0060
Minami, K., **14**-0275
Minami, S., **18**-0295
Minami, T., **10**-1123, **11**-0436, **12**-0319, **15**-0337, **15**-1011
Minami, Y., **19**-0592
Minamida, I., **12**-0639
Minamide, N., **11**-0101
Minamikawa, H., **16**-1422
Minari, M., **13**-0508
Minas da Piedade, M.E., **02**-0331
Minasyan, T.T., **19**-0387
Minasz, R.J., **10**-0329
Minato, A., **10**-1297
Minato, H., **12**-0040, **13**-0738, **13**-0748
Minato, M., **15**-1665, **16**-0645, **19**-0729
Minato, T., **15**-2004
Mincione, E., **19**-0056, **19**-0995
Minegishi, S., **10**-0028, **10**-0282
Minehan, T., **13**-0434
Mineur, C., **15**-2032
Mingardi, A., **15**-1099
Mingos, D.M.P., **07**-0105, **07**-0108, **10**-0471
Minidis, A.B.E., **19**-0538
Minière, S., **12**-0272
Minieri, P.P., **16**-2053
Minisci, F., **14**-0149, **11**-0183, **11**-0185, **11**-0262, **14**-0031, **14**-0094, **14**-0120, **14**-0138, **14**-0153, **14**-0155, **14**-0337, **14**-0338, **14**-0340, **14**-0341, **14**-0342, **14**-0343, **14**-0344, **14**-0347, **14**-0348, **15**-0050, **15**-1882, **19**-0120, **19**-0181, **19**-0255, **19**-0331, **19**-0612, **19**-0614, **19**-1047
Minkin, V.I., **02**-0092, **02**-0209, **02**-0231, **02**-0288, **02**-0378, **03**-0043, **05**-0327, **18**-0540, **18**-0893
Minkoff, G.J., **15**-1790
Minnaard, A.J., **15**-0387, **15**-0604, **15**-1103, **15**-1125, **15**-1131, **15**-1138
Minniear, A.B., **19**-0892
Minns, R.A., **15**-2209, **15**-2221
Mino, C., **16**-0086
Mino, T., **10**-1453, **13**-0482, **16**-0687, **18**-0352
Minoshima, T., **14**-0359
Minoshima, Y., **05**-0297
Minot, C., **01**-0048, **10**-0364
Minowa, N., **16**-0683
Minsky, A., **02**-0297, **02**-0298
Mintcheva, I., **04**-0306
Minton, M., **04**-0264
Mintz, M.J., **14**-0193
Minyaev, R.M., **18**-0540
Mio, M.J., **13**-0543
Mio, S., **15**-1092
Miocque, M., **11**-0514, **16**-0120, **16**-0196, **16**-0425
Mioduski, J., **18**-0642
Mioskowski, C., **10**-0848, **10**-1100, **10**-1110, **10**-1208, **10**-1798, **10**-1830, **12**-0318, **13**-0290, **15**-0252, **15**-0701, **15**-0733, **15**-1563, **15**-1939, **16**-0115, **16**-1181, **16**-1369, **16**-1381, **17**-0207, **17**-0316, **17**-0470
Miotti, U., **19**-1778
Mir, M., **13**-0066
Mirafzal, G.A., **16**-1371
Miranda, E.I., **10**-0777
Miranda, L.D., **15**-1244
Miranda, M.A., **14**-0069, **16**-2081
Mirbach, M.F., **15**-1494
Miré, M.-A., **16**-0878
Mirjalili, B.B.F., **10**-0642, **11**-0201
Mirkhani, V., **10**-0670, **15**-1829, **15**-1846
Mirkind, L.A., **14**-0418
Mironov, V.A., **18**-0526, **18**-0556
Mirowicz, M., **04**-0101
Mirrington, R.N., **10**-0799
Mirskova, A.N., **02**-0420, **10**-0261, **15**-0297, **15**-1608
Mirviss, S.B., **10**-1294, **12**-0447
Mirza, A.R., **13**-0411, **13**-0412
Mirza-Aghayan, M., **15**-0472, **15**-1039, **19**-0102
Mirzaei, F., **15**-0381
Misaki, T., **12**-0318, **16**-1639
Misawa, H., **06**-0079, **19**-0653
Misbach, P., **15**-0793
Miscione, G.P., **15**-2336
Miser, J.R., **13**-0703
Mißfeldt, M., **08**-0084
Mishima, H., **17**-0161
Mishima, K., **19**-1009, **19**-1144
Mishima, M., **05**-0314, **08**-0081, **10**-0027, **10**-0169, **10**-0170, **10**-0273, **10**-0274
Mishra, A., **05**-0403
Mishra, B.K., **19**-0296, **19**-0861
Mishra, R.K., **13**-0439
Mishra, S., **03**-0118
Mishriky, N., **17**-0224
Misiti, D., **04**-0059, **19**-1510
Mislow, K., **04**-0247, **02**-0249, **03**-0203, **04**-0001, **04**-0019, **04**-0033, **04**-0034, **04**-0087, **04**-0200, **04**-0202, **04**-0204, **04**-0247, **04**-0250, **04**-0504, **04**-0505, **05**-0230, **15**-0061, **18**-0737
Misokowski, C., **13**-0639
Mison, P., **10**-0181, **12**-0223, **19**-1245
Misra, S.C., **19**-1410
Missfeldt, M., **08**-0186
Mistry, J., **14**-0340
Misumi, A., **10**-1637
Misumi, S., **02**-0296
Misumi, Y., **16**-1163
Mita, N., **10**-1270
Mita, T., **15**-2130
Mitamura, S., **11**-0423, **11**-0425, **16**-1546
Mitani, M., **15**-1642, **19**-0605
Mitchel, A.R., **11**-0180
Mitchell, A.L., **15**-1069
Mitchell, C., **19**-0894
Mitchell, D., **10**-1801
Mitchell, D.J., **04**-0365, **10**-0020, **10**-0364, **10**-0367

Mitchell, D.K., **03**-0200, **03**-0201
Mitchell, D.L., **19**-0351
Mitchell, H.L., **12**-0605
Mitchell, J.A., **16**-1782
Mitchell, J.C., **14**-0243
Mitchell, L.H., **13**-0784
Mitchell, M.B., **14**-0340
Mitchell, M.J., **02**-0208, **02**-0223
Mitchell, M.L., **18**-0228
Mitchell, R.D., **02**-0234
Mitchell, R.H., **02**-0276, **02**-0280, **02**-0282, **02**-0298, **02**-0333, **16**-1957, **17**-0358
Mitchell, T.N., **12**-0276
Mitchell, T.R.B., **10**-0900, **18**-0618, **19**-0708
Mitin, A.V., **13**-0577
Mitnick, M.A., **19**-1334
Mitoma, Y., **19**-1447
Mitra, A., **18**-0471
Mitra, A.K., **16**-0097, **16**-1174, **16**-1192
Mitra, J., **03**-0029
Mitsch, R.A., **05**-0328, **15**-2311
Mitsky, J., **08**-0226
Mitsuboshi, T., **15**-0929
Mitsuda, N., **19**-1542
Mitsudera, H., **15**-1324
Mitsudo, K., **10**-1278, **15**-0730, **15**-1420
Mitsudo, T., **10**-0880, **10**-1845, **15**-0280, **15**-0281, **16**-0268, **19**-1119, **19**-1772
Mitsudo, T.-a., **10**-0788, **10**-1469, **15**-1467
Mitsuhashi, T., **10**-0404, **18**-0374, **18**-0694, **19**-0787
Mitsui, K., **10**-0221, **10**-1549, **16**-0878, **16**-1478
Mitsui, S., **15**-0400, **19**-1368, **19**-1369
Mitsuie, T., **16**-0687
Mitsunobu, O., **10**-0652, **10**-0702, **10**-0993, **16**-1655, **17**-0490
Mitsuya, H., **15**-0922
Mittelmeijer, M.C., **18**-0827
Mitten, J.V., **15**-0871
Mitton, C.G., **06**-0088
Mitzel, T.M., **16**-0598
Miura, K., **15**-0225, **15**-0392, **15**-0587, **15**-0737, **15**-0778, **16**-0183, **16**-1078, **16**-1079, **16**-1657
Miura, M., **10**-1852, **10**-1854, **13**-0338, **13**-0362, **13**-0452, **13**-0453, **15**-1360, **15**-1791, **15**-2372, **19**-0985, **19**-1371
Miura, T., **15**-0903, **19**-0155, **19**-1559, **19**-1774
Miura, Y., **05**-0258, **05**-0259, **10**-0896
Miwa, M., **13**-0604, **13**-0605
Miwa, T., **19**-1679
Miwa, Y., **15**-0394, **15**-1125
Miwata, H., **04**-0193
Mixan, C.E., **10**-0279
Miyabe, H., **16**-0933, **16**-0937, **16**-0938, **19**-1152
Miyabo, A., **05**-0117, **05**-0201
Miyachi, H., **15**-0604, **15**-0822
Miyadera, H., **18**-0374
Miyafuji, A., **15**-1831, **19**-0522
Miyagawa, N., **14**-0345
Miyagi, Y., **10**-1539
Miyaguchi, N., **19**-1624
Miyahara, I., **01**-0068
Miyahara, T., **19**-1659
Miyahara, Y., **08**-0187, **10**-1243, **19**-0068
Miyai, T., **19**-1359, **19**-1452
Miyaji, Y., **19**-1487
Miyake, A., **02**-0047, **15**-0442
Miyake, H., **10**-0785, **15**-0707, **15**-2045
Miyake, N., **15**-2084
Miyake, Y., **13**-0513
Miyamoto, H., **04**-0166, **16**-0547, **16**-0661, **16**-1070
Miyamoto, I., **02**-0295
Miyamoto, K., **13**-0362
Miyamoto, M., **19**-0592
Miyamoto, T., **15**-0804
Miyamura, K., **15**-0779
Miyano, M., **11**-0381
Miyano, N., **16**-0530, **16**-0538
Miyano, S., **04**-0175, **04**-0193, **15**-1158, **15**-2341, **16**-1282
Miyanohana, Y., **15**-0831
Miyasaka, T., **02**-0276
Miyashi, T., **15**-0157, **15**-2113, **18**-0601
Miyashia, H., **15**-0822
Miyashita, A., **15**-2201, **18**-0143
Miyashita, H., **15**-0604
Miyashita, M., **10**-1546, **10**-1803, **12**-0246, **15**-0253, **15**-1004, **15**-1055, **16**-1656, **16**-1684, **17**-0293, **19**-0900, **16**-0822
Miyata, A., **19**-0221
Miyata, K., **19**-1355
Miyata, M., **03**-0168, **04**-0179
Miyata, N., **16**-1089
Miyata, O., **15**-1260
Miyata, Y., **10**-0312
Miyatake, R., **15**-0849
Miyauchi, M., **03**-0186
Miyaura, N., **10**-1415, **10**-1416, **10**-1417, **12**-0451, **12**-0538, **13**-0471, **13**-0474, **13**-0476, **13**-0487, **13**-0625, **15**-0700, **15**-1022, **15**-1125, **15**-1126, **15**-1127, **15**-1156, **15**-1184, **16**-0698, **16**-0702, **16**-0906, **18**-0453, **18**-0457
Miyazaki, F., **13**-0399
Miyazaki, M., **16**-0364
Miyazaki, S., **16**-1727
Miyazaki, T., **02**-0036, **18**-0340, **19**-1244
Miyazaki, Y., **03**-0129
Miyazawa, E., **11**-0194, **16**-0353
Miyoshi, H., **15**-1714
Miyoshi, K., **13**-0617
Miyoshi, N., **12**-0246, **16**-0495, **16**-0661, **16**-0664, **16**-0765, **16**-1426
Miyoshi, S., **16**-1656
Miyoshi, T., **11**-0343
Mizhiritskii, M.D., **12**-0312, **19**-1548
Mizobe, Y., **19**-1241
Mizoguchi, T., **13**-0694
Mizokami, T., **13**-0705
Mizsak, S.A., **15**-0561, **16**-2109
Mizugaki, T., **15**-1791, **16**-0149, **19**-0120
Mizuguchi, Y., **12**-0694
Mizumura, M., **16**-1590
Mizuno, A., **10**-1798
Mizuno, H., **17**-0289
Mizuno, K., **03**-0027, **03**-0182, **05**-0289, **15**-0849, **15**-2252
Mizuno, M., **10**-1844, **16**-1314
Mizuno, N., **16**-0133, **19**-0120, **19**-0278, **19**-0571
Mizuno, S., **16**-0761
Mizuno, T., **11**-0542, **13**-0533, **16**-0579, **16**-1365
Mizuno, U., **19**-1659
Mizushima, E., **10**-1196, **15**-0209, **15**-0353
Mizushima, K., **10**-1845
Mizuta, M., **16**-1726
Mizuta, T., **16**-0545
Mizutani, H., **12**-0326
Mizutani, T., **16**-0148
Mladenova, M., **10**-1689
Młochowski, J., **19**-0129, **19**-0707
Mlosteń, G., **16**-1399
Mloston, G., **15**-1952
Mndzhoyan, O.L., **16**-0392, **16**-0393
Mo, H., **04**-0130

Mó, M., **02**-0008
Mo, Y., **05**-0033, **15**-0647
Mo, Y.K., **05**-0061, **10**-0117, **10**-0383, **11**-0014, **12**-0341, **14**-0169, **15**-0072, **18**-0748
Mo, Y.M., **05**-0052
Moad, G., **14**-0070
Mobbs, D.B., **19**-0298
Mobbs, R.H., **15**-0070, **15**-0072, **15**-0248, **15**-0317
Moberg, C., **07**-0116, **07**-0117, **10**-0663, **10**-1454, **16**-0687, **19**-1049
Möbius, K., **05**-0208
Mobley, T.A., **15**-1143
Mochalin, V.B., **02**-0182
Mochalina, E.P., **15**-0072
Mochalkin, A.I., **15**-1652
Möchel, T., **13**-0401
Mochida, K., **16**-1008, **19**-1481
Mochizuki, H., **15**-0502
Mochizuki, K., **15**-1676
Mochizuki, M., **16**-0670
Mock, W.L., **03**-0210, **15**-0486, **17**-0351, **17**-0352, **17**-0354, **18**-0239
Mock-Knoblauch, C., **15**-1828
Modak, J., **09**-0102
Modarelli, D.A., **05**-0351
Modena, G., **05**-0068, **10**-0237, **10**-0248, **10**-0258, **13**-0027, **15**-0021, **15**-0034, **15**-0035, **15**-0079, **15**-0082, **15**-0106, **15**-1639, **15**-1998, **17**-0013, **19**-0443, **19**-0791, **19**-0832, **19**-0834, **19**-0849, **19**-1778
Modi, D.P., **18**-0299, **19**-0054
Modro, A., **15**-0016, **15**-0087
Modro, T.A., **08**-0038
Moeini, L., **07**-0091
Moeller, K.D., **15**-0239
Moelwyn-Hughes, E.A., **10**-0599
Moerck, R.E., **15**-1998
Moerikofer, A.W., **15**-0650
Moersch, G.W., **12**-0435
Moffatt, F., **15**-2063
Moffatt, J.G., **11**-0516, **16**-1659, **19**-0160, **19**-0638, **19**-0647, **19**-0649
Moffett, K.K., **10**-0886
Mogali, S., **10**-0307, **19**-0939
Moggi, L., **07**-0011
Moghadam, M., **15**-1829
Moghaddam, F.M., **11**-0566, **12**-0070, **15**-1296, **16**-0144, **18**-0321, **19**-1147
Mogilaiah, K., **16**-1172
Mogren, T., **12**-0370
Mohacsi, E., **16**-1673
Mohadjerani, M., **13**-0227
Mohajer, D., **19**-0819
Mohajerani, B., **19**-0154
Mohamed, M., **18**-0683
Mohamed, N.M., **16**-0448
Mohamed, S.K., **11**-0176
Mohammadi, M., **15**-1296
Mohammadpoor-Baltork, I., **10**-0642, **10**-0670, **11**-0288, **16**-0063, **16**-0173, **16**-0313, **16**-1671, **16**-1739, **16**-1740, **19**-0035, **19**-0038, **19**-0039, **19**-0040, **19**-0335
Mohan, G.H., **10**-1140, **16**-2154, **19**-1382, **19**-1384
Mohan, J.M., **15**-1887
Mohan, K.V.V.K., **11**-0289
Mohan, L., **19**-0764
Mohan, R.S., **10**-0544, **16**-0071, **16**-0075, **16**-0160, **16**-0172, **16**-0174, **16**-0764, **16**-1671, **18**-0140, **18**-0146, **19**-0140
Mohanazadeh, F., **10**-1060, **16**-0063, **16**-1877
Mohanraj, S., **10**-1359
Mohanty, P.K., **16**-0744, **17**-0439, **19**-0692
Mohaptra, S., **10**-1380
Mohile, S.S., **11**-0213, **11**-0383
Mohler, D.L., **02**-0081
Mohr, B., **11**-0419
Mohr, P., **04**-0196
Mohrig, J.R., **10**-0392, **15**-0046, **15**-0409, **19**-0241
Mohsenzadeh, F., **16**-0129
Mohtahedi, M.M., **16**-0129
Moilliet, J.S., **11**-0314
Moineau, J., **13**-0404
Moinet, C., **12**-0716, **19**-1220
Moir, R.Y., **18**-0250
Moisak, I.E., **10**-1053
Moisan, L., **15**-0581
Moise, C., **19**-1099, **15**-1384, **19**-1669
Moiseenkov, A.M., **10**-0494, **15**-2024, **19**-0091
Moiseev, I.I., **19**-0721
Moiseikina, N.F., **11**-0496
Mojé, S., **16**-1898
Mojica, C., **19**-1011
Mojovic, L., **13**-0312
Mojtahedi, M.M., **16**-0913, **19**-0147, **19**-0242, **19**-1701
Mok, K., **15**-2105
Mokbel, L., **07**-0115
Mokhtar, R., **14**-0436
Mokhtari, B., **16**-1789
Mokhtari, M., **13**-0005
Mokrosz, J.L., **16**-1871
Mokrushin, V.S., **16**-1447
Mol, J.C., **18**-0826, **18**-0756, **18**-0826
Molander, G.A., **10**-1296, **10**-1415, **10**-1426, **10**-1427, **10**-1428, **10**-1454, **12**-0015, **12**-0470, **12**-0472, **13**-0322, **13**-0346, **13**-0354, **13**-0355, **13**-0451, **13**-0533, **13**-0564, **15**-0335, **15**-0347, **15**-0686, **15**-0728, **15**-0746, **15**-0767, **15**-0976, **15**-1187, **15**-1188, **15**-1234, **15**-2124, **15**-2347, **16**-0498, **16**-0823, **16**-0891, **19**-0900, **19**-1302, **19**-1524, **19**-1680
Molard, Y., **03**-0125
Molchanov, A.P., **02**-0205, **15**-2267, **15**-2277
Moldoványi, L., **19**-0250
Mole, T., **10**-1506, **15**-1146, **16**-0676, **16**-1974
Molina, G.A., **19**-1568
Molina, P., **10**-1181, **16**-0329, **16**-0434, **17**-0425
Molinari, F., **16**-1032, **19**-0232
Molinari, H., **10**-0470, **15**-1814
Molinaro, C., **15**-2337, **15**-2345, **16**-0712
Molinski, T.F., **15**-0474
Molitor, E., **16**-0130
Moll, G., **16**-1044
Molle, G., **16**-0478, **16**-0514
Møllendal, H., **03**-0054
Möller, F., **17**-0303, **17**-0304, **17**-0305
Mollère, P.D., **01**-0013
Möllerstedt, H., **02**-0185
Molnár, A., **17**-0172, **18**-0124
Moloney, M.G., **10**-1404
Molosnova, V.P., **16**-0446
Moloyama, Y., **16**-0641
Molter, K.E., **05**-0200, **10**-0051
Molvinger, K., **19**-1037
Molz, T., **04**-0471
Momany, F.A., **01**-0060
Momeni, A.R., **10**-1060, **16**-1877, **19**-0036
Momiyama, N., **12**-0202
Momose, D., **10**-1227
Monack, L.C., **13**-0070
Monagle, J.J., **16**-2068, **16**-2069, **16**-2070, **16**-2071, **19**-0639
Monahan, M.W., **15**-0031
Monahan, R., **10**-0826
Monasterios, J.R., **04**-0284, **15**-0016
Mondal, E., **10**-0561, **10**-0566, **16**-0255, **16**-0625
Mondal, M.A.S., **16**-1698

Mondal, S., **16**-1951
Mondon, M., **10**-1369
Monestel, R., **15**-0674
Monfared, H.H., **15**-1755
Monflier, E., **10**-0913, **15**-1381
Mongelli, N., **10**-0850
Mongin, F., **13**-0312, **13**-0319
Monković, I., **19**-0664
Monnier, M., **18**-0225
Monopoli, A., **13**-0399, **13**-0415
Monroe, B.M., **07**-0030, **07**-0044, **15**-2158
Monson, R.S., **17**-0157, **17**-0309, **17**-0460
Montagnon, T., **15**-2067, **17**-0297, **17**-0298
Montaigne, R., **15**-2212
Montaña, A.M., **07**-0099
Montanari, F., **04**-0038, **04**-0047, **05**-0253, **10**-0453, **10**-0456, **10**-0470, **10**-1065, **10**-1116, **13**-0281, **19**-0104, **19**-0109, **19**-0699
Montanucci, M., **13**-0103, **13**-0132
Montaudon, E., **10**-0741
Montavecchi, P.C., **15**-1912
Montchamp, J.-L., **15**-0378, **15**-0379
Monteiro, A.L., **10**-1419, **13**-0297, **13**-039, **13**-0444, **13**-0475, **13**-0481, **13**-0484, **15**-0798, **18**-0781
Monteith, M., **15**-1476
Montel, G., **03**-0158
Montelatici, S., **15**-0463
Montero, J.-L., **18**-0213
Monteux, D., **16**-0372
Montgomery, F.C., **18**-0283
Montgomery, J., **16**-0575, **16**-0727
Montgomery, L.K., **05**-0281, **10**-0189, **10**-0262, **15**-2182, **15**-2222, **18**-0077, **18**-0081
Montgomery, S.H., **16**-1014
Monthéard, J., **16**-1573
Monti, L., **15**-0125
Montierth, J.M., **14**-0312
Montillier, J.P., **12**-0477, **19**-1598
Montoro, R., **14**-0140
Montserrat, J.M., **13**-0016
Montury, M., **15**-0511
Moodie, R.B., **01**-0032, **11**-0029, **11**-0033, **11**-0041, **11**-0050, **11**-0054, **11**-0055, **11**-0083, **11**-0094, **11**-0096, **11**-0097, **11**-0119, **11**-0125, **11**-0144, **11**-0158, **11**-0161, **16**-0104, **16**-1597, **18**-0332, **18**-0336, **19**-0253
Moody, C.J., **02**-0267, **02**-0270, **10**-1121, **15**-0553, **15**-0554, **18**-0654, **18**-0718, **19**-1187, **19**-1242
Moody, E.M., **04**-0391, **04**-0393
Moody, H.M., **19**-1484
Mooij, J.J., **02**-0254
Mooiweer, H.H., **10**-1363
Moon, C.J., **15**-1834
Moon, R., **12**-0406
Moon, S., **07**-0080, **14**-0212, **15**-0130, **15**-0187, **15**-2210, **16**-1541
Moon, S.-S., **19**-0231
Moon, S.J., **19**-0992
Moonga, B.S., **11**-0607, **11**-0608
Moore, C., **12**-0664
Moore, D., **16**-0549
Moore, D.E., **07**-0048
Moore, D.R., **15**-0076
Moore, G.G., **10**-0698
Moore, G.J., **12**-0616
Moore, G.R., **19**-0713
Moore, H.W., **15**-2219, **15**-2226, **16**-2108
Moore, J.A., **16**-1565
Moore, J.S., **08**-0217, **13**-0711, **17**-0447, **18**-0800
Moore, J.W., **06**-0006, **06**-0053
Moore, K., **10**-0208
Moore, L.R., **13**-0502
Moore, M.L., **16**-0372
Moore, P.R., **15**-1680
Moore, P.T., **04**-0223, **17**-0249
Moore, R.E., **19**-1752
Moore, W.J., **19**-0562
Moore, W.M., **07**-0023, **19**-1689
Moore, W.R., **04**-0223, **04**-0487, **15**-2218, **17**-0249
Moorehead, A.W., **02**-0196
Moorhoff, C.M., **19**-0343
Moorman, A.E., **19**-0764
Moors, R.G., **17**-0053
Moorthy, J.N., **19**-0210
Moos, W.H., **16**-1823
Moosmayer, A., **05**-0234
Mootoo, D.R., **10**-0537
Moracci, F.M., **12**-0752
Moradi, W.A., **13**-0357
Morai, S., **15**-0830
Moralee, A.C., **15**-0820
Morales, J., **17**-0428
Morales, N.M., **04**-0221
Morales, O., **17**-0356, **17**-0357
Moran, D., **02**-0417, **05**-0337
Moran, K.D., **11**-0125
Moran, M., **15**-1887
Moran, P.J.S., **11**-0124, **15**-0625, **16**-0804, **19**-1021
Moran, W.J., **15**-1973, **19**-1395
Morand, P., **19**-1476, **19**-1479
Morandi, J.R., **15**-0466
Morandini, F., **10**-1511
Morao, I., **15**-0985, **15**-1944, **15**-1947, **15**-2109
Moravcová, J., **16**-1570
Moravsikiy, A., **12**-0278
Morchat, R., **17**-0507, **17**-0509
Mordas, D.M., **15**-1057
Mordini, A., **10**-1449, **12**-0395, **15**-1068, **16**-0217, **17**-0209, **17**-0209
More O'Ferrall, R.A., **05**-0070, **06**-0065, **06**-0087, **06**-0089, **08**-0128, **08**-0129, **10**-0390, **12**-0100, **17**-0003, **17**-0007, **17**-0046, **17**-0052
Moreau, C., **10**-0537, **19**-0247
Moreau, J., **16**-2015
Moreau, J.J.E., **04**-0026, **12**-0270
Moreau, N., **15**-0557
Moreau, P., **04**-0164
Moreira, A.P.D., **16**-0831
Morel, D., **12**-0670
Morel, Y., **13**-0077
Moreland Jr., W.T., **01**-0040, **09**-0050
Moreland, M., **16**-1235
Morelli, C., **16**-2102
Moreno, A., **07**-0121
Moreno, A., **15**-2022
Moreno-Dorado, F.J., **14**-0177, **15**-0284, **15**-1710
Moreno-Mañas, M., **13**-0365, **13**-0420, **13**-0481, **13**-0524, **13**-0525, **15**-1022
Morera, E., **10**-1848, **13**-0608, **19**-1374
Moretó, J.M., **10**-0602, **15**-0916, **15**-0998, **18**-0804
Moretti, I., **04**-0038, **16**-2122
Moretti, R., **12**-0230, **12**-0571
Moretto, A.F., **15**-2425
Morey, J., **19**-0138
Morgan, C.R., **19**-1763
Morgan, D.H., **14**-0214
Morgan, J.B., **07**-0118
Morgan, J.P., **18**-0781, **18**-0792
Morgan, J.W., **18**-0688
Morgan, M.M., **19**-0371
Morgan, T.D.B., **11**-0583
Morganti, S., **16**-0601

Mori, A., **10**-1198, **10**-1781, **10**-1782, **10**-1801, **12**-0287, **12**-0319, **13**-0293, **13**-0398, **13**-0439, **13**-0449, **13**-0450, **13**-0519, **13**-0538, **13**-0629, **14**-0323, **15**-0585, **15**-0589, **15**-1181, **16**-0751, **16**-1422, **16**-1546
Mori, A., **19**-1338
Mori, A.L., **10**-0534
Mori, H., **18**-0465
Mori, I., **10**-1522
Mori, K., **04**-0106, **04**-0134, **10**-1703, **19**-0120, **19**-1651
Mori, M., **10**-1458, **10**-1856, **15**-0766, **15**-0800, **15**-0811, **15**-1391, **15**-2363, **15**-2369, **15**-2428, **16**-0714, **16**-0905, **16**-1764, **18**-0789, **18**-0814, **18**-0830, **18**-0902, **19**-0371
Mori, N., **15**-2367, **15**-2375, **16**-0823, **16**-1119
Mori, S., **10**-1336, **10**-1617, **12**-0512, **13**-0613, **19**-1574
Mori, T., **10**-1595, **11**-0126, **11**-0140, **13**-0683, **15**-0742, **19**-1072, **19**-1108
Mori, Y., **14**-0379, **15**-0998, **15**-1025, **16**-1098, **16**-1491, **16**-1990
Moriarty, R., **19**-0844
Moriarty, R.M., **04**-0377, **05**-0406, **10**-0046, **10**-0848, **12**-0269, **12**-0719, **14**-0212, **15**-1605, **15**-1713, **15**-1882, **18**-0499, **19**-0203, **19**-0249, **19**-0406, **19**-0434, **19**-0480, **19**-0481, **19**-0483, **19**-0484, **19**-0485, **19**-0486, **19**-0846
Moriconi, E.J., **16**-2113, **16**-2114, **16**-2115
Morigaki, M., **02**-0326
Morihashi, K., **10**-0020
Morii, N., **15**-1461
Morikawa, A., **19**-0691
Morikawa, K., **15**-1693, **15**-1704
Morikawa, M., **10**-1849
Morimoto, C., **13**-0294
Morimoto, T., **03**-0130, **10**-1524, **12**-0113, **15**-0496, **15**-0777, **15**-1136, **15**-1448, **15**-1528, **15**-2084, **16**-0273, **19**-0688, **19**-0919
Morin, C., **12**-0455, **16**-0502
Morin, F.G., **04**-0163
Morinelli, T.A., **19**-1538
Morini, G., **14**-0120
Morioka, M., **16**-0664
Morisaki, H., **10**-0063, **10**-0202
Morisaki, Y., **10**-0788, **10**-0880
Morita, H., **16**-2088
Morita, J., **10**-1645
Morita, K., **19**-0156, **19**-0688
Morita, M., **12**-0754
Morita, N., **02**-0200, **05**-0045, **05**-0046, **15**-0365
Morita, R., **15**-1324
Morita, T., **10**-1134, **11**-0607, **19**-1367
Moritani, I., **10**-0908, **13**-0360, **13**-0420, **15**-2193, **17**-0088
Moritani, T., **05**-0351
Moritani, Y., **15**-0592
Moritz, K.L., **11**-0063
Moriuchi-Kawakami, T., **19**-1139
Moriwaki, M., **11**-0244, **11**-0425, **11**-0548
Moriyama, K., **09**-0012
Moriyasu, M., **02**-0390, **02**-0408
Moriyoshi, T., **18**-0148
Morizawa, Y., **10**-1263
Morizur, J., **14**-0386
Morken, J.P., **07**-0118, **15**-0706, **15**-2181, **17**-0187, **18**-0702, **19**-1760, **19**-1776
Morkovnik, A.S., **11**-0101, **11**-0102
Mormeneo, D., **16**-1759
Moro, M., **15**-1158, **16**-0892
Morokuma, K., **07**-0022, **10**-0202, **10**-1336, **15**-0115, **15**-0463, **16**-1844, **18**-0630
Moroz, A.A., **13**-0119
Morozova, I.D., **05**-0285
Morreale, A., **15**-1884, **15**-1890
Morrell, C.E., **10**-0239
Morrill, C., **18**-0792
Morrill, T.C., **04**-0208, **15**-0115
Morris Jr., P.E., **19**-0105
Morris, A.R., **09**-0085
Morris, A.R., **10**-0475
Morris, D.G., **01**-0051, **02**-0086, **08**-0095, **10**-0094, **12**-0254, **18**-0040, **18**-0387
Morris, G.A., **01**-0087, **13**-0505
Morris, G.F., **17**-0008
Morris, G.M., **19**-0380
Morris, G.W., **19**-0361
Morris, J.J., **03**-0015
Morris, K.P., **08**-0019, **14**-0204
Morris-Natschke, S., **16**-0493
Morrison III, W.H., **16**-2135
Morrison, A., **15**-1652, **15**-2116
Morrison, A.J., **15**-1429
Morrison, D.J., **12**-0319
Morrison, D.W., **16**-1069, **16**-1170
Morrison, G.A., **04**-0261, **04**-0263, **04**-0350, **04**-0387
Morrison, G.F., **10**-1763
Morrison, H., **07**-0054, **18**-0343
Morrison, H.A., **07**-0053
Morrison, J.D., **04**-0012, **04**-0026, **04**-0028, **04**-0045, **04**-0047, **04**-0134, **04**-0136, **04**-0137, **04**-0141, **04**-0145, **04**-0146, **04**-0149, **04**-0151, **04**-0202, **04**-0207, **04**-0208, **04**-0210, **04**-0211, **04**-0213, **04**-0214, **10**-1304, **10**-1638, **10**-1660, **10**-1686, **10**-1743, **12**-0074, **15**-0597, **15**-0599, **15**-0601, **15**-0674, **15**-0782, **15**-1093, **15**-1491, **15**-1584, **15**-1731, **15**-1820, **15**-1824, **15**-1826, **15**-2058, **16**-0489, **16**-0540, **16**-1013, **18**-0625, **19**-1014
Morrison, J.J., **16**-1034, **17**-0266
Morrison, M.A., **15**-0112
Morrison, R.T., **13**-0734, **14**-0105
Morriss, F.V., **12**-0736
Morrissey, M.M., **19**-0501
Morse, B.K., **18**-0015
Morse, C.S., **11**-0058
Morten, D.H., **10**-0082
Mortensen, J.Z., **18**-0696
Mortier, J., **15**-1119
Mortimer, C.T., **01**-0097
Mortimer, R., **18**-0458
Mörtl, M., **16**-0291
Morton, B.M., **07**-0044
Morton, D., **07**-0044
Morton, H.E., **10**-0614, **15**-1004, **19**-0195
Morton, R.C., **16**-1669
Mortreux, A., **13**-0626, **13**-0627, **15**-0602, **15**-0797, **15**-1381, **15**-1454, **19**-1718
Morzycki, J.W., **12**-0247, **19**-0058
Moscalenko, M., **16**-1426
Moseley, K., **15**-2405
Moser, W.H., **18**-0897, **18**-0905
Moses, L.M., **15**-0860
Mosettig, E., **15**-0437
Mosher, H.S., **04**-0105, **04**-0136, **04**-0206, **04**-0499, **05**-0158, **10**-0269, **10**-1057, **16**-0532, **16**-0540, **18**-0017, **18**-0098
Mosher, M.W., **14**-0260
Mosher, W.A., **15**-1166
Moskal, J., **16**-1200, **16**-1284
Moskalenko, M.A., **16**-1444

Moskau, D., **05**-0148, **18**-0642
Moskva, V.V., **15**-0039
Mosleh, A., **13**-0302
Moss, J.C., **15**-2210
Moss, R.A., **02**-0199, **05**-0327, **05**-0327, **05**-0367, **05**-0368, **05**-0372, **05**-0386, **05**-0391, **05**-0393, **05**-0409, **10**-0368, **10**-0389, **10**-1035, **12**-0346, **15**-2267, **15**-2268, **15**-2272, **15**-2275, **15**-2312, **15**-2317, **18**-0089, **18**-0090, **18**-0093
Moss, R.E., **04**-0241, **04**-0244, **08**-0186
Moss, R.J., **15**-1132, **17**-0147
Moss, S., **18**-0528
Mosset, P., **10**-1688, **16**-0874, **16**-0878
Mossman, C., **18**-0297
Mossman, C.J., **18**-0297
Mossoba, M.M., **07**-0067
Mostafavipoor, Z., **19**-0303
Mostefai, N., **19**-1045
Motallebi, S., **15**-0012
Motell, E.L., **06**-0064, **14**-0165
Motes, J.M., **05**-0136
Motherwell, W.B., **10**-1151, **12**-0247, **12**-0655, **13**-0581, **19**-0058, **19**-0436, **19**-1246, **19**-1540, **19**-1717
Motie, R.E., **16**-1514, **16**-1745
Motlagh, A.R., **10**-0897
Motoda, D., **15**-0731
Motofusa, S.-i., **15**-1159
Motohashi, S., **18**-0194
Motoi, M., **04**-0177
Motoki, S., **16**-0218
Motorina, I., **15**-1672
Motoyama, Y., **16**-0640
Motoyoshiya, J., **15**-0849, **16**-1307
Mott, L.J.L., **17**-0489
Mott, R.C., **12**-0157, **14**-0253
Motta, A.R., **18**-0776
Mottaghinejad, E., **19**-0092
Motti, E., **13**-0508
Motyka, L., **18**-0471
Moughamir, K., **10**-1865
Mouk, R.W., **18**-0196
Moule, D.C., **07**-0015
Moulijn, J.A., **18**-0756
Moulik, P.S., **08**-0191
Moulin, D., **15**-1125, **15**-1134, **19**-0789
Moulineau, C., **10**-1368
Moulines, F., **12**-0316
Moulines, J., **10**-0952
Moulton, B., **12**-0372
Moulton, W.N., **19**-0976
Mounier, C.E., **04**-0310
Mouri, M., **16**-1047, **16**-1418
Mouriño, A., **15**-1141
Mourning, M.C., **10**-0162, **17**-0023
Moussa, Z., **15**-0240
Moutet, J., **19**-0955
Moutou, J.-L., **16**-0847
Moutrille, C., **14**-0283
Mouvier, G., **15**-0068
Movahedi, Z., **10**-0663
Movassagh, B., **10**-0897, **16**-0053, **16**-0245, **16**-1629, **16**-1615
Movassaghi, M., **10**-1553, **19**-1353
Mowat, R., **11**-0265
Mowery, M.E., **13**-0520, **13**-0635
Mowery, M.W., **13**-0632
Moyano, A., **07**-0091, **15**-1437, **15**-2211, **15**-2364, **16**-0687, **17**-0416, **19**-1031
Moyer Jr., C.E., **11**-0641
Moynihan, H.A., **06**-0045
Mozdzen, E.C., **12**-0660, **19**-1492, **19**-1506
Mozingo, R., **15**-0437
Mozūraitis, R., **10**-0999
Mraz, T.J., **19**-0910
Mridha, N.K., **13**-0196
Mrowiec-Białoń, J., **15**-0150
Mrozack, S.R., **17**-0073
Mu, L., **10**-0403
Mu, R., **08**-0211
Muathen, H.A., **11**-0270
Mubarak, M.S., **19**-1334
Mucci, A., **08**-0219
Muchowski, J.M., **02**-0261, **13**-0702, **15**-1244, **16**-1709
Muci, A.R., **12**-0460, **15**-0698, **15**-0747, **15**-1827, **19**-0968
MuCullough, K.J., **15**-1941
Mudryk, B., **13**-0673
Muedas, C.A., **14**-0297, **15**-0847
Muehlbacher, M., **10**-1149
Mueller, A.M., **15**-1223
Mueller, B., **15**-0788
Mueller, J.A., **16**-0865, **19**-0120
Mueller, M.E., **05**-0246
Mueller, P.H., **15**-1945
Mueller, R.A., **15**-2350
Mueller, R.H., **18**-0677
Mueller, W.A., **09**-0090
Mueller, W.H., **15**-0021
Mueller-Westerhoff, U.T., **16**-1945
Muenster, L.J., **08**-0024
Muenter, J.S., **01**-0038, **08**-0233
Mues, C., **18**-0688
Muetterties, E.L., **15**-0446, **15**-0523, **19**-0015
Muezelaar, G.J., **10**-1437
Mügge, K., **18**-0540
Mugnoli, A., **02**-0285, **02**-0319, **17**-0056
Mühlstadt, M., **15**-0222
Muhsin, M., **17**-0067
Mui, J.Y., **05**-0380
Muir, D.M., **17**-0072, **17**-0097, **17**-0098
Mujsce, A.M., **10**-1319
Mukai, C., **15**-0238, **15**-0239, **15**-1442, **16**-0069
Mukai, T., **14**-0244, **15**-2322, **18**-0469, **18**-0470, **18**-0549, **18**-0601, **18**-0640
Mukaide, K., **15**-1719
Mukaiyama, T., **04**-0136, **10**-0992, **10**-1009, **10**-1089, **10**-1436, **10**-1511, **10**-1518, **10**-1535, **10**-1706, **10**-1805, **11**-0290, **11**-0324, **12**-0340, **15**-0184, **15**-0185, **15**-0197, **15**-0310, **15**-1043, **15**-1054, **15**-1055, **15**-1060, **15**-1838, **16**-0161, **16**-0256, **16**-0434, **16**-0490, **16**-0495, **16**-0683, **16**-0820, **16**-0994, **16**-0996, **16**-1011, **16**-1016, **16**-1052, **16**-1056, **16**-1077, **16**-1119, **16**-1125, **16**-1128, **16**-1129, **16**-1422, **16**-1426, **16**-1654, **16**-1656, **16**-1684, **16**-1716, **16**-1729, **16**-1788, **16**-1880, **16**-1937, **17**-0295, **17**-0487, **18**-0123, **18**-0440, **19**-0056, **19**-0243, **19**-0244, **19**-0480, **19**-0691, **19**-0870, **19**-1109, **19**-1113, **19**-1125, **19**-1128, **19**-1327, **19**-1661, **19**-1668, **19**-1702, **19**-1713
Mukerjee, A.K., **15**-2180, **16**-2094
Mukhametshin, F.M., **10**-1722, **12**-0699, **19**-1284
Mukherjee, C., **16**-1741
Mukherjee, D., **19**-0952
Mukherjee, R., **19**-0268
Mukherjee, S., **03**-0054
Mukherjee, S.B., **16**-0775
Mukherjee, S.K., **19**-0251
Mukhopadhyay, C., **19**-1190
Mukhopadhyay, K., **15**-1378
Mukhopadhyay, P.P., **15**-1277
Mukhopadhyay, T., **18**-0872
Mukkanti, K., **11**-0644
Mulder, J.A., **10**-0997
Mulder, J.J.C., **15**-2105
Mulder, P., **01**-0104, **02**-0024

Muldoon, J., **19**-0214
Muldowney, M.P., **15**-1902, **19**-1031
Mulhausen, H.A., **10**-0372
Mulholland, D.L., **02**-0348
Mulholland, K.R., **18**-0398, **18**-0399
Mullane, M., **16**-0030
Mullay, J., **01**-0024, **01**-0029
Mülle, P., **15**-2050
Mullen, A., **15**-1375, **15**-1381, **15**-1485
Mullen, D.G., **16**-1816
Müllen, K., **02**-0173, **02**-0254, **02**-0272, **02**-0274, **02**-0282, **02**-0305, **02**-0307, **02**-0319, **02**-0320, **02**-0333, **15**-0075, **18**-0637
Muller, B.L., **12**-0662
Muller, G., **10**-1454, **10**-1459
Muller, L.L., **15**-1883, **16**-1395, **16**-2076, **16**-2083, **16**-2094
Muller, M., **12**-0342
Muller, N., **02**-0375
Müller, B., **18**-0362
Müller, E., **05**-0234, **10**-0918, **14**-0273, **15**-2292, **15**-2323, **15**-2405, **18**-0234
Müller, E.P., **10**-1017
Müller, G., **01**-0011, **04**-0245
Müller, H., **15**-0501, **15**-0712, **19**-0056
Müller, H.R., **15**-0482
Müller, J., **05**-0053, -0143, **10**-0520
Müller, K., **02**-0066, **04**-0041, **18**-0619
Müller, M., **04**-0477, **12**-0608, **15**-2293, **16**-1500, **16**-2065, **19**-0504
Müller, P., **04**-0467, **10**-0011, **10**-0326, **10**-0333, **10**-0385, **10**-1565, **10**-1808, **12**-0239, **12**-0368, **15**-1887, **15**-1901, **16**-1436, **16**-1437, **16**-1564, **19**-0023, **19**-0028, **19**-0069
Müller, P., **19**-0247, **19**-0249, **19**-0250, **19**-0282, **19**-1348, **19**-1380
Müller, R.K., **17**-0420
Müller, S., **04**-0501
Müller, T., **05**-0008
Müller, T.E., **15**-0354
Müller, T.J.J., **15**-0910, **16**-1916
Müller, U., **02**-0158
Müller, W., **05**-0290, **10**-1033, **19**-0461
Müller, W.M., **03**-0112, **03**-0152, **04**-0244
Müllhofer, G., **17**-0059, **17**-0062
Mullie, F., **07**-0082
Mulligan, P.J., **18**-0195
Mulliken, R.S., **01**-0025, **02**-0375, **03**-0080, **03**-0081, **03**-0100, **07**-0014
Mullin, A., **10**-0267
Mullins, R.J., **15**-1160
Mulvaney, A.W., **19**-1515, **19**-1625
Mulvey, R.E., **13**-0654
Mulzer, J., **16**-1000, **17**-0412, **17**-0414, **17**-0416
Munavilli, S., **11**-0552
Munchausen, L.L., **15**-1945
Mundy, B.P., **16**-1064
Munechika, T., **10**-0207
Muneer, M., **07**-0062
Munekata, T., **17**-0321
Muneyuki, R., **10**-0171
Mungall, W.S., **04**-0193, **15**-1702
Munger, P., **12**-0512
Muñiz, K., **15**-1877, **19**-1028
Munjal, R.C., **02**-0199
Munn, N.M., **02**-0075
Muñoz, E., **15**-1119
Muñoz, E., **15**-1119
Muñoz, L., **12**-0214
Muñoz, L., **13**-0504
Muñoz, M.P., **15**-0818, **15**-0820
Muñoz-Muñiz, O., **16**-0688, **16**-1081
Munro, M.H.G., **15**-0562
Munson, M.S.B., **08**-0224
Münsterer, H., **12**-0223
Muntean, L., **02**-0428
Munyemana, F., **10**-1089
Münzel, N., **02**-0215
Mura, L.A., **10**-1748
Murabayashi, A., **18**-0697
Muraglia, E., **15**-1647
Muraglia, V., **10**-0169
Murahashi, S., **02**-0226, **10**-0900, **10**-0908, **10**-1012, **10**-1270, **10**-1291, **10**-1509, **10**-1795, **12**-0749, **14**-0246, **14**-0247, **14**-0395, **14**-0452, **16**-0430, **19**-0284, **19**-0288, **19**-0516, **19**-0896, **19**-1330
Murahashi, S.-I., **12**-0337, **12**-0733, **15**-1665, **16**-0931, **19**-0516, **19**-0569, **19**-0570, **19**-1624
Murahashi, T., **10**-1009
Murai, A., **10**-1347
Murai, S., **11**-0332, **11**-0414, **11**-0463, **12**-0246, **12**-0529, **13**-0532, **13**-0619, **15**-0726, **15**-0755, **15**-0777, **15**-0920, **15**-1473, **15**-1642, **15**-2443, **19**-0060, **19**-0747, **19**-1508
Murai, T., **10**-1280, **10**-1561, **15**-0748, **16**-1135, **16**-1245
Murakami, C., **19**-1005
Murakami, H., **10**-1123, **16**-2135
Murakami, M., **10**-1518, **10**-1771, **15**-0928, **15**-1409, **16**-1106, **16**-1125, **16**-2134, **19**-0221
Murakami, N., **15**-1324
Murakami, S., **16**-0765
Murakami, Y., **15**-0876, **16**-1854
Murakata, M., **10**-1639
Murakawa, K., **12**-0722
Muraki, M., **19**-1109, **19**-1113, **19**-1125
Muraki, T., **10**-0710
Muralha, V.S.F., **01**-0098
Murali, R., **15**-2043
Muralidhar, B., **19**-1117
Muralidharan, D., **15**-2119
Muralidharan, V.P., **16**-2084
Muralimohan, K., **13**-0589
Muramatsu, H., **15**-0598
Muramatsu, I., **16**-1625
Muramatsu, Y., **15**-1576
Murao, S., **19**-1032
Muraoka, K., **10**-1313, **19**-1339
Muraoka, M., **16**-0209, **16**-1032
Muraoka, T., **10**-1468, **10**-1469
Murari, M.P., **10**-1599
Murashima, T., **11**-0140
Murata, I., **02**-0131, **02**-0326, **07**-0021
Murata, K., **12**-0252, **15**-1004, **15**-1024, **19**-1042, **19**-1048
Murata, M., **10**-1217, **12**-0451, **12**-0452, **13**-0293, **13**-0633
Murata, S., **15**-1853, **16**-1125, **17**-0208
Murata, Y., **08**-0169, **15**-2069, **18**-0733
Murati, M.P., **10**-1505
Muratori, M., **19**-0823
Muratov, N.N., **16**-0448
Murawski, D., **18**-0866
Murayama, D.R., **02**-0226
Murchie, M.P., **03**-0113
Murcko, M.A., **04**-0279
Murdoch, J.R., **12**-0508
Murga, J., **16**-0996
Murguly, E., **04**-0072
Murhashi, S.-I., **18**-0363
Muri, D., **15**-1939
Murov, S., **16**-2085
Murphy, A., **15**-1729

Murphy, D.K., **10**-0497
Murphy, D.L., **11**-0235
Murphy, F., **16**-1239
Murphy, G.K., **12**-0368
Murphy, J.A., **11**-0363, **15**-1269, **19**-0206
Murphy, P.J., **10**-1487, **16**-1023, **16**-1342, **17**-0216
Murphy, R.B., **11**-0610
Murphy, T.J., **15**-2206
Murphy, W.S., **10**-1581, **12**-0515, **18**-0120
Murr, B.L., **06**-0080, **15**-2165
Murray, C.D., **13**-0745
Murray, C.J., **08**-0141, **15**-0325
Murray, K.J., **12**-0427, **15**-0491
Murray, K.K., **05**-0332
Murray, N.G., **14**-0438, **18**-0891
Murray, R.E., **12**-0545
Murray, R.W., **05**-0328, **10**-0968, **14**-0227, **14**-0228, **14**-0229, **14**-0232, **14**-0241, **15**-1744, **15**-1766, **15**-2155, **15**-2156, **15**-2157, **15**-2159, **15**-2161, **18**-0549, **19**-0010, **19**-0359, **19**-0369, **19**-0370, **19**-0371, **19**-0373, **19**-0374, **19**-0376, **19**-0378, **19**-0379, **19**-0488, **19**-0517, **19**-0756, **19**-0764, **19**-0767
Murrell, J.N., **01**-0001
Murry, J.A., **13**-0541, **13**-0606, **15**-2064
Murthy, Ch.V.S.R., **10**-0963, **16**-1476
Murty, M.S.R., **10**-0862, **10**-0958
Murugesan, V., **19**-0085
Musaev, D.G., **16**-1844
Musch, P.W., **02**-0084
Muscio Jr., O.J., **13**-0020, **15**-2219
Musco, A., **04**-0085
Musharraf, M.A., **19**-1103
Musker, W.K., **02**-0088, **17**-0247, **19**-0046, **19**-0850
Musser, C.A., **16**-0574
Musser, M.T., **10**-0285
Musso, H., **04**-0174, **04**-0175, **04**-0444, **04**-0446, **18**-0640, **19**-1571, **19**-1573
Musson, A., **11**-0136, **11**-0231
Mustanir, **10**-0027
Musumarra, G., **02**-0095, **10**-0079, **10**-0386, **10**-0386
Muszkat, K.A., **15**-2111
Mutai, K., **06**-0011
Mutch, A., **18**-0821
Muth, C.L., **19**-1506
Muthard, J.L., **02**-0352
Mutule, I., **13**-0499
Muthusamy, S., **12**-0369, **16**-0233
Muto, T., **15**-0777
Mutter, L., **17**-0145
Mutter, M., **16**-1817
Mutter, M.S., **16**-1303, **16**-1325
Mutti, S., **04**-0111
Muzart, J., **16**-0990, **19**-0218, **19**-0533, **19**-0537, **19**-0575, **19**-0576
Muzzi, R.M., **15**-1770
Myers, A.G., **10**-1659, **12**-0070, **13**-0370, **19**-1353, **19**-1483
Myers, B.J., **15**-2438
Myers, J.D., **17**-0363
Myers, M., **15**-1109, **16**-1410
Myers, M.M., **15**-0867
Myers, R.J., **01**-0081
Myhre, P.C., **05**-0020, **05**-0077, **10**-0183, **10**-0200, **10**-0208, **10**-0517, **11**-0010, **11**-0056, **11**-0058, **11**-0101, **15**-0098
Myint, Y.Y., **15**-1560
Myles, D.C., **10**-0734
Mynett, D.M., **16**-1540
Myoung, Y.C., **15**-0795
Myshenkova, T.N., **10**-1833
Mysík, P., **10**-1046

N'Gouela, S., **16**-0115
N'Guessan, T.Y., **18**-0225
N'Zemba, B., **07**-0118
Na, S., **15**-0395
Na, Y., **15**-1152, **15**-1374, **15**-1406, **19**-0120
Naab, P., **15**-0005, **15**-0030, **15**-0034
Naae, D.G., **15**-0017
Naan, M.P., **17**-0056
Naasz, R., **15**-1136, **16**-0787
Nababsing, P., **14**-0031
Nabana, T., **19**-0497
Nabeya, A., **10**-1733
Nacci, A., **13**-0399, **13**-0415
Nace, H.R., **17**-0123, **17**-0235, **17**-0242, **19**-0639
Nachod, F.C., **01**-0015, **01**-0089, **04**-0264, **04**-0268, **05**-0208, **05**-0219, **08**-0018, **08**-0040
Nachtigall, G.W., **10**-0066
Nada, F., **19**-0881
Nadal, B., **10**-1105
Nadeau, C., **10**-1858
Nadeau, E., **16**-0918
Nadelson, J., **16**-1894
Nadi, S., **14**-0150
Nadir, U.K., **10**-1568
Nadjo, L., **19**-0708
Nadkarni, D., **19**-1011
Nadler, E.B., **02**-0395, **02**-0397
Naef, R., **16**-0490
Naegele, W., **15**-0110
Naeimi, H., **10**-1161
Naemura, K., **04**-0065, **04**-0468, **04**-0470, **04**-0493, **10**-1511
Näf, F., **10**-1653, **15**-1172
Nafti, A., **12**-0223
Nagahara, K., **10**-1853, **15**-1262
Nagahara, S., **15**-0750, **18**-0143
Nagahara, T., **17**-0162
Nagai, T., **12**-0233
Nagai, K., **10**-1262, **15**-1125, **16**-0866, **16**-0894
Nagai, M., **05**-0201
Nagai, T., **05**-0231, **14**-0117, **16**-2147, **17**-0320
Nagai, Y., **10**-0513, **15**-1641, **15**-1925, **15**-2371, **19**-0010
Nagaiah, K., **16**-0068, **16**-1174
Nagaki, A., **15**-2135
Nagaku, M., **10**-0704
Nagano, H., **15**-0576, **15**-0595
Nagano, T., **10**-1298
Nagano, Y., **16**-1710
Nagao, K., **18**-0738
Nagao, S., **14**-0190
Nagao, Y., **04**-0136, **04**-0334, **16**-0232
Nagaoka, Y., **16**-1760
Nagarajan, K., **12**-0095
Nagarajan, M., **13**-0179, **16**-1671
Nagareda, K., **16**-0538, **16**-1294
Nagarkatti, J.P., **19**-0323
Nagasawa, K., **16**-1604
Nagasawa, M., **19**-1176
Nagasawa, T., **11**-0507
Nagase, H., **10**-0636, **12**-0326
Nagase, S., **10**-0202, **10**-1313, **16**-1294
Nagashima, H., **13**-0362, **15**-1064, 1, **19**-1094
Nagashima, T., **13**-0475, **15**-2302
Nagata, A., **15**-2379
Nagata, H., **15**-0823
Nagata, J., **15**-2194
Nagata, K., **16**-0364, **19**-1518
Nagata, M., **13**-0633
Nagata, R., **19**-0064
Nagata, T., **14**-0208, **14**-0213
Nagata, W., **11**-0390, **15**-1499, **15**-1502
Nagata, Y., **19**-1468, **19**-1492
Nagatomo, H., **18**-0359
Nagayama, S., **15**-1668, **16**-0609, **16**-0871, **16**-0944, **16**-1081, **16**-1083, **16**-1086, **16**-1117, **16**-1121, **16**-1122

Nagayoshi, M., **16**-1657
Nagel, C.J., **15**-1776
Nagel, M., **18**-0577, **18**-0578, **19**-0556
Nagendrappa, G., **15**-1844
Nageswar, Y.V.D., **10**-0546, **10**-0671, **19**-0200, **19**-0229
Nagino, C., **10**-0704
Nagira, K., **14**-0366, **14**-0368
Nagle, A.S., **10**-0859, **10**-0861, **16**-1867, **17**-0234
Nagorski, R.W., **12**-0091, **15**-1523
Nagraba, K., **15**-2159
Nagubandi, S., **11**-0395
Naguib, Y.M.A., **14**-0187
Nagura, T., **11**-0357
Nagy, J.B., **16**-1847
Nagy, O.B., **16**-1847
Nahabedian, K.V., **11**-0611
Nahm, S., **16**-1960, **16**-1967
Nahm, S.H., **15**-0969
Nahmany, M., **16**-1663
Naicker, K.P., **10**-1008, **13**-0389, **15**-1678, **16**-1831
Naicker, K.P., **19**-1758
Naidenov, S.V., **11**-0029
Naidu, B.N., **15**-1314
Naik, R.G., **15**-0684
Naik, S., **16**-1767
Naik, S.N., **13**-0723
Nailor, K.E., **15**-1278
Naimi-Jamal, M.R., **10**-1569, **16**-0913
Nair, D., **13**-0402
Nair, K.B., **15**-1651
Nair, L.G., **15**-1599, **15**-1624, **19**-0491, **19**-0730
Nair, R.V., **16**-1543
Nair, V., **15**-1532, **15**-1599, **15**-1624, **19**-0491, **19**-0730
Nairn, M.R., **15**-1682
Naito, M., **10**-1498
Naito, T., **07**-0041, **15**-1260, **15**-1275, **15**-2235, **16**-0933, **16**-0937, **16**-0938, **16**-0940, **16**-2083, **19**-1152
Najem, T.S., **16**-1571
Najera, C., **12**-0125, **16**-1784, **16**-1786, appendixA-0031
Najime, R., **10**-0952
Naka, T., **19**-0914
Nakabayashi, T., **19**-1152, **19**-1465
Nakada, M., **15**-2304, **16**-0560, **16**-0668
Nakada, S., **13**-0608
Nakadai, M., **16**-1054
Nakadaira, Y., **04**-0518, **05**-0245
Nakae, T., **12**-0337
Nakae, Y., **16**-1618
Nakagai, Y.-i., **15**-0766, **19**-1679
Nakagaki, R., **06**-0011
Nakagawa, H., **10**-0606
Nakagawa, J., **17**-0026
Nakagawa, K., **14**-0275, **15**-1275, **19**-0413
Nakagawa, M., **02**-0272, **02**-0286, **02**-0301, **02**-0304, **02**-0326, **02**-0327, **02**-0328, **04**-0065, **04**-0471, **14**-0175, **14**-0302, **15**-0989, **16**-0902, **17**-0088, **19**-1154
Nakagawa, S., **15**-1391
Nakagawa, T., **03**-0078, **12**-0721, **15**-0225, **15**-0392, **16**-1079
Nakahara, M., **03**-0004
Nakahara, S., **04**-0493
Nakahara, Y., **10**-1080
Nakahara, Y., **15**-1544
Nakahigashi, J., **15**-1520
Nakai, E., **18**-0735
Nakai, K., **10**-0234, **18**-0249
Nakai, M., **18**-0261, **19**-1618
Nakai, S., 09-II-0006, **15**-0707, **18**-0340
Nakai, T., **01**-0068, **15**-0889, **15**-0985, **15**-2064, **16**-1203, **16**-1487, **18**-0730, **18**-0732, **18**-0733, **18**-0735, **18**-0735
Nakai, Y., **03**-0045, **13**-0487
Nakaji, T., **07**-0058
Nakajima, T., **02**-0194
Nakajima, A., **10**-0584
Nakajima, K., **10**-1779, **11**-0622, **13**-0359, **15**-0799, **16**-2000
Nakajima, M., **15**-1693, **16**-1039, **18**-0238
Nakajima, N., **10**-1639, **14**-0452, **17**-0468, **19**-1154
Nakajima, O., **10**-0886
Nakajima, R., **15**-0819
Nakajima, S., **16**-1840, **18**-0153
Nakajima, S.-I., **18**-0144
Nakajima, T., **11**-0375, **11**-0376, **16**-1104
Nakajima, Y., **16**-1655, **19**-1022
Nakajo, M., **15**-1791
Nakama, T., **15**-0204
Nakamaye, K.L., **12**-0019
Nakamichi, N., **19**-0019
Nakamoto, K., **10**-0403, **10**-0440
Nakamura, A., **03**-0083, **10**-0788, **15**-2317, **16**-0452, **16**-1636, **19**-0480
Nakamura, E., **07**-0094, **10**-1336, **10**-1338, **10**-1358, **10**-1372, **10**-1463, **10**-1650, **13**-0595, **15**-0893, **15**-1063, **15**-1066, **15**-1974, **16**-0303, **16**-0581, **16**-1016, **19**-0479
Nakamura, H., **05**-0314, **10**-0274, **10**-1544, **15**-0223, **15**-1313, **16**-0871, **16**-0910
Nakamura, I., **15**-0179, **15**-0931
Nakamura, K., **04**-0163, **04**-0196, **11**-0189, **11**-0507, **13**-0538, **15**-1782, **16**-0518, **16**-0871, **16**-0910, **19**-1021, **19**-1022, **19**-1023
Nakamura, M., **02**-0296, **02**-0303, **15**-0893, **15**-2139
Nakamura, N., **02**-0220, **09**-0012, **13**-0778, **14**-0071
Nakamura, R., **13**-0605
Nakamura, S., **15**-0739, **15**-0786, **16**-1455, **19**-0999
Nakamura, T., **03**-0146, **08**-0200, **13**-0333, **13**-0438, **15**-1265, **15**-1267, **15**-1275, **15**-1645, **15**-1646, **16**-1127, **16**-1903
Nakamura, Y., **02**-0069, **10**-1044, **10**-1045, **11**-0216, **12**-0278, **15**-0811
Nakanishi, H., **18**-0637
Nakanishi, K., **04**-0117
Nakanishi, S., **10**-1503, **10**-1820
Nakano, A., **15**-0377
Nakano, H., **10**-1454
Nakano, K., **16**-1013
Nakano, M., **11**-0324, **13**-0762, **16**-1051, **16**-1788
Nakano, N., **15**-2065, **19**-0986
Nakano, S., **15**-0122
Nakano, T., **10**-0513, **15**-1641, **15**-1925, **16**-1727, **19**-0139
Nakano, Y., **15**-2368, **16**-1444
Nakao, J., **15**-0935
Nakao, R., **16**-1667
Nakao, S., **15**-2139
Nakao, T., **02**-0070
Nakaoka, K., **15**-2379
Nakashima, H., **11**-0323, **16**-0618, **16**-0640
Nakashima, K., **19**-0066
Nakashima, T., **10**-0311
Nakata, D., **19**-1578
Nakata, K., **10**-0273, **10**-0274, **15**-1836
Nakata, M., **15**-07, **19**-0637

Nakata, T., **16**-1661, **16**-1836, **17**-0241, **19**-1057
Nakatani, H., **15**-1380
Nakato, T., **19**-1624
Nakatsugawa, M., **16**-0687
Nakatsuji, M., **05**-0259
Nakatsuji, S., **02**-0326, **02**-0327, **02**-0328, **19**-0066
Nakatsuji, Y., **03**-0146
Nakatsuka, T., **19**-0056
Nakatsuka, Y., **16**-0618, **16**-0754, **16**-1006, **16**-1121
Nakaya, Y., **15**-2383
Nakayama, H., **07**-0058
Nakayama, J., **15**-1847, **17**-0364, 17-, **19**-0842, **19**-1565
Nakayama, M., **05**-0351, **15**-1642, **16**-1671
Nakayama, T., **18**-0396
Nakayasu, T., **11**-0357
Nakazaki M., **04**-0177
Nakazaki, A., **16**-1127
Nakazaki, M., **02**-0070, **04**-0020, **04**-0079, **04**-0468, **04**-0470, **04**-0493
Nakazawa, M., **18**-0229
Nakazawa, T., **02**-0326, **07**-0021, **14**-0373
Nakazono, Y., **13**-0617
Nakazumi, H., **09**-0064
Nakhapetyan, L.A., **15**-2281
Nakhshunov, V.S., **15**-0405
Nakmura, H., **17**-0382
Nakoji, M., **10**-1452
Nakova, E.P., **19**-1801
Nalbandyan, A.B., **19**-0701
Nalepa, C.J., **17**-0508
Nam, G.S., **16**-1994
Nam, H., **13**-0047
Nam, W., **19**-0463
Nam, G.S., **19**-1600
Namane, C., **19**-1243
Namanworth, E., **05**-0016, **05**-0050, **10**-0165, **10**-0374
Namavari, M., **10**-1055
Namba, K., **16**-0721
Namba, M., **19**-1152
Namboodiri, V., **13**-0495, **13**-0545
Namboodiri, V.V., **10**-0619
Nambu, H., **10**-1747, **10**-1750, **10**-1751, **10**-1755, **10**-1756, **12**-0252
Nambu, M., **15**-2066
Nambu, N., **11**-0013
Nametkin, N.S., **01**-0009, **18**-0761
Namiki, H., **12**-0326
Namy, J., **16**-2002
Namy, J.-L., **16**-0608, **16**-1363, **16**-1987, **19**-1648, **17**-0202, **18**-0143, **19**-0967, **19**-1670
Nan, Y., **15**-0245
Nanda, B., **10**-1013
Nanda, P., **11**-0429, **19**-0625
Nanda, S., **19**-1022
Nandakumar, M.V., **13**-0235
Nandanan, E., **15**-1694
Nandi, M., **15**-0762
Nandi, S., **01**-0025
Nandy, S.K., **16**-1474
Nangia, A., **16**-1321, **16**-1719
Nanjundaswamy, H.M., **16**-0307
Nanke, T., **10**-1826
Nanni, D., **15**-1258, **18**-0073, **18**-0300
Nano, G., **16**-1865
Nantz, M.H., **16**-1820
Naot, T., **19**-0284
Naota, T., **14**-0246, **14**-0247, **14**-0452, **16**-0430, **19**-0516, **19**-0570, **19**-1624
Naples, J.O., **16**-1655
Napolitano, E., **16**-0442, **17**-0188
Naqvi, S.M., **18**-0569
Nara, S., **11**-0196
Nara, S.J., **11**-0555, **16**-1170
Narang, C.K., **16**-1817
Narang, S.C., **10**-0757, **10**-1134, **10**-1176, **11**-0119, **11**-0133, **12**-0203, **16**-1523, **19**-1598
Narasaiah, A.V., **16**-0062
Narasaka, K., **10**-1706, **15**-1043, **15**-1055, **15**-1362, **15**-1423, **15**-1660, **15**-1697, **15**-2064, **16**-1077, **16**-1422, **19**-1056
Narashimhan, K.M., **18**-0137
Narashimhan, S., **19**-1071, **19**-1075
Narasimhan, C.S., **19**-0960
Narasimhan, M.S., **12**-0388
Narasimhan, N.S., **12**-0405
Narasimhan, S., **19**-1086, **19**-1091, **19**-1167, **19**-1300, **19**-1490
Naravane, A., **13**-0386
Narayan, R.S., **19**-0396
Narayan, S., **13**-0291
Narayana, A., **15**-1552
Narayana, C., **12**-0526, **15**-0654, **18**-0435, **19**-1598
Narayana, M., **15**-0510
Narayanan, B.A., **16**-0449
Narayanan, K.V., **10**-0232
Narayanan, R., **16**-1068
Nardello, V., **14**-0233
Nardi, M., **16**-1618
Narender Reddy, A.V., **19**-1262, **19**-1643
Narender, M., **19**-0229
Narender, N., **11**-0248, **11**-0256, **11**-0289, **16**-1672
Narender, R., **16**-2153, **17**-0440
Narin, S.Yu., **14**-0198
Narisada, M., **11**-0650
Narisano, E., **12**-0230
Narisawa, S., **15**-0985
Narita, K., **10**-1819, **15**-1341
Narita, N., **14**-0032, **14**-0105
Narita, S., **16**-1307
Naritomi, M., **13**-0362
Narkunan, K., **15**-1065, **16**-0163
Narsaiah, A.V., **09**-0115, **13**-0159, **16**-0068, **16**-0077, **16**-1171, **16**-1174, **17**-0441, **17**-0471, **19**-0212
Narsaiah, B., **19**-1193
Narsihmulu, Ch., **10**-0683, **13**-0405, **15**-0403, **15**-0438, **16**-0780, **16**-0784
Narula, A.P.S., **15**-0436
Narula, A.S., **12**-0454
Narusawa, H., **16**-0641
Naruse, M., **15**-1731
Naruse, Y., **18**-0466
Naruta, Y., **11**-0444, **15**-1991, **16**-0613, **19**-0258, **19**-0633
Narvaez, L.D., **11**-0120
Nascimento, M.de G., **16**-1632
Nash, E.G., **17**-0455
Nash, J.J., **17**-0240
Nashi, T., **10**-1161
Nasibov, S.S., **04**-0042
Nasielski, J., **12**-0040
Nasipuri, D., **15**-0541, **19**-0974
Naskar, D., **14**-0425, **16**-2121
Naso, F., **10**-1265, **10**-1325, **16**-1929, **17**-0013, **17**-0031, **17**-0056
Nasreen, A., **14**-0205, **16**-0087
Nass, D., **10**-0232
Nasserri, M.A., **10**-0679
Nassetta, M., **11**-0594
Nassimbeni, L.R., **03**-0169
Nata, A., **16**-0228
Natale, N.R., **16**-0361, **19**-0104, **19**-1151, **19**-1462
Natarajan, R., **10**-0530, **10**-0531
Natero, R., **05**-0212
Nathan III, E.C., **02**-0202, **02**-0203
Nathan, W.S., **02**-0369, **10**-0313
Näther, C., **15**-2293
Nation, A.J., **16**-0762
Natsume, H., **10**-1203
Natt, F., **11**-0464

Natta, G., **04**-0001
Nattier, B.A., **16**-0075, **16**-0160, **19**-0140
Naudet, M., **14**-0039, **14**-0179
Näumann, F., **16**-1058
Naumov, Yu.A., **11**-0496
Nauta, W.T., **05**-0231, **11**-0596
Navangul, H.V., **02**-0110
Navaro, O., **13**-0503
Navarrini, V., **11**-0185
Navarro, A., **10**-0925
Navarro, M., **13**-0304
Navarro, O., **13**-0509
Navarro-Ocaña, A., **12**-0213
Navarro-Vázquez, A., **18**-0627
Nave, P.M., **14**-0209
Naven, R.T., **03**-0132
Nawa, S., **11**-0343
Nay, B., **11**-0142
Nayak, A., **10**-1013
Nayak, B., **16**-1596
Nayak, M.K., **16**-1529
Nayak, S.K., **15**-1139, **19**-1708
Naylor, C.G., **17**-0015
Naylor, M., **18**-0370
Nayyar, N.K., **14**-0100
Nazareno, M.A., **10**-0097
Nazari, R., **19**-0146
Nazarov, I.N., **15**-0849
Nazarov, V.N., **10**-1089
Nazarova, N.E., **11**-0174
Nazarova, T.A., **15**-1652
Nazer, B., **19**-1107, **19**-1642
Nazran, A.S., **05**-0345, **14**-0049
Ncube, S., **18**-0435
Ndakala, A.J., **16**-1352
Ndibwami, A., **16**-0030
Neale, R.S., **15**-1608, **18**-0868
Neamati-Mazreah, N., **10**-0432
Nearhoof, E.H., **18**-0773
Neary, A.P., **11**-0112
Nebenzahl, L., **08**-0014, **08**-0053
Neber, P.W., **18**-0259
Nebois, P., **07**-0091
Nebzydoski, J.W., **10**-0152
Nechvatal, A., **14**-0172, **18**-0068
Neckers, D.C., **15**-2235, **16**-2083, **17**-0002, **17**-0527, **19**-1687, **19**-1689
Necşoiu, I., **19**-0631
Nédélec, J., **10**-1308
Nédélec, J.-Y., **10**-1228, **10**-1397, **13**-0304, **13**-0344, **15**-1162, **15**-1163, **16**-0570, **10**-1811, **10**-1818, **13**-0342
Nédélec, Y.-Y., **15**-2273
Nedugov, A.N., **10**-0806
Née, G., **10**-0485
Neelamkavil, S., **19**-0177
Neeland, E.G., **04**-0390
Neeman, M., **10**-0635
Neeraja, V., **15**-1906
Nefedov, B.K., **12**-0731, **15**-1375, **16**-1720
Nefedov, O.M., **05**-0227, **05**-0328, **05**-0370, **13**-0037, **15**-2315, **16**-1409
Nefedov, V.A., **13**-0256
Negashima, S., **19**-1447
Negele, S., **19**-0605
Negishi, E., **10**-1275, **10**-1326, **10**-1377, **10**-1378, **10**-1634, **10**-1749, **12**-0001, **12**-0296, **12**-0478, **12**-0573, **12**-0617, **12**-0620, **13**-0378, **13**-0552, **15**-0641, **15**-0683, **15**-0684, **15**-0685, **15**-0703, **15**-0705, **15**-0706, **15**-0778, **15**-0864, **15**-0906, **15**-0956, **15**-1102, **15**-1185, **18**-0420, **18**-0421, **18**-0423, **18**-0424, **18**-0440, **18**-0448, **18**-0449, **18**-0450
Negoro, N., **16**-1525, **17**-0373
Negoro, T., **15**-1540
Negri, D., **16**-0861
Negri, J.J., **15**-0497
Negri, J.T., **12**-0403
Négri, S., **10**-1850, **13**-0302
Neh, H., **15**-0616, **15**-1058
Nehru, K., **19**-0188, **19**-0809
Neibecker, D., **15**-1386
Neidigh, K.A., **16**-0357, **19**-1135
Neidle, S., **04**-0097
Neidlein, R., **04**-0467, **18**-0643
Neier, R., **18**-0683
Neighbors, M., **15**-1609
Neilands, O., **03**-0098
Neilson, D.G., **16**-0196
Neiman, L.A., **02**-0159
Neiman, M.B., **05**-0255
Neimann, K., **15**-1739
Neises, B., **16**-1665
Neiteler, G., **16**-0563
Neitzel, M.L., **18**-0247
Nekhoroshev, M.V., **16**-1607
Nelke, J.M., **19**-1728, **19**-1738
Nell, P.G., **16**-0491
Nelson, B.W., **14**-0028
Nelson, C.H., **19**-0470
Nelson, D.J., **12**-0488, **12**-0489, **15**-0089, **15**-0483, **15**-0653, **15**-1657, **15**-1982
Nelson, D.P., **03**-0108
Nelson, D.W., **15**-1696
Nelson, E.C., **16**-1269, **19**-0338
Nelson, E.D., **13**-0023
Nelson, G.C., **18**-0162
Nelson, G.L., **18**-0558
Nelson, J.A., **17**-0228
Nelson, J.D., **10**-0903
Nelson, J.V., **16**-0997, **16**-1013, **16**-1018, **18**-0601
Nelson, K.L., **11**-0051, **11**-0198
Nelson, N.T., **17**-0139
Nelson, P., **16**-1812
Nelson, P.G., **01**-0002
Nelson, R.B., **11**-0652
Nelson, S.F., **05**-0249, **05**-0326, **15**-1610, **15**-2063, **15**-2162
Nelson, S.G., **10**-1444, **16**-2075, **16**-2078, **19**-0968
Nelson, T.D., **13**-0469
Nelson, W.M., **15**-2165
Nelson-Reed, K.T., **12**-0279
Nemati, N., **16**-1174
Nemec, S., **13**-0272
Nemeth, L., **19**-0969
Nemo, T.E., **19**-0464
Nemoto, H., **10**-0234, **10**-1544, **16**-0782, **19**-0142, **19**-0541, **19**-1006, **19**-1058
Nemoto, T., **15**-1741, **15**-1796
Nendel, M., **15**-1994, **18**-0533
Nenitzescu, C.D., **11**-0408, **12**-0302, **15**-1648, **19**-0008, **19**-0627, **19**-0631
Neplyuev, V.M., **10**-1578, **12**-0194
Nepveux, F.J., **07**-0118
Neri, G., **19**-0960
Neri, O., **17**-0199
Neri, P., **03**-0123, **03**-0127, **03**-0128, **03**-0139, **04**-0066, **04**-0092, **04**-0162
Neri, S., **15**-1845
Neri, V., **15**-1751
Nerz-Stormes, M., **16**-1015, **16**-1023
Nesakumar, J.E., **18**-0137
Nesloney, C.L., **15**-0707
Nesmayanov, N.A., **16**-1301
Nesmeyanov, A.N., **02**-0166, **05**-0135, **10**-0243, **16**-1403
Nesterov, O.V., **16**-0190
Nestrick, T.J., **15**-0518
Net, G., **15**-1136
Neth, J.M., **04**-0342
Netherton, M.R., **13**-0350
Nething, M., **15**-0674
Netscher, T., **16**-2148
Neubauer, D., **15**-1378
Neuberg, M.K., **04**-0146, **15**-0597
Neuberger, K.R., **07**-0054
Neuenschwander, K., **19**-1468
Neuenschwander, M., **02**-0222

Neugebauer, F.A., **05**-0234, **05**-0321, **05**-0325
Neuman, P.N., **18**-0462
Neumann, A., **06**-0082
Neumann, B., **02**-0330, **05**-0174, **10**-1644
Neumann, C., **15**-2314
Neumann, F.W., **13**-0091
Neumann, G., **02**-0282
Neumann, H., **10**-0651, **12**-0619
Neumann, H.M., **16**-0523, **16**-0524, **16**-0525, **16**-0526, **16**-0963
Neumann, P., **02**-0061
Neumann, R., **11**-0482, **13**-0481, **15**-1739 **15**-1741, **15**-1756, **19**-0172, **19**-0181
Neumann, R.A., **16**-1299
Neumann, S., **04**-0151
Neumann, W.P., **05**-0236, **05**-0236, **05**-0237, **05**-0246, **16**-0967, **16**-2174, **19**-1307
Neumeister, J., **19**-0352
Neumeyer, J.L., **13**-0272
Neumüller, O., **14**-0235
Neunhoeffer, H., **16**-0329
Neunhoeffer, O., **13**-0165
Neurath, H., **16**-1816
Neureiter, N.P., **17**-0221, **17**-0346
Neuvonen, H., **16**-1557
Nevado, C., **15**-0818
Nevalainen, V., **16**-0983, **19**-1775, **19**-1776
Nevar, N.M., **10**-1670
Nevill, S.M., **05**-0308
Neville, A.G., **05**-0316
Nevitt, T.D., **15**-0005, **15**-0031
Newall, A.R., **10**-0638
Newbold, B.T., **19**-0294, **19**-0786, **19**-1278, **19**-1545, **19**-1632
Newcomb, M., **03**-0117, **04**-0164, **05**-0306, **05**-0307, **05**-0308, **05**-0310, **10**-0095, **10**-1686, **10**-1742, **14**-0038, **14**-0068, **14**-0070, **14**-0076, **14**-0078, **14**-0123, **15**-1221, **15**-1222, **15**-1283, **15**-1284, **18**-0075, **18**-0506, **18**-0613, **19**-1339
Newcomb, M.E., **12**-0594
Newcomb, R.C., **16**-1589
Newcombe, N.J., **15**-1680
Newham, J., **15**-0628
Newirth, T.L., **12**-0535
Newkirk, D.D., **14**-0121
Newkome, G.R., **16**-0309, **16**-2009
Newlands, S.F., **15**-0016
Newman Jr., R.C., **14**-0007
Newman, A., **16**-1021
Newman, C., **15**-0974, **15**-0986
Newman, D.A., **12**-0022
Newman, H., **15**-0170, **16**-0544
Newman, M.S., **04**-0068, **05**-0062, **05**-0075, **06**-0041, **10**-1794, **11**-0062, **12**-0682, **14**-0025, **16**-0320, **16**-0441, **16**-0445, **16**-1633, **16**-1937, **17**-0099, **18**-0031, **19**-0740
Newman, P.A., **09**-0027
Newman-Evans, R.H., **18**-0562
Newsom, I., **08**-0089, **08**-0186
Newton Jr., R.J., **15**-0491, **15**-0651
Newton, B.N., **10**-1482
Newton, C.G., **02**-0341, **19**-1129
Newton, J., **11**-0013
Newton, M.D., **02**-0216, **04**-0430
Newton, R.F., **07**-0044, **10**-0228
Newton, T.A., **15**-0098
Newton, T.W., **16**-1226
Ney, J.E., **19**-0285
Nezu, J., **19**-1542
Nečas, D., **12**-0689
Ng Lim, L.S., **18**-0338
Ng, C., **19**-0711, **19**-0712
Ng, J.S., **12**-0571
Ng, K.D., **13**-0310
Ng, K.M., **11**-0077
Ng, L., **15**-0086
Ng, L.-Y., **19**-0534
Ng, S.-S., **15**-1970
Ng, W.W., **15**-0093
Ngidi, E.L., **18**-0786
Ngo, D., **16**-1803
Ngo, H.L., **19**-1029
Ngoviwatchai, P., **14**-0037
Nguefack, C., **10**-1454, **19**-1050
Nguefack, J.-F., **10**-1780
Nguyen, H.N., **14**-0315
Nguyen, M.T., **18**-0306, **18**-0334, **18**-0593
Nguyen, N., **18**-0475
Nguyen, S.B.T., **15**-1908
Nguyen, S.L., **10**-1353, **10**-1546, **12**-0756, **13**-0505, **19**-0970, **19**-0972
Nguyen, T.V., **19**-1022
Ni, B., **18**-0809
Ni, J.X., **08**-0067
Ni, Z., **14**-0401, **19**-1580
Niat, M., **13**-0066
Nibbering, N.M.M., **16**-0027
Nibler, J.W., **15**-0488
Nicaise, O., **16**-0924
Nicaise, O.J.-C., **19**-1154
Nicasio, M.C., **12**-0366, **15**-2299, **19**-0548
Niccolai, G.P., **05**-0383, **19**-0042
Nice, L.E., **15**-1084
Nicholas, A.M. de P., **05**-0264
Nicholas, J.B., **05**-0095
Nicholas, K.M., **12**-0225, **15**-0330, **15**-0344, **19**-1362, **19**-1676
Nicholas, R.D., **18**-0018
Nicholls, B., **03**-0091, **19**-0597
Nicholls, D., **18**-0370
Nichols, M.A., **05**-0173, **08**-0213, **16**-0998
Nicholson, G., **04**-0175
Nicholson, L.W., **15**-0671
Nicholson, R.L., **10**-1640
Nickel, W., **04**-0517
Nickell, E.C., **19**-0368
Nickisch, K., **15**-0616, **15**-1058
Nickle, J.H., **19**-0249
Nicklow, R.A., **16**-0886
Nickon, A., **03**-0175, **05**-0126, **10**-0179, **10**-0189, **14**-0227, **15**-0135, **15**-2151, **17**-0280, **18**-0031, **18**-0088, **18**-0872, **18**-0873, **19**-1276, **19**-1519
Niclas, H., **10**-0408
Niclause, M., **19**-0701
Nicol, A.J., **13**-0782
Nicolaides, N., **19**-0250
Nicolaou, K.C., **10**-0743, **10**-1630, **15**-2067, **16**-0849, **16**-1651, **16**-1655, **17**-0297, **17**-0298, **19**-0624
Nicolas, E.C., **12**-0104
Nicolet, P., **03**-0015, **10**-0430, **10**-0430
Nicoletti, R., **10**-0901, **10**-0916
Nicolini, L., **13**-0504
Nicolopoulou, M., **14**-0033, **14**-0328
Nicoud, J.F., **04**-0155
Nidy, E.G., **10**-0742
Nie, J.J., **16**-1881
Nie, X., **19**-1032
Niederer, P., **13**-0704, **19**-1573
Niederhauser, A., **02**-0222
Niedermann, H., **15**-2047
Nieger, M., **02**-0299, **15**-1877
Nieh, M.T., **19**-1718
Nieh, T., **17**-0329
Niel, G., **16**-0697
Niele, F.G.M., **15**-1381
Nielsen, A., **05**-0255
Nielsen, A.T., **10**-1479, **11**-0132, **16**-0972, **17**-0113, **19**-0769, **19**-1532
Nielsen, J.K., **19**-1022

Nielsen, J.R., **04**-0283
Nielsen, K.E., **02**-0054
Nielsen, R.B., **15**-0708, **15**-0812
Nielsen, S.A., **03**-0105
Nielsen, S.F., **13**-0495
Niemczyk, M., **07**-0044
Niemeyer, H.M., **08**-0059, **08**-0069, **08**-0074
Nienhuis, D.M., **19**-0241
Nier, A.O., **04**-0253
Nierengarten, J.-F., **03**-0200, **03**-0207
Nierengarten, S.-F., **03**-0206
Nierlich, M., **03**-0139
Niess, R., **11**-0508
Niestroj, M., **16**-0967
Niethammer, K., **15**-2077
Nieuwenhuizen, W.F., **15**-0545
Nieuwenhuyzen, M., **18**-0672
Nifant'ev, E.Ye., **15**-1652
Nifant'ev, I.E., **13**-0377, **13**-0391
Nigam, A., **10**-1318, **19**-1339
Niggemann, M., **15**-1717
Nigh, W.G., **12**-0116, **14**-0301, **14**-0319, **14**-0371, **19**-0698
Nigmatullin, N.G., **16**-1463, **16**-1466
Nii, S., **10**-1196
Niimi, L., **16**-0380
Niimi, T., **15**-1961
Niimi, Y., **15**-1436
Niizuma, S., **16**-1277
Nikalje, M.D., **15**-1635, **19**-0752
Nikam, K., **10**-1161
Nikat, S.M., **19**-1442
Nikbaghat, K., **16**-0313
Nikeryasova, S.V., **11**-0496
Nikiforov, G.A., **02**-0411, **02**-0413
Nikishin, G.I., **04**-0360, **12**-0143, **12**-0677, **14**-0012, **14**-0162, **14**-0447, **16**-0153, **19**-0435, **19**-0606, **19**-1691
Nikitin, K.V., **13**-0601
Nikitin, V.I., **16**-1186
Nikitin, Yu.E., **16**-0398
Nikitina, T.V., **02**-0166
Nikje, M.M.A., **16**-0059
Niknam, K., **10**-0679, **10**-1161, **19**-0335
Nikoforov, A., **16**-0195
Nikolaev, V., **05**-0369
Nikolaev, V.A., **16**-2030
Nikolenko, L.N., **16**-0440
Nikolić, S., **02**-0106
Nikonova, L.A., **13**-0775
Nikoofar, K., **16**-1739
Nikrad, P.V., **19**-1212
Nikulicheva, T.I., **11**-0584
Nill, G., **04**-0170
Nilsson, A., **10**-0088, **11**-0010, **15**-0499, **16**-0289, **16**-0290
Nilsson, M., **02**-0379, **02**-0411, **10**-1353, **11**-0618, **13**-0256, **13**-0460
Nilsson, P., **07**-0117, **13**-0375, **13**-0392, **13**-0413
Nilsson, P.A., **15**-1244
Nimitz, J.S., **16**-1652, **16**-1655
Nimlos, M.R., **05**-0269
Nimmo, K., **10**-0534
Ninomiya, I., **07**-0041, **15**-1260, **15**-1275, **15**-2235, **16**-2083
Ninomiya, S., **10**-0350
Nir, M., **10**-0455
Nir, Z., **12**-0227, **18**-0824
Nisar, M., **17**-0327
Nisato, N., **13**-0462
Nishi, M., **10**-0992
Nishi, S., **14**-0442
Nishi, T., **10**-0252
Nishibayashi, Y., **10**-0793, **11**-0333, **15**-0808, **19**-1241
Nishibuchi, T., **10**-1503
Nishida, A., **14**-0175, **15**-0989, **16**-0902
Nishida, K., **15**-1837, **19**-0176
Nishida, M., **15**-2369, **15**-2428
Nishida, N., **15**-1292
Nishida, S., **04**-0422, **10**-1233, **15**-2193, **15**-2261, **19**-1725
Nishida, T., **15**-1831, **18**-0396
Nishida, Y., **07**-0058, **12**-0117, **19**-0518
Nishide, K., **10**-0798, **10**-0800, **19**-0161
Nishigaki, Y., **18**-0880
Nishiguchi, I., **11**-0542, **12**-0501, **15**-1336, **15**-1337, **15**-1921, **16**-1364, **19**-1678
Nishiguchi, T., **16**-1689, **19**-0109
Nishihama, S., **16**-1364
Nishihara, S., **16**-1759
Nishihara, Y., **10**-1781, **10**-1782, **12**-0287, **13**-0398, **13**-0449, **13**-0519, **14**-0323, **15**-0585, **15**-0589, **15**-0957
Nishii, S., **15**-1092
Nishii, Y., **12**-0318
Nishikata, T., **13**-0439, **15**-1126, **15**-1156
Nishikawa, S., **07**-0079
Nishikawa, T., **15**-0915, **15**-0942
Nishikawa, Y., **13**-0019
Nishiki, Y., **15**-0608
Nishikori, H., **15**-1829, **15**-1909, **16**-0183
Nishikubo, T., **10**-1171
Nishimae, S., **16**-0647
Nishimata, T., **15**-2363
Nishimori, N., **15**-0922, **15**-0923
Nishimoto, K., **10**-0273, **17**-0026
Nishimoto, M., **15**-0968
Nishimura, A., **16**-0933
Nishimura, J., **02**-0069, **05**-0092, **11**-0337, **15**-2341
Nishimura, K., **12**-0733, **12**-0749, **15**-1333
Nishimura, M., **15**-1904, **15**-1910
Nishimura, S., **15**-0530, **19**-1697
Nishimura, T., **12**-0132, **12**-0289, **13**-0139, **13**-0509, **16**-2025, **17**-0159, **19**-0120, **19**-0223, **19**-0719, **19**-1035
Nishina, H., **16**-0329
Nishinaga, A., **19**-0281
Nishinaga, T., **02**-0158
Nishino, A., **15**-0730
Nishino, F., **15**-0227
Nishino, H., **11**-0487, **15**-2154
Nishino, K., **16**-0382
Nishino, M., **16**-0620
Nishino, T., **10**-0828, **10**-1224, **13**-0040
Nishio, K., **16**-0755
Nishio, M., **15**-1561, **16**-0765, **18**-0352
Nishio, T., **10**-0779
Nishioka, K., **16**-0167
Nishioka, T., **09**-0078
Nishitani, K., **10**-1137, **16**-0687
Nishitani, S., **13**-0557, **15**-1400
Nishiuchi, M., **07**-0056
Nishiura, M., **15**-0804
Nishiwaki, N., **15**-1939, **16**-0920
Nishiwaki, Y., **12**-0210, **12**-0211
Nishiyama, H., **10**-0636, **15**-0730, **15**-0823, **15**-2300, **15**-2370, **16**-0640, **16**-0641
Nishiyama, K., **16**-0338, **19**-1408, **19**-1416
Nishiyama, T., **10**-0612, **10**-1230
Nishiyama, Y., **10**-0815, **10**-0828, **10**-0830, **10**-1224, **11**-0317, **13**-0040, **13**-0630, **15**-1561
Nishizawa, H., **10**-0581, **16**-1860

Nishizawa, K., **08**-0223
Nishizawa, M., **11**-0332, **15**-0829, **15**-1458, **15**-2371, **16**-1530
Nishizuka, A., **15**-1886
Nisimura, T., **13**-0667
Nitsche, R., **02**-0282, **02**-0284
Nitta, A., **15**-0612
Nitta, I., **10**-0074
Nitta, M., **15**-0321
Nittala, S.S., **15**-2153
Nitzschke, M., **16**-0204, **19**-1456
Niu, J., **02**-0347
Niu, Q.J., **16**-1908
Niu, Y., **07**-0046
Nivard, R.J.F., **16**-0214
Nivsarkar, M., **10**-0835
Niwa, H., **10**-1129, **15**-0608, **16**-0218, **19**-0400
Niwa, J., **01**-0033
Niwa, S., **16**-0493, **16**-1190
Niwa, Y., **16**-0871, **19**-1696
Niwayama, S., **16**-1544, **18**-0147, **18**-0461
Nixdorf, M., **04**-0437
Nixon, I.G., **02**-0078, **11**-0076
Niyazymbetov, M.E., **05**-0359
Nizar, M., **19**-0899
Niznik, G.E., **16**-2135, **17**-0481, **19**-1541
Njolito, E., **15**-0615
No, K., **03**-0123
Noack, K., **15**-0459
Noack, M., **15**-0323
Noall, W.I., **15**-1557
Noble, D.R., **11**-0158, **11**-0161
Nobre, S.M., **10**-1419, **13**-0481
Nobrega, J.A., **12**-0142
Nobutomo, M., **19**-1093
Nocanda, X.W., **16**-0805
Noda, K., **15**-1827, **15**-1909
Noda, T., **16**-1026
Nodari, N., **04**-0441
Node, M., **10**-0798, **10**-0800, **19**-0161, **19**-0176
Nodiff, E.H., **13**-0773
Noe, E.A., **04**-0391, **04**-0393, **04**-0423
Noe, M.C., **15**-1665, **15**-1696
Noels, A.F., **10**-0638, **15**-1643, **15**-1959
Nogami, G., **11**-0285
Nogami, H., **16**-1439
Nogami, T., **15**-2194
Nogi, T., **11**-0503, **11**-0504
Nógrádi, M., **04**-0001, **04**-0136, **04**-0146, **10**-1638, **10**-1686, **15**-0597, **16**-0489, **16**-1013, **19**-1014, **19**-1057
Noguchi, H., **18**-0147
Noguchi, S., **16**-0651
Noguchi, Y., **13**-0407, **16**-1653, **19**-0901
Nogue, D., **15**-2119
Nogueira, C.W., **15**-0944, **15**-1325
Noh, K., **15**-0820
Noheda, P., **15**-1361
Nohira, H., **18**-0143
Noirot, M.D., **12**-0742
Noji, S., **19**-0516, **19**-0569
Nojima, M., **10**-0220, **10**-1079, **10**-1086, **10**-1178, **10**-1313, **10**-1833, **15**-0168, **15**-1545, **15**-1623, **15**-1941, **16**-0450, **16**-1880, **16**-1883, **16**-2092, **18**-0754, **19**-0371, **19**-1339
Nokami, J., **15**-2337, **16**-0633, **16**-1004
Nokami, T., **10**-1278, **13**-0448
Nokkeo, S., **16**-2007
Nolan, G.S., **08**-0234
Nolan, S.P., **13**-0177, **13**-0192, **13**-0300, **13**-0341, **13**-0401, **13**-0480, **13**-0503, **13**-0509, **15**-0803, **16**-1682, **16**-1695
Nolen, R.L., **10**-1733, **10**-1741
Noll, K., **15**-0369, **18**-0472
Noller, H., **17**-0176
Noller, H., **17**-0314
Nolley Jr., J.P., **13**-0388, **13**-0417
Nolte, R.J.M., **16**-1776
Noltes, J.G., **03**-0083, **12**-0556, **18**-0329
Nome, F., **12**-0672, **16**-1863
Nomoto, M., **19**-1371
Nomoto, T., **02**-0301
Nomura, H., **10**-0273, **19**-0119, **19**-0245
Nomura, I., **16**-0069
Nomura, K., **19**-0066
Nomura, M., **15**-2372, **10**-1852, **10**-1854 **13**-0338, **13**-0362, **13**-0452, **13**-0453, **15**-1360, **19**-1371
Nomura, N., **10**-1446, **10**-1490, **15**-0762, **15**-0798
Nomura, R., **12**-0755, **16**-1727, **19**-1670
Nonhebel, D.C., **05**-0202, **14**-0001, **14**-0031, **14**-0066, **15**-0050, **15**-0052, **18**-0054
Nonogawa, M., **13**-0663
Nonoyama, N., **11**-0126, **11**-0301
Noorani, V.R., **19**-0965
Noordik, J.H., **02**-0254
Noori, G.F.M., **11**-0528
Norberto, F., **12**-0709
Norcross, R.D., **15**-2064, **16**-1018
Nordahl, Å., **15**-2039
Nordeen, C., **16**-1728
Nordlander, J.E., **10**-0159, **10**-0177, **10**-0279, **10**-0995, **15**-0022, **15**-0063, **18**-0018
Nordmann, G., **13**-0118
Noreen, A.L., **10**-0066
Norikate, Y., **10**-1260
Norin, T., **10**-1377
Norinder, U., **02**-0307, **02**-0326
Norisue, Y., **10**-0796
Norman, N.C., **01**-0009
Norman, O.L., **13**-0779
Norman, R.O.C., **05**-0208, **06**-0050, **10**-1320, **13**-0462, **14**-0153, **14**-0204, **15**-2050, **19**-0724
Norman, S.J., **16**-1511
Normant, H., **10**-0409, **10**-1656, **12**-0590, **12**-0620, **12**-0693, **15**-0467, **17**-0448, **19**-0478, **19**-0836
Normant, J., **10**-1297, **19**-1692
Normant, J.F., **06**-0016, **10**-0625, **10**-1245, **10**-1335, **10**-1339, **10**-1520, **10**-1525, **10**-1529, **10**-1530, **10**-1531, **10**-1543, **10**-1766, **12**-0499, **15**-0874, **15**-0888, **15**-0947, **15**-0949, **15**-0952, **15**-0954, **15**-0955, **15**-0959, **15**-1062, **15**-1092, **15**-1144, **16**-0389, **16**-0500, **18**-0231
Normark, J.R., **12**-0116
Normat, J.-F., **13**-0584
Norouzi, H., **10**-0821
Norrby, P.-O., **15**-1656, **15**-1696, **16**-0685
Norris, A.R., **13**-0003
Norris, D.J., **16**-1087
Norris, R.K., **05**-0313, **13**-0052
Norris, W.P., **19**-0769
Norsikian, S., **15**-0874, **15**-0888
Norsikian, S.L.M., **10**-1210
Nortey, S.O., **16**-1325
North, M., **12**-0337, **16**-1426, **16**-1436, **16**-1438, **16**-1444
Northrop, J.H., **18**-0121
Northrup, A.B., **16**-1036
Norton, H.M., **16**-1555
Norton, J.E., **15**-2057
Norton, J.R., **03**-0083, **10**-1251, **10**-1332, **10**-1841, **13**-0394, **14**-0443, **15**-0406, **15**-1477, **15**-1479, **15**-2292, **15**-2403, **18**-0835, **19**-1157
Norton, K.J., **04**-0313

Norton, S.H., **05**-0013
Nose, K., **16**-0871
Nose, M., **11**-0140
Nosek, J., **10**-1220
Noson, K., **19**-1045
Notario, R., **05**-0084
Nöth, H., **15**-0697
Noto, R., **15**-0224, **15**-0439, **15**-0439
Notz, W., **16**-0415, **16**-0917, **16**-1035, **16**-1036
Notzumoto, S., **18**-0730
Nour, A.R.O.A., **12**-0060
Noureldin, N.A., **19**-0099, **19**-0671, **19**-0851
Nourse, J.G., **04**-0129
Novak, I., **01**-0019
Novak, I., **05**-0252
Novak, M., **05**-0409
Novák, T., **15**-1001
Novák, Z., **13**-0537
Novi, M., **08**-0168, **17**-0056
Novikov, S.S., **05**-0327, **10**-1722, **12**-0699, **15**-1617, **15**-1987, **16**-2047, **19**-1185, **19**-1284
Novogrocki, G., **16**-0687
Novoselov, E.F., **18**-0325
Nowak, K., **13**-0677
Nowak, P., **12**-0423, **16**-1029
Nowicka-Scheibe, J., **03**-0013
Nowlan, V.J., **15**-0027
Nowotny, H., **04**-0173, **04**-0175
Nowrouzi, N., **10**-1807
Noyce, D.S., **04**-0323, **12**-0649, **15**-0025, **15**-0196, **15**-0219, **16**-1573, **17**-0415
Noyd, D.A., **10**-0089
Noyori, R., **04**-0149, **04**-0193, **10**-1221, **10**-1645, **12**-0265, **12**-0297, **15**-0596, **15**-0598, **15**-0607, **15**-1979, **15**-2198, **15**-2432, **16**-0161, **16**-0489, **16**-1013, **16**-1041, **16**-1125, **16**-1653, **17**-0208, **18**-0150, **18**-0368, **19**-0706, **19**-0816, **19**-1026, **19**-1027, **19**-1028, **19**-1048, **19**-1053, **19**-1322
Nozaki, H., **05**-0351, **10**-0811, **10**-1221, **10**-1257, **10**-1263, **10**-1341, **10**-1438, **10**-1709, **13**-0667, **15**-1118, **15**-1184, **16**-0148, **16**-0500, **16**-0508, **16**-0565, **16**-1066, **16**-1100, **16**-1235, **16**-1681, **17**-0343, **17**-0410, **18**-0737, **19**-0131, **19**-0133
Nozaki, K., **10**-1522, **11**-0498, **11**-0511, **15**-0611, **15**-1480, **15**-1492, **16**-0996, **19**-1038, **19**-1415
Nozawa, A., **16**-1759
Nozawa, K., **16**-1840, **19**-1021
Nozawa, S., **12**-0490, **15**-1189
Nozawa, Y., **02**-0304, **02**-0306
Noziri, M., **15**-0288
Nozoe, T., **02**-0162
Nsanzumuhire, C., **05**-0214
Nsenda, T., **11**-0512
Nshimyumkiza, P., **15**-2146
Nubbemeyer, U., **18**-0626
Nucciarelli, L., **19**-0732
Nüchter, M., **07**-0116
Nudelman, N.S., **12**-0532, **13**-0016, **13**-0618, **15**-0873, **16**-0843
Nuding, G., **14**-0415
Nugent, B.M., **15**-1278, **16**-0919
Nugent, S.T., **10**-1337
Nugent, W.A., **12**-0042, **15**-0577, **15**-0816, **15**-0820, **16**-0687, **19**-0308
Nugiel, D.A., **02**-0396, **02**-0397, **04**-0506
Nuhrich, A., **10**-0952
Nukada, T., **04**-272
Numata, T., **19**-1602, **19**-1778, **19**-1783, **19**-1785, **19**-1788
Nunami, K., **04**-0195
Nunes, J.J., **15**-2032
Nuñez, M.T., **19**-0408
Nuñez, O., **16**-0030
Núñez, A., **11**-0356
Nunn, M.I.T., **13**-0261
Nunn, M.J., **10**-1038
Nurgatin, V.V., **13**-0067
Nuridzhanyan, K.A., **10**-1034
Nurmi, T.T., **12**-0627, **15**-0877
Nurok, D., **04**-0169
Nury, P., **10**-1565
Nuss, J.M., **15**-2440
Nussim, M., **06**-0075, **16**-2085
Nutaitis, C.F., **15**-0499, **16**-0356, **16**-0374, **19**-0926, **19**-0935, **19**-1351, **19**-1351, **19**-1444
Nuteberg, D., **07**-0118
Nuzzo, R.G., **12**-0607
Nwaukwa, S., **18**-0343
Nwaukwa, S.O., **11**-0243, **19**-0674
Nyangulu, J.M., **15**-1602
Nyberg, A.I., **16**-1036
Nyberg, K., **14**-0270
Nyburg, S.C., **01**-0011, **15**-0093
Nyce, J.L., **17**-0014
Nye, M.J., **15**-2105, **18**-0204
Nyman, C.J., **14**-0444
Nyns, C., **17**-0358
Nystrom, R.F., **15**-0561

O'Brien, C., **11**-0113
O'Brien, D.F., **05**-0102
O'Brien, D.H., **05**-0130, **08**-0008, **10**-0374, **10**-0521
O'Brien, E.M., **16**-1986
O'Brien, J.L., **19**-0350, **19**-0351
O'Brien, M.J., **10**-1590
O'Brien, P., **08**-0208, **10**-1211, **17**-0218
O'Brien, S.C., **02**-0355
O'Connell, E., **18**-0397
O'Connor, B., **13**-0378, **19**-0708
O'Connor, C., **16**-1588, **16**-1596
O'Connor, C.J., **15**-1581, **16**-1600
O'Connor, G.L., **17**-0123
O'Connor, K.J., **15**-1909
O'Connor, S., **11**-0068, **13**-0653
O'Donnell, M.J., **13**-0581, **15**-2183, **15**-2184
O'Donoghue, A.C., **12**-0101
O'Donoghue, D.A., **18**-0307
O'Dowd, M.L., **12**-0398
O'Hagan, D., **03**-0011
O'Hara, R.K., **02**-0184
O'Leary, B., **02**-0008
O'Leary, D.J., **04**-0335
O'Leary, M.H., **16**-0018
O'Loane, J.K., **04**-0003
O'Mahony, C.P., **15**-1835
O'Mahony, D.J.R., **18**-0814
O'Meara, J.A., **10**-0706
O'Murchu, C., **19**-0358
O'Neal, H.E., **12**-0638, **17**-0122
O'Neal, H.R., **15**-2185, **15**-2216
O'Neil, I.A., **15**-1316, **17**-0482
O'Neill, J., **02**-0235
O'Neill, P., **02**-0397, **05**-0238, **10**-0492
O'Neill, T.H., **14**-0147
O'Shaughnessy, P., **15**-1905
O'Shaughnessy, P.N., **15**-0332
O'Shea, D.F., **10**-1514, **13**-0446
O'Shea, J.H., **19**-0830
O'Shea, K.E., **15**-2158
O'Shea, P.D., **13**-0742
O'Sullivan, B., **11**-0158, **11**-0161
O'Sullivan, M., **18**-0743, **18**-0744
O'Sullivan, M.B., **18**-0742
Oae, S., **05**-0119, **10**-0365, **10**-0372, **10**-0464, **10**-0771, **10**-1098, **12**-0639, **12**-0718, **13**-0082, **13**-0101, **13**-0113,

14-0355, **14**-0438, **15**-1892, **16**-0002, **16**-2142, **16**-2149, **17**-0065, **17**-0135, **18**-0261, **18**-0882, **18**-0884, **19**-0795, **19**-0834, **19**-0852, **19**-0871, **19**-1597, **19**-1598, **19**-1602, **19**-1604, **19**-1618, **19**-1620, **19**-1778, **19**-1783, **19**-1784, **19**-1785, **19**-1788, **19**-1791
Oakes, R.S., **09**-0107, **13**-0407, **15**-2036
Oakley, J.E., **10**-0379
Oare, D.A., **15**-1010, **15**-1013, **15**-1031, **15**-1032
Oba, M., **16**-0338, **19**-1408, **19**-1416
Obara, S., **15**-2065
Obara, Y., **10**-1825
Obayashi, R., **15**-1855
Obenius, U., **19**-1064, **19**-1065
Ober, M.H., **13**-0634
Oberender, H., **19**-0056
Oberhammer, H., **04**-0293, **04**-0371
Oberhauser, T., **11**-0232
Oberli, M.A., **18**-0578, **19**-0556
Oberlinner, A., **05**-0279, **14**-0006
Obeshchalova, N.V., **15**-0790
Obi, U., **07**-0079
Obika, S., **15**-0922, **15**-0923
Obraztsov, P.A., **15**-0183, **17**-0174
Obrecht, R., **17**-0480
Obushak, N.D., **13**-0731
Oçafrain, M., **10**-1818
Öcal, N., **16**-0066
Ocampo, R., **16**-0809
Occhiato, E.G., **10**-1414, **12**-0283, **16**-0687, **19**-1022
Occolowitz, J.L., **05**-0126
Ochal, Z., **10**-0892
Ochi, M., **19**-1392
Ochiai, H., **10**-1823, **16**-1903
Ochiai, K., **15**-1576
Ochiai, M., **04**-0334, **10**-0800, **10**-0846, **12**-0473, **15**-1850
Ochiai, O., **15**-1590
Ochiai, Yy., **19**-0142
Ochterski, J., **04**-0321
Oda, A., **15**-0872
Oda, J., **18**-0733
Oda, K., **15**-1837
Oda, M., **02**-0203, **10**-1227, **12**-0658, **13**-0462, **15**-0849, **15**-2322, **18**-0469, **18**-0470
Oda, N., **15**-1238
Oda, R., **11**-0518
Oda, T., **15**-0748, **19**-0516
Oda, Y., **19**-0570
Odaira, M., **11**-0493
Odaira, Y., **02**-0062, **02**-0064, **11**-0505
Odashima, K., **11**-0423, **15**-0604, **15**-0822, **15**-2367, **15**-2374
Ode, R.H., **19**-0661
Odedra, A., **15**-1783
Odell, K.J., **12**-0279
Odenkirk, W., **16**-1473
Oderaotoshi, Y., **15**-0390, **15**-1400, **15**-1904
Odinokov, V.N., **19**-0345
Odioso, R.C., **18**-0744
Odom, A.L., **15**-0352, **15**-0360
Oeckler, O., **02**-0340
Oediger, H., **17**-0303, **17**-0304, **17**-0305
Oehl, R., **11**-0469
Oehme, G., **15**-2422
Oelderik, J.M., **18**-0027
Oepen, G., **04**-0271
Oertle, K., **15**-0707, **16**-1652
Oesch, U., **04**-0163
Oeser, T., **04**-0427
Oestreich, M., **13**-0378, **15**-1323
Oestreich, T.M., **13**-0677
Offerhaus, R., **05**-0290
Offermann, K., **17**-0479
Offermanns, H., **19**-1792
Ofial, A.R., **10**-0009, **10**-0355, **10**-1673, **15**-0002
Ofori-Okai, G., **12**-0402
Ofstead, E.A., **18**-0756, **18**-0760, **18**-0824, **18**-0836
Ogasawara, K., **15**-1826, **16**-0251, **19**-0169, **19**-1382, **19**-1391, **19**-1489, **19**-1621
Ogasawara, M., **15**-0740, **15**-0932, **15**-1121, **15**-1130, **15**-1190, **15**-1871, **16**-1049
Ogata, I., **12**-0614
Ogata, Y., **11**-0306, **11**-0406, **11**-0485, **11**-0540, **11**-0551, **11**-0591, **11**-0622, **12**-0169, **12**-0170, **12**-0203, **12**-0714, **15**-1685, **15**-1733, **15**-1786, **16**-1445, **18**-0375, **19**-0010, **19**-0322, **19**-0780, **19**-1746, **19**-1767
Ogawa, A., **03**-0182, **10**-1826, **10**-1829, **13**-0615, **15**-0309, **15**-0312, **15**-1402, **15**-1855, **19**-1003, **19**-1302, **19**-1591, **19**-1650, **19**-1653, **19**-1695
Ogawa, C., **15**-1326, **16**-0914, **16**-0915
Ogawa, D., **16**-0458
Ogawa, H., **02**-0274, **02**-0295, **02**-0326, **10**-0627, **10**-0636, **10**-0902, **12**-0015, **12**-0547, **15**-0265
Ogawa, K., **04**-0455, **13**-0195, **19**-0255
Ogawa, M., **11**-0013, **14**-0402, **15**-1792, **19**-0139, **19**-1581
Ogawa, R., **15**-2384
Ogawa, S., **10**-0464, **13**-0082
Ogawa, T., **07**-0058, **10**-0790, **10**-1040, **13**-0256
Ogg Jr., R.A., **04**-0411
Ogi, K., **18**-0224
Ogibin, Y.N., **12**-0143
Ogibin, Yu.N., **19**-0435
Ogina, Y., **15**-1691
Ogino, H., **03**-0194
Ogino, T., **15**-1676, **15**-1679
Ogino, Y., **15**-1691
Ogiyama, H., **10**-1206
Ogle, C.A., **05**-0099, **05**-0151
Ogliaruso, M.A., **02**-0165, **16**-1648, **16**-1715, **17**-0423, **18**-0555
Ogo, T., **11**-0463
Ogoshi, H., **02**-0203
Ogoshi, S., **11**-0323, **15**-0802
Ogston, A.G., **04**-0253
Oguchi, T., **15**-1792
Oguchi, W., **16**-1104
Oguni, N., **04**-0193, **10**-1539, **10**-1797, **16**-0694
Ogura, H., **04**-0390, **16**-0436
Ogura, K., **03**-0193, **10**-1697, **10**-1698, **12**-0182, **12**-0695, **14**-0071, **15**-0056, **16**-1912, **19**-1606
Oguro, D., **16**-0828
Oguro, K., **12**-0534, **16**-1922
Oh, B.K., **10**-1549
Oh, C.H., **13**-0480, **13**-0569, **15**-0835, **15**-0837, **15**-0933, **15**-0934
Oh, C.R., **10**-0940
Oh, D.Y., **16**-0236
Oh, J.-H., **16**-1814
Oh, K.S., **13**-0506
Oh, L.M., **16**-0186
Oh, T., **15**-2042, **15**-2119
Oh, Y.J., **10**-0313
Oh, Y.S., **10**-0694
Ohanessian, G., **02**-0006, **02**-0041
Ohannesian, L., **11**-0263, **11**-0458, **12**-0156, **19**-1450
Ohara, M., **04**-0174
Ohara, S., **16**-1671, **16**-1801
Ohashi, A., **15**-0610
Ohashi, H., **10**-0815

Ohashi, Y., **10**-1630, **11**-0507, **15**-1420
Ohba, M., **14**-0071
Ohe, K., **13**-0328, **15**-0227, **15**-1159, **17**-0159, **19**-0120, **19**-0719, **19**-1745
Ohe, T., **13**-0328, **15**-1159
Óhegyi, G., **09**-0013
Ohfune, Y., **16**-0874
Ohga, T., **16**-0687, **19**-1032
Ohga,Y., **10**-0299
Ohhara, H., **17**-0343
Ohigashi, N., **15**-1061
Ohira, M., **10**-1328
Ohira, R., **15**-0319
Ohira, S., **05**-0351
Ohishi, H., **15**-1115
Ohishi, H., **15**-1115
Ohishi, M., **16**-1497
Ohishi, T., **13**-0314
Ohkata, K., **10**-0152, **16**-1228, **19**-1301
Ohkatsu, J., **14**-0006
Ohkawa, K., **10**-0513
Ohki, H., **16**-0645
Ohkoshi, N., **15**-0766
Ohkubo, H., **19**-0827
Ohkubo, K., **13**-0415
Ohkuma, T., **04**-0193, **19**-1027, **19**-1028
Ohlberg, D.A.A., **17**-0052
Ohlmeyer, M.J., **15**-0656, **15**-0697, **15**-0700
Ohloff, G., **14**-0228, **14**-0235, **15**-2156, **17**-0418, **18**-0551, **19**-0314
Ohlsson, L., **12**-0063
Ohme, R., **04**-0039
Ohmori, H., **15**-1236, **16**-1923, **19**-1089, **19**-1354
Ohmori, K., **19**-1274
Ohmura, T., **10**-1469
Ohnari, H., **19**-1301
Ohnesorge, M., **15**-2426
Ohno, A., **04**-0196, **11**-0189, **13**-0279, **15**-0625, **15**-2363, **16**-0002, **19**-1021, **19**-1022, **19**-1337
Ohno, H., **10**-0765, **10**-1801, **15**-0394, **15**-0779, **16**-1332
Ohno, K., **10**-0636, **14**-0443, **14**-0444, **14**-0450, **14**-0456, **17**-0327, **19**-1051
Ohno, M., **10**-1322, **16**-0686, **16**-1521, **18**-0147
Ohno, T., **15**-1336, **15**-1337
Ohno, Y., **16**-1282
Ohsaku, M., **07**-0022
Ohsawa, A., **16**-0364, **19**-1518
Ohsawa, K., **13**-0273
Ohsawa, T., **12**-0694, **19**-0279, **19**-1332, **19**-1542
Ohshima, M., **16**-0495, **19**-0056
Ohshima, T., **15**-1023, **15**-1741, **15**-1796, **16**-1044, **16**-1044
Ohshima, Y., **19**-0591
Ohshiro, Y., **10**-1214, **14**-0191, **15**-1464, **15**-1477, **19**-0591, **19**-1304
Ohshita, J., **10**-1126, **10**-1443, **14**-0284
Ohsugi, S.-i., **19**-0161, **19**-0176
Ohta, A., **13**-0128, **16**-0818
Ohta, C., **15**-1829, **19**-0823
Ohta, H., **10**-1509, **14**-0105, **14**-0281, **19**-1022
Ohta, K., **04**-0174
Ohta, M., **02**-0341, **02**-0421, **14**-0102, **15**-0238, **15**-1567, **17**-0407
Ohta, S., **16**-2015, **19**-1670
Ohta, T., **10**-0886, **10**-1453, **11**-0190, **15**-0598, **15**-0611, **15**-1492, **19**-1027, **19**-1093
Ohtaka, S., **19**-1651
Ohtake, H., **19**-0458
Ohtake, Y., **12**-0368
Ohtani, S., **15**-1254
Ohto, M., **19**-0065
Ohtsu, M., **15**-1892
Ohtsuka, Y., **15**-0569, **17**-0158, **19**-0923
Ohtsuki, N., **15**-2130
Ohwada, A., **11**-0196
Ohwada, T., **04**-0489, **11**-0477, **15**-0739
Ohya, S., **10**-1826, **19**-1302, **19**-1591
Ohya-Nishiguchi, H., **05**-0208
Ohyabu, Y., **11**-0412, **11**-0413
Ohyama, H., **16**-1004
Ohyama, T., **11**-0091
Ôi, S., **04**-0175, **15**-1158, **15**-1179, **15**-1179, **16**-0892
Oiarbide, M., **13**-0131, **15**-1310
Oida, T., **17**-0343
Oikawa, T., **15**-1146
Oisaki, K., **16**-0698
Oishi, A., **16**-2116
Oishi, M., **17**-0277
Oishi, T., **12**-0694, **15**-1697, **15**-1700, **16**-1332, **17**-0158, **19**-1057, **19**-1332, **19**-1542
Oishi, Y., **10**-0602
Ojanperä, I., **10**-0810
Ojha, N.D., **04**-0423
Ojima, I., **04**-0146, **15**-0428, **15**-0597, **15**-0705, **15**-0820, **15**-1138, **15**-1378, **15**-1491, **15**-1782, **15**-2391, **16**-1033, **19**-0847, **19**-0929
Ojima, J., **02**-0296, **02**-0303, **02**-0304, **02**-0306, **02**-0322, **02**-0328
Oka, K., **16**-1667
Oka, M., **06**-0040, **14**-0008, **18**-0182
Oka, M.-a., **15**-0802
Oka, S., **11**-0189, **13**-0279
Okabe, H., **07**-0043
Okabe, N., **10**-1849
Okabe, T., **15**-0993
Okachi, T., **15**-0982, **16**-0737
Okada, A., **10**-1460
Okada, H., **14**-0200
Okada, I., **10**-0906
Okada, K., **03**-0163, **11**-0390, **12**-0658, **14**-0244, **15**-0863
Okada, M., **10**-0828, **10**-1224, **14**-0442, **16**-1013, **16**-1127
Okada, S., **10**-0375, **11**-0267, **16**-1060, **16**-1272, **16**-2156, **19**-1677
Okahara, M., **03**-0146
Okai, K., **05**-0351
Okajima, M., **10**-1718
Okajima, S., **15**-0225
Okajima, T., **16**-2025
Okamoto, H., **10**-1871, **15**-0337
Okamoto, J., **16**-1923
Okamoto, K., **02**-0160, **02**-0199, **05**-0117, **05**-0201, **10**-0033, **10**-0060, **10**-0072, **10**-0073, **10**-0074, **10**-0084, **10**-0301, **10**-0309, **13**-0487, **15**-0420, **15**-2322, **18**-0469, **18**-0470
Okamoto, K., **18**-0643
Okamoto, M., **16**-2015
Okamoto, S., **15**-0768
Okamoto, T., **11**-0190, **11**-0244, **11**-0292, **12**-0120, **12**-0132, **12**-0144, **13**-0279, **13**-0776, **16**-1415, **16**-1826, **16**-1830, **19**-1089
Okamoto, Y., **02**-0070, **03**-0201, **04**-0087, **04**-0173, **04**-0175, **04**-0177, **09**-0020, **10**-1134, **18**-0904, **19**-1367, **19**-1679
Okamura, M.Y., **15**-2218
Okamura, W.H., **02**-0296
Okano, K., **13**-0202, **18**-0249, **18**-0585, **19**-1042
Okano, M., **04**-0459, **11**-0134, **11**-0406, **13**-0661, **15**-1536, **15**-1603, **15**-1711, **15**-1714, **15**-1716, **17**-0343, **19**-0471
Okano, N., **16**-1109

Okano, T., **10**-1849, **11**-0052, **15**-0611, **19**-0967
Okano, V., **16**-1445
Okarma, P.J., **04**-0519
Okauchi, T., **11**-0436
Okawa, M., **15**-0608
Okawara, M., **19**-0450, **19**-0732, **19**-1398
Okazaki, H., **15**-1118, **15**-1536
Okazaki, M., **02**-0326, **18**-0686
Okazaki, N., **11**-0569
Okazaki, R., **16**-0209, **16**-0218
Okazaki, T., **04**-0455, **05**-0084, **10**-0125, **11**-0022
Okazoe, T., **16**-0500, **16**-1365, **16**-1365
Okeda, T., **13**-0439
Okello, M., **09**-0114, **13**-0416
Okeyo, S., **11**-0257
Okhlobystin, O.Yu., **05**-0313, **11**-0101, **12**-0616, **16**-1607
Okimoto, M., **12**-0173, **16**-1459
Okino, T., **10**-1452, **15**-1004
Okovytyy, S., **17**-0206
Okraglik, R., **18**-0688
Oku, A., **12**-0386, **15**-0885, **16**-1116
Oku, K.-i., **10**-0676
Oku, M., **02**-0255, **12**-0068, **15**-1791
Okubo, H., **13**-0538
Okubo, K., **12**-0658, **13**-0415
Okubo, Y., **13**-0237
Okuda, F., **10**-0900, **13**-0281
Okuda, K., **13**-0782
Okuda, S., **15**-2389
Okuda, T., **15**-2116, **19**-0607
Okuhara, K., **16**-0540
Okukado, N., **10**-1378, **13**-0619
Okulova, V.F., **04**-0144
Okuma, K., **14**-0281
Okumoto, H., **14**-0359, **16**-0161, **16**-1759, **16**-2118, **17**-0161
Okumura, A., **11**-0569
Okuno, H., **18**-0228
Okura, I., **15**-0794
Okuro, K., **10**-1854, **15**-1460, **15**-1466
Okusako, Y., **10**-0154
Okuyama, K., **19**-0161, **19**-1670
Okuyama, S., **12**-0753
Okuyama, T., **05**-0065, **10**-0571, **10**-0575, **12**-0484, **15**-0107, **15**-1600
Okuyama, Y., **10**-1454
Okwuiwe, R., **16**-2143
Olagbemiro, T.O., **16**-1591
Olah, G.A., **02**-0156, **02**-0172, **02**-0206, **02**-0350, **03**-0083, **04**-0437, **05**-0002, **05**-0005, **05**-0007, **05**-0013, **05**-0014, **05**-0015, **05**-0016, **05**-0017, **05**-0018, **05**-0021, **05**-0022, **05**-0023, **05**-0024, **05**-0030, **05**-0031, **05**-0032, **05**-0034, **05**-0036, **05**-0037, **05**-0039, **05**-0040, **05**-0041, **05**-0047, **05**-0049, **05**-0052, **05**-0054, **05**-0056, **05**-0058, **05**-0060, **05**-0061, **05**-0063, **05**-0068, **05**-0075, **05**-0076, **05**-0077, **05**-0079, **05**-0083, **05**-0085, **05**-0087, **05**-0090, **05**-0091, **05**-0092, **05**-0093, **08**-0008, **08**-0015, **10**-0011, **10**-0041, **10**-0044, **10**-0115, **10**-0116, **10**-0117, **10**-0119, **10**-0129, **10**-0131, **10**-0139, **10**-0153, **10**-0165, **10**-0166, **10**-0167, **10**-0168, **10**-0172, **10**-0173, **10**-0181, **10**-0182, **10**-0187, **10**-0188, **10**-0191, **10**-0192, **10**-0197, **10**-0200, **10**-0205, **10**-0374, **10**-0380, **10**-0383, **10**-0391, **10**-0393, **10**-0394, **10**-0521, **10**-0528, **10**-0596, **10**-0649, **10**-1079, **10**-1080, **10**-1086, **10**-1089, **10**-1130, **10**-1132, **10**-1134, **10**-1147, **10**-1176, **10**-1178, **10**-1179, **10**-1180, **10**-1227, **11**-0003, **11**-0004, **11**-0013, **11**-0014, **11**-0015, **11**-0025, **11**-0026, **11**-0027, **11**-0029, **11**-0048, **11**-0063, **11**-0069, **11**-0091, **11**-0093, **11**-0099, **11**-0119, **11**-0133, **11**-0138, **11**-0149, **11**-0157, **11**-0177, **11**-0179, **11**-0198, **11**-0212, **11**-0214, **11**-0223, **11**-0224, **11**-0236, **11**-0263, **11**-0316, **11**-0319, **11**-0320, **11**-0337, **11**-0338, **11**-0346, **11**-0347, **11**-0352, **11**-0359, **11**-0361, **11**-0384, **11**-0406, **11**-0408, **11**-0416, **11**-0416, **11**-0420, **11**-0441, **11**-0446, **11**-0455, **11**-0458, **11**-0458, **11**-0460, **11**-0487, **11**-0490, **11**-0494, **11**-0523, **11**-0527, **11**-0529, **11**-0535, **11**-0546, **11**-0597, **11**-0604, **11**-0606, **11**-0636, **12**-0048, **12**-0050, **12**-0156, **12**-0203, **12**-0209, **12**-0302, **12**-0341, **12**-0342, **13**-0028, **13**-0096, **13**-0265, **14**-0169, **14**-0367, **15**-0008, **15**-0035, **15**-0072, **15**-0106, **15**-0168, **15**-0207, **15**-0253, **15**-0713, **15**-1545, **15**-1623, **15**-1628, **15**-1636, **15**-1648, **16**-0111, **16**-0116, **16**-0164, **16**-0185, **16**-0321, **16**-0450, **16**-0455, **16**-1294, **16**-1523, **16**-1880, **16**-1883, **16**-1884, **16**-1885, **16**-1950, **16**-2004, **16**-2043, **16**-2053, **17**-0169, **17**-0451, **18**-0007, **18**-0007, **18**-0009, **18**-0045, **18**-0048, **18**-0073, **18**-0104, **18**-0105, **18**-0108, **18**-0113, **18**-0117, **18**-0325, **18**-0378, **18**-0748, **19**-0008, **19**-0068, **19**-0643, **19**-0691, **19**-0773, **19**-0980, **19**-1443, **19**-1447, **19**-1450, **19**-1598, **19**-1605, **19**-1731, **19**-1753
Olah, G.S., **16**-1940
Olah, J.A., **05**-0013, **05**-0022, **05**-0030, **10**-0374, **10**-1086, **10**-1178, **11**-0069, **11**-0091, **11**-0494, **11**-0636, **12**-0341, **15**-0168, **15**-1545, **16**-1883, **18**-0007
Oldenziel, O.H., **16**-1199, **16**-1200, **19**-0405
Olefirowicz, E., **04**-0241
Olejnik, Z., **03**-0013
Olekhnovich, L.P., **02**-0378, **18**-0893
Olesker, A., **04**-0206
Oliva, A., **15**-2291, **16**-1032
Oliveira, G.R., **16**-0652, **16**-0871
Olivella, S., **15**-2090, **15**-2364
Oliver A.G., **15**-2065
Oliver, J.E., **16**-0527
Oliver, J.P., **05**-0145
Oliver, P.A., **15**-1733
Oliver, S.S., **10**-0147
Oliver, T.F., **14**-0261
Oliver, W.H., **15**-0083
Olivero, A., **15**-2439
Olivero, S., **15**-1236, **19**-1384
Olivi, N., **13**-0559
Olivier-Bourbigou, H., **08**-0113
Olivieri, A.C., **02**-0404
Olivo, H.F., **15**-1724
Olivucci, M., **15**-2105, **18**-0847
Öller, M., **17**-0256
Oller-López, J.L., **16**-0646
Ollevier, T., **10**-0925, **16**-0378, **16**-0918
Ollis, W.D., **02**-0341, **18**-0386, **18**-0389, **18**-0727, **18**-0729
Ollivier, C., **10**-0503, **15**-0664, **15**-1195, **15**-1235, **15**-1263, **15**-1264
Ollivier, J., **19**-1400, **12**-0426

Olmstead, H.D., **10**-1649, **10**-1652, **12**-0328, **12**-0420, **16**-0999
Olmstead, M.M., **02**-0364, **05**-0112, **13**-0579
Olmstead, W.N., **08**-0051, **10**-0336, **10**-0354
Olofson, R.A., **10**-1085, **10**-1187, **11**-0516, **16**-1303
Olofsson, B., **10**-0922
Olofsson, K., **07**-0117, **12**-0263, **12**-0264, **13**-0385
Olomucki, M., **10**-0991
Olsen, A.R.J., **10**-0003
Olsen, F.P., **08**-0127
Olsen, J.-C., **15**-2119
Olsen, R.K., **10**-1693, **16**-0233, **18**-0395
Olsen, R.S., **16**-1249
Olson, A.H., **18**-0110
Olson, J.M., **15**-0135
Olson, L.P., **18**-0589, **18**-0591
Olson, R.J., **11**-0235
Olsson, K., **10**-1703
Olsson, L., **10**-1529, **19**-1321
Olsson, L.F., **15**-0328
Olsson, R., **15**-2085
Olsson, T., **13**-0204
Olsson, T., **15**-1170
Olszowy, H.A., **04**-0340, **12**-0014
Oltay, E., **15**-1495
Oltra, J.E., **15**-1233, **16**-0646
Ölund, J., **19**-1332
Ölwegård, M., **17**-0050, **17**-0147
Omae, I., **03**-0083
Omar-Amrani, R., **13**-0200
Omata, T., **04**-0163
Omata, Y., **15**-1324
Omkaram, N., **04**-0142
Omori, H., **16**-0606
Omoto, K., **15**-1206, **15**-2049
Omoto, M., **19**-1338
Omura, H., **12**-0529, **13**-0619
Omura, K., **19**-0161, **19**-0165
Ona, H., **02**-0220
Onagi, H., **03**-0186
Onaka, M., **11**-0226, **15**-0982, **16**-0737
Onami, T., **12**-0224, **13**-0151, **17**-0293
Onan, K.D., **15**-1464
Ondruschka, B., **07**-0116
Ong, B.S., **15**-1803
Ong, H.H., **11**-0401
Oniciu, D.C., **02**-0092, **02**-0097
Onishi, H., **15**-0748
Onishi, T., **19**-0653
Onishi, Y., **10**-1093, **16**-0458, **19**-1359
Onistschenko, A., **10**-1563
Onitsuka, K., **10**-1469, **15**-1399, **15**-1407, **15**-1461, **15**-1469, **15**-1470
Onitsuka, S., **15**-2154
Ono, A., **19**-1212, **19**-1445
Ono, H., **15**-0993
Ono, M., **11**-0216
Ono, N., **10**-0785, **10**-1479, **10**-1484, **15**-2045, **17**-0069, **17**-0097, **17**-0113, **17**-0139, **19**-1530, **19**-1532, **19**-1536, **19**-1543
Ono, S., **18**-0363
Onoe, A., **15**-1536
Onomura, O., **05**-0250, **19**-1009, **19**-1144
Onopchenko, A., **19**-0422
Onoue, H., **14**-0275, **19**-0413
Onoue, T., **19**-0120, **19**-0719
Onozawa, S.-y., **15**-1359
Onsager, O., **10**-1221, **15**-0760, **15**-0793
Onuki, H., **15**-0158
Onuma, Y., **16**-0871, **16**-0873
Onyiriuka, S.O., **11**-0142
Ooi, T., **10**-0643, **10**-0713, **15**-0971, **15**-1001, **16**-1503, **16**-1691, **16**-1839, **18**-0143, **18**-0158, **19**-0155, **19**-1774
Ooka, H., **19**-1028
Ookawa, A., **10**-0984, **19**-1091
Oomkes, P.G., **16**-1202
Ooms, P.H.J., **16**-0214
Oono, K., **19**-0161
Oosterbeek, W., **09**-0064
Oosterhoff, L.J., **04**-0277, **15**-2105
Oosterwijk, R., **16**-1200
Oota, O., **16**-1167
Ootsuka, K., **16**-0183
Opalka, C.J., **16**-0423
Opgenorth, H., **14**-0357
Opitz, G., **15**-2190, **16**-1400, **16**-2109, **16**-2146, **16**-2147, **17**-0320
Oppenheimer, E., **14**-0448, **14**-0451
Ōki, M., **04**-0507, **03**-0045, **04**-0053, **04**-0057, **04**-0224, **04**-0227, **04**-0262, **04**-0264, **04**-0273, **04**-0324, **04**-0387, **04**-0458, **04**-0507, **04**-0509, **04**-0509, **06**-0056, **09**-0012, **09**-0012, **12**-0344
Ōkubo, M., **12**-0720, **16**-0530
Oppenlaender, T., **04**-0145
Oppenländer, T., **07**-0045, **07**-0054
Oppenländer, T., **18**-0463
Oppolzer, W., **04**-0136, **10**-1640, **10**-1641, **12**-0230, **12**-0577, **15**-0866, **15**-0961, **15**-0965, **15**-1957, **15**-1980, **15**-2002, **15**-2058, **15**-2063, **15**-2080, **15**-2241, **16**-1030, **16**-1378
Or, A., **15**-1536
Or, Y.S., **04**-0443
Orahovats, A., **17**-0015
Orban, J., **12**-0315
Orchin, M., **02**-0048, **07**-0010, **12**-0074, **15**-1494, **15**-2281, **19**-0020
Ordoñez, M., **18**-0232
Orena, M., **15**-1584, **19**-0090, **19**-0098
Orendt, A.M., **02**-0218
Orere, D.M., **16**-0093, **16**-1459
Orfanopoulos, M., **14**-0237, **14**-0238, **14**-0240, **14**-0241, **14**-0244, **16**-1485, **19**-1357, **19**-1450
Orfanos, V., **02**-0178
Orfanoupoulos, M., **19**-0234
Organ, M.G., **07**-0118, **10**-1448
Organopoulos, M., **15**-1767
Orioli, P., **16**-0976
Orita, A., **16**-1710
Oritani, T., **10**-0228, **18**-0301
Orito, K., **19**-0065
Orito, Y., **16**-1039
Oriyama, T., **19**-1327
Orizu, C., **16**-1426, **16**-1436
Orlando, V., **16**-1865
Orlinkov, A., **10**-1835, **14**-0139, **19**-0616
Orlova, G., **15**-2089
Orlović, M., **10**-0134
Ormiston, R.A., **02**-0090
Ornstein, P.L., **10**-0547
Orozco, M., **03**-0075, **03**-0076, **03**-0079
Orpen, A.G., **01**-0052, **01**-0070, **02**-0031, **04**-0239, **04**-0244, **04**-0249, **08**-0186
Orr, B.J., **04**-0280
Orr, G., **13**-0047
Orr, G.W., **03**-0059
Orsini, F., **15**-1758, **16**-0573
Orsini, M., **12**-0752, **16**-0757
Orsky, A.R., **08**-0151
Ortaggi, G., **19**-0056
Ortar, G., **10**-1848, **11**-0415, **13**-0608, **19**-1374
Ortega Schulte, C.M., **05**-0257
Ortega, F., **13**-0019, **16**-0016

Ortega, M., **19**-1706
Ortiz de Montellano, P.R., **14**-0082, **14**-0083, **18**-0058
Ortiz, M., **16**-0193
Ortiz, M.J., **18**-0570
Ortiz-Marciales, M., **17**-0428
Ortoleva, E., **02**-0319
Ortuño, R.M., **15**-2100, **15**-2244, **15**-2291
Orvedal, A.W., **02**-0246
Orville-Thomas, W.J., **03**-0037, **04**-0282
Orwig, B.A., **19**-0871
Orzech Jr., C.E., **18**-0021, **18**-0023
Osa, T., **19**-0689
Osakada, K., **15**-1181, **16**-0751, **19**-1479
Osaki, M., **15**-1055
Osako, K., **16**-1836
Osamura, Y., **13**-0050
Osanai, Y., **12**-0656
Osawa, E., **15**-0394, **18**-0114
Ōsawa, E., **04**-0275, **18**-0115
Osawa, S., **19**-1479
Osborn, C.L., **15**-2209
Osborn, J.A., **02**-0043, **15**-0407, **15**-0463, **15**-2202, **16**-1366, **16**-1367, **18**-0836, **19**-0120
Osborne, R., **10**-0533, **16**-1936
Osburn, P.L., **13**-0399
Osby, J.O., **10**-0988, **15**-0404, **15**-0571, **19**-1206
Oscarson, S., **10**-1123
Oshima, K., **10**-0846, **10**-1202, **10**-1257, **10**-1263, **10**-1393, **10**-1396, **10**-1398, **10**-1438, **10**-1498, **10**-1550, **10**-1625, **10**-1709, **12**-0224, **12**-0502, **13**-0317, **13**-0333, **13**-0429, **13**-0433, **13**-0438, **14**-0009, **15**-0305, **15**-0731, **15**-0737, **15**-0743, **15**-0863, **15**-0869, **15**-0915, **15**-0935, **15**-0942, **15**-0945, **15**-1206, **15**-1208, **15**-1252, **15**-1254, **15**-1265, **15**-1267, **15**-1645, **15**-1646, **15**-1858, **15**-1859, **15**-1876, **15**-2385, **15**-2427, **16**-0466, **16**-0500, **16**-0647, **16**-0669, **16**-0865, **16**-0992, **16**-0996, **16**-1235, **16**-1365, **19**-0127, **19**-0131, **19**-0133, **19**-0215, **19**-1415, **19**-1659, **19**-1666
Oshima, M., **19**-0899
Oshima, T., **15**-0159
Ōshima, T., **04**-0163
Oshisi, T., **11**-0341
Oshita, J., **10**-1418
Oshita, M., **12**-0543
Oshry, L., **12**-0651
Osipov, O.A., **08**-0149
Oskam, J.H., **18**-0768
Osman, M.A., **16**-1698
Osmialowski, B., **12**-0085
Osnabrug, S.J.M., **07**-0120
Osokin, Yu.G., **04**-0499
Osornio, Y.M., **15**-1244
Osowska-Pacewicka, K., **10**-0907, **15**-1879, **19**-0336, **19**-1275
Oßberger, M., **10**-1407
Ostapenko, A.G., **10**-1851
Ostercamp, D.L., **16**-0277
Østergaard, N., **15**-1667
Osterhout, M.H., **13**-0649, **19**-1149
Osterle, C., **04**-0118
Ostermann, G., **18**-0385, **18**-0387, **18**-0390, **18**-0396, **18**-0397
Ostermayer, F., **17**-0404
Ostrogovich, G., **16**-2071
Ostrovskii, V.A., **18**-0291, **18**-0305
Osuka, A., **13**-0135, **13**-0575, **19**-1534, **19**-1598, **19**-1744
Osuna, A.M.B., **15**-1488
Oswald, A.A., **15**-0110, **15**-0297, **19**-0779
Oswald, J., **12**-0611
Oswald, M.C., **16**-0160, **16**-0172, **18**-0140
Oswald, M.F., **16**-1407
Ota, K., **11**-0502
Ota, M., **19**-0823
Otake, H., **15**-1324
Otani, N., **17**-0487
Otani, S., **13**-0019, **16**-1826, **16**-1830
Otera, J., **10**-0714, **10**-0734, **10**-0811, **15**-1118, **16**-0148, **16**-1066, **16**-1100, **16**-1415, **16**-1677, **16**-1681, **16**-1710, **18**-0737, **19**-0653
Oth, J.F.M., **02**-0173, **02**-0274, **02**-0291, **02**-0291, **02**-0294, **02**-0298, **02**-0314, **02**-0315, **02**-0319, **02**-0324, **02**-0327, **04**-0440, **15**-2259, **15**-2359, **18**-0495, **18**-0634, **18**-0635, **18**-0637
Otimoto, K., **16**-0669
Otonnaa, D., **15**-1677
Otroshchenko, O.S., **13**-0455
Otsubo, K., **19**-0900
Otsubo, T., **02**-0295, **03**-0130
Otsuji, Y., **05**-0289, **10**-1503, **10**-1820
Otsuka, H., **03**-0126, **10**-1227, **13**-0462
Otsuka, M., **16**-1521
Otsuka, S., **04**-0136, **12**-0074
Ott, J., **16**-0147
Ott, K.C., **18**-0836
Ott, K.H., **18**-0614
Ott, W., **18**-0628
Ottaway, C., **08**-0084
Ottenbrite, R.M., **15**-2005, **15**-2044, **17**-0133
Ottenheym, J.H., **08**-0024
Ottenwaelder, X., **19**-0120
Otterbach, A., **04**-0444
Otteson, D., **15**-2103
Otto, C., **15**-2029
Otto, P., **15**-2185, **15**-2216, **15**-2225
Otto, S., **15**-2008, **15**-2029, **15**-2030, **19**-0653
Ottolina, G., **15**-1758, **19**-0824
Ottoni, O., **11**-0437, **11**-0438
Ottosson, H., **02**-0185, **10**-0061
Otvos, J.W., **15**-0449
Ou, W., **16**-0312
Ou, X., **18**-0317
Ou, Y., **10**-1549
Ouchi, A., **10**-1229
Oudenes, J., **10**-1645, **16**-0996
Ouellette, R.J., **10**-0171
Ouimet, N., **12**-0348
Ouk, S., **10**-0587
Oulevey, G., **11**-0450
Oullet, S.G., **10**-1555
Oullette, R.J., **15**-0186
Ounsworth, J.P., **04**-0387, **04**-0390
Ourévitch, M., **16**-0901
Ourisson, G., **10**-0208, **12**-0454, **18**-0085
Oussaid, A., **10**-1092, **19**-0564
Outram, J.R., **12**-0706
Outram, R.J., **15**-0311
Outurquin, F., **15**-0323
Ouvry, G., **15**-1209
Ovaska, T.V., **15**-0879, **15**-0883, **18**-0599, **19**-1485
Ovcharenko, I.V., **05**-0262
Ovcharenko, V.I., **05**-0254, **05**-0262
Øverås, A.T., **04**-0392
Overberger, C.G., **15**-2338, **18**-0582
Overchuk, N.A., **11**-0069, **11**-0604
Overman, J.D., **19**-1638
Overman, L.E., **10**-1649, **13**-0378, **15**-2044, **15**-2061, **18**-0618, **18**-0688, **18**-0689, **19**-1638, **18**-0690

Overton, K., **19**-0283
Overton, K.H., **10**-0228, **12**-0034
Owa, T., **11**-0436
Owaki, M., **19**-0690
Owczarczyk, Z., **13**-0674
Owen, N.L., **04**-0295
Owen, W.S., **10**-1676
Owens, G.S., **15**-1754
Owens, K.A., **18**-0630
Owens, P.H., **08**-0059
Owens, P.J., **14**-0409, **19**-1593
Owens, T.D., **15**-2065, **16**-0895
Owens, W.H., **19**-1118
Owsley, D.C., **19**-1728, **19**-1739
Owton, M.W., **15**-1917
Owton, W.M., **15**-1851
Owtschinnikow, J.A., **03**-203
Owuor, P.O., **15**-0063
Oxgaard, J., **15**-2013, **15**-2300
Oxley, P.W., **19**-1225
Oya, S., **16**-2119
Oyama, M., **15**-0922
Oyama, T., **12**-0452
Oyamada, H., **16**-1083, **19**-1091
Oyamada, J., **11**-0331
Oyola, Y., **15**-0667
Ozaki, F., **10**-0704
Ozaki, N., **15**-1064
Ozaki, S., **15**-1236, **16**-1756
Ozaki, S.-i., **19**-0825
Ozaki, Y., **05**-0371, **05**-0380
Ozanne, N., **16**-1244
Ozarde, P.S., **19**-1186
Ozasa, N., **16**-1094, **16**-1121
Ozawa, F., **10**-1123, **10**-1306, **10**-1868, **10**-1869, **10**-1871, **12**-0278, **12**-0319, **12**-0693, **13**-0177, **15**-0337
Ozawa, K., **11**-0517
Ozawa, M., **10**-1206, **15**-0354
Ozawa, S., **14**-0201
Ozawa, T., **15**-0115
Ozawa, Y., **11**-0607
Ozbalik, N., **14**-0387, **19**-0612, **19**-0613, **19**-0614
Özdemir, I., **15**-0813
Özdemïrhan, D., **19**-0493
Ozeki, N., **10**-0882
Ozier, I., **01**-0039
Özkan, I., **18**-0624
Ozkan, I., **15**-2200
Ozorio, A.A., **10**-1668
Ozretich, T.M., **15**-2218

Paatz, R., **10**-1835
Pabon, H.J.J., **10**-1614
Pac, C., **15**-2252
Pacansky, J., **02**-0213, **13**-0047, **16**-2108
Pace, A., **15**-1729
Pace, E.D., **19**-1254
Pachamuthu, K., **16**-1617
Pachón, L.D., **10**-0925
Pacifici, J.G., **18**-0203
Pack, S.K., **15**-0347
Packer, J., **08**-0030
Packer, J.E., **13**-0713
Paczkowski, M.A., **07**-0039
Padakanti, S., **11**-0438
Paddon-Row, M.N., **05**-0273, **16**-1022, **19**-0078
Padegimas, S.J., **11**-0191
Padias, A.B., **15**-2100
Padiya, K.J., **19**-1323
Padmaja, A., **16**-0052
Padmakumar, R., **15**-1027, **15**-1916, **16**-0775, **19**-0928
Padmanabhan, S., **19**-1598
Padmapriya, A.A., **16**-2159
Padmavathi, V., **16**-0052
Padmukumar, R., **11**-0426
Padwa, A., **02**-0086, **12**-0349, **13**-0233, **15**-1932, **15**-1951, **15**-1957, **15**-1965, **15**-1978, **15**-2000, **15**-2209, **18**-0574, **18**-0630
Padwa, A., **19**-1777
Pae, A.N., **10**-1516, **10**-1549, **16**-0605
Paetzold, J., **13**-0454, **15**-0278
Paetzold, P.I., **18**-0420
Pagani, G., **02**-0143
Pagani, G.A., **05**-0115
Pagano, A.S., **15**-1727
Pagano, S., **18**-0821
Page, I.D., **10**-0402
Page, M.A., **18**-0808
Page, M.I., **10**-0104, **11**-0164, **16**-0034
Page, P.C.B., **03**-0137, **10**-1693, **15**-1092, **15**-1782, **16**-0493, **16**-1413
Pagenkopf, B.L., **10**-1547, **15**-0604, **15**-1426, **15**-1444
Paget, W.E., **12**-0489
Pagington, J.S., **03**-0177
Pagni, R.M., **05**-0002, **08**-014, **10**-0807, **11**-0298, **13**-0489, **13**-0495, **13**-0545, **13**-0567, **14**-0309, **15**-1550, **15**-2040, **16**-0130, **16**-1876
Pagnoni, U.M., **12**-0114, **12**-0115, **12**-0119, **12**-0123, **12**-0152, **15**-1527, **15**-1602
Pai, C.-C., **15**-1480
Pai, C.K., **15**-2034
Pai, F., **19**-1056
Pai, G.G., **15**-0684
Paiaro, G., **04**-0084, **04**-0085
Paige, J.N., **17**-0227
Paik, C.H., **10**-0060, **19**-1569
Paik, S.-J., **15**-1993
Paike, N., **05**-0384
Pain, G.N., **12**-0659
Paine, A.J., **13**-0216, **13**-0269, **17**-0500
Painter, M.K., **19**-0378
Paisley, S.D., **10**-1437
Paixão, M.W., **16**-0687
Paju, A., **19**-0476
Pak, C.S., **17**-0528
Paknikar, S.K., **10**-0494
Pakrashi, S.C., **19**-1487
Pakulski, Z., **04**-0119
Pakusch, J., **18**-0403
Pal, B., **19**-1431
Pal, M., **10**-1780, **11**-0438, **13**-0387
Pal, R., **16**-1527
Pal, R.R., **15**-1016, **15**-1016
Pal, S., **15**-1783, **18**-0212
Palacios, F., **16**-0304
Palacios, J.C., **04**-0004, **08**-0118, **15**-2004, **15**-2097
Palacios, S.M., **07**-0096, **10**-0090, **13**-0052, **13**-0062, **13**-0065
Palani, N., **13**-0750
Palani, N., **18**-0565
Palano, D., **16**-1705
Palazzi, C., **18**-0361, **18**-0363
Palcios, J.C., **04**-0300, **04**-0303
Pale, P., **12**-0293, **15**-0247
Pale-Grosdemange, C., **16**-1806
Palenik, G.J., **13**-0010
Paleo, M.R., **05**-0186, **16**-0687
Palermo, R.E., **15**-1661, **15**-1858
Paleta, O., **10**-1046, **15**-1644
Paley, B.A., **12**-0481
Paley, R.S., **10**-1246
Palit, S.K., **10**-0490
Palit, S.R., **03**-0054
Palke, W.E., **01**-0006
Palkowitz, A.D., **16**-0706
Pallan, P.S., **10**-1068
Palm, D., **06**-0059
Palm, V.A., **10**-0443
Palma, P., **17**-0425
Palmer, B.W., **18**-0374
Palmer, D.A., **17**-0072
Palmer, G.J., **18**-0490
Palmer, H.B., **01**-0092
Palmer, J.D., **18**-0034
Palmer, K.W., **04**-0062
Palmer, M.H., **15**-0271
Palmer, M.J., **16**-1383
Palmere, R.M., **18**-0337

Palmieri, A., **16**-0327, **16**-0615, **16**-0808
Palmieri, G., **15**-1199
Palmieri, P., **18**-0073
Palombi, L., **10**-0716, **12**-0752
Palomero, M.A., **15**-2418
Palomo, C., **10**-1141, **13**-0131, **15**-1310, **16**-0339, **16**-0372, **16**-0598, **16**-0810, **16**-1664, **19**-0908
Palovich, M.R., **16**-0609
Palrisi, M.F., **04**-0092
Paluchowska, M.H., **16**-1871
Palucki, M., **19**-0823
Palumbo, G., **10**-1151, **16**-0147, **17**-0199
Palumbo, P.S., **17**-0350
Palumbo, R., **04**-0085
Pàmies, O., **15**-1136, **15**-1491
Pamment, M.G., **19**-0538
Pan, H.-Q., **15**-1212
Pan, J.-F., **16**-0788
Pan, L., **14**-0002
Pan, S.-F., **15**-0508, **15**-0566
Pan, W.-B., **15**-0481, **16**-1671
Pan, X., **10**-0979, **13**-0413, **16**-0687, **19**-1206
Pan, X.-W., **19**-1226
Pan, Y., **10**-0178, **13**-0558, **15**-0578, **19**-0059, **19**-0823, **19**-1028
Panarina, A.E., **15**-1315
Panaye, A., **09**-0074
Panda, A.K., **19**-0813
Panda, G., **02**-0360
Panda, M., **15**-0198
Pandell, A.J., **19**-0467
Pandey, B., **15**-2018
Pandey, G., **10**-0959, **10**-0961, **10**-1216, **15**-1217
Pandey, M.K., **10**-0961
Pandey, R.K., **15**-0298
Pandey, S.K., **16**-0233
Pandhi, S.B., **16**-2101
Pandiarajan, K., **10**-0740
Pandiarajan, P.K., **16**-0997
Pandiaraju, S., **16**-1158
Pandit, A.B., **17**-0477
Pandit, U.K., **15**-2017, **16**-0034
Pandya, S.U., **16**-0907, **16**-0928
Panek, E.J., **14**-0377
Panek, J.S., **10**-0564, **12**-0273, **16**-1414
Panethy, P., **17**-0045
Pang, M.-L., **16**-0170
Panicker, S.B., **15**-1532, **19**-0730
Panigrahi, A.K., **19**-0652
Panja, C., **10**-1587, **11**-0157
Pankayatselvan, R., **10**-1182
Pánkova, M., **17**-0015, **17**-0024, **17**-0026, **17**-0031, **17**-0096, **17**-0260
Pankratov, V.A., **16**-2066
Pankratova, K.G., **18**-0028
Pannala, M., **15**-0584
Pannecoucke, X., **15**-0323, **16**-1280
Pannell, D.K., **05**-0196
Panov, V.B., **11**-0101
Panova, Y.B., **18**-0011
Pansare, S.V., **10**-0633
Panshin, S.Y., **04**-0462
Panteleeva, I.Yu., **16**-0449
Panunzi, A., **04**-0085
Panunzi, B., **11**-0285, **15**-1569
Panunzio, M., **15**-2174
Panyachotipun, C., **10**-0187
Panzeri, A., **10**-1179
Paolucci, C., **04**-0470, **18**-0727, **16**-1459, **19**-1131
Papa, I., **10**-0084
Papa, P., **12**-0751
Papa, R., **10**-0171
Papadopoulos, M., **15**-2098, **16**-1482
Papageorgiou, G., **16**-0407
Papahatjis, D., **19**-1021
Papaioannou, C.G., **06**-0076
Papay, J.J., **10**-0136
Pape, M., **12**-0201
Pape, P.G., **19**-1319
Papeo, G., **10**-0707
Papoula, M.T.B., **13**-0581
Pappalardo, J.A., **10**-0852, **16**-0348, **16**-1949
Pappalardo, S., **03**-0139, **04**-0092
Pappas, B.C., **15**-2240
Pappas, J.J., **19**-0349
Pappas, R.S., **05**-0326
Pappas, S.P., **15**-2240, **18**-0494
Pappo, R., **15**-0992, **19**-0399
Paquer, D., **16**-0846, **16**-1398
Paquet, V., **16**-1372, **16**-1373
Paquette, L.A., **02**-0172, **02**-0173, **02**-0239, **02**-0241, **02**-0255, **02**-0349, **02**-0350, **02**-0352, **04**-0086, **04**-0088, **04**-0189, **04**-0193, **04**-0325, **04**-0442, **05**-0085, **10**-0152, **10**-0225, **10**-0269, **10**-1513, **12**-0188, **12**-0348, **12**-0665, **12**-0683, **12**-0684, **14**-0244, **15**-1997, **15**-1998, **15**-2052, **15**-2058, **15**-2078, **15**-2115, **15**-2116, **15**-2158, **15**-2232, **16**-0493, **16**-0591, **16**-2177, **17**-0344, **17**-0346, **17**-0518, **18**-0098, **18**-0128, **18**-0598, **18**-0599, **18**-0601, **18**-0606, **18**-0621, **18**-0634, **18**-0636, **18**-0638, **18**-0806, **18**-0837, **18**-0840, **18**-0842, **18**-0844, **18**-0845, **18**-0852, **18**-0855, **19**-0068, **19**-0343
Parac-Vogt, T.N., **11**-0121
Paradisi, C., **10**-0063
Paradkar, V.M., **10**-0993
Parady, T.E., **17**-0344
Paras, N.A., **11**-0353, **15**-1008
Paraskar, A.S., **19**-0752
Paraskewas, S., **16**-0132
Parcell, R.F., **18**-0259
Parchment, O.G., **02**-0418
Pardini, V.L., **19**-0862
Pardo, C., **10**-1049, **16**-0729
Pardo, D.G., **13**-0323, **13**-0586
Pardo, L., **19**-1022
Pardo, S.N., **11**-0389
Paré, J.R.J., **15**-2022
Paré, P.W., **16**-0782, **16**-0798, **16**-1001, **19**-0563
Parekh, S.I., **19**-1404
Parello, J., **18**-0156
Parfenova, M.N., **10**-0470
Parham, W.E., **12**-0354, **12**-0615, **15**-2263, **18**-0509
Parihar, J.A., **11**-0120
Parikh, J.R., **19**-0164
Parimala, G., **10**-0958
Parini, V.P., **03**-0093
Paris, J., **17**-0367
Parisel, O., **05**-0178
Pariser, R., **02**-0009
Parish, E.J., **15**-0665
Parish, S., **15**-0665
Parisi, L.M., **13**-0149
Parisi, M.F., **03**-0139
Park, B., **10**-0101
Park, C., **19**-0459
Park, C.-H., **13**-0309
Park, C.C., **19**-0120
Park, C.H., **03**-0147, **04**-0242, **04**-0246, **14**-0212
Park, C.M., **15**-0235, **15**-0262
Park, C.Y., **15**-1698
Park, D.J., **16**-1784
Park, E.J., **10**-1584
Park, E.S., **16**-0352
Park, G.-J., **03**-0185
Park, H., **15**-0762, **15**-0798, **18**-0274
Park, H.-g., **10**-1657, **15**-1302
Park, H.-J., **19**-0555, **19**-1042, **19**-1044
Park, H.G., **18**-0274
Park, H.S., **16**-0192, **16**-0823, **17**-0394, **19**-1165
Park, J., **02**-0403

Park, J., **15**-1079
Park, J.-N., **13**-0234
Park, J.-S., **12**-0295, **16**-1743
Park, J.C., **16**-0710
Park, J.H., **10**-1143, **15**-1411, **19**-0992
Park, J.K., **15**-1436
Park, J.Y., **10**-1083, **12**-0122, **19**-0555
Park, K., **10**-1489
Park, K.-M., **03**-0185
Park, K.H., **15**-1423, **16**-1751, **18**-0746, **18**-0749
Park, K.P., **10**-0245
Park, L., **19**-1326
Park, L.Y., **18**-0768
Park, M., **18**-0274
Park, M.-k., **10**-1657
Park, M.Y., **17**-0394
Park, O.-S., **11**-0269, **15**-1436
Park, R., **16**-0872
Park, S., **18**-0789, **19**-1339
Park, S.-D., **16**-1814
Park, S.-T., **10**-0551
Park, S.-U., **14**-0078
Park, S.B., **13**-0292, **13**-0368, **13**-0557
Park, S.J., **15**-0837, **15**-0934
Park, S.W., **15**-1834
Park, S.Z., **12**-0220
Park, W., **10**-0618, **16**-2025
Park, W.S., **10**-0089, **10**-0772, **19**-1016
Park, Y., **04**-0175
Park, Y.-S., **15**-1596
Park, Y.C., **15**-1371
Park, Y.J., **12**-0200, **15**-0494, **16**-1582
Park, Y.S., **10**-1281, **16**-0845
Párkányi, C., **02**-0004
Parker, A.J., **08**-0232, **08**-0240, **10**-0332, **10**-0338, **10**-0415, **10**-0693, **13**-0069, **17**-0068, **17**-0070, **17**-0072, **17**-0077, **17**-0097, **17**-0098
Parker, D., **03**-0119, **04**-0104, **04**-020, **15**-0401, **19**-0956
Parker, D.A., **10**-1353
Parker, D.G., **15**-0525, **18**-0378
Parker, J.K., **04**-0168, **04**-0287
Parker, K.A., **13**-0098
Parker, R.C., **07**-0080
Parker, R.E., **10**-0495, **13**-0086
Parker, R.J., **03**-0028
Parker, S.R., **11**-0488
Parker, V.D., **05**-0318, **06**-0033, **18**-0711
Parker, W.L., **15**-2419
Parks, C.R., **19**-0369
Parlanti, L., **19**-0204, **19**-1770
Parlato, S., **04**-0162
Parlman, R.M., **10**-1816, **19**-1529
Parmee, E.R., **13**-0193
Parmerter, S.M., **12**-0191
Parnes, Z.N., **02**-0156, **10**-1382, **15**-0401, **15**-0471, **15**-0514, **15**-0717, **16**-0182, **16**-0743, **19**-1303, **19**-1360, **19**-1450, **19**-1454
Parola, A., **07**-0032, **19**-1688
Parquette, J.R., **19**-0053
Parr, J., **15**-0431
Parr, J.E., **10**-1713
Parr, R.G., **02**-0009, **02**-0095, **02**-0110, **08**-0148, **08**-0155, **10**-0029, **10**-0032, **11**-0086
Parra-Hake, M., **16**-1438
Parrain, J.-L., **10**-1617, **12**-0272, **12**-0297, **15**-0766
Parratt, M.J., **04**-0030
Parrilli, M., **15**-1685
Parrinello, M., **18**-0316
Parrini, M., **16**-1156
Parris, G., **05**-0158, **05**-0167, **05**-0169
Parris, S., **13**-0229
Parrish, C.A., **13**-0123, **13**-0185
Parrish, D.A., **18**-0487
Parrish, D.R., **15**-1048, **16**-1072
Parrish, J.D., **16**-0821
Parrish, J.P., **13**-0449, **13**-0477
Parrot-Lopez, H., **03**-0125
Parrott, M.J., **14**-0001, **14**-0010, **14**-0012
Parrott, S.J., **16**-1486
Parry III, F.H., **15**-2213
Parry, K.A.W., **18**-0169
Pars, H.G., **12**-0706
Parshall, G.W., **11**-0116, **15**-1381, **16**-1348
Parson, A.F., **12**-0123
Parsonage, N.G., **03**-0105
Parsons Jr., G.H., **07**-0032, **19**-1688
Parsons, A.F., **10**-1225, **15**-1243, **15**-1244, **15**-1254, **15**-1929, **19**-1628
Parsons, J.A., **15**-0485
Parsons, J.L., **15**-0409, **15**-0574
Parsons, M., **11**-0314
Parsons, P.J., **18**-0670
Parsons, T., **16**-1438
Parsy, C.C., **15**-1771
Partch, R., **14**-0206
Partington, S.M., **12**-0663
Paruch, E., **10**-1538
Parvez, M., **04**-0161, **15**-0240
Pârvulescu, L., **15**-2210
Paryzek, Z., **19**-0371
Parziale, P.A., **18**-0551
Pascal, R., **16**-0123
Pascal, R.A., **06**-0066
Pascal Jr., R.A., **02**-0071, **02**-0073, **02**-0074, **02**-0101, **02**-0126
Pascali, V., **16**-0504
Pascali, V., **16**-0505
Pascard, C., **03**-0207, **04**-0244
Paschal, J.W., **16**-1323
Paschalis, P., **15**-0198
Paschmann, V., **18**-0631
Pascoe, J.D., **18**-0899
Pascone, J.M., **10**-0281
Pascual-Teresa, B., **15**-2099
Pasha, M.A., **10**-1528, **15**-1560, **16**-0307
Pashinnik, V.E., **16**-1887
Pashkovsky, F.S., **19**-1446
Pasquato, L., **15**-1998
Pasquet, M.J., **13**-0709
Pasquier, M.L., **04**-0205
Passacantilli, P., **19**-1088
Passarella, D., **16**-0687
Passarotti, C., **15**-0469
Pasta, P., **15**-1758, **19**-0759, **19**-0824
Pasteris, R.J., **18**-0861
Pastine, S.J., **11**-0326, **15**-0727
Pasto, D.J., **05**-0217, **05**-0244, **05**-0301, **10**-1290, **10**-1291, **10**-1651, **10**-1760, **15**-0005, **15**-0031, **15**-0106, **15**-0111, **15**-0112, **15**-0482, **15**-0486, **15**-0654, **15**-2219, **18**-0467, **18**-0534
Pastó, M., **10**-0921
Pastor, S.D., **16**-1190
Pastori, N., **16**-0141, **19**-0991, **19**-1657
Pastukhov, F.V., **16**-1969, **16**-1970
Pastukhova, I.V., **18**-0422
Pastushok, V.N., **10**-0470
Pasumansky, L., **13**-0172
Patai, S., **01**-0007, **01**-0009, **01**-0045, **01**-0072, **01**-0075, **02**-0038, **02**-0343, **03**-0001, **03**-0008, **03**-0047, **03**-0049, **03**-0050, **03**-0083, **03**-0094, **03**-0096, **03**-0101, **04**-0026, **04**-0032, **04**-0047, **04**-0064, **04**-0219, **04**-0261, **04**-0268, **04**-0350, **04**-0354, **04**-0471, **05**-0119, **05**-0145, **05**-0254, **05**-0255, **05**-0296, **05**-0297, **05**-0314, **05**-0316, **05**-0404, **07**-0044, **07**-0045, **07**-0050, **07**-0064, **08**-0043, **08**-0061, **08**-0156, **08**-0162,

08-0173, **08**-0178, **08**-0218, **08**-0223, **09**-0031, **09**-0032, **10**-0001, **10**-0115, **10**-0213, **10**-0289, **10**-0293, **10**-0373, **10**-0376, **10**-0384, **10**-0390, **10**-0391, **10**-0393, **10**-0423, **10**-0461, **10**-0494, **10**-0506, **10**-0520, **10**-0520, **10**-0585, **10**-0598, **10**-0615, **10**-0640, **10**-0658, **10**-0746, **10**-0749, **10**-0773, **10**-0780, **10**-0782, **10**-0839, **10**-0849, **10**-0852, **10**-0871, **10**-1005, **10**-1025, **10**-1034, **10**-1036, **10**-1061, **10**-1114, **10**-1265, **10**-1445, **10**-1479, **10**-1545, **10**-1693, **10**-1765 **10**-1785, **10**-1841, **11**-0037, **11**-0165, **11**-0227, **11**-0271, **11**-0444, **11**-0570, **11**-0581, **11**-0609, **11**-0623, **12**-0001, **12**-0002, **12**-0057, **12**-0059, **12**-0065, **12**-0066, **12**-0074, **12**-0083, **12**-0086, **12**-0222, **12**-0302, **12**-0306, **12**-0311, **12**-0388, **12**-0393, **12**-0424, **12**-0431, **12**-0432, **12**-0442, **12**-0474, **12**-0482, **12**-0504, **12**-0551, **12**-0564, **12**-0574, **12**-0582, **12**-0594, **12**-0638, **12**-0699, **13**-0037, **13**-0049, **13**-0052, **13**-0090, **13**-0129, **13**-0263, **13**-0660, **13**-0684, **13**-0687, **13**-0687, **13**-0688, **13**-0689, **13**-0690, **13**-0691, **13**-0693, **13**-0695, **14**-0125, **14**-0195, **14**-0217, **14**-0228, **14**-0246, **14**-0301, **14**-0302, **14**-0349, **14**-0397, **14**-0415, **14**-0443, **14**-0447, **15**-0001, **15**-0037, **15**-0037, **15**-0038, **15**-0039, **15**-0050, **15**-0075, **15**-0077, **15**-0079, **15**-0106, **15**-0294, **15**-0300, **15**-0314, **15**-0397, **15**-0435, **15**-0513, **15**-0572, **15**-0687, **15**-0705, **15**-0711, **15**-0760, **15**-0857, **15**-0947, **15**-0961, **15**-1215, **15**-1375, **15**-1477, **15**-1499, **15**-1517, **15**-1525, **15**-1624, **15**-1731, **15**-1790, **15**-1932, **15**-1932, **15**-1943, **15**-1980, **15**-1991, **15**-1992, **15**-2153, **15**-2156, **15**-2161, **15**-2166, **15**-2168, **15**-2234, **15**-2238, **15**-2261, **15**-2362, **16**-0002, **16**-0003, **16**-0014, **16**-0098, **16**-0098, **16**-0140, **16**-0196, **16**-0233, **16**-0266, **16**-0286, **16**-0287, **16**-0315, **16**-0425, **16**-0460, **16**-0464, **16**-0842, **16**-0851, **16**-0969, **16**-0972, **16**-1031, **16**-1169, **16**-1233, **16**-1255, **16**-1293, **16**-1421, **16**-1510, **16**-1549, **16**-1648, **16**-1658, **16**-1693, **16**-1715, **16**-1744, **16**-1755, **16**-1763, **16**-1844, **16**-1874, **16**-1891, **16**-2049, **16**-2094, **16**-2124, **17**-0003, **17**-0007, **17**-0047, **17**-0103, **17**-0122, **17**-0129, **17**-0145, **17**-0148, **17**-0172, **17**-0174, **17**-0243, **17**-0290, **17**-0300, **17**-0311, **17**-0344, **17**-0367, **17**-0387, **17**-0403, **17**-0424, **17**-0450, **17**-0458, **17**-0491, **17**-0502, **18**-0001, **18**-0099, **18**-0124, **18**-0124, **18**-0177, **18**-0194, **18**-0211, **18**-0215, **18**-0279, **18**-0290, **18**-0306, **18**-0395, **18**-0599, **18**-0617, **18**-0654, **18**-0695, **18**-0704, **18**-0739, **18**-0756, **18**-0874, **18**-0877, **18**-0881, **19**-0006, **19**-0021, **19**-0021, **19**-0048, **19**-0069, **19**-0252, **19**-0258, **19**-0280, **19**-0294, **19**-0387, **19**-0428, **19**-0633, **19**-0710, **19**-0738, **19**-0748, **19**-0786, **19**-0791, **19**-0795, **19**-0795, **19**-0812, **19**-0849, **19**-0913, **19**-0920, **19**-1095, **19**-1122, **19**-1136, **19**-1278, **19**-1348, **19**-1380, **19**-1482, **19**-1545, **19**-1561, **19**-1575, **19**-1595, **19**-1632, **19**-1636
Patat, F., **10**-0373, **10**-1114
Patchornik, A., **11**-0552, **16**-1817
Patel, B.A., **13**-0389
Patel, B.K., **16**-0149, **16**-1767, **19**-0702
Patel, B.P., **10**-0110
Patel, J.J.B., **19**-1238
Patel, K.M., **18**-0196
Patel, M., **15**-2102
Patel, P., **15**-0293
Patel, P.K., **10**-0719
Patel, R.C., **06**-0043, **06**-0049, **06**-0052, **06**-0053, **10**-1184
Patel, S., **19**-0296, **19**-0861
Patel, S.T., **15**-1830
Patel, S.V., **10**-1306
Patel, U.C., **15**-1444
Patel, V., **12**-0640
Pater, R H., **15**-1768, **15**-1786
Paternò, E., **15**-2244
Paterson, E.S., **10**-1545, **12**-0432, **12**-0474, **15**-0857, **16**-0003
Paterson, I., **16**-0647, **16**-1018, **16**-1032, **16**-1051
Pathak, D., **19**-1264
Pati, S.C., **19**-0622
Patil, G., **16**-1449
Patil, G.S., **10**-0101
Patil, K.M., **19**-1074
Patil, N.M., **13**-0203
Patil, N.S., **11**-0423
Patil, N.T., **15**-0892, **15**-0898
Patil, P.N., **16**-1543
Patil, P.S., **15**-1016
Patil, S.R., **15**-1716
Patil, V.D., **15**-0666
Patil, V.J., **16**-1270
Patinkin, S.H., **11**-0316
Patiño, R., **19**-0089
Patkar, L.N., **16**-1692
Paton, R.M., **15**-1932
Patonay, T., **12**-0322, **15**-1807
Patra, P.K., **11**-0336
Patricia, J.J., **12**-0626, **12**-0627, **15**-0877
Patrick, B.O., **02**-0366
Patrick, D.W., **17**-0290
Patrick, J.B., **19**-1501
Patrick, T.B., **11**-0310, **13**-0742, **14**-0129, **14**-0436, **15**-2257
Patrie, W.J., **19**-0135
Patro, B., **11**-0336, **15**-1269
Patsch, M., **18**-0385, **18**-0387, **18**-0390, **18**-0510
Pattabhi, V., **03**-0003
Pattenden, G., **10**-0718, **15**-0789, **15**-1271, **16**-1246
Patterson, D., **16**-2150
Patterson, D.B., **15**-0134
Patterson, J.M., **19**-0763
Patterson, S., **19**-1689
Patterson, W.I., **04**-0055
Pattison, F.L.M., **15**-1544
Pattison, J.B., **10**-1063
Pattison, V.A., **18**-0411, **18**-0414
Patton, D.S., **19**-1320
Patwardhan, B.H., **15**-0021
Patwari, S.B., **11**-0258
Patz, M., **16**-1020
Pau, C., **08**-0235
Pau, C.F., **15**-2044
Pauer, F., **05**-0175
Paugam, J.P., **15**-2273
Paugam, R., **15**-2119
Paukstelis, J.V., **04**-0233, **10**-1191, **16**-0295, **16**-0942, **19**-1140
Paul, D.B., **10**-1005, **15**-0397, **15**-1624
Paul, D.F., **11**-0275
Paul, E.W., **19**-0714

Paul, I.C., **02**-0258, **02**-0274, **02**-0325, **04**-0182, **04**-0187
Paul, K., **17**-0520, **17**-0522
Paul, N.C., **10**-0764
Paul, R., **15**-0404
Paul, S., **10**-0593, **11**-0429, **11**-0475, **11**-0554, **12**-0121, **19**-0625
Paul, V., **11**-0231, **11**-0234, **11**-0426
Pauling, L., **01**-0023, **05**-0280, **01**-0006
Paulmier, C., **12**-0244, **15**-0323, **17**-0290
Pauls, H.W., **13**-0503
Paulsen, H., **16**-1753
Paulson, J.F., **10**-0345
Paulson, K.L., **16**-1957
Paulus, E.F., **03**-0139
Pauluth, D., **12**-0081
Pauson, P.L., **02**-0166, **15**-1417, **15**-1429
Paust, J., **10**-0318
Pautex, N., **19**-0028
Pavam, C.H., **16**-0776
Paventi, M., **11**-0271, **11**-0272
Pavez, P., **13**-0110
Pavia, A.A., **10**-0646
Pavia, M.R., **16**-1823
Pavlenko, N.V., **19**-1069
Pavlides, V.H., **18**-0272
Pavlis, R.R., **14**-0045, **15**-1514, **18**-0081
Pavlov, S., **16**-1942
Pavlova, L.A., **10**-0522
Pavlova, N.N., **10**-0806
Pawar, D.M., **04**-0391, **04**-0393, **04**-0393
Pawar, S.S., **16**-0777
Pawełka, Z., **03**-0013
Payack, J.F., **13**-0237
Payeras, A.M., **19**-0181
Payne, A.H., **15**-0202
Payne, B.J., **18**-0146
Payne, D., **04**-0516
Payne, D.A., **12**-0116
Payne, G.B., **10**-0678, **15**-1776, **15**-1789
Payne, M.M., **15**-2394
Payne, M.T., **15**-0005
Payne, N.C., **10**-0290
Payzant, J.D., **10**-0336
Pazhenchevsky, B., **10**-0993
Pazos, J.F., **18**-0203
Pchelka, B.K., **18**-0362
Peach, M.E., **10**-0782, **13**-0129
Peachey, S.J., **04**-0028
Peacock, J.L., **14**-0071, **15**-1278
Peacock, S.C., **04**-0164
Peagram, M.J., **17**-0343
Pearce, G.T., **04**-0106
Pears, D., **19**-0894
Pearson, A.J., **03**-0086, **19**-0576
Pearson, D.E., **09**-0036, **10**-1185, **11**-0046, **11**-0224, **11**-0259, **11**-0423, **12**-0575
Pearson, D.P.J., **04**-0163
Pearson, M.M., **12**-0348
Pearson, R., **14**-0026, **14**-0183, **14**-0184
Pearson, R.G., **08**-0150, **06**-0006, **06**-0053, **08**-0041, **08**-0149, **08**-0151, **08**-0154, **08**-0219, **10**-0026, **10**-0339, **10**-0348, **10**-0398, **10**-1332, **15**-2103, **15**-2105
Pearson, R.J., **15**-2020
Pearson, S.C., **17**-0457
Pearson, W.H., **12**-0513, **12**-0565, **15**-1940, **18**-0298
Pease, A.R., **03**-0187
Pease, J.E., **16**-0494
Peat, A.J., **10**-1405
Peatt, A.C., **16**-0610, **16**-0883
Pecchi, S., **17**-0209
Pecher, J., **15**-1862, **19**-1056
Pechet, M.M., **12**-0729, **14**-0133, **14**-0134, **15**-1519, **18**-0870, **18**-0872
Pechhold, E., **05**-0171
Peclen, Y.J., **16**-2075
Pecoraro, J.M., **10**-0093
Pecul, M., **04**-0299
Peddada, L., **18**-0362
Pedersen, C.J., **03**-0101, **03**-0103
Pedersen, C.M., **16**-1873
Pedersen, H.L., **15**-0751
Pedersen, J.A., **10**-0092
Pedersen, K.J., **12**-0649, **16**-0157
Pedersen, P.R., **16**-0157
Pedersen, S.F., **15**-1825, **19**-1662, **19**-1663, **19**-1680, **19**-1698
Pedersen, T.M., **15**-2435, **16**-1314
Pedersen, U., **16**-1807
Pedersen, U.S., **16**-0220
Pederson, K.J., **12**-0084
Pedireddi, V.R., **08**-0011
Pedley, M.D., **08**-0191
Pedoussaut, M., **10**-1787, **16**-1542
Pedragosa-Moreau, S., **10**-0582
Pedregal, C., **15**-1006, **19**-1497
Pedrielli, P., **01**-0104
Pedrini, P., **19**-0232, **19**-0872
Pedro, J.R., **16**-0073, **16**-1528, **19**-0120
Pedrosa, R., **16**-0831, **16**-0837
Pedrosa, R., **16**-1962
Pedulli, G.F., **01**-0104, **01**-0110, **05**-0311, **15**-0705, **18**-0073, **19**-0120, **19**-0588
Pee, N.P., **12**-0190
Peel, J.B., **02**-0409
Peel, T.E., **08**-0015
Peeling, E.R.A., **11**-0153
Peeling, J., **03**-0054
Peerdeman, A.F., **04**-0097
Peerlings, H.W.I., **12**-0743
Peerzada, N., **11**-0403, **16**-0728
Pees, K.J., **15**-1146
Peet, N.P., **15**-2290, **16**-2011
Peeters, D., **15**-2003, **15**-2048
Peeters, H., **02**-0282
Peeters, H.L., **10**-0078
Pegg, G.G., **18**-0551
Pegg, N.A., **18**-0601
Pégot, B., **16**-0779
Pehk, T., **19**-0476
Pei, B.-G., **10**-0627, **10**-1788
Pei, C., **16**-1278
Pei, D., **16**-1962
Pei, J., **15**-2006, **16**-1081
Pei, T., **15**-0770, **15**-0890, **15**-0896
Pei, W., **16**-0769, **16**-0786
Peiffer, G., **14**-0180, **15**-0602, **19**-1021
Peiris, S., **05**-0126
Pel'kis, P.S., **10**-1034
Peled, P., **10**-0241
Pelikán, P., **14**-0004, **14**-0005
Pélinski, L., **16**-0687
Pelka, S., **13**-0186
Pellacani, L., **15**-1884, **15**-1889, **15**-1890
Pellerite, M.J., **08**-0014, **10**-0020, **10**-0353
Pellet, M., **10**-0540, **16**-1938
Pellet-Rostaing, S., **15**-0865
Pelletier, J.D., **10**-1074
Pelletier, W.M., **10**-0488
Pelliccia, A.R., **15**-1751
Pellissier, H., **04**-0190, **10**-1658, **13**-0045
Pellón, R.F., **16**-1192
Pelter, A., **04**-0079, **10**-1715, **10**-1757, **12**-0332, **12**-0427, **12**-0442, **14**-0392, **14**-0396, **15**-0636, **15**-0693, **15**-1183, **16**-0697, **16**-0996, **16**-1018, **16**-1812, **18**-0420, **18**-0420, **18**-0427, **18**-0428, **18**-0429, **18**-0432, **18**-0435, **18**-0435, **18**-0457, **18**-0459, **19**-0877, **19**-0882, **19**-0889, **19**-1077
Peltzer III, E.T., **17**-0363

Pena, J.M., **15**-0944
Pena, M.A., **13**-0620
Pena, P.C.A., **18**-0155
Peña, D., **15**-0604, **15**-0702
Peña, M.E., **11**-0125, **12**-0197, **12**-0700
Peña, M.R., **13**-0389
Peña-Cabrera, E., **12**-0256, **12**-0276
Penalva, V., **13**-0301
Penco, S., **19**-1374
Pendalwar, S.L., **15**-0470
Pendola, K.A., **13**-0143
Penenory, A., **05**-0237, **05**-0246
Peñéñory, A.B., **10**-0090, **10**-0787
Peng, J., **16**-0152, **18**-0317
Peng, S.-M., **19**-0746
Peng, X., **11**-0140
Peng, Y., **16**-1175, **16**-1772, **16**-1791
Peng, Y.-Y., **16**-1036
Peng, Z.-Z., **16**-0095
Penieres-Carrillo, G., **19**-0261
Penkett, C.S., **10**-1566
Penmasta, R., **10**-0046, **19**-0406, **19**-0481, **19**-0485, **19**-0846
Penn, J.H., **19**-1118
Pennella, F., **18**-0828
Penner, G.H., **03**-0054, **15**-2061
Penner-Hahn, J.E., **10**-1333
Pennetreau, P., **11**-0142
Penney, J.M., **13**-0535
Penninger, J.L.M., **15**-1495
Pennington, L., **18**-0272
Pensak, D., **14**-0029
Penso, M., **10**-0951, **13**-0324
Penso, M., **19**-1250
Penton Jr., H.R., **10**-0907
Penton, J.R., **11**-0033, **11**-0041, **11**-0050, **11**-0119, **11**-0167, **11**-0168
Penzien, K., **04**-0142
Peoples, P.R., **05**-0134
Pepermans, H., **15**-2407
Peppe, C., **16**-0233
Perales, J.B., **15**-0733
Peralez, E., **05**-0309
Percač, K., **10**-0116
Percec, V., **13**-0484
Perch, N.S., **15**-0774
Perchinunno, M., **14**-0347
Perchonock, C., **02**-0235
Perciaccante, R., **15**-1317
Percina, N., **10**-1100
Percy, J.M., **04**-0168, **04**-0287
Perdih, M., **04**-0101
Perdikomatis, G.P., **11**-0433
Perdoncin, G., **19**-0963
Peregudov, A.S., **13**-0152
Pereira, A.R., **16**-0475
Perelman, M., **16**-2109
Perepelkova, T.I., **03**-0001
Perera, S.A., **03**-0042
Peres, Y., **15**-1477
Perevalova, E.G., **02**-0166
Pereyre, M., **12**-0014
Perez Ossorio, R., **12**-0088
Perez, D., **15**-0590
Perez, F., **19**-0699
Pérez, A., **16**-0837
Pérez, D., **10**-1405
Pérez, E., **15**-1022
Pérez, I., **13**-0335
Pérez, J.A., **15**-1900
Pérez, J.M., **15**-2144
Pérez, M., **13**-0524
Pérez, P., **10**-0030, **10**-0031, **10**-0032, **13**-0686, **15**-1999, **15**-2099
Pérez, P.J., **12**-0366, **15**-2293, **15**-2299, **19**-0548
Pérez-Andrés, J.A., **17**-0163, **17**-0167, **17**-0400
Perez-Benito, J.F., **15**-1679
Pérez-Blanco, D., **16**-1215
Pérez-Castells, J., **15**-1430, **15**-1436, **15**-1438, **15**-1441, **15**-1443
Pérez-Encabo, A., **16**-0831, **16**-0837, **16**-1962
Pérez-Flores, J., **18**-0232, **15**-0370, **15**-2304
Perez-Rubalcaba, A., **16**-0527
Pérez-Serrano, L., **15**-1436, **15**-1438, **15**-1443
Perez-Torralba, M., **02**-0423
Pérez-Torrente, J.J., **04**-0061
Peri, F., **15**-0225
Periasamy, M., **04**-0160, **10**-0182, **12**-0453, **12**-0526, **13**-0168, **13**-0585, **13**-0664, **14**-0378, **15**-0654, **15**-0950, **15**-1389, **15**-1413, **16**-1973, **18**-0435, **19**-0017, **19**-0634, **19**-1488
Periasamy, M.P., **10**-0966, **16**-2124
Pericás, M.A., **02**-0346, **15**-1437
Pericàs, M.A., **07**-0091, **10**-0921, **15**-2211, **15**-2364, **16**-0687, **16**-0689, **17**-0416, **19**-1031
Perichon, J., **10**-1228, **10**-1854, **13**-0468, **10**-1308, **10**-1397, **10**-1442, **10**-1821, **13**-0337, **13**-0344, **13**-0614, **15**-1162, **15**-1388, **16**-0570, **16**-0716, **16**-1908
Périé, J.J., **15**-0327, **15**-0314
Peringer, P., **10**-1017
Perinis, M., **10**-0176
Pério, B., **16**-0144
Peris, E., **19**-0970
Peristeraki, A., **16**-1620
Perjéssy, A., **02**-0426
Perkampus, H., **11**-0004
Perkins, M.J., **04**-0234, **05**-0116, **05**-0211, **13**-0743, **13**-0748, **14**-0031, **14**-0033, **14**-0328, **14**-0329, **15**-0050, **15**-2261, **18**-0185, **19**-0614
Perkins, N.A., **11**-0369
Perković, T., **13**-0380
Perl, S., **02**-0065
Perlberger, J., **19**-0249
Perlin, A.S., **19**-0311
Perlmutter, P., **15**-0264, **15**-1478, **15**-1486, **15**-1501, **15**-1504, **16**-0798
Perlmutter-Hayman, B., **04**-0187
Pernazza, D., **16**-0757
Pérollier, C., **19**-0582
Perosa, A., **09**-0104, **10**-0884, **12**-0746, **13**-0406
Perraud, R., **16**-0539
Perret, R., **16**-1928
Perreten, J., **18**-0859
Perreux, L., **16**-1789
Perrier, H., **18**-0609
Perrin, C.L., **03**-0021, **03**-0034, **04**-0374, **04**-0375, **08**-0024, **11**-0028, **11**-0053, **11**-0100, **11**-0103, **11**-0105, **15**-2105, **16**-0030
Perrin, D.D., **08**-0018, **08**-0045, **08**-0160, **08**-0171
Perrio, S., **12**-0242, **19**-0823
Perriot, P., **18**-0231
Perron R., **10**-0460
Perrot, M., **19**-1099, **19**-1105
Perroux, Y., **16**-0396, **16**-1735
Perry, D.A., **16**-0210
Perry, M.C., **15**-0425
Perry, N.B., **18**-0022, **18**-0102
Perry, R.A., **12**-0640
Perry, S.S., **02**-0218
Person, W.B., **03**-0080, **03**-0081, **03**-0100, **04**-0385
Persson, B.A., **15**-0289
Persson, E.S.M., **10**-1293, **10**-1438
Persson, I., **08**-0146
Persson, J., **10**-0854
Persson, P., **08**-0146

Perst, H., **10**-0110, **10**-0380, **10**-0739
Persy, G., **02**-0331, **02**-0381, **05**-0408, **07**-0021
Pertici, P., **15**-1693
Pertsikov, B.Z., **14**-0097
Perumal, P.T., **11**-0474, **15**-0675, **15**-2119, **15**-2142, **18**-0312, **18**-0442, **19**-0209
Perumal, S., **11**-0541
Peruncheralathan, S., **17**-0434
Perutz, R.N., **02**-0171
Peruzzini, M., **15**-0279, **15**-2406
Pervez, H., **11**-0142
Pervukhina, N.V., **05**-0262
Pesce, G., **10**-0819, **10**-1530
Pesce, L., **13**-0582
Pesce, M., **19**-0960
Pesch, J., **15**-1368, **16**-0724
Pescitelli, G., **04**-0120
Petasis N.A., **13**-0265, **16**-1349, **16**-1353, **16**-1355, **16**-1356, **16**-1357, **11**-0157, **11**-0157, **13**-0096
Petch, W.A., **13**-0770
Pete, J., **16**-1655, **19**-1412
Pete, J.-P., **15**-1049
Pete, J.P., **16**-0009, **16**-1492
Pète, J., **17**-0278
Peter, D., **18**-0169
Peter, R., **10**-1381, **16**-0493
Peter-Katalinić, J., **04**-0244
Peters, D., **02**-0191, **04**-0419, **13**-0495, **15**-0788
Peters, D.A.V., **15**-1544
Peters, D.G., **19**-1334
Peters, E.-M., **08**-0084
Peters, E.N., **05**-0092, **09**-0009, **10**-0133, **10**-0198
Peters, G.A., **16**-0197
Peters, J.A., **19**-1098
Peters, K., **02**-0243, **04**-0294, **05**-0231, **08**-0084, **08**-0186, **10**-1662
Peters, K.S., **07**-0032, **10**-0067, **16**-2087
Peters, N.K., **15**-0544
Peters, S.J., **02**-0242
Petersen, B.L., **05**-0077
Petersen, C.J., **03**-0103
Petersen, H.E., **18**-0257
Petersen, J.M., **18**-0262
Petersen, J.S., **04**-0148, **15**-0680, **16**-1050
Petersen, M.R., **18**-0676
Petersen, N.O., **16**-1659
Petersen, S.B., **03**-0077
Petersen, W.C., **19**-1219
Peterson Jr., M.R., **01**-0048
Peterson, B., **17**-0233
Peterson, D., **10**-1542, **12**-0589
Peterson, D.J., **12**-0565, **16**-1232
Peterson, G.A., **19**-1374
Peterson, H.J., **05**-0071, **08**-0121, **15**-0724
Peterson, J.O., **19**-0942
Peterson, J.R., **02**-0352, **04**-0088, **15**-1715, **15**-1882, **19**-0852
Peterson, K.B., **15**-2090
Peterson, K.P., **15**-0387, **15**-1363
Peterson, M.J., **10**-0606
Peterson, M.L., **14**-0418
Peterson, M.R., **12**-0087
Peterson, P.E., **05**-0021, **10**-0113, **10**-0114, **10**-0116, **10**-0136, **10**-0282, **10**-0383, **15**-0016, **15**-0269, **18**-0250
Peterson, R.T., **15**-1042
Petersson, A., **15**-0924
Pethrick, R.A., **04**-0277
Petillo, P.A., **04**-0241
Petiniot, N., **10**-0638
Petit, A., **07**-0111, **10**-0468, **13**-0109, **16**-0372, **16**-1644, **16**-1689, **18**-0715
Petit, F., **15**-0602, **15**-0797, **19**-1718
Petit, J., **10**-0060
Petit, M., **15**-2386, **19**-1718
Petit, Y., **10**-1542, **15**-1092, **18**-0692
Petneházy, I., **16**-1808, **17**-0488
Peto, A.G., **11**-0416, **11**-0446
Petra, D.G.I., **19**-1022
Petragnani, N., **10**-1611, **12**-0245
Petrašiūnas, G.L.R., **16**-0218
Petricci, E., **07**-0119
Petricci, S., **10**-0951, **13**-0324
Petrich, J.W., **12**-0087
Pétrier, C., **12**-0609, **15**-1142, **15**-1142, **16**-0479, **16**-0645
Petrillo, G., **08**-0168, **17**-0056
Petringa, A., **03**-0139
Petrini, M., **10**-0845, **15**-1289, **16**-0108, **16**-0113, **16**-0487, **16**-0615, **16**-1666, **17**-0160, **19**-0666, **19**-1206, **19**-1586
Petro, C., **05**-0075, **10**-0051, **10**-0178, **10**-0184
Petrosyan, V.E., **05**-0359
Petrosyan, V.S., **12**-0047
Petrov, A.A., **15**-0060, **15**-0081, **15**-0222, **15**-1611, **15**-1638, **15**-1932, **16**-1309
Petrov, A.D., **16**-1943
Petrov, E.S., **08**-0160, **15**-1199
Petrov, M.L., **15**-1932
Petrovanu, M., **12**-0414
Petrovich, J.P., **19**-1691
Petrovlskii, P.V., **13**-0152
Petrovski, Ž., **10**-1562
Petrovskii, P., **10**-1835, **19**-0616
Petrzilka, M., **15**-2003, **18**-0676
Pettersen, D., **17**-0216
Petterson, R.C., **16**-1869, **18**-0085, **18**-0855, **18**-0868
Pettersson, C., **04**-0175
Pettersson, G., **04**-0175
Pettersson, M., **04**-0297
Pettiette-Hall, C.L., **19**-0016
Pettit, R., **02**-0348
Pettit, G.H., **11**-0518
Pettit, G.R., **11**-0635, **14**-0398, **19**-1467, **19**-1467, **19**-1469, **19**-1576
Pettit, L.D., **03**-0083
Pettit, R., **02**-0132, **02**-0211, **02**-0227, **02**-0229, **02**-0348, **04**-0441, **15**-2199, **18**-0500, **18**-0501, **18**-0502, **18**-0638
Pettit, R.J., **16**-1348
Pettitt, D.J., **17**-0225
Pettus, T., **15**-1724
Petty, J.D., **10**-0482
Petty, R., **01**-0041
Peverley, J., **15**-1175
Pevzner, M.S., **14**-0358
Pews, R.G., **04**-0423
Peyerimhoff, S.D., **07**-0015
Peyman, A., **05**-0231
Peynircioglu, N.B., **05**-0116
Peyrat, J.-F., **10**-1051, **13**-0325, **13**-0559
Peyroux, E., **13**-0445
Pezacki, J.P., **05**-0384
Pfab, J., **12**-0706
Pfaltz, A., **04**-0149, **10**-1471, **13**-0399, **13**-0419, **15**-1136, **15**-2304, **19**-0538, **19**-1155, appendixA-0033
Pfau, M., **15**-0971, **15**-1044, **15**-1044
Pfeffer, M., **10**-0875
Pfeffer, P.E., **10**-0693, **10**-1690, **12**-0208, **16**-1252, **16**-1694, **16**-2039
Pfeifer, K.-H., **02**-0082
Pfeifer, L.A., **13**-0378
Pfeifer, W.D., **10**-0256
Pfeiffer, D., **15**-0686
Pfeiffer, M., **13**-0237
Pfeiffer, P.Z., **17**-0009
Pfeiffer, S.S., **11**-0651
Pfennig, D.R., **10**-1222
Pfenninger, A., **15**-1820
Pfister, J.R., **10**-0906, **18**-0280

Pfister, X., **19**-1028
Pfitzner, K.E., **19**-0160, **19**-0647
Pflüger, F., **12**-0277
Pflum, D.A., **15**-0604
Pfohl, W.F., **10**-1234
Pfordte, K., **14**-0289
Pfrengle, W., **16**-2133
Pfriem, S., **04**-0437, **17**-0512
Pfyffer, J., **15**-2050
Pgaltz, A., **15**-0605
Phadke, R., **11**-0380
Pham, K.M., **16**-0361
Pham, S.M., **16**-1126
Pham, T.N., **10**-0091, **10**-0095, **12**-0627 **12**-0631, **19**-1339
Phan, N.T.S., **13**-0497
Phansavath, P., **19**-1028
Phanstiel IV, O., **18**-0563
Phanstiel, O., **18**-0509
Phelan, N.F., **02**-0048
Phelps, J.C., **15**-1641
Phelps, M.E., **10**-1055
Phenix, B., **13**-0272
Philip Jr., J.B., **14**-0448
Philip, D., **15**-2020
Philip, H., **18**-0056
Philippi, K., **15**-1735
Philippot, K., **10**-1459
Philips, J.C., **08**-0049, **10**-0269, **17**-0356, **17**-0357, **18**-0098
Philips, N.G., **15**-2426
Phillips, A.M.F., **18**-0354
Phillips, B., **15**-1801
Phillips, B.A., **11**-0399
Phillips, B.T., **17**-0462
Phillips, C.J., **16**-0925
Phillips, D.D., **05**-0138
Phillips, D.L., **15**-2333, **15**-2340
Phillips, D.R., **03**-0165
Phillips, E., **19**-0192
Phillips, G.W., **16**-1195
Phillips, H., **10**-0006, **10**-0007
Phillips, I.M., **15**-2065, **15**-2266
Phillips, J.B., **02**-0276
Phillips, J.H., **15**-0292
Phillips, J.N., **05**-0043
Phillips, L., **04**-0285
Phillips, N.H., **12**-0629
Phillips, O.A., **15**-0162
Phillips, R., **11**-0083
Phillips, R.B., **18**-0623
Phillips, R.E., **01**-0041
Phillips, R.R., **12**-0193
Phillips, R.S., **19**-1022
Phillips, W.G., **19**-0647, **19**-0648
Phillips, N.H., **05**-0181
Philouze, C., **16**-1385
Philp, D., **03**-0205
Phopase, J., **13**-0347, **16**-2179
Photis, J.M., **17**-0518
Phukan, P., **16**-0904
Pi, J., **15**-1030
Pi, R., **12**-0421, **12**-0550
Piacenti, F., **10**-1837, **15**-1375
Piacenti, F., **15**-1477
Pialssã, C., **15**-0944
Piancatelli, G., **15**-1558, **19**-0080, **19**-0204, **19**-0732, **19**-0735, **19**-1770
Piantini, U., **16**-0684
Piao, F., **19**-1189
Piarulli, U., **16**-1417
Piatak, D.M., **11**-0635, **19**-0408
Piattelli, M., **03**-0123, **03**-0127, **03**-0128, **03**-0139, **04**-0092
Piazza, C., **10**-1354
Piber, M., **10**-1406
Piccirilli, J.A., **04**-0252
Piccolo, O., **10**-1511, **11**-0376, **11**-0508
Picher, M.T., **15**-2057
Pichler, S., **07**-0103
Pick, R.M., **10**-0724
Pickard, P.L., **16**-0955
Pickardt, J., **15**-2172
Pickering, D., **05**-0140
Pickering, D.A., **11**-0335
Pickering, R.A., **10**-0756
Pickles, G.M., **13**-0095
Picoul, W., **16**-1230
Picq, D., **10**-1044
Picquet, M., **18**-0814
Picraccini, D., **15**-1526
Pictet, A., **11**-0400
Pidathala, C., **16**-1063
Pidcock, A., **12**-0279
Pidgeon, C., **10**-0783
Pielartzik, H., **04**-0477
Pielichowski, J., **10**-0590
Pienta, N., **10**-0184
Pienta, N.J., **05**-0075, **10**-0051
Pieraccini, D., **10**-0411, **11**-0242
Pierce, M.E., **19**-1054
Pierini, A.B., **10**-0090, **10**-0787, **13**-0052, **13**-0061, **13**-0343, **13**-0589
Pierini, M., **12**-0083
Pierlot, C., **14**-0233
Piermatti, O., **15**-2006
Pierre, J., **04**-0243, **16**-0539, **19**-1062
Pierre, J.-L., **19**-0189
Pierres, C., **15**-2145
Pierri, F., **14**-0039
Pierrot, M., **19**-0371
Piers, E., **10**-1802, **12**-0548, **15**-1117, **18**-0484
Piers, W.E., **12**-0319, **19**-1142
Piersanti, G., **15**-2174
Pierson, C., **14**-0154
Pierson, G.O., **18**-0203
Piet, J.J.N., **15**-1663
Pieter, R., **19**-1281
Pietra, F., **02**-0156, **02**-0162, **04**-0063, **04**-0155, **13**-0013, **13**-0057
Pietra, S., **13**-0072, **19**-0777, **19**-1544
Pietrasanta, F., **10**-0179
Pietraszkiewicz, M., **03**-0101
Pietroni, B., **15**-0848
Pietroni, B.R., **11**-0334
Pietropaolo, R., **19**-0960
Pietrusiewicz, K.M., **18**-0811
Pietsek, D.J.J., **17**-0073
Piette, L.H., **14**-0204, **15**-0058
Piettre, S., **15**-2182, **15**-2222
Piffl, M., **05**-0183
Pigeon, P., **10**-1047, **17**-0307
Pigou, P.E., **10**-0045
Piguel, S., **15**-1591
Pigulla, M., **15**-0150
Pihko, P.M., **16**-1036
Pihlaja, K., **10**-0598, **10**-0658, **10**-0749, **10**-1061, **16**-1658
Pike, D.C., **16**-0015, **16**-1512
Pike, K.G., **15**-1429, **19**-0126
Pikul, S., **04**-0135
Pikulin, S., **18**-0561, **18**-0562
Pilard, S., **10**-0952
Pilati, T., **02**-0268, **02**-0277
Pilcher, G., **01**-0093, **01**-0094, **01**-0099
Pilichowska, S., **10**-0992
Pilipauskas, D.R., **10**-1187
Pilkiewicz, F.G., **15**-2275
Pilkington, J.W., **18**-0035
Pillai, C.N., **15**-0855
Pillai, S., **10**-0876
Pillai, S.M., **15**-0792
Pillai, T.P., **12**-0707, **12**-0708
Pillai, U.R., **15**-1747, **15**-1748
Pillai, V.N.R., **16**-1817
Pilli, R.A., **16**-1350
Pilling, M.J., **05**-0304
Pilot, J.F., **16**-1262, **16**-1302
Pimentel, G.C., **03**-0001, **03**-0032, **05**-0275, **05**-0276
Pinchuk, A.N., **16**-0699
Pincock, J.A., **05**-0308, **15**-0005, **15**-0016, **15**-0087, **17**-0507, **17**-0509, **18**-0848, **19**-0121
Pincock, R.E., **04**-0094, **04**-0187, **04**-0449, **05**-0279, **10**-0146, **10**-0149, **10**-0150, **10**-0151, **10**-1236
Pinder, A.R., **19**-1290, **19**-1301

Pindur, U., **05**-0053, **10**-0520, **15**-2029, **19**-1727
Pine, R.D., **16**-1348
Pine, S.H., **13**-0759, **13**-0764, **13**-0766, **16**-1348, **16**-1351, **18**-0380, **18**-0383, **18**-0391
Pinel, C., **10**-0604
Piñero, L., **17**-0428
Pines, H., **12**-0057, **12**-0065, **15**-0314, **15**-0722, **15**-0723, **15**-0724, **15**-0791, **17**-0140, **17**-0176, **18**-0056, **19**-0027, **19**-0424
Pineschi, M., **10**-0814, **10**-0953, **10**-1564
Pinet, S., **16**-0907, **16**-0928
Pinetti, A., **12**-0115, **12**-0123, **15**-1527, **15**-1602
Ping, Y.Y., **16**-0842
Ping-Guo, M., **15**-0441
Pinhas, A.R., **12**-0757, **18**-0502, **19**-0840
Pinhey, J.T., **11**-0658, **13**-0264, **14**-0330
Pinho e Melo, T.M.V.D., **15**-2133
Pinho, P., **15**-0387, **15**-2119, **19**-1028
Pini, D., **04**-0120, **16**-0831
Pinkerton, A.A., **02**-0402
Pinkerton, A.B., **15**-0366, **15**-0815, **15**-1152, **16**-0569
Pinkerton, F.H., **10**-0895
Pinkus, A.G., **12**-0147, **16**-0541
Pinnick, H.W., **10**-0285, **16**-0105, **19**-0479, **19**-0699
Pino, P., **10**-1837, **12**-0304, **13**-0598, **14**-0443, **15**-0598, **15**-1375, **15**-1375, **15**-1477, **15**-1489, **15**-1491, **15**-1499, **15**-1504, **15**-2362, **18**-0837
Pinschmidt Jr., R.K., **15**-2111, **18**-0498
Pinson, J., **13**-0054, **13**-0127
Pinto, D.C.G.A., **07**-0121
Pinzani, D., **17**-0209
Pioch, R.P., **12**-0431
Piotrowska, H., **12**-0212, **12**-0338, **15**-2443
Piotrowski, A.M., **16**-0500
Piqué, C., **15**-2304
Piquer, Ma.J.A., **07**-0091
Piqueras, M.C., **02**-0185
Piqueur, J., **10**-0873
Piras, D., **07**-0123
Piras, P.P., **19**-1400
Pires, E., **15**-2038
Pirkle, W.H., **04**-0170, **04**-0173, **04**-0175, **04**-0176, **04**-0197, **04**-0207, **04**-0210, **04**-0211, **04**-0255, **15**-0485
Pirogowa, G.N., **17**-0149
Pironti, V., **19**-0759
Pirozhkov, S.D., **10**-1833, **15**-1375, **18**-0422
Pirrung, F.O.H., **15**-0913
Pirrung, M.C., **16**-1014
Pisanenko, D.A., **15**-0024
Pisano, D., **02**-0095
Pisano, L., **19**-1537
Pischel, U., **02**-0158
Pískala, A., **16**-1303
Piskunova, Z., **10**-0263
Pistarà, V., **16**-0049, **16**-0242
Pistorius, R., **14**-0419
Piszkiewicz, L., **14**-0058
Pitacco, G., **16**-0287
Pitcher, R.G., **04**-0203
Pitchumani, K., **19**-0806
Piteau, M., **10**-1187
Pitman, I.H., **12**-0726
Pitram, S.M., **18**-0905
Pitre, S., **19**-1054
Pitre, S.V., **19**-0595
Pitteloud, R., **18**-0676
Pitter, S., **15**-0343
Pittman Jr., **05**-0002
Pittman Jr., C.U., **02**-0207, **05**-0002, **05**-0035, **05**-0038, **05**-0039, **05**-0049, **05**-0050, **05**-0061, **10**-0119, **15**-0108
Pitts Jr., J.N., **07**-0001, **07**-0011, **07**-0027, **07**-0038, **07**-0044, **07**-0065, **19**-1687, **19**-1689
Pitts, M.R., **10**-1121, **15**-0553, **15**-0554, **19**-1187, **19**-1242
Pitzer, K.S., **04**-0382
Pitzer, R.M., **04**-0278
Piva, O., **12**-0165, **15**-0151, **19**-0533
Piveteau, E., **12**-0508
Pivsa-Ast, S., **13**-0338
Pizey, J.S., **10**-0634, **10**-0740, **10**-0853, **11**-0282, **11**-0282, **11**-0290, **11**-0445, **11**-0467, **12**-0112, **13**-0657, **13**-0659, **14**-0144, **14**-0173, **14**-0206, **14**-0250, **15**-0188, **15**-0402, **15**-0635, **15**-1537, **15**-1565, **15**-1714, **16**-0261, **16**-1877, **19**-0010, **19**-0010, **19**-0022, **19**-0289, **19**-0879, **19**-1291
Pizzano, A., **15**-0611
Pizzo, F., **10**-0672, **10**-0944, **10**-1152, **10**-1167, **15**-1681, **15**-1819, **15**-2006, **19**-1258
Pizzolatti, M.G., **12**-0716
Pizzotti, M., **12**-0748, **19**-1748
Pla-Quintana, A., **13**-0365, **13**-0420
Place, D., **03**-0172
Plachky, M., **17**-0199
Plackett, J.D., **18**-0727
Planas, A., **18**-0186
Plancher, J.M., **10**-0549
Planinsek, Z., **19**-0687
Plankl, W., **12**-0680
Plante, R., **11**-0594
Plaquevent, J., **04**-0136
Plaquevent, J.C., **17**-0315
Plat, M., **10**-1023
Plate, A.F., **18**-0614
Plath, P., **18**-0019
Plato, M., **05**-0208
Platone, E., **11**-0262
Platts, J.A., **03**-0002
Platz, M.S., **05**-0375
Platz, M.S., **05**-0384, **05**-0407, **05**-0409, **05**-0345, **05**-0352, **05**-0365, **05**-0369, **05**-0386, **05**-0408, **18**-0219
Plaut, H., **10**-0688
Plavšić, D., **02**-0106, **05**-0152
Plé, G., **02**-0428, **04**-0076, **10**-1405, **17**-0315
Pleiss, M.A., **10**-0993
Pleixats, R., **13**-0481, **13**-0524, **13**-0525
Plénat, F., **10**-0179
Plenio, H., **13**-0539
Plepys, R.A., **19**-0921
Pleskov, Y.V., **15**-0540
Plesnicar, B., **15**-1731
Plesničar, B., **15**-1726, **18**-0352
Plessi, L., **15**-1667, **19**-0391
Plesske, K., **02**-0168
Pletcher, D., **19**-0104
Pletcher, W.A., **04**-0493
Pletnev, A.A., **13**-0624
Plexats, R., **13**-0420
Plieninger, H., **15**-2076, **19**-0446
Plietker, B., **15**-1414, **15**-1717
Plinke, G., **02**-0298
Plotkin, M.A., **13**-0181
Plourde, G.L., **15**-2061
Pluim, H., **15**-1806
Plum, H., **15**-2001
Plumb, J.B., **19**-0202
Plumeré, P., **04**-0163
Plumet, J., **16**-1429, **18**-0781
Plummer, B.F., **16**-0135
Plummer, E.L., **04**-0106
Plummer, M., **18**-0860
Plunian, B., **15**-1119
Plusquellec, D., **16**-1713
Plzak, K., **05**-0140
Poater, J., **02**-0154

Pobiner, H., **19**-0336
Pochapsky, T.C., **04**-0173, **04**-0175
Pochini, A., **11**-0388
Pöchlauer, P., **10**-1017
Pock, R., **15**-0029, **15**-1637, **15**-1927
Pocker, Y., **10**-0084, **12**-0412, **12**-0673, **15**-0030, **16**-0044, **18**-0148, **18**-0149
Podlech, J., **16**-2117
Podoplelov, A.V., **10**-1314
Podraza, K.F., **10**-1646
Poehlein, B.W., **15**-1729
Poeth, T., **10**-1242
Pogodin, S., **02**-0360
Pogorelyi, V.K., **03**-0014, **03**-0044, **03**-0049
Pohl, D.G., **14**-0152, **14**-0153, **14**-0158
Pohl, M., **16**-1500, **16**-2065
Pohmakotr, M., **19**-0477
Poignée, V., **04**-0467
Poindexter, M.K., **18**-0514
Pointdexter, G.S., **07**-0118
Poirer, M., **19**-1186
Poirier, D., **10**-1074
Poirier, J., **10**-1269, **11**-0142, **12**-0311, **16**-1233
Poirier, R.A., **02**-0281, **12**-0087, **15**-2062
Poisson, J.-F., **15**-0874
Pojarliev, P., **15**-1004, **16**-0414, **16**-1036
Pojer, P.M., **15**-0402, **19**-1528
Pokrovskaya, S.V., **16**-1462
Pola, J., **19**-0363, **19**-0381
Polach, S.A., **12**-0367
Polanc, S., **16**-1684, **16**-1708
Polanyi, J.C., **06**-0013
Polanyi, M., **15**-0452, **16**-1552
Polasek, M., **13**-0237
Polavarapu, P.L., **04**-0112
Polášek, M., **02**-0407
Polborn, K., **15**-0702, **16**-0889
Poleshchuk, O.Kh., **03**-0080
Polet, D., **10**-1295, **10**-1471, **15**-1136, **15**-1137
Polezhaeva, N.A., **02**-0089, **16**-1402
Poli, G., **10**-1449
Poli, M., **10**-0481
Poli, S., **19**-0232
Poliakoff, M., **09**-0106
Poliart, C.D., **08**-0087
Polichnowski, S.W., **18**-0836
Poling, B., **15**-2292
Poliskie, G.M., **19**-1289
Politanskii, S.F., **10**-1075
Politzer, I.R., **10**-1733, **10**-1736
Politzer, P., **02**-0035
Polivkova, J., **04**-0110
Polizzi, C., **15**-0363
Polk, D.E., **13**-0617
Polla, E., **10**-0134
Pollack, R.M., **05**-0114, **12**-0059, **12**-0060, **12**-0095, **16**-1573, **16**-1593
Pollart, D.F., **17**-0184
Pollart, K.A., **19**-0351
Pollastri, M.P., **10**-1099
Pollenz, R.S., **18**-0487
Pollet, P., **15**-0614
Polleux, P., **12**-0368
Pollex, A., **18**-0405
Pollicino, S., **04**-0470, **16**-0926, **18**-0727
Pollini, G.P., **15**-2179
Pollock, C.M., **16**-0966
Pollock, L., **04**-0384
Polniaszek, R., **16**-1828, **16**-1833
Polshettiwar, V., **10**-0835, **16**-0216
Polster, R., **12**-0414
Polston, N.L., **18**-0447
Polt, R.L., **12**-0409
Poltarzewski, Z., **19**-0960
Pomarès, O., **19**-0247
Pomerantz, M., **01**-0080
Pommelet, J., **17**-0358
Pommer, H., **16**-1255, **16**-1337
Pommier, J., **02**-0421
Ponaras, A.A., **10**-0662
Ponaskik Jr., J.A., **10**-1453
Ponde, D.E., **16**-1683
Ponec, R., **03**-0063, **09**-0061, **15**-2105, **19**-0360
Ponomarchuk, M.P., **10**-1318, **19**-0630
Ponomareva, E.A., **10**-0033, **10**-0406
Ponomarov, A.B., **13**-0534, **13**-0619
Pons, J., **19**-1658, **19**-1710
Pons, J.-F., **15**-1254
Ponsold, K., **09**-0043
Ponti, F., **19**-0098, **19**-0440
Ponticello, G.S., **04**-0206
Pook, L.M., **14**-0020
Poole Jr., C.P., **05**-0208
Poole, H.G., **11**-0152
Poon, C., **02**-0243
Poon, N.L., **15**-0205, **15**-0265, **16**-0192
Poon, Y.C., **01**-0011
Poondra, R.R., **13**-0442
Poonia, N.S., **03**-0101
Poonian, M.S., **18**-0039
Pooyan, M., **10**-1161
Popa, C., **18**-0648
Popa, V., **03**-0083
Pope, W, J., **04**-0028
Popik, V.V., **16**-2030
Pople, J.A., **02**-0028, **01**-0052, **02**-0009, **02**-0014, **02**-0016, **02**-0103, **02**-0207, **02**-0371, **04**-0285
Popov, A.F., **10**-0263
Popov, E.M., **02**-0032, **02**-0036
Popov, S.I., **16**-0440
Popovitz-Biro, R., **13**-0481
Popp, F.D., **19**-1129
Poppinger, D., **05**-0024
Porai-Koshits, B.A., **11**-0583
Poranski Jr., C.F., **13**-0008
Porcelloni, M., **16**-0949, **18**-0800
Porcheddu, A., **10**-1091, **16**-1703, **16**-1790, **16**-1948, **16**-2102, **19**-0171, **19**-0186, **19**-0677, **19**-1073
Porcu, G., **07**-0042
Pore, D.M., **16**-1157
Pore, V.S., **15**-1535
Poretti, M., **15**-0450
Porri, L., **18**-0825
Porshnev, Yu.N., **02**-0182
Porta, F., **12**-0748, **19**-1748
Porta, O., **14**-0031, **14**-0094, **14**-0341, **14**-0344, **16**-0009, **16**-0141, **19**-0991, **19**-1657, **19**-1658, **19**-1663, **19**-1665
Portella, C., **16**-0009, **16**-1062, **16**-1492
Porter J.R., **16**-0865
Porter, C.R., **18**-0182
Porter, D.W., **10**-1211
Porter, G., **19**-1690
Porter, G.B., **07**-0011
Porter, H.K., **19**-1202
Porter, H.Q., **01**-0013
Porter, J.R., **16**-0865
Porter, N.A., **05**-0268, **14**-0014, **14**-0091, **15**-0065, **15**-1050, **15**-1096, **15**-1198, **15**-1207
Porter, R.D., **05**-0041, **05**-0091, **11**-0014
Porter, T.A., **12**-0382
Portlock, D.E., **10**-0981
Portnoy, M., **10**-1822, **13**-0607, **15**-1433
Portnoy, R.C., **10**-1733
Portoghese, P.S., **16**-1469
Porzi, G., **10**-0900, **10**-0916
Posey, I.Y., **10**-1622, **12**-0420
Poshkus, A.C., **16**-2170
Posner, B.A., **17**-0343

Posner, G.H., **10**-0664, **10**-0803, **10**-1334, **10**-1335, **10**-1338, **10**-1340, **10**-1342, **10**-1344, **10**-1351, **10**-1352, **10**-1369, **10**-1370, **10**-1436, **10**-1540, **15**-1042, **15**-1063, **15**-1072, **15**-1073, **15**-1087, **15**-1091, **15**-1093, **15**-1103, **15**-1967, **15**-2165, **16**-1148, **16**-1289, **16**-1892, **16**-1893, **16**-1894, **17**-0240
Posner, J., **18**-0204
Pospelov, M.V., **19**-0345
Poss, K.M., **18**-0665
Possel, O., **10**-1668
Post, A.J., **18**-0343
Posteher, F., **04**-0434
Poster, H., **10**-0707
Postigo, J.A., **18**-0481
Postovskii, I.Ya., **13**-0220, **13**-0638
Potapov, V.M., **04**-0144
Potapova, I.M., **16**-1186
Potdar, M.K., **11**-0213, **11**-0383
Potenza, J.A., **02**-0199
Potier, P., **16**-0402
Potini, C., **10**-0685
Potter, A., **14**-0116, **14**-0138
Potter, G.J., **15**-1557
Potter, N.H., **19**-0691
Potter, S.E., **18**-0386
Pötter, B., **01**-0096
Potthast, A., **16**-0370
Potts, A.W., **01**-0016, **01**-0019
Potts, K.T., **02**-0196, **15**-1046
Potvin, P.G., **03**-0119
Pouilhès, A., **15**-2146
Poulin, O., **15**-1125
Poulsen, C.S., **18**-0789
Poulter, C.D., **05**-0050, **10**-1149, **18**-0280, **18**-0537
Poulter, S.R., **04**-0422, **15**-0465
Poulton, D.J., **18**-0048
Poupaert, J.H., **19**-1791, **19**-1796
Poupart, M., **12**-0348
Poupart, M.A., **16**-1655
Poupko, R., **04**-0382, **18**-0619, **18**-0637
Pourali, A.R., **19**-0762
Pourbaix, C., **16**-0703
Pourcin, J., **18**-0225
Pourde II, G.W., **18**-0487
Poutsma, M.L., **14**-0024, **14**-0062, **14**-0125, **15**-0108, **15**-0142, **15**-1516, **19**-1465
Poux, M., **16**-0122
Pouységu, L., **11**-0193
Powell, A.L., **19**-1763, **19**-1765
Powell, D.A., **13**-0294
Powell, D.L., **02**-0342, **03**-0051
Powell, D.R., **12**-0469
Powell, H.K.J., **09**-0030
Powell, J.W., **17**-0280
Powell, M.F., **06**-0062, **06**-0087, **08**-0104, **08**-0105
Powell, M.T., **15**-0425
Powell, N.A., **10**-1782, **16**-0561
Powell, P., **03**-0083
Powell, R.E., **01**-0002
Power, P.P., **05**-0112, **05**-0175
Powers, D.B., **16**-0706
Powers, J.P., **04**-0357, **04**-0370, **05**-0278
Powers, J.W., **19**-0640
Poyer, J.L., **05**-0260
Poynton, A.J., **18**-0688
Pozebon, D., **13**-0397
Pozharskii, A.F., **02**-0148, **13**-0676
Pozsgay, V., **12**-0697
Pozzi, G., **13**-0404, **19**-1050, **19**-1776
Prabagaran, N., **15**-1329, **18**-0787
Prabhakar, S., **15**-1891, **15**-1907, **16**-0027
Prabhakaran, E.N., **13**-0181, **15**-1278
Prabhu, A.V., **16**-0581
Prabhu, K.P., **16**-0267
Prabhudas, B., **16**-0589
Pracejus, H., **04**-0136, **15**-0265
Pradaux, F., **16**-0646
Pradeille, N., **15**-0323
Pradhan, S.K., **19**-0962
Prados, P., **19**-1173
Praeger, D., **04**-0329
Prager, R.H., **10**-1758, **15**-0647, **16**-2166
Prajapati, D., **09**-0107, **10**-0591, **10**-0843, **10**-1394, **15**-1018, **16**-0149, **16**-0234, **16**-0395, **16**-0882, **16**-0927, **16**-1176, **16**-1182, **16**-1253, **16**-1902, **16**-1997, **18**-0313, **19**-0306, **19**-1264, **19**-1268, **19**-1554, **19**-1694
Prakash, G.K.S., **05**-0002, **05**-0014, **05**-0044, **05**-0058, **05**-0083, **05**-0085, **05**-0090, **05**-0093, **08**-0015, **10**-0119, **10**-0139, **10**-0173, **10**-0181, **10**-0182, **10**-0191, **10**-0200, **10**-1132, **10**-1179, **10**-1180, **11**-0119, **11**-0157, **11**-0212, **11**-0223, **11**-0236, **11**-0346, **11**-0420, **11**-0535, **12**-0048, **12**-0050, **12**-0156, **12**-0341, **12**-0341, **13**-0096, **13**-0265, **14**-0367, **15**-1628, **16**-0111, **16**-0185, **16**-0455, **16**-1940, **16**-1950, **16**-2043, **16**-2053, **19**-0773, **19**-1443, **19**-1447
Prakash, I., **12**-0719, **19**-0406, **19**-0645, **19**-0846
Prakash, O., **10**-0848, **15**-1605, **16**-1708, **19**-0203, **19**-0480, **19**-0483, **19**-0484, **19**-0844
Prakash, P.K.S., **11**-0473
Prakash, S.J., **10**-0958
Prall, M., **18**-0627
Praly, J., **04**-0366
Prandi, J., **18**-0143
Prasad, A.R., **10**-0958, **10**-1195, **14**-0308, **16**-1531
Prasad, A.S.B., **19**-1488
Prasad, B.A.B., **10**-0684, **16**-1453
Prasad, B.V., **02**-0422
Prasad, C.S.N., **10**-1849
Prasad, E., **19**-0984, **19**-0989
Prasad, K., **11**-0254, **16**-1825
Prasad, K.G., **19**-1071
Prasad, R., **15**-1936
Prasad, R.S., **19**-1515, **19**-1625
Prashad, M., **13**-0179, **19**-0680
Prashanthi, M., **16**-1172
Prasuna, G., **16**-1321
Pratelli, C., **04**-0120
Prather, J., **19**-1390
Prati, F., **16**-2122
Pratt, A.C., **18**-0852
Pratt, B.C., **15**-1503
Pratt, D.A., **02**-0024, **05**-0268
Pratt, D.V., **02**-0395, **18**-0682
Pratt, D.W., **04**-0295
Pratt, E.F., **10**-0655
Pratt, J.R., **10**-0895
Pratt, L.M., **05**-0172, **05**-0252, **08**-0211, **08**-0212, **10**-0307, **16**-1021, **19**-0939
Pratt, R.J., **12**-0032
Pratt, W.E., **04**-0432
Praveen, C., **19**-0703
Prechtl, F., **15**-1769, **19**-0504
Preda, D.V., **18**-0521
Pregel, M.J., **16**-2146
Preiss, T., **16**-1918
Prelog, V., **03**-0203, **04**-0043, **04**-0098, **04**-0131, **04**-0132, **04**-0164, **18**-0051
Premalatha, K., **16**-0279
Press, J.B., **10**-1129
Presser, N., **18**-0499
Pressman, D., **17**-0010
Prestat, G., **10**-1208, **10**-1499
Preston, S.B., **10**-1759
Preto, R.J., **06**-0076
Pretty, A.J., **18**-0386

Pretzer, W., **02**-0259, **02**-0265, **02**-0266
Preuss, H., **15**-0048
Prevost, C., **12**-0605, **16**-1403, **10**-0229
Prévost, N., **18**-0057
Prewitt, M.L., **14**-0089
Prewo, R., **04**-0460
Prezhdo, O.V., **02**-0152
Pri-Bar, I., **10**-1822, **12**-0737, **13**-0600, **19**-0661
Pric, J.M., **12**-0052
Price, A., **13**-0456
Price, C.C., **13**-0707
Price, D.A., **15**-1973
Price, G.J., **07**-0066, **07**-0082
Price, J.D., **04**-0482, **15**-1722, **15**-1724, **15**-2282
Price, M.D., **19**-1033
Price, M.J., **15**-0047
Price, R., **13**-0269, **13**-0280
Price, R.C., **17**-0064, **19**-1466
Price, W.C., **01**-0016
Priebe, H., **10**-1007
Priego, J., **10**-1454, **16**-0687, **16**-0688
Priesner, C., **10**-0391, **10**-0396
Priest, D.N., **17**-0157, **17**-0460
Priest, W.J., **04**-0411
Priester, W., **12**-0399
Prieto, J.A., **10**-1643, **15**-1741
Prieto, M., **13**-0504
Prieto, O., **16**-0687
Prieto, P., **13**-0413, **15**-1944
Prieto, R., **15**-0788
Prikazchikova, L.P., **15**-0045
Prilezhaeva, E.N., **15**-0049, **15**-0118
Prim, D., **13**-0470
Prince, A.A.M., **18**-0312
Prince, R.H., **14**-0457
Principe, L.M., **15**-1419, **15**-1449
Pring, M., **15**-0005
Pringle, P.G., **15**-1136
Prins, T.J., **19**-0894
Prins, W.L., **17**-0002
Prinsen, W.J.C., **04**-0067, **04**-0069
Prinzbach, H., **04**-0447, **12**-0375, **15**-2196, **15**-2196, **15**-2232, **15**-2241, **16**-2148, **19**-0068
Prior, D.V., **03**-0015
Prior, M.J., **16**-1236
Prisyahnyuk, V., **15**-1242
Pritchard, D.E., **05**-0273
Pritchard, G.J., **12**-0402
Pritchard, J.G., **16**-1770
Pritt, J.R., **10**-0280, **10**-0402
Pritzkow, H., **05**-0180
Pritzkow, W., **15**-0024, **15**-1735
Privett, O.S., **19**-0368
Priya kumar, U.D., **16**-0008
Probasco, E.K., **15**-0135
Probst, D.A., **18**-0813
Procházka, M., **10**-1796
Procopio, A., **10**-0545, **10**-1123, **15**-0875, **16**-1618
Procopiou, P.A., **10**-0717, **10**-0732, **10**-0994, **18**-0793
Procter, G., **16**-1023, **18**-0896
Prodger, J.C., **10**-1693, **15**-0900, **15**-1092
Prodolliet, J., **19**-0361
Proença, M.F.J.R.P., **11**-0528
Prokes, I., **11**-0230
Prokipcak, J.M., **10**-0212
Prokof'ev, A.K., **05**-0370, **13**-0037
Prokopiou, P.A., **19**-1410, **19**-1411
Prolingheuer, E., **18**-0027
Proops, W.R., **14**-0305
Proskow, S., **04**-0018, **15**-2227, **15**-2228
Pross, A., **01**-0112, **05**-0378, **08**-0142, **09**-0001, **10**-0078, **10**-0090, **10**-0304, **10**-0854
Pross, E., **10**-0458
Proto, A., **15**-1741, **15**-1822
Protopopova, M.N., **12**-0370, **15**-2302
Protschuk, G., **16**-2012
Provencal, D.P., **10**-1640
Proverb, R.J., **17**-0494
Prudent, N., **04**-0139
Pruett, R.L., **15**-1477
Pruitt, J.R., **15**-0266
Pruitt, K.M., **13**-0012, **13**-0086
Prunier, L., **10**-0208
Pruss, G.M., **17**-0092
Pryor, W.A., **05**-0202, **06**-0064, **14**-0001, **14**-0027, **14**-0062, **14**-0093, **18**-0054, **19**-0353, **19**-0356
Przemetchi, V., **19**-0631
Przheval'skii, N.M., **18**-0691
Przystas, T.J., **10**-0530, **10**-0536
Psaro, R., **19**-0958
Psarras, T., **05**-0103, **08**-0062
Ptock, A., **19**-1723
Pu, L., **16**-0549, **16**-0687, **16**-0549
Puar, M.S., **10**-0333
Pucheault, M., **12**-0334, **15**-1132
Pucher, R., **16**-2015
Puchta, R., **02**-0105, **02**-0417
Puckette, T.A., **16**-1195
Pudjaatmaka, H., **08**-0059, **08**-0064
Pudovik, A.N., **16**-0213
Puerta, J.E., **10**-0488
Puerta, M.C., **15**-0284
Pugh, J.K., **08**-0215
Pugh, R.L., **14**-0457
Pugia, M.J., **10**-0470
Pugin, B., **19**-0221
Puglia, G., **11**-0385, **11**-0388, **11**-0491
Puglis, J., **19**-1295
Pugnaud, S., **15**-2102
Pugsley, J.S., **19**-0218
Puigjaner, C., **19**-1031
Pujol, M.D., **10**-0923, **19**-0708
Puke, C., **16**-1300
Pulay, A., **17**-0058
Pulley, S.R., **15**-2410
Pullman, A., **02**-0003, **02**-0007
Pullman, B., **02**-0093, **02**-0174, **02**-0204
Pullmann, T., **13**-0539
Pulpoka, B., **03**-0140
Pumphrey, N.W.J., **01**-0087
Pungente, M.D., **10**-0758
Puniani, E., **16**-0798
Punna, S., **13**-0494
Punniyamurthy, T., **16**-0143, **19**-0120, **19**-0572, **19**-0681
Punta, C., **19**-0120, **19**-0588
Punzalan, E.R., **12**-0617
Punzi, A., **10**-1770, **16**-1924
Pupowicz, D., **15**-2349
Pupyshev, V.I., **15**-0181
Purcell, J., **14**-0351
Purcell, K.F., **10**-0443
Purchase, M., **16**-1562
Purdham, J.T., **10**-0148
Purdie, N., **04**-0117
Purdon, J.G., **15**-0485
Purmort, J.I., **12**-0413
Purnell, H., **10**-0916, **15**-0268
Purohit, V.G., **10**-1621
Purpura, M., **10**-1429
Purrington, S.T., **11**-0310, **11**-0311, **12**-0137, **12**-0160, **12**-0178, **14**-0129
Pursiainen, J., **03**-0170
Puterbaugh, W.H., **10**-1284, **13**-0764, **16**-1141
Putinas, J.M., **16**-2137
Pütter, R., **10**-0615, **10**-0616
Putz, G.J., **10**-0279
Putzas, D., **08**-0084
Puza, M., **11**-0116
Puzitskii, K.V., **10**-1833, **15**-1375, **18**-0422
Py, S., **15**-1009
Pyatin, B.M., **10**-0380, **10**-0686

Pyatnitskii, Yu.I., **19**-0412
Pye, C.C., **15**-2062
Pyne, S.G., **16**-1189, **16**-1490
Pyor, W.A., **15**-0050
Pyreseva, K.G., **12**-0709
Pyron R.S., **15**-2096, **15**-2098
Pyryalova, P.S., **19**-1180
Pytkowicz, J., **15**-1136
Pyun, C., **10**-1417
Pyun, S.-J., **10**-1197, **14**-0388
Pyykkö, P., **01**-0002

Qabar, M.N., **15**-1256
Qadir, M., **13**-0401
Qaseer, H.A., **15**-1534
Qi, H., **15**-0065
Qi, J.Y., **15**-1844
Qi, N., **19**-1652
Qian, C., **10**-1170, **15**-1741, **16**-0397
Qian, H., **15**-0233
Qian, M., **12**-0296
Qian, R., **16**-0631
Qian, X., **16**-0435, **16**-1175, **16**-1772
Qian, Z., **13**-0255
Qian, Z.-s., **19**-1040
Qiao, K., **15**-0719
Qiao, X., **02**-0074
Qin, B., **16**-1438
Qin, J., **16**-0932
Qing, F.-L., **16**-0451
Qing, F.L., **15**-0244, **15**-1671
Qiu, L.-Q., **15**-0604
Qiu, L.Q., **15**-1844
Qiu, M., **15**-2301
Qiu, X., **16**-1172
Qiu, Z., **11**-0439, **15**-2436
Qu, Z., **19**-1633
Quach, T.D., **10**-0629, **13**-0215, **13**-0533
Quack, M., **04**-0003
Quadbeck, G., **15**-0265
Quadrelli, P., **15**-1043
Quadri, M.L., **17**-0369
Quai, M., **16**-1258
Quallich, G.J., **19**-1032
Quan, L.G., **15**-2372, **16**-0566
Quan, P.M., **13**-0216, **13**-0467, **15**-1989
Quang, Y.V., **15**-1964
Quaranta, E., **16**-1842
Quartieri, S., **15**-1951
Quast, H., **10**-1000, **12**-0476, **18**-0642
Quayle, O.R., **16**-1555
Quayle, P., **11**-0492
Que Jr., L., **15**-1666
Queen, A., **10**-0079, **10**-0084
Queffelec, J., **15**-2181
Quéguiner, G., **13**-0312, **13**-0319
Querci, C., **15**-1730, **19**-0461
Quesnel, Y., **10**-0549
Quesnelle, C.A., **13**-0326
Quest, D.E., **12**-0688
Qui, N.T., **12**-0537
Quian, Y., **16**-0684
Quici, S., **05**-0253, **10**-0469, **10**-0470, **13**-0404, **19**-0109, **19**-0182, **19**-0185, **19**-1050, **19**-1776
Quiclet-Sire, B., **15**-0385
Quideau, S., **11**-0193
Quiles, F., **18**-0875
Quillinan, A.J., **10**-1769
Quinero, L., **10**-1162
Quinet, C., **15**-0316
Quiniou, H., **16**-0209
Quinkert, G., **04**-0136, **18**-0863
Quinn, H.W., **03**-0083
Quiñoá, E., **04**-0106, **04**-0108, **04**-0109
Quiñonero, D., **13**-0021
Quint, S., **10**-0886, **16**-1684
Quintanar-Audelo, M., **16**-1081
Quintard, J., **16**-2004
Quintavalla, A., **15**-2056
Quintero, L., **16**-0688
Quintin, J., **13**-0308
Quiram, E.R., **15**-0110
Quirante, J., **15**-1240
Quirion, J.-C., **16**-1280
Quirk, R.P., **08**-0033, **08**-0118
Quiroga-Feijoo, M.L., **16**-0527
Qureshi, M.I., **04**-0494

Ra, C.S., **12**-0684
Raab, V., **08**-0088
Raab, W., **10**-1662
Raabe, D., **11**-0321
Raabe, G., **01**-0009, **15**-1810, **16**-0687
Raaen, V.F., **10**-0079, **18**-0040, **18**-0056
Rabalais, J.W., **01**-0013
Raban, M., **04**-0032, **04**-0200, **04**-0202, **04**-0204, **04**-0250
Rabbat, P., **10**-1062
Rabenstein, D.L., **02**-0250
Raber, D.J., **10**-0053, **10**-0057, **10**-0079, **10**-0170, **10**-0279, **10**-0727
Rabeyrin, C., **10**-1454
Rabideau, P.W., **02**-0359, **02**-0360, **02**-0362, **02**-0363, **04**-0349, **15**-0533, **15**-0538, **15**-0544, **15**-0546
Rabinovich, D., **02**-0292
Rabinovich, E.A., **12**-0061
Rabinovitch, B.S., **05**-0339, **12**-0380
Rabinovitz, M., **02**-0172, **02**-0184, **02**-0272, **02**-0274, **02**-0297, **02**-0298, **02**-0332, **04**-0071, **05**-0052, **10**-0455, **10**-0457, **15**-0532, **15**-0969, **17**-0307, **19**-1166, **19**-1179
Rabinowitz, J.L., **15**-1513, **18**-0337
Rabinowitz, M., **02**-0245
Rabinowitz, R., **16**-1289
Rabjohn, N., **04**-0516, **19**-0468, **19**-0553
Rablen, P.R., **01**-0108, **02**-0037, **04**-0302, **04**-0305, **04**-0309, **16**-2016
Racela, W., **08**-0023
Racher, S., **07**-0080
Racherla, U.S., **12**-0557, **15**-0660, **15**-0672, **16**-0707, **18**-0252
Rachon, J., **12**-0612, **18**-0019
Rachoń, J., **05**-0356
Rack, E.P., **14**-0051, **15**-1514
Raczynska, E.D., **12**-0085
Raczyńska, E.D., **08**-0087
Rad, A.A.R., **18**-0321
Rad, M.N.S., **16**-1789
Radeglia, R., **04**-0039
Radell, J., **03**-0159
Rademacher, L.E., **17**-0395
Rademacher, P., **04**-0266, **04**-0458
Radford, D.V., **03**-0099
Radhakrishna Murti, P.S., **19**-0622
Radhakrishna, A., **12**-0227
Radhakrishna, A.S., **18**-0272
Radhakrishna, P., **16**-1671
Radhakrishnan, K.V., **13**-0303
Radhakrishnan, U., **13**-0562, **15**-0854, **15**-1389, **15**-2372, **15**-2379
Radi, M., **07**-0119
Radics, L., **04**-0225
Radinov, R., **15**-1050
Radivoy, G., **19**-1311
Radke, C.M., **18**-0643
Radke, K.R., **13**-0195
Radkiewicz-Poutsma, J.L., **18**-0369
Radkowski, K., **15**-0475
Radlick, P., **02**-0255, **18**-0268, **19**-0446
Radner, F., **11**-0101, **11**-0135, **1**-0160
Radom, L., **02**-0186, **01**-0112, **02**-0014, **02**-0028, **02**-0172,

04-0285, **05**-0024, **08**-0234, **15**-0538, **18**-0219
Radtke, R., **19**-0023
Radzik, D.M., **17**-0240
Radziszewski, J.G., **05**-0269, **02**-0218, **04**-0497, **04**-0498
Raecke, B., **11**-0622
Raeppel, S., **13**-0608
Raevskii, O.A., **03**-0150, **03**-0110
Rafati, M., **19**-0246
Rafei, M., **16**-1646
Rafel, S., **16**-0772, **16**-0777, **16**-0797
Rafferty, P., **16**-1954
Rafikov, S.R., **16**-1463
Ragagnin, G., **15**-1843, **19**-0182
Ragain, R.M., **10**-0208
Ragauskas, A.J., **05**-0126
Raghavachari, K., **10**-0206
Raghavan, A.S., **18**-0473, **18**-0544
Raghavan, K.V., **11**-0248, **11**-0256, **16**-1672, **19**-0781
Raghavan, M., **19**-0735
Raghavan, S., **19**-0857
Raghavendra, S., **10**-1570
Ragi, A., **19**-0813
Ragnarsson, U., **10**-0992
Ragoussis, N., **16**-0982, **19**-1021
Ragoussis, V., **16**-0982
Ragunathan, K.G., **03**-0118
Rahaim Jr., R.J., **11**-0657
Raheem, I.T., **07**-0123
Rahim, Md.A., **16**-1357
Rahimizadeh, M., **15**-2366
Rahm, A., **12**-0014
Rahman, A., **19**-1316, **19**-1487
Rahman, A.-u., **10**-0860
Rahman, M., **19**-0251
Rahman, S.M.A., **10**-0765
Rahn, B.J., **10**-1296
Rai, A.N., **10**-0631
Rai, R., **12**-0268
Rai, R.S., **19**-1097
Raimondi, L., **15**-1697, **15**-1939
Raimondi, M., **02**-0006, **02**-0121
Rainer, J.D., **15**-1268
Raines, R.T., **06**-0048
Rainier, J.D., **18**-0816
Rainka, M.P., **18**-0726
Rainsford, A.E., **17**-0444
Rainville, D.P., **12**-0015, **15**-0651
Rairama, R., **16**-0562
Raithby, P.R., **03**-0017
Raj, K.S., **10**-0958, **10**-1195
Raj, C.P., **15**-2023
Raja, R., **19**-1028
Rajabi, J., **19**-0151
Rajadhyaksha, S.N., **19**-0764
Rajagopal, D., **16**-1068
Rajagopal, R., **11**-0237, **13**-0415, **13**-0491
Rajagopal, S., **05**-0409, **10**-0449, **10**-0451, **19**-0831
Rajagopalan, R., **19**-0602
Rajagopalan, S., **15**-1186
Rajakumar, P., **04**-0077
Rajan Babu, T.V., **15**-1492
Rajan, S., **12**-0209, **13**-0589
RajanBabu, T.V., **15**-0052, **15**-0762, **15**-0798, **15**-0820, **15**-1182, **15**-0844
Rajanna, K.C., **11**-0122
Rajappa, S., **16**-1692, **18**-0701
Rajaram, J., **15**-0436
Rajaram, S., **19**-1640
Rajasekaran, K., **19**-0831
Rajasekhar, K., **10**-0823
Raje, P.S., **16**-0386
Rajender, A., **19**-0857
Rajendran, V., **07**-0089
Rajewski, R.A., **09**-0094
Rajkumar, A.B., **15**-0586
Rajkumar, G.A., **19**-0085
Rajkumar, M., **10**-0942
Rajogopal, R., **11**-0131
Rajput, A.S., **01**-0077
Raju, A.K., **16**-0383
Rajzmann, M., **05**-0313, **10**-0443
Rakhit, S., **13**-0272, **15**-1125
Rakhmankulov, D.L., **05**-0053, **10**-0528, **16**-1470
Rakitin, O.A., **13**-0687
Rákos, L., **10**-0663
Rakshit, A.B., **08**-0237
Raksis, J.W., **18**-0267
Raksit, A.B., **10**-0345, **10**-0346
Raley, J.H., **18**-0083
Ralph, E.K., **08**-0220
Ralte, S.L., **16**-0125
Ram, R.N., **16**-0388
Ram, S., **16**-0371, **19**-1203, **19**-1448
Ram, S.R., **19**-1208, **19**-1257, **19**-1259, **19**-1547
Rama Rao, A.V., **16**-0249, **18**-0330, **19**-1018
Rama, K., **10**-1528
Ramachandar, T., **10**-0958, **16**-1618, **19**-0692
Ramachandraiah, G., **11**-0239, **11**-0296
Ramachandran, J., **16**-0846
Ramachandran, P.V., **15**-0645, **15**-0674, **16**-0699, **19**-1016, **19**-1018, **19**-1054, **19**-1260
Ramachary, D.B., **16**-0877
Ramadas, S.R., **16**-0846
Ramaiah, M., **14**-0001
Ramaiah, D., **07**-0062, **07**-0063
Ramaiah, P., **19**-0773
Ramakers, J.E., **04**-0485
Ramakrishnan, V.T., **12**-0707, **17**-0386
Ramalingam, T., **10**-0556, **16**-0149, **19**-0302, **19**-1253, **19**-1758
Ramalingam, V.T., **16**-0167
Ramamurthy, V., **05**-0409, **07**-0019, **07**-0021, **07**-0039, **07**-0044, **11**-0558, **14**-0229, **15**-2157, **15**-2235
Raman, J.V., **02**-0054
Ramana, A.V., **19**-1266
Ramana, C.V., **18**-0309
Ramana, K.V., **16**-0088, **19**-1266
Ramana, M.M.V., **11**-0120
Ramanathan, B., **15**-0360
Ramanathan, C.R., **04**-0160
Ramarao, C., **15**-0420, **15**-1667, **19**-0128, **19**-0894
Ramart-Lucas, P., **18**-0130
Ramaseshan, M., **15**-0318
Ramaswamy, S., **18**-0563
Rambaud, D., **15**-0718
Rambaud, M., **12**-0621
Rambo, E., **15**-1805
Ramchandani, R.K., **13**-0410
Ramdan, M., **16**-1644
Ramesh, C., **13**-0399, **13**-0604, **13**-0605, **16**-0322, **16**-1526, **16**-1527, **16**-1532, **17**-0442
Ramesh, G., **10**-1109
Ramesh, M., **14**-0387
Ramesh, P., **10**-0680
Rameshkumar, C., **15**-1389, **15**-1413
Raminelli, C., **12**-0290
Ramirez, F., **16**-1262, **16**-1289, **16**-1302
Ramminger, C., **18**-0781
Rammler, D.H., **16**-1716
Rammoorty, V., **19**-1614
Ramnarayan, K., **19**-0960
Ramnauth, J., **13**-0272, **15**-1125, **17**-0511
Ramón, D.J., **16**-0687
Ramondenc, Y., **10**-1405
Ramontini, M., **16**-0392
Ramos, A., **18**-0570, **18**-0858
Ramos, B., **17**-0379
Ramos, E.C., **15**-1077

Ramos, J., **17**-0155
Ramos, J.H.R., **10**-1800, **15**-1334, **15**-2150
Rampalli, S., **15**-0878
Rampi, R.C., **13**-0157
Rampoldi, A., **10**-0347
Ramsay, D.A., **01**-0052
Ramsay, O.B., **04**-0001, **17**-0042
Rämsby, S., **16**-1827
Rämsch, R.Y., **16**-1497
Ramsden, C.A., **02**-0010, **02**-0341
Ramsden, H.E., **12**-0457
Ramsden, P.D., **04**-0161
Ramsey, B., **05**-0052, **10**-0165, **10**-0166
Ramsey, B.G., **01**-0013
Ramu, R., **16**-1527
Rana, K.K., **11**-0246, **11**-0247, **15**-0255
Rana, S., **16**-0363
Ranaivosata, J.-L., **05**-0299
Rancourt, J., **05**-0242, **15**-0053
Rand, M.H., **16**-0044
Randad, R.S., **16**-0493, **16**-0706
Randall, L.H., **02**-0054
Rander, K.D., **11**-0191
Randić, M., **02**-0109, **02**-0096, **04**-0417
Randl, S., **18**-0781, **18**-0792
Randolph, C.L., **15**-0707
Rane, A.M., **10**-0777, **15**-1665
Raner, K.D., **07**-0115, **14**-0116 **14**-0119, **14**-0122, **14**-0163
Ranes, E., **11**-0145
Rang, H., **04**-0437
Rangaishenvi, M.V., **15**-0670, **19**-1527
Ranganathan, D., **15**-2185, **18**-0733, **19**-0397
Ranganathan, K., **15**-1241
Ranganathan, S., **15**-2185, **18**-0733, **19**-0397
Ranganayakulu, K., **05**-0051
Rangappa, K.S., **06**-0084
Rangarajan, R., **19**-0558
Rani, K.S., **10**-1216
Rani, N., **10**-0848
Rank, B., **19**-0325
Rankin, K.N., **19**-0671
Ranu, B., **19**-0927, **19**-0937
Ranu, B.C., **10**-0812, **10**-0829, **10**-1223, **11**-0418, **15**-0191, **15**-0191, **15**-0480, **15**-0567, **15**-0570, **15**-0582, **15**-0617, **15**-1059, **15**-1332, **16**-0048, **16**-0369, **16**-0578, **16**-0597, **16**-1522, **16**-1524, **16**-1829, **17**-0212, **17**-0372, **17**-0374, **18**-0138, **19**-0895, **19**-0932, **19**-0937, **19**-0944, **19**-1133, **19**-1336, **19**-1377
Rao, A.B., **19**-1022
Rao, A.J., **16**-0766
Rao, A.S., **10**-0494
Rao, B.N., **11**-0558
Rao, C.G., **09**-0009, **10**-0179, **10**-0320, **15**-0666
Rao, C.N.R., **02**-0377, **03**-0067
Rao, C.T., **10**-1107, **10**-1131
Rao, C.V., **16**-1531
Rao, D.P., **13**-0575
Rao, D.V., **11**-0594, **19**-0554
Rao, G.V., **10**-0909, **19**-1270, **19**-1382, **19**-1637, **19**-1693
Rao, H.S.P., **15**-1311, **16**-0162
Rao, J.M., **10**-0601, **15**-2252, **18**-0429, **18**-0435, **19**-1031, **19**-1555
Rao, K., **10**-0958
Rao, K.R., **10**-0546, **10**-0579, **10**-0671, **10**-0925, **10**-0927, **10**-0958, **19**-0032, **19**-0200, **19**-0229, **16**-0125
Rao, K.V., **10**-1195
Rao, K.V.R., **19**-0121
Rao, M.L.N., **13**-0327, **13**-0336
Rao, M.S., **16**-0871, **16**-1374
Rao, M.V., **16**-0089
Rao, N.V., **10**-1138, **16**-0084, **16**-0337, **16**-1781
Rao, P.B., **15**-1791, **15**-1807, **15**-1812, **16**-1321, **18**-0361
Rao, P.D., **16**-0771
Rao, P.P., **10**-1195
Rao, P.S., **19**-1193
Rao, R., **11**-0233
Rao, R.J., **10**-1123, **19**-1555
Rao, R.S., **11**-0435, **15**-2134
Rao, S.A., **14**-0378, **15**-0950, **15**-0953, **16**-0645
Rao, S.N., **10**-0459
Rao, T.S., **11**-0273
Rao, V.D., **04**-0160
Rao, V.V.R., **14**-0395, **15**-0665
Rao, V.V.V.N.S.R., **19**-1193
Rao, Y.S., **19**-0110
Raphael, R.A., **04**-0451
Rapoport, H., **13**-0741, **16**-1817, **16**-1823, **16**-2024, **19**-0470, **19**-1088
Raposo, C., **15**-1938
Rapp, M.W., **10**-0430
Rappa, A., **13**-0676, **15**-0550
Rappe, A.K., **15**-1761, **04**-0397
Rappe, C., **12**-0140, **12**-0141, **17**-0344, **18**-0194, **18**-0202, **18**-0205, **18**-0209
Rappé, A.K., **18**-0836
Rappoport, Z., **05**-0254, **01**-0009, **01**-0045, **02**-0038, **02**-0343, **02**-0381, **02**-0393, **02**-0394, **02**-0395, **02**-0396, **02**-0397, **02**-0399, **02**-0405, **03**-0097, **03**-0125, **04**-0026, **04**-0047, **04**-0408, **04**-0409, **04**-0410, **04**-0421, **04**-0431, **04**-0435, **04**-0464, **04**-0506, **05**-0068, **05**-0119, **05**-0136, **05**-0241, **05**-0314, **05**-0316, **05**-0404, **07**-0064, **08**-0061, **08**-0071, **09**-0032, **10**-0115, **10**-0136, **10**-0237, **10**-0240, **10**-0241, **10**-0242, **10**-0244, **10**-0245, **10**-0247, **10**-0248, **10**-0249, **10**-0255, **10**-0265, **10**-0266, **10**-0293, **10**-0315, **10**-0391, **10**-0403, **10**-0423, **10**-0440, **10**-0839, **10**-1036, **10**-1265, **10**-1785, **11**-0227, **11**-0370, **11**-0444, **12**-0059, **12**-0083, **12**-0086, **12**-0095, **12**-0699, **13**-0027, **13**-0037, **13**-0049, **13**-0052, **13**-0691, **14**-0301, **15**-0035, **15**-0037, **15**-0038, **15**-0039, **15**-0050, **15**-0075, **15**-0077, **15**-0106, **15**-0435, **15**-0513, **15**-0572, **15**-0705, **15**-1499, **15**-1790, **15**-1932, **15**-1986, **15**-1991, **15**-2234, **15**-2261, **15**-2283, **16**-0012, **16**-0972, **16**-1166, **16**-1169, **16**-1421, **16**-2124, **17**-0047, **17**-0055, **17**-0056, **17**-0148, **17**-0300, **17**-0367, **17**-0387, **17**-0424, **17**-0450, **17**-0458, **18**-0159, **19**-0021, **19**-0258, **19**-0633, **19**-0738, **19**-0795, **19**-0812, **19**-0920, **19**-1166, **19**-1179, **19**-1561
Raptis, M., **19**-0250
Rasanen, M., **04**-0297
Rashatasakhon, P., **13**-0233
Rashchupkina, Z.A., **10**-1598
Rasheed, M.A., **18**-0608, **19**-0857
Rashid, S.M.K., **15**-2164
Rasmussen, J.K., **10**-1650, **10**-1662, **12**-0199, **12**-0311, **16**-1233, **16**-1425, **16**-2110
Rasmussen, J.R., **12**-0013
Rasmussen, K.G., **16**-0944
Rasmussen, S.C., **13**-0195
Rasmussen, S.E., **10**-0005, **11**-0424
Rasmussen, T., **16**-0685
Rasne, R.M., **15**-1029, **15**-1041
Raspin, K.A., **14**-0457
Raspoet, G., **18**-0306

Rassat, A., **05**-0208, **05**-0258, **16**-1290, **19**-0962
Rassias, G.A., **15**-1782
Rassu, G., **16**-0984
Rasteikiene, L., **15**-1601
Rastelli, A., **15**-1731, **15**-1733, **15**-1736, **15**-1944, **15**-1951, **19**-0519
Rastetter, W.H., **15**-1728
Raston C.L., **09**-0084, **09**-0120, **09**-0121, **10**-1321, **12**-0574, **12**-0579, **12**-0582, **15**-0947, **16**-0610, **16**-0883
Rasul, G., **05**-0093, **11**-0119, **11**-0236
Ratajczak, F., **19**-0189
Ratajczak, H., **03**-0037, **18**-0028, **18**-0046
Ratajczyk, T., **04**-0299
Ratcliffe, A.J., **10**-0537
Ratcliffe, P.D., **16**-1383, **19**-0126
Ratcliffe, R., **10**-1118, **19**-0079
Rath, N.P., **07**-0062
Rathjen, H., **12**-0345
Rathke, M.W., **04**-0512, **10**-1633, **10**-1745, **10**-1746, **10**-1751, **10**-1754, **10**-1761, **12**-0176, **12**-0487, **15**-1183, **16**-0809, **16**-0812, **16**-1133, **16**-1235, **16**-1249, **16**-2006, **16**-2013, **16**-2015, **16**-2019, **16**-2020, **18**-0422, **18**-0425, **18**-0430, **18**-0431, **19**-0059, **19**-0841
Rathmell, R.E., **15**-0887
Rathore, R., **10**-1331, **19**-0272, **19**-0560
Ratnam, K.R., **10**-1131
Ratnasamy, P., **13**-0399
Ratovelomanana, V., **10**-1297
Ratovelomanana-Vidal, V., **19**-1028
Ratts, K.W., **15**-0397
Ratusky, J., **11**-0622, **11**-0623, **11**-0624, **11**-0625
Rau, A., **18**-0616
Rau, H., **07**-0009
Rau, M., **15**-0036
Raubo, P., **19**-1395
Raucher, D.J., **15**-2406
Rauchfuss, T.B., **16**-0213
Raudenbusch, W., **17**-0404, **17**-0456
Rauhut, M.M., **06**-0035, **06**-0036, **13**-0755
Rauk, A., **01**-0101, **04**-0033, **04**-0036, **04**-0247, **04**-0285, **05**-0078, **08**-0144, **10**-0280, **12**-0232, **18**-0166
Rauleder, G., **18**-0028
Raulins, N.R., **18**-0594, **18**-0654
Raunio, E.K., **15**-0047
Rausch, B.J., **15**-1447
Rausch, M.D., **02**-0166, **12**-0392
Raut, S.V., **17**-0265
Rautenstrauch, C.W., **09**-0089
Rautenstrauch, V., **14**-0237, **18**-0407, **18**-0729, **18**-0730, **18**-0738, **19**-0962, **19**-0964
Ravard, A., **17**-0315
Ravasio, N., **19**-0958
Raveendran, P., **09**-0095
Ravenek, W., **15**-1494
Ravenscroft, M.D., **13**-0036
Ravichandran, S., **19**-0646
Ravikumar, K.S., **19**-0938, **19**-0948
Ravindran, N., **12**-0492, **12**-0494, **15**-0659, **18**-0447
Ravindran, T., **19**-1282
Ravindranath, B., **16**-1769, **17**-0197
Ravindranath, N., **16**-1526, **16**-1527, **16**-1532
Ravindranathan, M., **09**-0009, **10**-0133, **10**-0320, **15**-0792, **18**-0106, **18**-0107
Ravindranathan, T., **10**-1068, **15**-1887, **15**-2185, **16**-0243, **18**-0450
Raw, A.S., **19**-1680
Raw, S.A., **16**-1278, **16**-1407
Rawal, V.H., **10**-1026, **13**-0332, **14**-0298, **15**-2003, **15**-2132, **18**-0513
Rawalay, S.S., **19**-0664
Rawat, M., **15**-2412
Rawdah, T.N., **05**-0002
Rawlinson, D.J., **11**-0183, **14**-0149, **14**-0196, **14**-0246, **14**-0249, **14**-0251, **15**-1608, **18**-0865
Rawson, R.J., **15**-2330
Ray Jr., W.J., **13**-0779
Ray, A., **19**-1607
Ray, C.A., **15**-2123
Ray, G.C., **18**-0825
Ray, R., **15**-1660
Ray, S., **16**-1610
Ray, T., **19**-0576
Rayadh, A., **15**-1029, **15**-1328
Rayanakorn, M., **10**-0916, **15**-0268
RayMahasay, S., **11**-0054
Raymo, F.M., **02**-0312, **03**-0200
Raymond, K.N., **02**-0254
Rayner, C.M., **09**-0107, **13**-0407, **13**-0426, **15**-2036
Raynie, D.E., **09**-0093
Raza, A., **16**-0744
Razdan, R.K., **14**-0378
Razin, V.V., **16**-1680
Razinger, M., **04**-0101
Razumovskii, S.D., **19**-0345, **19**-0357, **19**-0359
Razuvaev, G.A., **09**-0020, **12**-0438, **14**-0293
Razzuk, A., **13**-0080
Rea, D.G., **04**-0378
Read de Alaniz, J., **16**-0726
Read, D., **04**-0248, **04**-0249
Read, R.A., **17**-0094
Read, R.W., **10**-1027
Read, T.O., **13**-0086
Reader, J.C., **15**-2083
Readio, P.D., **14**-0040, **14**-0183, **15**-0124
Readman, J.M., **11**-0057
Readshaw, S.A., **04**-0366, **04**-0367
Ready, J.M., **10**-0583
Reagan, J., **19**-0352
Reagan, M.T., **08**-0122, **19**-1276
Reale, A., **19**-1714
Reardon Jr., E.J., **12**-0080, **15**-2350
Reardon, R.C., **05**-0406
Rebbert, R.E., **07**-0049
Rebeiro, G.L., **11**-0432, **18**-0716
Rebek Jr., J., **03**-0150, **15**-2025
Rebek, J., **16**-1799, **16**-1817, **18**-0615
Rebeller, M., **19**-1421
Reber, G., **01**-0011
Rebiere, F., **15**-2064, **19**-0822
Rebolledo, F., **19**-1022
Reboul, E., **16**-1078
Recca, A., **19**-1714
Rechsteiner, B., **16**-0294
Recktenwald, G., **19**-1689
Recupero, F., **19**-0120, **19**-0181, **19**-0331, **19**-0588, **19**-0612, **19**-1047
Reddy, A.C., **10**-0854
Reddy, A.S., **16**-1747
Reddy, A.V.N., **10**-1030
Reddy, B.G., **15**-2007
Reddy, B.M., **12**-0738, **16**-0149
Reddy, B.S.N., **19**-1268
Reddy, B.S.P., **19**-1268

Reddy, B.V.S., **09**-0115, **10**-0556, **10**-0682, **10**-0822, **10**-0823, **10**-0865, **10**-0958, **10**-0963, **10**-1195, **10**-1550, **10**-1570, **11**-0219, **11**-0435, **13**-0147, **13**-0159, **13**-0655, **14**-0308, **15**-1004, **15**-1035, **15**-1327, **15**-1340, **15**-1606, **15**-2134, **16**-0149, **16**-0167, **16**-0169, **16**-0233, **16**-0279, **16**-0324, **16**-0332, **16**-0383, **16**-0604, **16**-0763, **16**-0871, **16**-1174, **16**-1175, **16**-1476, **16**-1531, **17**-0366, **17**-0399, **18**-0301, **18**-0608, **18**-0662, **19**-0031, **19**-0032, **19**-0302, **19**-1551, **19**-1594, **19**-1758
Reddy, C.K., **15**-1143
Reddy, Ch.G., **10**-1131
Reddy, Ch.K., **10**-0231
Reddy, Ch.R., **10**-1123, **16**-0093, **16**-0355, **19**-1453, **19**-1555
Reddy, Ch.S., **10**-0823, **16**-0176, **16**-1172
Reddy, Ch.V., **15**-1001, **19**-0781
Reddy, D.R., **19**-0483
Reddy, D.S., **03**-0070, **18**-0297, **19**-0682, **19**-1382
Reddy, E.B., **16**-0333
Reddy, E.J., **16**-0930
Reddy, G.D., **15**-1217, **15**-2231
Reddy, G.J., **11**-0333, **19**-1032, **19**-1035
Reddy, G.R., **16**-1172, **16**-1747
Reddy, G.S., **10**-1139, **16**-0080, **16**-0252, **16**-1348, **16**-1608, **16**-1611, **16**-1748, **16**-1906, **16**-2154, **19**-0864, **19**-1599
Reddy, G.S.K., **19**-1195
Reddy, G.S.K.K., **10**-0930, **16**-0604
Reddy, G.V., **19**-1193, **19**-1270
Reddy, G.V.S., **10**-0909, **19**-1637
Reddy, J.P., **19**-1149
Reddy, J.S.S., **15**-2134
Reddy, K.B., **10**-0930, **14**-0308
Reddy, K.L., **19**-1195
Reddy, K.V., **16**-0052, **16**-1404, **18**-0701
Reddy, L.R., **10**-0579, **10**-0925, **10**-0927, **10**-0958
Reddy, M.A., **10**-0546, **10**-0579, **10**-0925, **10**-0927, **10**-0958, **19**-0200
Reddy, M.M., **16**-1341, **16**-1748, **19**-1551
Reddy, M.R., **16**-1973
Reddy, M.S., **16**-0784, **19**-0229
Reddy, M.S.K., **16**-0090
Reddy, M.V., **16**-0093, **16**-1618, **19**-1237
Reddy, M.V.R., **16**-0699, **19**-0595
Reddy, N.K., **15**-1552
Reddy, N.P., **12**-0748, **13**-0174, **19**-0219
Reddy, N.R., **13**-0405, **16**-0784
Reddy, N.V., **16**-1172
Reddy, P.G., **12**-0732
Reddy, P.M., **13**-0655
Reddy, P.N., **15**-0270
Reddy, P.P., **16**-0329, **19**-0682
Reddy, P.S., **19**-1541
Reddy, P.S.M.M., **10**-0560
Reddy, P.S.N., **16**-0329, **19**-0682
Reddy, P.S.R., **16**-0871
Reddy, P.T., **15**-1004, **16**-0324, **16**-1175, **19**-1022, **19**-1031
Reddy, P.V., **10**-0958
Reddy, R., **15**-0933
Reddy, R.M., **16**-0807
Reddy, R.S., **15**-0612
Reddy, R.T., **19**-0823
Reddy, S., **11**-0587
Reddy, T.I., **16**-1178
Reddy, V.L.N., **10**-0680
Reddy, V.P., **11**-0119, **15**-2049, **18**-0548
Reddy, V.R., **12**-0738, **16**-0149
Reddy, Y.K., **13**-0346
Reddy, Y.R., **18**-0606
Redecker, T., **05**-0174
Redgrave, A.J., **15**-1724
Redlich, O., **03**-0160
Redlich, S., **13**-0380
Redman, R.P., **17**-0052, **17**-0102
Redmond, W., **13**-0717
Redmore, D., **17**-0510, **18**-0159, **18**-0174, **18**-0194, **18**-0217, **18**-0237, **18**-0569
Redpath, J., **15**-0878
Redvanly, C.S., **18**-0224
Redwine, O.D., **05**-0219
Ree, B., **05**-0050, **10**-0198
Reece, P.A., **10**-1758
Reed, C.A., **09**-0111, **05**-0008, **05**-0009, **08**-0106
Reed, D., **13**-0654
Reed, D.W., **14**-0188
Reed, J.N., **12**-0512
Reed, K.W., **18**-0362
Reed, L.L., **02**-0163
Reed, R., **12**-0591
Reed, R.G., **19**-1334
Reed, S.A., **04**-0389
Reed, S.C., **05**-0351
Reedich, D.E., **17**-0508
Reedijk, J., **10**-0925, **19**-0183
Reek, J.N.H., **13**-0177, **19**-1022
Reents Jr., W.D., **11**-0101
Rees, C.W., **02**-0267, **02**-0270, **05**-0327, **15**-1894, **15**-2325
Rees, J.H., **01**-0042
Rees, L., **11**-0142
Rees, T.C., **15**-0867
Reese, C.B., **11**-0556, **12**-0354, **16**-0093, **16**-1459, **18**-0509, **19**-1130
Reese, O., **15**-1104
Reetz, M.T., **10**-1381, **10**-1383, **10**-1389, **10**-1508, **10**-1613, **10**-1624, **11**-0427, **13**-0397, **14**-0049, **15**-0413, **15**-0600, **15**-0926, **15**-1125, **15**-1134, **16**-0492, **16**-0493, **16**-0519, **16**-0520, **16**-0564, **16**-0580, **16**-0647, **16**-0677, **16**-0679, **16**-0684, **16**-0709, **16**-0946, **16**-1033, **16**-1077, **16**-1088, **16**-1090, **16**-1204, **17**-0199, **18**-0892, **18**-0893, **19**-0027
Reeve, W., **08**-0050, **17**-0395
Reeves, R.L., **16**-0099, **16**-0266, **16**-0969
Reeves, W.P., **10**-1006, **11**-0233
Refvik, M.D., **19**-1525
Regen, S.L., **07**-0080, **07**-0087, **10**-0469, **10**-0470, **10**-0709, **10**-0808, **17**-0307, **19**-0099
Reger, D.L., **15**-0417
Reggel, L., **15**-0549
Reginato, G., **15**-1068, **16**-0217, **17**-0209, **17**-0209
Regis, R.R., **12**-0187
Regitz, M., **01**-0009, **04**-0479, **05**-0364, **05**-0381, **10**-0390, **12**-0214, **13**-0693, **15**-2360, **16**-2165, **17**-0281, **17**-0496, **18**-0215, **18**-0495, **18**-0496, **18**-0643, **19**-0297
Régnier, S., **18**-0308
Regnourf-de-Vains, J.-B., **03**-0125
Regulski, T.W., **15**-0016
Rehan, A.H., **16**-1303
Rehborn, D.C., **13**-0479
Rei, M., **15**-0259, **15**-0260
Reibenspies, J.H., **15**-0425
Reich, C.J., **10**-0517
Reich, H.J., **05**-0119, **05**-0141, **05**-0177, **05**-0181, **10**-0114, **10**-1714, **12**-0245, **12**-0629, **15**-1113, **17**-0290, **17**-0292, **17**-0293, **18**-0733, **19**-0827

Reich, I.J., **12**-0245
Reich, I.L., **10**-0114, **17**-0293
Reich, S.D., **10**-0148
Reichard, D.W., **05**-0126
Reichardt, C., **10**-0399, **10**-0428, **10**-0430, **10**-0443, **10**-0445, **10**-0446, **10**-0447, **14**-0114
Reichel, C.J., **16**-0405
Reichenbach, T., **15**-0862
Reichenbacher, P.H., **18**-0043
Reichle, R., **18**-0024
Reichle, W.T., **12**-0001
Reichlin, D., **15**-2063
Reichmanis, E., **02**-0257, **02**-0274
Reichwein, J.F., **15**-1444
Reid, C.G., **14**-0269
Reid, C.S., **10**-1549
Reid, D.H., **02**-0131, **19**-0254
Reid, D.J., **10**-0079
Reid, E.E., **16**-1782
Reid, G., **03**-0114
Reid, I., **12**-0072
Reid, M., **16**-1278
Reid, S.N., **16**-1138
Reider, P.J., **04**-0197, **09**-0105, **13**-0237, **13**-0385, **13**-0504, **15**-0440, **15**-1038, **16**-0280, **19**-0673, **19**-0678, **19**-1148
Reiding, D.J., **11**-0596
Reif, L., **11**-0603
Reiff, H., **16**-1056
Reiffers, S., **19**-1738
Reihs, S., **15**-1839
Reijnders, P.J.M., **10**-1252
Reikhsfel'd, V.O., **15**-2362
Reimlinger, H., **12**-0057
Rein, B.M., **10**-1096, **13**-0252
Rein, T., **14**-0252, **16**-1308, **16**-1314
Rein, T., **16**-1326
Reinecke, M.G., **13**-0049
Reinehr, D., **15**-0866
Reineke, C.E., **18**-0044
Reinhardt, L.A., **05**-0326
Reinheimer, J.D., **13**-0086
Reinhold, U., **16**-0857
Reinhoudt, D.N., **03**-0101, **03**-0113, **03**-0172, **15**-2166
Reinke, L.A., **05**-0260
Reinmuth, O., **10**-1231, **10**-1321, **10**-1536, **12**-0558, **12**-0574, **16**-0464, **16**-0842, **16**-0851, **16**-0951, **16**-1921, **16**-1931, **16**-1934
Reis, H., **15**-1378
Reis, Ö., **13**-0349, **19**-0494
Reisch, J., **15**-0359
Reisdorf, D., **19**-0836
Reisenauer, H.P., **02**-0164
Reiser, O., **16**-1158, **16**-1308
Reiser, O.B., **16**-1326
Reisse, J., **07**-0075, **07**-0076, **07**-0080, **07**-0082, **16**-0578
Reisser, M., **15**-0757
Reissig, H., **04**-0410, **15**-0128
Reissig, H.-U., **16**-0671, **16**-0735
Reißig, H.-U., **16**-0736
Reist, E.J., **10**-1119, **17**-0220
Reister, S., **11**-0240
Reiter, M., **15**-0229
Reitman, M., **13**-0548
Reitsma, B.H., **04**-0127, **04**-0146, **15**-0597
Reitz, A.B., **16**-1255, **16**-1298, **16**-1303, **16**-1323, **16**-1324, **16**-1325
Reitz, D.B., **05**-0124, **10**-1720
Reitz, O., **06**-0061
Reitz, R.R., **18**-0844
Reitz, T.J., **10**-0993
Rekasheva, A.F., **10**-0520, **10**-0573
Rekker, R.F., **11**-0613
Rekowski, V., **05**-0290
Rele, S., **19**-1708, **19**-1716
Rella, M.R., **19**-0235
Reller, A., **15**-0459
Remanick, A., **18**-0100
Remar, J.F., **10**-0803
Rembaum, A., **02**-0026
Remenar, J.F., **12**-0422
Remennikov, G., **10**-0355
Remington, R.B., **02**-0062
Remion, J., **16**-1879
Remizova, T.B., **18**-0182
Remorova, A.A., **11**-0332
Rempala, P., **05**-0392
Remuson, R., **10**-1216
Ren, J., **16**-0270
Ren, L., **15**-1394
Ren, P., **12**-0359, **12**-0361, **15**-2432
Ren, P.-D., **15**-0508, **15**-0566, **16**-0655, **16**-0663, **19**-1325
Ren, P.D-D., **19**-1226
Ren, R.X., **10**-1088, **13**-0126, **13**-0270, **16**-0312, **18**-0317
Ren, S.-K., **19**-0082
Ren, S.K., **18**-0154
Ren, Z., **16**-1172
Renaldo, A.F., **18**-0618
Renard, G., **10**-0179
Renard, M., **19**-1796
Renard, P.-Y., **10**-0848
Renaud, J.-L., **10**-1463, **10**-1534, **15**-0428, **19**-1684
Renaud, P., **10**-0503, **15**-0664, **15**-1195, **15**-1235, **15**-1263, **15**-1264, **15**-1266, **17**-0299
Renaud, R.N., **11**-0116
Renaut,P., **15**-1972
Rendenbach, B.E.M., **15**-1042
Render, D., **16**-0034
Rendleman, J., **14**-0033, **14**-0328
Renehan, M.F., **15**-1773, **15**-1835
Renes, G., **04**-0283
Renga, J.M., **12**-0245, **17**-0293
Renger, B., **10**-1721, **13**-0166, **19**-1281
Renk, E., **14**-0102, **14**-0130, **17**-0452
Renko, Z.D., **15**-1716
Renneboog, R., **08**-0232
Renneke, R.F., **14**-0282, **19**-0061
Rennels, R.A., **11**-0182, **13**-0642, **13**-0643
Renner, R., **14**-0169
Rennick, L.E., **15**-0406
Rennie, R.A.C., **15**-0401, **19**-0873
Reno, D.S., **04**-0175, **04**-0197
Renslo, A.R., **15**-2036, **15**-2125
Rentea, C.N., **19**-0631
Renton, P., **13**-0272
Rentzsch, M., **10**-0133
Renugopalakrishnan, V., **04**-0302
Renz, M., **18**-0350
Répási, J., **13**-0537
Repic, O., **11**-0254, **16**-1825, **19**-0680
Répichet, S., **11**-0423
Repinskaya, I.B., **15**-0623
Repič, O., **10**-0721, **13**-0179, **15**-2331
Reppe, C., **12**-0142
Reppe, W., **15**-2362
Requin, F., **04**-0127, **04**-0146, **15**-0597
Řeřicha, R., **17**-0026
Rerick, M.N., **19**-0874, **19**-1388, **19**-1389
Resek, J.E., **19**-0052
Reshef, D., **15**-0220
Reshotova, I.G., **15**-0533
Resmini, M., **15**-2017
Resnick, P., **12**-0192
Resouly, S.M., **13**-0298, **13**-0529
Respess, W.L., **15**-1063
Respondek, J., **16**-1328
Resta, S., **15**-0899, **15**-1855
Rétey, J., **10**-1179

Rettig, S., **04**-0390
Réty, J., **04**-0151
Reuben, D.M.E., **19**-1063
Reuchlein, H., **02**-0084
Reucroft, J., **16**-1323
Reuliaux,V., **16**-1847
Reum, M.E., **15**-2277
Reuman, M., **10**-1307, **12**-0405
Reusch, W., **18**-0196, **19**-1426, **19**-1457
Reuss, R.H., **12**-0155, **19**-0479
Reutov, O.A., **04**-0025, **05**-0099, **05**-0100, **05**-0129, **08**-0013, **08**-0014, **10**-0242, **10**-0341, **10**-0478, **10**-0484, **10**-0488, **10**-0489, **10**-0490, **10**-0769, **10**-1310, **12**-0002, **12**-0017, **12**-0034, **12**-0037, **12**-0043, **12**-0045, **12**-0506, **12**-0626, **12**-0670, **13**-0267, **15**-0030, **15**-0263, **16**-1301, **16**-2059, **18**-0026, **18**-0028, **18**-0035, **18**-0044, **18**-0046, **18**-0250, **18**-0250, **18**-0408
Reutov, V.M., **05**-0130
Reuvers, J.T.A., **17**-0296
Reuwer Jr., J.F., **12**-0099
Revetllat, J., **12**-0087
Revial, G., **15**-1044
Revis, A., **16**-1076
Revuelta, J., **19**-1231
Rewicki, D., **05**-0100, **08**-0014
Rey, M., **15**-2213, **18**-0389
Rey, P., **05**-0291, **15**-0375
Reye, C., **12**-0593, **15**-0290, **13**-0481
Reymond, J.-L., **15**-1759
Reymond, S., **10**-1155
Reynolds, G.F., **12**-0040
Reynolds, J., **12**-0717
Reynolds, J.D., **09**-0049
Reynolds, N.J., **16**-0472
Reynolds, N.T., **19**-0704
Reynolds, W.F., **01**-0042, **02**-0036, **09**-0041, **09**-0052, **09**-0064
Reynolds-Warnhoff, P., **19**-0975
Reza-Elahi, S., **15**-0520
Rezaei, H., **15**-1983
Rezaeifard, A.-R., **19**-0819
Rezai, N., **18**-0314
Rezende, M.C., **08**-0083, **10**-0725 **10**-0850, **11**-0495, **12**-0672, **16**-1632, **16**-1863, **16**-1863
Reznikov, V.A., **05**-0254, **05**-0261, **05**-0262
Rheault, T.R., **15**-1216
Rhee, C.K., **19**-0943, **19**-0945, **19**-0947
Rhee, E.S., **18**-0740, **18**-0752, **18**-0753
Rhee, H., **18**-0327, **19**-0309
Rhee, I., **12**-0529, **13**-0617, **13**-0619
Rhee, S., **15**-0712, **18**-0417
Rheingold, A.L., **15**-1871, **16**-0154, **16**-1352
Rho, M.M., **09**-0009
Rhoads, S.J., **18**-0594, **18**-0654
Rhode, O., **19**-0480
Rhodes, C.J., **05**-0245, **05**-0323
Rhodes, R.A., **10**-1187
Rhodes, S., **10**-0499
Rhodes, Y.E., **10**-0148, **10**-0150, **10**-0198, **19**-0847
Rhom, D., **10**-0239
Rhyoo, H.Y., **19**-1042, **19**-1044
Riant, O., **15**-2064, **19**-1045, **19**-1684
Riazi-Kermani, F., **16**-0578
Ribagorda, M., **12**-0470, **13**-0354, **13**-0355
Ribas, J., **03**-0076, **03**-0079
Ribbons, D.A., **15**-1721
Ribe, S., **09**-0092, **18**-0661
Ribeiro, A.A., **16**-0998
Ribeiro, C.M.R., **15**-0277, **16**-0831
Riber, D., **15**-1338
Ribo, J., **18**-0222
Ricci, A., **01**-0042, **10**-1495, **13**-0098, **15**-1068, **16**-0217, **16**-0926, **17**-0209
Ricci, M., **15**-1730, **19**-0456, **19**-0461
Rice, G., **02**-0364
Rice, J.E., **02**-0062
Rice, K., **15**-2439
Rice, K.C., **11**-0531, **16**-0148
Rice, S.A., **06**-0008
Rice, S.N., **05**-0403
Rich, A.E., **16**-0284
Rich, J.D., **14**-0423
Rich, N., **04**-0378
Richard J.P., **08**-0063
Richard, C., **05**-0354
Richard, C.S., **19**-1250
Richard, J.P., **05**-0011, **05**-0019, **05**-0094, **05**-0096, **10**-0001, **10**-0058, **10**-0083, **10**-0084, **10**-0294, **12**-0044, **12**-0101, **18**-0304
Richard, T.J., **15**-1728
Richards Jr., C.A., **05**-0331
Richards, A.C., **01**-0087
Richards, C.J., **16**-1432
Richards, D.H., **10**-0764
Richards, J.J., **13**-0522
Richards, K.E., **11**-0083, **11**-0107
Richards, M., **19**-1186
Richards, R.M., **04**-0090
Richards, S.N., **19**-0253
Richards, W.G., **02**-0014
Richardson, D.B., **05**-0377, **12**-0383
Richardson, D.E., **10**-0403, **10**-0728, **15**-1793
Richardson, J., **16**-1386
Richardson, K.S., **02**-0008, **05**-0025, **16**-0044
Richardson, P.F., **15**-1530, **18**-0362
Richardson, P.R., **15**-1529
Richardson, W.H., **05**-0306, **12**-0638, **14**-0084, **17**-0122, **19**-1716
Richarz, W., **10**-0900
Riche, C., **15**-2234
Richens, D.T., **19**-0611
Richert, S.A., **19**-0609
Richey Jr., H.G., **05**-0034, **05**-0035, **05**-0047, **05**-0048, **05**-0050, **05**-0068, **05**-0108, **05**-0118, **10**-0129, **10**-0132, **10**-0188, **10**-0192, **13**-0028, **15**-0035, **15**-0106, **15**-0860, **15**-0861, **15**-0862, **15**-0867, **16**-0468, **16**-0516, **16**-0574, **16**-0925, **18**-0590
Richey, J.M., **05**-0068, **13**-0028, **15**-0035, **15**-0106
Richheimer, S.L., **10**-1737
Richman, J.E., **10**-1614, **10**-1698, **15**-1348
Richmond, G.D., **10**-1589
Richmond, M.I., **16**-0687
Richter, M.J., **15**-1769
Richter, R., **10**-1089, **16**-1755
Richter, W.J., **12**-0109
Richter-Addo, G.B., **15**-1616
Rickards, B., **15**-1444, **15**-1445
Rickborn, B., **10**-0227, **10**-0497, **10**-1542, **12**-0002, **12**-0424, **12**-0504, **12**-0551, **15**-0187, **17**-0147, **17**-0475, **18**-0094, **18**-0255, **19**-0930
Rickter, D.O., **18**-0025
Rico, I., **10**-1006
Rico, J.G., **19**-1680, **19**-1709
Ridd, J.H., **01**-0042, **11**-0029, **11**-0030, **11**-0041, **11**-0042, **11**-0043, **11**-0064, **11**-0083, **11**-0095, **11**-0101, **11**-0104, **11**-0119, **11**-0125, **11**-0148, **11**-0156, **11**-0273, **11**-0577, **11**-0639, **12**-0699, **13**-0696, **13**-0697, **13**-0698

Riddell, F.G., **04**-0319, **04**-0354, **04**-0357, **04**-0382
Rideout, D., **09**-0091
Rideout, D.C., **15**-2029
Rider, H.D., **10**-1033
Ridvan, L., **03**-0185
Rieber, M., **12**-0414
Rieche, A., **11**-0488, **11**-0489, **13**-0244, **13**-0245, **13**-0247
Ried, W., **16**-1183, **16**-2047, **17**-0513
Riede, J., **01**-0011
Riedel, M., **16**-0292
Riedel, O., **11**-0622
Riediker, M., **16**-0684
Riefling, B., **14**-0382
Rieger, A.L., **14**-0183, **14**-0184
Rieger, D.L., **16**-1015
Rieger, H., **19**-0267
Rieger, R., **15**-2061
Riego, J.M., **16**-1686, **18**-0308
Riehl, J.J., **12**-0315
Rieke, R.D., **10**-1227, **12**-0561, **12**-0595, **12**-0597, **12**-0598, **12**-0599, **12**-0600, **12**-0601, **12**-0602, **13**-0465, **16**-0564, **16**-0812, **16**-0817, **16**-1899, **16**-1907, **16**-1908, **19**-1654, **19**-1710
Rieker, A., **05**-0230, **05**-0234, **13**-0704, **19**-1573
Riela, S., **15**-0224
Riemenschneider, J.L., **10**-0181
Riemenschneider, K., **15**-0101
Rienkena, E., **19**-1334
Rienstra-Kiracofe, J.C., **01**-0025, **05**-0385
Riera, A., **07**-0091, **10**-0921, **15**-1437, **15**-2364, **16**-0687, **19**-1031
Riera, J., **05**-0256
Riermeier, T.H., **13**-0162, **16**-0344, **16**-0373, **19**-1158
Ries, M., **15**-1919
Riesen, A., **18**-0480
Riesz, P., **07**-0067, **15**-0028
Rieth, R.D., **13**-0306
Rietz, E.G., **10**-0527
Riezebos, G., **19**-0368
Rifi, M.R., **02**-0155, **10**-1241
Rigamonti, J., **13**-0717
Rigaudy, J., **14**-0219, **15**-2155
Rigby, J.H., **10**-0614, **15**-1256, **15**-1272, **15**-2438, **15**-2438, **19**-0027
Rigby, R.D.G., **11**-0658
Riggleman, S., **13**-0510
Riggs, N.V., **02**-0186
Righetti, P.P., **15**-0961, **15**-1043, **8**-0708
Righi, G., **10**-0685, **10**-1150, **10**-1153, **10**-1172, **15**-1690, **17**-0213, **19**-1088
Righi, P., **15**-0225, **16**-0255, **16**-1151
Rigo, B., **13**-0735
Rigo, P., **17**-0267
Riguera, R., **04**-0106, **04**-0108, **04**-0109, **04**-0110
Rihs, G., **04**-0447, **16**-0684
Riley, C.M., **17**-0463
Riley, D.P., **19**-0801
Riley, E.F., **16**-1150
Riley, T., **12**-0098
Rimbault, C.G., **14**-0244
Rimkus, A., **15**-1138
Rimmelin, J., **15**-2091
Rimmelin, P., **08**-0019
Rinalde, S., **11**-0457
Rinaldi, C., **18**-0697
Rinaldi, P.L., **04**-0206
Rinaldi, S., **16**-0521
Rinaudo, J., **13**-0748
Rinderknecht, H., **16**-1719
Rinehart Jr., K.L., **02**-0166, **11**-0063, **12**-0562, **16**-0836, **17**-0501
Ring, D.F., **12**-0380
Ring, R.N., **15**-0076
Rintoul, G.B., **16**-0612
Riordan, J.C., **16**-1597
Riordan, J.D., **08**-0123
Riordan, P.D., **19**-1558
Ríos, J.V., **19**-0799
Ripin, D.H.B., **15**-0663
Ripka, W.C., **10**-1078, **16**-0447
Ripoll, J., **02**-0412
Ripoll, J.L., **15**-2086, **16**-0263
Rippon, D., **19**-0192
Riquet, E., **10**-1413
Risberg, E., **15**-2123
Risbood, P.A., **19**-0934
Risch, N., **04**-0144, **16**-0406
Rische, J., **15**-0341
Rische, T., **15**-0340
Rise, F., **04**-0392
Risgaard, T., **16**-1164
Risitano, F., **15**-1937
Rispens, M.T., **19**-0536
Rispens, T., **15**-2019
Rissanen, K., **03**-0120, **03**-0170
Rist, Ø., **14**-0441
Ritchie, C.D., **05**-0378, **06**-0053, **06**-0087, **08**-0099, **08**-0116, **08**-0126, **09**-0060, **10**-0329, **10**-0350
Ritchie, E., **19**-1528
Ritchie, G.L.D., **02**-0140
Ritieni, A., **10**-0992
Rittberg, B.R., **17**-0445
Ritter, J.J., **16**-2053
Ritter, R.H., **12**-0386
Ritter, W., **04**-0290
Rittner, R., **04**-0353
Rivard, D.E., **12**-0693
Rivera, I., **10**-1415
Rivera, N.R., **15**-0615, **16**-0280
Rivera-Fortin, M.A., **16**-2082, **16**-2088
Rivero, M.R., **10**-1428, **15**-1418
Rivero, R., **10**-0978
Riveros, J.M., **08**-0224, **08**-0231, **08**-0234, **10**-0009, **16**-1566
Rivers, G.T., **17**-0271
Rivers, P., **04**-0050
Riviere, H., **13**-0389, **15**-1170, **15**-1168, **16**-1893
Rizk, M., **18**-0730
Rizzo, C.J., **15**-2029, **15**-2030
Ro, R.S., **17**-0069, **17**-0388, **17**-0401
Roach, S.L., **10**-0543, **15**-0786
Roark, W.H., **18**-0056
Robaugh, D.A., **05**-0225
Robb, E.W., **07**-0105
Robb, M.A., **15**-2105, **15**-2211, **15**-2244, **18**-0847
Robbins, C.R., **13**-0775
Robbins, H.M., **10**-0078, **10**-0079
Robbins, J.D., **18**-0854
Robbins, M.D., **16**-1585, **17**-0092
Robbins, T.A., **03**-0172
Robert, F., **15**-1437, **15**-1452
Robert, M., **05**-0303
Robert-Peillard, F., **15**-1903
Roberti, M., **16**-1260
Roberts, B.P., **10**-0741, **12**-0436, **12**-0447, **14**-0054, **14**-0058, **14**-0059, **14**-0098, **15**-0754, **15**-1353, **15**-1367, **19**-1301, **19**-1415
Roberts, D.D., **10**-0193, **10**-0194
Roberts, D.K., **17**-0093, **17**-0094
Roberts, D.W., **15**-2220
Roberts, E., **12**-0370
Roberts, F.E., **10**-0060, **16**-0230
Roberts, J.D., **01**-0040, **02**-0223, **04**-0286, **04**-0417, **04**-0510, **05**-0171, **05**-0307, **06**-0056, **09**-0050, **10**-0200, **10**-0316, **10**-0635, **13**-0038, **13**-0079, **13**-0091, **14**-0103, **15**-2166, **15**-2222
Roberts, J.L., **15**-1686, **16**-0996

Roberts, J.T., **14**-0408, **17**-0445, **19**-1592
Roberts, K., **10**-0325, **10**-0326, **10**-0438, **10**-0439
Roberts, K.A., **16**-1572
Roberts, L., **15**-1271
Roberts, R., **10**-0392, **18**-0705
Roberts, R.M., **11**-0316, **11**-0362, **11**-0378, **11**-0598, **18**-0706
Roberts, R.M.G., **11**-0598, **11**-0599, **15**-0005
Roberts, R.S., **16**-1312
Roberts, S., **13**-0172, **15**-2213
Roberts, S.M., **10**-0228, **15**-1813, **15**-1817, **15**-2213, **18**-0155, **18**-0362
Roberts, T.D., **16**-2162
Roberts, V.A., **15**-2433
Roberts, W.J., **15**-1358
Robertson, A., **13**-0491
Robertson, D.E., **10**-0582
Robertson, G.B., **01**-0064, **04**-0480
Robertson, J., **15**-1175, **15**-1247, **18**-0159, **18**-0175
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Robertson, J.M., **02**-0060
Robertson, K.N., **19**-0121
Robertson, P.W., **15**-0083, **15**-1538
Robertson, R.E., **06**-0057, **06**-0070, **06**-0086, **06**-0087, **10**-0033, **10**-0034, **10**-0078, **10**-0208, **10**-0517, **16**-2143, **19**-1739
Robertson, W.G.P., **16**-0191
Robey, R.L., **19**-0405
Robiette, A.G., **04**-0441
Robiette, R., **15**-2003, **15**-2048
Robin, M.B., **01**-0015, **01**-0016
Robin, S., **15**-0234, **19**-0240
Robin, Y., **10**-1854
Robins, M.J., **19**-1402
Robinson, B., **18**-0714
Robinson, C.N., **09**-0078
Robinson, D.A., **18**-0493
Robinson, D.L., **04**-0316, **04**-0351
Robinson, E.A., **11**-0484
Robinson, G.C., **10**-0055, **10**-0066
Robinson, G.M., **18**-0721
Robinson, G.W., **07**-0015
Robinson, J.A., **04**-0151
Robinson, J.E., **10**-0886, **10**-0903, **10**-1469
Robinson, J.K., **06**-0062
Robinson, J.W., **01**-0018
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Robinson, L., **10**-0422
Robinson, L.A., **18**-0135
Robinson, M.J.T., **01**-0087, **04**-0357, **18**-0116
Robinson, P.J., **16**-1172, **18**-0169
Robinson, R., **02**-0098, **16**-1140, **18**-0721
Robinson, R.A., **08**-0052
Robinson, R.E., **18**-0813
Robinson, R.I., **15**-1687
Robinson, R.M., **05**-0402
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Robson, J.H., **16**-2059
Robson, M.J., **18**-0159
Robson, R., **16**-0132
Robveille, S., **13**-0089
Robvieux, F., **15**-2446
Robyr, C., **16**-1189
Rocco, C., **03**-0127
Roček, J., **19**-0023, **19**-0249, **19**-0250, **19**-0251, **19**-0251, **19**-0404, **19**-0710, **19**-0711, **19**-0712
Rocha, j.B.T., **15**-0944
Roche, D., **11**-0254
Rochester, C.H., **08**-0046, **03**-0001, **08**-0010, **08**-0116, **08**-0124, **08**-0126
Rochlin, E., **12**-0083, **16**-1166
Rochon, F., **18**-0362
Rochow, E.G., **12**-0573
Rockett, J., **12**-0431
Rocklin, D., **14**-0007
Rockstuhl, A., **15**-1573
Rodeheaver, G.T., **19**-0728
Rodehorst, R., **14**-0448, **19**-0079
Rodewald, H., **04**-0437
Rodewald, L.B., **18**-0116
Rodewald, P.G., **15**-1921
Rodger, A., **04**-0128
Rodger, P.M., **04**-0128
Rodgers, A.S., **15**-2311
Rodgers, L.R., **06**-0066
Rodgers, M.A., **14**-0228, **15**-2156
Rodig, A., **05**-0180
Rodin, J.O., **15**-2095
Rodina, L.L., **18**-0211, **18**-0218
Rodkin, M.A., **11**-0297
Rodler, M., **02**-0402, **13**-0047
Rodrguez, M.A., **18**-0592
Rodrigo-Chiner, J., **15**-1199
Rodrigue, A., **03**-0113
Rodrigues, D.C., **18**-0655
Rodrigues, J.A.R., **11**-0124, **15**-0625, **16**-0804, **19**-1021
Rodrigues, J.P., **16**-0276
Rodrigues, O.E.D., **12**-0294, **15**-0216, **15**-0291, **16**-0687
Rodrigues, R., **12**-0245
Rodriguez, A., **15**-0902, **17**-0379
Rodriguez, A.L., **10**-1410, **13**-0646, **15**-0901
Rodriguez, D., **15**-2050, **19**-1077
Rodriguez, H.R., **10**-1284, **12**-0388, **13**-0641
Rodriguez, J., **12**-0074
Rodriguez, M.L., **19**-0601
Rodríguez, B., **10**-0921
Rodríguez, D., **10**-1392, **10**-1402, **14**-0310
Rodríguez, J.F., **11**-0268
Rodríguez, J.R., **10**-0925, **15**-0827, **18**-0791
Rodríguez, M.A., **12**-0486, **15**-1547, **19**-1706, **19**-1706
Rodríguez, N., **17**-0228
Rodríguez-García, C., **15**-2291
Rodríguez-Otero, J., **18**-0464
Rodríguez-Ranera, C., **16**-0729
Rodríguez-Solla, H., **15**-2346, **17**-0163, **17**-0167, **17**-0400
Rodríguez-Vicente, A., **16**-0729
Rodriques, K.E., **15**-1593
Rodriquez, M., **07**-0123
Rodríquez, M.A., **15**-2416
Roduner, E., **05**-0245
Roe Jr., R., **15**-2213, **15**-2214
Roe, D.C., **15**-1504
Roe, S.P., **05**-0144
Roecker, L., **06**-0062
Roelens, S., **04**-0205
Roelofs, N.H., **18**-0520
Roelofsen, D.P., **16**-0275, **16**-0290
Roengsumran, S., **11**-0598
Roeper, M., **15**-1381
Roesch, K.R., **15**-2397
Roeterdink, F., **13**-0049
Roger, P., **19**-1243
Rogers, D., **04**-0097
Rogers, D.W., **01**-0091, **02**-0039, **02**-0051, **02**-0331, **02**-0352, **02**-0353, **04**-0462
Rogers, D.Z., **10**-0664
Rogers, G.A., **16**-0026
Rogers, H.R., **12**-0605, **12**-0630, **19**-0727
Rogers, M., **12**-0069
Rogers, M.T., **05**-0149, **05**-0280
Rogers, P., **10**-0534
Rogers, R.D., **18**-0601
Rogers, R.J., **12**-0605, **13**-0721
Rogers, W.J., **17**-0459
Rogers-Evans, M., **10**-1272

Rogic, M.M., **19**-1054
Rogić, M.M., **10**-1745, **10**-1746, **10**-1747, **10**-1749, **10**-1750, **10**-1751, **10**-1753, **10**-1754, **10**-1761, **12**-0487, **15**-1183, **19**-0343
Roginskii, V.A., **05**-0265
Roglans, A., **13**-0365, **13**-0420, **13**-0525, **15**-1022
Rogne, O.B., **16**-2143, **16**-2150, **16**-2155
Rogozhin, S.V., **04**-0173, **10**-0522, **16**-1816
Rogozhnikova, O.Yu., **11**-0029
Roh, E.J., **10**-0940, **11**-0325, **15**-1834
Roh, S.-G., **03**-0185
Rohatgi-Mukherjee, K.K., **07**-0001
Rohr, W., **16**-1669, **19**-1132
Rohrbaugh, P.E., **13**-0086
Rohrer, C., **19**-1645
Röhrig, P., **02**-0295
Röhrling, J., **16**-0370
Rohwer, M.B., **16**-0772
Roitman, J.N., **12**-0029
Rojas, J., **15**-0302
Rojo, J., **19**-1173
Rokhlin, E.M., **16**-0041, **16**-1255
Roland, J.R., **11**-0616
Roland, S., **15**-1136, **16**-0868
Rolando, C., **10**-1865, **19**-0841
Rölfing, K., **16**-0580
Roling, P.V., **16**-0527
Rolla, F., **10**-0453, **10**-0983, **10**-1065, **10**-1116, **15**-0173, **17**-0369, **19**-0104, **19**-1256
Rollet, P., **13**-0541
Rollin, Y., **10**-1821, **13**-0468
Rollmann, C., **19**-1022
Roloff, A., **10**-1168
Rolston, J.H., **15**-0013
Rom, R., **18**-0630
Roman, E., **16**-1278
Roman, F., **18**-0875, **18**-0876
Roman, S.A., **10**-0136
Romanelli, M.G., **02**-0165, **17**-0423
Romanenko, V.D., **01**-0009
Romano, A., **19**-0232
Romano, L.J., **14**-0160
Romanova, V.S., **19**-1303
Romanovich, A.Ya., **19**-0091
Romański, J., **16**-1399
Romão, C., **18**-0354
Rombolà, O., **13**-0228
Rombouts, G., **13**-0187
Romea, P., **16**-1015, **16**-1794, **16**-1940, **19**-1272
Romeo, A., **19**-0134
Romeo, R., **16**-1618
Romera, J.L., **10**-0856
Romero, J.A.C., **10**-1433
Romero, J.R., **19**-0579
Romero, R.H., **15**-1428
Romers, C., **04**-0354, **04**-0365
Romesberg, F.E., **05**-0188, **08**-0202, **08**-0203, **08**-0205, **12**-0422
Romine, J.L., **16**-0493
Rømming, C., **13**-0689, **16**-0211
Romney-Alexander, T.M., **13**-0268
Romo, D., **15**-2245, **16**-2075
Romsted, L.S., **10**-0529
Ron E., **15**-0980
Ron, M., **06**-0075
Rona, P., **10**-1429, **15**-2430
Rona, R.J., **10**-1542
Ronald, B.P., **18**-0148
Ronald, R.C., **16**-0443
Ronan, B., **16**-1189
Roncaglia, F., **12**-0152
Roncin, J., **05**-0273
Ronco, G., **10**-0060
Rondan, N.G., **02**-0352, **05**-0124, **15**-2433, **18**-0482, **18**-0669, **18**-0852
Rondanin, R., **16**-1260
Rondestvedt Jr., C.S., **10**-0513, **13**-0732, **19**-1223
Rongsi, C., **02**-0120
Ronman, P., **16**-2135
Rönn, M., **10**-1300, **15**-0230
Rönnqvist, M., **03**-0057
Ronzini, L., **16**-1929
Roobeek, C.F., **12**-0343, **15**-0134
Rooney, J.J., **15**-0451, **18**-0113, **18**-0117, **18**-0618, **18**-0836
Rooney, J.R., **11**-0142
Roos, B.O., **05**-0332
Roos, E.C., **16**-1734
Roos, G.H.P., **16**-0771
Root, K.S., **12**-0606
Roothaan, C.C.J., **01**-0003, **02**-0009
Rop, D., **10**-0481
Roper, T.D., **16**-1048
Ropp, G.A., **11**-0620
Ropp, S., **15**-0229
Roque, J., **10**-0148
Roque, J.-P., **10**-0646, **18**-0213
Roque, J.P., **16**-0228, **19**-0247
Roques, N., **11**-0220, **11**-0423, **16**-2029, **19**-1318
Ros, F., **10**-1602
Rosa, E., **12**-0709, **13**-0504
Rosa, J.N., **16**-0779
Rosado, I., **10**-0777
Rosado, O., **16**-1770, **18**-0876
Rosales, A., **15**-1233, **16**-0646
Rosas, N., **10**-1247
Rosati, O., **10**-0563, **10**-0925, **12**-0723, **15**-1365, **15**-1625, **16**-0149, **16**-1842, **19**-0668
Rosauer, K.G., **16**-0991
Rösch, N., **15**-1734, **15**-1738, **15**-1934, **19**-0114
Roschangar, F., **13**-0649, **16**-1780
Roscher, N.M., **14**-0207
Roschmann, K.J., **15**-1832
Rose, A., **03**-0190
Rose, J., **03**-0080
Rose, J.B., **17**-0012
Rose, M., **13**-0233
Rose, M.E., **10**-0589, **10**-1582
Roseblade, S., **15**-1247
Roselló, A.L., **19**-0120
Rosen, P., **10**-1653
Rosen, W., **02**-0255
Rosenau, T., **16**-0370
Rosenbaum, C., **18**-0717
Rosenberg, A., **01**-0039
Rosenberg, A.M., **16**-1564
Rosenberg, D.E., **13**-0737
Rosenberg, J.L., **02**-0348
Rosenberg, R.E., **02**-0037
Rosenberg, S.D., **12**-0457
Rosenberger, M., **02**-0184
Rosenblatt, D.H., **15**-1610, **19**-0748
Rosenblum, L.D., **16**-1980
Rosenblum, M., **02**-0171, **10**-1634, **13**-0756
Rosencrantz, D.R., **16**-1466
Rosenfeld, J., **05**-0020, **18**-0022
Rosenfeld, J.C., **18**-0511
Rosenfeld, M.N., **13**-0718, **19**-0267
Rosenfeld, S.M., **02**-0061, **12**-0651
Rosenman, H., **14**-0449
Rosenmund, K.W., **15**-0437
Rosenquist, N.R., **09**-0062, **09**-0063
Rosenstein, I.J., **14**-0091
Roses, J.B., **18**-0599
Rosingana, M., **16**-1833
Rosini, C., **04**-0114, **15**-1136, **15**-1693, **16**-0687, **19**-0823
Rosini, G., **15**-0225, **16**-1149, **16**-1666, **19**-1206, **19**-1532
Roskamp, E.J., **12**-0331, **16**-1802, **16**-1837, **16**-1838, **19**-1698
Roskos, P.D., **18**-0345
Rösler, K., **19**-0023

Rosnati, V., **19**-1427, **19**-1465
Rosner, T., **13**-0399, **13**-0419, **15**-0615
Rosokha, S.V., **11**-0019
Ross Jr., B., **19**-0609
Ross, C.B., **16**-1471
Ross, D.A., **13**-0702
Ross, D.S., **11**-0125, **11**-0154, **19**-0253
Ross, M.M., **02**-0356
Ross, N.A., **16**-0815
Ross, P., **10**-0010
Ross, S.D., **13**-0003, **13**-0086
Ross, S.K., **09**-0106
Rossa, L., **17**-0516
Rossall, B., **16**-2143
Rosset, S., **15**-1136, **15**-1137
Rossetti, Z.L., **04**-0332
Rossi, E., **15**-2423
Rossi, I., **16**-0750
Rossi, J.C., **15**-0375, **15**-1685
Rossi, L., **10**-0716, **10**-0785, **10**-1153, **12**-0745, **12**-0752
Rossi, L.I., **19**-0805
Rossi, M., **16**-1260, **19**-0117
Rossi, M.H., **16**-0315
Rossi, R., **04**-0064, **10**-0790, **10**-1418, **13**-0473, **13**-0536, **18**-0825
Rossi, R.A., **10**-0090, **10**-0094, **10**-0787, **11**-0647, **13**-0052, **13**-0061, **13**-0065, **13**-0248, **13**-0343, **13**-0588, **13**-0589, **19**-1376
Rossi, R.C., **16**-0776
Rossiter, B.E., **15**-1169, **15**-1820
Rossky, P.J., **10**-0071
Rösslein, L., **04**-0196
Rössler, K., **13**-0713
Rossy, P.A., **19**-1294
Rostami, A., **19**-0860
Rostovshchikova, T.N., **15**-0023, **15**-0169
Rotello, V.M., **13**-0504
Rotem, M., **15**-0280
Rotermund, G.W., **15**-0685
Rotger, C., **13**-0021
Roth, W.R., **18**-0621
Roth, A.S., **15**-0548
Roth, B.D., **16**-0349, **19**-1468
Roth, E.A., **01**-0074
Roth, G.P., **10**-1361, **12**-0256, **12**-0276
Roth, H.D., **02**-0259, **02**-0264, **05**-0318, **05**-0395, **07**-0001, **12**-0384, **12**-0385, **15**-2322, **18**-0469, **18**-0470
Roth, J.A., **11**-0650
Roth, M., **15**-0066
Roth, P., **15**-1895, **15**-2119
Roth, W., **04**-0068, **12**-0655
Roth, W.R., **05**-0290, **10**-0175, **15**-2232, **18**-0526, **18**-0538, **18**-0551, **18**-0552, **18**-0554, **18**-0559, **18**-0590, **18**-0631, **18**-0633, **18**-0849
Rothbard, J., **19**-0601
Rothenberg, G., **13**-0481, **14**-0085
Rothenberg, M.E., **10**-0084
Rother, H., **15**-2219
Rothgery, E.F., **15**-2283
Rothman, E.S., **16**-1694
Rothrock, T.S., **18**-0179
Rothstein, S.D., **13**-0195
Rothwell, I.P., **15**-0973
Rotinov, A., **17**-0131
Rotiroti, L., **11**-0285
Rotstein, D., **19**-1295
Röttele, H., **02**-0274, **02**-0314
Rotter, H.W., **08**-0084
Rottländer, M., **10**-1406
Rouden, J., **16**-0436, **16**-1765, **16**-1925
Rouessac, A., **15**-2086
Rouessac, F., **15**-2086
Rouget, E., **16**-0531
Rouillard, M., **19**-1245
Roulleau, F., **16**-1713
Roumestant, M., **10**-1435
Roumian, C., **10**-0833
Rounds, W.D., **16**-0137, **16**-1775
Roush, W.R., **04**-0124, **15**-1980, **16**-0493, **16**-0561, **16**-0699, **16**-0706, **16**-0710
Rousseau, A.D., **07**-0054
Rousseau, B., **15**-0581, **19**-0905
Rousseau, G., **15**-0234, **15**-1587, **15**-1592, **15**-1857, **16**-1275, **19**-0240
Roussel, A., **15**-2213
Roussel, C., **03**-0015, **04**-0505, **09**-0065, **09**-0068
Roussel, M., **19**-0725
Rousset, C.J., **12**-0617, **15**-0799, **15**-0864
Rousset, L., **15**-1065
Rousset, S., **12**-0272
Routier, S., **19**-1627
Routledge, A., **15**-1243
Rouvray, D.H., **04**-0260
Roux, M.C., **15**-1111
Roux-Schmitt, M., **16**-1213
Rovira, C., **05**-0256
Rovis, T., **15**-1368, **15**-1368, **15**-1370, **16**-0723, **16**-0724, **16**-0726, **16**-0733, **16**-1985, **16**-1986, **16**-1990, **19**-0704, **19**-1386
Rowan, S.J., **03**-0185
Rowe Jr., C.A., **12**-0063
Rowe, D.J., **16**-1278
Rowe, J.R., **14**-0138
Rowe, K., **18**-0432
Rowe, K., **18**-0432
Rowland Jr., S.P., **12**-0094
Rowland, B.I., **18**-0876
Rowland, C., **05**-0285
Rowland, F.S., **18**-0070, **18**-0224
Rowland, N.E., **02**-0274
Rowland, S.P., **02**-0398
Rowlands, D.A., **11**-0445
Rowlands, M., **12**-0332
Rowley, A.G., **16**-1323, **19**-1420, **19**-1424, **19**-1546, **19**-1603
Rowley, D.H., **18**-0852
Rowsell, E., **13**-0440
Roy, A., **13**-0441
Roy, A.H., **13**-0318
Roy, C.D., **17**-0390
Roy, D.A., **14**-0353
Roy, F., **11**-0041
Roy, G., **16**-1241
Roy, J., **18**-0744
Roy, P., **12**-0198
Roy, R.R., **16**-1707
Roy, S., **14**-0285, **14**-0425, **14**-0426, **16**-0715, **16**-2121, **19**-0447
Roy, S.C., **11**-0246, **11**-0247, **12**-0635, **15**-0255, **16**-0177, **16**-0646
Roy, U.V., **15**-2218
Royer, A.C., **15**-1588
Royo, A.J., **15**-2038
Royo, J., **19**-0799
Rozantsev, E.G., **05**-0228, **05**-0255
Rozantsev, G.G., **05**-0327
Rozas, I., **08**-0012
Rozen, S., **10**-1003, **10**-1041, **11**-0266, **11**-0291, **11**-0312, **11**-0537, **12**-0111, **12**-0137, **12**-0138, **14**-0129, **14**-0133, **14**-0134, **14**-0136, **15**-1519, **15**-1545, **15**-1582
Rozenberg, V.I., **16**-0687
Rozental, E., **10**-0023, **19**-0158
Rozhkov, I.N., **14**-0130, **15**-1109, **15**-1622
Rozhkov, V.V., **11**-0180
Rozsondai, B., **05**-0227
Rozwadowska, M.D., **16**-1499
Ruane, M., **17**-0070, **17**-0072, **17**-0077

Ruano, J.L.G., **10**-1800, **15**-1334, **15**-2150
Ruano, M., **10**-1472
Ruasse, M., **05**-0378, **09**-0021, **15**-0012, **15**-0014, **15**-0016, **16**-2140
Ruasse, M.-F., **19**-0815
Ruban, S.G., **14**-0116
Rubenstein, P.A., **08**-0059
Rubin, A.E., **15**-1696
Rubin, M., **10**-1432, **10**-1784, **15**-0738, **15**-0843, **15**-2357, **15**-2379, **19**-1451
Rubin, M.B., **07**-0044, **15**-2320
Rubin, R.M., **18**-0640
Rubina, M., **15**-0803, **15**-2379, **10**-1069
Rubino, M.E., **15**-1766
Rubinshtein, B.I., **14**-0164
Rubinstein, H., **15**-1866
Rubio, E., **15**-0357
Rubio, V., **16**-1413
Ruble, J.R., **18**-0637
Rubottom, G.M., **12**-0157, **14**-0253, **16**-0838, **19**-0010, **19**-0311, **19**-0479
Rubow, M., **15**-1636, **15**-1637
Rucando, D., **10**-1792, **15**-2436
Ruch, R.R., **19**-0976
Rüchardt, C., **01**-0107, **04**-0294, **04**-0294, **04**-0386, **04**-0406, **05**-0231, **05**-0232, **05**-0246, **05**-0267, **05**-0279, **05**-0298, **10**-0083, **13**-0033, **13**-0744, **14**-0006, **14**-0062, **14**-0357, **15**-0265, **18**-0035, **18**-0074, **18**-0377, **18**-0403, **18**-0404, **19**-0023, **19**-1562
Ruck, R.T., **05**-0373, **05**-0376, **15**-0987, **17**-0461
Rücker, C., **04**-0426, **04**-0438, **15**-2096
Rücker, G., **04**-0426
Rückert, A., **18**-0784
Ruckle Jr., R.E., **12**-0217, **12**-0348
Rudakov, E.S., **10**-0202, **10**-0424, **10**-0425
Rudchenko, V.F., **04**-0042
Rudd, E., **15**-1649
Rudd, M.T., **15**-0836
Ruden, R.A., **15**-1171
Ruderman, W., **14**-0161
Rüdiger, V., **03**-0110
Rudkevich, D.M., **12**-0699
Rudler, H., **12**-0692, **18**-0836
Rudloff, E. von, **19**-0390
Rudloff, I., **14**-0280
Rudolf, K., **18**-0484
Rudolph, J., **15**-1777, **15**-1859, **16**-0703, **16**-1551
Rudorf, W., **15**-1943, **16**-0200, **16**-0433, **16**-1250
Rudorf, W.-D., **15**-1052
Rudrawar, S., **10**-0923, **10**-0926
Rudy, T.P., **14**-0113
Rudzińsci, J., **17**-0045
Rüedi, G., **18**-0577, **18**-0578, **19**-0556
Rueping, M., **16**-1161
Rufa, L., **19**-1750
Rufanov, K.A., **15**-1959
Rufińska, A., **05**-0163
Ruge, B., **07**-0045
Rüger, C., **12**-0742
Rüger, W., **15**-0086
Ruggiero, P.L., **15**-0856
Rugmini, P., **15**-1027, **15**-1916, **19**-0928
Rühl, T., **05**-0139
Ruhland, T., **13**-0077
Ruhlandt-Senge, K., **05**-0175
Rühlmann, K., **19**-1736
Ruholl, H., **19**-0319
Ruiz, A., **15**-1136
Ruiz, J., **16**-1964
Ruiz, J.R., **13**-0576
Ruiz, R., **16**-0073, **19**-0120
Ruiz-Hitzky, E., **10**-0699
Ruiz-López, M.F., **15**-2059
Ruiz-Pérez, C., **04**-0467
Rule, H.G., **13**-0457
Rulin, F., **15**-1724
Rull, M., **16**-1583
Rumbo, A., **18**-0828
Rummens, F.H.A., **17**-0137
Rumthao, S., **10**-0894
Runcio, A., **19**-0226
Rundel, W., **10**-0918
Rundle, R.E., **05**-0159
Runsink, J., **15**-1368, **16**-0724
Ruo, T.C.S., **14**-0045
Ruoho, A.E., **11**-0201, **11**-0292, **11**-0302, **16**-0046, **16**-0083
Ruostesuo, J., **10**-0331
Rupilius, W., **15**-1484
Ruprecht, H., **19**-0386
Rusch, G.M., **18**-0164
Rush, D.J., **04**-0302, **04**-0308
Rusiniak, L., **15**-2298
Ruske, W., **11**-0523, **11**-0527
Russ, M., **16**-1889
Russel, G.A., **18**-0068
Russell, A.E., **19**-1760
Russell, A.T., **16**-1023, **16**-1276
Russell, C.J., **16**-1107
Russell, C.R., **05**-0130
Russell, G.A., **05**-0208, **05**-0313, **05**-0316, **10**-0089, **10**-1315, **10**-1602, **11**-0340, **12**-0717, **13**-0052, **13**-0666, **14**-0037, **14**-0062, **14**-0088, **14**-0090, **14**-0115, **14**-0117, **14**-0121, **14**-0183, **14**-0183, **14**-0225, **14**-0381, **15**-0513, **19**-1788
Russell, J.A., **10**-0093
Russell, K.C., **18**-0487
Russell, K.E., **13**-0003
Russell, R.A., **19**-0078
Russell, R.K., **02**-0255
Russell, R.L., **11**-0178, **18**-0224
Russell, S.W., **19**-0057
Russell, T., **16**-0587
Russell-King, J., **18**-0022, **18**-0102
Russell-Maynard, J.K.L., **10**-1054
Russey, E., **19**-1243
Russo, A., **19**-0615
Russo, M., **15**-0232
Russo, T.J., **10**-0490
Ruszkay, S.J., **19**-0696
Ruther, F., **19**-0470
Rutherford, D.R., **13**-0020
Rutherford, J.L., **05**-0182, **08**-0199, **08**-0207, **13**-0642, **13**-0643, **18**-0726
Rutherford, K.G., **13**-0717
Ruthven, D.M., **19**-0934
Rutjes, F.P.J.T., **15**-0395, **18**-0813
Rutjes, P.J.T., **12**-0273
Rutledge, P.S., **12**-0161, **14**-0431, **15**-1557, **15**-1589, **15**-1603, **15**-1604, **15**-1626, **15**-1631, **15**-1686
Rüttimann, A., **17**-0411
Ruwet, M., **17**-0176
Ruzicka, L., **15**-0781, **16**-2051, **18**-0111
Ruzsicska, B.P., **05**-0358
Ruzziconi, R., **17**-0031, **17**-0033, **17**-0051, **17**-0052, **17**-0110, **19**-0845
Ryabokobylko, Yu.S., **13**-0256
Ryabov, A.D., **13**-0360
Ryabova, K.G., **10**-1833, **18**-0422
Ryabova, V., **13**-0309
Ryabstev, M.N., **15**-0030
Ryan, K.M., **15**-1835
Ryan, P.W., **15**-0549
Ryang, H.S., **14**-0117
Ryang, M., **12**-0529, **12**-0535, **13**-0617, **13**-0619, **15**-1343
Rybakova, N.A., **11**-0526
Ryberg, P., **17**-0038

Rybinskaya, M.I., **02**-0144, **02**-0166, **10**-0243
Rychlý, J., **14**-0004, **14**-0005
Rychnovsky, S.D., **04**-0357, **04**-0370, **05**-0140, **05**-0253, **05**-0278, **10**-1782, **14**-0080, **15**-1000, **16**-1478, **18**-0607, **19**-0179
Rychtman, A.C., **08**-0001
Rycroft, D.S., **02**-0402
Rydon, H.N., **10**-1095
Rylander, P.N., **14**-0259, **14**-0445, **15**-0401, **15**-0406, **15**-0414, **15**-0461, **15**-0628, **15**-0792, **15**-1662, **16**-0345, **19**-0013, **19**-0875, **19**-0899, **19**-0956, **19**-1076, **19**-1097, **19**-1136, **19**-1186, **19**-1239, **19**-1316, **19**-1349
Rynbrandt, R.H., **17**-0357
Ryou, S.S., **14**-0061
Rys, P., **11**-0028, **11**-0096
Rytting, J.H., **03**-0108
Ryu, D.H., **15**-2012, **16**-1436
Ryu, E.K., **10**-0625, **17**-0426
Ryu, H.-C., **10**-1624, **13**-0329, **13**-0330, **13**-0517, **13**-0568, **13**-0623
Ryu, I., **10**-1827, **10**-1829, **10**-1840, **10**-1853, **12**-0529, **13**-0557, **13**-0615, **13**-0619, **15**-0309, **15**-0312, **15**-1262, **15**-1400, **15**-1782, **15**-1896, **15**-1910, **16**-1892, **19**-0060, **19**-0591, **19**-0607
Ryu, J.-S., **15**-0335, **15**-1868
Ryu, K., **15**-0622
Ryu, Z.H., **10**-0404, **16**-1512
Ryzhkov, L.R., **05**-0297
Rzasa, R.M., **15**-2124
Rzepa, H., **10**-0179
Rzepa, H.S., **16**-0027

Saá, C., **14**-0310, **15**-2389
Saá, J.M., **12**-0389, **13**-0237, **13**-0299, **19**-0138
Saaby, S., **16**-0899
Saadioui, M., **03**-0139
Saalfrank, R.W., **15**-1839
Saavedra, J.E., **12**-0699
Sabacky, M.J., **04**-0151, **05**-0233, **15**-0426
Sabat, M., **15**-1871, **15**-2074
Sabek, O., **11**-0104
Sabesan, A., **16**-0541
Sabesan, S.I., **16**-1728
Sabharwal, A., **19**-0471
Sabin, J.R., **03**-0055
Sabitha, G., **10**-0930, **10**-0942, **10**-0958, **16**-0090, **16**-0763, **16**-1341, **9**-1594
Sablier, M., **05**-0206
Sabol, M.A., **04**-0029, **16**-2141
Sabol, M.R., **19**-0472
Sabourault, N., **15**-0733
Saboureau, C., **13**-0614
Sabu, K.R., **17**-0438
Saburi, H., **10**-1123
Saburi, M., **15**-0598, **19**-1479
Sacchetti, A., **16**-0687
Sacchetti, G., **19**-0872
Sacha, H., **16**-1013
Sachdev, H.S., **17**-0419
Sacher, E., **01**-0043
Sachs, D.H., **19**-1319
Sachs, F., **16**-1254
Sacks, C.E., **16**-0092
Sackur, O., **18**-0207
Sadakane, M., **16**-2118
Sadakari, N., **02**-0295
Sadalai, A., **19**-0752
Sadana, A., **16**-1708
Sadashiv, K., **10**-0682, **13**-0147
Sadavarte, V.S., **10**-0774, **10**-1107, **11**-0430, **16**-1602, **16**-1681, **16**-1684, **17**-0438, **19**-0988
Sadayori, N., **10**-1544, **15**-2372
Sadd, J.S., **05**-0341
Sadeghi, M.M., **10**-0898, **16**-0063, **16**-1740, **19**-0035, **19**-0036, **19**-0038, **19**-0039, **19**-0040
Sadeghipour, M., **14**-0294
Sadek, P.C., **11**-0335
Sadekov, I.D., **03**-0043
Sadhu, K.M., **10**-1417, **16**-1393
Sadighi, J.P., **13**-0183, **13**-0188, **13**-0306
Sadílek, M., **02**-0407
Sadlej, J., **04**-0299
Sadow, A.D., **15**-1320
Sadowski, J.S., **13**-0122
Sadri, A.R., **11**-0598
Sadun, C., **15**-1751
Sadykov, A.S., **13**-0455
Sadykov, R.A., **15**-1617
Saeed, M.A., **17**-0126
Saegusa, T., **10**-0919, **10**-1806, **12**-0731, **14**-0442, **15**-1506, **15**-2351, **19**-0843, **19**-0848, **19**-1767
Saejueng, P., **12**-0295
Saeki, H., **16**-1655
Saeki, N., **16**-1361
Saeki, T., **13**-0565
Saeki, Y., **10**-0154, **10**-0273, **10**-0274, **10**-0403, **10**-0440, **10**-0441
Saeman, M.C., **18**-0778
Saengchantara, S.T., **18**-0482
Saenger, W., **03**-0174, **03**-0176, **03**-0178, **16**-1520
Saenz, J., **13**-0211
Sæthre, L.J., **15**-0096
Saettel, N.J., **15**-2013
Safaei, H.R., **19**-0808
Safarov, M.G., **16**-1463, **16**-1466
Safarowsky, O., **03**-0183
Safavi, A., **10**-0665, **10**-0681
Safavy, K.K., **10**-0060
Saferstein, R., **10**-0109
Saffert, A., **19**-0547
Safonova, I.L., **15**-2281
Safont, V.S., **15**-2057
Sagal, J.F., **10**-1099
Sagal, J.F., **18**-0814
Sagar, A.D., **19**-0324
Sagatys, D.S., **17**-0157
Sagawa, Y., **15**-1054
Sagdeev, R.Z., **10**-1314
Saha, B., **15**-2304
Saha, C., **12**-0402
Saha, J.G., **11**-0068, **13**-0744
Saha, M., **15**-0191, **15**-1059
Saha-Möller, C., **15**-1741
Saha-Möller, C.R., **15**-1791, **15**-1807, **15**-1812, **15**-1828, **15**-1832, **18**-0361, **19**-0205, **19**-0211, **19**-0237, **19**-0540, **19**-0542, **19**-0547
Sahab, S., **17**-0234
Sahai, M., **16**-1875
Sahali, Y., **15**-2249
Sahara, T., **19**-0990, **19**-1143
Sahasrabudhe, K., **18**-0297
Sahjiki, H., **15**-0411
Sahle-Demessie, E., **15**-1747, **15**-1748
Sahli, A., **19**-0717
Sahli, M.S., **17**-0126
Sahm, W., **14**-0377
Sahu, P.R., **10**-0566, **16**-0255
Sahu, S.G., **10**-1587
Sahyun, M.R.V., **17**-0081, **17**-0261, **19**-1432
Saidi, M.R., **10**-1569, **15**-1293, **16**-0129, **16**-0913, **19**-0147, **19**-0242, **19**-1701
Saigo, K., **13**-0424, **15**-0154, **15**-1055, **15**-1439, **16**-0256, **16**-0650, **16**-0824, **16**-0828, **16**-0859, **16**-1128, **18**-0129, **19**-0691

Saikachi, H., **02**-0274
Saikia, A.K., **16**-1696
Saikia, P., **10**-0843, **16**-1997
Saimoto, H., **14**-0402, **19**-1581
Sain, B., **15**-1899, **15**-2180, **16**-0390, **16**-2094, **19**-0114, **19**-0782, **19**-0783, **19**-0785
Saindane, M., **12**-0251, **16**-0530
Saini, R.K., **19**-0089, **19**-0113, **19**-0207, **19**-0798, **19**-0918
Sainsbury, D.M., **10**-0179
Sainsbury, M., **13**-0456, **14**-0286
Saint, R.E., **12**-0362
Saint, S.L., **12**-0362
Saint-Clair, J.-F., **13**-0516
Saiparakash, P.K., **11**-0122
Saishō, **11**-0504
Saito, A., **16**-0906, **18**-0301
Saito, E., **16**-0430
Saito, H., **15**-0778
Saito, I., **15**-2153, **15**-2155, **19**-0064
Saito, K., **10**-0300, **16**-0651, **16**-1451, **18**-0129, **18**-0301
Saito, M., **16**-0329
Saito, N., **15**-0766, **15**-2032
Saito, S., **02**-0402, **04**-0276, **04**-0301, **11**-0332, **11**-0412, **11**-0413, **15**-0931, **15**-1391, **15**-2084, **15**-2128, **15**-2171, **15**-2388, **15**-2401, **16**-0545, **16**-0855, **16**-1029, **16**-1046, **16**-1054, **16**-1060, **17**-0162, **17**-0285, **18**-0702, **19**-0014, **19**-0965
Saito, T., **10**-0785, **10**-1515, **14**-0246, **15**-1665, **16**-1384
Saito, Y., **10**-0171
Saitô, S., **10**-0084
Saitoh, A., **15**-1136
Saitoh, T., **12**-0694, **15**-0310, **19**-0986
Saitou, K., **15**-0625
Saiz, J.L., **08**-0131
Saičić, R.N., **10**-1562
Sajiki, H., **11**-0644, **15**-0576
Sajimon, M.C., **07**-0062, **07**-0063
Sajus, L., **19**-0701
Sakabe, M., **13**-0010
Sakabe, Y., **12**-0619
Sakaguchi, K.-e., **10**-1465
Sakaguchi, S., **10**-0606, **12**-0210, **12**-0211, **13**-0371, **13**-0401, **15**-0377, **15**-0621, **15**-0756, **15**-0763, **15**-0937, **15**-1210, **15**-1404, **15**-1757, **15**-1842, **16**-1444, **16**-2060, **19**-0095, **19**-0315, **19**-0552, **19**-0580, **19**-0593
Sakai, D., **16**-1503
Sakai, H., **15**-1520
Sakai, K., **15**-0985
Sakai, M., **10**-0152, **10**-1796, **11**-0630, **12**-0547, **13**-0281, **15**-0502, **15**-1336, **18**-0840, **18**-0843
Sakai, N., **13**-0541, **15**-1480, **15**-1492, **16**-0553
Sakai, S., **16**-0434, **17**-0487, **19**-0922
Sakai, T., **13**-0362, **15**-1297, **19**-1021, **19**-1355
Sakairi, M., **16**-1384
Sakaitani, M., **10**-1227
Sakajiri, T., **10**-0597
Sakaki, K., **19**-1620
Sakaki, T., **03**-0123
Sakakibara, H., **16**-0638
Sakakibara, K., **09**-0076
Sakakibara, N., **15**-0800, **18**-0814, **18**-0830
Sakakibara, T., **11**-0493, **11**-0505
Sakakibara, Y., **10**-1796, **12**-0547, **13**-0279, **13**-0281, **13**-0282, **15**-0502
Sakakura, T., **10**-1870, **10**-1872, **11**-0506, **14**-0365, **19**-0061
Sakakura, Y., **16**-2156
Sakamoto, K., **15**-2337, **16**-0871
Sakamoto, M., **04**-0166, **10**-1453, **13**-0482, **16**-0687
Sakamoto, S., **03**-0185, **03**-0189, **03**-0210, **05**-0160, **16**-1041, **19**-1677
Sakamoto, T., **07**-0083, **11**-0194, **11**-0196, **11**-0342, **13**-0273, **15**-0204, **15**-0354, **16**-0353, **16**-0687
Sakamura, H., **19**-1176
Sakane, S., **18**-0340
Sakat, S., **16**-1937
Sakata, G., **16**-0303
Sakata, S., **16**-0830
Sakata, Y., **02**-0274, **02**-0296, **15**-1567, **15**-1792, **19**-0130
Sakdarat, S., **10**-0614
Sakighi, J.P., **15**-0476
Sakizadeh, K., **10**-0079, **10**-0081, **10**-0386
Sakthivel, K., **15**-0994, **16**-0415, **16**-1036
Sakuma, K., **08**-0203
Sakuma, S., **15**-1127
Sakuraba, H., **16**-1190
Sakuraba, S., **15**-0607
Sakurada, I., **15**-1568, **15**-1874
Sakuragi, H., **06**-0011, **07**-0022
Sakuragi, R., **15**-0876
Sakurai, H., **04**-0503, **04**-0518, **05**-0245, **05**-0249, **10**-1134, **10**-1260, **13**-0294, **13**-0481, **15**-1139, **15**-1175, **15**-2252, **16**-0761, **16**-1017, **19**-1367
Sakuratani, K., **19**-0193, **19**-0526
Sala, R., **15**-0469
Saladino, R., **15**-1751
Salagre, P., **18**-0278
Salahuddin, S., **19**-1259
Salakhov, M.S., **15**-1980
Salakhutdinov, N.F., **11**-0088
Salaman, A.M., **16**-0426
Salaris, M., **16**-1790
Salaskar, A., **16**-0825
Salaun, J.R., **18**-0209
Salaün, J., **16**-0159, **18**-0159, **19**-1400, **19**-1730
Salazar, J.A., **14**-0208
Salbaum, H., **16**-1344
Sale, A.A., **10**-0656
Salehi, P., **10**-0655, **10**-0663, **10**-0668, **10**-0897, **16**-2054, **18**-0314, **19**-0080, **19**-0084, **19**-0866
Salehzadeh, S., **12**-0705
Salem, G., **10**-1321, **12**-0574, **12**-0582, **15**-0947
Salem, L., **04**-0137, **04**-0469, **05**-0285, **07**-0039, **15**-2105
Salem, M.R., **16**-1141
Salem, R.B., **15**-0970, **16**-1450
Salemnick, G., **12**-0227
Salerno, G., **12**-0734, **15**-0243, **15**-0304, **15**-0361
Sales, M., **16**-1027, **16**-1431
Salfeld, J.C., **13**-0461
Salgaonkar, P.D., **19**-0810
Salim, J.R., **16**-1863
Salinger, R., **05**-0103, **08**-0062
Salinger, R.M., **05**-0158, **12**-0569, **16**-0540
Salisbury, K., **18**-0855
Sall, D.J., **10**-0993
Saller, H., **02**-0057
Salmón, M., **10**-1247
Salmon-Legagneur, F., **18**-0130
Salmond, W.G., **01**-0021
Salomaa, P., **10**-0506, **10**-0520, **10**-0574, **10**-0598, **10**-0658, **10**-0749, **10**-1061, **16**-0098, **16**-1658
Salomon, C., **15**-1486
Salomon, C.J., **18**-0287
Salomon, M.F., **10**-0744, **10**-1511

Salomon, R.G., **10**-0744, **10**-1507, **11**-0389, **19**-0447
Salomone, A., **16**-0473
Salomone, R.A., **16**-2115
Salov, B.V., **13**-0107
Saltiel, J., **07**-0054, **18**-0463
Saluja, P.P.S., **10**-0184
Salunkhe, A.M., **12**-0519, **19**-1260
Salunkhe, M.M., **11**-0213, **11**-0383, **11**-0555, **15**-1016, **16**-0058, **16**-1170, **16**-1543, **19**-0324, **19**-1323
Saluzzo, C., **10**-1125, **15**-0865, **16**-1933
Salvador, J., **19**-1479
Salvadori, P., **04**-0120, **15**-1136, **15**-1693, **16**-0831
Salvataore, R.N., **17**-0234
Salvatella, L., **15**-2054
Salvatella, L., **15**-2059
Salvatore, R.N., **10**-0826, **10**-0859, **10**-0861, **10**-0889, **10**-0973, **16**-1867
Salvi, N.A., **19**-1022
Salvino, J.M., **08**-0199
Salzbrunn, S., **11**-0157, **13**-0096
Salzer, A., **05**-0145
Salzmann, T.N., **12**-0240, **17**-0294
Salzner, U., **04**-0372, **04**-0373, **04**-0375
Sam, D.J., **10**-0462, **19**-0388
Samajdar, S., **11**-0143, **16**-0072, **16**-0231, **16**-0283, **19**-0224
Samanich, D., **15**-1677
Samant, S.D., **11**-0303, **16**-1779
Samanta, A., **07**-0022
Samanta, S., **10**-0812, **10**-0829, **15**-0567, **15**-0570, **16**-0597, **19**-0932, **19**-1336
Samanta, S.K., **18**-0690
Samanta, T., **19**-0247, **19**-0249
Sambri, L., **10**-0931, **10**-1064, **11**-0457, **15**-1018, **15**-1105, **15**-1289, **16**-0521, **16**-0615, **16**-1618, **17**-0160, **19**-0997
Samec, J.S.M., **19**-1146
Sames, D., **11**-0326, **13**-0307, **13**-0504, **15**-0727, **19**-0286
Samii, Z.K.M.A.E., **15**-1851
Samimi, H.A., **19**-0144
Samitov, Yu.Yu., **06**-0056
Samizu, K., **19**-0169
Samkoff, N., **13**-0734, **14**-0105
Sammakia, T., **10**-0539
Sammelson, R.E., **17**-0263
Sammes, M.P., **03**-0045, **17**-0506
Sammes, P.G., **10**-0993, **13**-0128, **15**-0962, **15**-2235, **16**-1323, **18**-0872
Sammis, G.M., **15**-1335
Sammonds, L., **16**-1021
Samoilova, N.A., **16**-1816
Samoilova, R., **05**-0263
Samoilova, Z.E., **04**-0036
Samokhvalov, G.I., **15**-0064
Samoshin, V.V., **04**-0333, **04**-0360, **16**-0673
Sampedro, D., **15**-2416, **18**-0592
Sample Jr., T.E., **15**-2087
Sampler, E.P., **03**-0137
Sampoli, M., **08**-0129
Samsel, E.G., **15**-0515
Samuel, C.J., **18**-0854
Samuel, D., **13**-0758
Samuel, O., **16**-1189
Samuel, P.A., **18**-0397
Samuelsson, B., **10**-1089, **10**-1096, **10**-1591, **19**-0775
Samuilov, Ya.D., **15**-1932
Samuni, U., **19**-0360, **19**-0381
San Filippo Jr., J., **10**-0743, **10**-1350, **11**-0579, **12**-0631, **14**-0160, **14**-0377, **18**-0749, **18**-0751, **19**-0098
Sanada, T., **13**-0450
Sanbri, L., **15**-0875
Sancassan, F., **04**-0314, **04**-0384, **08**-0168
Sanchez Jr., G.V., **11**-0327, **15**-2398
Sanchez, A.M., **11**-0558
Sanchez, B.L., **13**-0764
Sanchez, C., **16**-1662
Sanchez, M. de N. de M., **16**-0027
Sanchez, M.G., **18**-0676
Sanchez, R., **16**-0273, **16**-1813
Sanchez, R.A., **15**-0115, **16**-1460
Sánchez, A., **11**-0356
Sánchez, B., **15**-1225
Sánchez, F., **10**-0729
Sánchez, L.R., **10**-0133
Sánchez-Baeza, F., **19**-0384
Sanda, J.C., **04**-0502
Sandall, J.P.B., **11**-0101, **11**-0577
Sandefur, B.J., **10**-0889
Sandefur, L.O., **15**-1091
Sander, G.E.C., **16**-1869
Sander, M.R., **11**-0560
Sander, W., **04**-0477, **05**-0207, **19**-0364
Sanderfer, P.O., **17**-0503
Sanders, A.W., **05**-0177
Sanders, C.J., **15**-1885, **15**-1905
Sanders, D.P., **18**-0778, **18**-0781
Sanders, L.A., **15**-0135
Sanders, W.J., **15**-0292
Sanderson, J.R., **17**-0520, **17**-0522, **17**-0523, **17**-0524
Sanderson, R.T., **01**-0023, **01**-0027
Sanderson, W.A., **18**-0017
Sanderson, W.R., **15**-1771
Sandford, G., **11**-0314, **16**-0454
Sandhu, J.S., **10**-0591, **10**-0843, **15**-1002, **15**-1018, **15**-2180, **16**-0149, **16**-0234, **16**-0395, **16**-1176, **16**-1182, **16**-1253, **16**-1902, **16**-1997, **16**-2094, **17**-0384, **18**-0313, **19**-0306, **19**-1264, **19**-1268, **19**-1433, **19**-1554, **19**-1757
Sandifer, R.M., **16**-1057
Sandler, S.R., **10**-0751, **18**-0167, **18**-0509
Sandorfy, C., **03**-0001
Sandoval, C., **10**-1554
Sandoval, C.A., **19**-1028
Sandri, E., **04**-0470, **18**-0727
Sandri, J., **10**-1096
Sandri, S., **19**-0090, **19**-0098
Sandrinelli, F., **12**-0242, **19**-0823
Sandrock, G., **10**-0068
Sands, R.D., **09**-0011
Sandström, J., **04**-0227, **04**-0228, **04**-0274, **04**-0505, **04**-0515
Sandström, M., **08**-0146
Sandu, J.S., **10**-1394, **16**-0927, **19**-1694
Sanematsu, F., **10**-0063
SanFilippo, L.J., **17**-0516, **17**-0526
Sanford, M.S., **18**-0833, **19**-0513, **19**-0527
Sang, X., **10**-0855
Sanganee, H.J., **10**-1640
Sangani, P.K., **19**-0586
Sangiorgi, C., **18**-0300
Sangster, D.F., **14**-0195
Sangu, K., **15**-2377
Sanière, L., **15**-1902
Sankararaman, S., **10**-0565, **11**-0101, **16**-1099, **18**-0137
Sannicolo, F., **18**-0714, **13**-0424
Sano, A., **14**-0008
Sano, H., **10**-1825, **15**-0707
Sano, T., **10**-0993
Sanrame, C.N., **05**-0113
Sans, J., **13**-0274
Sansano, J.M., **15**-0878

Sanseverino, A.M., **15**-0178, **15**-1576
Sansom, P.J., **16**-0104
Sansone, E.B., **19**-1232
Sansoulet, J., **10**-0589, **10**-0973, **16**-1542, **17**-0307
Santa, L.E., **16**-0480
Santaballa, J.A., **12**-0084
Santacruz-Juárez, E., **10**-1162
Santagostino, M., **19**-0198, **19**-0199
Santamaria, J., **14**-0219
Santana, M., **19**-1438
Santaniello, E., **15**-0520, **16**-1687, **19**-0098, **19**-0440, **19**-1091
Santarsiero, B.D., **15**-0012
Santella, N., **18**-0601
Santelli, M., **10**-0886, **10**-1420, **10**-1617, **10**-1658, **13**-0045, **13**-0367, **13**-0399, **13**-0401, **13**-0445, **13**-0539, **13**-0541, **13**-0560, **15**-0766, **15**-1175, **15**-2169, **16**-0642, **16**-1798, **19**-0371, **19**-1658, **19**-1710
Santhakumar, V., **10**-1423
Santhi, V., **19**-1031
Santi, C., **15**-0230, **15**-0273
Santi, R., **13**-0582
Santiago, A.N., **10**-0094
Santiago, B., **10**-1416, **12**-0336
Santiago, C., **11**-0028
Santiago, M.V., **18**-0875
Santiesteban, H., **10**-0801
Santinelli, F., **15**-1819
Santini, S., **11**-0470
Santo, K., **16**-1425
Santoni, G., **16**-1308
Santora, B.P., **15**-0419
Santos, A.G., **15**-2046, **16**-0779
Santos, J.G., **13**-0110
Santos, L.S., **16**-1350
Santos, M., **11**-0268
Santos, R.C.D., **15**-1950
Santos, R.P., **15**-1120
Santosusso, T.M., **19**-0644
Santra, M., **10**-1868
Santry, D.P., **02**-0016
Santry, L.J., **10**-0536, **16**-0027
Sanuki, R., **15**-0604, **15**-0822
Sanz, D., **02**-0423
Sanz-Tejedor, A., **11**-0268
Saporovskaya, M.B., **04**-0169, **04**-0209
Sapountzis, I., **13**-0225
Sapra, P., **13**-0170
Sarabi, S., **16**-0063
Saraf, S.D., **11**-0393
Sarancha, V.N., **10**-1075
Sarandeses, L.A., **10**-1392, **10**-1402, **13**-0335, **13**-0620, **15**-1141
Sarangi, C., **10**-1013
Sarapa, D., **10**-0544
Saraswathy, V.G., **18**-0137
Saravanan, P., **16**-0171, **16**-0233, **16**-1618
Saravanan, V., **16**-1741
Saravanani, P., **11**-0341
Sard, H., **18**-0586
Sarda, P., **19**-1361
Sardarian, A.-R., **19**-0145
Sardina, F.J., **05**-0186, **16**-0687
Sarel, S., **10**-0192, **15**-0144
Sarel-Imber, M., **10**-0192
Sargent, G.D., **10**-0148, **10**-0150, **10**-0173, **15**-0026, **15**-0028, **18**-0104
Sargent, M.V., **02**-0093, **02**-0272, **02**-0298, **18**-0371
Saritha, B., **16**-0780
Sarkar, A., **10**-1223, **10**-1417, **15**-0191, **15**-0617, **16**-0369, **16**-1524, **17**-0372, **19**-1133
Sarkar, A.K., **12**-0035
Sarkar, B.R., **15**-1378
Sarkar, D.C., **16**-0048, **16**-1522, **19**-0944
Sarkar, T.K., **16**-1474
Sarkice, A.Y., **08**-0119
Sarkis, G., **10**-0208
Sarma, D.N., **17**-0201
Sarma, J.C., **15**-1199, **16**-0233, **16**-0358, **17**-0332
Sarma, K.D., **11**-0643
Sarmah, G.K., **19**-0230
Sarmah, P., **10**-1108
Sarner, S.F., **17**-0495
Sarshar, S., **15**-2058
Sartamaría, J., **15**-2025
Sarthou, P., **10**-0489, **10**-0490
Sartillo-Piscil, F., **10**-1162
Sartoré, G., **16**-1570, **11**-0385, **11**-0388, **11**-0409, **11**-0491, **11**-0497, **15**-1770, **16**-0233, **16**-0255, **16**-1151, **19**-0532, **19**-0823
Sartorio, R., **15**-1770, **19**-0823
Sartoris, N., **15**-2210
Sarussi, S.J., **19**-1012, **19**-1200
Sarvari, M.H., **11**-0423, **14**-0277, **16**-0311, **16**-0325, **17**-0439, **17**-0443
Sarzi-Amade, M., **15**-1736, **19**-0519, **15**-1731, **15**-1733
Sasabe, H., **03**-0182
Sasahara, T., **12**-0619
Sasai, H., **10**-0672, **15**-1808, **16**-1008, **16**-1043
Sasaki, H., **10**-1416, **15**-1829, **15**-1829, **16**-0552
Sasaki, K., **11**-0630, **12**-0547, **13**-0279, **13**-0466, **13**-0782, **14**-0200, **14**-0204, **15**-0502, **16**-1017, **19**-0635, **19**-1004
Sasaki, M., **10**-1546, **10**-1803, **13**-0208, **18**-0904
Sasaki, R., **16**-0452, **16**-1358
Sasaki, S., **10**-1438, **16**-1880
Sasaki, T., **10**-1322
Sasaki, Y., **03**-0138, **10**-1655, **15**-0281
Sasakura, K., **11**-0390, **11**-0524, **11**-0525, **16**-1057
Sasaoka, A., **16**-1036
Sasaoka, M., **02**-0394, **14**-0190
Sasaoka, S., **10**-1440, **19**-1244
Sasayama, H., **10**-0886
Sashima, M., **18**-0342
Sashiwa, H., **14**-0402, **19**-1581
Sasidharan, M., **17**-0150, **19**-0594
Sasmal, P.K., **16**-0065, **16**-1027
Sass, R.L., **02**-0080
Sassaman, M.B., **16**-0185, **19**-1511
Sasse, M.J., **19**-1225
Sasson, S., **15**-2113,
Sasson, Y., **10**-0458, **10**-0610, **10**-0699, **10**-1017, **10**-1073, **11**-0260, **11**-0482, **14**-0085, **17**-0307
Sastry, G.N., **02**-0361, **02**-0360, **16**-0008
Sastry, K.A.R., **12**-0495
Sastry, V.V.S.K., **16**-0846
Satchell, D.P.N., **08**-0146, **10**-0523, **10**-0557, **10**-0559, **11**-0452, **11**-0527, **12**-0302, **12**-0306, **12**-0412, **15**-0182, **15**-0205, **15**-0265, **15**-0265, **15**-0290, **15**-0368, **16**-0014, **16**-0104, **16**-0190, **16**-0191, **16**-0192, **16**-0421, **16**-1513, **16**-1514, **16**-1515, **16**-1516, **16**-1723, **16**-1745, **16**-1844
Satchell, R.S., **08**-0146, **10**-0523, **10**-0559, **12**-0302, **12**-0306, **15**-0182, **15**-0205, **15**-0265, **15**-0368, **16**-0014, **16**-0104, **16**-0190, **16**-0191, **16**-0192, **16**-0421, **16**-1844
Satgé, J., **01**-0009
Sathe, S.S., **15**-2350
Sathe, V.T., **16**-1152
Satheesh, G., **10**-1550
Sathyanarayana, B.K., **04**-0127, **04**-0146, **15**-0597
Satish, A.V., **08**-0084

Sato, A., **15**-0743, **18**-0549, **18**-0701
Sato, F., **04**-0193, **10**-1376, **12**-0534, **14**-0379, **15**-0710, **15**-0801, **15**-0819, **15**-0946, **15**-1146, **15**-1437, **15**-2176, **15**-2368, **15**-2408
Sato, H., **15**-2037, **15**-2044, **16**-1078
Sato, K., **10**-0676, **11**-0517, **11**-0651, **12**-0473, **13**-0050, **13**-0462, **15**-0209, **15**-0528, **15**-1641, **15**-1662, **18**-0729, **19**-0706, **19**-0816
Sato, K.-I., **15**-0309, **15**-0312
Sato, M., **10**-1376, **10**-1415, **12**-0534, **13**-0218, **13**-0348, **13**-0408, **13**-0557, **14**-0379, **15**-0700, **15**-1146, **15**-1187, **15**-1886, **16**-1922
Sato, N., **13**-0287, **16**-1455
Sato, O., **13**-0408, **18**-0127, **18**-0316
Sato, R., **16**-0329
Sato, S., **07**-0058, **11**-0216, **14**-0071, **16**-0353, **19**-1391
Sato, T., **10**-0714, **10**-0811, **10**-1511, **12**-0300, **15**-0146, **15**-0680, **15**-0755, **15**-1118, **15**-1220, **15**-1254, **16**-0167, **16**-0237, **16**-0490, **16**-0923, **16**-1025, **16**-1066, **16**-1100, **16**-1618, **16**-1929, **18**-0368, **18**-0517, **18**-0737, **19**-1072, **19**-1108, **19**-1713
Sato, Y., **10**-1458, **11**-0110, **13**-0762, **13**-0764, **15**-0766, **15**-1135, **15**-2363, **15**-2375, **15**-2428, **16**-0714, **16**-0905, **16**-2119, **18**-0830
Satoh, A., **11**-0522
Satoh, H., **14**-0359, **15**-1436
Satoh, J.Y., **10**-0227, **11**-0297, **12**-0162, **12**-0175, **15**-1685
Satoh, M., **10**-1416
Satoh, T., **10**-1852, **11**-0260, **13**-0338, **13**-0452, **13**-0453, **14**-0170, **15**-2372, **16**-1220, **18**-0194, **19**-1168, **19**-1371, **19**-1487
Satoh, Y., **15**-1187, **16**-0696, **16**-2100, **18**-0276
Satsumabayashi, K., **12**-0117, **19**-0518
Sattely, E.S., **18**-0780, **18**-0792, **18**-0808
Satti, A.M., **12**-0060
Satti, N.K., **16**-1832
Sattur, P.B., **16**-2110
Satyamurthy, N., **10**-1055
Satyanarayana, T., **16**-0766
Saucy, G., **18**-0676
Sauer, D.R., **13**-0488
Sauer, E.L.O., **10**-1555
Sauer, G., **16**-1072
Sauer, J., **10**-1312, **13**-0088, **13**-0251, **15**-1932, **15**-1980, **15**-2001, **15**-2032, **15**-2088, **15**-2096, **15**-2101, **15**-2137, **15**-2166, **15**-2261
Sauermann, D., **15**-1549
Sauermann, G., **05**-0147, **05**-0153
Sauers, R.R., **05**-0059, **05**-0391, **05**-0393, **08**-0152, **10**-0009
Sauerwald, M., **10**-1624
Saugé, L., **19**-1627
Saullo, P., **10**-0411
Saulnier, M.G., **10**-0855
Saumtally, I., **12**-0303
Saunders Jr., W.H., **06**-0059, **10**-0393, **12**-0098, **17**-0003, **17**-0006, **17**-0007, **17**-0026, **17**-0027, **17**-0028, **17**-0031, **17**-0032, **17**-0057, **17**-0060, **17**-0062, **17**-0064, **17**-0065, **17**-0073, **17**-0083, **17**-0084, **17**-0090, **17**-0096, **17**-0097, **17**-0101, **17**-0174, **17**-0245, **17**-0387, **18**-0035, **18**-0282, **18**-0283, **18**-0656, **18**-0658, **18**-0872, **19**-0835
Saunders, D.G., **05**-0279
Saunders, M., **02**-0235, **02**-0365, **04**-0462, **05**-0002, **05**-0020, **05**-0097, **05**-0098, **10**-0181, **10**-0200, **10**-0201, **10**-0968, **15**-2070, **18**-0002, **18**-0008, **18**-0022, **18**-0027, **18**-0042, **18**-0049, **18**-0511, **18**-0640
Saupe, T., **08**-0089, **08**-0182, **08**-0183, **08**-0184
Sauriat-Dorizon, H., **18**-0809
Saus, A., **19**-1800
Sausker, J.B., **15**-1107
Saussine, L., **15**-1795
Sauter, F., **11**-0642
Sauthier, M., **15**-1454
Sauvage, J., **19**-1743
Sauvage, J.-P., **03**-0181, **03**-0197, **03**-0200, **03**-0201, **03**-0206, **03**-0207, **04**-0242
Sauve, D.M., **15**-0468
Sauvé, G., **16**-2157, **19**-1384
Savage, G.P., **15**-1939
Savall, B.M., **16**-0561
Savarin, C., **13**-0144, **13**-0480, **13**-0566
Saveant, J.-M., **05**-0303
Savéant, J., **10**-0090, **13**-0052, **13**-0054, **13**-0058, **13**-0089, **13**-0127
Savéant, J.-M., **13**-0052, **13**-0056
Savedoff, L.G., **10**-0334
Savel'yanov, V.P., **10**-1089
Savel'yanova, R.T., **10**-1089
Savelli, G., **10**-0407, **10**-0701, **11**-0470, **15**-1681, **15**-1819
Savelova, V.A., **16**-2155, **16**-2170
Savenko, T.V., **15**-1735
Savenkov, N.F., **15**-1652
Savige, W.E., **19**-0790
Savignac, M., **15**-0774, **15**-0977, **19**-1622, **19**-1622
Saville, B., **10**-0838, **12**-0715
Savin, V.I., **04**-0044, **16**-0530
Savinykh, Yu.V., **10**-0315
Savle, P.S., **15**-1840
Savoia, D., **12**-0693
Sawa, Y., **12**-0535, **15**-1343
Sawada, A., **19**-1298, **19**-1308
Sawada, D., **16**-1439
Sawada, M., **05**-0378, **10**-0063, **10**-0170, **10**-0329
Sawada, S., **04**-0459
Sawada, T., **10**-0507, **15**-2304
Sawada, Y., **18**-0904
Sawaguchi, M., **10**-1044, **10**-1045, **15**-1520, **15**-1548
Sawaki, R., **16**-0714
Sawaki, Y., **15**-1786, **18**-0375, **19**-0322, **19**-0383
Sawama, Y., **18**-0139
Sawamoto, H., **15**-1115
Sawamura, M., **16**-1190
Sawaya, H.S., **16**-1289
Sawistowska, M.H., **15**-0484
Sawyer, D.T., **19**-0609
Sawyer, J.S., **12**-0568, **13**-0167, **15**-2353
Sawyer, R., **19**-0645
Sawyer, T.K., **16**-1823
Saxena, I., **16**-0358
Saxena, M.P., **19**-0352
Saxena, N., **19**-0560
Saxton, R.G., **02**-0239
Sayal, P.K., **19**-0471
Sayama, S., **17**-0293
Sayce, I.G., **19**-0005
Sayed, S.H., **15**-1720
Sayer, J.M., **16**-0099, **16**-0316, **16**-0317
Sayigh, A., **10**-0012
Sayigh, A.A.R., **16**-2071
Sayles, D.C., **10**-1227
Sayo, N., **15**-0611, **19**-1027
Sayrac, T., **02**-0204, **14**-0258

Sayre, L.M., **12**-0041
Sbarbati, N.E., **12**-0535
Scafato, P., **15**-1136, **16**-0687
Scaiano, J., **07**-0001
Scaiano, J.C., **05**-0113, **05**-0285, **07**-0001, **07**-0047, **14**-0097, **14**-0118, **14**-0216, **18**-0073
Scaiano, J.J., **05**-0310
Scalzi, F.V., **12**-0168
Scamehorn, R.G., **13**-0594, **18**-0198
Scamuzzi, B., **10**-0790
Scanio, M.J.C., **15**-2435
Scanlan, T.S., **10**-0802
Scannon, P.J., **08**-0069, **08**-0074
Scarborough Jr., R.M., **10**-0801, **19**-0590
Scardovi, N., **15**-0225
Scarpati, R., **15**-1941
Scarpello, J.T., **13**-0402
Scarpi, D., **16**-0687, **19**-1022
Scartozzi, M., **15**-0384
Scattergood, A., **12**-0465, **12**-0467
Scerer Jr., K.V., **18**-0463
Scettri, A., **15**-1558, **15**-1818, **16**-0756, **19**-0080, **19**-0732, **19**-0735, **19**-0823
Schaad, L.J., **02**-0095, **02**-0107, **02**-0223, **03**-0001, **12**-0099
Schaaf, T.K., **15**-1585
Schaafsma, S.E., **16**-0043
Schaal, W., **07**-0118
Schaap, A., **10**-1536, **15**-2159
Schaap, A.P., **15**-2164
Schaap, L.A., **15**-0722
Schaart, B.J., **12**-0604
Schaasberg-Nienhuis, Z.R.H., **11**-0204
Schachtschneider, J.H., **15**-2199, **18**-0500
Schade, C., **05**-0072, **05**-0131, **05**-0146, **12**-0396, **12**-0550, **15**-1636
Schade, G., **16**-1287
Schade, O., **05**-0207
Schade, P., **02**-0320
Schädler, H.D., **17**-0476
Schadt, F.L., **10**-0158, **10**-0162, **10**-0282, **10**-0421, **10**-0433
Schaefer III, H.F., **01**-0011, **01**-0025, **02**-0252, **02**-0062, **02**-0172, **02**-0251, **02**-0261, **02**-0262, **02**-0417, **04**-0279, **05**-0331, **05**-0332, **05**-0337, **05**-0383, **05**-0385, **07**-0015, **15**-0011, **16**-1844
Schaefer, A.D., **16**-1851
Schaefer, F.C., **16**-0012, **16**-0197
Schaefer, J.P., **02**-0163, **10**-1096, **13**-0252, **16**-1412, **16**-2022, **19**-0470, **19**-0599
Schaefer, T., **03**-0054
Schaefer, W., **04**-0504
Schaeffer, M.W., **03**-0072
Schaeffer, W.D., **04**-0022, **10**-0397
Schäfer, B., **15**-1975
Schäfer, G., **10**-0430, **10**-0446
Schäfer, H., **14**-0419, **18**-0411, **18**-0413, **19**-0250
Schäfer, H.J., **14**-0156, **14**-0415, **15**-1998, **17**-0514, **19**-0319, **19**-0598
Schäfer, L., **03**-0031
Schäfer, U., **04**-0437, **17**-0512
Schäfer, W., **04**-0490, **15**-2255, **15**-2256, **15**-2260, **18**-0494
Schäfer-Ridder, M., **02**-0260
Schaffers, T., **18**-0631
Schaffner, K., **11**-0560, **18**-0856, **18**-0860, **18**-0863
Schaffrodt, H., **18**-0019
Schakel, M., **10**-0711, **15**-0043, **15**-2072, **18**-0590
Schaleger, L.L., **10**-0534
Schaller, C., **12**-0348
Schaller, J., **15**-2050
Schaller, R., **16**-1873, **16**-2041
Schallner, O., **05**-0086
Schaltegger, A., **18**-0190
Schambach, R.A., **11**-0615
Schamlz, H.-G., **15**-1017
Schamp, N., **16**-1224
Schank, K., **10**-0746, **10**-0839, **13**-0687, **16**-2034, **19**-0812
Schanze, K., **05**-0409
Schapiro, V., **15**-2231
Scharf, D.J., **15**-2350
Scharf, G., **11**-0634
Scharf, H., **15**-2001, **15**-2235
Schat, G., **12**-0566, **12**-0585
Schatz, B., **18**-0705
Schatz, J., **15**-2137
Schaub, B., **16**-1259, **16**-1324, **16**-1328
Schaub, F., **15**-1080
Schauble, J.H., **15**-1543, **19**-0733, **19**-1001
Schauder, J.R., **17**-0222
Schauer, M., **03**-0072
Schaumann, E., **15**-2231, **16**-0002, **16**-0004, **16**-2095, **16**-2096
Schaus, J.V., **12**-0273
Schaus, S.E., **10**-1804, **16**-0801, **16**-1188
Scheer, J.C., **17**-0132
Scheeren, H.W., **15**-2043
Scheeren, J.W., **11**-0460, **15**-2191, **16**-0214, **16**-2081
Scheffer, A., **15**-1788
Scheffer, J.R., **04**-0142, **05**-0285, **16**-2093
Scheffler, K., **05**-0234
Scheffold, R., **17**-0216
Scheibye, S., **16**-0211, **16**-0212, **16**-0220
Scheidt, F., **10**-0226
Scheidt, K.A., **04**-0124, **15**-1322, **15**-1339, **15**-1368, **16**-0724, **16**-1944
Scheinbaum, M.L., **18**-0559
Scheiner, P., **17**-0505
Scheiner, S., **03**-0020
Scheinmann, F., **10**-1769, **18**-0654
Scheiper, B., **10**-1330
Scheithauer, S., **16**-1724
Schell, F.M., **18**-0344
Schellenberg, K.A., **16**-0356
Schellenberger, H., **19**-0326
Schellman, J.A., **04**-0268
Schelpe, A., **15**-0170
Schemenaur, J.E., **19**-1001
Schenck, G.O., **14**-0235, **15**-2151
Schenck, T.G., **18**-0689
Schenerman, M.A., **19**-1181
Schenk, W.A., **15**-1849
Schenk, W.N., **16**-1537
Schenkluhn, H., **15**-2429
Schepers, R.G., **18**-0868
Schepp, N.P., **02**-0383, **02**-0385, **02**-0386, **12**-0097, **12**-0150
Scheppele, S.E., **06**-0076, **10**-0170, **18**-0104
Scherer, P., **12**-0035, **12**-0036
Scherrer, R.A., **13**-0249
Schertler, P., **04**-0435
Schetty, G., **18**-0132
Scheuermann, H., **04**-0369
Scheuermann, J.E.W., **10**-0955
Scheuplein, S.W., **18**-0735
Scheurer, P.G., **10**-0510
Schiano, A.-M., **16**-1505
Schiavelli, M.D., **10**-0232, **10**-0253, **10**-1411, **15**-0219
Schick, H., **10**-0488
Schick, U., **12**-0274
Schieb, T., **02**-0284
Schiemenz, G.P., **16**-1256, **16**-1264
Schiess, M., **16**-0407, **16**-1681
Schiess, P.W., **17**-0403

Schiesser, C.H., **04**-0358, **05**-0080, **05**-0082, **12**-0614, **14**-0244, **15**-0103
Schiff, H., **12**-0462
Schiffers, R., **18**-0703
Schijf, R., **11**-0460
Schikora, E., **05**-0357
Schildknegt, K., **18**-0297
Schill, G., **03**-0180, **03**-0192, **03**-0194, **03**-0195, **04**-0093, **10**-1698
Schilling, P., **14**-0169
Schilling, W., **16**-1655
Schimmel, H., **10**-0355
Schimperna, G., **16**-1077
Schindbauer, H., **16**-1810
Schindler, S.R., **16**-1342
Schinke, U., **18**-0750
Schinz, H., **16**-2051
Schinzer, D., **15**-1175, **19**-1022
Schipper, P., **10**-0152
Schippers, P.H., **04**-0216
Schiraldi, D.A., **11**-0629
Schirmer, H., **15**-2413
Schissler, D.O., **15**-0448
Schlag, E.W., **03**-0072, **05**-0339, **07**-0022
Schlama, T., **13**-0554
Schlapbach, A., **16**-0697
Schläpfer-Dähler, M., **04**-0460
Schlatter, A., **19**-1042
Schlatter, M.J., **04**-0465
Schlegel, H.B., **01**-0100, **04**-0306, **05**-0121, **10**-0020, **10**-0364, **14**-0036, **14**-0068
Schleifenbaum, A., **02**-0076
Schleker, W., **15**-2001
Schlemenat, A., **18**-0849
Schlemper, H., **08**-0084, **17**-0306
Schlenk Jr., W., **04**-0102, **04**-0165, **05**-0157
Schlenk, W., **05**-0157
Schlessinger, R.H., **10**-1614, **10**-1698, **15**-1348
Schleth, F., **19**-1310
Schleyer, P.v.R., **01**-0010, **01**-0033, **01**-0048, **01**-0054, **02**-0014, **02**-0040, **02**-0092, **02**-0099, **02**-0104, **02**-0105, **02**-0156, **02**-0207, **02**-0251, **02**-0261, **02**-0262, **02**-0309, **02**-0311, **02**-0338, **02**-0339, **02**-0350, **02**-0354, **02**-0371, **02**-0417, **03**-0051, **03**-0052, **03**-0058, **03**-0060, **03**-0083, **04**-0372, **04**-0373, **04**-0492, **05**-0002, **05**-0013, **05**-0022, **05**-0024, **05**-0030, **05**-0034, **05**-0037, **05**-0040, **05**-0047, **05**-0050, **05**-0054, **05**-0060, **05**-0068, **05**-0076, **05**-0078, **05**-0079, **05**-0083, **05**-0087, **05**-0101, **05**-0124, **05**-0131, **05**-0146, **05**-0148, **05**-0154, **05**-0176, **05**-0194, **05**-0337, **05**-0385, **06**-0080, **08**-0008, **08**-0110, **08**-0233, **10**-0011, **10**-0041, **10**-0051, **10**-0053, **10**-0057, **10**-0079, **10**-0082, **10**-0119, **10**-0120, **10**-0128, **10**-0129, **10**-0131, **10**-0133, **10**-0153, **10**-0157, **10**-0158, **10**-0162, **10**-0164, **10**-0170, **10**-0173, **10**-0177, **10**-0178, **10**-0181, **10**-0184, **10**-0188, **10**-0192, **10**-0196, **10**-0197, **10**-0199, **10**-0201, **10**-0206, **10**-0208, **10**-0254, **10**-0256, **10**-0257, **10**-0279, **10**-0280, **10**-0281, **10**-0282, **10**-0318, **10**-0320, **10**-0326, **10**-0374, **10**-0380, **10**-0393, **10**-0394, **10**-0399, **10**-0421, **10**-0433, **10**-1112, **10**-1538, **11**-0004, **12**-0009, **12**-0396, **12**-0407, **12**-0421, **12**-0550, **12**-0655, **12**-0687, **13**-0028, **13**-0048, **14**-0101, **15**-0035, **15**-0106, **15**-0140, **15**-0630, **15**-0647, **15**-1947, **15**-2196, **18**-0002, **18**-0007, **18**-0009, **18**-0018, **18**-0029, **18**-0045, **18**-0048, **18**-0100, **18**-0105, **18**-0113, **18**-0114, **18**-0115, **18**-0116, **18**-0118, **18**-0119, **18**-0509, **18**-0510, **18**-0511, **18**-0624, **19**-0008, **19**-1286
Schlicher, J.W., **19**-1184
Schlingloff, G., **18**-0363
Schlitt, R., **18**-0708
Schlögl, K., **04**-0078, **04**-0083, **04**-0175
Schlögl, R., **15**-0459
Schlosberg, R.H., **05**-0023, **05**-0031, **11**-0014
Schlosser, M., **10**-1312
Schlosser, M., **11**-0040, **12**-0391, **12**-0394, **12**-0395, **12**-0424, **12**-0551, **16**-1259, **16**-1282, **16**-1297, **16**-1303, **16**-1323, **16**-1324, **16**-1328, **16**-1329, **16**-1330, **16**-1331, **17**-0024, **17**-0026, **17**-0209, **17**-0310, **18**-0418
Schlubach, H.H., **15**-1620
Schlummer, B., **15**-0389
Schlund, R., **12**-0062
Schlüter, A., **04**-0431
Schlüter, K., **15**-0094
Schmalstieg, L., **02**-0282
Schmalz, D., **02**-0321, **05**-0148
Schmalzing, D., **04**-0175
Schmelzer, A., **04**-0416
Schmerling, L., **15**-0713, **15**-0725, **15**-1636
Schmickler, H., **02**-0102, **02**-0284, **02**-0295, **02**-0320, **02**-0326, **02**-0330
Schmid, B., **16**-0147
Schmid, C.R., **19**-0109
Schmid, G.H., **10**-0122, **10**-0134, **15**-0001, **15**-0016, **15**-0021, **15**-0022, **15**-0026, **15**-0079, **15**-0087
Schmid, H., **15**-2112, **18**-0526, **18**-0621, **18**-0654, **18**-0686, **18**-0691, **18**-0705, **18**-0705
Schmid, J., **19**-0366
Schmid, M., **18**-0686
Schmid, P., **13**-0013, **13**-0014
Schmid, W., **15**-0939
Schmidbaur, H., **04**-0513
Schmidlin, J., **15**-1166
Schmidlin, R., **05**-0324
Schmidt, A., **12**-0623
Schmidt, A.H., **02**-0347, **16**-1889, **18**-0495, **19**-1605
Schmidt, B., **18**-0779, **19**-1692
Schmidt, C., **15**-2098
Schmidt, D., **18**-0641
Schmidt, D.M., **13**-0773
Schmidt, E.K.G., **18**-0590, **18**-0590
Schmidt, E.W., **14**-0273
Schmidt, F., **16**-0703
Schmidt, G., **04**-0389, **19**-0081
Schmidt, G.M.J., **02**-0292, **04**-0142
Schmidt, H., **04**-0473, **19**-0598
Schmidt, J., **10**-1236
Schmidt, J.A.R., **10**-1552
Schmidt, K., **02**-0284
Schmidt, L.M., **04**-0313
Schmidt, M.W., **01**-0010
Schmidt, R., **19**-1341
Schmidt, R.D., **11**-0180
Schmidt, R.R., **02**-0239, **05**-0135, **10**-1734, **15**-2122, **15**-2139
Schmidt, S., **10**-1644
Schmidt, S.E., **10**-0859
Schmidt, S.P., **10**-1089
Schmidt, T., **12**-0077, **19**-1008
Schmidt, U., **16**-1652, **16**-1655
Schmidt, W., **02**-0224, **15**-2073, **15**-2111
Schmidtchen, F.P., **04**-0243, **04**-0245

Schmiedel, R., **02**-0206, **03**-0202, **10**-1640
Schmitt, A.C., **19**-0584
Schmitt, E., **19**-1465
Schmitt, R.J., **12**-0709
Schmittberger, T., **16**-1543
Schmittel, M., **05**-0298, **18**-0487
Schmitter, J., **10**-1437
Schmittou, E.R., **10**-0517
Schmitz, C., **17**-0289
Schmitz, E., **04**-0038, **16**-0140, **18**-0866
Schmitz, P.H., **10**-1664
Schmitz, R., **15**-1167, **19**-1210, **19**-1536
Schmitz, R.F., **10**-0711
Schmolke, B., **18**-0590
Schmuff, N.R., **05**-0143, **10**-1478
Schmutzler, R., **12**-0365
Schnabel, W., **02**-0158
Schnack, L.G., **10**-0318, **18**-0507
Schneemeyer, L.F., **03**-0053
Schneider, A., **18**-0116
Schneider, C., **10**-0945, **10**-1546, **15**-1104, **18**-0603
Schneider, D.R., **18**-0506
Schneider, F., **05**-0208
Schneider, G., **08**-0067
Schneider, H., **01**-0042, **04**-0330, **09**-0010, **10**-0192, **15**-0013, **15**-1735, **19**-0461
Schneider, H.-J., **03**-0110, **04**-0389
Schneider, J.A., **04**-0141
Schneider, K., **04**-0501, **18**-0496
Schneider, M., **19**-0241
Schneider, M.F., **18**-0804
Schneider, M.P., **18**-0615, **18**-0616
Schneider, P., **12**-0577
Schneider, R., **13**-0198, **13**-0199, **13**-0200, **15**-1636, **19**-1312
Schneider, S., **07**-0022
Schnell, H., **05**-0231, **11**-0386
Schnell, H.W., **05**-0042
Schnider, P., **10**-1659
Schnöckel, H., **04**-0477
Schnorrenberg, G., **16**-1820
Schnurpfeil, D., **15**-1573
Schnyder, A., **11**-0512
Schöbel, G., **16**-1227
Schobert, R., **18**-0672
Schoch, J., **18**-0891
Schoeller, W.W., **11**-0013
Schoemaker, H.E., **15**-0395, **15**-0913, **18**-0813, **19**-1022
Schoenberg, A., **10**-1849, **10**-1852
Schoeneck, W., **13**-0682
Schoffstall, A.M., **15**-1932
Schofield, K., **11**-0029, **11**-0033, **11**-0041, **11**-0050, **11**-0054, **11**-0055, **11**-0083, **11**-0094, **11**-0096, **11**-0097, **11**-0119, **18**-0332, **18**-0336
Scholes, G., **19**-0438
Scholl, M., **18**-0767, **18**-0781, **18**-0832
Scholl, P.C., **19**-0603
Schöllkopf, U., **04**-0136, **10**-0318, **12**-0009, **15**-2262, **16**-1197, **16**-1198, **16**-1286, **18**-0385, **18**-0387, **18**-0389, **18**-0390, **18**-0396, **18**-0397, **18**-0410, **18**-0411, **18**-0413, **18**-0504, **18**-0510, **18**-0730
Scholte, A.A., **10**-0996
Scholz, D., **12**-0243
Scholz, M., **05**-0319
Scholz, U., **13**-0119
Schomäcker, R., **11**-0013
Schomaker, J.M., **15**-1673
Schomaker, V., **02**-0228
Schön, M., **16**-0490
Schön, U., **16**-0429
Schönberg, A., **07**-0041, **12**-0073, **15**-0050, **15**-2151, **15**-2235, **16**-1397, **19**-1687
Schönberger, A., **19**-0262
Schönleber, D., **18**-0616
Schönowsky, H., **14**-0320
Schoofs, A.R., **04**-0214, **10**-0227
Schoolenberg, J., **15**-0409, **15**-0574
Schore, N.E., **14**-0312, **15**-2362, **19**-1033
Schossig, J., **18**-0396
Schotte, L., **12**-0141
Schotten, T., **13**-0485
Schoustra, B., **17**-0002
Schowen, K.B., **16**-1465
Schowen, R.L., **06**-0088, **06**-0087, **16**-0020, **16**-1465, **16**-1494, **16**-1593, **16**-1594
Schrader, W., **11**-0427
Schrage, K., **15**-0453
Schräpler, U., **19**-1736
Schreader, L., **19**-1368
Schreck, J.O., **09**-0071, **09**-0081
Schrecken, H., **14**-0377
Schreckenberg, M., **10**-1664, **15**-1368, **16**-0724
Schreer, M., **16**-0563
Schreiber, J., **10**-0723, **10**-1175, **12**-0035, **16**-0402, **16**-0404, **17**-0420, **19**-0250
Schreiber, M.R., **17**-0090
Schreiber, S.L., **15**-2235, **19**-0200, **19**-0352
Schreibmann, A.A.P., **19**-1645
Schreier, P., **19**-0540, **19**-0542, **19**-0547
Schreiner, H., **02**-0260
Schreiner, P.R., **05**-0315, **10**-1112, **14**-0003, **14**-0142, **14**-0150, **15**-0855, **15**-2378, **18**-0627
Schriesheim, A., **05**-0043, **11**-0316, **11**-0384, **12**-0063, **13**-0667, **17**-028, **17**-0288, **19**-0336, **19**-079, **19**-0869
Schrimpf, M.R., **12**-0469
Schrive, J., **14**-0233
Schriver, G.W., **05**-0002, **10**-0177
Schrock, R.R., **16**-1367, **18**-0755, **18**-0756, **18**-0762, **18**-0768, **18**-0775, **18**-0780, **18**-0792, **18**-0800, **18**-0808, **18**-0822, **18**-0828, **18**-0829, **18**-0836
Schröder, B., **18**-0850
Schröder, F., **15**-0965
Schröder, G., **02**-0274, **02**-0298, **02**-0314, **02**-0324, **04**-0193, **15**-1702, **18**-0634, **18**-0635, **18**-0637, **19**-0361, **19**-0375
Schröder, M., **03**-0114, **15**-1656, **16**-0647
Schröder, U., **16**-1198
Schrøder, S., **17**-0005
Schroeck, C.W., **16**-1387, **16**-1388
Schroeder, G.M., **10**-1632, **10**-1628
Schroeder, H.E., **03**-0103
Schroeder, J.D., **10**-0948, **19**-0175, **19**-0679
Schroeter, S., **14**-0235
Schroeter, S., **14**-0235
Schroll, G., **10**-0910, **15**-0468
Schroth, W., **02**-0118, **17**-0476, **19**-1794
Schrott, W., **12**-0509
Schrumpf, G., **04**-0281, **10**-1536
Schubert, H., **04**-0143
Schubert, P.F., **07**-0079, **07**-0081, **07**-0088
Schubert, R.M., **19**-0903
Schubert, U., **04**-0513, **15**-0783

Schubert, W.M., **02**-0370, **11**-0045, **11**-0271, **11**-0443, **11**-0609, **11**-0610, **14**-0447, **15**-0025, **19**-0428
Schuchardt, U., **19**-0611
Schuda, P.F., **15**-2126
Schug, R., **15**-2223
Schugar, H.J., **02**-0199
Schuld, C.L., **15**-1722
Schulenberg, J.W., **02**-0401, **18**-0874
Schuler, R.H., **05**-0273, **05**-0280
Schulman, D.R., **16**-0040
Schulman, E.M., **16**-0040
Schulman, J.M., **04**-0430
Schulman, M.F., **15**-0631
Schulmeier, B., **11**-0233
Schulmeier, B.E., **15**-2088
Schult, K.E., **15**-0359
Schulte II, J.P., **18**-0808, **19**-1010, **19**-1315
Schulte, T., **19**-1310
Schulte-Elte, K.H., **12**-0662, **14**-0237
Schulte-Frohlinde, D., **07**-0054
Schultz, A.G., **05**-0322, **15**-0537, **18**-0184, **18**-0471, **18**-0860
Schultz, F., **11**-0610
Schultz, H.P., **16**-2050
Schultz, J.C., **05**-0073
Schultz, M., **19**-0056
Schultz, M.J., **16**-0865, **19**-0120
Schultz, P.G., **07**-0118, **18**-0604
Schultz, R.A., **03**-0101
Schultz, S.C., **15**-0409
Schultze, L.M., **16**-2099
Schulz, E., **19**-1028
Schulz, H., **19**-0482, appendixA-0017
Schulz, J.G.D., **19**-0422
Schulz, L., **10**-1605
Schulz, M., **19**-0503
Schulz, W.H., **02**-0284
Schulz-von Itter, N., **10**-0567
Schulze, P.D., **05**-0344
Schulze, S.M., **18**-0601
Schulze, V., **16**-0491
Schumacher, R., **16**-1419
Schuman, M., **18**-0818
Schumann, H., **11**-0360, **12**-0614, **13**-0322, **15**-0767
Schumann, R.C., **16**-1018
schumann, W., **10**-0860
Schummer, A., **04**-0243
Schummer, D., **18**-0233
Schüngel, F.-M., **05**-0315
Schürer, S.C., **18**-0774
Schurig, V., **04**-0037, **04**-0173, **04**-0175, **04**-0211
Schurz, K., **01**-0011
Schüssler, H., **16**-1716, **16**-1799
Schüßler, M., **19**-0503
Schuster, A., **04**-0434
Schuster, D.I., **07**-0064, **15**-2238, **15**-2254, **18**-0856, **18**-0861
Schuster, G.B., **01**-0042, **05**-0347, **05**-0401, **14**-0244
Schuster, H.F., **04**-0135, **04**-0481, **10**-0231, **15**-0106, **15**-0443, **15**-2183, **16**-2091, **17**-0378, **18**-0171, **18**-0695
Schuster, I.I., **05**-0088
Schuster, P., **03**-0001
Schut, J., **14**-0404, **19**-1587
Schütte, H., **10**-0317
Schütz, T., **16**-0576
Schüürmann, G., **10**-0410
Schwab, J.W., **16**-1565
Schwab, P., **18**-0766
Schwab, P.A., **15**-1786
Schwab, W., **18**-0462
Schwamborn, M., **02**-0260
Schwan, A.L., **19**-1525
Schwarm, M., **19**-1082
Schwartz, A., **04**-0196
Schwartz, H.S., **10**-0724
Schwartz, J., **12**-0245, **15**-0706, **15**-1150, **15**-1151, **16**-1348, **16**-1367, **17**-0413, **19**-1665
Schwartz, J.L., **18**-0696
Schwartz, L.H., **18**-0046
Schwartz, L.M., **08**-0164
Schwartz, M., **04**-0282
Schwartz, M.A., **19**-1230
Schwartz, R.A., **12**-0398
Schwartz, S., **08**-0019
Schwartz, S.J., **18**-0429
Schwartzman, L.H., **19**-1184
Schwarz, H., **05**-0002, **05**-0067, **10**-0133, **10**-0488, **18**-0077, **19**-0064
Schwarz, J., **08**-0075, **19**-0602
Schwarz, L., **13**-0299
Schwarz, M.J., **16**-1466
Schwarz, R., **15**-1052
Schwarz, S., **10**-0488
Schwarz, W., **13**-0704, **16**-2108
Schwarzenbach, D., **02**-0402
Schwarzenbach, K., **15**-2323
Schwebel, H., **10**-0848
Schweig, A., **02**-0204, **02**-0215, **04**-0473
Schweikert, N., **03**-0194
Schweinsberg, F., **14**-0043
Schweiter, M.J., **15**-1824
Schweitzer, D., **02**-0308
Schweizer, E.E., **15**-2263, **17**-0259
Schweizer, T., **01**-0042
Schweizer, W.B., **04**-0295, **04**-0504, **05**-0191, **05**-0192, **12**-0036, **16**-0407
Schwellnus, K., **16**-1204
Schwemlein, H.P., **03**-0083
Schwendeman, R.H., **01**-0052 **01**-0078
Schwenker, R.P., **07**-0028
Schweppe, A., **19**-0830
Schwesinger, R., **08**-0084, **08**-0186, **17**-0306
Schwetlick, K., **12**-0742, **14**-0223, **14**-0292
Schwier, T., **10**-1432, **15**-0738
Schwierz, H., **03**-0188
Schwyzer, R., **16**-1579
Sciacovelli, O., **17**-0031
Scilly, N.F., **16**-1971
Sclafani, J.A., **13**-0530
Sclove, D.B., **18**-0203
Scoccitti, T., **19**-1142
Scola, P.M., **10**-0899, **15**-2122
Scopes, D.I.C., **15**-0364
Scopes, P.M., **04**-0102
Scorrano, G., **05**-0070, **08**-0009, **08**-0111, **08**-0129, **16**-1576
Scott J.L., **09**-0084
Scott, A.P., **02**-0186
Scott, A.D., **10**-0003, **16**-1562
Scott, A.I., **13**-0299
Scott, A.P., **18**-0219
Scott, C.B., **10**-0349, **17**-0194
Scott, D.A., **15**-0197, **15**-0202, **15**-0588
Scott, F.L., **05**-0054
Scott, I.L., **15**-1428
Scott, J.A., **08**-0223, **08**-0231, **08**-0236
Scott, J.L., **09**-0120, **16**-1172, **18**-0490
Scott, J.M.W., **06**-0057, **10**-0033, **10**-0034, **10**-0078, **11**-0587
Scott, J.W., **04**-0134, **04**-0136
Scott, K.J., **17**-0094
Scott, K.W., **18**-0758, **18**-0760, **18**-0762
Scott, L.T., **02**-0271, **02**-0319, **02**-0353, **02**-0358, **02**-0360, **16**-1655, **18**-0062, **18**-0520, **18**-0521, **18**-0646, **18**-0520
Scott, M.D., **17**-0446
Scott, M.K., **12**-0691
Scott, P., **15**-0332, **15**-1885
Scott, R.M., **18**-0396
Scott, S.L., **15**-0315, **19**-0074
Scott, W.B., **04**-0449, **10**-1236

Scott, W.J., **10**-1305, **10**-1346, **10**-1347, **12**-0256, **12**-0257, **12**-0259, **12**-0276, **13**-0389
Scouten, C.G., **10**-0182
Scremin, M., **16**-1632
Screttas, C.G., **09**-0059, **10**-1852, **12**-0392, **12**-0542, **14**-0411, **14**-0413, **16**-0965, **18**-0192, **19**-0974
Screttri, A., **15**-0232, **15**-1741, **15**-1822
Scribner, R.M., **10**-1078, **16**-0447
Scriven, C.E., **19**-1725
Scriven, E.F.V., **05**-0396, **05**-0411 **10**-1005, **10**-1011, **11**-0148, **12**-0236, **15**-1932, **16**-1622, **18**-0282, **19**-1256
Scully Jr., F.E., **19**-0662
Seabury, M., **15**-2219
Seabury, N.J., **13**-0075
Sealy, J.M., **19**-1671
Seapy, D.G., **10**-1089
Searle, C.E., **17**-0498
Searle, R., **02**-0059
Sears, P.G., **08**-0231
Seayad, A.M., **15**-0333, **15**-0342, **16**-0306, **16**-0344
Seayad, J., **15**-0314
Sebastian, J.F., **01**-0047
Sebastian, R., **03**-0054
Sebastián, R.M., **15**-1022
Sebastiani, G.V., **11**-0279, **17**-0031, **17**-0033, **17**-0051, **17**-0110
Sebban, M., **12**-0599
Sebti, S., **15**-1001, **15**-1029
Sechrest, R.C., **04**-0362
Seco, J.M., **04**-0106, **04**-0108, **04**-0109
Seconi, G., **12**-0045
Secor, R.M., **04**-0185
Sedaghat-Herati, M.R., **10**-0308, **11**-0029
Seddighi, B., **10**-0655, **10**-0668
Seddon, K.R., **09**-0109, **09**-0111, **13**-0415
Sedelmeier, G., **15**-2196
Sederholm, C.H., **04**-0323
Sedlmeier, J., **19**-0721
Sedrani, R., **10**-1520, **15**-1092
Seebach, D., **04**-0131, **04**-0132, **04**-0136, **04**-0424, **05**-0148, **05**-0191, **05**-0192, **10**-0558, **10**-1666, **10**-1667, **10**-1693, **10**-1697, **10**-1701, **10**-1703, **10**-1708, **10**-1721, **10**-1731, **10**-1767, **12**-0240, **12**-0619, **15**-1042, **15**-1114, **15**-2103, **16**-0246, **16**-0407, **16**-0520, **16**-1014, **16**-1149, **16**-1681, **16**-2012, **16**-2035, **19**-0742, **19**-1281, **19**-1692, **19**-1710
Seeboth, H., **13**-0093, **13**-0244, **13**-0245, **13**-0247
Seekircher, R., **19**-0422
Seel, C., **03**-0202
Seeley, D.A., **15**-2112
Seelhammer, T., **13**-0291
Seely, F.L., **14**-0020
Seeman, J.I., **04**-0267, **09**-0012, **18**-0485
Seetz, J.W.F.L., **12**-0566, **12**-0583
Sefcik, M.D., **12**-0051
Seferin, M., **15**-0798, **18**-0781
Segal, G.A., **02**-0016
Segall, Y., **15**-0498
Seganish, W.M., **10**-1212, **13**-0632, **13**-0637
Segebarth, N., **07**-0075,l **07**-0080
Seger, A., **19**-1034
Seghrouchni, L., **16**-0555, **16**-1917
Segi, M., **16**-1104
Segmuller, B., **04**-0519
Segoe, K., **10**-1806
Segorbe, M.M., **12**-0262
Segovia, A., **19**-0355
Segre, A., **03**-0079
Seguineau, P., **16**-1306
Segura, P., **09**-0078, **11**-0614
Segura, R.C.M., **19**-1021
Sehgal, A., **18**-0667
Sehgal, C., **07**-0079
Sehgal, C.M., **07**-0079
Sehmi, P., **05**-0006, **06**-0047
Seib, R.C., **10**-0170, **17**-0035
Seibel, W.L., **10**-0993, **17**-0324
Seibl, J., **10**-0015
Seiche, W., **15**-1481, **15**-1491
Seid, M., **18**-0275
Seidel, B., **15**-2182, **15**-2222
Seidel, C.F., **16**-2051
Seidel, D., **16**-1161
Seidel, G., **13**-0472, **18**-0828
Seidel, W.C., **15**-1504
Seidl, P., **10**-0148
Seigal, B.A., **18**-0779
Seiji, Y., **13**-0770
Seijo, E., **16**-1140
Seikaly, H.R., **15**-0182, **15**-0205, **15**-0265
Seiler, P., **03**-0045
Seiler, S.T., **04**-0431
Seip, H.M., **02**-0030, **04**-0261, **04**-0317, **04**-0350
Seip, R., **03**-0050
Seites, P.G., **10**-1183
Seitz Jr., E.P., **10**-1430
Seitz, G., **02**-0206
Seitz, T., **16**-1765
Seitz, W., **04**-0038
Sekar, G., **10**-0684, **10**-0925, **10**-0956, **10**-0962, **15**-2297, **19**-0535
Sekhar, Ch.V.R., **16**-0616
Sekhar, K.C., **11**-0394, **19**-1214
Seki, A., **15**-0994, **16**-0978
Seki, H., **03**-0193
Seki, M., **16**-1981, **16**-1989, **16**-1990
Seki, T., **19**-1766, **19**-1773
Seki, Y., **10**-0170
Sekiguchi, A., **04**-0503, **05**-0179, **05**-0317, **10**-0785, **13**-0538
Sekiguchi, S., **11**-0169, **13**-0015, **13**-0155, **16**-1593
Sekiguchi, Y., **15**-1004, **16**-1036
Sekine, A., **15**-1023
Sekiya, A., **10**-1306, **13**-0263, **13**-0279, **13**-0710, **15**-0176
Sekiya, K., **10**-1372
Sekiya, M., **10**-1524, **16**-0273, **18**-0249
Sekljic, H., **16**-1774
Selby, D.W., **10**-0228
Selegue, J.P., **02**-0366
Seliger, H.H., **15**-2165
Selikson, S.J., **19**-1422
Selim, A., **10**-1640
Selinka, C., **02**-0084
Selitsianos, D., **16**-1310
Sell, T., **15**-0413, **19**-0983
Sella, A., **10**-0321
Sellers, C., **13**-0717
Sellers, S.F., **18**-0589
Sello, G., **15**-1758
Selman, C.M., **12**-0013
Selman, S., **18**-0188
Seltzer, R., **10**-0488, **10**-0489
Seltzer, S., **15**-2088, **15**-2094
Selva, A., **14**-0341
Selva, M., **09**-0104, **10**-0412, **10**-0884, **12**-0746, **13**-0406, **19**-0339
Selvakumar, K., **13**-0399, **19**-1703
Selve, C., **10**-0908
Selvi, S., **11**-0473
Selwood, T., **16**-1559
Selzle, H.L., **03**-0072
Semenov, A.O., **14**-0118
Semenow, D., **10**-0394
Semenow, D.A., **13**-0038, **13**-0079
Semigran, M.J., **19**-1719

Semmelhack, M.F., **02**-0053, **10**-1251, **10**-1253, **10**-1255, **13**-0361, **13**-0462, **13**-0596, **15**-0230, **15**-2429, **17**-0340, **19**-0109
Semmingsen, D., **02**-0346
Semones, A.M., **13**-0463
Sen Gupta, K.K., **19**-0711
Sen Gupta, S., **19**-0711
Sen Sharma, D.K., **10**-0178
Sen, A., **14**-0261
Sen, D., **03**-0105
Sen, K.D., **01**-0022, **01**-0024, **01**-0028
Sen, S., **15**-2410
Sen, S.E., **10**-0543, **15**-0786
Senanayake, C.B.W., **12**-0260
Senanayake, C.H., **16**-0462, **19**-1207
Senatore, L., **16**-2144, **16**-2145
Senboku, H., **10**-1863, **14**-0439, **15**-1387, **17**-0383
Senda, T., **15**-1130
Senda, Y., **15**-0122
Senders, J.R., **04**-0440, **15**-2359
Sendijarević, V., **10**-0060, **17**-0035
Senet, J., **10**-1187
Seneviratne, V., **19**-0768
Seng, F., **16**-1343, **16**-1408
Senglet, N., **19**-0614
Sengupta, D., **12**-0688
Sengupta, K.K., **19**-0247, **19**-0249
Sengupta, S., **12**-0404, **13**-0365, **13**-0540, **13**-0726, **16**-1951
Senju, T., **16**-0491
Senn, M., **12**-0109, **14**-0123
Sennhenn, P.C., **15**-1777, **15**-1859
Senthilkumar, P., **17**-0477
Senthilnathan, V.P., **05**-0345
Senzaki, M., **15**-2084
Senzaki, Y., **15**-2322, **18**-0469, **18**-0470, **18**-0643
Seo, J.W., **10**-0501
Seo, K., **16**-1530
Seo, S., **04**-0206
Seoane, G., **15**-1724, **15**-2282
Seoane, P., **15**-1969
Seomoon, D., **10**-1402, **13**-0620, **15**-0820, **15**-0918
Seppelt, K., **01**-0096
Seppo, E., **18**-0052
Seqyad, A., **15**-1378
Sera, A., **06**-0051, **09**-0086, **10**-0475, **17**-0031, **19**-1254
Seradj, H., **10**-0568, **16**-0160, **16**-0166, **16**-0175, **16**-0255, **16**-1623
Sercel, A.D., **16**-0349
Serdyuk, L., **17**-0257
Sereda, G.A., **15**-1541
Sérée de Roch, I., **19**-0701
Seregin, I.V., **13**-0309
Seregina, V.F., **13**-0107
Serelis, A.K., **15**-0104
Sergeev, N.M., **04**-0333
Sergeev, G.B., **12**-0609, **15**-0023, **15**-0169, **15**-0181
Sergeeva, N.S., **12**-0731
Sergeeva, Z.I., **19**-1279
Sergeyev, S., **15**-0152
Sergi, V., **10**-0534
Sergovskaya, N.L., **15**-1574
Serguchev, Yu.A., **19**-0433
Seri, N., **03**-0130
Serino, C., **10**-1281
Serita, K.-i., **16**-0380
Serizawa, H., **15**-1187
Serizawa, Y., **10**-0811
Serjeant, E.P., **08**-0018, **08**-0160
Serra, M., **18**-0278
Serra-Zanetti, F., **17**-0425
Serratosa, F., **02**-0346, **02**-0347, **16**-1583
Serravalle, M., **11**-0185, **14**-0120, **14**-0340, **14**-0363
Serva, L., **19**-1243
Servano, J., **16**-0689
Servesko, J.M., **15**-0594
Servi, S., **15**-0520
Servino, E.A., **13**-0425
Servis, K.L., **10**-0178, **15**-2103, **18**-0471
Sesana, G., **14**-0344
Sesenoglu, Ö., **19**-0320
Seshadri, S., **14**-0188
Seshita, T., **10**-1230
Sessions, R.B., **04**-0239, **04**-0240, **04**-0241, **04**-0244
Sestanj, K., **11**-0391
Sestelo, J.P., **10**-1392, **10**-1402, **13**-0335, **13**-0620
Seter, J., **10**-0151
Seth, S., **17**-0265
Seth-Paul, W.A., **09**-0047
Sethi, A., **15**-2041
Sethi, K., **16**-1213
Sethi, P., **16**-2031
Sethna, S., **11**-0380, **11**-0416, **11**-0441
Sethofer, S.G., **10**-0923
Sethuraman, M.R., **11**-0419
Setiarahardjo, I.U., **13**-0012
Seto, C.T., **16**-0687
Seto, H., **13**-0255
Seto, K., **13**-0583
Setoguchi, H., **15**-0929
Settambalo, R., **11**-0355
Setzer, W.N., **05**-0148
Seubert, J., **18**-0497
Seubold Jr., F.H., **18**-0055, **18**-0065
Severin, T., **15**-1167, **19**-0605, **19**-1210, **19**-1536
Seville, J.P.K., **15**-1950
Sevin, A., **14**-0314, **15**-2234, **18**-0052, **18**-0118
Sevlapalam, N., **16**-1688
Sevrin, M., **10**-1089
Sewald, N., **15**-1138
Sexsmith, S.R., **15**-2403
Sexton, A., **12**-0580, **12**-0597
Sexton, G., **08**-0101
Sexton, K.E., **19**-1077
Seybold, G., **02**-0222, **02**-0224, **18**-0042
Seybold, P.G., **08**-0175
Seydel, R., **11**-0351
Seyden-Penne, J., **08**-0149, **15**-1001 **15**-1111, **16**-1213, **17**-0112, **19**-0010, **19**-0874, **19**-0913, **19**-1062, **19**-1291
Seyferth, D., **05**-0380, **12**-0354, **12**-0376, **12**-0528, **12**-0568, **15**-1344, **15**-1345, **15**-2269, **15**-2271, **15**-2272, **16**-0510, **16**-0511, **16**-1282, **19**-1306
Seyler, J.K., **15**-0417
Sezen, B., **13**-0307, **19**-0286, **19**-0493, **19**-0494
Seçen, H., **10**-0939
Sfouggatakis, C., **18**-0905
Sfulcini, A., **15**-0961
Sha, C., **16**-0542
Sha, C.-K., **15**-0908, **15**-1246, **15**-1249
Shaabani, A., **19**-0149, **19**-0565, **19**-0566, **19**-0808
Shaafi, E., **19**-0092
Shaapuni, D.Kh., **19**-1360
Shabana, R., **16**-0211, **19**-1791
Shabangi, M., **19**-1302, **19**-1671
Shackleton, T.A., **15**-0515
Shadakshari, U., **15**-1139
Shaefer, C.G., **19**-1098
Shäfer, W., **02**-0204
Shaffer, D.K., **14**-0207
Shafran, Yu.M., **16**-1447
Shah, A.C., **16**-1809
Shah, M.H., **12**-0167, **16**-2106
Shah, M.M., **11**-0381
Shah, N.M., **11**-0380
Shah, R.C., **11**-0381
Shah, R.D., **16**-0362
Shah, S.K., **10**-1714
Shah, S.T.A., **10**-0786
Shahak, I., **10**-1017, **10**-1146
Shahi, S.P., **16**-0114, **19**-0595

Shaik, S., **10**-0854, **14**-0079, **15**-2105
Shaik, S.S., **02**-0006, **02**-0041, **08**-0142, **10**-0089, **10**-0100, **10**-0358
Shaikh, N., **10**-1297
Shaikh, N.S., **15**-1294
Shain, S.A., **16**-0022
Shainyan, B.A., **02**-0420, **10**-0237, **10**-0244, **10**-0261, **19**-1789
Shair, M.D., **18**-0657
Shakespeare, W.C., **04**-0486, **13**-0228
Shakhidayatov, Kh., **12**-0057
Shakirov, M., **11**-0013
Shakirov, M.M., **18**-0006, **18**-0011
Shakoori, A., **19**-0861
Shalaev, V.K., **15**-2077, **19**-0837
Sham, T.-K., **19**-0121
Shamma, M., **10**-0803, **15**-1585
Shamsipur, M., **19**-0039
Shamsuddin, K.M., **19**-1103
Shang, X., **16**-1136
Shang, Z., **14**-0060
Shani, A., **02**-0259, **02**-0265
Shank, R.S., **15**-2329
Shankar, B.K.R., **04**-0443
Shanklin, J.R., **16**-1195, **16**-1387, **16**-1388
Shanklin, M.S., **15**-1480
Shanmugam, P., **10**-1546
Shanmugasundaram, M., **13**-0432, **15**-2373, **15**-2387
Shannon, I.J., **17**-0265
Shannon, P.J., **19**-1487
Shannon, P.T., **07**-0054
Shao, C., **15**-2421
Shao, D., **16**-0663
Shao, H., **16**-1001, **19**-0563
Shao, J.-G., **15**-2004
Shao, L., **18**-0667
Shao, L.-Y., **16**-0095
Shao, M.-Y., **16**-0687
Shapiro, B.L., **02**-0101
Shapiro, G., **16**-1733
Shapiro, I.O., **05**-0104
Shapiro, J., **18**-0487
Shapiro, M.J., **04**-0130
Shapiro, R.H., **17**-0268, **17**-0269, **17**-0273, **17**-0274
Shapland, P., **15**-0668
Shapley, J.R., **15**-2202
Sharada, D.S., **16**-0807
Sharanin, Yu.A., **16**-1409
Sharf, B., **07**-0022
Sharf, V.Z., **16**-1470
Sharghi, H., **10**-0679, **10**-1161, **10**-1165, **11**-0423, **11**-0549, **14**-0277, **16**-0311, **16**-0325, **17**-0443, **18**-0323, **18**-0660
Sharifi, A., **16**-0129, **16**-0144
Sharifi, T., **11**-0029
Sharma, A.K., **19**-1787
Sharma, D.K., **07**-0053
Sharma, G.T., **09**-0074
Sharma, G.V.M., **10**-1131, **16**-0781, **16**-0795, **16**-1671, **16**-1684, **18**-0702
Sharma, J.P., **19**-0080, **19**-0249
Sharma, L., **16**-1529
Sharma, M., **18**-0564, **19**-0096, **19**-0469
Sharma, N.K., **16**-1195, **19**-0584
Sharma, P., **10**-1247, **15**-2007
Sharma, P.A., **19**-1018
Sharma, P.K., **14**-0079
Sharma, R., **16**-1957, **19**-1485
Sharma, R.B., **10**-0178
Sharma, R.K., **14**-0333
Sharma, R.P., **10**-1013, **17**-0198, **17**-0201, **17**-0332, **19**-0934
Sharma, R.R., **10**-1279
Sharma, S., **10**-1355, **10**-1367, **12**-0570, **16**-1757
Sharma, S.D., **16**-1893, **16**-2101
Sharma, S.N., **19**-0463
Sharma, U., **15**-1002, **15**-2434
Sharma, V., **15**-1605, **16**-1708
Sharma, V.B., **16**-0390, **19**-0114, **19**-0783
Sharma, V.K., **19**-1212
Sharma, V.L., **19**-1491
Sharnin, G.P., **13**-0067
Sharp, D.W.A., **05**-0088
Sharp, J.T., **13**-0745, **15**-1355
Sharp, K.G., **05**-0346
Sharp, M.J., **13**-0305
Sharp, R.L., **15**-0647, **15**-0650, **15**-0669
Sharpe, L.R., **13**-0594
Sharpless, K.B., **04**-0193, **07**-0122, **10**-0494, **10**-0496, **10**-0498, **10**-0678, **10**-0819, **10**-0866, **10**-1018, **10**-1502, **10**-1504, **10**-1542, **12**-0223, **12**-0224, **12**-0248, **14**-0189, **15**-1564, **15**-1658, **15**-1661, **15**-1691, **15**-1692, **15**-1693, **15**-1696, **15**-1698, **15**-1699, **15**-1701, **15**-1702, **15**-1704, **15**-1731, **15**-1741, **15**-1760, **15**-1777, **15**-1795, **15**-1820, **15**-1821, **15**-1822, **15**-1824, **15**-1825, **15**-1826, **15**-1858, **15**-1859, **15**-1860, **15**-1861, **15**-1864, **15**-1865, **15**-1866, **15**-1876, **16**-1387, **17**-0290, **17**-0293, **17**-0329, **19**-0079, **19**-0470, **19**-0471, **19**-0473, **19**-0474, **19**-0590, **19**-0600, **19**-0732, **19**-0734, **19**-0902, **19**-1718
Sharts, C.M., **10**-0511, **10**-1041, **10**-1042, **10**-1145, **12**-0727, **15**-0166, **15**-1542, **15**-1621, **15**-2166, **15**-2209, **15**-2272
Shastin, A.V., **15**-1918
Shatavsky, M., **10**-0130
Shatenshtein, A.I., **05**-0104, **05**-0148, **11**-0114, **12**-0061
Shaterian, H.R., **10**-0848
Shatkina, T.N., **18**-0026
Shatskaya, V.A., **16**-2155
Shaughnessy, E.A., **15**-2064
Shaughnessy, K.H., **13**-0502
Shaw, A., **18**-0509
Shaw, C., **16**-1840
Shaw, J.E., **10**-0693, **13**-0103, **13**-0134
Shaw, J.T., **16**-1053, **16**-1145, **16**-1161
Shaw, M.J., **11**-0313
Shaw, W.J., **19**-0608
Shchegolev, A.A., **18**-0002
Shchukina, M.V., **16**-2143
She, X., **13**-0413, **15**-1773, **15**-1774
Shea, H.A., **13**-0502
Shea, K.J., **04**-0491, **14**-0041, **14**-0042, **14**-0045, **15**-0142, **18**-0081, **18**-0620, **18**-0623, **18**-0650
Shearer, G.O., **15**-1732
Shearer, H.M.M., **02**-0228
Shearing, D.J., **17**-0056
Sheats, G.F., **11**-0098
Sheats, J.E., **13**-0028, **13**-0030, **13**-0719
Shebaldova, A.D., **15**-2199, **18**-0500, **18**-0756
Shechter, H., **05**-0387, **10**-1786, **15**-1619, **15**-2329, **16**-2162, **17**-0269, **17**-0280, **19**-0419, **19**-0664
Sheeba, V., **15**-1624, **19**-0730
Sheehan, J.C., **10**-0983, **10**-1000, **16**-1796
SheHon, D.R., **16**-0821
Sheikh, H., **10**-0725
Sheikh, M.Y., **19**-0213
Shein, S.M., **10**-1314, **13**-0216
Shekarriz, M., **10**-0681, **10**-1799, **15**-1577, **15**-1848
Shekhar, R., **13**-0487
Shekhtman, N.M., **04**-0363
Shelby, Q., **13**-0482

Sheldon, C.G., **12**-0323, **16**-1371
Sheldon, R.A., **14**-0196, **14**-0214, **14**-0217, **14**-0246, **14**-0432, **15**-1655, **15**-1739, **15**-1750, **15**-1753, **16**-1841, **18**-0350, **18**-0355, **18**-0379, **19**-0181, **19**-0183, **19**-0225, **19**-0273, **19**-0433, **19**-0718
Sheldrake, P., **15**-0536
Sheldrick, G.M., **05**-0143
Sheldrick, W.S., **04**-0271
Shell, B., **19**-0429
Shellhamer, D.F., **15**-0004, **15**-0033
Shelly, D.P., **11**-0567, **13**-0742
Shelly, K.P., **12**-0095
Shelton, J.R., **15**-0069, **16**-0400
Shelton, K.W., **18**-0487
Shemyakin, M.M., **02**-0159, **12**-0718, **16**-1255, **18**-0885, **18**-0888
Shen, C., **19**-0159
Shen, C.-X., **16**-0451
Shen, C.-Y., **15**-1246
Shen, C.C.C., **05**-0130
Shen, G.S., **16**-1351
Shen, H., **15**-2435
Shen, J., **12**-0342, **16**-0687
Shen, J.-h., **16**-0687
Shen, J.H., **15**-1826
Shen, K., **15**-2105, **18**-0557
Shen, L., **10**-0997, **15**-1124, **16**-0699
Shen, S., **02**-0199, **05**-0386
Shen, W., **10**-1409, **12**-0308, **13**-0507, **13**-0514
Shen, X., **16**-2078
Shen, X.-P., **03**-0133
Shen, Y., **11**-0328, **11**-0358, **16**-0810, **16**-0811, **16**-0834, **16**-1428
Shene, A.L., **17**-0178
Sheng, R., **02**-0120
Sheng, S., **15**-0214
Sheng, S.J., **18**-0073
Shenglof, M., **13**-0322
Shenhav, H., **15**-0077
Shepelavy, J.N., **12**-0235
Shepherd, B.D., **01**-0011
Shepherd, J.P., **15**-1676
Shepherd, R., **18**-0032
Shepherd, R.G., **13**-0071
Sheppard, A.C., **19**-0480, **19**-0501, **19**-0736, **19**-0830
Sheppard, H.C., **11**-0113
Sheppard, N., **02**-0034, **02**-0037, **05**-0088
Sheppard, P.J., **11**-0072
Sheppard, W.A., **10**-0511, **10**-1041, **10**-1042, **10**-1145, **11**-0616, **13**-0460, **13**-0691, **15**-0166, **15**-1542, **15**-1621, **15**-2272, **19**-1763
Sheradsky, T., **12**-0222, **12**-0227
Sherbine, J.P., **14**-0413
Sheridan, P.M., **08**-0197
Sheridan, R.S., **02**-0213, **04**-0320, **04**-0497, **05**-0328, **05**-0355, **05**-0386, **05**-0392, **05**-0400, **06**-0033, **17**-0422, **17**-0508
Sherlock, A.E., **15**-0900
Sherman, J.C., **03**-0171, **03**-0172, **03**-0173
Sherman, S.C., **11**-0629
Sherman, V.W., **14**-0454
Sherrill, C.D., **03**-0073, **03**-0074
Sherrington, D.C., **15**-1694, **15**-1823, **16**-1817, **16**-1822
Sherrod, S.A., **06**-0074
Sherwin, M.A., **18**-0641
Shestopalov, A.M., **16**-1409
Sheu, C., **18**-0461, **19**-0609
Sheu, H., **10**-0437
Sheu, J., **15**-2061, **15**-2136
Sheu, R.G., **18**-0895
Shevchuk, V.U., **10**-1075
Shevelev, S.A., **10**-0483, **11**-0180
Shevlin, P.B., **05**-0350, **14**-0046, **17**-0139, **18**-0073
Shezad, N., **13**-0407, **13**-0426, **15**-2036
Shi, F., **13**-0097, **16**-0067, **16**-0152
Shi, J., **10**-1390
Shi, L., **13**-0162, **16**-0298, **16**-0645, **16**-0834, **16**-1266, **19**-1384, **19**-1673
Shi, M., **10**-1864, **15**-1137, **15**-1902, **16**-0687, **16**-0773, **16**-0782, **16**-0785, **16**-0789, **16**-0791, **16**-0796, **16**-0800, **16**-0802, **16**-0866, **16**-0897, **18**-0581
Shi, Q., **15**-1125
Shi, Q.-Z., **19**-0568
Shi, W.-J., **15**-1136
Shi, W.J., **10**-1386
Shi, X.-X., **16**-0253
Shi, Y., **15**-0352, **15**-0578, **15**-1740, **15**-1767, **15**-1768, **15**-1772, **15**-1773, **15**-1774, **15**-1775, **15**-2343, **16**-1794, **18**-0157
Shi, Z., **15**-0287, **16**-0044, **19**-1120
Shi-ike, T., **16**-0437
Shia, K.-S., **10**-1494, **15**-1100, **16**-1067
Shiba, T., **15**-1461
Shibagaki, M., **19**-1287
Shibahara, F., **11**-0498, **15**-1492
Shibakami, M., **03**-0168, **13**-0710, **15**-0176, **04**-0179
Shibanuma, T., **16**-0434, **17**-0487
Shibasaki, M., **10**-0672, **10**-0743, **13**-0379, **13**-0399, **15**-0994, **15**-1023, **15**-1303, **15**-1568, **15**-1741, **15**-1796, **15**-1808, **15**-1874, **16**-0687, **16**-0698, **16**-0898, **16**-1008, **16**-1041, **16**-1043, **16**-1044, **16**-1272, **16**-1426, **16**-1438, **16**-1439, **19**-1677
Shibata, I., **15**-0622, **15**-1061, **16**-0376, **16**-0377, **16**-0382, **16**-0617, **16**-0638, **16**-0822, **16**-0871, **16**-1904, **19**-1001, **19**-1101, **19**-1139, **19**-1298, **19**-1308
Shibata, J., **16**-1129
Shibata, K., **10**-0881, **15**-0906, **16**-0666, **16**-0711, **16**-0719
Shibata, N., **19**-178, **19**-1783
Shibata, T., **04**-0422, **10**-0439, **10**-1406, **13**-0324, **13**-0613, **15**-0983, **15**-1336, **15**-1445, **15**-1448, **15**-1457, **15**-1691, **15**-1914, **15**-1915, **15**-2012, **15**-2383
Shibatmoi, K., **10**-1470, **12**-0158, **16**-0640
Shibli, A., **10**-1385
Shibutani, M., **02**-0296, **02**-0303, **02**-0328
Shibuya, A., **15**-0350
Shibuya, I., **16**-2116
Shibuya, K., **19**-1610
Shibuya, S., **15**-1247, **19**-1283
Shida, J., **10**-0916
Shida, S., **12**-0346
Shida, T., **05**-0284
Shie, J.-J., **14**-0278
Shieh, C.H., **16**-2108
Shieh, J.J., **02**-0080
Shieh, W.-C., **10**-0721, **13**-0487
Shields, G.C., **08**-0170, **08**-0175
Shields, G.P., **03**-0017
Shiers, J.J., **10**-0246
Shiga, H., **15**-2369
Shiga, N., **10**-0882
Shiga, Y., **19**-1307
Shigemasa, T., **18**-0131
Shigemasa, Y., **14**-0402, **19**-1581
Shigemura, K., **11**-0013

Shigemura, M., **08**-0169
Shigetani, T., **02**-0036
Shigeyoshi, Y., **10**-1627
Shih, C., **10**-0394
Shih, J., **10**-1180
Shih, J.G., **05**-0083
Shih, N.C., **15**-0488
Shih, N.Y., **03**-0210
Shih, T.L., **16**-1018
Shih, Y., **11**-0447, **11**-0607
Shih, Y.-K., **13**-0753
Shiina, I., **16**-0820, **16**-1011, **16**-1119, **16**-1129, **16**-1656, **16**-1684, **16**-1788
Shijo, M., **04**-0175
Shikaura, J., **15**-1238
Shikimi, M., **15**-0154
Shillaker, B., **10**-0084
Shim, C.S., **09**-0021, **10**-0304, **16**-1509
Shim, E., **13**-0620
Shim, S.B., **12**-0696
Shim, S.C., **10**-1626, **13**-0599, **16**-2120
Shim, W.H., **11**-0325
Shim, S.C., **10**-1500
Shima, K., **15**-0319
Shimabayashi, A., **16**-2015
Shimada, H., **19**-1678
Shimada, M., **11**-0434
Shimada, S., **11**-0418, **11**-0442, **13**-0321, **13**-0327, **13**-0336, **15**-0380 **18**-0517
Shimada, T., **13**-0538, **15**-0211, **15**-0745, **15**-0787, **15**-1719, **18**-0143
Shimagaki, M., **17**-0241
Shimamura, T., **16**-1129
Shimamura, Y., **12**-0695
Shimane, K., **16**-1361
Shimanouchi, T., **10**-1157
Shimanskaya, M.V., **15**-2274
Shimao, I., **18**-0882, **18**-0890
Shimasaki, C., **17**-0289
Shimazaki, M., **18**-0158
Shimazaki, R., **13**-0293
Shimizu, A., **19**-1301
Shimizu, H., **15**-1935 **16**-0490, **16**-1121, **16**-1124, **17**-0161, **19**-0120, **19**-0823, **19**-1162, **19**-1744
Shimizu, I., **10**-1630, **11**-0342, **17**-0327, **18**-0189, **19**-0060, **19**-0899
Shimizu, K., **10**-1322, **15**-0993, **15**-1391
Shimizu, K.-i., **13**-0481, **16**-1685
Shimizu, M., **10**-1080, **10**-1149, **10**-1154, **15**-1544, **15**-2298, **16**-0666, **16**-0711, **16**-0719, **16**-0819, **16**-0871, **16**-0921, **16**-1114, **16**-1384, **19**-0732, **19**-0990, **19**-1021, **19**-1143, **19**-1610, **19**-1667, **19**-1696
Shimizu, N., **10**-0163
Shimizu, R., **10**-1783
Shimizu, S., **03**-0138, **10**-1655, **19**-1022
Shimizu, T., **10**-0919, **16**-1661, **16**-1836, **16**-1981, **16**-1989, **19**-0827
Shimizu, Y., **13**-0415, **16**-1904
Shimobayashi, A., **13**-0281
Shimoda, K., **15**-0626, **16**-1545
Shimoji, K., **10**-1709, **16**-1235
Shimonaka, K., **11**-0323, **16**-2156
Shimomoto, A., **16**-1036
Shin, C., **02**-0421
Shin, C., **10**-1516
Shin, D., **15**-0252
Shin, D.-S., **16**-1381, **19**-0523
Shin, J., **05**-0092
Shin, K.K., **07**-0012
Shin, S., **15**-0844
Shin, S.I., **10**-0859, **10**-0973, **13**-0449, **16**-1867
Shin, W.C., **10**-1031
Shin, Y.-J., **16**-0690
Shin-ike, T., **14**-0013
Shinada, T., **16**-0874
Shindo, M., **10**-1617, **16**-0858, **16**-2119
Shine, H.J., **05**-0318, **11**-0502, **11**-0543, **11**-0546, **11**-0562, **11**-0570, **11**-0579, **11**-0585, **11**-0586, **11**-0590, **11**-0602, **11**-0639, **13**-0754, **13**-0759, **13**-0769, **13**-0773, **18**-0185, **18**-0654, **18**-0656, **18**-0658, **18**-0714, **18**-0739, **18**-0740, **18**-0741, **18**-0742, **18**-0743, **18**-0746, **18**-0749, **18**-0750, **18**-0751, **18**-0752, **18**-0753, **18**-0881, **18**-0891
Shiner Jr., V.J., **06**-0069, **06**-0072, **06**-0073, **06**-0080, **06**-0082, **06**-0088, **10**-0059, **10**-0060, **10**-0070, **10**-0134, **10**-0170, **10**-0208, **10**-0327, **10**-0382, **10**-0430, **12**-0637, **17**-0006, **17**-0035, **17**-0064, **18**-0018, **19**-0975, **19**-0977
Shiner, C.S., **05**-0126, **10**-0743
Shiner, V.J., **10**-0202, **10**-0208
Shingaki, T., **12**-0233
Shingare, M.S., **10**-0660
Shingu, H., **10**-0073, **10**-0074, **10**-0084, **10**-0309
Shingū, K., **04**-0065
Shinhama, K., **14**-0355
Shinkai, S., **03**-0122, **03**-0123, **03**-0126, **07**-0058, **13**-0770, **19**-1574
Shinkarenko, N.V., **14**-0228, **15**-2156
Shinmen, M., **13**-0557
Shinmyozu, T., **03**-0129
Shinoda, H., **02**-0036
Shinoda, K., **15**-0707, **19**-0361
Shinohara, A., **15**-1719
Shinohara, T., **18**-0357, **18**-0363
Shinohara, Y., **16**-1228
Shinokubo, H., **14**-0009, **10**-1202, **10**-1396, **10**-1498, **10**-1550, **10**-1625, **13**-0317, **13**-0333, **13**-0429, **13**-0433, **15**-0305, **15**-0731, **15**-0743, **15**-0863, **15**-0915, **15**-0935, **15**-1206, **15**-1208, **15**-1252, **15**-1254, **15**-1265, **15**-1645, **15**-1646, **15**-2385, **15**-2427, **16**-0466, **16**-0647, **16**-0865, **16**-0992, **19**-0127, **19**-1666
Shinozaki, H., **17**-0427
Shintani, R., **15**-0592, **15**-1125, **16**-1941
Shioiri, T., **10**-1798, **12**-0068, **12**-0512, **15**-1791, **15**-1807, **16**-0947, **16**-1032, **16**-1221, **16**-1225, **16**-1229, **16**-1314, **16**-1392, **18**-0216, **18**-0231, **19**-0487
Shiono, M., **16**-0434, **17**-0487, **18**-0440
Shiotsuki, M., **10**-1453
Shipman, M., **10**-0246, **18**-0057
Shippey, M.A., **17**-0199
Shirae, Y., **13**-0482
Shiragami, T., **10**-0965, **15**-0319
Shirai, M., **10**-0894, **13**-0407, **13**-0415, **15**-1324
Shirai, N., **13**-0762, **13**-0764
Shirai, R., **12**-0108
Shirai, Y., **15**-1807, **16**-1229
Shiraishi, D., **15**-0288
Shiraishi, H., **19**-1663
Shiraishi, T., **10**-1243, **15**-1037
Shiraishi, Y., **18**-0685
Shirakawa, E., **11**-0329, **12**-0284, **13**-0430, **15**-0210, **15**-1492
Shirakawa, K., **12**-0497
Shirakawa, S., **03**-0138, **16**-1101
Shirasaka, K., **15**-2366
Shirasaka, T., **16**-1487
Shireman, B.T., **16**-1054
Shiri, M., **11**-0299

Shirini, F., **16**-0096, **19**-0087
Shirley, D.A., **12**-0400
Shirley, I.M., **15**-0420, **15**-1667
Shirley, R.L., **17**-0517
Shiro, M., **04**-0334, **12**-0368
Shiro, M., **16**-1117
Shirokawa, S.-i., **16**-1127
Shirokova, N.P., **18**-0305
Shirota, Y., **15**-2194
Shiroyama, M., **19**-0322
Shirwaiker, G.S., **18**-0644
Shirzi, J.S., **19**-0242, **19**-1701
Shishido, K., **16**-2119
Shishido, T., **10**-0896, **15**-0371, **15**-0732
Shitani, R., **15**-1140
Shiue, J.-S., **19**-1670
Shivakawa, S., **19**-1004
Shivanyuk, A., **03**-0120
Shivaramayya, K., **15**-1295
Shivasankar, K., **16**-1701
Shivini, F., **12**-0705
Shizuka, H., **11**-0594
Shklover, V., **05**-0263
Shkmoda, K., **19**-1022
Shkurko, O.P., **09**-0020
Shlyapintokh, V.Ya., **14**-0228, **15**-2156
Shner, V.F., **13**-0107
Shoaf, C.J., **19**-1182
Shoair, A.G., **19**-0394
Shobe, D., **18**-0162
Shodai, H., **10**-1230
Shoel, S.Md.A., **15**-2399
Shoemaker, M.J., **18**-0390
Shohamy, E.B., **17**-0056
Shoji, M., **15**-2139, **19**-0505, **19**-0507
Shokol, V.A., **16**-1309
Sholle, V.D., **05**-0228, **05**-0255
Shönberg, A., **15**-2436
Shone, R.L., **06**-0076, **11**-0648
Shono, T., **10**-1719, **14**-0284, **16**-0645, **16**-1491, **17**-0371, **17**-0435, **18**-0011, **19**-0319, **19**-0862, **19**-1563, **19**-1691, **19**-1699
Shook, B.C., **17**-0164, **17**-0165
Shook, C.A., **18**-0576
Shook, D.A., **12**-0218
Shoosmith, J., **05**-0275
Shoppee, C.W., **10**-0133, **15**-0124
Shore, N., **07**-0044
Shore, P.A., **14**-0202
Shorokhodov, V.I., **11**-0294
Short, E.L., **11**-0607
Short, K.M., **15**-2438
Short, R.P., **16**-1034
Shorter, J., **08**-0136, **08**-0149, **09**-0016, **09**-0019, **09**-0020, **09**-0038, **09**-0041, **09**-0058, **09**-0061, **09**-0078, **10**-0350, **10**-0443, **16**-0424
Shortridge, R.W., **04**-0412
Shostakovskii, M.F., **10**-0661, **15**-0047, **15**-0049, **15**-0250, **15**-0295
Shoup, T.M., **12**-0444, **16**-0494
Shovshinev, S.V., **15**-1574
Shpan'ko, I.V., **16**-0015
Shpan'ko, L.V., **13**-0086
Shreeve, J.M., **12**-0136, **15**-1533
Shriner, R.H., 09-II-0006
Shriner, R.L., **04**-0001, **04**-0013, 09-II-0006
Shtamburg, V.G., **04**-0042
Shteingarts, V.D., **11**-0012, **13**-0106, **14**-0203, **18**-0250
Shtern, M.M., **10**-0242
Shtern, V.Ya., **12**-0203
Shu, C., **10**-0294
Shu, L., **15**-0966, **15**-1740, **15**-1773, **15**-1774, **15**-1775
Shubashree, S., **13**-0147
Shubert, D.C., **10**-1296
Shubin, V.G., **11**-0013, **18**-0002, **18**-0006, **18**-0011, **18**-0030, **18**-0035, **18**-0250
Shudo, K., **11**-0190, **11**-0477
Shue, R.S., **13**-0417
Shue, Y.-J., **10**-0881
Shuekhgeimer, G.A., **15**-1987
Shuford, R.J., **15**-0465
Shuikin, N.I., **15**-0713, **19**-1373
Shukla, M.R., **16**-1543
Shukla, R., **03**-0118, **18**-0079, **18**-0473
Shukla, V.G., **19**-0810
Shukun, H., **19**-1370
Shul'pin, G.B., **02**-0166
Shulman, E.M., **16**-1148
Shulman, G.P., **17**-0143
Shulman, J.I., **16**-1329
Shulman, N., **13**-0084
Shults, R.H., **10**-1290, **10**-1291
Shulyupin, M.O., **15**-0373, **15**-0382
Shumaker, S.H., **18**-0329
Shumate, K.M., **18**-0462
Shundo, R., **15**-1921
Shundo, T., **10**-1503
Shunmugasundaram, A., **05**-0378
Shusherina, N.P., **15**-2003
Shushunov, V.A., **12**-0432, **12**-0438
Shustov, G.V., **04**-0036, **04**-0039, **10**-0367
Shute, R.E., **13**-0177, **13**-0407, **13**-0492
Shuto, S., **16**-1277
Shutt, G.R., **10**-0007
Shuttleworth, S., **10**-0647
Shvartsberg, M.S., **13**-0119, **14**-0319
Shvekhgeimer, G.A., **15**-1617
Shvets, V.F., **14**-0118
Shvets, V.I., **04**-0159
Shvets,V.F., **14**-0116
Shvo, Y., **15**-0220, **15**-0280, **15**-0436
Shyamsunder, T., **10**-0958, **15**-0403, **15**-0438
Si, Y.-G., **16**-0550, **16**-0869
Siahaan, T.J., **15**-1082
Siam, K., **03**-0031
Siani, G., **12**-0083
Sibelle, E.C., **11**-0440
Sibi, M.P., **14**-0030, **15**-1050, **15**-1096, **15**-1107, **15**-1216, **15**-1962, **15**-2066, **16**-0687, **16**-1737, **16**-1957
Sibille, S., **10**-1397
Sicher, J., **04**-0451, **10**-0208, **17**-0007, **17**-0015, **17**-0018, **17**-0021, **17**-0022, **17**-0024, **17**-0025, **17**-0096, **17**-0389
Sicken, M., **02**-0295
Sicking, W., **01**-0090, **15**-2060
Sickles, B.R., **13**-0044
Sicre, J.E., **10**-0284
Siddall, J.B., **15**-1080
Siddhanta, A.K., **02**-0402, **12**-0097
Siddiquei, A.S., **11**-0073
Siddiqullah, Md., **12**-0465, **12**-0467
Siddons, D.C., **18**-0419
Sidhu, H., **17**-0036
Sidhu, R.S., **18**-0733
Sidler, J.D., **18**-0411
Sidot, C., **13**-0613
Siebeneicher, H., **15**-0355
Siebenhaar, B., **16**-1177
Sieber, A., **17**-0457
Sieber, P., **16**-1579
Sieber, S., **05**-0078, **10**-0120, **10**-0208
Sieber, W., **15**-2112, **16**-1461
Siebert, W., **02**-0170
Sieburth, S.M., **18**-0601
Sieburth, S.Mc.N., **15**-0758, **15**-2436, **16**-1947
Sieck, R., **10**-1033
Sieczkowski, J., **03**-0092
Siedle, A.R., **15**-2419

Siedlecka, R., **19**-0129
Siegbahn, P.M., **05**-0332
Siegel, A., **12**-0406
Siegel, C., **16**-1032
Siegel, E., **10**-0747
Siegel, H., **12**-0620
Siegel, J., **04**-0019, **04**-0504, **19**-1362
Siegel, J.J., **11**-0079
Siegel, J.S., **02**-0072, **02**-0082, **02**-0359, **03**-0200, **08**-0169, **11**-0080
Siegel, M.G., **04**-0163
Siegel, S., **15**-0451
Siegert, P., **16**-2065
Siegfried, B., **10**-0333, **10**-1808, **13**-0733, **14**-0354, **16**-1564, **19**-0665, **19**-1567
Siegfried, R., **10**-0178
Siegfried, S., **18**-0672
Siegl, W.O., **10**-1812
Siegmann, K., **10**-1333, **14**-0390
Siehl, H., **05**-0067, **06**-0072, **10**-0200
Sieler, J., **04**-0054
Siemeling, U., **05**-0174
Siemers, N.O., **19**-1680
Siemsen, P., **14**-0300
Sierakowski, C., **18**-0090
Sies, C.W., **11**-0057
Siesel, D., **11**-0371
Sieskind, O., **11**-0344
Sifniades, S., **12**-0206
Sigalas, M.P., **05**-0055
Sigalov, M., **12**-0083
Sigeev, A.S., **13**-0152
Siggel, L., **15**-2440
Siggel, M.R., **02**-0056, **08**-0171
Sigman, M.E., **05**-0401
Sigman, M.S., **15**-2363, **16**-0865, **19**-0120, **19**-0218
Signorella, S., **13**-0521
Sih, C.J., **04**-0180, **19**-1020
Siklosi, M.P., **12**-0660
Sikora, D.J., **02**-0166
Sikorski, J.A., **18**-0453
Sikorski, W.H., **15**-1113
Silber, E., **15**-2103
Silber, J.J., **13**-0013
Silber, P., **15**-2243
Silberman, L., **06**-0015
Silberman, R.G., **02**-0197
Silbermann, J., **12**-0631
Silbert, L.S., **10**-0693, **10**-0747, **10**-1690, **12**-0208, **14**-0151, **16**-1252, **16**-1694, **16**-2039
Silbey, R., **07**-0022
Silcoff, E.R., **16**-0975, **16**-1044
Sild, S., **02**-0112
Silina, A., **10**-1675
Silks III, L.A., **18**-0871
Sill, P., **15**-0834
Sill, P.C., **15**-1444, **15**-1445
Silla, E., **10**-0232
Sillion, B., **15**-1566, **19**-0674
Silovani, A., **16**-0687
Silva Jr., J.F., **18**-0210
Silva, A.M.S., **07**-0121
Silva, D. de O., **16**-0293
Silva, M.A., **15**-2004
Silveira Jr., A., **18**-0440
Silveira, C.C., **12**-0290, **12**-0294, **15**-0216, **15**-0291
Silveira, G.P.C., **16**-0776
Silveira, P.B., **13**-0297
Silver, D.M., **15**-2105
Silver, M.E., **16**-1852
Silver, M.S., **10**-0203, **17**-0081
Silverberg, L.J., **19**-1027
Silverman, S.B., **19**-1450
Silversmith, E.F., **03**-0175, **15**-2222, **16**-1148
Silverstein, R.M., **04**-0106, **04**-0256
Silverthorn, W.E., **03**-0083, **03**-0091
Silverton, J.V., **02**-0270
Silverwood, H.A., **19**-0020
Silvester, M.J., **11**-0310
Silvestri, M.G., **10**-1503
Silvi, B., **08**-0198
Sim, T.B., **15**-0568
Simal, F., **15**-1643, **15**-1959
Simamura, O., **18**-0374, **19**-0787, **19**-1565
Simandan, T., **10**-0974
Simándi, L.I., **14**-0301, **19**-0398, **19**-0738
Simandoux, J., **15**-0024
Simchen, G., **10**-1524, **16**-0943
Sime, J.M., **08**-0034
Simić, O., **15**-2065
Simkin, B.Ya., **02**-0092, **02**-0209, **02**-0231, **02**-0288, **05**-0327
Simmons, H.E., **02**-0032, **02**-0255, **04**-0230, **04**-0242, **04**-0246, **10**-0462, **12**-0235, **13**-0038, **15**-2227, **15**-2228, **15**-2327, **15**-2328, **15**-2333, **15**-2336, **19**-0388
Simmons, M.C., **05**-0377, **12**-0383
Simmons, R., **18**-0781
Simms, J.A., **15**-0047
Simms, N., **10**-1634
Simões, J.A.M., **01**-0098
Simon, A., **02**-0340
Simon, E.S., **19**-1246
Simon, H., **04**-0151, **06**-0059, **17**-0059, **17**-0062, **17**-0254
Simon, J., **11**-0157, **13**-0096
Simon, J.A., **16**-2059
Simon, J.D., **10**-0067
Simon, K., **05**-0177
Simon, W., **04**-0163
Simon, W.M., **13**-0177, **16**-1581
Simonelli, F., **19**-1425
Simonet, B., **15**-1587
Simonetta, M., **01**-0007, **01**-0072, **02**-0260, **02**-0268, **02**-0277, **02**-0285, **02**-0319, **13**-0010, **15**-2103
Simoni, D., **16**-1260
Simonneaux, G., **15**-2307
Simonoff, R., **19**-1513
Simonot, B., **15**-1592
Simonov, A.M., **13**-0676
Simons, H.E., **02**-0052
Simons, J., **05**-0327
Simons, J.H., **16**-0446
Simons, R.W., **15**-1595
Simova, S., **16**-0487
Simpkins, N.S., **10**-1639, **12**-0105, **12**-0108, **15**-0040, **15**-0311, **16**-0851, **16**-1236
Simpson, C.C., **11**-0073
Simpson, C.F., **11**-0072
Simpson, G.R., **08**-0180
Simpson, G.W., **15**-1939, **17**-0035
Simpson, I.D., **10**-1566
Simpson, J.H., **10**-1400
Simpson, J.M., **18**-0590
Simpura, I., **16**-0983, **19**-1775, **19**-1776
Sims, J.J., **19**-0446
Sims, L.B., **06**-0063, **06**-0069, **17**-0058, **17**-0128
Sims, L.L., **15**-0124
Simson, J.M., **12**-0233
Sinclair, J.A., **14**-0396, **15**-1188, **18**-0453, **18**-0455
Sindona, G., **10**-0545
Sinegovskaya, L.M., **04**-0295
Sineokov, A.P., **15**-1966
Singaram, B., **10**-0893, **10**-0923, **10**-1417, **12**-0516, **12**-0519, **13**-0172, **15**-0670, **15**-0671, **15**-0674, **15**-0675, **15**-1187, **16**-0997, **18**-0433, **18**-0442, **18**-0443, **18**-0456, **19**-0026, **19**-0161, **19**-0416, **19**-0888, **19**-0939, **19**-0953, **19**-1126, **19**-1154, **19**-1172, **19**-1271, **19**-1498, **19**-1499, **19**-1527
Singaram, S., **15**-0693, **19**-0888
Singer, L.A., **16**-2084

Singer, M.S., **16**-0540
Singer, R.A., **02**-0374, **13**-0177, **13**-0188, **13**-0473
Singer, S.P., **12**-0224, **15**-1876, **17**-0290
Singh, A., **07**-0080, **07**-0087, **10**-0808
Singh, A.K., **16**-0125
Singh, B.P., **10**-0168, **10**-1089, **15**-0253, **16**-1523, **18**-0073, **19**-1605
Singh, D.U., **16**-1779
Singh, G., **16**-1282
Singh, G.P., **15**-1795
Singh, H.K., **12**-0212, **19**-1346
Singh, J., **10**-0474, **10**-1071, **10**-1624, **15**-0694, **16**-0993, **16**-1071, **19**-0096, **19**-0469, **19**-0471, **19**-0925
Singh, J.O., **13**-0013
Singh, K., **10**-0603
Singh, M., **19**-0488, **19**-0756
Singh, M.P., **19**-1643
Singh, N., **19**-0143
Singh, N.K., **12**-0338
Singh, P., **12**-0160
Singh, P.N.D., **05**-0402
Singh, P.R., **10**-1318, **13**-0713, **14**-0357, **16**-1779, **19**-1339
Singh, R., **11**-0619, **16**-1682
Singh, R.P., **11**-0341, **15**-0620
Singh, S., **03**-0067, **11**-0314, **15**-0344, **15**-2439, **16**-2007, **19**-1288, **19**-1607
Singh, S.K., **19**-0397
Singh, S.P., **10**-0848, **12**-0636, **18**-0126
Singh, U.K., **13**-0178
Singh, V., **10**-0474, **10**-1070, **10**-1624, **12**-0254, **16**-0993
Singh, V.K., **10**-0684, **10**-0925, **10**-0956, **10**-0959, **10**-0961, **10**-0962, **11**-0341, **15**-1794, **15**-2297, **16**-0171, **16**-0233, **16**-0549, **16**-0614, **16**-1453, **16**-1618, **19**-0167, **19**-0535, **19**-1014
Singh, J., **10**-1070
Singhal, G.H., **17**-0171
Singhal, N., **19**-0210
Singleton, D.A., **15**-0967, **15**-0662, **15**-2004, **15**-2088, **15**-2115
Singleton, D.M., **17**-0139
Sinha, J., **14**-0440
Sinha, P., **14**-0285
Sinha, S., **11**-0322, **19**-0948
Sinha, S.C., **16**-1055, **18**-0727
Siniscalchi, F.R., **19**-0823
Sinisterra, J.V., **19**-1022, **19**-1762
Sinke, G.C., **01**-0093
Sinn, H., **15**-1549
Sinnige, H.J., **15**-0126
Sinnokrot, M.O., **03**-0073, **03**-0074
Sinnott, M.L., **10**-0402, **16**-0029, **16**-0030
Sinnreich, J., **15**-1598
Sinou, D., **10**-0802, **10**-1100, **10**-1453, **10**-1454, **10**-1780, **13**-0404, **15**-0598, **18**-0761, **19**-1050, **19**-1776
Sinoway, L., **10**-1351
Sinya, J., **15**-0535
Sipe Jr., H.J., **11**-0215
Sipos, G., **05**-0083, **16**-1227
Siquet, C., **11**-0276
Sirieix, J., **10**-1407
Siriwardana, A.I., **15**-0179, **15**-0931
Sirkecioglu, O., **16**-1609
Sirlin, C., **04**-0164
Sirna, A., **19**-0056
Sirokmán, F., **16**-1227
Siroky, M., **10**-1796
Sirol, S., **19**-1045
Sironi, M., **02**-0121
Siska, S.J., **04**-0140
Siskos, M.G., **11**-0433
Sisti, A.J., **10**-0303, **15**-0016, **15**-1562, **18**-0163, **18**-0164, **18**-0165, **18**-0349
Sita, L.R., **04**-0148, **16**-1050
Sitnikov, A.A., **13**-0377, **13**-0391
Sitzmann, M.E., **19**-0769
Siu, T., **15**-1893
Sivakamasundari, S., **16**-0191
Sivakumar, M., **17**-0477, **19**-0676
Sivakumar, S., **04**-0160
Sivanand, P.S., **16**-0267
Sivappa, R., **16**-1679
Sivaram, S., **10**-1376, **15**-0792
Sivasankar, S., **16**-1152
Sivasankaran, K., **15**-0432
Six, C., **18**-0772
Sixma, F.L.J., **11**-0377, **11**-0605, **17**-0132, **19**-0357
Sixxa, H., **16**-0370
Sizan, O.E., **10**-1851
Sjöberg, B., **16**-0201
Sjöberg, K., **10**-0453, **16**-0201
Sjöholm, Å., **15**-1280, **15**-0323
Sjöholm, R., **16**-0562
Sjöström, M., **09**-0029
Skamoto, I., **10**-1704
Skarnulis, A.J., **12**-0580, **12**-0597
Skarżewski, J., **16**-2009, **19**-0129
Skattebøl, L., **11**-0472, **15**-2281
Skell, P.S., **14**-0188, **05**-0329, **05**-0342, **09**-0047, **09**-0050, **10**-0203, **10**-0393, **10**-0394, **12**-0596, **14**-0040, **14**-0041, **14**-0041, **14**-0042, **14**-0045, **14**-0118, **14**-0163, **14**-0183, **14**-0185, **14**-0188, **15**-0055, **15**-0057, **15**-0124, **15**-0142, **15**-1514, **15**-2280, **15**-2311, **15**-2313, **15**-2316, **17**-0043, **17**-0116, **17**-0127, **18**-0020, **18**-0043, **18**-0047, **18**-0081, **18**-0167, **19**-0836
Skelton, B.W., **10**-0652
Sket, B., **12**-0126, **19**-0633
Skidmore, J., **15**-1813, **15**-1817, **18**-0155
Skinner, C.J., **11**-0314
Skinner, G.A., **11**-0053, **11**-0105
Skinner, I.A., **12**-0080
Skjaerbaek, N., **13**-0187
Sklarz, B., **19**-0010, **19**-0311
Sklorz, C.A., **16**-0647
Skobel, H., **15**-1346
Skobeleva, S.E., **03**-0037
Skoglund, M., **12**-0058
Skolnik, H., appendixA-0001
Skonieczny, S., **16**-2146
Skorcz, J.A., **13**-0574
Skorobogatova, E.V., **15**-0280
Skovronek, H., **16**-1869
Skowronska, A., **15**-1845, **16**-0432
Skrabal, P., **11**-0028, **13**-0036
Skrydstrup, T., **15**-1338, **16**-0419
Skrypnik, Yu.G., **16**-2146
Skulski, L., **11**-0284, **11**-0286
Skvarchenko, V.R., **15**-2077
Skwarczynski, M., **15**-0829
Sky, A.F., **05**-0245
Slack, D.A., **12**-0006
Slade, J., **04**-0170
Sladkov, A.M., **13**-0534
Slae, S., **17**-0046
Slagle, J.D., **10**-1099
Slama, F.J., **10**-0383
Slater, C.D., **06**-0026, **09**-0078, **18**-0708
Slaugh, L.H., **10**-1320, **14**-0454, **18**-0064, **18**-0075, **18**-0083
Slavin, J., **16**-1946

Slawin, A.M.Z., **02**-0312, **10**-0246, **15**-1782, **16**-0493
Slayden, S.W., **12**-0446, **18**-0454
Slebocka-Tilk, H., **15**-0008, **15**-0012, **15**-0022, **15**-1523, **16**-1059
Ślebocka-Tilk, H., **16**-1595, **16**-1596
Slee, T.S., **04**-0416
Sleezer, P.D., **12**-0034
Slegeir, W., **18**-0502
Sleiter, G., **11**-0010
Slieker, L.M., **10**-1469
Slinckx, G., **18**-0509
Slingenfelter, D.S., **04**-0163
Śliwińska, A., **15**-0391
Sliwinski, W.F., **10**-0320, **18**-0509
Sloboda-Rozner, D., **15**-1741
Slocum, D.W., **05**-0099, **12**-0406, **13**-0640, **13**-0641
Slocum, M.G., **12**-0406
Slopianka, M., **10**-0466, **15**-2172
Slotin, L., **04**-0253
Slowinski, F., **15**-2442
Ślusarska, E., **10**-0993
Slutsky, J., **17**-0495
Smadja, W., **15**-0106
Smail, F.R., **09**-0106
Small Jr., V.M., **10**-0731
Small, A., **18**-0573
Small, L.E., **08**-0231, **12**-0661
Small, P.A., **11**-0109
Smalley, R.E., **02**-0355, **02**-0356
Smalley, R.K., **18**-0281
Smallridge, A.J., **11**-0146, **15**-0624, **15**-1486, **15**-1504, **19**-1021, **19**-1022
Smat, R.J., **17**-0008
Smejkal, J., **16**-1811
Smentowski, F.J., **12**-0717
Smerz, A., **15**-1768
Smerz, A.K., **15**-1766, **15**-1769, **19**-0488
Smid, J., **05**-0130
Smidrkal, J., **13**-0484
Smidt, J., **08**-0024, **19**-0721
Smidt, S.P., **15**-0605
Smietana, M., **12**-0318, **15**-1563
Smil, D.V., **10**-1423, **16**-0741, **16**-0742
Smiles, S., **13**-0777
Smiley, R.A., **10**-0486, **10**-1786
Smirnov, V.V., **15**-0023, **15**-0169, **15**-0181
Smirnyagin, V.A., **15**-1617
Smissman, E.E., **16**-1465, **16**-1469, **17**-0125, **18**-0206
Smit, P.J., **14**-0353
Smit, W.A., **15**-0001, **15**-0021, **15**-2024
Smith, R.A.J., **15**-1067
Smith III, A.B., **10**-0519, **18**-0903, **10**-0801, **15**-1092, **18**-0757, **18**-0903, **18**-0905, **18**-0906, **18**-0907, **19**-0590
Smith III, M.R., **13**-0097, **19**-1572
Smith III, W.J., **04**-0124, **13**-0167, **19**-1357
Smith Jr., W.N., **12**-0592
Smith, A., **13**-0427
Smith, A.C., **11**-0120
Smith, A.D., **10**-1640, **19**-1515, **19**-1625
Smith, A.L., **10**-1725
Smith, A.S., **16**-1937
Smith, B., **19**-0269
Smith, B.D., **04**-0311, **04**-0313
Smith, B.H., **04**-0078
Smith, B.T., **18**-0297
Smith, C., **18**-0727
Smith, C.D., **12**-0436, **18**-0415, **18**-0416
Smith, C.J., **13**-0177
Smith, C.P., **16**-1262, **16**-1302
Smith, C.R., **08**-0024
Smith, C.V., **14**-0157
Smith, D.A., **15**-0501, **15**-0849
Smith, D.C., **16**-0221
Smith, D.F., **12**-0660
Smith, D.F., **16**-0514
Smith, D.G., **19**-1099
Smith, D.H., **04**-0129
Smith, D.J.H., **10**-1860, **19**-0726, **19**-1099
Smith, D.K., **13**-0752
Smith, D.M., **02**-0298, **10**-1433, **14**-0353
Smith, D.R., **02**-0312
Smith, D.T., **16**-0494
Smith, E.M., **10**-1739
Smith, F., **07**-0101
Smith, F.E., **07**-0101
Smith, F.C., **17**-0265
Smith, F.R., **13**-0457
Smith, G., **15**-0962, **18**-0738
Smith, G.D., **04**-0293, **17**-0017
Smith, G.G., **12**-0643, **17**-0122, **17**-0133, **17**-0145, **17**-0492, **17**-0493, **18**-0594, **18**-0654
Smith, G.M., **15**-2027
Smith, G.T., **03**-0011
Smith, G.V., **15**-0456, **15**-0465
Smith, G.V., **17**-0344
Smith, H.D., **12**-0218
Smith, H.E., **04**-0268
Smith, H.L., **18**-0271
Smith, H.W., **15**-2301
Smith, J., **16**-1787
Smith, J.A., **15**-1817
Smith, J.A.S., **11**-0469
Smith, J.D., appendixA-0036
Smith, J.G., **10**-0376, **17**-0082, **17**-0206
Smith, J.S., **17**-0008
Smith, J.W., **03**-0050, **08**-0173, **08**-0218
Smith, K., **10**-0462, **10**-1715, **10**-1757, **11**-0123, **11**-0136, **11**-0142, **11**-0231, **11**-0276, **12**-0332, **12**-0402, **12**-0427, **12**-0442, **12**-0489, **14**-0392, **14**-0396, **15**-0636, **15**-1183, **16**-0661, **16**-0697, **16**-0996, **16**-1018, **16**-1426, **18**-0420, **18**-0427, **18**-0428, **18**-0432, **18**-0435, **18**-0437, **19**-0877, **19**-0882, **19**-0889, **19**-0996, **19**-1077
Smith, L.A., **13**-0015, **16**-1837
Smith, L.C., **18**-0872
Smith, L.I., **16**-0673
Smith, L.R., **16**-1872
Smith, M., **15**-0533, **16**-1659
Smith, M.A., **06**-0013, **16**-1621
Smith, M.B., **04**-0098, **04**-0110, **04**-0274, **04**-0316, **04**-0330, **04**-0351, **04**-0491, **05**-0162, **05**-0164, **05**-0170, **06**-0014, **10**-0236, **10**-0472, **10**-0864, **10**-0974, **10**-0974, **10**-1103, **11**-0257, **15**-0400, **15**-1106, **15**-1200, **15**-1216, **15**-1255, **15**-1692, **15**-1724, **15**-1820, **15**-1968, **15**-1983, **15**-2003, **15**-2021, **15**-2034, **15**-2046, **15**-2057, **15**-2061, **15**-2080, **15**-2136, **16**-0962, **16**-0970, **16**-1029, **16**-1075, **16**-1272, **16**-1932, **17**-0283, **19**-0911, **19**-1025, **19**-1582
Smith, M.D., **19**-0128
Smith, M.L., **17**-0006, **17**-0064
Smith, M.R., **10**-0118, **19**-0801
Smith, N.W., **10**-1211
Smith, P., **05**-0200
Smith, P.A.S., **11**-0510, **12**-0706, **17**-0496, **18**-0160, **18**-0263, **18**-0282, **18**-0284, **18**-0292, **18**-0335, **18**-0373
Smith, P.J., **06**-0084, **10**-1748, **17**-0059, **17**-0062, **17**-0065
Smith, P.L., **15**-2074
Smith, P.M., **10**-0600, **16**-1439
Smith, R.A., **12**-0174

Smith, R.A.J., **11**-0487, **15**-1066, **15**-1169, **15**-1174
Smith, R.C., **10**-0544, **16**-0160, **16**-1671
Smith, R.D., **15**-2328, **15**-2336
Smith, R.D.J., **09**-0096
Smith, R.F., **17**-0446, **18**-0238
Smith, R.G., **05**-0233, **10**-1482, **19**-1531
Smith, R.J., **04**-0137
Smith, R.K., **04**-0170
Smith, R.N.M., **12**-0045
Smith, R.R., **18**-0825
Smith, R.S., **10**-0539, **10**-1296, **15**-0948, **16**-0676
Smith, S., **10**-0060, **10**-0070
Smith, S.C., **08**-0191, **15**-0420, **15**-1007, **15**-1667, **18**-0419, **19**-0475
Smith, S.F., **10**-0017
Smith, S.G., **10**-0334, **10**-0335, **10**-0419, **10**-0490, **13**-0644, **15**-1170, **16**-0527, **16**-0538, **17**-0035
Smith, S.M., **15**-0786
Smith, S.V., **04**-0391, **04**-0393
Smith, T.A.D., **15**-1782
Smith, T.D., **15**-0483
Smith, T.L., **12**-0496
Smith, W.B., **10**-0126, **14**-0419
Smith, W.E., **11**-0486, **18**-0180
Smith, W.N., **10**-1768
Smith-Palmer, T., **15**-1626
Smitha, G., **16**-0176
Smithen, C.E., **15**-2325
Smithers, R., **12**-0428, **15**-1175, **16**-0743
Smithers, R.H., **16**-1282
Smithies, A.J., **15**-1271
Smolina, T.A., **18**-0044, **18**-0250
Smolinsky, G., **05**-0399, **05**-0400, **12**-0234, **17**-0491, **17**-0493, **18**-0553
Smolko, K.I., **16**-0879
Smonou, I., **14**-0244, **19**-0234, **19**-1007, **19**-1357
Smoot, J., **19**-1638
Smoter, N.J., **16**-0174
Smrcina, M., **13**-0237
Smrtka, M., **10**-1792
Smulik, J.A., **15**-0805
Smushkevich, Yu.I., **19**-0441
Smyth, M.P., **16**-0687
Smyth, R.L., **16**-2143
Smyth, T., **10**-0637
Smyth, T.A., **19**-0429, **19**-0430
Snagovskii, Yu.S., **16**-1855
Snaith, R., **13**-0654
Snapper, M.L., **15**-1204, **16**-0417, **16**-0865, **16**-0865, **16**-1439, **16**-1457, **18**-0584, **18**-0779, **18**-0789
Snatzke, G., **04**-0119, **04**-0268
Snavely, K., **09**-0094
Sneddon, H.F., **16**-0341, **16**-1428
Sneeden, R.P.A., **16**-0842
Sneen, R.A., **10**-0076, **10**-0077, **10**-0078, **10**-0079, **10**-0085, **10**-0086, **14**-0207, **16**-1564, **17**-0036
Snell, R.L., **15**-2242
Snider, B.B., **15**-0936, **15**-0972, **15**-0980, **15**-2184, **16**-1483, **16**-1484, **19**-0065
Snieckus, V., **10**-1272, **10**-1283, **10**-1284, **12**-0405, **12**-0407, **12**-0512, **13**-0326, **13**-0471, **13**-0641, **15**-0961, **8**-0764
Snoble, K.A.J., **15**-1171, **16**-1301
Snook, M.E., **19**-0255
Snoonian, J.R., **05**-0352
Snow, A.W., **16**-0188
Snow, D.H., **10**-0285
Snow, J.T., **18**-0446
Snow, J.W., **16**-0340
Snow, R.A., **02**-0352
Snowden, D.J., **15**-0887
Snowden, M., **18**-0369
Snowden, R.L., **12**-0662
Snushall, B., **03**-0210
Snyckers, F., **11**-0009
Snyder Jr., R.C., **10**-0194
Snyder, C., **12**-0442
Snyder, C.H., **14**-0393
Snyder, D.C., **10**-1094
Snyder, E.I., **10**-0160, **10**-1096, **10**-1102, **15**-0562, **17**-0031
Snyder, E.S., **10**-1742
Snyder, G.A., **04**-0508
Snyder, H.R., **13**-0751
Snyder, J.K., **04**-0202, **15**-1697, **15**-2102, **15**-2444
Snyder, J.P., **02**-0093, **02**-0094, **02**-0100, **02**-0191, **02**-0227, **02**-0248, **02**-0341, **02**-0347, **10**-1334, **10**-1365, **15**-1169, **19**-0871
Snyder, L., **15**-0815
Snyder, L.C., **10**-0131
Snyder, S.A., **15**-2067
Soai, K., **10**-0984, **10**-1009, **15**-1055, **16**-0490, **16**-0493, **16**-0565, **16**-0686, **16**-0830, **16**-1190, **19**-1091, **19**-1481
Soares, V.C.D., **16**-0276
Sobczyk, L., **03**-0013
Sobery, W., **12**-0377
Sobhani, S., **19**-0040, **19**-0145
Sobkowiak, A., **19**-0609
Sobolev, A.N., **03**-0124
Sobrio, F., **16**-0436
Socaci, C., **02**-0428
Soçen, H., **10**-0939
Soccolini, F., **16**-1225
Sock, O., **13**-0614
Sodeoka, M., **16**-0408
Södergren, M.J., **15**-1901, **17**-0219, **19**-0536
Soderquist, J., **10**-0777
Soderquist, J.A., **10**-0777, **10**-1415, **10**-1416, **12**-0563, **15**-0649, **15**-0652, **15**-0667, **15**-0675, **15**-1665, **19**-1031
Soejima, T., **16**-1491
Soell, P.S., **19**-0338
Soeta, T., **16**-0894, **16**-0908
Sofia, M.J., **15**-0282
Sōfuku, S., **16**-1625
Soga, T., **10**-1805
Sogon, T., **19**-1338
Soheili, A., **13**-0541, **13**-0637
Sohmiya, H., **07**-0083, **07**-0098
Sohn, E., **11**-0434
Sohn, S.-M., **16**-1174
Sohn, S.C., **10**-0313
Soja, P., **12**-0241
Sojka, S.A., **15**-1805
Sokolov, V.I., **04**-0001, **04**-0025, **04**-0463, **12**-0016, **15**-0263, **16**-2059
Sokolova, T.N., **15**-0280
Sokołowska, J., **16**-0858
Solà, L., **15**-2364, **16**-0689
Solà, M., **02**-0154
Solabannavar, S.B., **16**-1157
Solash, J., **10**-0212, **10**-0395
Solastiouk, B., **12**-0725
Soldaini, G., **19**-0767
Soldermann, N., **18**-0683
Soldevilla, A., **18**-0592
Solé, D., **15**-0916
Soler, A., **16**-0329
Soler, T., **16**-0854
Solis-Oba, A., **10**-1124
Solladié, G., **10**-1057, **10**-1588, **15**-1376, **16**-0489, **16**-1130
Solladié, N., **03**-0181
Solladié-Cavallo, A., **16**-0391
Sollenberger, P.Y., **16**-0103, **16**-0315
Sølling, T.I., **16**-0047
Sollner, K., **07**-0078
Solly, R.K., **14**-0045, **18**-0551
Solodenko, W., **16**-0429
Solodova, K.V., **11**-0174
Solomon, J.J., **10**-0184

Solotnov, A.F., **03**-0110
Solov'ev, V.P., **03**-0110
Solov'yanov, A.A., **05**-0099, **05**-0129, **05**-0130, **10**-0242, **10**-0341, **12**-0670, **18**-0408
Soloveichik, S., **19**-0001
Soloway, A.H., **12**-0450
Solsky, R.L., **17**-0056
Solter, L.E., **12**-0398
Solv'yanov, A.A., **16**-0523
Soman, R., **15**-1651, **19**-0348
Somanathan, R., **16**-1438
Somasunderam, A., **15**-1385
Somayaji, V., **12**-0492
Somayajulu, G.R., **02**-0036
Sombret, B., **14**-0233
Sombroek, J., **02**-0278
Somers, J.J., **15**-0758
Somers, P.K., **16**-0849
Somerville, R.F., **15**-1589
Somfai, P., **05**-0081, **10**-0922, **15**-0323, **15**-1280, **15**-1895, **15**-2123, **18**-0419, **18**-0545
Sominsky, L., **19**-0158
Sommazzi, A., **19**-1419
Sommer, H.Z., **10**-0866
Sommer, J., **05**-0014, **05**-0016, **08**-0015, **08**-0019, **10**-0374, **11**-0460, **12**-0048, **12**-0049, **12**-0342, **15**-1148, **18**-0035
Sommer, K., **15**-0926
Sommer, L.H., **10**-0060, **10**-1312, **12**-0431
Sommers, A.H., **10**-1582
Somorjai, G.A., **15**-0457
Son, B., **03**-0107
Son, C.U., **15**-1439
Son, E.-C., **13**-0565
Son, H.S., **16**-0360
Son, S.U., **15**-1423, **15**-1431, **15**-1432, **15**-1436, **15**-1439, **15**-1993
Son, T., **10**-1869
Son, Y.-C., **19**-0239
Son, Y.C., **04**-0110, **15**-2034
Sonawane, H.R., **18**-0212, **19**-0463
Soncini, A., **02**-0083
Sondengam, B.L., **16**-0356
Sondheimer, F., **02**-0093, **02**-0243, **02**-0259, **02**-0265, **02**-0272, **02**-0273, **02**-0274, **02**-0287, **02**-0291, **02**-0293, **02**-0296, **02**-0298, **02**-0300, **02**-0301, **02**-0304, **02**-0305, **02**-0324, **02**-0326, **02**-0327, **02**-0328, **14**-0303
Sone, T., **13**-0770
Song, B.D., **16**-1511, **16**-1763
Song, C., **13**-0353
Song, C.-S., **10**-1327, **10**-1852, **13**-0610
Song, C.E., **10**-0411, **10**-0501, **10**-0940, **11**-0325, **15**-1695, **15**-1834
Song, G., **16**-0435, **16**-1175, **16**-1772, **16**-1791, **19**-0784
Song, H., **13**-0378
Song, H.-J., **10**-1793
Song, H.-Y., **16**-0738
Song, I.H., **19**-0440
Song, J.J., **16**-0462
Song, K., **10**-0002
Song, K.-S., **01**-0109, **01**-0111
Song, M., **16**-0575
Song, Q., **15**-1455, **15**-1456
Song, S.-E., **14**-0011, **16**-0960
Song, S.-J., **16**-1174
Song, S.H., **19**-1474
Song, W., **05**-0095
Song, W.M., **19**-0962
Song, X., **13**-0431
Song, Y., **12**-0454, **16**-0349, **16**-1433
Song, Y.-L., **12**-0455
Song, Y.H., **19**-0137
Song, Y.L., **12**-0452
Song, Z., **13**-0644, **16**-1485, **19**-0673, **19**-0678
Song, Z.-L., **19**-0082
Song, Z.L., **18**-0134, **18**-0157
Songstad, J., **08**-0149, **10**-0302, **10**-0487
Songster, M., **16**-0135
Soni, N.R., **10**-1131
Soni, P., **10**-0569, **16**-0051
Sonmor, E.R., **19**-1142
Sonnenberg, F.M., **17**-0015
Sonnet, P.E., **07**-0054, **16**-1144, **17**-0192, **17**-0220, **17**-0337, **17**-0360
Sonnichsen, G., **06**-0076,. **08**-0064
Sono, M., **19**-0461
Sono, S., **12**-0518
Sonobe, H., **15**-1442
Sonoda, A., **10**-1509, **14**-0395, **19**-0896, **19**-1330
Sonoda, K., **15**-0732
Sonoda, N., **03**-0157, **10**-0815, **10**-0828, **10**-0830, **10**-1224, **10**-1561, **10**-1826, **10**-1827, **10**-1829, **10**-1853, **11**-0317, **12**-0246, **12**-0529, **12**-0735, **13**-0040, **13**-0615, **13**-0619, **13**-0630, **14**-0013, **15**-0309, **15**-0312, **15**-1262, **15**-1402, **15**-1855, **16**-1892, **19**-0060, **19**-0607, **19**-0747, **19**-1591
Sonoda, T., **10**-0465, **13**-0022
Sonoda, Y., **15**-0742
Sonogashira, K., **13**-0536
Soong, L.T., **15**-0562
Sooriyakumaran, R., **07**-0086
Sopchik, A., **14**-0188
Sorato, C., **15**-1691
Sørbye, K., **10**-0766
Sordo, J.A., **16**-2112
Sordo, T.L., **16**-2112
Sorensen, C.M., **16**-1709
Sorensen, J.B., **03**-0012
Sorensen, T.S., **03**-0061, **04**-0231, **05**-0037, **05**-0051, **05**-0078, **10**-0124, **10**-0280, **10**-0430, **10**-0444, **17**-0392, **18**-0007, **18**-0166
Sørensen, P.E., **10**-0530, **16**-0044, **16**-0157
Sorenson, M.E., **15**-1314
Sorger, K., **05**-0176
Soriano, J.M., **16**-1786
Sorimachi, K., **16**-0901
Sorm, F., **11**-0622
Sorokin, A.B., **19**-0582
Sorokin, V.D., **15**-1572, **15**-1580
Sorokin, V.I., **15**-0030, **18**-0714
Sorokina, L.P., **19**-1111, **19**-1767
Sorrenti, P., **16**-1149
Sorriso, S., **13**-0688, **13**-0689
Sosa-Rivadeneyra, M., **16**-0688
Sośnicki, J.G., **15**-1299
Sosnovsky, G., **11**-0183, **14**-0012, **14**-0149, **14**-0196, **14**-0224, **14**-0246, **14**-0249, **14**-0251, **14**-0262, **14**-0291, **15**-1608, **16**-0118, **17**-0523, **18**-0865
Sosounk, S.E., **15**-1541
Sotiriou, C., **19**-0337
Sotomatsu, T., **08**-0169
Sotomayor, N., **16**-1964
Sott, R., **08**-0208, **16**-0470
Soucy, C., **19**-1479
Soufi, J., **15**-2172
Soula, G., **10**-0463
Soufiaoui, M., **19**-0222
Soulen, R.L., **02**-0241
Souma, Y., **10**-1014, **15**-1379, **15**-1380
Soumillion, J.P., **14**-0116
Soundararajan, N., **05**-0384, **05**-0386, **16**-1833
Soundararajan, R., **12**-0488, **12**-0489, **15**-0089, **15**-0661
Souppe, J., **16**-2002, **19**-0967, **19**-1670
Sousa, J.A., **19**-0350

Sousa, L.R., **04**-0163, **04**-0164, **18**-0854
South, J.A., **13**-0133
Southern, J.M., **15**-1316, **16**-1909
Southwick, P.L., **02**-0398, **12**-0094, **18**-0249, **18**-0722
Souto-Bachiller, F.A., **02**-0214
Souček, J., **15**-0705
Sowa Jr., J.R., **13**-0480
Sowerby, R.L., **10**-1653
Sowin, T.J., **19**-0195
Sowinski, A.F., **14**-0160
Sozzani, P., **19**-1091
Spaar, R., **10**-0251
Spackman, I.H., **17**-0061
Spada, G.P., **04**-0187
Spaeth, E.C., **11**-0358
Spagnol, M., **10**-0884, **19**-1028
Spagnol, M.D., **10**-1492
Spagnolo, P., **12**-0512, **15**-1912, **18**-0300
Spaller, M.R., **15**-2302
Spanedda, M.V., **16**-0901
Spanget-Larsen, J., **02**-0180
Spangler, C.W., **18**-0480, **18**-0526, **18**-0556
Spangler, D.P., **10**-1365
Spaniol, T.P., **03**-0120
Spanka, G., **04**-0458
Spannenberg, A., **15**-0608
Sparacino, M.L., **16**-1709
Sparapany, J.J., **17**-0062
Sparfel, D., **19**-0279
Sparks, T., **18**-0670
Spatola, A.F., **11**-0645
Spawn, C., **10**-1150
Spear, R.J., **05**-0036, **05**-0039, **10**-0167, **10**-0200, **11**-0013
Specht, H., **02**-0215
Speck, D.H., **03**-0102
Speckamp, W.N., **12**-0273, **15**-0913, **16**-1734
Spector, M.L., **12**-0740
Speer, H., **05**-0135
Spehar, A., **19**-1295
Speier, J.L., **15**-0705
Speizman, D., **10**-0350
Spek, A.L., **13**-0237, **15**-2072, **16**-0833, **19**-0216
Spellmeyer, D.C., **15**-0103, **18**-0461, **18**-0483, **18**-0484
Spencer, A., **13**-0361
Spencer, C.M., **02**-0312
Spencer, J.B., **15**-0163, **15**-1305, **15**-1306, **15**-1307, **15**-1308, **19**-1560
Spencer, J.L., **15**-2431
Spencer, K.L., **16**-2075
Spencer, N., **03**-0204, **03**-0205
Spencer, T.A., **17**-0052
Spencer, W.T., **13**-0522
Spengler, T., **11**-0400
Spenser, I.D., **17**-0457
Sperandio, A., **17**-0213
Sperandio, D., **18**-0799
Speranza, M., **10**-0009, **10**-0259, **10**-0260, **17**-0095
Spero, D.M., **12**-0368, **15**-2292
Sperrle, M., **15**-0815
Sperry, L., **15**-0242
Speth, D.R., **19**-0470
Spevak, P., **19**-1262, **19**-1643
Spey, S.E., **15**-2301
Speziale, A.J., **16**-1222, **16**-1872
Spialter, L., **10**-0852, **16**-0348
Spialtr, L., **16**-1949
Spicciarich, D., **19**-1172
Spicer, L.D., **19**-1448
Spietschka, E., **18**-0221
Spiewak, J.W., **17**-0357
Spiliotis, V., **19**-1021
Spillane, W.J., **11**-0567
Spillett, R.E., **11**-0073
Spilling, C.D., **16**-1189, **19**-1204
Spillner, C.J., **05**-0050
Spina, E., **16**-2143
Spina, K.P., **10**-1048
Spinacé, E.V., **19**-0611
SPindler, F., **15**-0615
Spinelli, D., **08**-0168
Spinetti, L.M., **19**-1022
Spinicelli, L.F., **12**-0208, **16**-0107
Spino, C., **15**-1983, **16**-0471
Spirikhin, L.V., **14**-0383
Spirin, Yu.L., **14**-0110
Spitzer, R., **04**-0382
Spitzer, U.A., **19**-0110, **19**-0403, **19**-0409, **19**-0467
Spitzin, V.I., **17**-0149
Spitznagel, G.W., **05**-0101
Spletzer, E.G., **19**-0840
Spogliarich, R., **19**-0960
Spohn, R.J., **12**-0528
Spokes, G.N., **13**-0047
Spolaore, B., **17**-0216
Spoor, P., **10**-1471
Spoors, P.G., **16**-0186
Spotnitz, R.M., **19**-0623
Spracklin, D.K., **04**-0390
Spratt, R., **04**-0038
Sprecher, M., **10**-0012, **16**-0180
Spreti, N., **10**-0407
Spring, F.S., **18**-0111
Springer, D.M., **16**-1534
Springer, G., **08**-0147
Springer, J.P., **04**-0206
Springer, W.R., **18**-0198
Sprott, K.T., **15**-2012
Sprout, C.M., **16**-0687
Sprügel, W., **19**-0650
Sprules, T.J., **18**-0608
Spruyt, P., **13**-0559
Spryskov, A.A., **11**-0044, **11**-0202, **16**-2143
Spurlock, L.A., **07**-0079
Spurlock, S., **19**-0446
Sputore, S., **19**-0198
Squillacote, M., **04**-0320, **04**-0469
Squillacote, M.E., **04**-0342, **10**-0200
Squire, R.H., **18**-0891
Squires, R.R., **02**-0024, **05**-0101, **05**-0107, **05**-0126, **12**-0641
Sraidi, K., **03**-0015
Srebnik, M., **10**-1160, **12**-0516, **15**-0642, **15**-0643, **15**-0645, **15**-0674, **18**-0422
Sreekumar, R., **11**-0426, **15**-1027, **15**-1916, **19**-0928
Sreevivas, P., **18**-0702
Sridhar, M., **16**-2153, **18**-0289, **19**-1641
Sridharan, S., **10**-0312, **17**-0035
Sridharan, V., **15**-0806, **15**-0878, **15**-1476
Srihari, P., **19**-1613
Srikanth, A., **15**-1844
Srikrishna, A., **19**-1393
Srinavasa, G.R., **19**-1749
Srinivas, C., **19**-1613
Srinivas, Ch., **13**-0655, **16**-0169
Srinivas, D., **13**-0399, **16**-0080, **16**-1175, **16**-1341, **16**-1906
Srinivas, G., **19**-0017
Srinivas, K.A., **13**-0105, **15**-1763
Srinivas, K.V.N.S., **16**-0333, **16**-1647
Srinivas, P., **10**-0851, **19**-0705
Srinivas, R., **10**-0556, **16**-0149, **19**-0302, **19**-1253, **19**-1758
Srinivasan, C., **05**-0378, **11**-0541, **19**-0831
Srinivasan, K.V., **11**-0131, **11**-0231, **11**-0234, **11**-0237, **11**-0426, **13**-0415, **13**-0491, **13**-0723
Srinivasan, M., **19**-0376
Srinivasan, N.S., **19**-0731
Srinivasan, P.S., **16**-0846
Srinivasan, R., **04**-0429, **07**-0054, **08**-0140, **15**-2232, **16**-0125, **19**-0100

Srinivasu, P., **11**-0248, **11**-0256, **16**-1672
Srirangam, J.K., **13**-0211
Srisailas, M., **04**-0077
Srivastava, N., **15**-1287
Srivastava, P.C., **12**-0495
Srivastava, R., **13**-0399
Srivastava, R.C., **15**-2180, **16**-2094
Srivastava, R.G., **19**-0694
Srivastava, R.R., **10**-1168, **15**-0254, **16**-1711
Srivastava, R.S., **12**-0225, **15**-0330, **15**-1386
Srivastava, S., **15**-0119, **16**-0006, **19**-1339
Srivastava, S.K., **10**-0861, **11**-0225
Srivastava, V., **16**-1610
Srogi, J., **16**-1976, **13**-0144, **13**-0504, **13**-0566, **16**-1976, **19**-1229
Sromek, A.W., **13**-0309, **15**-0356, **15**-2357
Srzić, D., **05**-0152
St. Jean Jr., D.J., **15**-1234
St. Pierre, M.J., **07**-0036
Staab, E., **15**-1841
Staab, H.A., **02**-0308, **03**-0029, **04**-0073, **05**-0231, **05**-0321, **05**-0325, **08**-0089, **08**-0182, **08**-0183, **08**-0184, **08**-0186, **08**-0186, **11**-0459, **15**-0005, **15**-0030, **15**-0034, **16**-1669, **19**-1132
Staas, W.H., **07**-0079
Stabba, R., **15**-0793
Staben, S.T., **15**-0978
Stabinsky, Y., **18**-0738
Stabler, S.R., **16**-1709
Stacey, F.W., **15**-0297, **15**-1518
Stach, H., **16**-1859, **18**-0159
Stachel, S.J., **19**-1464
Stachissini, A.S., **16**-0308, **16**-0315
Stack, D.E., **12**-0561, **12**-0601, **16**-1899
Stack, T.D.P., **15**-1729
Stackhouse, J., **04**-0034
Stadler, A., **07**-0103, **07**-0106, **10**-0703, **13**-0241
Stadmüller, S., **16**-2086, **16**-2087
Staemmler, V., **02**-0216
Stafford, D.G., **15**-2296
Stahl, D., **05**-0067
Stahl, F., **02**-0311, **13**-0048
Stahl, M., **19**-1727
Stahl, N., **03**-0019
Stahl, R.E., **04**-0078
Stahl, S.S., **10**-0980, **15**-0334, **16**-1732
Stahl-Larivière, H., **04**-0127, **04**-0146, **15**-0597
Stähle, M., **12**-0395
Stahly, B.C., **13**-0669
Stahly, G.P., **13**-0669
Staib, R.R., **15**-2122
Stairs, R.A., **19**-0628, **19**-0629
Stakem, F.G., **13**-0361
Staklis, A., **18**-0271
Staley, R.H., **05**-0075, **08**-0223, **10**-0184
Staley, S.W., **02**-0246, **04**-0423, **05**-0099, **05**-0126, **15**-0632
Stalick, W.M., **12**-0057, **12**-0065, **15**-0314, **15**-0722, **15**-0724, **19**-0027, **19**-0424
Stalinski, K., **15**-1245
Staliński, K., **15**-1242
Stalke, D., **02**-0084, **05**-0176, **13**-0237
Stallman, J.B., **15**-0879
Stals, J., **01**-0053
Stam, C.H., **02**-0063, **10**-0317, **11**-0615
Stambuli, J.P., **13**-0482
Stamhuis, E.J., **16**-0103
Stamm, H., **10**-1563
Stammann, G., **15**-0030
Stammler, H.-G., **05**-0174
Stamp, L., **15**-2402
Stampfer, W., **19**-1022
Stan, M.A., **10**-1444
Stanbury, P., **15**-2213, **15**-2217
Stanchev, S., **16**-0647
Standen, M.C., **16**-1382
Standen, S.T., **10**-0542
Stanetty, P., **10**-1268, **16**-0476, **18**-0362, **18**-0362
Stanforth, S P., **12**-0276
Stanforth, S.P., **13**-0581
Stang, P.J., **05**-0068, **05**-0347, **05**-0363, **10**-0248, **10**-0249, **10**-0381, **10**-1411, **11**-0337, **12**-0441, **13**-0027, **13**-0536, **13**-0562, **15**-0035, **15**-0106, **16**-1572, **17**-0326
Stangeland, E.L., **19**-0939, **10**-0487
Stanger, A., **02**-0006, **02**-0065, **02**-0082
Staninets, V.I., **15**-0092
Stanković, S., **16**-0085, **19**-0299, **19**-0509, **19**-0510
Stanley, J.H., **14**-0454
Stanley, J.P., **14**-0062, **18**-0740
Stanley, L.M., **16**-0687
Stanovnik, B., **15**-1932
Stansbury, H A., **14**-0305
Stanton, J.F., **02**-0252
Stanton, M.G., **16**-1680
Stanway, S.J., **17**-0210
Staples, M.A., **02**-0192
Staples, R.J., **16**-1138
Staral, J., **10**-0116
Staral, J.S., **02**-0172, **02**-0206, **10**-0200, **11**-0015
Starcher, P.S., **15**-1801
Starer, I., **10**-0203, **18**-0020, **18**-0047
Starikov, E.B., **03**-0069
Starikova, Z.A., **16**-0687
Staring, E.G.J., **16**-2077, **16**-2079
Stark, B.P., **17**-0421, **17**-0499, **17**-0502, **17**-0510, **17**-0516
Stark, H., **04**-0136
Stark, T.J., **17**-0139
Starks, C.M., **10**-0453, **10**-0454, **10**-0610, **10**-0696, **10**-1047, **10**-1619, **10**-1787, **15**-2274, **16**-1225, **16**-1255
Starner, W.E., **16**-0853
Starnes Jr., W.H., **19**-0438
Starnes, S.D., **08**-0165
Staros, J.V., **18**-0493
Staroscik, J., **10**-0227
Staroverov, V.B., **18**-0627
Staude, E., **10**-0373, **10**-1114
Staudinger, H., **19**-1273
Stauffer, R.D., **17**-0340
Stavber, S., **11**-0287, **11**-0304, **11**-0311, **12**-0127, **12**-0131, **19**-0687
Stavchansky, S., **16**-1835
Staveley, L.A.K., **03**-0105
Stavenger, R., **10**-1155
Stavenger, R.A., **10**-1642, **16**-1126
Stavrescua, R., **07**-0095
Stears, N.D., **11**-0029
Stec, W.J., **16**-1306
Stecher, H., **04**-0198
Steckel, T.F., **17**-0395
Steckhan, E., **10**-0567, **10**-1243, **14**-0415, **15**-2093, **19**-0621
Steed, J.M., **03**-0072
Steel, A.J., **14**-0058, **14**-0098
Steel, P.J., **15**-0134, **15**-0138, **15**-0138, **16**-0495, **16**-0645, **17**-0035
Steele, B.R., **10**-1852, **12**-0542, **16**-0965
Steele, F., **02**-0416
Steele, R.B., **16**-0500
Steele, W.R.S., **08**-0086
Steele, W.V., **04**-0234
Steenken, S., **05**-0011, **09**-0067, **10**-0040, **10**-0329

Steensma, R.W., **16**-2178
Steenwinkel, P., **04**-0092
Steere, J.A., **07**-0097, **16**-1173
Štefane, B., **10**-1538, **16**-1684, **16**-1708
Stefanelli, S., **15**-1697
Stefani, A., **14**-0095
Stefani, H.A., **15**-1325, **16**-0293
Steffens, C., **15**-0894
Steffens, H.C., **17**-0218
Stefinovic, M., **18**-0764
Stegel, F., **11**-0010, **13**-0008
Stegemann, J., **02**-0174
Stegemeyer, H., **04**-0068
Steglich, W., **16**-1622, **16**-1665
Stegmann, V.R., **16**-2088, **16**-2089, **19**-0211
Stéhelin, L., **10**-0208
Stehle, N., **10**-1281
Stein, A.R., **10**-0060, **10**-0078, **10**-0079, **10**-0084, **16**-2125
Stein, D., **19**-1306
Stein, K., **18**-0538
Stein, M., **05**-0230
Stein, R.L., **12**-0609
Stein, S.E., **05**-0225
Stein, Z., **01**-0067
Steinauer, R., **16**-1643
Steinbach, R., **10**-1381, **10**-1383, **10**-1389, **10**-1508, **16**-0493
Steinbeck, K., **12**-0354, **12**-0624
Steinberg, H., **10**-0317, **11**-0605, **16**-0043, **19**-1755
Steiner, A., **15**-1813
Steiner, D., **10**-0923
Steiner, E., **02**-0083, **15**-1642
Steiner, G., **15**-2223, **15**-2228
Steiner, P.R., **12**-0658
Steiner, R.P., **18**-0462
Steiner, T., **03**-0003, **03**-0013, **03**-0036, **03**-0069
Steinman, D.H., **15**-1972
Steinmann, J.E., **15**-0292
Steinmetz, A., **19**-0411
Steinmetz, M.G., **07**-0054
Steinmetz, R., **15**-2235
Steinreiber, A., **10**-0703
Steliou, K., **16**-1655
Stella, L., **05**-0243, **05**-0245, **18**-0865
Stelter, E.D., **11**-0028
Stelzer, F., **15**-0818
Stelzer, O., **13**-0237
Stemerick, D.M., **10**-0899
Stemke, J.E., **17**-0270, **17**-0275
Stemmler, T.L., **10**-1333
Stemp, G., **15**-1680
Stenberg, V.I., **11**-0557, **11**-0594
Stengel, P.J., **19**-1524
Stengel, T., **15**-2384
Stenkula, M., **15**-0276
Stensiö, K., **19**-0079
Stensland, P., **17**-0119
Stent, M.A.H., **10**-1538, **17**-0179
Stenzel, J., **11**-0257
Stenzel, W., **13**-0485
Stepanov, N.F., **15**-0181
Stephan, E., **10**-0079
Stephan, H., **03**-0139
Stephan, M., **16**-1852
Stéphan, E., **16**-0469
Stephani, R., **11**-0253
Stephens, J.R., **12**-0674
Stephens, P.J., **04**-0114, **04**-0118
Stephens, R.D., **13**-0534
Stephenson, B., **10**-0269, **10**-1057, **18**-0098
Stephenson, C., **18**-0609
Stephenson, C.R.J., **12**-0370
Stephenson, D.S., **04**-0369
Stephenson, G.A., **15**-1006
Stephenson, L.M., **14**-0227, **14**-0237, **14**-0241, **15**-0969, **15**-2431, **16**-1485, **19**-0470
Stephenson, P.T., **16**-1506
Stepien, B.T., **02**-0188
Stepukhovich, A.D., **18**-0054
Stercho, Y.P., **19**-1494
Stergiades, I.A., **16**-0474
Sterk, H., **15**-2216
Sterling, H.J., **16**-1894
Sterling, J.J., **10**-1352, **10**-1370, **15**-1073
Stermitz, L.F., **18**-0512
Stern, A.G., **18**-0088
Stern, C.L., **15**-1868, **15**-1869, **15**-1871
Stern, E.W., **12**-0740
Sternbach, D.D., **10**-0992, **10**-1712
Sternberg, H.W., **15**-1377
Sternfeld, F., **15**-1724
Sternhell, S., **04**-0510, **14**-0330
Sternson, L.A., **12**-0716, **13**-0770
Sterrenburg, J.G., **18**-0771
Stetter, H., **10**-1664, **12**-0624, **15**-1346, **15**-1368, **16**-0724, **16**-1497
Stetter, H., **16**-1498
Stévenart-De Mesmaeker, N., **18**-0729
Stevenazzi, A., **15**-1417, **15**-1440
Stevens, A.E., **18**-0836
Stevens, C.L., **10**-0212, **15**-0369, **17**-0171, **17**-0389, **19**-0081
Stevens, E.D., **13**-0177
Stevens, E.S., **04**-0127, **04**-0146, **15**-0597
Stevens, I.D.R., **05**-0384, **10**-0334, **15**-2232, **17**-0072
Stevens, I.W., **05**-0019
Stevens, J.A., **13**-0019
Stevens, J.B., **08**-0123, **16**-1597
Stevens, K.D., **15**-0030
Stevens, M.F.G., **12**-0712
Stevens, R.M., **10**-0995
Stevens, R.R., **17**-0247, **17**-0279
Stevens, R.V., **06**-0041, **19**-0132, **19**-0241
Stevens, R.W., **16**-1016
Stevens, T.S., **11**-0568, **13**-0759, **13**-0773, **18**-0001, **18**-0282, **18**-0380, **18**-0384, **18**-0412
Stevens, W., **11**-0460, **11**-0461, **16**-1624, **16**-1625
Stevens, W.R., **15**-1504
Stevenson, C.D., **02**-0219, **02**-0242
Stevenson, D.P., **15**-0449
Stevenson, G.R., **02**-0093, **02**-0334
Stevenson, J.P., **05**-0305
Stevenson, P., **10**-1243
Stevenson, R., **18**-0111
Stevenson, S., **02**-0364
Stevenson, T., **10**-1641
Stevenson, T.A., **04**-0402
Steward, O.W., **15**-1101, **17**-0181
Stewart, A.T., **19**-1764
Stewart, D.R., **03**-0131
Stewart, E.T., **01**-0003
Stewart, I.C., **15**-1321
Stewart, J.D., **18**-0362
Stewart, J.J.P., **02**-0018, **15**-2090
Stewart, J.M., **16**-1819
Stewart, L.E., **03**-0107
Stewart, L.J., **11**-0298
Stewart, R., **01**-0032, **03**-0024, **08**-0001, **08**-0024, **08**-0025, **08**-0026, **08**-0048, **08**-0135, **08**-0140, **12**-0095, **19**-0002, **19**-0247, **19**-0249, **19**-0250, **19**-0325, **19**-0467
Stewart, S.K., **12**-0493
Stewart, T.E., **04**-0106
Stewen, U., **05**-0237, **05**-0246
Sticca, R.P., **18**-0487
Stick, R.V., **10**-1089
Stickley, K.R., **05**-0321
Stickney, C.A., **19**-0585

Stien, D., **15**-0344, **15**-1282
Stiff, C.M., **16**-0858
Stigliani, W.M., **04**-0465
Stiles, A.W., **19**-1130
Stiles, M., **13**-0047, **15**-2075, **16**-1246, **16**-1247, **18**-0035
Stiles, P.J., **04**-0126, **03**-0099
Still, I.W.J., **19**-1619, **19**-1620
Still, W.C., **04**-0141, **10**-1726, **15**-0655, **16**-1575
Stille, J.K., **10**-1260, **10**-1361, **10**-1400, **10**-1411, **10**-1412, **10**-1439, **10**-1822, **10**-1824, **12**-0256, **12**-0259, **12**-0276, **12**-0278, **12**-0279, **13**-0239, **13**-0389, **13**-0619, **15**-1477, **16**-1016, **16**-1904, **17**-0015, **17**-0328
Stille, J.R., **16**-1002, **18**-0608, **18**-0608
Stillings, M.R., **15**-2050
Stilz, H.U., **16**-0006
Stimson, V.R., **12**-0071
Stinson, S.R., **19**-0877
Stiriba, S.-E., **15**-2304
Stirling, C.J.M., **02**-0089, **04**-0029, **04**-0047, **04**-0048, **05**-0119, **06**-0012, **09**-0005, **10**-0225, **10**-0263, **10**-0378, **10**-0400, **10**-0824, **10**-0839, **10**-1599, **10**-1636, **10**-1713, **15**-0021, **16**-1402, **17**-0003, **17**-0046, **17**-0049, **17**-0052, **17**-0102, **17**-0115, **18**-0460, **18**-0738, **19**-0795, **19**-0812
Stivers, E.C., **12**-0099
Stock, L.M., **01**-0042, **08**-0233, **10**-0314, **11**-0024, **11**-0030, **11**-0045, **11**-0047, **11**-0081, **11**-0089, **11**-0090, **11**-0092
Stöckel, K., **02**-0328
Stöckigt, J., **16**-1256
Stöcklin, G., **13**-0713
Stockmann, H., **15**-2050
Stockton, J.D., **15**-2213
Stocky, T.P., **19**-1077
Stoddard, G.J., **18**-0620
Stoddart, J.-F., **03**-0185, **03**-0189, **02**-0312, **03**-0101, **03**-0184, **03**-0186, **03**-0187, **03**-0191, **03**-0200, **03**-0204, **03**-0205, **04**-0164
Stodola, F.H., **16**-1599
Stoessel, S.J., **13**-0389
Stofer, E., **14**-0434
Stoffer, J.O., **10**-0208
Stofko Jr., J.J., **18**-0049, **18**-0615
Stohrer, W., **10**-0228
Stoicheff, B.P., **01**-0071, **02**-0034, **02**-0037
Stojiljković, A., **19**-0274
Stokes, S., **17**-0186
Stokes, S.S., **18**-0584
Stoll, M., **16**-2051
Stolle, A., **19**-1400
Stolle, W.T., **16**-1208
Stolow, A., **05**-0120, **06**-0013
Stolow, R.D., **04**-0369
Stoltz, B.M., **10**-1631, **17**-0279
Stolz, L.A., **18**-0657
Stolz-Dunn, S., **13**-0422
Stone, A.J., **18**-0522
Stone, D.A., **16**-1732
Stone, F.G.A., **02**-0177, **12**-0276, **15**-2431
Stone, J.M.R., **04**-0378
Stone, R.M., **09**-0036
Stoneberg, R.L., **19**-1100
Stoner, E.J., **10**-0606
Stoos, F., **19**-0023
Storch, D.M., **02**-0019
Storch, E.C., **16**-0826
Storer, J.W., **17**-0052
Storer, R.I., **16**-1738
Storesund, H.J., **18**-0022, **18**-0102
Storey, J.M.D., **16**-1952
Stork, G., **05**-0188, **10**-0226, **10**-0227, **10**-0228, **10**-0564, **10**-1058, **10**-1259, **10**-1636, **10**-1647, **10**-1650, **10**-1653, **10**-1662, **10**-1668, **10**-1674, **10**-1678, **10**-1683, **10**-1684, **12**-0409, **12**-0420, **15**-0781, **15**-1351, **15**-1688, **15**-2082, **16**-1071, **16**-1282
Storr, R.C., **15**-2103, **15**-2166, **18**-0471
Story, P.R., **02**-0350, **10**-0129, **10**-0131, **14**-0265, **17**-0520, **17**-0521, **17**-0522, **17**-0524, **19**-0369, **19**-0376, **19**-0379
Story, R.R., **18**-0105
Stothers, J.B., **05**-0125, **05**-012, **06**-0067, **18**-0194
Stotskii, A.A., **11**-0125
Stott, P.E., **03**-0101
Stotter, P.L., **12**-0154
Stottlemeyer, T.R., **07**-0068
Stotz, E.H., **04**-0253
Stotz, D.S., **10**-0490
Stoughton, R.W., **04**-0056
Stout, C.W., **15**-2138
Stoute, V., **18**-0374
Stoutland, P.O., **10**-0359
Stowell, J.C., **05**-0099, **10**-1193, **15**-0992, **16**-0464, **16**-0969
Stoy, P., **15**-1940
Stoyanov, E., **08**-0106
Stoye, D., **16**-1753
Strachan, A.N., **11**-0098, **11**-0150
Strachan, W.M.J., **18**-0887, **19**-0350
Strachan, W.S., **18**-0111
Stracke, M.P., **15**-1325
Stragies, R., **18**-0789
Strand, J.W., **10**-0878, **11**-0186
Strange, J.H., **04**-0382
Stranne, R., **10**-1454
Strassner, T., **15**-0267, **15**-1933
Straszewski, J.P., **16**-1357
Stratakis, M., **12**-0420, **14**-0238, **14**-0240
Stratford, P.W., **16**-0690
Strating, J., **15**-0008, **19**-1738
Stratton, B., **05**-0378
Straub, T.S., **15**-1799
Strauss, C.R., **07**-0105, **07**-0115, **07**-0116, **11**-0191, **19**-0966
Strauss, H.L., **04**-0323
Strauss, M.J., **13**-0008, **13**-0009
Strauss, U., **01**-0094
Strausz, O.P., **05**-0358, **15**-1785, **15**-2213, **18**-0222, **18**-0224, **18**-0226
Strawn, K.G., **19**-0765
Strazzari, S., **05**-0215
Strazzolini, P., **12**-0701, **16**-1712, **19**-0226
Streck, R., **18**-0756
Street, L.J., **12**-0370
Streeter, D.L., **18**-0121
Strege, P.E., **02**-0045, **02**-0046, **10**-1448, **10**-1450
Streib, H., **13**-0763
Streib, W.E., **15**-2406
Streicher, H., **05**-0092
Streicher, W., **13**-0083, **13**-0752
Streiner, T., **03**-0048
Streith, J., **15**-1642, **16**-0326, **18**-0480
Streitwieser Jr., A., **01**-0049, **02**-0002, **02**-0026, **02**-0056, **02**-0115, **04**-0022, **05**-0099, **05**-0130, **05**-0134, **05**-0150, **06**-0083, **07**-0015, **08**-0013, **08**-0014, **08**-0053, **08**-0058, **08**-0059, **08**-0064, **08**-0067, **08**-0068, **08**-0069, **08**-0070, **08**-0071, **08**-0073, **08**-0074, **08**-0171, **10**-0008, **10**-0060, **10**-0088, **10**-0283, **10**-0397, **10**-0420, **11**-0603

Streitwieser, A., **02**-0023, **04**-0312, **05**-0193, **05**-0194, **08**-0060, **08**-0074, **08**-0080, **08**-0212, **08**-0215, **10**-0001, **10**-0270, **10**-0277, **10**-0287, **10**-1597, **12**-0420, **16**-0463
Strekowski, L., **14**-0346, **16**-1235
Strelenko, Y.A., **04**-0360
Strickland, J.B., **16**-0697
Strickland, S.M.S., **18**-0871
Strieter, E.R., **13**-0178
Strijtveen, B., **04**-0205
Strine, J., **13**-0272
Stringer, O.D., **19**-0827
Stroh, R., **11**-0350, **11**-0351
Strohmeier, W., **12**-0088, **15**-0406
Strologo, S., **13**-0582
Ström, P., **16**-1827
Strömberg, S., **13**-0393
Stromquist, P., **19**-1616
Strömqvist, M., **16**-0290
Strongin, R.M., **13**-0730
Stroud, M.A., **11**-0072
Stroud, S.G., **19**-0411, **19**-0462
Strouf, O., **19**-0874
Štrouf, O., **19**-0010
Strozier, R.W., **02**-0352, **15**-0080, **15**-2005
Struass, C.R., **13**-0413
Strub, H., **02**-0218
Struchkov, Y., **05**-0263
Strukelj, M., **15**-0021
Strunk, S., **18**-0418
Struzynski, C.P., **10**-0855
Stryker, J.M., **12**-0533, **13**-0628, **16**-1073, **16**-1073
Strzalko, T., **15**-1001
Stuart, A.M., **15**-1488
Stuart, R.S., **12**-0055
Stubbs, C.A., **19**-0132
Stubbs, M.E., **18**-0645
Stuber, F.A., **19**-0554
Stucchi, E., **15**-1068
Stuchal, F.W., **10**-0285
Stuckwisch, C.G., **15**-1932
Stucky, G., **05**-0159
Studabaker, W.B., **15**-2287
Stüdemann, T., **10**-1384
Studer, A., **14**-0391, **18**-0056, **19**-1310, **19**-1686
Studer, M., **11**-0512, **16**-1177
Studzinskii, O.P., **10**-0390
Stuermer, R., **12**-0460
Stull, D.R., **01**-0093
Stupp, S.I., **17**-0447
Sturino, C.F., **18**-0816
Sturla, S.J., **15**-0973, **15**-1439
Sturmer, D., **10**-0134
Stürmer, R., **15**-0698, **16**-0706
Stutchbury, J.E., **16**-0191
Styler, S.A., **10**-0886
Styring, P., **13**-0497
Stępień, B.T., **02**-0137
Su, A.C.L., **15**-0796
Su, B.M., **05**-0150
Su, C., **16**-1170
Su, F.-Y., **16**-1640
Su, H., **17**-0216
Su, J., **15**-1926, **19**-0378
Su, L., **15**-1147
Su, M., **12**-0288, **15**-0177, **16**-1320
Su, M.-D., **18**-0591
Su, M.D., **04**-0168, **04**-0287
Su, Q., **10**-1390, **15**-0065
Su, T.M., **10**-0320, **18**-0509, **18**-0510, **18**-0511
Su, W., **10**-0618, **10**-0772, **12**-0631, **16**-0687, **16**-0884, **19**-0820, **19**-1705
Suanders Jr., W.H., **17**-0092
Suarez, A., **12**-0277
Suarez, J., **10**-1643
Suarez, P.A.Z., **09**-0110, **16**-0276
Suárez, A., **15**-0611
Suárez, E., **14**-0208, **17**-0154
Subba Rao, B.C., **12**-0442, **19**-0993, **19**-1634
Subba Rao, G., **15**-0533
Subba Rao, G.S.R., **11**-0365
Subba Rao, O., **05**-0405
Subba Rao, Y.V., **11**-0644
Subba Reddy, B.V., **10**-1549, **10**-1574, **11**-0195, **16**-0090, **19**-1253, **19**-1613
Subbaraj, A., **05**-0405
Subbaraman, J., **10**-0372
Subbaraman, L.R., **10**-0372
Subbarao, Y.T., **16**-1679
Subbotin, O.A., **04**-0333, **09**-0034
Subong, A.P., **19**-0751
Subotkowski, W., **11**-0562, **18**-0658, **18**-0751, **18**-0891
Subrahmanya, M., **10**-0680
Subrahmanyam, C., **12**-0492
Subramaniam, B., **09**-0094
Subramanian, L.R., **05**-0068, **10**-0248, **10**-0249, **10**-0381, **10**-0791, **10**-1362, **11**-0471, **13**-0027, **15**-0035, **15**-0106, **16**-2057
Subramanian, R., **05**-0386, **10**-1089, **10**-1621
Subrmanyam, R.V.K., **10**-0909
Suchan, S.D., **10**-1222
Suchanek, P., **16**-1056
Suchkov, V.V., **10**-1089
Suckling, C.J., **11**-0142
Suda, H., **04**-0177
Suda, K., **10**-0567, **18**-0144, **18**-0153, **18**-0342
Suda, M., **02**-0179, **02**-0220, **16**-1289
Suda, S., **16**-0183
Sudalai, A., **10**-0660, **10**-1068, **11**-0234, **11**-0426, **13**-0410, **15**-0299, **15**-1635, **15**-1887, **15**-1897, **16**-1152, **16**-1674, **16**-1683, **19**-0330, **19**-0594
Sudha, R., **16**-1099, **18**-0137
Sudo, R., **10**-0906
Sudo, T., **15**-0745
Sudrik, S.G., **18**-0212
Sue, R.E., **12**-0579
Suehiro, T., **14**-0096
Suemitsu, R., **10**-1654, **10**-1815, **10**-1817, **12**-0532, **12**-0540, **13**-0617
Suenaga, M., **03**-0129
Suenaga, T., **10**-1453, **15**-2063
Suenaga, Y., **16**-1788
Suenram, R.D., **19**-0361, **19**-0383
Suga, S., **10**-1718, **10**-1844, **11**-0375, **11**-0376, **14**-0299, **15**-2135
Suga, T., **17**-0216
Sugahara, H., **18**-0500
Sugahara, N., **15**-0160
Sugai, T., **19**-1022
Sugamoto, K., **15**-0203, **15**-0204
Sugano, M., **16**-0644
Sugasawa, S., 09-II-0006, **17**-0459
Sugasawa, T., **11**-0390, **11**-0524, **11**-0525, **11**-0530, **16**-1057
Sugathapala, P.M., **15**-2438
Sugawara, A., **18**-0143
Sugawara, M., **10**-0310, **10**-1204, **15**-2348
Sugawara, S., **15**-2379
Sugawara, Y., **13**-0415
Sugden, J.K., **19**-1238
Sugden, S., **10**-0313
Suggs, J.W., **14**-0455, **19**-0080
Sugi, Y., **13**-0599, **13**-0604, **13**-0605, **13**-0608
Sugihara, H., **15**-1300, **15**-1888, **19**-1779
Sugihara, T., **11**-0332, **13**-0380, **13**-0453, **15**-0829, **15**-1427, **15**-1458, **15**-2371, **16**-1530
Sugihara, Y., **07**-0021, **15**-1847, **17**-0364

Sugimoto, A., **03**-0027, **16**-1220
Sugimoto, H., **10**-0713, **16**-1691
Sugimoto, M., **16**-1455
Sugimoto, O., **12**-0588
Sugimoto, T., **10**-1868, **15**-1711, **15**-1941, **15**-2117, **18**-0363
Sugino, E., **19**-1283
Suginome, H., **10**-0874, **10**-1258, **10**-1415, **15**-0321, **18**-0338, **19**-0065
Suginome, M., **10**-0689, **16**-0713, **16**-1106, **16**-1442, **16**-2127
Sugita, N., **13**-0613, **19**-1745
Sugita, T., **11**-0376, **12**-0619, **17**-0026
Sugiura, F., **11**-0485
Sugiura, M., **10**-1462, **15**-1304, **15**-1326, **15**-1390, **16**-0909, **16**-0914, **16**-0915
Sugiura, T., **05**-0297, **10**-1630
Sugiyama, E., **16**-0376, **16**-0377, **19**-1139
Sugiyama, J., **14**-0268
Sugiyama, T., **15**-1559
Sugoh, K., **12**-0754
Suguro, M., **13**-0293, **13**-0439
Suh, D.J., **10**-0864
Suh, G., **15**-1478
Suh, J.M., **16**-0947
Suh, W.H., **19**-1044
Suh, Y.S., **16**-0817
Suh, W.H., **15**-1438
Suhendra, M., **19**-1187
Suhr, H., **13**-0084
Sui, J.K., **19**-1033
Suib, S.L., **19**-0238
Suk, J.Y., **18**-0218
Sukai, A.K., **16**-0061, **16**-0062
Sukata, K., **10**-0971, **16**-1425, **16**-2046
Sukcharoenphon, K., **02**-0417
Sukhanov, N.N., **10**-1583
Sukhmolinova, L.I., **10**-1782
Sukirthalingam, S., **15**-0878
Sukumar, R., **10**-0660
Sukumaran, K.B., **18**-0471
Sulbaran de Carrasco, M.C., **19**-1717
Sulfab, Y., **11**-0029
Sulikowski, G.A., **12**-0301, **12**-0356, **15**-1092
Sulikowski, M.M., **12**-0356
Sullins, D.W., **16**-0989
Sullivan, A.B., **19**-0871
Sullivan, A.C., **19**-0118
Sullivan, D.F., **16**-1133, **16**-1235, **16**-2019, **19**-0059
Sullivan, E.L., **16**-2172
Sullivan, G.R., **02**-0101, **04**-0208
Sullivan, P.J., **05**-0205
Sullivan, R.J., **11**-0305
Sulmon, P., **16**-1224
Sultana, S.S., **10**-0683, **13**-0405, **16**-0780
Sultanbawa, M.U.S., **17**-0415
Sulzbach, H.M., **02**-0251, **02**-0261, **02**-0262
Sulzbach, R.A., **12**-0554
Sumarta, L., **15**-1679
Sumi, S., **19**-0106
Sumida, N., **16**-0167
Sumida, S.-i., **16**-0633
Sumihara, H., **16**-2028
Sumino, M., **16**-2015
Sumino, Y., **10**-1826, **19**-1591
Suminov, S.I., **15**-0314
Sumitani, N., **14**-0071, **15**-0056
Sumitra, G., **16**-0252
Sumiya, T., **10**-1825, **19**-0505
Summerhays, K.D., **08**-0226
Summers, B., **14**-0106, **14**-0108
Summerville, R.H., **10**-0254, **10**-0257
Sumonja, M., **02**-0238
Sumpter, C.A., **02**-0271
Sumrell, G., **15**-1513
Sun, C., **08**-0212, **12**-0498
Sun, F., **04**-0231
Sun, G.-F., **16**-0662
Sun, G.-r., **15**-1744
Sun, J., **15**-0421, **16**-1768, **19**-0823
Sun, K.-L., **16**-0349
Sun, L., **10**-0002
Sun, N., **10**-1454
Sun, S.F., **16**-0106
Sun, W., **16**-0420, **16**-0947
Sun, W.-H., **15**-2421
Sun, X., **05**-0182, **10**-0098, **12**-0422, **15**-0762, **15**-0850, **15**-1690, **16**-0233, **16**-2175
Sun, Y., **05**-0375, **13**-0480, **13**-055, **15**-0239, **15**-0434, **15**-0615, **19**-1028
Sun, Y.-K., **19**-1028
Suna, E., **12**-0106, **13**-0499
Sunagawa, M., **16**-2025
Sunay, U., **10**-0801
Sundaralingam, M., **05**-0087
Sundararajan, G., **10**-0925, **15**-1329, **18**-0787
Sundararaman, P., **19**-0708
Sundberg, J.E., **13**-0589
Sundberg, R.J., **18**-0714
Sundermeier, M., **13**-0288
Sundén, H., **16**-1036, **19**-0506
Sunderhaus, J.D., **10**-0690
Sundermeier, M., **13**-0274
Sundermeier, U., **19**-0238
Sundermeyer, J., **08**-0088, **15**-1738
Sundgren, A., **10**-1123
Sung, B.S., **15**-1439
Sung, D.D., **16**-1512
Sung, D.W.L., **16**-0690
Sung, H.R., **15**-0934
Sung, S.-y., **10**-1401, **10**-1471, **15**-1177, **16**-0596, **16**-0599
Šunjić, V., **04**-0146, **10**-0891, **15**-0597
Sunkel, J., appendixA-0024, appendixA-0023
Sunko, D.E., **06**-0069, **06**-0072, **06**-0076, **10**-0116, **10**-0120, **10**-0185, **10**-0208
Sunner, J., **10**-0416
Sunoj, R.B., **18**-0220
Suorsa, T., **03**-0170
Superchi, S., **04**-0114, **16**-0687
Superchi, S., **19**-0823
Suppan, P., **07**-0032, **19**-1690
Surampudi, V., **11**-0157
Surapaneni, R., **15**-2068
Surendra, K., **10**-0546, **10**-0671, **19**-0200
Suresh, C.H., **02**-0029, **15**-0099
Suresh, S., **19**-0594
Suri, J.T., **16**-0917
Suri, K.A., **16**-1832
Suri, O.P., **16**-1832
Suri, S.C., **12**-0709
Suriaatmaja, M., **19**-0394
Suriano, J.A., **15**-1425
Surivet, J.-P., **15**-0814
Surman, P.W.J., **02**-0201
Surmina, L.S., **10**-1598
Suroweic, M., **19**-0817
Surprenant, S., **16**-1240
Surridge, J.H., **11**-0297, **13**-0622, **15**-1536
Surville, R. De, **19**-0748
Surzur, J., **10**-1227, **15**-0052, **18**-0076, **19**-0255
Suschitzky, H., **13**-0460, **13**-0715, **13**-0717, **16**-0434, **19**-0010, **19**-0298
Sushko, T.P., **18**-0218
Suslick, K.S., **07**-0066, **07**-0069, **07**-0070, **07**-0071, **07**-0072, **07**-0079, **07**-0081, **07**-0088, **19**-0525
Suslova, E.N., **15**-0308, **19**-1789
Süss, H.U., **02**-0179, **02**-0180
Süsse, M., **16**-1858

Sustmann, R., **05**-0243, **05**-0245, **05**-0290, **15**-2044, **15**-2060, **15**-2088, **15**-2096, **15**-2179, **19**-1532
Susuki, S., **05**-0277
Susuki, T., **10**-0441
Susz, P.B., **11**-0450
Sütbeyaz, Y., **10**-0939, **19**-0392
Suter, C., **18**-0537
Sutherland, A.G., **17**-0347
Sutherland, A.J., **12**-0271
Sutherland, I.O., **03**-0101, **03**-0151, **04**-0163, **18**-0386, **18**-0389, **18**-0727, **18**-0729, **19**-1467
Sutherland, J.K., **15**-0782
Sutherland, R.G., **05**-0396, **07**-0079
Sutthivaiyakit, S., **10**-0900, **19**-0708
Suttle, N.A., **16**-2143
Sutton, A.E., **18**-0779
Sutton, L.E., **01**-0087
Suvorov, N.N., **19**-0441
Suwa, T., **15**-0622, **16**-0376, **16**-0377, **16**-0382, **16**-0638, **19**-1139
Suwiński, J., **13**-0041
Suyama, T., **16**-1708
Suzui, A., **19**-0373
Suzuka, T., **10**-1460
Suzuki, A., **10**-1415, **10**-1416, **10**-1417, **10**-1836, **11**-0358, **12**-0490, **12**-0518, **12**-0538, **13**-0471, **13**-0474, **13**-0476, **13**-0625, **13**-0705, **13**-0718, **14**-0096, **15**-0168, **15**-0636, **15**-0694, **15**-0700, **15**-1183, **15**-1184, **15**-1187, **15**-1189, **15**-1191, **15**-1192, **16**-0696, **16**-1135, **16**-1759, **17**-0161, **18**-0420, **18**-0429, **18**-0435, **18**-0441, **18**-0447, **18**-0453, **18**-0457
Suzuki, D., **15**-2368, **15**-2408
Suzuki, H., **10**-0790, **10**-0906, **10**-1040, **10**-1201, **11**-0119, **11**-0126, **11**-0140, **11**-0301, **11**-0626, **12**-0503, **13**-0135, **13**-0146, **13**-0254, **13**-0256, **13**-0575, **13**-0683, **13**-0752, **14**-0402, **15**-0993, **16**-0661, **16**-0686, **19**-1534, **19**-1581, **19**-1598, **19**-1744
Suzuki, K., **10**-0584, **10**-1297, **13**-005, **14**-0202, **15**-1829, **16**-0490, **18**-0013, **18**-0158, **18**-0244, **18**-0249, **19**-1274
Suzuki, M., **10**-1645, **10**-1697, **10**-1825, **15**-1136, **16**-0161, **16**-1125, **17**-0208, **18**-0150
Suzuki, N., **15**-0799, **15**-08, **15**-0958, **19**-1445
Suzuki, R., **16**-0381
Suzuki, S., **06**-0083, **10**-1561, **14**-0299, **16**-1195, **19**-0653, **19**-1168, **19**-1487
Suzuki, T., **10**-0550, **10**-0676, **10**-1655, **12**-0117, **13**-0155, **13**-0415, **15**-0212, **15**-0839, **15**-0993, **15**-0998, **15**-1115, **16**-0668, **16**-1041, **16**-1044, **16**-1685, **16**-2023, **18**-0359, **19**-0156, **19**-0518, **19**-0688, **19**-0900
Suzuki, Y., **13**-0321, **13**-0327, **16**-1225, **19**-1487
Svanholm, U., **18**-0711
Svedas, V., **04**-0151
Svendsen, B.H., **15**-0751
Svendsen, J.S., **15**-1691, **15**-1701, **15**-1866
Svensen, H., **13**-0681
Svensson, M., **13**-0393, **13**-0396
Svensson, S., **15**-0096
Svensson, T., **18**-0040
Sveshnikova, E.B., **07**-0028
Svetlakov, N.V., **10**-1053
Svinivas, D., **16**-1608
Sviridov, S.I., **15**-1574
Svoboda, J.J., **05**-0032, **05**-0056, **05**-0061
Svoboda, M., **17**-0018, **17**-0030, **17**-0031, **17**-0096, **17**-0260, **17**-0389
Svyatkin, V.A., **04**-0333
Swafford, A.M., **15**-1588
Swafford, R.L., **18**-0855
Swager, T.M., **03**-0190, **05**-0224
Swain, C.G., **06**-0088, **09**-0062, **09**-0063, **09**-0064, **10**-0349, **10**-0622, **11**-0274, **12**-0099, **12**-0648, **13**-0028, **13**-0030, **13**-0719, **13**-0721, **16**-1731, **19**-1763, **19**-1765
Swain, C.J., **05**-0142
Swain, M.S., **09**-0062, **09**-0063
Swallow, S., **16**-0759
Swamer, F.W., **16**-2014
Swami, S.S., **17**-0429, **19**-0979, **19**-0988
Swaminathan, S., **10**-0232, **12**-0682, **16**-1068, **19**-1018
Swamy, N.R., **10**-0958
Swamy, T., **11**-0219, **19**-0031, **19**-0032
Swan, G.A., **12**-0679
Swan, J.M., **10**-0832, **10**-0838
Swann, B.P., **19**-0405
Swann, E., **18**-0718
Swansborough, K.F., **19**-0010
Swanson, D.R., **12**-0617
Swanson, E., **15**-2410
Swanson, J.C., **17**-0031
Swanson, S.B., **13**-0103
Swanwick, M.G., **19**-1211
Swapna, G.V.T., **15**-2252
Swarbrick, M.E., **18**-0419, **18**-0687
Swärd, K., **13**-0389
Swarnalakshmi, S., **19**-1075, **19**-1300
Swart, E.R., **10**-0084
Swartz, J.E., **13**-0059
Swartz, T.D., **10**-0179
Swartzendruber, J.K., **12**-0224
Swarup, S., **10**-0368
Sweany, R.L., **15**-0515
Sweat, F.W., **19**-0638
Swedlund, B.E., **10**-0001, **11**-0271, **15**-1626, **15**-1631
Swedo, R.J., **19**-0251
Sweeney, A., **10**-0226
Sweeney, J.B., **15**-0275
Sweeney, W.A., **02**-0370, **11**-0443
Sweeney, Z.K., **16**-0733
Sweeting, L.M., **04**-0207, **04**-0208
Sweetman, B.J., **16**-0229
Swensen, W.E., **16**-1285
Swerdloff, M.D., **19**-0343
Swern D., **14**-0221, **10**-0740, **10**-0746, **10**-0747, **12**-0438, **14**-0196, **14**-0224, **14**-0246, **14**-0249, **15**-0027, **15**-1726, **19**-0161, **19**-0162, **19**-0165, **19**-0644, **19**-0648, **19**-0700, **19**-0716, **19**-1787
Swett, L.R., **10**-1582, **16**-1728
Swierczewski, G., **10**-1511
Świerczek, K., **13**-0041
Swiger, R.T., **10**-0285
Swinborne-Sheldrake, R., **02**-0130
Swinbourne, E.S., **17**-0122
Swindell, C.S., **10**-0110, **10**-1532
Swindell, R.T., **10**-0134
Swinnen, D., **16**-1786
Swisher, J.V., **17**-0356
Swiss, K.A., **16**-1024
Switzer, C., **15**-1042
Swiątek, A., **16**-1399
Swoboda, W., **19**-0371
Sy, A.O., **18**-0267
Syamala, M.S., **11**-0558
Syatkovskii, A.I., **15**-2287

Sydnes, L.K., **17**-0313
Sygula, A., **02**-0360, **02**-0363
Sygula, R., **02**-0360
Sylvander, L., **05**-0245
Symons, M.C.R., **02**-0376, **03**-0037, **05**-0142, **05**-0273, **05**-0284, **05**-0318, **10**-0034
Synerholm, M.E., **10**-0013, **18**-0688
Syper, L., **18**-0371, **19**-0622, **19**-0626
Syriopoulos, G.T., **10**-1505
Szabo, A.L., **16**-1552
Szabo, H., **14**-0271
Szabo, W.A., **16**-2110
Szabó, A., **13**-0537
Szabó, K.J., **16**-0611
Szabó, Z.G., **06**-0046
Szafran, M., **02**-0095
Szajáni, B., **17**-0488
Szarek, W.A., **04**-0363
Szczygielska-Nowosielska, A., **16**-1655
Szeimies, G., **04**-0491, **10**-0199, **19**-0711
Szeja, W., **10**-0654
Szejtli, J., **03**-0175, **03**-0177
Szele, I., **06**-0076, **11**-0165, **11**-0170, **13**-0035, **13**-0685
Szentpály, L.-v., **10**-0032
Szentpály, L.V., **10**-0029
Szeto, C.-P., **16**-1074
Szeto, W.T.A., **16**-1886
Szeverenyi, N.M., **05**-0189, **12**-0420
Szeverényi, Z., **19**-0398
Szilagyi, P., **05**-0061
Szilagyi, S., **10**-0571
Szillat, H., **15**-0818
Szmant, H.H., **15**-1852, **19**-1464
Szmuszkovicz, J., **10**-0722, **10**-1674, **10**-1678
Szöllõsy, Á., **16**-1212
Szöllőy, Á., **15**-1491
Szucs, S.S., **15**-0861
Szulejko, J.E., **08**-0146, **10**-0010
Szumigala Jr., R.H., **13**-0266, **13**-0504
Szwarc, H., **18**-0416
Szwarc, M., **05**-0012, **05**-0313, **10**-0053
Szymanski, M.J., **15**-0967
Szymoniak, J., **12**-0329, **15**-0881, **15**-1384, **16**-0856, **16**-1115, **16**-1411, **16**-1481, **16**-1482, **19**-1669
Taagepera, M., **04**-0240, **08**-0219, **08**-0226, **08**-0235
Taba, K.M., **04**-0349
Tabacco, S.A., **10**-1433
Tabaei, M.H., **10**-0568
Tabanella, S., **15**-1884
Tabar-Hydar, K., **19**-0088, **19**-0102, **19**-0147, **19**-0153
Tabata, A., **15**-1536, **15**-1714
Tabata, H., **19**-0761
Tabata, M., **14**-0396
Tabata, T., **18**-0338
Taber, D.F., **10**-1610, **11**-0419, **12**-0217, **12**-0348, **12**-0356, **12**-0358, **12**-0654, **15**-0820, **15**-0871, **15**-0961, **15**-1980, **15**-2366, **19**-0168, **19**-1027, **19**-1464
Taber, T.R., **16**-0997, **16**-1013, **16**-1018
Tabet, J.-C., **15**-1452
Tabuchi, H., **11**-0551, **11**-0591
Tabuchi, N., **15**-1341, **16**-0651
Tabuchi, T., **17**-0202, **19**-1418
Tabushi, I., **02**-0326, **03**-0101, **03**-0174, **12**-0112, **14**-0144, **15**-1733, **19**-0780
Tacconi, G., **15**-2122, **15**-2179, **18**-0708
Tachi, K., **16**-0620
Tachibana, A., **12**-0087
Tachibana, K., **16**-2092
Tada, M., **11**-0328, **12**-0015, **15**-0241, **15**-1508, **19**-1375
Tada, N., **14**-0190
Tadaki, M., **13**-0448
Tadanier, J., **18**-0028
Taddei, M., **07**-0042, **07**-0123, **13**-0098, **16**-2102, **19**-1073
Tadjer, A., **02**-0245
Tae, E.L., **05**-0365
Tae, J.S., **15**-1371
Taeger, E., **12**-0590
Taeschler, C., **10**-0124
Tafesh, A.M., **15**-1381
Taffer, I.M., **10**-0500
Taft, B.R., **15**-0594
Taft, R.W., **03**-0015, **03**-0016, **05**-0052, **05**-0092, **08**-0132, **08**-0160, **08**-0161, **08**-0176, **08**-0217, **08**-0219, **08**-0223, **08**-0226, **08**-0235, **09**-0020, **09**-0037, **09**-0047, **09**-0050, **09**-0051, **09**-0052, **09**-0054, **09**-0055, **09**-0059, **09**-0063, **10**-0429, **10**-0432, **10**-0443, **10**-0448, **10**-0448, **10**-0524, **15**-0028, **16**-1591
Taga, T., **10**-0234, **15**-0394, **15**-1125, **19**-1745
Tagaki, W., **12**-0639, **14**-0202, **16**-2149
Tagarelli, A., **10**-0545, **15**-0875
Tagat, J.R., **16**-2178
Tagaya, H., **10**-0716, **19**-1461
Taggi, A.E., **12**-0124, **12**-0167, **16**-2103, **16**-2105, **17**-0318, **19**-1273
Tagliavini, E., **12**-0693, **16**-0750
Tagliavini, G., **16**-0645
Taguchi, H., **13**-0448, **16**-0508, **16**-1235, **16**-1357, **17**-0410
Taguchi, K., **16**-0290
Taguchi, T., **08**-0200, **10**-0992, **10**-1819, **12**-0179, **15**-0839, **15**-1164, **15**-1341, **15**-1590, **16**-0651, **18**-0701, **19**-0848
Taguchi, Y., **15**-1228, **16**-2116
Tahmasebi, D.P., **10**-0655
Tahshiro, M., **19**-1447
Tai, A., **04**-0001, **04**-0136, **15**-0155, **15**-0158, **18**-0363
Tai, C.-L., **16**-1067
Tai, J.J., **10**-0202
Tai, W.T., **18**-0209
Taigounov, A.A., **19**-0933
Taigounov, I.R., **19**-0933
Taiji, T., **10**-0886, **10**-1453
Taillades, J., **15**-0375
Taillefer, M., **11**-0656, **13**-0578
Taira, A., **15**-1179
Taira, S., **15**-0794
Tait, B.D., **15**-0120
Tait, S.J.D., **19**-0104
Tajbakhsh, M., **10**-1082, **13**-0227, **16**-0055, **16**-0063, **16**-0145, **19**-0150, **19**-0861
Tajik, H., **11**-0288
Tajima, K., **16**-1716
Tajima, M., **17**-0427
Tajmehri, H., **11**-0288
Takaba, D., **16**-1274
Takabe, K., **16**-1196
Takabe, K., **19**-0661
Takacs, J.M., **15**-0795
Takacs, J.M., **15**-0810, **16**-1144
Takada, E., **15**-1191
Takada, H., **16**-1385
Takada, S., **18**-0487
Takada, S.C.S., **16**-0276
Takada, T., **15**-1139
Takagaki, T., **19**-1332
Takagi, H., **16**-1274
Takagi, J., **19**-0706

Takagi, K., **10**-1039, **10**-1244, **10**-1406, **13**-0279, **13**-0281, **13**-0282, **13**-0324, **13**-0466, **15**-0983, **15**-1445, **15**-1448, **15**-1457, **15**-2383
Takagi, M., **16**-0239, **19**-1339
Takagi, R., **16**-1228
Takagi, Y., **10**-1215, **12**-0714
Takagishi, H., **15**-2393
Takagishi, S., **12**-0391, **16**-0161
Takaguchi, Y., **16**-1307
Takahahsi, T., **15**-2404
Takahara, J.P., **16**-0495
Takahara, P.M., **19**-1663
Takahashi, E., **15**-1576
Takahashi, G., **12**-0284
Takahashi, H., **10**-1709, **16**-0686, **16**-0823, **19**-0414, **19**-0761
Takahashi, J., **17**-0072
Takahashi, K., **02**-0047, **10**-1454, **10**-1630, **15**-1847, **16**-1940, **19**-0279, **19**-0870, **19**-1287
Takahashi, M., **19**-0215
Takahashi, N., **15**-0794
Takahashi, O., **15**-0156
Takahashi, S., **10**-1469, **11**-0260, **13**-0583, **15**-1399, **15**-1407, **15**-1461, **15**-1468, **15**-1469, **15**-1470, **19**-1087
Takahashi, T., **10**-1378, **10**-1378, **10**-1524, **10**-1779, **13**-0359, **15**-0225, **15**-0392, **15**-0706, **15**-0740, **15**-0799, **15**-0841, **15**-0864, **15**-0956, **15**-0957, **15**-0958, **15**-1892, **15**-1904, **15**-2380, **15**-2424, **16**-0664, **16**-1426, **16**-2000, **18**-0488, **18**-0803
Takahashi, T.T., **10**-0227, **15**-1559
Takahashi, Y., **10**-1834, **10**-1836, **11**-0358, **12**-0173, **15**-0157, **19**-0690
Takahata, H., **19**-0142, **19**-0541
Takahori, T., **15**-2010, **16**-1007
Takai, K., **15**-2276, **16**-0500, **16**-0565, **16**-1365, **16**-1368, **19**-0044, **19**-0133
Takai, T., **15**-0185, **15**-1838, **16**-0823, **19**-0480
Takai, Y., **10**-0063, **10**-0170, **15**-0502, **16**-0683
Takaishi, N., **19**-0461
Takaki, K., **10**-0896, **15**-0371, **15**-0732, **15**-1330
Takakis, I.M., **10**-0148, **15**-0187
Takaku, M., **11**-0368
Takakura, M., **19**-1659
Takakura, N., **16**-0189
Takamatsu, K., **11**-0038
Takami, K., **10**-1393, **12**-0502, **13**-0433
Takamine, K., **19**-1649, **19**-1663
Takamizawa, S., **19**-1177
Takamori, M., **10**-1205
Takamoto, N., **01**-0069
Takamoto, Y., **10**-1040
Takamura, N., **13**-0694
Takanami, T., **10**-0567, **18**-0144, **18**-0153
Takano, H., **10**-1215
Takano, K., **11**-0189
Takano, M., **15**-2304
Takano, S., **15**-1826, **16**-0251, **19**-0169, **19**-1391
Takanohashi, Y., **19**-1487
Takao, H., **11**-0332, **15**-0829, **15**-1458, **15**-2371
Takaoka, K., **19**-1534
Takaoka, R., **04**-0166
Takaoka, T., **17**-0472
Takasaki, K., **10**-0504
Takase, K., **15**-1561, **17**-0343
Takase, M., **19**-1091
Takashima, K., **10**-0009, **16**-1566
Takasu, K., **15**-1292, **15**-1641, **15**-2167
Takasugi, J.J., **16**-1281
Takasuka, M., **16**-1472
Takata, T., **03**-0182, **19**-0834
Takatsuki, H., **16**-1116
Takatsuto, S., **04**-0119
Takaya, A., **04**-0127, **04**-0146, **15**-0597
Takaya, H., **15**-0598, **15**-0611, **15**-1480, **15**-1492, **15**-2198, **19**-1026, **19**-1027
Takaya, H., **19**-1038
Takaya, J., **16**-0409, **16**-1103
Takaya, K., **19**-1774
Takaya, Y., **15**-1121, **15**-1130, **15**-1190
Takayama, R., **07**-0056
Takayanag, H.i., **19**-0415
Takazawa, O., **16**-0995
Takeba, M., **15**-1402
Takechi, N., **16**-0572
Takeda, A., **15**-2363, **15**-2372, **15**-2379, **19**-1021, **19**-1355
Takeda, H., **15**-1359
Takeda, K., **11**-0650, **16**-0436, **18**-0904
Takeda, M., **10**-1104, **15**-0371, **15**-1080, **19**-1478
Takeda, T., **10**-1205, **10**-1215, **13**-0448, **15**-0801, **15**-0914, **15**-1836, **16**-0452, **16**-1357, **16**-1358, **16**-1361, **16**-1729, **19**-0287
Takeda, Y., **15**-1237
Takegami, Y., **10**-1844, **10**-1845, **19**-1119, **19**-1772
Takehara, A., **10**-1454
Takehira, K., **15**-0371, **15**-0732, **10**-0896
Takei, H., **10**-1436, **16**-1937
Takei, I., **19**-1241
Takeishi, S., **16**-1026
Takemiya, A., **15**-1782
Takemoto, K., **03**-0157, **03**-0168, **04**-0179
Takemoto, T., **19**-0072
Takemoto, Y., **10**-1452, **15**-0922, **15**-0923, **15**-1004, **15**-1670, **19**-0480
Takemura, H., **03**-0129
Takemura, S., **19**-0637
Takenaka, N., **19**-1684
Takenaka, Y., **10**-1703
Takeno, H., **19**-1028
Takenoshita, H., **10**-1805
Takeoka, Y., **03**-0051, **15**-0779
Takeshima, T., **16**-0209
Takeshita, M., **15**-0624
Takeshita, T., **08**-0233, **14**-0133, **14**-0134, **17**-0014
Takeuchi, H., **05**-0231, **11**-0189, **19**-1035, **19**-1650
Takeuchi, K-i., **05**-0111
Takeuchi, K., **02**-0158, **02**-0160, **04**-0455, **05**-0084, **05**-0117, **05**-0201, **10**-0125, **10**-0299, **10**-0301, **10**-0439, **13**-0599, **15**-1459, **15**-2322, **16**-1323, **18**-0469, **18**-0470, **18**-0643
Takeuchi, M., **14**-0071
Takeuchi, N., **15**-1792
Takeuchi, R., **10**-0882, **10**-0902, **10**-0916, **10**-1822, **15**-1390, **15**-2383
Takeuchi, S., **14**-0402, **19**-1581
Takeuchi, T., **15**-1567
Takeuchi, Y., **01**-0087, **03**-0101, **15**-0465
Takeyama, T., **16**-0507, **16**-0509
Takezawa, E., **19**-0315
Takezawa, F., **15**-2300
Takhi, M., **16**-1618
Taki, H., **19**-0284
Takido, T., **10**-0819
Takigawa, T., **10**-1703
Takikawa, H., **16**-1046
Takimoto, M., **15**-0766, **15**-0811, **15**-1391
Takinami, S., **18**-0447
Takino, T., **10**-0150
Takiyama, N., **15**-2347, **16**-0518

Takizawa, J.-i., **19**-0475
Takizawa, S., **19**-0142
Takizawa, Y., **14**-0268
Takizawa, Y., **16**-0978
Takken, H.J., **17**-0275
Taktak, S., **16**-0571
Takui, T., **05**-0258
Takuma, Y., **19**-1176
Takumi, H., **10**-0641
Talami, S., **18**-0460
Talbert, J., **16**-1897
Talbot, R.J.E., **16**-0014, **16**-1510, **16**-1516, **16**-1588
Talbott, R., **11**-0610
Tale, R.H., **19**-1074
Talinli, N., **16**-1609
Tallant, M., **12**-0301
Tallarico, J.A., **15**-1204
Talley, J.J., **10**-0300
Talley, P., **12**-0500
Tallier, C., **16**-1961
Talukdar, B., **16**-1767
Talukdar, S., **16**-0336, **19**-1463, **19**-1623, **19**-1648, **19**-1716
Talybov, G.M., **15**-0261
Tam, I., **18**-0503
Tam, J.P., **16**-1818
Tam, K., **04**-0407
Tam, N.C., **19**-1609
Tam, W., **15**-2173, **15**-2441
Tam, W.W., **19**-0132
Tamada, M., **19**-0605
Tamagaki, S., **14**-0202
Tamagawa, K., **02**-0030
Tamagnan, G., **15**-1092
Tamaki, K., **16**-1078
Tamami, B., **10**-0936, **10**-1164, **15**-1848, **16**-0079, **17**-0432, **19**-0917
Tamamura, H., **10**-0234
Tamao, K., **10**-0688, **10**-1250, **10**-1297, **10**-1565, **13**-0565, **15**-0816, **16**-0509, **18**-0828
Tamaru, Y., **10**-0881, **10**-1498, **10**-1823, **14**-0279, **15**-1594, **16**-0666, **16**-0711, **16**-0719, **16**-1903, **18**-0738
Tamborra, P., **06**-0012
Tamborski, C., **12**-0616
Tamburin, H.J., **18**-0590
Tamhankar, B.V., **11**-0249
Tamiaki, H., **15**-2257
Tamm, C., **04**-0196, **19**-0475
Tamm, M., **02**-0161, **03**-0036, **03**-0069, **12**-0365
Tamm, T., **10**-0215
Tämm, K., **10**-0215
Tamura, H., **15**-2197
Tamura, K., **18**-0148
Tamura, M., **10**-1294, **10**-1320, **10**-1797, **13**-07, **14**-0374, **15**-0176, **15**-1054, **15**-1060
Tamura, O., **15**-1237, **16**-1261
Tamura, R., **05**-0277, **10**-1479, **19**-1536
Tamura, S., **06**-0067
Tamura, Y., **10**-0850, **11**-0521
Tan, B., **04**-0292
Tan, C.-H., **04**-0121, **04**-0122, **04**-0123
Tan, C.-W., **16**-1029, **16**-1030
Tan, G., **16**-1644
Tan, J., **11**-0398
Tan, K.-T., **16**-0610
Tan, K.L., **16**-0559
Tan, L.C., **10**-0807, **16**-1876
Tan, L.K., **11**-0451, **15**-1652
Tan, L.Y., **05**-0275
Tan, S.L., **14**-0188
Tan, T.-L., **12**-0094
Tan, X.J., **15**-1826
Tan, Z., **16**-0462, **19**-1633
Tanabe, K., **03**-0072, **10**-0882
Tanabe, M., **10**-1654, **17**-0418
Tanabe, Y., **12**-0318, **16**-1095, **16**-1134, **16**-1636, **16**-1639, **16**-2017, **16**-2018, **16**-2028, **16**-2156
Tanaka, A., **10**-1137, **12**-0754, **18**-0301
Tanaka, C., **19**-1398
Tanaka, D., **13**-0370, **15**-0766
Tanaka, F., **15**-1004, **16**-0917, **16**-1035
Tanaka, H., **13**-0297, **14**-0190, **15**-1665, **15**-1855, **15**-2064, **16**-0645, **16**-0670, **16**-2118, **18**-0488, **19**-0029, **19**-0460, **19**-1489
Tanaka, I., **11**-0594
Tanaka, J., **13**-0010, **16**-0600, **17**-0247
Tanaka, K., **01**-0067, **01**-0068, **01**-0069, **04**-0163, **09**-0120, **09**-0122, **10**-0336, **10**-1463, **15**-1369, **15**-1594, **16**-0547, **16**-0661, **16**-0686, **16**-0793, **16**-1070, **16**-1203, **18**-0465, **19**-0220, **19**-0859, **19**-0956, **19**-0981, **19**-1176
Tanaka, M., **02**-0070, **05**-0179, **10**-1014, **10**-1412, **10**-1827, **10**-1868, **10**-1870, **10**-1872, **11**-0476, **11**-0506, **12**-0108, **12**-0531, **12**-0614, **13**-0174, **13**-0321, **13**-0327, **13**-0336, **13**-0619, **14**-0365, **15**-0209, **15**-0353, **15**-0376, **15**-0381, **15**-1359, **15**-1379, **15**-1654, **15**-1662, **16**-0670, **16**-1167, **16**-2044, **19**-0061, **19**-0607
Tanaka, N., **06**-0081, **10**-0313
Tanaka, R., **05**-0258, **05**-0259, **07**-0022, **15**-0079, **15**-0337, **15**-0946, **15**-2368
Tanaka, S., **04**-0079, **10**-1123, **10**-1169, **10**-1498, **10**-1797, **15**-1941, **15**-2383, **16**-0373, **16**-1496
Tanaka, T., **05**-0317, **10**-0765, **11**-0244, **13**-0321, **13**-0327, **13**-0328, **15**-0779, **15**-1115, **15**-1184, **16**-1880, **19**-0541
Tanaka, W., **16**-0818
Tanaka, Y., **10**-1453, **15**-0755, **19**-1283
Tandon, A., **16**-1610
Tanemura, K., **10**-0550, **12**-0117, **19**-0518
Tang, C., **16**-0777
Tang, D., **19**-1401
Tang, D.Y.H., **05**-0281, **18**-0081
Tang, F.Y., **14**-0093
Tang, H., **10**-1443
Tang, J., **10**-1550, **15**-0863, **16**-0150
Tang, K., **12**-0402
Tang, K.-H., **15**-1218, **15**-1270
Tang, L., **15**-1004
Tang, M.-H., **10**-0924
Tang, M.-W., **15**-1768
Tang, P.W., **15**-1170
Tang, Q., **13**-0343
Tang, R., **18**-0737
Tang, R.H., **14**-0093
Tang, S., **04**-0292, **15**-0231
Tang, T.P., **16**-0895, **16**-0896
Tang, W., **15**-0412, **15**-0425, **15**-0603
Tang, X.-Q., **16**-0727
Tang, Y., **15**-0856, **15**-1122, **16**-0835, **16**-0911, **16**-1267, **16**-1394
Tang, Y.S., **02**-0383, **08**-0057, **08**-0105
Tang, Z., **16**-1037
Tang, Z.-Y., **13**-0511
Tangari, N., **16**-0504, **16**-0506
Tange, H., **19**-0981
Tangestaninejad, S., **10**-0670, **15**-1829, **15**-1846
Tanguy, G., **10**-1820, **10**-1845
Tani, H., **10**-0906, **14**-0402, **19**-1581, **19**-1598
Tani, K., **11**-0155, **12**-0074
Tani, M., **13**-0371, **13**-0401
Tani, R., **19**-0014
Tani, S., **10**-0846, **16**-0608, **18**-0732, **19**-1578

Tanida, H., **10**-0146, **10**-0161, **10**-0170, **10**-0171, **17**-0069
Tanigaki, K., **18**-0225
Tanigawa, Y., **10**-0908, **10**-1009, **10**-1012, **10**-1291, **10**-1509, **14**-0254
Taniguchi, H., **10**-0252, **11**-0370, **11**-0493, **11**-0505, **17**-0321, **19**-1663
Taniguchi, K., **19**-1649
Taniguchi, M., **11**-0368, **15**-0604, **15**-0822
Taniguchi, N., **13**-0151, **15**-0932, **16**-1655
Taniguchi, S., **10**-0375
Taniguchi, T., **19**-1621
Taniguchi, Y., **02**-0295, **10**-1009, **10**-1012, **10**-1169, **15**-1330
Tanikaga, R., **19**-1779
Tanikawa, S., **10**-0060, **10**-0074, **15**-1711, **17**-0343
Tanimoto, Y., **19**-1053
Tanino, K., **10**-1546, **10**-1803, **15**-0971, **15**-0989
Tanio, M., **10**-0850
Tanizawa, D., **19**-1139
Tanji, K., **12**-0588
Tank, R.T., **14**-0271
Tankguchi, N., **13**-0140
Tankguchi, T., **19**-1382
Tanko, J., **04**-0410, **15**-0128, **18**-0161, **18**-0569, **18**-0580, **18**-0614
Tanko, J.M., **04**-0422, **05**-0216, **05**-0305, **14**-0058, **14**-0118, **14**-0128, **14**-0163, **14**-0294
Tann, C.-H., **12**-0285
Tanna, C.H., **18**-0537
Tanner, D., **05**-0081, **02**-0307, **02**-0326, **13**-0187, **16**-0858, **18**-0545
Tanner, D.D., **14**-0045, **14**-0138, **14**-0158, **14**-0183, **14**-0188, **18**-0076, **19**-1346, **19**-1533
Tanner, M.E., **02**-0212
Tanoury, G.J., **19**-1207
Tantillo, D.J., **03**-0063, **15**-2081, **18**-0540, **18**-0620, **18**-0639
Tanturli, R., **15**-1693
Tanuma, M., **19**-0842
Tanyeli, C., **19**-0493, **19**-0494, **19**-0495
Tanzawa, T., **17**-0413
Tanzella, D.J., **18**-0676
Tao, B., **10**-1155, **13**-0480, **13**-0501
Tao, E.V.P., **15**-0269
Tao, F., **12**-0454, **13**-0108
Tao, W.-T., **15**-1157
Tapi, O., **10**-0232
Tapia, J., **04**-0372
Tapolczay, D., **15**-1271
Tapolczay, D.J., **15**-1316
Tapuhi, E., **02**-0383, **08**-0057, **12**-0147
Tapuhi, Y., **04**-0187
Taqian-Nasab, A., **11**-0134
Tarakanova, A.V., **18**-0614
Tarama, K., **15**-0417
Tararov, V., **16**-0344, **16**-1426
Tararov, V.I., **16**-1436, **16**-1438, **19**-1158
Tarbell, D.S., **11**-0039, **19**-0868
Tarbin, J.A., **19**-0770
Tarbit, B., **13**-0504
Tardella, P.A., **15**-1884, **15**-1889, **15**-1890
Tardif, O., **15**-0734
Tardy-Delassus, A., **11**-0464
Tarhouni, R., **12**-0621
Tarino, J.Z., **13**-0749
Tarr, A.W., **06**-0013
Tarrade, A., **15**-1902
Tarrant, P., **15**-2170
Tarratt, H.J.F., **18**-0116
Tarrian, T., **10**-0663
Tartakovskii, V.A., **19**-1185
Tartakovsky, E., **04**-0366
Tarygina, L.K., **13**-0256
Taschner, E., **10**-1174
Taschner, M.J., **15**-2058, **18**-0362, **19**-1468
Tashika, H., **10**-1817
Tashino, Y., **19**-0709
Tashiro, H., **19**-1447
Tashiro, M., **10**-0507, **11**-0595, **15**-0523
Tashtoush, H., **05**-0060, **11**-0455
Tasinazzo, M., **16**-1426
Tasler, S., **13**-0163
Tasneem, Ali, M.M., **11**-0122
Tasneem, Rajanna, K.C., **11**-0473
Tatai, J., **15**-1001
Tatamidani, H., **10**-1862, **19**-1508, **16**-1977, **16**-1978
Tatchell, A.R., **19**-1245
Tateishi, A., **14**-0268
Tateiwa, J.-i., **16**-1472
Tatemitsu, H., **02**-0304, **02**-0306
Taticchi, A., **02**-0149, **15**-1985, **15**-2003
Tatlock, J.H., **19**-0740
Tatlow, J.C., **15**-1518
Tato, J.V., **12**-0700
Tatsami, K., **15**-1504
Tatsukawa, A., **10**-0552, **10**-1595
Tatsuki, S., **18**-0685
Tatsumi, A., **11**-0140
Tatsumi, K., **12**-0278
Tatsumi, T., **15**-0224
Tatsuzawa, M., **16**-0829
Taube, H., **15**-0529
Tauh, P., **15**-1222
Taura, K., **01**-0068
Taurins, A., **16**-0427
Tautermann, C., **10**-0766
Tautou, H., **10**-0733
Tavares, P., **15**-0634
Taveras, A.G., **05**-0322
Taverner, S.J., **09**-0109
Tavernier, D., **04**-0131
Tawaka, K., **15**-2366
Tawaka, S., **16**-0608
Tawara, Y., **02**-0203
Taya, H., **16**-1689
Taya, K., **10**-0627, **10**-0636, **16**-0260
Tayal, S.R., **10**-1318
Tayama, E., **16**-1839
Tayama, O., **15**-0377, **15**-0756
Tayano, T., **16**-0696
Taylor, A., **18**-0670
Taylor, B., **16**-0057
Taylor, B.F., **04**-0372
Taylor, C.K., **14**-0118
Taylor, D., **10**-0621
Taylor, D.K., **04**-0433
Taylor, D.R., **08**-0073, **10**-0231, **15**-0106, **15**-2219, **17**-0378
Taylor, E.A., **10**-0907
Taylor, E.C., **11**-0229, **13**-0099, **13**-0100, **13**-0263, **13**-0283, **13**-0284, **13**-0660, **14**-0336, **14**-0370, **14**-0431, **16**-1412, **16**-1605, **16**-2008, **16**-2042, **18**-0231, **19**-0405, **19**-1798
Taylor, E.J., **19**-1462
Taylor, G.A., **18**-0894
Taylor, H.T., **15**-1649
Taylor, J.A., **14**-0316
Taylor, J.B., **16**-1405, **16**-1406
Taylor, J.E., **15**-1675, **15**-1677, **19**-1570
Taylor, J.M., **11**-0262
Taylor, J.W., **10**-0078
Taylor, K.F., **16**-0993
Taylor, K.G., **05**-0347
Taylor, M., **19**-1148
Taylor, M.J., **02**-0201
Taylor, M.S., **11**-0402, **15**-1003
Taylor, N.J., **15**-1124, **16**-0467
Taylor, P.C., **16**-1384
Taylor, P.G., **11**-0097, **15**-0293, **16**-1234, **16**-1237

Taylor, P.J., **03**-0015, **09**-0047
Taylor, P.N., **04**-0249
Taylor, P.W., **04**-0389
Taylor, R., **01**-0052, **01**-0070, **02**-0031, **02**-0355, **02**-0371, **03**-0017, **03**-0023, **03**-0025, **03**-0029, **03**-0045, **09**-0028, **11**-0001, **11**-0029, **11**-0045, **11**-0049, **11**-0065, **11**-0072, **11**-0073, **11**-0075, **11**-0108, **11**-0112, **11**-0203, **11**-0214, **11**-0271, **11**-0364, **11**-0449, **11**-0609, **11**-0612, **11**-0626, **11**-0631, **11**-0660, **12**-0645, **13**-0658, **17**-0122, **17**-0133, **17**-0134, **17**-0145, **17**-0191, **17**-0493, **19**-0401, **19**-1689
Taylor, R.A., **15**-0419
Taylor, R.B., **04**-0516
Taylor, R.C., **13**-0086
Taylor, R.E., **16**-0665
Taylor, R.E.R., **13**-0713
Taylor, R.J., **04**-0207
Taylor, R.J.K., **10**-0542, **15**-0886, **15**-0952, **15**-1090, **15**-1791, **16**-0264, **16**-0341, **16**-0365, **16**-1278, **16**-1292, **16**-1407, **17**-0343, **17**-0347, **18**-0815, **19**-0685
Taylor, R.L., **10**-0150
Taylor, R.T., **15**-0482
Taylor, S., **15**-1724
Taylor, S.J., **15**-2181
Taylor, S.K., **11**-0335, **14**-0372
Taylor, S.K., **16**-1852
Taylor, W.C., **15**-2158, **19**-1528, **19**-1713
Taylor, P.G., **01**-0045
Tazaki, M., **11**-0517, **16**-0239
Tazoe, M., **16**-0666
Tchoubar, B., **15**-0467, **18**-0207, **19**-1062
Teach, E.G., **15**-1595
Teasley, M.F., **15**-2162
Tebbe, F.N., **16**-1348
Teberekidis, V.I., **05**-0055
Tedder, J.M., **01**-0001, **05**-0202, **11**-0173, **11**-0174, **11**-0617, **14**-0001, **14**-0050, **14**-0062, **14**-0116, **14**-0186, **15**-0090, **15**-0100, **18**-0068
Tedesco, A., **13**-0487
Tedford, M.C., **16**-1521
Tedjo, E.M., **17**-0296
Tedrow, J.S., **15**-0604, **16**-0733, **16**-1053, **16**-1145
Tee, O., **11**-0106
Tee, O.S., **11**-0271, **11**-0272, **15**-0547
Teeter, J.S., **15**-1630
Tehrani, K.A., **16**-1354
Teimouri, F., **19**-0565
Teimouri, M.B., **19**-0808
Teissier, P., **18**-0076
Teixeira, R.R., **11**-0657
Tejedor, D., **16**-1911, **19**-0334
Tejero, T., **16**-0929
Tejero, T., **19**-1692
Tekavec, T.N., **15**-2441
Tekawa, M., **18**-0189
Teki, Y., **05**-0258, **05**-0259
Tel, L.M., **04**-0285
Teleman, O., **16**-1214
Teles, J.H., **15**-1368, **16**-0724
Telford, R.P., **19**-1102, **19**-1200, **19**-1223
Teller, R.G., **15**-0446
Telschow, J.E., **19**-0475
Temme, H., **19**-1536
Temme, O., **19**-1028
Temnikova, T.I., **14**-0097
Temperini, A., **15**-0273
Tempesta, M.S., **04**-0516
Temple Jr., D.L., **10**-1741, **10**-1744
Temple, R.D., **15**-1790
Templeton, D.H., **02**-0254
Templeton, J.L., **15**-1900
Ten Hoeve, W., **04**-0024
ten Brink, G.-J., **18**-0350, **18**-0355, **19**-0225
Tenaglia, A., **19**-0457
TenBrink, R., **10**-0481
Tencer, M., **16**-1059
Teng, L., **18**-0406
Tennant, G., **13**-0782
Tennyson, R.L., **16**-2075
Tenud, L., **10**-0015
Teo, K.E., **12**-0140
Tepe, J., **11**-0421
Tepper, M., **13**-0237
ter Borg, A.P., **18**-0549
ter Halle, R., **15**-0865, **19**-1028
ter Wiel, J., **15**-1789
Terada, M., **13**-0237, **15**-0985, **15**-2064, **16**-0901, **16**-1487
Terada, T., **19**-0139
Terai, H., **12**-0337
Teraji, T., **15**-2193
Terakawa, E., **10**-0125
Terakura, K., **18**-0316
Teranishi, A.Y., **12**-0248, **15**-1760, **16**-0999, **17**-0293, **19**-0732
Teranishi, H., **15**-1238
Teranishi, S., **10**-0712, **13**-0420, **19**-0109, **19**-0129, **19**-1718
Terao, J., **10**-1196, **10**-1294, **10**-1303, **10**-1384, **15**-0872
Terao, T., **12**-0346
Terao, Y., **13**-0452, **15**-1932, **18**-0249, **19**-1371
Teraoka, Y., **15**-1238
Terasaki, S., **19**-1212
Terashima, S., **15**-2185, **17**-0239
Teratani, S., **10**-0627, **10**-0636, **15**-0265
Terec, A., **02**-0428
Terefenko, E.A., **16**-1946
Terekhova, L.N., **15**-0849
Terenghi, G., **11**-0491
Terent'ev, A.B., **18**-0069, **18**-0080, **18**-0084
Terent'ev, A.O., **12**-0143
Terent'eva, G.A., **10**-0315
Tereschenko, G.F., **18**-0293
Ternansky, R., **15**-2439
Ternansky, R.J., **18**-0601
Ternovskoi, L.A., **15**-1544
Tero-Kubota, S., **05**-0317
Terpko, M.O., **19**-1200
Terpstra, J.W., **10**-0756, **18**-0242
Terrano, D., **19**-0529
Terranova, E., **19**-0457
Terrell, C.R., **16**-0416
Terrell, R., **10**-1674, **10**-1678, **16**-1851
Terrett, N.K., **16**-1506
Terrier, C., **15**-1476
Terrier, F., **08**-0107, **08**-0172, **10**-0366, **10**-0368, **13**-0005, **13**-0008, **13**-0009, **13**-0671
Terstegen, F., **15**-2293
Terstiege, I., **12**-0266, **12**-0266
Teschner, M., **12**-0240
Tesoro, G.C., **15**-0076
Testa, A., **13**-0406
Testa, B., **04**-0001
Testaferri, L., **10**-1306, **13**-0103, **13**-0132, **13**-0135, **14**-0326, **15**-0230, **15**-0273, **19**-0492
Tester, J.W., **15**-2036
Teston-Henry, M., **08**-0146
Tewson, T.J., **11**-0029
Texier, F., **10**-0265, **15**-1964
Texier-Boullet, F., **07**-0111, **16**-0294, **16**-0411
Tey, C., **16**-1940
Teyssié, P., **10**-0638
Tezuka, H., **04**-0459
Tezuka, T., **14**-0032, **14**-0105, **18**-0549
Tezuka, Y., **01**-0069, **19**-0787
Thacher, A.F., **18**-0551
Thadani, A., **05**-0348
Thadani, A.N., **10**-1423, **16**-0740, **16**-0741, **16**-0742

Thakkar, M., **15**-2007
Thakur, A.J., **17**-0384, **19**-0306
Thakur, V.V., **15**-1897
thakur, A.J., **18**-0313
Thakuria, J.A., **19**-1757
Thaler, W.A., **14**-0039, **14**-0125, **14**-0176, **15**-0171
Thalji, R.K., **15**-0927
Thalmann, A., **16**-1652
Tham, F.S., **09**-0111
Thamatloor, D.A., **18**-0220
Thames, S.F., **10**-0895
Than, C., **11**-0118
Thanh, B.T., **16**-1022
Thanh, G.V., **18**-0773
Thanos, J., **04**-0151
Thathagar, M.B., **13**-0481
Thavonekham, B., **10**-1345, **10**-0706
Thayumanavan, R., **15**-0994, **15**-1004, **16**-0917
Thayumanavan, S., **05**-0187
Thea, S., **16**-1571, **16**-2146
Theaker, G., **11**-0174, **11**-0617
Thebtaranonth, C., **15**-0052, **16**-0972
Thebtaranonth, Y., **15**-0052, **16**-0972, **18**-0386, **18**-0729
Thede, K., **13**-0424
Theis, M., **12**-0397
Thelan, P.J., **18**-0867
Theobald, D.W., **04**-0316, **04**-0351
Theophanides, T., **11**-0453
Therien, M.J., **12**-0508
Théron F., **12**-0065, **15**-0047, **18**-0617, **18**-0695
Thetford, D., **10**-0993, **13**-0128
Thevenin, P., **13**-0503
Thewissen, D.H.M.W., **15**-0522
Thi, H.C.G., **04**-0467
Thi, M.P.N., **10**-0385
Thiaw-Woaye, A., **16**-0595
Thibblin, A., **06**-0059, **06**-0062, **10**-0061, **10**-0080, **10**-0217, **17**-0004, **17**-0035, **17**-0036, **17**-0045, **17**-0050, **17**-0052, **17**-0056, **17**-0062, **17**-0147
Thibonnet, J., **12**-0272
Thickitt, C.P., **15**-1905
Thiebaud, S., **10**-0587
Thiébault, A., **13**-0054, **13**-0058, **13**-0089, **13**-0127, **13**-0343
Thiebes, C., **13**-0265
Thiede, R.J., **16**-0106
Thiel, O.R., **15**-0314
Thiel, W., **02**-0015, **02**-0018
Thiele, G.F., **02**-0320
Thielecke, W., **10**-1605, **15**-1927
Thieme, P.C., **16**-1255
Thier, W., **15**-0482
Thiéry, V., **11**-0382
Thies, I., **12**-0655
Thies, O., **16**-0967
Thies, R.W., **04**-0481, **18**-0583
Thieser, R., **10**-0458
Thijs, L., **06**-0032
Thijs, L., **16**-0687
Thilmont, N., **10**-1820
Thinggaard, J., **16**-1873
Thirase, G., **05**-0153
Thirot, G., **08**-0160
Thirsk, C., **12**-0456
Thiruvazhi, M., **18**-0576
Thiruvengadam, T.K., **12**-0285
Thobe, J., **16**-1264
Thoer, A., **11**-0481
Thomas IV, B.E., **15**-0963, **15**-0970, **15**-0971
Thomas, A., **13**-0200, **15**-1694
Thomas, A.A., **07**-0122, **15**-2088
Thomas, A.F., **18**-0676
Thomas, A.P., **10**-1431
Thomas, A.W., **19**-0264
Thomas, B., **07**-0054
Thomas, B.R., **19**-1439
Thomas, C., **19**-0120
Thomas, C.B., **13**-0462, **15**-1921, **18**-0078, **19**-0724, **19**-1797
Thomas, C.R., **15**-1518
Thomas, C.W., **10**-0519, **16**-1057
Thomas, D.W., **10**-1086, **16**-1883
Thomas, E., **13**-0325
Thomas, F., **09**-0010
Thomas, G., **19**-1097
Thomas, J.A., **11**-0572, **11**-0575
Thomas, J.M., **10**-0916, **15**-0268
Thomas, J.M., **19**-1028
Thomas, K.G., **07**-0063
Thomas, L., **13**-0503
Thomas, M.J., **15**-0515
Thomas, P.J., **10**-0322, **10**-1551, **17**-0049, **17**-0052, **17**-0102
Thomas, P.N., **11**-0094
Thomas, R., **02**-0212, **16**-1306
Thomas, R.C., **06**-0015
Thomas, R.D., **05**-0150, **05**-0151, **05**-0196, **08**-0202
Thomas, R.J., **16**-0021, **16**-0022, **16**-1596
Thomas, R.M., **10**-1139, **19**-1384
Thomas, S., **10**-0893, **13**-0172, **15**-1532, **19**-1172
Thomas, S.D., **15**-1721
Thomas, S.J., **10**-0637
Thomas, T.D., **02**-0056, **08**-0171, **08**-0234, **15**-0096
Thomas, W.A., **04**-0345
Thomassin, R., **11**-0451, **16**-2052
Thomazeau, C., **08**-0113
Thomm, E.W.C.W., **12**-0726
Thommen, W., **14**-0237
Thompson, A., **19**-0120
Thompson, A.L.S., **13**-0714
Thompson, A.S., **18**-0302
Thompson, C.M., **05**-0099, **10**-0482
Thompson, D.F., **13**-0411
Thompson, D.H.P., **10**-1254
Thompson, D.J., **10**-1832, **12**-0074, **15**-0401
Thompson, H.W., **15**-1168
Thompson, J., **12**-0406, **17**-0415
Thompson, J.A., **10**-0161, **19**-0361
Thompson, J.A., **19**-0377
Thompson, J.E., **19**-1761
Thompson, J.T., **10**-0060, **10**-0395
Thompson, K.L., **15**-0260
Thompson, L.A., **16**-1823
Thompson, L.H., **07**-0085
Thompson, M., **01**-0013
Thompson, M.M., **19**-0015
Thompson, N., **15**-1730
Thompson, Q.E., **19**-0347
Thompson, S.R., **15**-1882
Thomsen, I., **10**-0949, **16**-0212, **16**-0220
Thomsen, I.B., **16**-1873
Thomson, P., **18**-0670
Thomson, R.H., **05**-0226, **11**-0444, **19**-0258, **19**-0633
Thomson, S.J., **15**-0457
Thonchant, S., **15**-1910
Thondorf, I., **03**-0124, **03**-0130
Thongsornkleeb, C., **18**-0406
Thorarensen, A., **10**-1300
Thorburn, S., **11**-0073
Thorez, A., **15**-1381
Thorhauge, J., **15**-1097
Thorn, D.L., **15**-0816
Thorn, M.G., **15**-0973
Thorne, M.P., **17**-0133
Thornton, D.E., **18**-0224
Thornton, E.R., **06**-0074, **06**-0088, **15**-2061, **16**-1010, **16**-1015, **16**-1023, **16**-1032, **19**-0483
Thornton, S.D., **16**-0836

Thorpe, D.H., **11**-0593
Thorpe, F.G., **13**-0095
Thorsen, M., **16**-1807
Thorsen, P.T., **19**-1487
Thottumkara, A.P., **19**-0201
Thozet, A., **16**-2132
Threadgill, M.D., **19**-1566
Thudium, F., **09**-0015
Thuéry, P., **03**-0139
Thuillier, A., **16**-1398
Thulin, B., **02**-0307
Thummel, R.P., **12**-0087
Thurkauf, A., **16**-0148
Thurmaier, R.J., **15**-0014
Thurner, A., **17**-0209
Thweatt, J.G., **12**-0116, **15**-2189
Thyagarajan, B.S., **14**-0335, **18**-0654
Thyagarajan, G., **16**-1309, **18**-0295
Tian, F., **05**-0306
Tian, H., **15**-1773, **15**-1774, **19**-0573
Tian, H.-Y., **16**-1092
Tian, Q., **15**-2363
Tian, Q.-S., **19**-1675
Tian, S., **15**-0335, **15**-1872
Tian, S.-K., **16**-1443, **16**-1626
Tian, W.Q., **19**-1273
Tian, X., **15**-0278
Tian, Y., **13**-0242, **15**-1885
Tichenor, G.J.W., **15**-0047
Tichy, M., **03**-0037, **03**-0038, **10**-0208
Tidwell, T.T., **02**-0238, **04**-0421, **04**-0499, **04**-0511, **05**-0055, **05**-0066, **09**-0007, **10**-0083, **10**-0209, **10**-0294, **15**-0024, **15**-0027, **15**-0079, **15**-0117, **15**-0182, **15**-0205, **15**-0222, **15**-0265, **15**-0368, **16**-0514, **16**-1059, **16**-1572, **16**-2112, **17**-0035, **17**-0317, **19**-0161, **19**-0638
Tiecco, M., **10**-0798, **10**-1114, **10**-1306, **13**-0103, **13**-0132, **13**-0135, **14**-0109, **14**-0326, **15**-0230, **15**-0273, **19**-0492
Tiekink, E.R., **12**-0614
Tiekink, E.R.T., **15**-1939
Tierney, J., **07**-0116
Tierney, J.P., **07**-0106, **07**-0117
Tietz, H., **12**-0742
Tietze, L.F., **13**-0424, **16**-0234
Tijani, J., **15**-1403
Tijerina, T., **16**-1348
Tikwe, L., **04**-0517
Tillack, A., **13**-0162, **14**-0280, **15**-0314, **15**-0320, **15**-0331, **15**-0343, **15**-0348, **15**-0351
Tille, A., **15**-0265
Tillement, O., **19**-1312
Tillett J.G., **16**-1559
Tilley, T.D., **15**-0729, **16**-0947
Tillyer, R.D., **15**-0615, **15**-1038, **18**-0719
Tilstam, U., **19**-0067
Timberlake, J.W., **05**-0216
Timko, J.M., **04**-0164
Timm, D., **19**-0056
Timmer, K., **15**-0522
Timmerman, P., **03**-0172
Timmers, D.A., **15**-2297
Timmins, G., **05**-0126, **06**-0086, **10**-0179, **12**-0054
Timmons, C., **15**-1896, **16**-0980
Timmons, C.J., **18**-0512
Timmons, D.J., **15**-2355
Timmons, R.J., **15**-0487
Timms, A.W., **14**-0351, **14**-0352
Timms, P.L., **12**-0596
Timokhin, V., **15**-1219
Timokhin, V.I., **14**-0081, **17**-0138
Timokhina, L.V., **16**-0208
Timony, P.E., **13**-0253
Tin, K., **12**-0183
Tinant, B., **16**-1224
Tindall, C., **15**-0275
Ting, J., **10**-0803, **10**-1342
Tingoli, M., **10**-1306, **10**-1532, **11**-0285, **13**-0103, **13**-0132, **13**-0135, **15**-1569, **19**-0492
Tinnemans, A.H.A., **15**-2235
Tinsley, A.S., **13**-0403
Tinucci, L., **11**-0508
Tipper, C.F.H., **05**-0359, **06**-0008, **06**-0046, **06**-0049, **06**-0052, **06**-0053, **06**-0054, **07**-0044, **08**-0096, **08**-0102, **08**-0135, **10**-0213, **11**-0001, **11**-0108, **11**-0203, **11**-0214, **11**-0271, **11**-0543, **11**-0609, **11**-0612, **11**-0626, **11**-0631, **11**-0660, **12**-0002, **12**-0024, **12**-0038, **12**-0057, **12**-0424, **12**-0504, **12**-0551, **12**-0638, **13**-0003, **13**-0658, **14**-0062, **14**-0214, **15**-0001, **15**-0050, **15**-0451, **15**-1932, **15**-1980, **15**-2166, **16**-0014, **16**-1510, **16**-1516, **16**-1549, **16**-1560, **16**-1588, **17**-0003, **17**-0007, **17**-0037, **17**-0039, **17**-0057, **17**-0122, **17**-0176, **18**-0471, **18**-0526, **18**-0569, **18**-0594, **18**-0739, **19**-0002, **19**-0701
Tipping, A.E., **18**-0852
Tippmann, E.M., **05**-0375
Tipsword, G.E., **10**-1365
Tipton, A.K., **15**-1666
Tipton, T.J., **05**-0279
Tiria, C., **16**-1735, **16**-0396
Tirouflet, J., **19**-1099
Tirpak, R.E., **16**-1249, **16**-2013
Tishbee, A., **04**-0170, **04**-0175
Tissandié, S., **19**-1243
Tissot-Croset, K., **10**-1295, **10**-1295
Tissue, G.T., **18**-0281
Titov, A.I., **12**-0205
Titov, E.V., **09**-0048
Titov, M.I., **16**-1215
Titov, Yu.A., **15**-0533, **18**-0194
Titova, S.P., **11**-0582
Tius, M.A., **16**-0474
Tiwari, H.P., **10**-0049, **19**-0080, **19**-0249
Tjen, K.C.M.F., **15**-0395
Tkachuk, R., **02**-0142
Tkatchenko, I., **15**-2431
Tkatchouk, E., **14**-0322
To, D.C.M., **15**-1811
Toader, D., **17**-0257
Tobe, M.L., **10**-0090, **10**-0092, **13**-0052
Tobe, Y., **02**-0062, **02**-0064
Tobey, S.W., **02**-0204, **16**-0022
Tobias, M.A., **15**-0134
Tobiason, F.L., **01**-0078
Tobisu, M., **15**-2443
Tobito, Y., **19**-0732
Tobler, H.J., **02**-0183
Toblert, T.L., **16**-0955
Tocher, D.A., **04**-0348, **04**-0516
Tochtermann, W., **02**-0064, **04**-0387
Toczko, A.G., **17**-0056
Toda, A., **15**-0394
Toda, F., **01**-0067, **01**-0068, **01**-0069, **03**-0163, **03**-0166, **04**-0163, **04**-0164, **04**-0166, **09**-0120, **09**-0122, **10**-0641, **16**-1070, **16**-1380, **16**-2021, **16**-2023, **18**-0131, **19**-0915, **19**-0981, **19**-1756
Toda, M., **19**-1434
Toda, N., **15**-0945
Toda, T., **15**-2322, **18**-0469, **18**-0470
Todaro, L.J., **04**-0348
Todd, D., **19**-1429
Todd, G.P., **17**-0145
Todd, H.E., **14**-0095
Todd, M.J., **10**-0049
Todda, F., **05**-0277
Todeschini, R., **02**-0319
Todesco, P.E., **13**-0078, **16**-0272, **19**-0832
Todo, H., **10**-1384

Todres, Z.V., **02**-0254, **05**-0313, **06**-0034
Toekelt, W.G., **15**-0725
Togni, A., **15**-1320, **16**-0684, **16**-1190
Togo, H., **10**-0710, **11**-0285, **14**-0174, **14**-0345, **19**-0193, **19**-0497, **19**-0526, **19**-0709, **19**-1597, **19**-1598, **19**-1602, **19**-1629
Toh, H.T., **14**-0133, **14**-0134
Tohda, Y., **13**-0536, **15**-1939
Tohjo, T., **19**-1781
Tohyama, Y., **15**-0989
Toi, H., **19**-0896, **19**-1330
Töke, L., **15**-1042, **15**-1001, **16**-1212, **16**-1808, **17**-0209, **17**-0488
Token, K., **10**-0170
Toker, J.D., **15**-1955
Tökes, L., **10**-1429
Toki, T., **10**-1561
Tokitoh, N., **15**-0624, **15**-0625, **15**-0627
Tokiyama, H., **12**-0144
Tokles, M., **04**-0202, **15**-1697
Tokuda, M., **10**-0874, **10**-1258, **10**-1863, **13**-0436, **14**-0439, **15**-0321, **15**-1387, **17**-0383
Tokuda, Y., **11**-0542
Tokue, R., **16**-0436
Tokumaru, K., **07**-0022, **14**-0105, **16**-1225, **10**-0830, **13**-0630
Tokunaga, M., **04**-0193, **15**-0212, **19**-0823
Tokunaga, N., **12**-0078, **15**-1140, **15**-1154
Tokunaga, Y., **19**-0667
Tokuno, E., **19**-0848
Tokura, N., **05**-0231, **10**-1833, **14**-0117, **16**-2147, **17**-0320, **18**-0754, **19**-1343
Tokutake, N., **18**-0194
Tokuyama, H., **13**-0202, **16**-1990, **18**-0678
Tolbert, L.M., **11**-0629, **15**-1994, **15**-2096
Toldy, L., **04**-0225
Tolgyesi, W.S., **05**-0015, **11**-0029, **11**-0404, **11**-0636
Tolkachev, O.N., **19**-1801
Tollabi, M., **10**-1453
Tollenaere, J.P., **09**-0047
Tolman, C.A., **15**-0464, **15**-1504, **15**-1504
Tolomelli, A., **15**-1317
Tolson, T.J., **10**-1505
Tolstaya, T.P., **10**-1782
Tolstikov, G.A., **10**-1438, **14**-0383, **15**-0704, **15**-0706, **15**-2195, **15**-2429, **19**-0345
Tolstikova, L.L., **15**-0308
tom Dieck, H., **04**-0175, **15**-2402
Tom, N.J., **13**-0177, **16**-1581
Toma, L., **18**-0708
Toma, M., **07**-0095
Toma, S., **07**-0093, **11**-0230, **15**-1017, **19**-0567
Toma, Š., **07**-0092, **16**-0331, **13**-0169
Tomalia, D.A., **05**-0052
Tomari, M., **17**-0490
Tomaru, J.-i., **11**-0140
Tomás, J., **18**-0186
Tomás, M., **15**-2415
Tomaselli, G.A., **16**-2143
Tomasik, P., **09**-0038
Tomasik, W., **12**-0706, **19**-0480
Tomasini, C., **15**-1099
Tomaszewski, J.E., **16**-0540
Tomatsu, A., **19**-0637
Tombo, G.M.R., **16**-0147
Tomezsko, E.S., **19**-0462
Tomi, K., **19**-1119
Tomilov, A.P., **19**-0010
Tomilov, Y.V., **15**-2315
Tomimoto, K., **11**-0267
Tomimura, T., **05**-0259
Tominack, B.J., **07**-0119, **13**-0541, **13**-0546
Tominaga, Y., **16**-1953
Tomino, I., **19**-1053
Tomioka, A., **04**-0301
Tomioka, H., **05**-0336, **05**-0337, **05**-0371, **05**-0380, **18**-0228, **19**-0131, **19**-0133
Tomioka, K., **02**-0199, **04**-0149, **12**-0691, **15**-1042, **15**-1092, **15**-1093, **15**-1095, **15**-1125, **15**-1297, **15**-1333, **15**-1693, **15**-1773, **15**-2063, **16**-0418, **16**-0858, **16**-0894, **16**-0908, **16**-1314, **16**-1760
Tomioka, T., **11**-0651, **11**-0651
Tomita, K., **13**-0782
Tomita, M., **18**-0295
Tomita, N., **16**-0931
Tomita, S., **19**-0169
Tomita, Y., **10**-1820
Tomizawa, G., **12**-0190
Tomkins, R.P.T., **02**-0204
Tomlinson, I.A., **15**-2141
Tommasino, M.L., **18**-0145
Tomo, Y., **16**-1195
Tomoda, S., **04**-0229, **11**-0038, **16**-0491
Tomoika, H., **18**-0222
Tomooka, K., **15**-0889, **18**-0013
Tomori, H., **13**-0183
Tonachini, G., **05**-0120
Tonellato, U., **05**-0068, **10**-0248, **13**-0027, **14**-0027, **15**-0035, **15**-0079, **15**-0082, **15**-0087, **15**-0106
Toneva, R., **19**-0954
Tong, K.-H., **15**-1762
Tong, P.-E., **15**-1133
Tong, W., **16**-1172
Tong, X., **15**-0845
Tongco, E.C., **16**-2053
Tongpenyai, N., **10**-0900
Toniolo, L., **11**-0478
Tonks, L., **13**-0411, **13**-0412
Tonogaki, K., **18**-0789
Tonsbeeck, C.H.T., **11**-0613
Toops, D., **18**-0601
Top, S., **16**-2058
Topley, B., **10**-0014
Topolski, M., **05**-0356, **12**-0426, **12**-0610
Toppet, S., **15**-2213
Topping, C.M., **15**-1084
Topsom, R.D., **01**-0042, **01**-0052, **08**-0161, **08**-0235, **09**-0002, **09**-0039, **09**-0049, **09**-0051, **09**-0052, **09**-0055, **09**-0064
Tor, Y., **10**-1024
Torchy, S., **16**-0366, **16**-0368, **19**-0965
Torck, B., **15**-0024
Tordeux, M., **16**-0453
Tordo, P., **05**-0214
Toreki, R., **18**-0762
Torenius, H.M., **09**-0117, **13**-0271
Torgov, I.B., **15**-0849
Tori, M., **19**-0461
Tori-i, A., **10**-0507
Torigoe, M., **14**-0400, **19**-1579
Torii, S., **10**-1805, **14**-0190, **14**-0359, **15**-1665, **16**-0161, **16**-0645, **16**-2118, **19**-0401, **19**-0745
Torii, T., **15**-0998
Torisawa, Y., **11**-0522
Toriumi, Y., **04**-0301
Toriyama, F., **12**-0287
Tormo, J., **16**-1502
Toro-Labbé, A., **10**-0031, **10**-0032
Toroioli, S., **10**-0672
Török, B., **19**-1460
Toromanoff, E., **04**-0138, **16**-0005, **16**-0011
Torossian, G., **10**-1620
Torraca, K.E., **13**-0123, **13**-0124

Torre, G., **04**-0038, **16**-2122
Torregiani, E., **10**-1064, **15**-1018, **15**-1289, **17**-0160
Torrell, E., **13**-0471
Torres, E.C., **17**-0155
Torres, G., **15**-1741
Torres, L.E., **06**-0016
Torres, M., **15**-1785, **18**-0222
Torres, T., **10**-0729
Torres, W., **15**-1741
Torssell, K., **19**-0439, **19**-0647, **19**-0648, **19**-0649
Torssell, K.B.G., **10**-0768, **15**-1932, **19**-1556
Tortajada, A., **19**-0840
Tortioli, S., **10**-0672
Tortorelli, V.J., **15**-2316
Toru, T., **16**-1455, **19**-0999
Torupka, E.J., **10**-1236
Tosaka, E., **18**-0244
Tosaki, S.-y., **15**-1741
Toscano, J.P., **05**-0369
Toscano, R.A., **04**-0361
Toscano, V.G., **18**-0630
Toshida, N., **15**-1448
Toshikawa, S., **15**-2276, **19**-0044
Toshima, K., **15**-0749
Toshimitsu, A., **04**-0459, **10**-1565, **11**-0134, **13**-0661, **19**-0471
Tosi, G., **15**-2350
Toste, F.D., **10**-1448, **15**-0814, **15**-0815, **15**-0825, **15**-0978, **15**-1321, **15**-1446, **15**-2435
Tosun, A., **19**-0494
Toteva, M.M., **05**-0096
Toteva, M.M., **10**-0058
Toth, A., **17**-0053
Toth, B.R., **10**-0179
Toth, I., **15**-0598
Tóth, G., **19**-0440
Tóth, J., **19**-1215
Toto, S.D., **10**-1089
Totten, G.E., **19**-0847
Tottie, L., **10**-0663
Touchard, F.P., **16**-1333
Touillaux, R., **16**-1239
Toullec, J., **02**-0379, **02**-0383, **02**-0384, **02**-0405, **04**-0096, **08**-0009, **10**-0531, **12**-0084, **12**-0095, **12**-0099, **15**-0016, **15**-0251
Toupet, L., **02**-0428
Tour, J.M., **11**-0293, **15**-0470, **16**-0500, **19**-0753
Toussaint, O., **19**-0436
Towne, T.B., **15**-0231
Townes, J.A., **15**-2181
Townley, E.R., **18**-0872
Towns, D.L., **05**-0138
Townsend, J.M., **16**-1387, **18**-0032
Townsend, R.-J., **15**-2432
Townsend, R.J., **15**-2303
Townson, M., **14**-0053
Toy, P.H., **05**-0308, **14**-0068, **14**-0076, **19**-0178
Toyao, A., **15**-1237
Toyoda, M., **19**-0723
Toyoda, T., **11**-0390, **11**-0524, **11**-0525, **16**-1057
Toyokuni, T., **19**-1217
Toyosaki, T., **12**-0755
Toyoshima, T., **10**-1306
Toyota, K., **13**-0177
Toyota, M., **15**-0769
Toyota, S., **04**-0273, **16**-1070, **16**-2021, **19**-1756
Tozer, M.J., **15**-2071
Traas, P.C., **17**-0275
Trabanco, A.A., **10**-0856
Trabocchi, A., **10**-1414, **12**-0283
Tracey, M.R., **10**-0997
Trachtenberg, E.N., **19**-0468, **19**-0470, **19**-0553
Trachtman, M., **02**-0028
Tracz, S., **15**-1534
Trætteberg, M., **02**-0050, **02**-0051
Trahanovsky, W.S., **10**-0134, **12**-0116, **12**-0203, **12**-0671, **14**-0209, **14**-0301, **14**-0319, **14**-0371, **15**-0186, **15**-1726, **17**-0290, **18**-0352, **18**-0733, **19**-0002, **19**-0010, **19**-0073, **19**-0103, **19**-0311, **19**-0329, **19**-0391, **19**-0426, **19**-0436, **19**-0590, **19**-0622, **19**-0698, **19**-0827
Trainor, R., **15**-1685
Trainor, R.W., **07**-0116, **07**-0105
Tramontano, A., **19**-1053
Tramontini, M., **04**-0136, **10**-0264, **10**-0388, **16**-0392, **16**-0392, **19**-0951
Tramper, H.S., **19**-1345
Tran, H.Q., **05**-0326
Tran, M.B., **10**-1433
Tran, V., **15**-1958
Tran-Dube, M.B., **15**-1368, **16**-0724
Tranter, G.E., **04**-0005
Trappel', L.N., **10**-1583
Trattner, R.B., **16**-0015
Trauner, D., **15**-0850, **18**-0688
Trauthwein, H., **15**-0314, **15**-0343, **15**-0348
Trautwein, H., **18**-0074
Traverse, J.F., **16**-0865
Travis, B.R., **15**-1673, **19**-0341, **19**-0396, **19**-0676
Traylor, T.G., **12**-0008, **12**-0009, **12**-0040, **15**-0114, **15**-0117, **19**-1571, **19**-1573
Traynelis, V.J., **13**-0665, **19**-0661
Traynham, J.G., **05**-0004, **11**-0053, **14**-0039, **14**-0041, **14**-0043, **14**-0109, **18**-0085
Traynor, L., **11**-0607
Treager, J.C., **02**-0237
Trebalón, L., **17**-0485
Trecker, D.J., **11**-0560, **15**-1726, **15**-1742, **15**-2151, **15**-2209, **15**-2235, **18**-0628, **19**-0011, **19**-0047, **19**-0070, **19**-0345, **19**-0553, **19**-0588, **19**-0638
Trécourt, F., **13**-0312, **13**-0319
Treffers, H.P., **16**-1558
Trehan, S., **15**-0792, **16**-1426
Tremaine, P.H., **16**-0119
Tremblay, J.P., **14**-0045
Tremblay, M.-C., **16**-0471
Tremble, J., **10**-1429
Tremelling, M.J., **13**-0597
Trémillon, B., **12**-0341
Tremmel, J., **05**-0227
Trépanier, V.E., **11**-0332
Treptow, B., **04**-0427, **15**-0910
Trevillyan, E.A., **12**-0410, **12**-0411
Trevisan, R., **13**-0681
Trewhella, M.A., **15**-0624, **19**-1021, **19**-1022
Triantafyllou, A.S., **11**-0433
Tribedi, U., **15**-1534
Trifan, D.S., **18**-0103
Trifilieff, E., **12**-0454
Trifonova, A., **19**-1155
Trimble, L.A., **12**-0230
Trimitsis, G.B., **10**-0481
Trinajstic, N., **02**-0115
Trinajstić, N., **02**-0106, **02**-0414
Trincado, M., **15**-0357
Trindle, C., **15**-2105
Tripathy, P.B., **10**-1417
Tripathy, R., **15**-2061
Tripathy, S., **13**-0161
Tripoli, R., **11**-0363, **12**-0320, **19**-0206
Tripolone, M., **16**-2143
Tripoulas, N.A., **10**-0995
Tristram, E.W., **16**-0310
Tritle, G.L., **10**-0170
Trivedi, G.K., **15**-1936
Trivedi, N.J., **16**-1768

Trofimenko, S., **12**-0366, **15**-2293, **15**-2299, **19**-0548
Trofimov, B.A., **04**-0295, **10**-0661, **10**-0775, **10**-1517, **15**-0250
Trofimov, M.I., **01**-0029
Trogolo, C., **14**-0071, **15**-0899, **15**-1258, **15**-1855, **15**-1922, **15**-1924
Troisi, L., **15**-1768, **15**-2164
Troitskii, N.A., **12**-0143
Trombetti, A., **15**-0488
Trombini, C., **12**-0693, **16**-0601
Tromelin, A., **11**-0550
Trometer, J.D., **10**-1557, **17**-0052
Tromp, J., **11**-0615
Tronche, C., **05**-0307, **14**-0123
Tröndlin, F., **13**-0033, **19**-1562
Troost, J.J., **17**-0474
Tropitzsch, R., **17**-0353
Trost, B.M., **02**-0045, **02**-0046, **02**-0047, **02**-0089, **02**-0329, **04**-0206, **04**-0407, **05**-0143, **06**-0016, **10**-0802, **10**-0907, **10**-1441, **10**-1446, **10**-1447, **10**-1448, **10**-1450, **10**-1471, **10**-1478, **10**-1485, **10**-1492, **10**-1588, **10**-1628, **10**-1632, **10**-1648, **10**-1856, **12**-0077, **12**-0081, **12**-0240, **12**-0240, **12**-0253, **12**-0513, **13**-0418, **13**-0536, **13**-0667, **14**-0254, **15**-0366, **15**-0396, **15**-0477, **15**-0741, **15**-0755, **15**-0800, **15**-0807, **15**-0814, **15**-0815, **15**-0816, **15**-0836, **15**-0905, **15**-0910, **15**-1152, **15**-1446, **15**-1850, **15**-1914, **15**-1915, **15**-1969, **15**-1971, **15**-1972, **15**-2044, **15**-2435, **16**-0168, **16**-0179, **16**-0416, **16**-0569, **16**-0903, **16**-0975, **16**-1042, **16**-1044, **16**-1054, **16**-1162, **16**-1189, **16**-1376, **16**-1378, **16**-1402, **16**-1406, **16**-1652, **16**-1697, **17**-0233, **17**-0294, **17**-0294, **18**-0112, **18**-0235, **18**-0727, **18**-0831, **19**-0023, **19**-0027, **19**-0053, **19**-0130, **19**-0444
Trost, M.K., **18**-0831
Trotman, S., **19**-0334
Trotman-Dickenson, A.F., **08**-0219, **14**-0110, **14**-0112
Trotter, J., **01**-0075, **03**-0172, **04**-0142, **04**-0390, **04**-0450, **05**-0285
Troung, A., **19**-0535
Troupel, M., **10**-1811, **10**-1818, **13**-0142
Troutman, M.V., **15**-0425
Troyansky, E.I., **04**-0360, **14**-0162, **19**-0606
Trozzolo, A.M., **05**-0328, **05**-0345, **14**-0034
Trshiska, Ya, **18**-0325
Truax, D.R., **04**-0261, **04**-0350
Truce, W.E., **10**-0238, **10**-0261, **10**-1713, **10**-1748, **11**-0476, **12**-0208, **13**-0773, **13**-0775, **13**-0779, **13**-0783, **15**-0044, **15**-0045, **15**-0047, **15**-0047, **15**-0048, **15**-0049, **15**-1089, **15**-1598, **15**-1600, **16**-0230, **16**-1403, **16**-2147, **17**-0320, **18**-0381
Trudell, M.L., **13**-0179, **18**-0242, **19**-0107, **19**-1630
Trueblood, K.N., **02**-0271
Truesdale, L.K., **12**-0223, **16**-0240
Truhlar, D.G., **06**-0006, **06**-0022
Trullinger, T.K., **19**-1423
Trumbull, E.R., **17**-0243, **17**-0250, **17**-0258
Trumper, P.K., **15**-1092
Truong, A., **16**-2091
Truong, P.N., **01**-0010
Trupp, B., **04**-0438
Truscheit, E., **17**-0303
Trusty, S., **10**-0534
Trzoss, M., **04**-0137, **18**-0807
Trzupek, L.S., **12**-0535
Ts, C.e., **04**-0410
Tsadjout, A., **12**-0723
Tsai, C., **12**-0498
Tsai, C.-C., **16**-1359, **16**-1360
Tsai, F.Y., **15**-2424
Tsai, J.H., **03**-0083
Tsai, M., **04**-0021, **19**-0015
Tsai, Y., **10**-1232
Tsai, Y.-C., **10**-0881
Tsai, Y.-M., **15**-1218, **15**-1247, **15**-1270
Tsanaktsidis, J., **10**-0045, **12**-0655, **14**-0434, **15**-1279
Tsang, G.T.Y., **10**-0290
Tsang, R., **16**-0009
Tsang, S.C., **19**-0192
Tsang, W., **05**-0265
Tsangaris, M.N., **15**-1570
Tsao, K.-L., **10**-0272
Tsao, M.-L., **05**-0407, **10**-0275, **10**-0440
Tsarev, D.A., **13**-0514
Tsaroom, S., **10**-1017
Tschaen, D., **10**-1128
Tschaen, D.M., **15**-1038, **19**-0673, **19**-0678
Tschamber, T., **18**-0480
Tscheschlok, K., **15**-1927
Tschuikow-Roux, E., **05**-0339
Tschumper, G.S., **01**-0025
Tse, A., **08**-0223
Tse, C., **15**-0128, **18**-0161, **18**-0569, **18**-0580, **18**-0614
Tse, C.-L., **19**-1404
Tse, M.K., **15**-1764
Tsel'eva, M.A., **15**-0867
Tselinskii, I.V., **10**-1035, **12**-0711, **19**-0786
Tseng, C.C., **04**-0147, **10**-1509, **10**-1656
Tseng, C.K., **15**-1595
Tseng, L.T., **16**-0006
Tseng, S.-L., **16**-0687
Tseng, W.-H., **15**-1246
Tsibouklis, J., **10**-0999
Tsipouras, A., **04**-0207
Tsir, Ya., **16**-1943
Tso, H., **15**-2087
Tsogoeva, S.B., **15**-1033
Tsou, T.T., **13**-0462
Tsoucaris, G., **04**-0164, **04**-0165
Tsubaki, K., **03**-0130, **10**-1463, **17**-0435, **19**-1563
Tsuboi, S., **10**-1548, **19**-1021
Tsubouchi, A., **13**-0448, **16**-1361
Tsubouchi, H., **16**-1771
Tsuboya, N., **15**-2401
Tsuchida, M., **12**-0714, **19**-0156, **19**-0688
Tsuchida, Y., **14**-0096, **19**-1618
Tsuchihashi, G., **10**-1697, **10**-1698, **12**-0181, **12**-0182, **12**-0186, **18**-0013, **18**-0158, **19**-1606
Tsuchimoto, T., **11**-0329, **12**-0284, **15**-0210, **15**-0912, **18**-0245
Tsuchiya, K., **10**-1196
Tsuchiya, S., **01**-0083
Tsuchiya, T., **11**-0423, **12**-0658, **14**-0435, **16**-1914, **16**-2116
Tsuchiya, Y., **10**-0950, **15**-0730, **15**-0993, **16**-1422, **16**-1426
Tsuda, T., **14**-0442, **15**-0849
Tsuge, H., **15**-1791, **15**-1807
Tsuge, O., **10**-1034, **15**-1932
Tsuge, S., **19**-1108
Tsugeno, A., **10**-0299, **10**-0439
Tsugoshi, T., **11**-0521
Tsui, S.K., **17**-0065
Tsuji, H., **16**-0606
Tsuji, J., **04**-0167, **10**-1445, **10**-1447, **10**-1630, **10**-1653,

10-1849, **12**-0537, **13**-0362, **14**-0259, **14**-0443, **14**-0444, **14**-0450, **14**-0456, **15**-0792, **15**-1381, **15**-1641, **15**-1665, **16**-0645, **16**-1004, **17**-0327, **17**-0327, **19**-0060, **19**-0414, **19**-0415, **19**-0718, **19**-0729, **19**-0899, **19**-1307
Tsuji, K., **10**-0063, **16**-1771
Tsuji, S., **10**-1627, **16**-0237
Tsuji, T., **04**-0422, **10**-0146, **10**-0161, **10**-0992, **10**-1233, **12**-0159, **15**-2261, **19**-0644, **19**-1573
Tsuji, Y., **10**-0440, **10**-0441, **10**-0442, **10**-0900, **10**-0902, **10**-0916, **10**-1206, **10**-1797, **10**-1822, **19**-1247
Tsujigami, T., **19**-1022
Tsujimoto, M., **14**-0201
Tsukada, N., **10**-1544, **12**-0300, **15**-2379
Tsukagoshi, T., **15**-0780
Tsukahara, J., **09**-0012
Tsukamoto, H., **13**-0348
Tsukamoto, M., **15**-0596
Tsukayama, M., **07**-0056
Tsukazaki, M., **19**-0122, **19**-0123
Tsukinoki, T., **15**-0523
Tsukube, H., **16**-1521
Tsukuda, M., **12**-0619
Tsukada, N., **15**-0929
Tsukuda, T., **13**-0481
Tsukurimichi, E., **17**-0289
Tsumaki, H., **10**-0785, **16**-1754
Tsumiyama, T., **19**-0288
Tsumura, S., **19**-0521
Tsunawaki, S., **13**-0707
Tsuneishi, H., **15**-0158
Tsuno, Y., **05**-0314, **09**-0061, **10**-0063, **10**-0154, **10**-0163, **10**-0169, **10**-0170, **10**-0273, **10**-0274, **10**-0311, **10**-0403, **10**-0440, **10**-0441, **10**-0442, **11**-0172, **18**-0270
Tsunoda, K., **11**-0487
Tsunoda, T., **10**-0704, **10**-1704, **16**-0161, **16**-1274, **18**-0685
Tsunoi, S., **10**-1827, **10**-1829, **15**-1262, **19**-0607
Tsuritani, T., **19**-1666
Tsurugi, J., **19**-1468, **19**-1492
Tsurugi, K., **10**-1446
Tsuruoka, Y., **19**-1212
Tsuruta, H., **18**-0640
Tsuruta, T., **14**-0006
Tsushima, K., **10**-1347
Tsushima, S., **12**-0224
Tsushima, T., **12**-0159
Tsutsui, H., **10**-0965
Tsutsui, M., **12**-0001
Tsutsui, Y., **15**-2135
Tsutsumi, K., **15**-1448
Tsutsumi, S., **12**-0535, **12**-0735, **13**-0617, **15**-1343, **15**-1642, **19**-0747
Tsutsumi, T., **19**-1038
Tsuzuki, H., **15**-0523
Tsuzuki, S., **03**-0072
Tsuzuki, T., **03**-0072
Tsvelikhovsky, D., **16**-0891
Tsvetkov, E.N., **03**-0143
Tsyganov, D., **15**-0961
Tu, C.-H., **15**-1100
Tu, S.-J., **16**-0054, **19**-1090
Tu, Y.-Q., **13**-0162, **16**-0298, **19**-0082, **19**-1673
Tu, Y.Q., **18**-0134, **18**-0154, **18**-0157, **19**-1042, **19**-1043, **19**-1384
Tuaillon, J., **15**-1611
Tubergen, M.W., **15**-0167
Tuccarbasu, S., **14**-0427
Tuchiya, Y., **15**-2300
Tucker, B., **10**-1089, **16**-2071
Tucker, C.E., **09**-0112, **10**-1333, **15**-2041
Tucker, G.P., **11**-0204
Tucker, J.A., **15**-1057
Tucker, J.L., **15**-0497
Tucker, J.R., **15**-2288
Tucker, O., **14**-0288
Tucker, R.B., **19**-0632
Tuddenham, D., **02**-0267
Tueting, D., **16**-1904
Tufariello, J.J., **04**-0232, **19**-0448
Tufon, C., **13**-0012
Tuinstra, H.E., **18**-0778
Tuji, H., **10**-0490
Tuladhar, S.M., **10**-0046, **15**-1854
Tulchinsky, M.L., **16**-0675
Tuleen, D.L., **14**-0040, **14**-0049, **14**-0183
Tuli, D., **10**-1582
Tullman, G.M., **14**-0427
Tullock, C.W., **10**-1078, **16**-0447
Tumas, W., **05**-0106, **12**-0664, **17**-0064
Tumi, S.O., **14**-0437
Tümmler, B., **03**-0144
Tuncay, A., **19**-0525
Tuncay, C.I., **19**-0525
Tüncher, W., **19**-0290
Tundo, A., **18**-0073
Tundo, P., **09**-0104, **10**-0412, **10**-0470, **10**-0884, **10**-1583, **12**-0746, **13**-0406, **19**-0339
Tung, C., **17**-0515
Tung, C.C., **16**-1222
Tung, H., **19**-0609
Tung, J.C., **04**-0313
Tung, J.S., **13**-0741
Tunge, J.A., **18**-0675
Tunney, B.H., **13**-0239
Tunoori, A.R., **16**-1784, **19**-1127
Tuong, H.B., **16**-1328
Tuong, T.D., **13**-0216
Tureček, F., **02**-0407
Turk, A., **10**-1256
Turk, M.R., **02**-0242
Turkenburg, L.A.M., **02**-0062, **10**-0317
Turkevich, J., **15**-0448
Turkut, E., **19**-0494
Turley, P.C., **16**-0043, **18**-0201
Turnbull, K., **01**-0009, **10**-1005, **10**-1011, **19**-1256, **19**-1620
Turner, A.B., **19**-0021, **19**-0022
Turner, D.W., **01**-0013
Turner, H.W., **13**-0177, **19**-0218
Turner, J.M., **16**-0917
Turner, J.O., **05**-0049, **08**-0035
Turner, J.V., **12**-0315, **16**-1668, **18**-0729
Turner, L.M., **05**-0135, **12**-0032
Turner, N.J., **13**-0442
Turner, R.B., **04**-0495
Turos, E., **16**-1835, **18**-0527
Turro, N.J., **05**-0208, **05**-0285, **05**-0289, **05**-0335, **05**-0368, **07**-0001, **07**-0019, **07**-0021, **07**-0025, **07**-0029, **07**-0039, **07**-0039, **07**-0040, **07**-0044, **07**-0046, **10**-1370, **14**-0161, **14**-0229, **15**-0154, **15**-2157, **15**-2161, **15**-2235, **15**-2239, **15**-2242, **15**-2254, **15**-2283, **15**-2312, **16**-0043, **16**-2084, **17**-0515, **17**-0527, **18**-0201, **18**-0202, **18**-0205, **18**-0236, **18**-0495, **19**-1687
Turský, M., **12**-0689
Turteltaub, J.S., **19**-0235
Turunen, B.J., **16**-1784
Tuszynski, W.J., **10**-0178
Tuulmets, A., **16**-0527
Tverezovsky, V.V., **16**-1959
Tweddle, N.J., **16**-2114
Tweedie, V.L., **19**-1383
Twiddle, S.J.R., **12**-0456
Twieg, R.J., **13**-0202
Twigg, M.V., **10**-1832, **12**-0074, **15**-0401

Twigger, H.L., **16**-1954
Twitchett, H., **16**-1756
Twitchin, B., **12**-0315
Tye, H., **13**-0271, **16**-1654
Tykwinski, R.R., **17**-0325
Tyltin, A.K., **15**-2088
Tymonko, S.A., **19**-0140, **13**-0567
Tymoschenko, M.F., **13**-0305
Tyobeka, T.E., **11**-0216
Tyrlik, S., **19**-1712
Tyuleneva, V.V., **16**-1255
Tyurina, L.A., **15**-0181
Tyutyulkov, N., **02**-0245
Tzalis, D., **16**-0546

Uang, B.-J., **16**-1438
Uang, S., **16**-0697
Ubukata, M., **17**-0468
Uccello-Barretta, G., **16**-0831
Ucciani, E., **14**-0039, **14**-0179
Uchibori, Y., **13**-0255
Uchic, J.T., **10**-0318, **18**-0508
Uchida, A., **14**-0373
Uchida, M., **10**-1817, **16**-1195
Uchida, N., **10**-0084
Uchida, T., **06**-0051, **09**-0086, **10**-0475, **10**-1464, **15**-1711, **15**-1961, **15**-2300, **15**-2304, **16**-1826, **16**-1830, **18**-0363
Uchida, Y., **05**-0119, **15**-0598
Uchimaru, T., **03**-0072
Uchimura, H., **15**-0730
Uchino, N., **10**-1796, **13**-0281
Uchiro, H., **16**-1052, **16**-1119, **19**-0901, **19**-1596
Uchiyama, K., **11**-0215
Uchiyama, M., **15**-0739, **15**-1564
Uda, H., **16**-1017
Udenfriend, S., **14**-0202
Ue, N., **10**-0882
Ueba, M., **10**-1515, **19**-1359, **19**-1452
Uebel, J.J., **10**-0223
Uebelhart, P., **05**-0319
Ueda, A., **18**-0643
Ueda, H., **13**-0010, **13**-0198
Ueda, K., **02**-0064, **05**-0084, **10**-1856, **18**-0139
Ueda, M., **11**-0215, **16**-0702, **16**-0906, **16**-0933, **16**-0937, **16**-0938, **16**-0940, **19**-1152
Ueda, N., **19**-1700
Ueda, T., **18**-0678
Ueda, W., **13**-0583
Ueda, Y., **15**-1314
Uedo, E., **16**-1060, **19**-0014
Uehara, S., **19**-0605
Uehara, T., **15**-1939
Uehlin, L., **16**-1106
Uehling, D.E., **15**-1060
Ueki, H., **10**-1558
Uemoto, K., **10**-1704, **15**-0288
Uemura, M., **03**-0091
Uemura, S., **04**-0459, **10**-0793, **11**-0134, **11**-0333, **12**-0289, **13**-0139, **13**-0263, **13**-0285, **13**-0328, **13**-0513, **13**-0659, **13**-0660, **13**-0661, **15**-0227, **15**-1159, **15**-1536, **15**-1603, **15**-1714, **15**-1716, **16**-1472, **17**-0159, **19**-0120, **19**-0223, **19**-0471, **19**-0719, **19**-1241, **19**-1651, **19**-1745
Uemura, T., **15**-0611, **19**-1038
Uemura,S., **13**-0509
Uenishi, J., **18**-0360, **19**-0907, **19**-1307
Ueno, H., **19**-1337
Ueno, K., **13**-0617
Ueno, M., **08**-0188, **16**-0381, **16**-1121
Ueno, S., **13**-0532
Ueno, T., **10**-0074
Ueno, Y., **19**-0450, **19**-0732, **19**-1398
ueno, M., **15**-2167
Ueshima, T., **19**-1767
Ueta, M., **15**-0802
Ueyama, K., **15**-1125
Uff, B.C., **18**-0352, **18**-0376, **19**-1129
Uffer, P.M., **04**-0462
Ufret, L., **17**-0428
Ugai, T., **16**-1496
Ugalde, J.M., **16**-0832
Uggerrud, E., **03**-0054
Uggerud, E., **10**-0054
Ugi, I., **10**-0967, **15**-0547, **16**-2124, **16**-2128, **16**-2131, **16**-2133, **17**-0479, **17**-0480
Uglova, E.V., **12**-0017
Ugo, R., **11**-0505
Uguen, D., **16**-1543, **18**-0436, **19**-0508
Uh, H., **10**-0724
Uhm, S.J., **16**-0812
Uhm, S.T., **12**-0599
Uhm, T.S., **16**-1512
Ujaque, G., **15**-2057
Ujihara, Y., **16**-1196
Ujikawa, O., **16**-1488, **16**-1489
Ukai, K., **15**-0945, **16**-1365
Ukaji, Y., **19**-0592
Ukhin, L.Yu., **13**-0534
Ukita, T., **04**-0334, **15**-1691
Ulan, J.G., **15**-0501
Ulich, L.H., **16**-1881
Ullenius, C., **10**-1353, **13**-0460, **15**-1094, **15**-1170, **18**-0629
Ullman, E.F., **13**-0758
Ullrich, E.C., **19**-1683
Ulman, M., **18**-0833
Ulmen, J., **18**-0637
Ulmer II, C.W., **15**-0849
Ulrich, G., **05**-0291
Ulrich, H., **15**-2184, **16**-1755, **16**-2071, **16**-2076, **16**-2094, **19**-0554
Ulrich, P., **10**-0613, **16**-1328
Ulrich, W., **18**-0632
Um, I., **10**-0358, **10**-0368
Um, I.-H., **10**-0369
Um, I.H., **16**-0015
Um, S.Y., **15**-0835
Uma, R., **19**-0120
Umani, F., **14**-0071, **15**-1258
Umani-Ronchi, A., **10**-1469, **12**-0693, **16**-0504, **16**-0505, **16**-0506, **16**-1434
Umbreit, M.A., **17**-0329, **19**-0471, **19**-1718
Umeda, S., **16**-0687
Umemoto, T., **12**-0190
Umen, M.J., **12**-0560, **15**-1071, **15**-1088
Umeno, M., **13**-0255, **18**-0880
Umino, A., **15**-2304
Umpleby, J.D., **15**-0867
Undheim, K., **15**-1049
Unelius, C.R., **10**-0999
Uneyama, K., **12**-0639, **15**-2376, **19**-1156
Ungaro, R., **11**-0388
Unger, D., **10**-0156
Unger, S.H., **09**-0062, **09**-0063, **09**-0065, **09**-0068
Ungváry, F., **12**-0611, **15**-1495, **15**-1496, **15**-1497, **16**-0536
Unibertsitatea, E.H., **16**-0832
Unni, M.K., **15**-0669
Uno, F., **17**-0269
Uno, M., **13**-0583
Untch, K.G., **02**-0103, **02**-0316, **10**-1798
Unterberg, H., **02**-0307
Untiedt, S., **05**-0351
Unverferth, K., **12**-0742
Uozumi, Y., **10**-0691, **10**-1470, **13**-0487, **15**-0201, **18**-0692, **19**-1041
Uphade, B.S., **13**-0410
Uphade, T.S.S., **15**-1887
Uppalla, L.S., **10**-0774, **10**-1107, **16**-1159, **16**-1602, **16**-1681, **16**-1684
Upton, C.J., **15**-0142
Upton, T.H., **18**-0836

Ura, Y., **16**-2000
Urabe, H., **15**-0801, **15**-0819, **15**-0946, **15**-1437, **15**-2176, **15**-2368, **15**-2408
Uraguchi, D., **10**-1469, **16**-0901
Urasaki, I., **11**-0306
Urata, H., **10**-1854
Urawa, Y., **16**-1912
Urban, F.J., **18**-0734
Urban, R.S., **18**-0191
Urbanek, L., **14**-0103
Urbano, F.J., **13**-0576
Urbanowicz, J.H., **16**-0137, **16**-1775
Urbanski, T., **12**-0212, **12**-0338
Urbas, L., **15**-1004, **16**-0397, **16**-1149
Urbańska, N., **16**-1391
Urch, C.J., **19**-0122, **19**-0123
Urey, H.C., **16**-0038
Urgaonkar, S., **13**-0177, **13**-0179, **13**-0558
Uriarte, A.K., **07**-0054
Uriel, C., **15**-1224
Uriz, P., **18**-0278
Urks, M., **16**-2168
Urove, G.A., **19**-1334
Urpí, F., **16**-0109, **16**-1015, **16**-1015, **16**-1759, **16**-1794, **16**-1940, **19**-1272
Urry, W.H., **14**-0290
Ursprung, J.J., **18**-0109
Usacheva, G.M., **04**-0044
Usai, M., **13**-0532
Usano, A., **16**-1036
Usher, L.C., **18**-0792
Ushida, S., **16**-0613
Ushiki, S., **16**-1190
Ushino, T., **05**-0084
Ushio, H., **16**-0686
Ushio, Y., **19**-1392
Ushioda, N., **18**-0542, **19**-1392
Uskoković, M., **04**-0203
Usorov, M.I., **19**-0441
Usov, V.A., **16**-0208
Ustynyuk, N.A., **15**-1959
Ustynyuk, T.K., **18**-0194
Ustynyuk, Yu.A., **09**-0034, **15**-0280, **15**-0867
Usugi, S., **15**-0305
Usugi, S.-i., **10**-1398
Usui, H., **10**-1512
Usui, S., **04**-0270
Usui, Y., **15**-1662
Usuki, J., **15**-1439
Usyatinskii, A.Ya., **13**-0263, **13**-0660
Utaka, M., **19**-1021, **19**-1355
Uteniyazov, K., **18**-0250
Uthe, J.F., **11**-0379
Utimoto, K., **15**-0737, **15**-0945, **15**-1184, **15**-1290, **16**-0500, **16**-0683, **16**-0823, **16**-0996, **16**-1365, **16**-1365, **16**-1368, **19**-1415, **19**-1659
Utley, J.H.P., **11**-0043, **11**-0045, **14**-0415
Utsonomiya, M., **15**-0333
Utsugi, M., **15**-2304
Utsunomiya, D., **10**-0965
Utsunomiya, M., **13**-0179, **15**-0329, **15**-0333
Uyeda, R.T., **04**-0242, **12**-0063
Uyehara, T., **10**-0676, **15**-1085, **15**-1170
Uyeo, S., **18**-0295
Uzan, R., **11**-0010, **19**-0708
Uzick, W., **05**-0236, **05**-0236
Uziel, J., **19**-0789
Uzio, D., **05**-0383, **19**-0042

V'yunov, K.A., **15**-0001
Vaal, M.J., **16**-1538
Vaccaro, L., **10**-0672, **10**-0944, **10**-1152, **10**-1167, **15**-2006, **19**-1258
Vaccaro, P.H., **04**-0015
Vadivel, S.K., **19**-1641
Vågberg, J.O., **10**-0226
Vaghei, R.G., **16**-0055
Vahrenholt, F., **15**-2179
Vaichunaite, B.K., **12**-0718, **18**-0885
Vaid, B.K., **12**-0719
Vaid, R.K., **12**-0719
Vaidya, R.A., **10**-0467
Vaidyanathan, R., **05**-0253, **16**-1803, **16**-2161, **19**-0179
Vaidyanathaswamy, R., **15**-0510
Vail, O.R., **10**-0135
Vaino, A.R., **15**-1752
Vairamani, M., **15**-1532, **18**-0872
Vaish, S.P., **16**-0318
Vajda, E., **05**-0227
Vakulrskaya, T., **05**-0263
Valacchi, M., **17**-0209
Valad, B., **19**-1050
Valange, P., **04**-0440, **15**-2359, **15**-2359
Valeev, E.F., **03**-0073
Valencia, S., **19**-0969
Valenciano, J., **12**-0271
Valenta, Z., **19**-0012
Valentí, E., **15**-2211, **17**-0416
Valentin, E., **16**-0287
Valentine Jr., D., **04**-0136
Valentine Jr., D.J., **04**-0045
Valentine, J.S., **10**-0743, **19**-0463
Valenzuela, J., **05**-0325
Valerga, P., **15**-0284
Valette, G., **19**-0478
Valgimigli, L., **05**-0311
Valicenti, J.A., **17**-0389
Valko, L., **14**-0004, **14**-0005
Vallecchi, M.E., **19**-1022
Vallee, Y., **16**-0928
Valleé, R.E., **03**-0052
Vallée, Y., **15**-1009, **16**-0907, **16**-1456
Vallin, K.S.A., **12**-0286, **13**-0415
Vallribera, A., **15**-1022
Valls, J., **04**-0136
Valot, F., **10**-0884, **16**-1778
Valoti, E., **11**-0376, **11**-0508
Valters, R., **06**-0011
Valters, R.E., **02**-0424
Valverde, S., **10**-1530, **15**-1224, **15**-1718
Van Albada, M.P., **11**-0636
Van Allen, D., **13**-0240
Van Alsenoy, C., **03**-0031
Van Atta, R.E., **19**-0976
Van Auken, T.V., **04**-0074, **04**-0167, **17**-0501
Van Brunt, M.P., **15**-1583
Van Buren II, W.D., **12**-0208
Van Calsteren, M.-R., **15**-2022
Van Cleave, W.C., **11**-0041
Van de Weghe, P., **10**-1015, **16**-1082
Van Der Mensbrugghe, A., **16**-1847
Van der Eycken, E., **07**-0118, **07**-0119, **07**-0121, **15**-2022
Van der Kelen, G.P., **12**-0506
van der Lugt, C., **05**-0223
van der Plas, H.C., **13**-0049
Van Dine, G.W., **10**-0196, **10**-0318, **18**-0510
Van Doren, J.M., **10**-0344
Van Duyne, G., **02**-0353
Van Eenam, D.N., **13**-0764
Van Eenoo, M., **17**-0199, **17**-0200
Van Engen, D., **02**-0071, **02**-0101
Van Hoozer, R., **17**-0158
Van Horn, D.E., **10**-1378, **15**-0956
Van Horn, W.F., **19**-1598
Van Lente, M.A., **11**-0265
Van Maarseveen, J.H., **18**-0813
Van Mele, B., **15**-2091
Van Nieuwen hze, M.S., **15**-1692
Van Peppen, J.F., **15**-0458
Van Santen, R.A., **15**-1798

Van Sickle, D.E., **15**-2095
Van Tamelen, E.E., **12**-0692
Van Vliet, M.C.A., **15**-1750
Van Vranken, D.L., **12**-0352
van Albada, M.P., **11**-0210
van Bac, N., **11**-0655
van Beilen, J., **19**-0546
van Beilen, J.B., **19**-0543
van Bekkum, H., **09**-0018, **15**-0407, **16**-0275, **16**-0290, **19**-0195, **19**-1098
van Bergen, T.J., **11**-0520
van Bommel, A.J., **04**-0097
van Brussel, J.J.M., **10**-0925
van Dam, P.B., **18**-0827
van de Putte, T., **15**-0407
van de Ven, L.J.M., **18**-0566
van Deidhuizen, J.J., **17**-0309
van den Aardweg, G.C.N., **18**-0826
van den Berg, J., **04**-0283
van den Berg, M., **15**-0604, **19**-0073, **19**-0391, **19**-0426, **19**-0590
van den Hark, T.E.M., **02**-0254
van den Heuvel, M., **16**-0431
van den Hoven, B.G., **15**-1487
van der Donk, W.A., **15**-0200, **15**-0696
van der Ent, A., **15**-0463
van der Eyken, E., **13**-0547
van der Gen, A., **04**-0092, **10**-1620, **16**-1318, **16**-1423
van der Heiden, R., **15**-0502
van der Kerk, G.J.M., **03**-0083, **16**-0833
van der Kerk, S.M., **06**-0012
van der Lugt, W.T.A.M., **15**-2199, **18**-0500
van der Maas, **03**-0036
van der Maeden, F.P.B., **19**-1755
van der Meer, R., **16**-1698
van der Plas, H.C., **01**-0087, **13**-0049, **13**-0219, **13**-0638, **13**-0677
van der Pol, C., **16**-0774
van der Sluis, M., **16**-0864
van der Vecht, J.R., **10**-0317
van der Veen, J.M., **11**-0484
van der Veen, L.A., **15**-1483
van der Wel, H., **16**-0027
van der Zeeuw, A.J., **12**-0310
van Doorn, J.A., **08**-0019, **08**-0023, **18**-0048, **18**-0379
van Dorp, D.A., **19**-0368
van Duijneveldt, F.B., **03**-0025
van Duijneveldt-van de Rijdt, J.G.C.M., **03**-0025
van Duynhoven, J.P.M., **03**-0172
van Echten, E., **16**-1200
van Eerden, J., **03**-0113
van Eikkema Hommes, N.J.R., **10**-1538, **12**-0584
van Elburg, P., **16**-1318
van Eldik, R., **17**-0067
van Emster, K., **18**-0014
van Es, A., **11**-0460, **11**-0461, **16**-1624, **16**-1625
van Es, D.S., **13**-0177
van Eyk, S.J., **16**-0495, **16**-0645
van Halteren, B.W., **11**-0312
van Helden, R., **10**-0712
van Hijfte, L., **15**-2145
van Houwelingen, H.C., **09**-0057
van Klaveren, M., **10**-1438
van Koten, G., **10**-0875, **10**-1438, **11**-0615, **12**-0559
van Kruchten, E.M.G.A., **18**-0096
van Leeuwen, P.W.N.M., **13**-0177, **13**-0369, **15**-1483, **19**-1022
van Lenthe, J.H., **10**-1538, **13**-0048
van Leusen, A.M., **10**-1668, **16**-1199, **16**-1200, **16**-1202, **16**-1284
van Leusen, D., **12**-0352, **16**-1199, **16**-1200
van Melick, J.E.W., **16**-1843
van Niel, M.B., **10**-1693, **16**-1413
van Opdenbosch, N.J., **04**-0398
van Otterlo, W.A.L., **18**-0786
van Raayen, W., **08**-0024
van Rantwijk, F., **15**-0407, **16**-1841
van Schaick, E.J.M., **04**-0283
van Soolingen, J., **15**-0532
van Staden, M., **19**-0143
van Staveren, C.J., **03**-0113
van Strijdonck, G.P.F., **13**-0369
van Tamelen, E.E., **02**-0248, **02**-0250, **10**-1102, **10**-1263, **10**-1502, **10**-1504, **14**-0398, **15**-0485, **15**-0487, **15**-0782, **15**-1585, **15**-2260, **16**-0106, **18**-0494, **19**-0446, **19**-0909, **19**-1455, **19**-1576
van Veggel, F.C.J.M., **03**-0113, **03**-0172
van Veldhuizen, B., **01**-0087
van Vliet, M.C.A., **15**-1739, **15**-1753
van Vranken, D.L., **15**-0393, **15**-0733
van Vuuren, E., **18**-0771
van Wageningen, A.M.A., **03**-0172
van Well, R., **19**-1289
van Zijl, A.W., **10**-1374
van Zijl, P.C.M., **02**-0062
van Zoeren, C., **19**-0241
Vanajatha, G., **19**-0772
Vance, R.L., **18**-0669
Vander Jagt, D.L., **10**-0179
Vandercammen, J., **07**-0082
Vanderesse, R., **10**-1243, **13**-0462, **14**-0401, **19**-1580
Vanderpool, S., **18**-0589
Vanderslice, C.W., **19**-1295
Vanderstraeten, P.E., **13**-0504
VanDerveer, D., **12**-0688, **16**-1034, **18**-0121, **18**-0122
VanderWerf, C.A., **16**-1304
Vanemon, P., **19**-0708
VanHorn, W.F., **19**-0871
Vanier, N.R., **05**-0105
Vankar, Y.D., **10**-1086, **10**-1107, **10**-1131, **10**-1178, **11**-0460, **15**-0168, **15**-0564, **15**-1545, **15**-2007, **16**-0111, **16**-0114, **16**-1617, **16**-1883, **17**-0451, **19**-0595, **19**-0643
Vankelecom, I.F.J., **13**-0402, **19**-0120
Vanlandeghem, K., **16**-0977
Vanlierde, H., **15**-2213
VanNieuwenhze, M.S., **04**-0124
Vanquickenborne, L.G., **18**-0306, **18**-0334
VanRheenen, V., **15**-1660
Vančik, H., **10**-0116, **10**-0120, **10**-0185, **10**-0208
Vaquero, J.J., **12**-0271, **13**-0544
Vara Prasad, J.V.N., **15**-0636, **15**-0646, **15**-0673, **15**-0675, **15**-0677, **15**-0857, **18**-0444
Varadarajan, A., **02**-0348, **02**-0351
Varala, R., **15**-1020, **18**-0357
Varalakshmy, N.R., **19**-0965
Varasi, M., **10**-0707
Vardanyan, I.A., **19**-0701
Vardapetyan, S.K., **19**-0387
Varea, T., **15**-1199
Varela, J.A., **15**-0702, **15**-2389
Varescon, F., **15**-1795
Varga, S.L., **04**-0206
Vargaftik, M.N., **19**-0721
Vargas, J.R., **18**-0657
Varghese, B., **10**-0925, **18**-0787
Varghese, J.P., **10**-1385
Varick, T.R., **05**-0308, **14**-0078, **15**-1221
Varkony, T.H., **19**-0454

Varma, M., **10**-0554, **16**-1528, **17**-0115
Varma, R.K., **15**-1585
Varma, R.S., **07**-0111, **10**-0554, **10**-0619, **10**-1008, **13**-0389, **15**-0563, **15**-1373, **15**-1678, **15**-1747, **15**-1748, **16**-0244, **16**-0271, **16**-0297, **16**-0375, **16**-1149, **16**-1178, **16**-1528, **16**-1831, **19**-0033, **19**-0089, **19**-0113, **19**-0207, **19**-0798, **19**-0918, **19**-0922, **19**-1112, **19**-1215, **19**-1758
Vartanyan, S.A., **12**-0065
Varughese, P., **10**-0335
Varvak, A., **17**-0204
Vasapollo, G., **10**-1855, **12**-0747, **15**-1385, **15**-1385, **15**-1398, **15**-1401, **15**-1466
Vasbinder, M.M., **16**-0800
Vasco, V., **15**-0170
Vasconcellos, M.L., **16**-1120
Vasella, A., **19**-0470
Vasella, T., **14**-0391
Vasil'ev, A.A., **15**-1574
Vasil'ev, G.S., **15**-0049
Vasil'eva, S.P., **16**-0182, **19**-0741
Vasil'tsov, A.M., **10**-0775
Vasin, V.A., **16**-1680
Vasíšková, S., **17**-0026
Vaskan, R.N., **16**-0485
Vasquez, E., **13**-0591
Vasquez, P.C., **19**-0234
Vass, A., **19**-1215
Vassar, V.C., **15**-0428
Vasse, J.-L., **16**-1230
Vassie, S., **10**-0156, **18**-0024
Vassilikogiannakis, G., **10**-1630, **15**-2067
Vastra, J., **15**-1133
Vasu, J., **15**-1936
Vasudevan, A., **15**-0208, **18**-0273
Vasudevan, S., **16**-2088
Vatèle, J.-M., **10**-1122, **15**-0221
Vater, H., **10**-0226
Vathke-Ernst, H., **15**-1979
Vaughan, C.W., **13**-0079
Vaughan, H.L., **16**-1585
Vaughan, J., **08**-0030, **11**-0083
Vaughan, K., **12**-0712
Vaughan, L.G., **12**-0568
Vaughan, T.A., **11**-0045
Vaughn, W.L., **15**-0265
Vaultier, M., **10**-0952, **11**-0431, **12**-0518, **15**-1119, **15**-2305
Vaushan, D.E.W., **19**-1028
Vauthey, E., **07**-0032
Vauthey, I., **16**-1778
Vayjooee, M.H.B., **15**-0290
Vayner, G., **18**-0606
Vayron, P., **10**-0848
Vaziri-Zand, F., **10**-0589
Vazquez, B., **14**-0322
Vázquez, E., **13**-0413
Vázquez, J., **19**-0300
Vázquez, S., **04**-0490
Vázquez-Villa, H., **10**-0669
Vdovin, V.M., **18**-0761
Veal, K.T., **15**-1248
Veale, C.A., **16**-0849
Vecchiani, S., **15**-1531
Veciana, J., **05**-0256
Vedantham, P., **16**-2072
Vedder, C., **13**-0237
Vedejs, E., **12**-0106, **12**-0469, **15**-0668, **15**-1688, **15**-1733, **15**-1932, **16**-0210, **16**-0246, **16**-0247, **16**-1208, **16**-1293, **16**-1296, **16**-1301, **17**-0195, **17**-0340, **18**-0727, **19**-0475, **19**-1428, **19**-1503
Vederas, J.C., **12**-0230, **19**-0161
Vedernikov, A.N., **15**-1904
Veenland, J.U., **11**-0636
Veenstra, J.S., **15**-0680
Veeravagu, P., **16**-1480, **17**-0117
Veerkamp, T.A., **08**-0024
Veglia, A.V., **11**-0558
Vegter, G.C., **14**-0103
Vekemans, J.A.J.M., **19**-0216
Vel'der, Ya.L., **14**-0383
Velaparthi, U., **10**-0855
Velasco, L., **10**-1247
Veldkamp, A., **15**-1696
Velichko, F.K., **15**-1640
Velker, J., **18**-0683
Vellekoop, A.S., **15**-1169
Velluz, L., **04**-0136, **04**-0268
Velmathi, S., **19**-1300
Velu, S., **16**-1152
Velu, S.E., **15**-1084
Velusamy, S., **16**-0143, **19**-0120, **19**-0572
Venanzi, L.M., **16**-0147
Venier, C.G., **12**-0180, **19**-0821
Venimadhavan, S., **12**-0095
Venkatachalam, C.S., **11**-0659, **19**-1334
Venkatachalam, T.K., **12**-0639
Venkataiah, B., **16**-0556, **16**-1638, **16**-1700, **10**-1497
Venkatakrishnan, P., **19**-0210
Venkataraman, D., **12**-0295, **13**-0102, **13**-0201, **13**-0240
Venkataraman, K., **16**-1655, **16**-1879
Venkataraman, S.K., **10**-1380
Venkataramani, P.S., **19**-0694
Venkatasubramanian, N., **19**-0247
Venkatathri, N., **13**-0399
Venkatesan, K., **04**-0453, **15**-2235, **16**-0007
Venkateswarlu, A., **10**-1144, **16**-1328
Venkateswarlu, Y., **10**-0680, **10**-0958
Venkatraman, L., **04**-0160, **15**-2066
Venkatraman, M.S., **19**-0119, **19**-0703, **19**-1190
Venkatraman, S., **13**-0297, **13**-0324, **15**-1155, **15**-1158
Vennall, G.P., **15**-0974, **15**-0986, **16**-0743
Vennesland, B., **04**-0253
Ventre, C., **05**-0365
Ventura, S., **11**-0185, **14**-0340
Venturello, C., **15**-1662
Venturello, P., **10**-1583
Venturi, M., **03**-0184
Venturini, A., **05**-0121, **15**-2211
Venturo, V.A., **03**-0072
Venugapal, C., **16**-0167
Venugopal, D., **10**-0680
Venugopal, M., **18**-0312
Venugopalan, P., **16**-0052
Vera, E.L., **10**-0997
Veracini, S., **08**-0014
Verardo, G., **12**-0701
Verardo, G., **17**-0267
Verbicky Jr., J.W., **14**-0452
Verbicky, C.A., **18**-0790
Verbit, L., **04**-0021
Verboom, R.C., **15**-0289
Verboom, W., **03**-0172
Verbrugge, C., **14**-0393
Verchere, J., **10**-0366
Verdaguer, X., **15**-1437, **19**-1133, **19**-1472
Verdecchia, M., **10**-0716
Verdonck, L., **12**-0506
Verducci, J., **02**-0424
Veregin, R.P., **03**-0054
Verenchikov, S.P., **14**-0012
Vereshchagin, A.N., **04**-0349, **16**-0153, **19**-1691
Vereshchagin, L.I., **19**-0010
Verevkin, S.P., **04**-0386
Verhé, R., **10**-0293, **10**-1233, **12**-0110, **15**-2261
Verhelst, W.F., **15**-0218
Verhoeven, J.W., **06**-0012, **07**-0031, **15**-0103
Verhoeven, T.R., **02**-0047, **13**-0237, **15**-1741

Verkade, J.G., **04**-0127, **04**-0146, **13**-0177, **13**-0179, **13**-0558, **13**-0592, **15**-0597, **15**-2361, **16**-0748, **16**-0774, **16**-1154, **16**-1180, **16**-1690, **16**-1694
Verkade, P.E., **09**-0018
Verkruijsse, H.D., **10**-0999, **10**-1726, **12**-0396, **12**-0421, **12**-0483, **16**-1898
Verlhac, J., **16**-2004
Verma, M., **15**-1787
Verma, S.D., **02**-0192
Vermeer, P., **10**-0230, **10**-1349, **10**-1363, **12**-0500, **12**-0544, **15**-0951
Vermeeren, H.P.W., **17**-0132
Vermehren, J., **10**-0259
Vermeij, R.J., **02**-0068
Vermeulen, T., **04**-0156
Vermont, G.B., **13**-0734, **14**-0105
Verna, F., **15**-0424
Vernigor, E.M., **19**-0837
Vernin, G., **13**-0736, **13**-0743, **14**-0326
Vernon, C.A., **10**-0222, **17**-0069
Vernon, J.M., **13**-0037, **15**-1996
Vernon, N.M., **17**-0052
Verny, M., **12**-0065, **18**-0617
Verny, M., **18**-0695
Veronese, D., **16**-0776
Verpeaux, J., **13**-0127, **19**-0841
Verpeaux, J.-N., **13**-0315, **17**-0287
Verpeaux, J.N., **10**-1486, **13**-0058, **13**-0343
Verrall, R.E., **07**-0079
Verrinder, D.J., **10**-0212
Versichel, W., **03**-0025, **03**-0029
Versluis, L., **15**-1494
Verter, H.S., **19**-0329
Verveer, P.C., **07**-0120
Verza, E., **15**-0520
Verzas, M.K., **15**-0208
Verzele, M., **16**-0182
Vescovi, A., **19**-0204, **19**-1770
Veselov, V.Ya., **10**-0361, **10**-0363
Veselovskaia, I.K., **13**-0246
Veselovskii, A.B., **19**-0091
Veselovskii, V.V., **19**-0091, **15**-2024
Vesley, G.F., **17**-0527
Vessière, R., **12**-0065, **15**-0047, **16**-0329, **18**-0617, **18**-0695
Vest, G., **16**-1813
Vestling, M.M., **17**-0048, **17**-0052
Veszprém, T., **18**-0593
Vetter, A.H., **19**-1133
Vetter, W., **03**-0195
Veverková, E., **16**-0331
Veyron B., **10**-1044
Večeřa, M., **16**-1570
Vial, L., **15**-0865
Viala, J., **10**-1096m **16**-0004, **16**-0206
Vianello, P., **10**-0707
Vianello, R., **08**-0120
Vianna, J.F., **12**-0672
Viau, R., **05**-0119
Vibet, A., **16**-0004
Vibhute, Y.B., **11**-0258
Vicart, N., **10**-1405
Vice, S.F., **10**-1286, **13**-0442
Vicens, J., **03**-0123, **03**-0136, **03**-013, **03**-0140
Vichard, D., **12**-0352
Vicia, M.S., **13**-0192, **13**-0177
Vickery, B., **19**-0440
Vickery, B.D., **16**-0759
Vico, R., **11**-0654
Vida, J.A., **18**-0722
Vidal, J.-P., **18**-0156
Vidal, M., **15**-0562
Vidal, S., **14**-0105
Vidal-Ferran, A., **19**-1031
Vidrine, D.W., **05**-0021, **10**-0136
Viehe, H.G., **01**-0007, **04**-0440, **04**-0471, **05**-0243, **05**-0245, **10**-1765, **11**-0175, **12**-0065, **12**-0416, **12**-0483, **12**-0483, **13**-0037, **13**-0049, **14**-0301, **15**-0050, **15**-0079, **15**-0216, **15**-0217, **15**-0435, **15**-1964, **15**-1992, **15**-2182, **15**-2222, **15**-2233, **15**-2260, **15**-2308, **15**-2308, **15**-2359, **15**-2362, **16**-1183, **17**-0289, **17**-0311, **17**-0358, **18**-0729, **19**-0840, **19**-1795
Vieira, A.S., **12**-0290
Vieira, N.M.L., **10**-1151
Viel, S., **03**-0079
Vierfond, J., **11**-0514
Vierhapper, F.W., **01**-0087, **04**-0347
Viertler, H., **15**-1770, **19**-0862
Vieta, R.S., **18**-0613
Vietmeyer, N.D., **18**-0485
Vig, O.P., **16**-1893
Viggiano, A.A., **10**-0345
Vignola, N., **10**-0753, **10**-1592, **10**-1687, **16**-1063
Vijayakumaran, K., **19**-0081
Vijh, A.K., **14**-0415
Vila, X., **15**-1240
Vilaivan, T., **16**-0874
Vilaplana, M.J., **10**-1181, **17**-0425
Vilar, E.T., **11**-0471, **16**-2057
Vilarrasa, J., **15**-0302, **16**-0109, **16**-1015, **16**-1583, **16**-1759, **16**-1794, **16**-1857, **16**-1940, **19**-1272
Vilasís, I., **16**-1015
Villa, M., **11**-0607
Villa, P., **10**-0060
Villa, R., **19**-0232
Villa, V., **10**-1179
Villacampa, M., **15**-2144
Villacorta, G.M., **10**-1357
Villani, C., **04**-0052, **04**-0059, **13**-0407
Villani, R., **15**-1641
Villanova, L., **11**-0614
Villar, F., **15**-1266, **17**-0299
Ville, G., **10**-0224
Villegas, C., **10**-1162
Villemin, D., **13**-0490, **13**-0516, **16**-1644, **16**-1718, **18**-0828, **18**-0836, **19**-0639
Villieras, J., **10**-1529, **10**-1530, **12**-0499, **12**-0620, **12**-0621, **12**-0622, **15**-0954, **16**-1306, **18**-0231
Villiers, C., **19**-1727
Villiers, P., **10**-1405
Vilsmaier, E., **10**-0317, **17**-0353, **19**-0650
Vimara, E., **14**-0363
Vinader, V., **10**-1471
Vinatoru, M., **07**-0095
Vincens, M., **15**-0562
Vincent Jr., B.F., **19**-1150, **19**-1227
Vincent, B.R., **05**-0144
Vincent, G., **13**-0209, **16**-2132
Vincent, M.A., **02**-0418, **18**-0667
Vincent, R.L., **03**-0059
Vines, S.M., **12**-0477
Vineyard, B.D., **04**-0151, **15**-0426
Vingiello, F.A., **11**-0393
Vink, J.A.J., **19**-1219
Vinnik, M.I., **08**-0116, **15**-0183, **17**-0174, **18**-0320
Vinod, M.P., **13**-0410
Vinod, T.K., **19**-0201
Vinograd, L.Kh., **16**-0810
Vinogradov, A.N., **14**-0220
Vinogradov, M.G., **14**-0012, **14**-0447
Viola, A., **17**-0494, **18**-0617, **18**-0695
Viout, P., **10**-0217, **10**-1620, **16**-1593, **16**-1594

Virgil, S., **15**-1693
Virtanen, J., **10**-0331
Vis, J.-M., **18**-0355
Visali, B., **16**-1174
Vishnyakova, T.B., **03**-0014
Vishnyakova, T.P., **16**-0422
Vishwakarma, L.C., **19**-0498, **19**-0500, **15**-0653
Visigalli, M., **16**-1705
Viski, P., **19**-0398, **19**-0465
Vismara, E., **11**-0262, **14**-0120, **14**-0337, **14**-0338, **14**-0342, **14**-0343, **14**-0348, **15**-1199
Visnick, M., **16**-1235
Visser, G.W.M., **11**-0312
Visser, J.P., **04**-0485
Visser, M.S., **18**-0814
Viswajanani, R., **19**-1393
Viswanathan, G.S., **16**-1477
Viswanathan, R., **13**-0181
Vitale, A.A., **10**-0868, **12**-0532
Vitale, A.C., **18**-0163
Vitale, D.E., **17**-0052
Vitale, M., **10**-1499
Vitale, M.A., **09**-0088, **10**-0477
Vitali, D., **13**-0013
Vite, G.D., **16**-0009
Vítek, A., **17**-0026
Vítek, J., **19**-0363
Viti, S.M., **04**-0193
Vitins, P., **17**-0495
Vitrone, J., **19**-0343
Vitt, S., **10**-1835, **14**-0139, **19**-0616
Vitt, S.V., **04**-0169, **04**-0209
Vittal, J.J., **16**-0590
Vittimberga, B.M., **18**-0056
Vitullo, V.P., **10**-0312, **17**-0035, **18**-0186
Vivanco, S., **15**-1944
Vivarelli, P., **02**-0058
Vivekananda, S., **02**-0407
Viyayakrishna, K., **10**-0925
Vizza, F., **15**-2406
Vlaar, C.P., **15**-1777, **15**-1859
Vlaar, M.J.M., **15**-2072
Vladuchick, S.A., **15**-2327
Vladuchick, W.C., **15**-2044
Vlasov, V.M., **13**-0076
Vliegenthart, J.A., **03**-0025
Vlietstra, E.J., **16**-1776
Vo-Quang, Y., **15**-2277
Vo-Thanh, G., **15**-0930, **16**-0779, **18**-0809
Vodichka, L., **18**-0325
Voelter, W., **04**-0119, **10**-0786
Voet, J.G., **04**-0454
Vofsi, D., **15**-1536, **15**-1598, **15**-1642
Vogel, A., **02**-0277
Vogel, D.E., **10**-0687, **15**-0346
Vogel, E., **02**-0173, **02**-0175, **02**-0248, **02**-0259, **02**-0260, **02**-0261, **02**-0263, **02**-0264, **02**-0265, **02**-0266, **02**-0274, **02**-0275, **02**-0277, **02**-0278, **02**-0282, **02**-0284, **02**-0295, **02**-0319, **02**-0320, **02**-0326, **02**-0330, **02**-0333, **03**-0183, **04**-0467, **15**-2322, **16**-0997, **16**-1018, **17**-0303, **18**-0468, **18**-0468, **18**-0469, **18**-0470, **18**-0472, **18**-0614, **18**-0645, **18**-0645
Vogel, G., **05**-0149
Vogel, G.C., **03**-0054
Vogel, H., **15**-1353
Vogel, I.A., **19**-1741
Vogel, P., **05**-0002, **13**-0243, **13**-0296, **15**-2238, **16**-2168, **18**-0002, **18**-0022, **18**-0027, **18**-0037, **18**-0042
Vogel, P.C., **10**-0070
Vogel, R., **13**-0578
Vogel, S., **11**-0013
Vogel, W., **08**-0018
Vogelfanger, E., **10**-0174
Vogels, C.M., **19**-1609
Vogelzang, M.W., **17**-0132
Vogl, E.M., **13**-0593
Vogler, E.A., **12**-0609, **18**-0303
Vogt, C.E., **13**-0361
Vogt, M., **15**-1741
Vogtle, F., **03**-0210
Vögtle, E., **03**-0101
Vögtle, F., **02**-0061, **02**-0299, **03**-0101, **03**-0112, **03**-0119, **03**-0144, **03**-0145, **03**-0152, **03**-0183, **03**-0188, **03**-0198, **03**-0202, **04**-0067, **04**-0164, **04**-0244, **04**-0509, **10**-0808, **14**-0415, **16**-1210, **17**-0516
Voigt, K., **12**-0274
Voigtländer, D., **11**-0427
Voigtmann, U., **18**-0789
Voisey, M.A., **05**-0380
Voitenko, Z.V., **15**-2088
Voitsekhovskaya, I.Yu., **16**-1811
Vol'kenshtein, Yu.B., **11**-0404
Vol'pin, M.E., **02**-0159, **02**-0203, **12**-0013, **13**-0222, **15**-0406, **15**-2310, **19**-1295, **19**-1303
Volant, F., **15**-0682
Volante, R.P., **13**-0236, **13**-0266, **13**-0504
Volatron, F., **16**-1789
Vold, R.L., **03**-0161
Vold, R.R., **03**-0161
Volger, H.C., **10**-0712, **12**-0010, **15**-0134, **15**-2257
Volkman, S.K., **16**-0896
Vollhardt, J., **05**-0143
Vollhardt, K.P.C., **02**-0076, **02**-0006, **02**-0023, **02**-0081, **02**-0208, **07**-0119, **15**-0430, **15**-2362, **15**-2400, **15**-2402, **15**-2403, **16**-1335, **17**-0227
Vollmar, A., **11**-0058
Vollmer, J.J., **15**-2103, **18**-0471
Volmer, M., 09-II-0006
Volod'kin, A.A., **11**-0013, **18**-0187
Volodarsky, L.B., **05**-0254, **05**-0261
Volovik, S.V., **15**-0092
Volpe, T., **15**-1044
Volpin, M.E., **16**-0842
Volpp, W., **19**-0366
Völter, H., **04**-0225
Volz, H., **02**-0236, **05**-0042, **05**-0092, **05**-0231
Von Lehman, T., **10**-0137
Von Rein, F.W., **15**-0862
Von Seebach, M., **04**-0339
von Brachel, H., **15**-0961
von dem Bussche-Hünnefeld, C., **16**-1823
von Felten, W.C., **10**-0171
von J. Hinz, A., **14**-0006
von Matt, P., **15**-2064
von Nagy-Felsobuki, E., **09**-0052
von Pechmann, H., **11**-0380
von Puttkamer, H., **02**-0319
von Raumer, M., **07**-0032
von Ross, B., **02**-0225
von Schenck, H., **13**-0375, **13**-0396
von Schnering, H., **04**-0294
von Schnering, H.G., **02**-0243, **05**-0231, **08**-0084, **08**-0186, **10**-1662
Vonderheid, C., **10**-1662
Vontor, T., **10**-0083
Voorhees, K.J., **17**-0492
Vorbrüggen, H., **10**-0723, **13**-0653, **13**-0676, **14**-0337, **16**-1622, **16**-1655
Vorlop, K.-D., **16**-1422
Vorogushin, A., **15**-2410
Voronenkov, V.V., **04**-0499, **14**-0220
Voronkov, M., **05**-0263
Voronkov, M.G., **03**-0114, **15**-0297, **15**-0308, **15**-1608, **16**-0208
Voronkov, M.V., **10**-0897
Vorozhtsov Jr., N.N., **11**-0605

Vos, T.J., **17**-0309
Vossius, D., **18**-0285
Vosswinkel, M., **05**-0407
Vostell, M., **16**-1195
Vostrikova, O.S., **15**-0704, **15**-0706
Vostrowsky, O., **16**-1255, **16**-1336, **17**-0353
Voter, A.F., **02**-0216
Vött, V., **10**-0136
Vottero, C., **11**-0142
Vottero, G.P., **12**-0599
Vovsi, B.A., **15**-2184, **17**-0319
Vowinkel, E., **10**-0650
Voyle, M., **13**-0128
Voynov, G.H., **19**-1485
Vrancken, E., **10**-1538, **10**-1550, **17**-0217
Vrang, L., **07**-0118
Vrcek, V., **05**-0097
Vreeke, M., **10**-0103
Vreugdenhil, A.D., **05**-0162
Vrielink, A., **10**-0078
Vrielink, J.J., **10**-0711, **15**-0043
Vriend, J., **05**-0223
Vrček, V., **10**-0142
Vu, A.T., **15**-0820, **15**-2391
Vu, B.T., **15**-1939
Vukov, R., **10**-0148
Vukov, R., **19**-0445
Vul'fson, N.S., **16**-0810
Vyas, P.V., **11**-0239
Vyas, R., **15**-1898
Vyas, V.A., **17**-0059
Vypel, H., **14**-0129
Vyse, N., **15**-1435
Vyskoc, F., **07**-0115
Vyskocil, S., **13**-0237
Vysotskaya, N.A., **14**-0195

Waack, R., **12**-0413
Wabnitz, T.C., **15**-1306, **15**-1307, **15**-1308
Wack, H., **12**-0124, **12**-0167, **15**-2180, **16**-2103, **16**-2105, **17**-0318, **19**-1273
Wada, E., **10**-1595
Wada, F., **13**-0362, **13**-0724
Wada, F., **14**-0364, **14**-0366, **14**-0368
Wada, K., **10**-0788, **19**-1476
Wada, M., **10**-0993, **16**-0645, **16**-0661, **16**-0664, **16**-0765, **16**-1426, **19**-1001, **19**-1022
Wada, R., **16**-0698
Wada, S., **16**-0661
Wada, T., **15**-0154, **15**-0160
Wada, Y., **19**-1559
Wadamoto, M., **16**-1094, **16**-1121
Waddell, S.T., **04**-0431, **15**-0143
Wade Jr., L.E., **18**-0630
Wade, A.M., **18**-0688
Wade, K., **02**-0171, **05**-0145, **12**-0001, **12**-0050, **12**-0341
Wade, P.A., **10**-1483, **15**-0473
Wade, R.C., **19**-0882, **19**-0889
Wadgaonkar, P.P., **11**-0249, **16**-0058, **16**-1157, **19**-1254, **19**-1442
Wadman, S., **10**-1532
Wadsworth Jr., W.S., **16**-1305, **16**-1306
Wadsworth, K.J., **15**-1024, **15**-1132, **16**-1982
Waegell, B., **04**-0387, **12**-0074, **15**-2326, **17**-0272, **18**-0197, **19**-0457, **19**-1339, **19**-1341
Wagatsuma, N., **10**-0804
Wagaw, S., **13**-0174
Wagemann, W., **02**-0278
Wagenknecht, J.H., **19**-1099
Wager, C.A., **16**-1662, **19**-0983, **19**-0987
Wager, T.T., **19**-0983
Wagerle, Ty.R., **12**-0167
Wagle, D.R., **16**-1655, **16**-1879
Wagner, A., **02**-0260, **10**-1100, **10**-1110, **10**-1830, **13**-0290, **13**-0639, **15**-0733, **15**-1939, **16**-0115, **17**-0470
Wagner, C.D., **15**-0449
Wagner, C.K., **06**-0066
Wagner, G., **01**-0011
Wagner, G.W., **16**-1247
Wagner, H., **02**-0221, **02**-0222, **10**-0484, **18**-0506
Wagner, J., **04**-0036
Wagner, J.M., **10**-0888
Wagner, K., **10**-0391, **10**-0396, **17**-0513
Wagner, P.J., **05**-0289, **07**-0024, **07**-0037, **07**-0044, **07**-0046, **07**-0047, **07**-0048, **07**-0049, **07**-0052
Wagner, R.S., **01**-0057
Wagner, U., **04**-0119
Wagner, W.M., **05**-0362
Wagner-Jauregg, T., **15**-2073
Wagnon, J., **15**-1074
Wähälä, K., **10**-0810
Waheed, N., **19**-1487
Wahl Jr., G.H., **01**-0048, **13**-0028, **13**-0034
Wai, C.M., **09**-0098
Wai, J.S.M., **15**-1691
Wai, W., **17**-0504
Wailes, J.S., **15**-1773, **15**-1782
Wainschel, L.A., **11**-0092
Wainwright, P.G., **15**-1807, **15**-1809, **15**-1815
Wait, A.R., **09**-0047
Waite, B.A., **08**-0037
Wakabayashi, A., **15**-1458, **15**-2371
Wakabayashi, K., **14**-0009, **15**-0869, **15**-1208, **15**-1254
Wakabayashi, S., **07**-0021
Wakabayashi, T., **16**-0260, **16**-1083
Wakabyashi, H., **16**-0827
Wakahara, Y., **16**-1066
Wakai, C., **03**-0004
Wakamatsu, H., **18**-0755
Wakamatsu, K., **15**-0157
Wakamatsu, T., **13**-0678
Wakasa, M., **07**-0033
Wakasa, N., **19**-1177
Wakasugi, K., **16**-1636, **16**-1639
Wakatsuki, Y., **15**-0212, **15**-0734, **15**-0804, **15**-2405, **19**-0823
Wakefield, B., **05**-0156, **05**-0244
Wakefield, B.J., **05**-0148, **12**-0415, **12**-0474, **12**-0552, **12**-0558, **12**-0594, **13**-0460, **13**-0651, **16**-1944, **19**-1347
Wakharkar, R.D., **10**-0660, **11**-0255, **13**-0410
Waki, Y., **13**-0297
Wakiji, I., **15**-0808
Wakisaka, K., **10**-0804
Wakita, A., **15**-0048
Wakita, M., **03**-0078
Wakita, T., **15**-1159
Wakselman, C., **10**-1369, **16**-0453
Wakselman, M., **17**-0146
Wakui, H., **13**-0452
Walba, D.M., **03**-0192, **03**-0200, **04**-0089, **04**-0090, **10**-0912
Walborsky, H.M., **05**-0135, **05**-0136, **05**-0197, **05**-0270, **05**-0356, **10**-0966, **10**-1296, **10**-1505, **10**-1599, **12**-0018, **12**-0032, **12**-0426, **12**-0605, **12**-0610, **12**-0612, **12**-0614, **12**-0684, **14**-0378, **14**-0456, **14**-0457, **15**-0631, **15**-2063, **16**-2124, **16**-2135, **17**-0481, **18**-0019, **19**-1541
Walburn, J.J., **12**-0457
Wälchli, R., **12**-0669
Wald, S.A., **19**-1207
Walde, A., **12**-0395
Waldeck, D.H., **07**-0055
Walden, F.A., **10**-0060
Walden, P., **06**-0042, **10**-0004

Walder, L., **17**-0216
Waldmann, H., **18**-0717
Waldvogel, E., **13**-0503
Wale, P.D., **16**-1597
Wales, D.J., **18**-0522
Walfort, B., **02**-0084
Waligorska, M., **17**-0052
Walker, B.J., **16**-1306
Walker, D., **11**-0039, **19**-0022
Walker, E.C., **19**-0708
Walker, E.R.H., **19**-0874
Walker, F., **05**-0167, **05**-0168
Walker, F.H., **04**-0432
Walker, F.J., **10**-0678
Walker, F.W., **16**-0524
Walker, H., **15**-0359
Walker, K.A.M., **10**-0794, **15**-0423, **15**-0466, **19**-1128
Walker, L.E., **17**-0446
Walker, M.A., **10**-0704, **16**-1018, **17**-0204
Walker, M.P., **18**-0344
Walker, W.E., **10**-0902
Walkowiak, W., **03**-0107
Wall, A., **11**-0160, **17**-0349
Wall, D.K., **16**-2048
Wall, J.S., **15**-0076
Walla, P., **13**-0326
Wallace, B., **16**-1486
Wallace, D.J., **13**-0236, **13**-0272
Wallace, E.M., **11**-0410
Wallace, O.B., **16**-1534
Wallace, R.G., **18**-0288
Wallace, R.H., **19**-0962
Wallace, R.W., **05**-0279
Wallace, T.J., **16**-2147, **17**-0286, **17**-0320, **19**-0336, **19**-0793, **19**-0869
Wallace, T.L., **17**-0288
Wallace, T.W., **18**-0482
Wallen, S.L., **09**-0095
Wallenfels, K., **10**-1785, **15**-1499, **16**-1421, **17**-0424, **17**-0458
Waller, F.D., **17**-0248
Waller, F.J., **10**-0282, **10**-0383, **11**-0137, **19**-0115
Wallin, A.P., **12**-0409
Walling, C., **10**-0177, **11**-0540, **12**-0436, **14**-0016, **14**-0103, **14**-0118, **14**-0120, **14**-0164, **14**-0176, **14**-0183, **14**-0184, **14**-0188, **14**-0193, **14**-0197, **16**-0529, **19**-0255
Walling, C., **19**-0273
Wallis, E.S., **18**-0266
Wallis, S.R., **17**-0495
Wallner, O.A., **16**-0611
Wallon, A., **04**-0244
Wallraff, G.M., **04**-0469
Waloch, C., **16**-0879
Walsgrove, J., **19**-1042
Walsh Jr., E.J., **18**-0238, **18**-0599, **19**-1100
Walsh, A.D., **01**-0028, **07**-0015, **15**-0085
Walsh, C.T., **18**-0362
Walsh, H.G., **14**-0212, **19**-0434
Walsh, L.M., **16**-0783
Walsh, P.A., **02**-0388
Walsh, P.J., **15**-1699, **15**-2337, **16**-0568, **16**-0632, **16**-0646, **16**-0687, **16**-0688, **16**-0717, **16**-1438
Walsh, R., **05**-0351, **05**-0380, **15**-0181, **18**-0087, **18**-0571, **18**-0590, **18**-0647
Walsh, T.D., **10**-0060, **10**-0088
Walsh, W.L., **18**-0249
Walspurger, S., **15**-1148
Walter, D., **18**-0411
Walter, D.S., **15**-1271
Walter, D.W., **18**-0056
Walter, H., **06**-0072, **12**-0590
Walter, R., **13**-0456
Walter, R.I., **16**-0534
Walter, W., **04**-0225, **16**-0004, **16**-0188
Walter, W.F., **14**-0398, **19**-1576
Walters, M.A., **18**-0579, **18**-0685
Walters, M.E., **19**-1376
Walters, M.J., **18**-0126
Walthall, D.A., **08**-0100
Walton, D.R.M., **11**-0032, **12**-0476, **13**-0616, **14**-0317, **14**-0318, appendixA-0036
Walton, H.F., **02**-0344
Walton, J.C., **05**-0202, **05**-0210, **14**-0001, **14**-0031, **14**-0070, **15**-0050, **15**-0052, **15**-0090, **15**-0100, **15**-1218, **18**-0054, **19**-1310, **14**-0001
Waltz, K.M., **16**-0632
Waluk, J., **12**-0087
Wambsgans, A., **18**-0868
Wan, B., **16**-0687
Wan, C.-W., **13**-0478
Wan, H., **15**-1137
Wan, J.K.S., **05**-0314, **07**-0044
Wan, K., **18**-0023
Wan, P., **08**-0038, **15**-0256
Wan, W.B., **02**-0289, **02**-0302
Wan, X., **19**-1028
Wan, Y., **13**-0174, **13**-0602, **19**-1631
Wan, Z., **10**-1444, **16**-2075
Wan, Z.-K., **15**-2102
Wan,Y., **10**-0813
Wang H.H., **07**-0081
Wang, B., **15**-0775, **15**-2127, **19**-0277, **19**-1002
Wang, B.M., **18**-0134, **18**-0157
Wang, C., **08**-0163, **12**-0498, **13**-0365, **15**-1405, **15**-1456, **16**-0168
Wang, C.-C., **15**-0761, **15**-1145
Wang, C.-J., **15**-1137, **15**-1902, **16**-0782, **16**-0866
Wang, C.-L., **19**-0292
Wang, C.C-Y., **15**-1490
Wang, C.J., **10**-1078, **16**-0447
Wang, C.S., **16**-2163
Wang, D., **15**-2340, **16**-0875, **16**-1092, **16**-1985, **19**-1028
Wang, D.-K., **16**-0851, **16**-0871, **16**-0911
Wang, D.-q., **15**-2333
Wang, F., **08**-0194, **13**-0558, **15**-0272, **15**-0615, **19**-0082, **19**-0784, **19**-1042, **19**-1375
Wang, F.-S., **15**-1249
Wang, G., **15**-0287, **16**-0147, **16**-0154, **16**-1352
Wang, G.-W., **02**-0365, **02**-0366, **15**-1034, **15**-2070
Wang, G.L., **12**-0668
Wang, G.P., **08**-0060
Wang, G.Y., **10**-0175
Wang, H., **13**-0171, **13**-0359, **15**-0578, **15**-0793, **15**-1004, **15**-2414, **16**-0687
Wang, H.-F., **13**-0439
Wang, H.-s., **16**-0687
Wang, H.-W., **16**-0420, **16**-0947
Wang, H.H., **07**-0088
Wang, I., **15**-1787
Wang, J., **05**-0187, **05**-0285, **10**-1453, **12**-0370, **13**-0299, **15**-0434, **15**-0806, **15**-1137, **15**-2031, **16**-0684, **16**-0872, **16**-1008, **16**-1352, **16**-1713, **16**-1833, **18**-0758, **19**-1028, **19**-1584, **19**-1585, **19**-1633
Wang, J.-C., **15**-1970
Wang, J.-G., **19**-0568
Wang, J.-T., **01**-0111
Wang, J.-X., **07**-0118, **10**-0833, **12**-0298, **13**-0414, **16**-1714, **16**-1913, **16**-1915, **16**-1920
Wang, J.-x., **16**-1919
Wang, J.C., **03**-0208
Wang, J.Y.C., **14**-0148
Wang, K., **05**-0248, **12**-0250, **15**-2414
Wang, K.K., **15**-0653, **18**-0453, **18**-0458, **19**-1059

Wang, L., **03**-0020, **10**-0509, **10**-1271, **10**-1409, **13**-0145, **13**-0320, **13**-0443, **13**-0495, **13**-0539, **13**-0545, **13**-0549, **13**-0567, **14**-0309, **15**-1693, **16**-2175, **19**-1190, **19**-1199, **19**-1601
Wang, L.-C., **15**-2175, **16**-0722
Wang, L.-X., **10**-1386, **15**-0604, **15**-1136, **15**-1885, **19**-1028
Wang, L.L., **02**-0243
Wang, Li.C., **15**-1229
Wang, M., **13**-0162, **13**-0549, **15**-0272, **15**-1373, **16**-0298, **16**-0667, **16**-1494, **16**-1993, **19**-1199, **19**-1673
Wang, M.-L., **07**-0089
Wang, M.-X., **16**-0124
Wang, M.D., **12**-0750
Wang, N., **15**-1944
Wang, P.A., **15**-0538, **15**-0539
Wang, P.G., **16**-0682, **16**-0767, **16**-0774, **16**-0777, **16**-1036
Wang, P.S., **05**-0342
Wang, Q., **11**-0119, **11**-0236, **11**-0535, **12**-0454, **13**-0108, **15**-1000, **15**-1101, **15**-1628, **16**-0455, **17**-0181, **19**-1443
Wang, R., **15**-1125, **15**-1213, **16**-0549, **16**-0552, **16**-0687
Wang, R.-T., **15**-0388
Wang, S., **09**-0098, **18**-0362, **19**-1206
Wang, S.H., **19**-1043
Wang, S.L.B., **15**-1926
Wang, S.Y., **07**-0079
Wang, T., **02**-0241, **03**-0148, **11**-0436, **12**-0099, **13**-0187, **19**-0175, **19**-0679
Wang, T.C., **10**-0571, **12**-0084
Wang, T.S., **10**-1582
Wang, W., **08**-0098, **08**-0105, **08**-0108, **12**-0250, **12**-0627, **15**-0425, **15**-0877, **16**-0510, **16**-0511, **16**-0645, **16**-1266
Wang, W.-B., **15**-0527, **16**-1837, **16**-1838
Wang, W.-H., **15**-1136
Wang, W.-h., **08**-0109
Wang, X., **08**-0193, **11**-0557, **15**-0765, **15**-0818, **15**-0890, **15**-0896, **15**-1014, **15**-1254, **15**-1361, **15**-2211, **15**-2354, **16**-0687, **16**-0762, **16**-0987, **16**-1996, **17**-0257, **17**-0379, **18**-0735
Wang, X.-C., **15**-1778
Wang, X.-j., **11**-0398
Wang, X.-L., **13**-0500
Wang, X.-R., **16**-0687
Wang, X.-X., **19**-0292
Wang, X.-Y., **19**-0291, **19**-0292
Wang, Y., **13**-0488, **10**-1460, **13**-0237, **15**-1004, **15**-1696, **15**-2245, **16**-0154, **16**-1266, **16**-1313, **16**-1352, **18**-0483, **18**-0483, **19**-0688, **19**-1269, **19**-1539
Wang, Y.-C., **19**-1314
Wang, Y.-F., **13**-0138, **13**-0228
Wang, Y.-G., **13**-0156
Wang, Y.-H., **13**-0544
Wang, Y.-L., **19**-0291, **19**-0292, **19**-1635
Wang, Y.-M., **16**-0170
Wang, Y.-X., **10**-0038
Wang, Y.A., **19**-1273
Wang, Z., **10**-1453, **12**-0514, **13**-0148, **13**-0390, **15**-0917, **15**-1822, **16**-0649, **16**-0654, **16**-0661, **16**-0748, **16**-0831, **16**-1993, **16**-2180, **19**-0037, **19**-1017, **19**-1054, **19**-1660
Wang, Z.-M., **15**-1658, **15**-1693, **15**-1704
Wang, Z.-X., **02**-0105, **15**-1767, **15**-1768
Wang,W., **16**-0511
Wann, S.R., **10**-0532, **19**-1487
Wannberg, J., **11**-0513
Wannere, C.S., **02**-0040
Wanzlick, H.-W., **05**-0357
Waratuke, S.A., **15**-0973
Warawa, E.J., **19**-0075
Warburton, M.R., **15**-2219
Ward Jr., W.J., **16**-1294
Ward, A., **18**-0520
Ward, D.E., **15**-2008, **16**-1027, **16**-1431, **19**-0943, **19**-0945, **19**-0947
Ward, D.G., **08**-0038
Ward, E.L.M., **11**-0492
Ward, F.E., **15**-1768
Ward, H.R., **04**-0487, **05**-0218, **05**-0219, **05**-0221, **10**-1314, **10**-1318, **12**-0627, **12**-0628, **18**-0493
Ward, J.F., **12**-0565
Ward, J.P., **11**-0351, **18**-0760, **19**-0057, **19**-0352
Ward, J.S., **18**-0638
Ward, P., **18**-0185
Ward, R.S., **04**-0136, **04**-0190, **17**-0392
Ward, R.W., **15**-0962
Ward, T.J., **18**-0381
Ward, T.R., **16**-0147
Wardell, J.L., **10**-0773, **10**-0780, **10**-1545, **12**-0388, **12**-0388, **12**-0415, **12**-0432, **12**-0474, **12**-0474, **12**-0549, **12**-0559, **12**-0564, **12**-0594, **12**-0615, **13**-0656, **15**-0294, **15**-0857, **15**-0873, **16**-0003, **16**-0645, **19**-1595, **19**-1636
Ware, J.C., **12**-0040
Waring, A.J., **08**-0118, **18**-0034, **18**-0035, **18**-0185
Waring, C., **19**-0434, **19**-0438
Waring, M.J., **15**-0202, **15**-0588, **15**-1680
Warkentin, J., **05**-0384, **05**-0394, **05**-0394, **14**-0074, **15**-1259, **15**-1945, **17**-0417, **17**-0500
Warmuth, R., **03**-0132
Warner, B.P., **16**-0745
Warner, C.D., **12**-0683
Warner, C.R., **18**-0238
Warner, P.M., **02**-0357, **04**-0491, **18**-0487, **18**-0489, **18**-0491, **18**-0639, **18**-0643
Warnet, R., **15**-0046
Warnet, R.J., **15**-0134
Warnhoff, E.W., **05**-0125, **12**-0140, **15**-2264, **18**-0094, **18**-0194, **18**-0209, **18**-0241, **19**-0975
Warpehoski, M.A., **19**-0473
Warren, C.T., **16**-1556
Warren, H.B., **02**-0358
Warren, J.A., **04**-0267
Warren, R.W., **18**-0116
Warren, S., **16**-1327, **18**-0032, **18**-0250, **19**-1778
Warren, S.E., **15**-0112
Warrener, R.N., **15**-2235, **19**-0078
Warrick, P., **06**-0062
Warrington, J.M., **18**-0599
Warshawsky, A., **11**-0552
Wartenberg, F.-H., **15**-1250
Wartini, A.R., **05**-0325
Wartski, L., **15**-1001, **15**-1111, **15**-1112, **15**-1114, **15**-2119
Waseda, T., **16**-1968
Waser, J., **15**-0345
Washiyama, M., **15**-1064
Wassef, W.N., **16**-1514, **16**-1515
Wassen, J., **02**-0173, **02**-0274
Wasserman, A., **15**-1980
Wasserman, B., **10**-0333
Wasserman, E., **02**-0235, **02**-0236, **03**-199, **05**-0289, **05**-0328, **05**-0342, **05**-0345, **05**-0399, **05**-0400, **18**-0824, **18**-0825
Wasserman, H.H., **12**-0645, **14**-0227, **14**-0227, **14**-0228,

14-0229, **14**-0241, **15**-2151, **15**-2155, **15**-2156, **15**-2157, **15**-2159, **15**-2161, **15**-2283, **16**-0043, **18**-0201, **18**-0347, **19**-0440, **19**-0477, **19**-0554
Wassermann, B.C., **12**-0614
Wasserscheid, P., **09**-0109
Wassmundt, F.W., **11**-0191
Waszczylo, Z., **06**-0084, **10**-0313
Wat, E.K.W., **10**-1252
Watanabe, A., **16**-0338, **18**-0150, **18**-0363
Watanabe, F., **11**-0292, **11**-0650
Watanabe, H., **10**-1303, **10**-1384, **12**-0534, **15**-2304, **16**-1004
Watanabe, J., **10**-0567
Watanabe, M., **01**-0068, **15**-1004, **15**-1024, **16**-0565, **16**-1357
Watanabe, N., **12**-0326, **12**-0368, **15**-1603
Watanabe, S., **10**-0676, **10**-1217, **12**-0169, **12**-0452, **13**-0293, **13**-0633, **15**-1808, **16**-0917, **19**-0825
Watanabe, S.-i., **10**-1137
Watanabe, T., **10**-0828, **10**-1224, **13**-0476, **13**-0619, **15**-1847, **16**-1854, **19**-0650
Watanabe, W.H., **10**-0661
Watanabe, Y., **10**-0552, **10**-0880, **10**-0900, **10**-0902, **10**-0916, **10**-0992, **10**-1822, **10**-1844, **10**-1845, **13**-0764, **15**-0280, **15**-0281, **15**-0340, **15**-0374, **15**-1467, **16**-0268, **19**-0999, **19**-1119, **19**-1247, **19**-1772
Watanuki, K., **10**-0612
Wataya, Y., **16**-0381
Waterhouse, A., **10**-1290, **10**-1291
Waterlot, C., **13**-0735
Waters, D.L., **18**-0559
Waters, D.N., **11**-0608
Waters, W.A., **10**-1320, **14**-0234, **14**-0319, **19**-0002, **19**-0247, **19**-0256, **19**-0325, **19**-1211, **19**-1748
Wathey, B., **07**-0116
Watkin, D.J., **02**-0163
Watkin, J.G., **16**-0745
Watkins, C.J., **07**-0026
Watkinson, M., **10**-0955
Watson Jr. C.R., **17**-0326
Watson, A.J., **11**-0118
Watson, B.T., **15**-0708
Watson, D.G., **01**-0052, **01**-0070, **02**-0031
Watson, H B., **12**-0088
Watson, I.D.G., **10**-0886, **10**-0957
Watson, J.M., **18**-0706
Watson, M.P., **18**-0690
Watson, S.P., **15**-1429
Watson, S.W., **17**-0178
Watson, T.W., **02**-0402
Watson, W.H., **03**-0112
Watt, A.N., **10**-0693
Watt, C.I.F., **12**-0663, **12**-0664, **19**-0007, **19**-1763
Watt, D.S., **10**-1610, **10**-1615, **14**-0258, **16**-2088, **19**-0472, **19**-0662, **19**-1422
Watts, D.W., **16**-0424
Watts, I.M., **05**-0380
Watts, L., **02**-0211, **02**-0229, **04**-0441
Watts, P.C., **16**-1248
Watts, W.E., **05**-0067, **05**-0083, **11**-0568, **13**-0759, **13**-0773, **15**-1417, **16**-1635, **18**-0001, **18**-0282, **18**-0380
Waugh, J.S., **02**-0101
Wawzonek, S., **18**-0867
Waxman, B.H., **15**-0187
Wayda, A.L., **02**-0254
Waykole, L., **10**-0826, **16**-0530, **16**-2177
Wayman, M., **12**-0726
Waymouth, R., **15**-0598
Waymouth, R.M., **04**-0149, **10**-1455, **15**-0778
Wayne, R.P., **14**-0228, **15**-2156
Wayner, D.D.M., **01**-0089, **01**-0101, **05**-0310, **19**-1533
Weakley, T.J.R., **05**-0064, **02**-0289, **02**-0289
Wearing, J.T., **19**-0767
Weast, R.C., **05**-0265, **14**-0166
Weatherwax, A., **15**-2180
Weaver, S.L., **15**-2219
Weaver, W.M., **10**-0333, **11**-0119, **19**-0640
Weavers, L.K., **07**-0074
Webb H.M., **08**-0224
Webb, C.F., **15**-2117
Webb, D., **11**-0628
Webb, G., **15**-0451, **15**-0457
Webb, G.G., **10**-0183, **10**-0200
Webb, H.M., **08**-0191, **08**-0219
Webb, K.S., **16**-1148, **19**-0696
Webb, K.S., **19**-0768
Webb, T.R., **16**-0112
Webb, V.L., **04**-0336
Weber, A., **16**-2034
Weber, E., **03**-0101, **03**-0112, **03**-0144, **03**-0145, **03**-0155, **03**-0156
Weber, E.J., **16**-0494, **16**-0743
Weber, H., **02**-0257
Weber, J., **19**-0241
Weber, J.C., **19**-0068
Weber, J.L., **02**-0204
Weber, L., **02**-0045, **02**-0046, **10**-1448, **10**-1450
Weber, P., **14**-0063
Weber, R.T., **05**-0293
Weber, S., **10**-0317
Weber, T., **04**-0136, **11**-0375
Weber, W.P., **10**-0453, **10**-0610, **10**-0696, **10**-0784, **10**-0967, **10**-1047, **10**-1619, **10**-1787, **15**-1676, **15**-2274, **16**-1232, **16**-1255, **16**-2046, **19**-1616
Webster, B., **15**-2172, **16**-2080
Webster, J.R., **18**-0077
Webster, O.W., **02**-0144, **15**-1986
Weckerle, B., **19**-0540
Wedegaertner, D.K., **12**-0017, **14**-0458
Weedon, A.C., **12**-0080, **15**-2238, **15**-2248, **16**-0218, **19**-1001
Weedon, B.C.L., **19**-0074
Weeds, S.M., appendixA-0038
Weeks, D.P., **10**-0533, **10**-0536, **16**-1936
Weerasooriya, U., **12**-0348
Weetman, J., **15**-2058
Wege, D., **18**-0039
Weglein, R.C., **18**-0031
Wegner, G., **11**-0419
Wehle, D., **04**-0322, **04**-0369
Wehmeyer, R.M., **12**-0599, **16**-1899
Wehmschulte, R.J., **05**-0175
Wehn, P.M., **12**-0228
Wehner, G., **16**-1205, **17**-0256
Wehner, W., **03**-0144
Wei, B., **13**-0414, **16**-1913, **16**-1915, **16**-1919, **16**-1920
Wei, C., **10**-1776, **16**-0296, **16**-0297, **16**-0299, **16**-0603, **16**-0887, **16**-0890
Wei, D., **19**-1520
Wei, H.-X., **15**-1609, **15**-1613, **15**-1881, **16**-0769, **16**-0782, **16**-0785, **16**-0798, **16**-1001, **19**-0563
Wei, H.X., **16**-0786
Wei, J., **12**-0440
Wei, J.-W., **15**-1288

Wei, L.-L., **15**-0481, **15**-0918, **15**-1056, **15**-1286, **15**-1690, **15**-1706, **16**-1005, **16**-1108
Wei, L.-M., **15**-0481, **15**-0918, **16**-1671
Wei, L.L., **16**-0410
Wei, Q., **15**-0287
Wei, S., **16**-1258
Wei, T., **19**-1054
Wei, X., **15**-0886, **15**-1791, **16**-1292
Wei, Z.-L., **19**-1021, **19**-1022
Wei, Z.-Y., **16**-1792
Wei, Z.Y., **10**-1523
Weiberth, F.J., **16**-0952
Weichold, O., **13**-0484
Weickhardt, K., **12**-0352
Weickhardt, K., **18**-0363
Weidert, P.J., **04**-0193
Weidmann, B., **16**-0520
Weidmann, H., **16**-0813, **19**-1645, **19**-1715
Weidmann, R., **04**-0214
Weidner, J., **10**-0317
Weidner-Wells, M.A., **15**-1939
Weigand, B., **16**-0234
Weigand, K., **13**-0186
Weigel, H., **11**-0216
Weigel, L.O., **19**-1098
Weigert, F.J., **04**-0417
Weigmann, H., **16**-1297
Weil, T.A., **13**-0598
Weiler, L., **04**-0387, **04**-0390, **10**-0758, **16**-1168, **18**-0797
Weill-Raynal, J., **04**-0136, **10**-1749, **18**-0420
Weinberg, D.S., **10**-1096
Weinberg, H.R., **19**-0010
Weinberg, N., **16**-0044
Weinberg, N.L., **19**-0010
Weinberg, W.H., **13**-0177
Weinberger, B., **10**-1845
Weiner, B., **15**-1323
Weiner, D.P., **10**-0582
Weiner, H., **10**-0086
Weiner, L., **15**-1756
Weiner, M.A., **05**-0149
Weiner, P.K., **05**-0332
Weiner, S.A., **13**-0666
Weingarten, H., **13**-0120, **16**-0274, **16**-0289, **16**-1805
Weinheimer, A.J., **15**-0492
Weinhold, F., **02**-0023
Weinig, P., **16**-0684
Weinkauff, D.J., **04**-0151
Weinkötz, S., **16**-2088
Weinlich, J., **04**-0478
Weinman, S.A., **04**-0031
Weinmann, H., **19**-0067
Weinreb, S.M., **10**-0899, **15**-0344, **15**-0387, **15**-1282, **15**-1583, **15**-1641, **15**-2122, **16**-0343, **16**-1729, **16**-1835, **16**-1960, **16**-1967, **18**-0817, **19**-0395
Weinshenker, N.M., **19**-0159
Weinstein, R.D., **15**-2036
Weinstein, R.M., **16**-0510, **16**-0511
Weinstein, S., **04**-0170, **04**-0172, **04**-0188, **17**-0047
Weinstock, L.M., **12**-0216
Weintraub, L., **16**-1851
Weinwurzel, D.H., **10**-0209
Weinwurzel, D.H., **10**-0209
Weirich, R., **13**-0456
Weise, A., **10**-0408
Weiser, J., **04**-0326
Weisgerber, G., **10**-1835
Weisman, G.R., **04**-0207, **04**-0241, **05**-0231
Weisman, R.B., **05**-0298
Weismiller, M.C., **19**-0501
Weiss, A., **14**-0102
Weiss, A.W., **01**-0003
Weiss, B., **13**-0036
Weiss, D.S., **07**-0025, **07**-0044, **15**-2235
Weiss, E., **05**-0131, **05**-0147, **05**-0153, **05**-0161
Weiss, J., **02**-0064, **10**-0014, **16**-1720
Weiss, K., **14**-0352
Weiss, M.M., **13**-0378
Weiss, R., **05**-0063, **05**-0075, **10**-0391, **10**-0396, **11**-0424, **11**-0454
Weiss, R.C., **15**-0433
Weiss, R.G., **10**-1096, **11**-0557
Weiss, S., **04**-0276, **10**-0871
Weissbach, O., appendix**A**-0024
Weissberger, A., **04**-0102, **06**-0006, **06**-0022, **06**-0030, **06**-0037, **06**-0038, **06**-0041, **06**-0052, **06**-0053, **06**-0056, **06**-0058, **06**-0059, **08**-0160, **09**-0016, **15**-0401, **19**-0873
Weissbuch, I., **04**-0102, **04**-0188
Weissenbach, P., **11**-0034
Weisser, H.R., **18**-0725
Weissermel, K., **15**-1579
Weissman, H., **13**-0431
Weissman, P.M., **19**-1115
Weissman, S., **10**-1128
Weissman, S.A., **15**-0675, **19**-1018
Weitl, F.L., **10**-0060
Weitz, E., **15**-1788
Weitz, I.S., **15**-0532
Weitzberg, M., **15**-2165
Welch, C.J., **04**-0176, **09**-0105
Welch, D.S., **16**-0794
Welch, J., **10**-1086, **10**-1178, **16**-1883
Welch, J.T., **15**-0168, **15**-1545
Welch, M.J., **14**-0436
Welch, S.C., **19**-1376
Welch, S.L., **13**-0498
Welch, T.R., **18**-0609
Welder, C., **19**-1339
Welker, C.H., **18**-0688
Welker, M.E., **15**-0430
Well, P.R., **09**-0037
Weller, A., **07**-0017
Weller, H.N., **19**-0241
Weller, T., **16**-2012
Weller, W.T., **16**-1650
Welling, L.L., **16**-0248
Wellmann, J., **10**-1243
Wells, A.P., **02**-0092, **02**-0114
Wells, J.I., **10**-0150
Wells, P.R., **01**-0029, **09**-0006, **09**-0016, **09**-0018, **09**-0047, **10**-0351, **11**-0073, **14**-0043
Wells, S., **10**-0392
Wells, W.E., **10**-0382
Welsh, K.M., **14**-0161
Welsher, T.L., **02**-0210
Welter, T.R., **18**-0852
Welton, T., **09**-0109, **09**-0111, **15**-0525, **15**-0531, **15**-2041
Welvart, Z., **06**-0069, **12**-0695, **16**-0540, **16**-1190, **18**-0413, **18**-0416
Wen, J.Q., **12**-0102
Wen, X., **16**-0834
Wen, X., **19**-1186, **14**-0060
Wenchen, H., **02**-0120
Wendel, K., **02**-0223
Wender, I., **10**-1837, **12**-0304, **13**-0598, **14**-0443, **15**-0549, **15**-1375, **15**-2362, **18**-0837
Wender, P., **15**-1377, **15**-1477, **15**-1499, **15**-1504
Wender, P.A., **15**-1422, **10**-1560, **10**-1653, **15**-0775, **15**-0842, **15**-0877, **15**-1421, **15**-2235, **15**-2435, **15**-2439, **15**-2440, **16**-1459, **18**-0575, **18**-0601, **18**-0799
Wenderoth, B., **10**-1381, **10**-1389, **16**-0493
Wendling, F., **16**-1137
Wendschuh, P.H., **18**-0485
Wendt, M.D., **04**-0124
Wengenroth, H., **12**-0646
Wenjie, H., **02**-0120
Wenke, G., **19**-0847

Wenkert, E., **10**-1306, **10**-1511, **10**-1521, **10**-1532, **15**-0867, **15**-1985, **15**-2350, **19**-0587, **19**-1436
Wennerbeck, I., **04**-0228
Wennerström, O., **02**-0295, **02**-0305, **02**-0307, **02**-0326
Wensing, M., **12**-0625
Went, C.W., **10**-1676
Wentrup, C., **04**-0476, **04**-0486, **04**-0497, **04**-0498, **05**-0383, **05**-0407, **06**-0038, **10**-0479
Wentworth Jr., P., **12**-0327, **15**-1955
Wentworth, A.D., **12**-0327
Wenz, G., **04**-0175
Wenzel, T.T., **02**-0254
Wenzinger, G.R., **10**-0150
Wepster, B.M., **02**-0058, **09**-0064, **11**-0051, **11**-0159
Werkman, C.H., **04**-0253
Wermeckes, B., **19**-0482
Wermer, M., **05**-0212
Werner, E.A., **10**-0863
Werner, H., **02**-0169, **12**-0345, **12**-0345
Werner, N.D., **14**-0047, **16**-1571
Werner, T., **19**-0490
Werner, U., **03**-0152, **04**-0244
Werner, W., **16**-1634
Werness, P.G., **02**-0080
Wernett, P.C., **16**-1295
Wersel, O.A., **15**-2112
Werstiuk, N.H., **05**-0125, **05**-0126, **06**-0086, **10**-0179, **12**-0054, **17**-0280, **17**-0390, **18**-0475
Werth, R.G., **18**-0100
Werthemann, L., **18**-0676
Wertz, D.W., **04**-0382
Wertz, J.E., **05**-0208
Wescott, S.A., **15**-0696
Weskamp, T., **10**-1303
West, C.T., **19**-1303, **19**-1450
West, F.G., **12**-0368, **15**-0852, **15**-0853, **15**-1412, **16**-1313
West, J.C., **11**-0117
West, K., **08**-0147
West, K.N., **10**-0411
West, P., **12**-0413
West, P.R., **04**-0479
West, R., **01**-0009, **01**-0011, **01**-0012, **02**-0342, **02**-0346, **02**-0347, **03**-0051, **05**-0149, **12**-0399, **15**-2197, **18**-0900
Westaway, K., **07**-0101
Westaway, K.C., **06**-0069, **06**-0081, **06**-0084, **06**-0085, **07**-0101, **10**-0313, **10**-0327, **10**-0414
Westaway, S.M., **10**-1404
Westberg, H.H., **18**-0840, **18**-0843, **19**-0446
Westbrook J.A., **16**-1188
Westcott, S.A., **15**-0696, **19**-1609
Westdorp, I., **19**-1727
Westerberg, G., **09**-0108
Westerkamp, J.F., **16**-2064
Westerlund, C., **10**-1275
Westerman, P.W., **05**-0039, **05**-0063, **05**-0075, **05**-0092, **11**-0013
Westermann, E., **13**-0397
Westermann, J., **10**-1381, **10**-1383, **10**-1508, **15**-0616, **15**-1058, **16**-0493, **16**-0677
Westheimer, F.H., **10**-0526, **12**-0648, **16**-0290, **19**-0248, **19**-0250
Westhus, M., **18**-0777
Westlake, P.J., **19**-1533
Westley, J.W., **04**-0169, **04**-0209
Westman, F., **15**-0264
Westman, G., **16**-0798
Westman, J., **07**-0116
Westmijze, H., **12**-0500, **12**-0544, **5**-0951
Westmoreland, I., **15**-1905
Weston, J., **05**-0183
Weston, J.B., **11**-0097
Westphal, J., **15**-2076
Westrum Jr., E.F., **01**-0093
Westwood, D., **16**-0493, **16**-1413
Westwood, N.P.C., **01**-0013
Westwood, S.W., **14**-0097
Wette, M., **18**-0567
Wetter, H., **12**-0035, **12**-0036, **15**-0707
Wetterich, F., **05**-0242, **14**-0057, **14**-0092
Wetterling, M., **12**-0414
Wettermark, G., **04**-0219
Wetzel, D.M., **05**-0123
Wetzel, W.H., **17**-0133
Wever, R., **19**-1022
Wexler, S., **14**-0230, **14**-0234, **15**-2158
Wey, S.-J., **15**-1909
Weyerstahl, P., **10**-0242, **10**-0760
Weygand, F., **17**-0254
Weyler Jr., W., **15**-2219
Weymuth, C., **19**-0556
Whaite, K., **16**-1597
Whalen, D.L., **05**-0114
Whalen, E.J., **15**-0135
Whalen, R., **14**-0154
Whaley, W.M., **11**-0400
Whalley, E., **15**-0024
Whalley, W., **17**-0491, **18**-0599, **18**-0704
Whang, D., **03**-0185
Whangbo, M., **01**-0001, **04**-0365, **05**-0121
Wharton, P.S., **18**-0205
Whatley, L.S., **03**-0051
Wheatley, P.J., **03**-0090
Wheeler, C., **10**-0411
Wheeler, D.M.S., **15**-0134
Wheeler, O.H., **16**-1770, **17**-0087, **17**-0100, **18**-0875, **18**-0876, **19**-0628, **19**-0913, **19**-1095, **19**-1482
Wheeler, R.A., **15**-1826
Whelan Jr., W.P., **10**-0012
Whelan, H.M., **16**-1954
Whelan, J., **15**-1361
Wheland, G.W., **02**-0001, **02**-0129, **02**-0140, **04**-0001, **04**-0126, **18**-0012, **18**-0030
Wheless, K., **19**-1385
Whetten, R.L., **02**-0356
Whiffen, D.H., **01**-0053
Whimp, P.O., **04**-0480
Whipple, L.D., **12**-0017
Whitby, R.J., **15**-0778
Whitcombe, G.P., **19**-0123
Whitcombe, N.J., **13**-0364
White, A.D., **19**-0123
White, A.H., **10**-0652
White, A.J.P., **03**-0186, **03**-0187, **03**-0200
White, A.M., **05**-0041, **05**-0060, **05**-0090, **08**-0008, **10**-0187, **10**-0528, **18**-0108
White, A.W., **11**-0222, **15**-0877
White, C.G.H., **04**-0348
White, C.T., **04**-0153, **16**-1034
White, D.H., **14**-0436
White, D.N.J., **18**-0432
White, D.R., **16**-1219
White, E.H., **07**-0026, **10**-0049, **10**-0393, **10**-0395, **10**-0907, **17**-0243, **18**-0099
White, E.P., **15**-1538
White, F., **10**-1725
White, H.S., **11**-0576, **11**-0580
White, J., **18**-0160
White, J.B., **15**-0502
White, J.D., **04**-0493, **10**-0661
White, J.M., **01**-0064, **04**-0241, **08**-0186, **16**-1784, **17**-0281, **19**-1127
White, K.B., **19**-0203
White, K.S., **18**-0681
White, L.S., **13**-0402
White, M.G., **11**-0629
White, M.A., **15**-1879, **19**-0121

White, M.C., **19**-0539
White, P., **19**-0043
White, P.D., **16**-1642, **16**-1643
White, P.S., **04**-0361
White, P.S., **15**-2356
White, R., **15**-2202
White, R.F.M., **11**-0013
White, R.W., **19**-0350, **19**-0351
White, S., **10**-1661
White, S.B., **11**-0215
White, V.A., **11**-0587
White, W., **05**-0386
White, W.A., **16**-0274, **16**-0289
White, W.N., **10**-0226, **11**-0570, **11**-0574, **11**-0576, **11**-0577, **11**-0578, **11**-0580, **18**-0654, **18**-0708, **18**-0710
Whitehead M.A., **08**-0151
Whitehead, A.J., **15**-0311
Whitehead, M., **18**-0272
Whiteling, S.C., **17**-0035
Whitener, G.D., **07**-0119
Whitesell, J.K., **04**-0136, **04**-0196, **04**-0264, **10**-1656, **10**-1674, **10**-1686
Whitesell, M.A., **10**-1656, **10**-1674
Whitesides, G.M., **04**-0151, **04**-0208, **05**-0171, **05**-0171, **10**-1334, **10**-1350, **12**-0013, **12**-0535, **12**-0605, **12**-0605, **12**-0606, **12**-0611, **13**-0122, **14**-0375, **14**-0377, **14**-0378, **15**-0467, **15**-1063, **15**-1172, **16**-1521, **16**-1687, **19**-0727
Whitesides, T., **19**-0446
Whitfield, D.M., **04**-0272
Whitham, G.H., **15**-0187, **16**-1236, **17**-0343
Whiting, A., **12**-0456
Whiting, A., **12**-0493
Whiting, M.C., **03**-0091, **10**-0217, **10**-0280, **10**-0402, **10**-1050, **15**-0445, **16**-0300, **17**-0280, **18**-0022, **18**-0102
Whitlock Jr., H.W., **10**-1649, **18**-0110
Whitman, D.W., **02**-0217
Whitman, G.M., **15**-0315, **15**-1503
Whitmire, K.H., **16**-2088
Whitmore, F.C., **10**-0397, **15**-0030, **16**-0513, **18**-0003, **18**-0013
Whitney, C.C., **18**-0446, **18**-0447
Whitney, D.B., **16**-1818
Whitney, G.C., **10**-1636
Whitney, S., **12**-0560
Whitney, T.A., **19**-1616
Whittaker, D., **05**-0002, **10**-0638, **18**-0096, **18**-0211, **19**-0975, **19**-0977
Whittaker, D.T.E., **10**-1225, **15**-1254
Whittaker, G., **18**-0523
Whittaker, M., **16**-1654
Whitten, C.E., **10**-1352, **10**-1370, **15**-1072, **15**-1073, **16**-1893, **16**-1894
Whittington, B.I., **15**-0134, **15**-0138
Whittle, A.J., **11**-0217, **11**-0423
Whittle, A.J., **12**-0163
Whittle, R.R., **16**-1303
Whitworth, S.M., **03**-0061, **10**-0280
Whyman, R., **15**-1494
Wibaut, J.P., **19**-0357
Wibbeling, B., **16**-1300, **16**-2088
Wiberg, A., **02**-0431
Wiberg, K.B., **01**-0089, **01**-0108, **02**-0037, **02**-0041, **02**-0056, **04**-0015, **04**-0118, **04**-0278, **04**-0279, **04**-0302, **04**-0305, **04**-0308, **04**-0321, **04**-0336, **04**-0388, **04**-0402, **04**-0404, **04**-0405, **04**-0409, **04**-0418, **04**-0420, **04**-0424, **04**-0431, **04**-0432, **04**-0435, **04**-0448, **04**-0465, **04**-0519, **04**-0519, **05**-0047, **06**-0053, **08**-0013, **08**-0166, **08**-0167, **08**-0193, **10**-0150, **10**-0192, **10**-0195, **10**-0197, **10**-0199, **10**-0201, **10**-0324, **10**-1235, **14**-0165, **15**-0131, **15**-0141, **15**-0143, **17**-0422, **18**-0042, **18**-0162, **18**-0623, **18**-0876, **19**-0002, **19**-0003, **19**-0004, **19**-0247, **19**-0250, **19**-0251, **19**-0311, **19**-0425, **19**-0466, **19**-0467, **19**-0630, **19**-0711
Wiberg, N., **01**-0009, **01**-0011, **15**-0488
Wicenec, C., **16**-2174
Wicha, J., **19**-0408
Wick, A., **17**-0411
Wickberg, B., **16**-1958
Wickham, G., **12**-0035, **12**-0037
Wicks, G.E., **19**-0771
Widdison, W.C., **14**-0457
Widdowson, D.A., **10**-1852, **12**-0403, **13**-0282, **13**-0501, **13**-0718, **15**-1721
Widehem, R., **10**-0913
Wideman, L.G., **19**-0836
Widenhoefer, R.A., **15**-0226, **15**-0233, **15**-0764, **15**-0765, **15**-0770, **15**-0774, **15**-0818, **15**-0820, **15**-0890, **15**-0896, **15**-0896
Widhalm, M., **04**-0175, **15**-0596, **16**-0687
Widing, H.F., **01**-0046, **09**-0059
Widmer, J., **10**-0781, **10**-1482, **19**-1531
Wiechell, H., **17**-0326
Wiechert, R., **16**-1072
Wiedemann, W., **15**-2322, **18**-0469, **18**-0470, **18**-0507
Wiegand, N.H., **18**-0646
Wiegers, K.E., **17**-0031
Wieghardt, K., **03**-0115, **14**-0321
Wieland, D.M., **10**-1542, **10**-1557
Wieland, G., **16**-0943
Wieland, H., **02**-0282
Wieland, L.C., **10**-0544
Wieland, P., **04**-0043, **19**-1067
Wiemer, D.F., **10**-1150
Wiering, J.S., **15**-1806
Wieringa, J.H., **15**-0008
Wiersum, U.E., **17**-0229, **18**-0519
Wiesboeck, R., **17**-0042
Wiese, K.-D., **15**-1481
Wieser, H., **04**-0261
Wieser, H., **04**-0350
Wieser, J.D., **01**-0062
Wieser, K., **19**-0605
Wiest, H., **15**-2001, **15**-2101
Wiest, O., **04**-0311, **15**-2013, **15**-2093, **15**-2231
Wieting, R.D., **05**-0075, **10**-0184
Wife, R., **13**-0577
Wife, R.L., **02**-0274, **15**-2050
Wigal, C.T., **15**-1171
Wigfield, D.C., **16**-1561, **19**-0951, **19**-1060, **19**-1063
Wiggin, C.J., **19**-0074
Wiggins, G., appendixA-0039
Wiglesworth, C., **19**-0472
Wijers, H.E., **10**-0826
Wijkens, P., **10**-1363
Wijnberg, J.B.P.A., **19**-1022
Wijnen, J.W., **15**-2035
Wilbur, D.S., **15**-2226
Wilby, A.H., **15**-0518, **19**-1232
Wilby, J., **17**-0084
Wilcox Jr., C.F., **02**-0327, **02**-0353
Wilcox, A.L., **10**-0768
Wilcox, C.F., **01**-0042, **10**-0178, **10**-1636
Wilcox, C.S., **15**-1938, **18**-0677

Wilcoxen, K., **13**-0430
Wild, D., **15**-2076
Wilder Jr., P., **18**-0101
Wildsmith, E., **10**-0992
Wildt, H., **18**-0849
Wilen, S.H., **03**-0203, **04**-0001, **04**-0009, **04**-0098, **04**-0100, **04**-0115, **04**-0116, **04**-0117, **04**-0126, **04**-0156, **04**-0156, **04**-0157, **04**-0158, **04**-0259, **04**-0274, **04**-0316, **04**-0351, **04**-0376, **04**-0424, **10**-0109
Wiley, D.W., **15**-0073, **15**-2192
Wiley, G.A., **10**-0170, **10**-1096, **13**-0252
Wiley, P.F., **10**-0077
Wilfred, C.D., **16**-0341
Wilhelm, E., **15**-1637
Wilhelm, R., **13**-0501
Wilhelm, R.S., **10**-1337, **10**-1355, **10**-1356, **10**-1540, **12**-0570, **15**-1075, **15**-1076
Wilk, B.K., **10**-1801, **16**-1165, **16**-1518
Wilk, K.A., **17**-0031, **17**-0064, **17**-0072
Wilke, G., **10**-1251, **15**-0501, **15**-0712, **15**-0793, **15**-2429, **15**-2431, **15**-2431
Wilke, J., **04**-0471
Wilkerson, C.R., **16**-1993
Wilkins, C.L., **15**-0016, **16**-1469
Wilkins, J.M., **12**-0560, **16**-0581
Wilkins, R.F., **16**-0407
Wilkinson C., **18**-0756
Wilkinson, A.L., **11**-0083
Wilkinson, B.L., **16**-1637
Wilkinson, D.E., **16**-1538
Wilkinson, F., **07**-0011
Wilkinson, G., **02**-0043, **12**-0276, **14**-0444, **15**-0407, **15**-0410, **15**-0416, **15**-0463
Wilkinson, H.S., **19**-1207
Will, B., **15**-1841
Willard, A.K., **18**-0677, **18**-0687
Willard, G.F., **17**-0177
Willard, J.E., **14**-0137
Willaredt, J., **08**-0084
Willaredt, R.P., **13**-0742
Willcott III, M.R., **18**-0591
Willcott, M.R., **18**-0590
Willem, R., **15**-2407
Willett, G.D., **02**-0409
Willey, P.R., **14**-0413
Willi, A.V., **06**-0068, **06**-0082, **08**-0135, **11**-0612, **11**-0613, **17**-0003, **17**-0062
Williams II, T.C., **16**-0386
Williams Jr., J.M., **05**-0138, **10**-0535, **17**-0348, **17**-0353
Williams Jr., L.P., **18**-0120
Williams Jr., V.Z., **18**-0114, **18**-0116
Williams, A., **09**-0083, **16**-0015, **16**-0424, **16**-1569, **16**-1570, **16**-1571, **16**-2067, **16**-2143, **16**-2146, **17**-0486
Williams, A.D., **15**-1047
Williams, A.J.S., **19**-1244
Williams, A.L., **15**-1278, **16**-0947
Williams, D., **03**-0200, **15**-1677
Williams, D.A., **12**-0013, **12**-0015, **15**-1254
Williams, D.J., **02**-0270, **02**-0312, **03**-0184, **03**-0186, **03**-0187, **16**-0493, **18**-0427, **19**-0058
Williams, D.L.H., **02**-0392, **10**-0518, **10**-0750, **10**-0755, **10**-0756, **11**-0037, **11**-0158, **11**-0161, **11**-0543, **11**-0570, **11**-0572, **11**-0575, **11**-0581, **11**-0583, **11**-0584, **12**-0195, **12**-0196, **12**-0197, **12**-0198, **12**-0699, **13**-0032, **13**-0075, **13**-0698, **13**-0699, **13**-0770, **18**-0739, **18**-0883
Williams, D.R., **10**-0614, **10**-1661, **15**-1160, **19**-0708, **19**-1149
Williams, E.D., **19**-0977
Williams, F., **05**-0326
Williams, F.J., **10**-0151, **18**-0846
Williams, F.V., **08**-0219
Williams, G.D., **15**-2297
Williams, G.H., **11**-0589, **13**-0736, **14**-0027, **14**-0031, **14**-0288, **14**-0325
Williams, G.J., **19**-0370
Williams, G.J., **19**-0374
Williams, G.R., **02**-0191
Williams, I.D., **15**-1825, **19**-0583
Williams, J., **08**-0147
Williams, J.K., **15**-2192
Williams, J.L.R., **15**-2252
Williams, J.M., **03**-0053, **13**-0274, **15**-0446
Williams, J.M.J., **10**-0897, **10**-1463, **13**-0400, **13**-0411, **13**-0412, **15**-0904, **17**-0001
Williams, K., **15**-1049
Williams, K.B., **05**-0094
Williams, K.J., **10**-0916, **15**-0268
Williams, L., **14**-0452
Williams, L.M., **16**-0848
Williams, M.J., **16**-0340
Williams, M.R.V., **19**-1171
Williams, N.H., **04**-0342
Williams, P.H., **15**-1776, **15**-1789, **18**-0366
Williams, R., **16**-0777
Williams, R.V., **02**-0290
Williams, R.E., **10**-0173, **12**-0050, **12**-0341, **16**-1817, **16**-2010
Williams, R.H., **18**-0449
Williams, R.J., **17**-0124, **17**-0144
Williams, R.M., **04**-0134, **16**-1448
Williams, R.O., **15**-1393, **17**-0015
Williams, R.V., **02**-0280, **15**-1997, **18**-0642
Williams, T., **04**-0203
Williams, T.J., **15**-2435
Williams, W.G., **18**-0075
Williamson, D.G., **19**-0357
Williamson, D.H., **15**-0406
Williamson, J.S., **16**-0357, **19**-1135
Williamson, K.L., **01**-0033
Williard P.G., **08**-0199, **04**-0235, **04**-0246, **05**-0173, **05**-0188, **05**-0191, **05**-0191, **08**-0211, **08**-0212, **08**-0213, **10**-0342, **10**-0798, **19**-0235
Willis Jr., J.N., **04**-0385
Willis Jr., W.W., **17**-0292
Willis, A.C., **02**-0241
Willis, B.J., **17**-0525
Willis, C., **15**-0485
Willis, C.R., **19**-1301, **19**-1415
Willis, D.M., **13**-0730
Willis, J.B., **10**-0313
Willis, M.C., **10**-0621, **15**-0993
Willner, I., **02**-0172, **02**-0184, **02**-0274, **02**-0297
Willoughby, C.A., **19**-1154
Wills, M., **15**-1814, **19**-1042
Willson, T.M., **16**-0743
Willy, W.E., **04**-0381, **10**-1048
Wilsey, S., **18**-0533
Wilshire, C., **16**-1422
Wilson Jr., E.B., **04**-0296, **19**-0288
Wilson, A.A., **10**-0060, **10**-0395
Wilson, A.C., **12**-0509
Wilson, B., **08**-0238
Wilson, C.C., **03**-0070
Wilson, C.L., **12**-0026, **12**-0027
Wilson, C.V., **14**-0425
Wilson, D., **15**-0878
Wilson, D.R., **03**-0156

Wilson, E.B., **02**-0035, **03**-0051, **04**-0265, **10**-1240
Wilson, F.X., **10**-1538, **17**-0179
Wilson, G.E., **15**-2190
Wilson, H., **05**-0378, **10**-0372, **10**-0408
Wilson, H.R., **17**-0527
Wilson, J., **13**-0491
Wilson, J.D., **02**-0100, **16**-1805
Wilson, J.G., **10**-1544
Wilson, J.M., **12**-0664
Wilson, J.N., **15**-0449
Wilson, J.R.H., **19**-0118
Wilson, J.S., **19**-1402
Wilson, J.Z., **10**-0614
Wilson, K.R., **04**-0094, **04**-0187
Wilson, L.J., **15**-1464
Wilson, M., **15**-1254, **19**-1628
Wilson, M.A., **15**-1581
Wilson, N.D.V., **10**-0726
Wilson, N.H., **15**-2322, **18**-0469, **18**-0470
Wilson, P.W., **05**-0346
Wilson, R.M., **05**-0285, **07**-0047, **07**-0048
Wilson, S.E., **18**-0840, **18**-0845
Wilson, S.L., **14**-0244
Wilson, S.R., **15**-2334, **18**-0901
Wilson, T., **16**-0743
Wilson, V.P., **15**-0167
Wilt, J.C., **10**-1466
Wilt, J.K., **18**-0056
Wilt, J.W., **14**-0087, **15**-0052, **15**-0102, **18**-0054, **18**-0380
Wilterdink, R.J., **17**-0524
Wilzbach, K.E., **04**-0440
Wilzbach, K.E., **18**-0494
Wimmer, E., **18**-0669
Wims, A.I., **19**-0423
Winand, R., **16**-0578
Winans, C.G., **02**-0101
Winchester, W.R., **05**-0154, **05**-0155, **12**-0370
Wind, R.A., **05**-0223
Winemiller, M.D., **05**-0182
Winer, A.M., **05**-0275
Wingard, A.K., **17**-0240
Wingert, H., **12**-0441, **15**-2360, **18**-0495, **18**-0496
Wingrove, A.S., **05**-0138
Winiarski, J., **13**-0670, **13**-0674
Winikov, E.H., **09**-0037
Wink, D., **15**-0463
Wink, D.J., **02**-0254, **15**-0843
Winkel, L., **13**-0454
Winkler, A., **10**-1599
Winkler, H.J.S., **03**-0090, **04**-0074, **04**-0167
Winkler, J.D., **04**-0235, **04**-0246
Winkler, T., **10**-1089, **15**-1642, **16**-1393, **18**-0658
Winn, C.L., **16**-0783, **16**-1384
Winnik, M.A., **06**-0011, **10**-0450, **18**-0374
Winotai, C., **19**-0477
Winotapan, C., **16**-0874
Winstein, S., **02**-0348, **02**-0350, **02**-0350, **04**-0347, **05**-0126, **10**-0055, **10**-0060, **10**-0062, **10**-0066, **10**-0066, **10**-0070, **10**-0105, **10**-0106, **10**-0107, **10**-0123, **10**-0130, **10**-0131, **10**-0132, **10**-0134, **10**-0148, **10**-0152, **10**-0156, **10**-0158, **10**-0170, **10**-0171, **10**-0174, **10**-0177, **10**-0216, **10**-0282, **10**-0334, **10**-0419, **10**-0427, **10**-0430, **12**-0008, **12**-0009, **12**-0034, **17**-0010, **17**-0035, **17**-0069, **17**-0070, **17**-0072, **17**-0077, **17**-0116, **18**-0015, **18**-0028, **18**-0055, **18**-0076, **18**-0103
Winter, A.H., **05**-0410
Winter, J.E., **15**-1731
Winter, J.G., **11**-0587
Winter, J.J.G., **15**-1680
Winter, J.N., **05**-0296
Winter, M.J., **15**-2362
Winter, P.R., **05**-0269
Winter, R.A.E., **17**-0338, **17**-0342
Winter, R.E.K., **18**-0472
Winter, R.L., **14**-0048
Winter, S.B.D., **16**-1601
Winter, S.R., **10**-1814, **10**-1843, **10**-1844
Winter, W., **05**-0230
Winterfeldt, E., **15**-0048
Winterfeldt, E., **15**-0079, **15**-0088, **18**-0691, **19**-0010
Winterman, D.R., **08**-0086
Wintermute, R.D., **18**-0126
Winum, J.-Y., **18**-0213
Wipf, P., **09**-0092, **10**-0235, **15**-0907, **15**-2016, **16**-0687, **18**-0661, **18**-0679
Wipff, G., **05**-0121
Wipke, W.T., **18**-0115, **18**-0535
Wippel, H.G., **16**-1305
Wireko, F., **04**-0142
Wirschun, W.G., **16**-1457
Wirth, T., **14**-0140, **15**-1591, **19**-0197
Wirthwein, R., **13**-0049
Wirz, J., **07**-0021, **02**-0331, **02**-0381, **02**-0383, **02**-0386, **02**-0412, **05**-0408, **08**-0057, **12**-0084, **12**-0097, **12**-0101, **12**-0150, **15**-0215
Wischmeyer, U., **15**-0778
Wise, L.D., **04**-0325, **19**-1357
Wiseman, J.R., **04**-0493, **04**-0494, **04**-0496, **10**-0044, **10**-0572
Wishnok, J.S., **18**-0493
Wiskott, E., **15**-2196
Wiskur, S.L., **10**-1422
Wisotsky, M.J., **05**-0048, **05**-0061, **08**-0022
Wistrand, L., **13**-0115
Wistrand, L.-G., **13**-0675, **13**-0725, **14**-0270
Wistuba, E., **18**-0035, **18**-0377
Witanowski, M., **05**-0171
Witanowski, M., **05**-0171
Witherington, J., **10**-1538
Witholt, B., **19**-0543, **19**-0544, **19**-0545, **19**-0546, **19**-1501
Witt, K.E., **19**-1720
Witt, O.N., **11**-0035
Witte, K., **10**-0212, **10**-0229
Wittenberg, R., **16**-1976
Wittenberger, S.J., **15**-1004, **16**-1634
Wittig, C.M., **15**-0030
Wittig, G., **04**-0475, **04**-0478, **04**-0484, **05**-0151, **08**-0145, **10**-1285, **12**-0414, **13**-0037, **13**-0759, **13**-0763, **14**-0361, **15**-2077, **15**-2323, **16**-1056, **16**-1255, **16**-1286, **16**-1297, **16**-1337, **17**-0193, **17**-0255, **18**-0408
Wittman, M., **10**-0855
Wittman, M.D., **19**-0756
Wittmann, D.K., **10**-1607
Witulski, B., **15**-2382, **15**-2384
Witz, M., **11**-0314
Witzel, H., **05**-0053, **10**-0520
Wladislaw, B., **19**-1782
Wligus, C.P., **16**-0130
Wlodarczak, L., **15**-1643
Wlostowski, M., **10**-1801
Włostowska, J., **15**-2268
Wnuk, T.A., **10**-0964
Wo, S., **10**-1797
Wodrich, M.D., **02**-0040
Woell, J.B., **10**-1859, **10**-1860, **10**-1861
Woerpel, K.A., **10**-1433, **15**-0736, **15**-2297
Woggon, W., **19**-0470
Woggon, W.-D., **19**-1042
Wohl, J., **15**-1166
Wohl, R.A., **17**-0406
Wohlhieter, G.E., **15**-1213
Wojciechowski, B.J., **19**-0371

Wojciechowski, K., **10**-1580, **13**-0672
Wojciechowski, M., **10**-0065
Wojcik, J.M., **13**-0591
Wojnarowski, W., **10**-0318, **18**-0509
Wojtkowiak, B., **09**-0016
Wojtkowski, P.W., **10**-1651, **10**-1760, **10**-1760
Wójtowicz, H., **19**-0707
Wolber, G.J., **10**-0228
Wolckenhauer, S.A., **15**-1000
Wold, S., **09**-0029, **10**-0178, **12**-0063
Woldhuis, A.F., **11**-0199
Wolf, A.D., **10**-0188
Wolf, A.P., **11**-0311, **13**-0752, **14**-0051, **18**-0029, **18**-0119, **18**-0557
Wolf, C., **05**-0351, **13**-0504, **13**-0544
Wolf, D.C., **18**-0262
Wolf, G.C., **15**-1600
Wolf, J.F., **05**-0092, **08**-0223, **08**-0235, **19**-0691
Wolf, L.B., **15**-0395
Wolf, M.A., **16**-0494
Wolf, P., **15**-0075
Wolf, S., **07**-0097, **16**-1173
Wolf, S.A., **15**-0084
Wolf, W., **14**-0333, **14**-0335
Wolfarth, E.F., **18**-0710
Wolfe Jr., J.R., **10**-0088
Wolfe, J.F., **13**-0052, **13**-0589, **16**-1648, **16**-1715
Wolfe, J.P., **13**-0174, **13**-0175, **13**-0183, **13**-0188, **13**-0198, **13**-0473, **19**-0285
Wolfe, S., **04**-0285, **04**-0285, **04**-0365, **05**-0119, **05**-0120, **05**-0121, **10**-0020, **10**-0358, **10**-0364, **10**-0367, **10**-0989, **10**-1158, **15**-1674, **15**-1674, **16**-0044, **16**-1213, **19**-0408, **19**-1788
Wölfel, G., **10**-0870
Wolfenden, J.H., **11**-0109
Wolff, C., **02**-0064, **04**-0091
Wolff, H.P., **04**-0119
Wolff, M.A., **15**-0647, **15**-0650
Wolfinger, M.D., **17**-0346
Wolford, L.T., **10**-1032
Wolford, R.K., **08**-0231
Wolfrom, M.L., **19**-0344
Wolfsberg, M., **02**-0218, **06**-0059
Wolfson, A., **19**-0120
Wolinsky, J., **12**-0164, **16**-1465, **19**-1582
Wolk, J.L., **10**-0023, **10**-0319
Wolke, S.I., **13**-0481
Wolkoff, P., **17**-0304
Wolkowski, J.P., **13**-0583
Wollenberg, R.H., **16**-1652, **16**-1655
Wollmann, T.A., **16**-1025
Wollweber, D., **05**-0290
Wolman, Y., **08**-0156, appendixA-0001
Wolner, D., **19**-0065
Wolochowicz, I., **19**-1712
Wolovsky, R., **02**-0272, **02**-0273, **02**-0291, **14**-0303, **18**-0824, **18**-0825
Wolter, D., **14**-0292
Wolter, M., **13**-0118, **13**-0232
Wolters, E.T.M., **16**-1843
Wolthius, E., **19**-1465
Won, C.M., **11**-0613
Won, H.S., **15**-0835
Wong, A., **09**-0105
Wong, C., **16**-1521
Wong, C.-H., **16**-0627, **16**-1687
Wong, C.K., **14**-0406, **19**-1589
Wong, C.M., **10**-1685, **16**-0250, **18**-0209, **19**-1364
Wong, C.-H., **10**-1642
Wong, H., **11**-0436, **19**-0664
Wong, H.C., **17**-0234
Wong, H.L., **15**-1885
Wong, H.N.C., **02**-0243, **03**-0155, **04**-0407, **04**-0410, **05**-0324, **15**-0128, **17**-0192, **18**-0161, **18**-0569, **18**-0580, **18**-0614
Wong, H.S., **10**-1451
Wong, J.C.Y., **18**-0816
Wong, K.-T., **10**-1155, **12**-0459
Wong, K.-Y., **15**-1133, **15**-1762
Wong, K.-y., **16**-0687
Wong, M., **07**-0070
Wong, M.-K., **15**-1746, **15**-1768, **15**-1773, **15**-1779, **15**-1768
Wong, M.S., **17**-0234
Wong, M.Y.H., **19**-0975
Wong, N.R., **18**-0520
Wong, R.J., **17**-0073
Wong, S.C., **08**-0123
Wong, S.M., **12**-0030
Wong, T., **17**-0192
Wong-Ng, W., **01**-0011
Woo, E.P., **02**-0291, **02**-0327
Woo, J.C., **19**-0231
Woo, J.C.S., **18**-0719
Woo, L.K., **16**-1371
Wood Jr., B.F., **15**-2090
Wood, C.D., **18**-0836
Wood, D.E., **14**-0040
Wood, F.K., **15**-1024
Wood, H.G., **04**-0253
Wood, J., **13**-0114
Wood, J.L., **02**-0080, **03**-0067, **16**-0343
Wood, J.T., **11**-0616
Wood, L.S., **05**-0342
Wood, M.L., **18**-0288
Wood, M.R., **12**-0313
Wood, N.F., **10**-0571
Wood, P.D., **05**-0384
Wood, S.E., **18**-0255
Wood, T.R., **16**-1881
Woodall, T.M., **19**-1032
Woodard, D.L., **11**-0311, **12**-0178
Woodard, R.A., **15**-0280
Woodard, R.W., **04**-0021
Woodard, S.S., **04**-0193, **15**-1821, **15**-1826
Woodburn, H.M., appendixA-0001
Woodbury, R.P., **16**-2019
Woodbury, R.P., **19**-0059
Woodcock, D.J., **10**-0393, **17**-0243, **18**-0099
Woodcock, H.L., **05**-0337
Woodford, B., **16**-1021
Woodgate, P.D., **12**-0161, **14**-0431, **15**-1557, **15**-1581, **15**-1589, **15**-1603, **15**-1604, **15**-1626, **15**-1631, **19**-1435
Woodgate, S.D., **15**-1603
Woodling, R.E., **19**-1018
Woodnutt, D.J., **18**-0896
Woodruff, R.A., **16**-1603
Woods, K.W., **15**-1733
Woodward, R.B., **15**-1683, **15**-2053, **15**-2098, **15**-2103, **15**-2106, **15**-2114, **15**-2116, **15**-2258, **17**-0355, **18**-0393, **18**-0474, **18**-0476, **18**-0525, **18**-0526, **18**-0531, **18**-0622
Woodward, S., **08**-0159, **15**-1136, **15**-1687, **16**-0632, **19**-1030, **19**-1032
Woodworth, C.W., **01**-0048, **15**-0630
Woodworth, R.C., **05**-0329, **15**-2280, **15**-2313
Woody, R.W., **04**-0117
Woolf, J., **15**-2041
Woolf, L.I., **17**-0108, **17**-0118
Woolley, G.T., **10**-0228
Woosley, J., **10**-0807
Worakun, T., **10**-1243
Worden, S., **19**-1335
Workman, P.S., **16**-0659
Worley, J.W., **16**-0004
Worm, K., **11**-0462
Wormser, H.C., **14**-0335

Worrall, J.M., **04**-0372
Worrell, J.H., **10**-0859
Worsch, D., **04**-0164
Worthley, S., **19**-1738
Wothers, P.D., **04**-0454
Wotiz, J.H., **12**-0065, **13**-0080
Wovkulich, P.M., **10**-1511
Woźniak, M., **13**-0677
Wray, V., **04**-0285, **10**-0495
Wright, A., **18**-0900
Wright, B.B., **05**-0328
Wright, D.B., **15**-2219
Wright, D.G., **17**-0116
Wright, D.L., **18**-0792, **18**-0808
Wright, D.R., **17**-0128
Wright, G.F., **02**-0134, **16**-2059
Wright, G.J., **09**-0053, **11**-0057, **11**-0083, **11**-0083, **11**-0107
Wright, J.A., **15**-1430
Wright, J.M., **18**-0487
Wright, M., **17**-0343
Wright, M.E., **10**-1824
Wright, P.T., **15**-2071
Wright, S.C., **02**-0006, **15**-0515
Wright, S.W., **16**-0224
Wrighton, M., **07**-0054
Wrighton, M.S., **15**-0707
Wristers, J., **15**-2199, **18**-0500
Wroble, R.R., **19**-1422
Wrobleski, A., **18**-0298
Wroblewski, A.E., **04**-0127, **04**-0146, **15**-0597
Wu, A., **14**-0169, **14**-0367, **16**-2004, **17**-0168, **17**-0169, **17**-0170, **18**-0117, **19**-1731
Wu, B., **13**-0503, **15**-1471
Wu, C., **11**-0409
Wu, C.Y., **08**-0029, **08**-0031
Wu, D.K., **16**-1219
Wu, E.S.C., **17**-0340
Wu, F., **16**-0687
Wu, G., **10**-0430, **10**-0444, **19**-1186
Wu, H., **16**-1258, **16**-1362, **16**-1644, **19**-1263
Wu, H.-C., **19**-1560
Wu, H.-H., **16**-0150
Wu, H.-P., **15**-0603, **15**-0604
Wu, J., **09**-0105, **10**-0674, **10**-0924, **10**-1571, **13**-0385, **13**-0443, **16**-1258, **19**-1028, **19**-1148
Wu, J.X., **10**-1088
Wu, J.-D., **16**-1067
Wu, J.-S., **10**-0879
Wu, J.H., **15**-1050, **15**-1096
Wu, J.X., **13**-0126, **13**-0270
Wu, L., **10**-0584
Wu, L.-L., **19**-1644
Wu, M.-J., **15**-0481, **15**-0918
Wu, M.-S., **15**-2373, **15**-2387
Wu, M.-Y., **15**-0933
Wu, M.H., **10**-0677
Wu, M.J., **16**-1671
Wu, P., **12**-0370, **18**-0687
Wu, Q.-Q., **16**-0253
Wu, R., **16**-0500
Wu, S., **04**-0180, **10**-1273, **10**-1279, **10**-1309, **15**-0286, **15**-0603, **15**-0821, **15**-0966, **17**-0060, **19**-1028
Wu, S.-H., **15**-0508, **15**-0566, **16**-0662
Wu, T., **12**-0598
Wu, T.-F., **15**-0519, **19**-1042
Wu, T.R., **16**-0699
Wu, T.Y.H., **07**-0118
Wu, W., **15**-0422, **15**-0744, **16**-1155, **19**-1617
Wu, W.-X., **15**-0065
Wu, X., **11**-0245, **19**-1042, **19**-1631
Wu, X.-M., **15**-0985
Wu, X.-Y., **15**-1773
Wu, Y., **03**-0133, **10**-1391, **13**-0237, **15**-1230, **18**-0735, **19**-0952
Wu, Y.-C., **16**-1671
Wu, Y.-D., **15**-1696, **15**-1939, **15**-2118, **16**-1037
Wu, Y.-g., **16**-1538
Wu, Y.-H., **16**-1360
Wu, Y.-J., **07**-0120, **13**-0138, **13**-0213, **13**-0345
Wu, Y.-W., **18**-0061, **06**-0077
Wu, Z., **10**-0509, **13**-0005, **13**-0341, **13**-0711, **15**-1766, **15**-1768, **15**-1773, **16**-0444, **16**-0457, **16**-0459, **16**-0700, **19**-1199
Wu, Z.-W., **10**-0879
Wuchrer, M., **18**-0822
Wudl, F., **02**-0356
Wüest, H., **18**-0407, **19**-0451
Wulf, C.M., **18**-0611
Wulff, C., **16**-0234
Wulff, W.D., **10**-0151, **15**-1926, **15**-2412, **18**-0361, **19**-1374
Wulfman, D.S., **13**-0684, **13**-0690, **13**-0693, **14**-0349, **15**-2292, **17**-0281
Wüllner, R., **18**-0646
Wunderli, A., **18**-0658
Wunderlich, D., **15**-0723
Wunderlich, K., **10**-0739
Würthwein, E.-U., **04**-0070, **16**-0292
Wustrow, D.J., **19**-1357
Wuts, P.G.M., **10**-0613, **10**-0895, **16**-1578, **16**-1761
Wuyts, H., **12**-0465
Wuyts, S., **19**-0120
Wuzik, A., **13**-0237
Wyatt, J.K., **18**-0487
Wyatt, J.L., **05**-0284
Wyatt, P.A.H., **07**-0016
Wyatt, R.J., **01**-0087
Wyckoff, J.C., **12**-0724, **14**-0065, **14**-0154
Wylie, W.A., **13**-0018
Wyman, B.M., **15**-1513
Wyman, D.P., **14**-0148
Wyman, W.E., **18**-0280
Wyn-Jones, E., **04**-0277, **04**-0282
Wynberg, H., **04**-0024, **04**-0010, **04**-0136, **04**-0149, **04**-0186, **11**-0480, **14**-0404, **15**-0008, **15**-1806, **16**-0103, **16**-0695, **16**-2077, **16**-2079, **19**-1587, **19**-1738
Wynn, T., **16**-0643, **16**-1110
Wynne, J.H., **16**-0188
Wynne-Jones, K.M.A., **16**-0044
Wysocki, D.C., **02**-0316
Wysong, R.D., **11**-0259

Xi, C., **10**-1779, **15**-0799, **16**-2000
Xi, F., **19**-1181
Xi, Z., **15**-0799, **15**-1455, **15**-1456
Xia, A.X., **15**-0272
Xia, C., **10**-0737, **19**-0573
Xia, C.-G., **10**-0932, **10**-1163, **13**-0112, **15**-1288, **15**-1309, **15**-1319, **15**-1765, **16**-0420, **16**-0947
Xia, G., **16**-0640, **19**-1684
Xia, L., **02**-0392
Xia, L.-J., **10**-0924
Xia, M., **10**-1425, **13**-0356, **13**-0437
Xia, W., **12**-0292, **16**-0835
Xia, W.-J., **19**-0082
Xia, W.J., **19**-1384
Xia, X., **10**-0018
Xian, M., **18**-0906
Xiang, B., **05**-0182, **15**-2296
Xiang, J., **10**-1773, **15**-1405
Xiao, C., **12**-0437
Xiao, D., **15**-0610, **19**-1155
Xiao, J., **10**-1457, **13**-0496, **13**-0498, **15**-1488, **19**-1042
Xiao, J.-P., **19**-0292
Xiao, L., **10**-0737
Xiao, W., **16**-0354
Xiao, W.-J., **15**-1398, **15**-1401
Xiao, Y., **09**-0113, **15**-2041
Xiaoding, X., **18**-0826

Xiaofeng, G., **02**-0120
Xiaohui, Z., **10**-0592
Xidos, J.D., **15**-2062
Xie, C., **05**-0293
Xie, D., **12**-0275, **13**-0424
Xie, H., **15**-0287, **19**-0241
Xie, J.-H., **15**-0604, **15**-1136, **19**-1028
Xie, L., **12**-0098, **12**-0419, **16**-0977
Xie, Q., **12**-0581
Xie, R., **19**-1035
Xie, R.-G., **13**-0206, **16**-0549
Xie, W., **16**-1962
Xie, X., **13**-0413, **15**-0772
Xie, Y., **02**-0251, **18**-0503
Xie, Y.-X., **13**-0542, **15**-2372
Xie, Y.-Y., **19**-0528
Xin, X.-Q., **19**-0141
Xin, Y., **10**-0467, **16**-0834
Xing, L., **15**-0604
Xiong, H., **12**-0598
Xiong, W., **16**-0552
Xiong, Y., **10**-0046, **13**-0645
Xiu, C.-G., **19**-0617
Xodo, L.E., **04**-0333
Xu, B., **18**-0581
Xu, C., **10**-1326
Xu, C.-Z., **19**-0617
Xu, D., **15**-1658, **15**-1693, **15**-1704, **16**-1825
Xu, D.Q., **10**-0594
Xu, F., **15**-1038
Xu, G., **13**-0156, **15**-0425
Xu, H., **16**-0767
Xu, J., **16**-0462, **16**-0549, **16**-0552, **16**-0628, **16**-0774, **19**-1054
Xu, J.-H., **13**-0177, **13**-0558
Xu, K.-C., **16**-0590
Xu, L., **10**-1453, **10**-1457, **15**-1125, **19**-0107, **19**-1630
Xu, L.-W., **10**-0932, **10**-1163, **13**-0112, **15**-1288, **15**-1309, **15**-1319
Xu, M.-H., **19**-1697
Xu, Q., **15**-1379, **15**-1380, **16**-0687
Xu, Q.-h., **19**-0919
Xu, Q.-Y., **15**-1509
Xu, R., **16**-0645
Xu, W., **15**-2016, **16**-1910
Xu, X., **15**-0354, **15**-1614, **15**-1896, **15**-1944, **16**-0661, **16**-0798, **16**-0980, **17**-0385
Xu, X.-H., **19**-1644
Xu, Y., **12**-0171
Xu, Y.-J., **15**-1128
Xu, Y.-M., **16**-0791, **16**-0796, **16**-0802, **16**-0897
Xu, Y.;Lu, M., **19**-0174
Xu, Z., **03**-0133, **15**-0710, **16**-0549, **16**-0552
Xu, Z.-B., **13**-0171
Xu, Z.-N., **19**-0093, **19**-0094
Xu, Z.Y., **10**-0594
Xue, D., **15**-0575
Xue, L., **04**-0349
Xuong, N.D., **11**-0655

Yabe, A., **10**-1229
Yabe, M., **15**-1341
Yablokov, V.A., **18**-0376
Yabu, M., **16**-0617
Yadani, N., **10**-1796
Yadav, J.C., **18**-0662
Yadav, J.S., **09**-0115, **10**-0556, **10**-0682, **10**-0822, **10**-0823, **10**-0862, **10**-0865, **10**-0930, **10**-0942, **10**-0958, **10**-0963, **10**-1195, **10**-1549, **10**-1550, **10**-1570, **10**-1574, **11**-0195, **11**-0219, **11**-0394, **11**-0435, **13**-0147, **13**-0159, **13**-0655, **14**-0308, **15**-1004, **15**-1035, **15**-1327, **15**-1340, **15**-1606, **15**-2134, **16**-0065, **16**-0080, **16**-0090, **16**-0149, **16**-0167, **16**-0169, **16**-0233, **16**-0252, **16**-0279, **16**-0324, **16**-0332, **16**-0383, **16**-0604, **16**-0749, **16**-0763, **16**-0871, **16**-0930, **16**-1174, **16**-1175, **16**-1374, **16**-1476, **16**-1531, **16**-1608, **16**-1611, **16**-1748, **16**-1906, **17**-0366, **17**-0399, **17**-0439, **18**-0301, **18**-0608, **19**-0031, **19**-0032, **19**-0302, **19**-0864, **19**-1022, **19**-1031, **19**-1214, **19**-1253, **19**-1541, **19**-1551, **19**-1594, **19**-1599, **19**-1613, **19**-1758
Yadav, L.D.S., **10**-0626
Yadav, V.K., **10**-1177, **11**-0332, **15**-0829, **15**-1791, **15**-1800, **16**-0008
Yadav-Bhatnagar, N., **13**-0224
Yadov, J.S., **16**-1341
Yaeger, D.B., **15**-0004, **15**-0033
Yager, W.A., **05**-0328, **05**-0342, **05**-0345, **05**-0399, **05**-0400
Yaghmaie, F., **15**-0458
Yagi, K., **15**-0158, **15**-2427
Yagi, M., **19**-0915
Yagihashi, F., **18**-0338
Yagodin, V.G., **18**-0713
Yaguchi, Y., **15**-1586
Yagupol'skii, L.M., **16**-0448
Yahner, J.A., **16**-2038
Yajima, H., **04**-0212
Yakabe, S., **12**-0113, **15**-0496, **15**-1528, **19**-0688, **19**-0919
Yakebayashi, M., **13**-0380
Yakobson, G.G., **11**-0339, **13**-0076, **13**-0085, **17**-0308
Yakovleva, O.P., **04**-0372
Yakura, T., **18**-0360
Yakushina, L.M., **15**-0295
Yalovskaya, A.I., **10**-1087
Yamabe, S., **10**-0375, **15**-0828, **15**-2004, **15**-2197, **16**-0464, **18**-0071
Yamabe, T., **05**-0111, **12**-0087
Yamada, C., **05**-0275
Yamada, H., **18**-0488, **19**-1254
Yamada, I., **15**-1125
Yamada, J., **15**-1170, **15**-1843, **16**-1905
Yamada, K., **10**-1129, **10**-1415, **15**-0828, **16**-1639
Yamada, K.-i., **15**-1125, **15**-1297, **16**-0418
Yamada, M., **10**-0702, **10**-1805, **15**-1427, **16**-0816, **16**-1839
Yamada, N., **10**-1797
Yamada, S., **04**-0145, **12**-0588, **12**-0691, **12**-0695, **13**-0694, **16**-1686
Yamada, T., **12**-0546, **15**-0185, **15**-0569, **15**-1697, **15**-1886, **15**-2130, **16**-0731, **16**-1422, **19**-0029, **19**-0480, **19**-0661, **19**-0901, **19**-0923
Yamada, Y., **04**-0193, **10**-122, **10**-1823, **12**-022, **14**-0279, **16**-2024
Yamada, Y.M.A., **16**-1043, **19**-0761
yamada, M., **10**-1137
Yamaga, T., **15**-0621
Yamagami, M., **12**-0718, **18**-0884
Yamagishi, F.G., **18**-0391
Yamagiwa, N., **15**-1303, **16**-1041
Yamago, S., **15**-1974
Yamaguchi, F., **04**-0169, **13**-0019
Yamaguchi, H., **03**-0186, **17**-0369, **18**-0840, **18**-0843
Yamaguchi, J., **19**-0287, **19**-0505, **19**-0507
Yamaguchi, J.-i., **16**-1708
Yamaguchi, K., **03**-0185, **03**-0189, **03**-0197, **03**-0210, **05**-0160, **13**-0399, **15**-1731, **15**-1741, **15**-1745, **15**-1951, **16**-0133, **16**-1041, **16**-1914, **19**-0120, **19**-0278, **19**-0571, **19**-1677

Yamaguchi, M., **10**-0831, **10**-1777, **11**-0330, **12**-0069, **13**-0538, **15**-0612, **15**-0780, **15**-1011, **15**-1037, **15**-1427, **16**-1488, **16**-1489, **16**-1655, **16**-1968, **17**-0202, **18**-0331, **19**-0900, **19**-1302, **19**-1358, **19**-1418
Yamaguchi, R., **10**-0882, **10**-0905, **11**-0357, **13**-0663, **15**-0558, **17**-0175, **19**-0690
Yamaguchi, S., **04**-0107, **04**-0202, **16**-0823, **19**-0934
Yamaguchi, T., **14**-0008
Yamaguchi, Y., **05**-0331, **15**-1136, **16**-1491
Yamaichi, A., **15**-1114
Yamaji, M., **10**-0712
Yamakawa, K., **16**-0938, **16**-1220, **18**-0194
Yamakawa, T., **15**-0750
Yamakawa, Y., **15**-0280, **15**-0281
Yamaki, T., **15**-0804
Yamamiya, Y., **10**-0704
Yamamoto H., **16**-0645
Yamamoto, A., **10**-1306, **10**-1868, **10**-1869, **10**-1871, **11**-0342, **12**-0278, **12**-0693, **14**-0299, **16**-0620, **16**-0713, **16**-1106, **16**-1442, **18**-0189, **19**-1769
Yamamoto, C., **19**-1679
Yamamoto, D., **04**-0282
Yamamoto, G., **02**-0322, **03**-0045, **04**-0507, **10**-0404, **12**-0344
Yamamoto, H., **10**-0935, **10**-1040, **10**-1120, **10**-1257, **10**-1260, **10**-1438, **10**-1490, **10**-1522, **10**-1550, **10**-1637, **10**-1637, **10**-1709, **11**-0412, **11**-0413, **12**-0158, **12**-0202, **12**-0368, **12**-0521, **14**-0208, **14**-0213, **15**-0223, **15**-0704, **15**-0707, **15**-0750, **15**-0786, **15**-0971, **15**-1741, **15**-2009, **15**-2063, **15**-2344, **16**-0150, **16**-0508, **16**-0618, **16**-0626, **16**-0640, **16**-0640, **16**-0657, **16**-0676, **16**-0754, **16**-0844, **16**-0855, **16**-1006, **16**-1029, **16**-1046, **16**-1047, **16**-1051, **16**-1054, **16**-1094, **16**-1096, **16**-1121, **16**-1235, **16**-1328, **16**-1329, **16**-1418, **16**-1487, **16**-1530, **16**-1671, **16**-1785, **16**-1801, **17**-0162, **17**-0277, **17**-0410, **18**-0143, **18**-0158, **18**-0339, **18**-0340, **18**-0341, **18**-0551, **19**-0946, **19**-0965, **19**-1244, **19**-1684
Yamamoto, I., **13**-0314
Yamamoto, J., **16**-0268, **18**-0702, **18**-0880
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Yamamoto, M., **15**-1731, **18**-0229, **18**-0465, **19**-0934
Yamamoto, N., **10**-0672, **10**-1453
Yamamoto, O., **18**-0637
Yamamoto, S., **10**-1375, **12**-0319, **12**-0473, **16**-1759, **18**-0440
Yamamoto, S.-y., **16**-1892
Yamamoto, T., **03**-0129, **04**-0229, **10**-1440, **10**-1868, **10**-1871, **12**-0246, **12**-0278, **13**-0218, **16**-0209
Yamamoto, Y., **10**-0234, **10**-0958, **10**-1126, **10**-1261, **10**-1375, **10**-1443, **10**-1509, **10**-1544, **13**-0303, **13**-0667, **14**-0395, **15**-0179, **15**-0211, **15**-0350, **15**-0354, **15**-0362, **15**-0745, **15**-0766, **15**-0771, **15**-0787, **15**-0823, **15**-0854, **15**-0892, **15**-0898, **15**-0931, **15**-0938, **15**-0940, **15**-1082, **15**-1085, **15**-1092, **15**-1126, **15**-1156, **15**-1170, **15**-1313, **15**-1391, **15**-1439, **15**-2171, **15**-2363, **15**-2370, **15**-2372, **15**-2372, **15**-2379, **15**-2384, **15**-2388, **15**-2389, **15**-2393, **15**-2401, **16**-0491, **16**-0493, **16**-0566, **16**-0613, **16**-0871, **16**-0910, **16**-0911, **16**-1017, **16**-1032, **16**-1905, **18**-0429, **18**-0733, **19**-0747, **19**-0896, **19**-1006, **19**-1058, **19**-1330, **19**-1337, **19**-1451, **19**-1678, **19**-1679
Yamamoto, Y., **15**-2379
Yamamura, G.-h., **16**-1892
Yamamura, H., **15**-0707, **16**-0600
Yamamura, K., **03**-0101, **10**-1795
Yamamura, M., **10**-1270
Yamamura, S., **10**-1815, **19**-1434
Yamanaka, H., **19**-0244
Yamanaka, M., **04**-0061, **14**-0175, **15**-0989, **15**-1063, **16**-0902
Yamanaka, R., **19**-1022, **19**-1023
Yamanashi, M., **15**-0808
Yamane, M., **15**-1362
Yamaoka, M., **19**-1387
Yamaoka, Y., **15**-0394, **10**-1418
Yamasaki, A., **11**-0328
Yamasaki, K., **05**-0351, **13**-0430, **15**-1024
Yamasaki, M., **15**-0983
Yamasaki, N., **15**-0155
Yamasaki, R., **10**-0652
Yamasaki, S., **10**-1093, **15**-1568, **15**-1874
Yamase, Y., **11**-0422, **11**-0452
Yamashina, N., **12**-0538
Yamashita, A., **12**-0067, **19**-1772
Yamashita, F., **15**-0735
Yamashita, H., **15**-0238, **15**-0239
Yamashita, K., **10**-0882, **12**-0087, **15**-1457
Yamashita, M., **10**-1304
Yamashita, M., **10**-1453, **10**-1654, **10**-1697, **10**-1815, **10**-1817, **10**-1845, **12**-0532, **12**-0540, **13**-0617, **16**-0086, **18**-0352, **19**-1119, **19**-1606, **19**-1670
Yamashita, S., **16**-0645
Yamashita, T., **10**-0729, **10**-0965, **16**-1990
Yamashita, Y., **15**-1935, **15**-2128, **16**-1121, **16**-1124
Yamataka, H., **05**-0314, **06**-0067, **10**-0027, **10**-0170, **10**-0202, **16**-0530, **16**-0535, **16**-0538, **16**-1294, **19**-0974
Yamatake, T., **19**-0475
Yamato, E., **17**-0459
Yamato, M., **04**-0275, **05**-0351
Yamauchi, A., **12**-0720
Yamauchi, H., **19**-1254, **15**-0923, **19**-0650
Yamauchi, S., **16**-0452, **19**-0922
Yamaura, Y., **12**-0386
Yamawaki, J., **10**-0171, **10**-0971, **16**-2045, **19**-0106
Yamazaki, A., **10**-1779
Yamazaki, H., **10**-1719, **13**-0615, **15**-1262, **15**-2236, **15**-2247, **15**-2405, **15**-2405, **19**-0899, **19**-1306
Yamazaki, J., **14**-0096
Yamazaki, N., **16**-0436

Yamazaki, O., **13**-0321, **13**-0327
Yamazaki, S., **15**-0828, **15**-2197, **16**-0464, **19**-0275, **19**-0276, **19**-0281, **19**-0287, **19**-0420, **19**-0636, **19**-0800
Yamazaki, T., **10**-0678, **10**-1558, **15**-0849
Yamazaki, Y., **19**-0276
Yambushev, F.D., **04**-0044
Yamdagni, R., **08**-0224, **08**-0225, **08**-0226, **08**-0227
Yampolsky, I.V., **16**-1969, **16**-1970
Yamshita, Y., **16**-0935
Yan, J., **04**-0130, **10**-0509, **19**-0341, **19**-1199
Yan, L., **04**-00399
Yan, M., **13**-0206, **15**-1133, **15**-1136, **15**-1138, **15**-1509
Yan, S., **05**-0372, **12**-0346, **16**-0278
Yan, T.-H., **16**-1029, **16**-1030, **16**-1360, **19**-1314, **16**-1359
Yan, W., **16**-0552
Yan, W.-J., **16**-0549
Yan, Y.-L., **12**-0145, **15**-0867, **15**-0891
Yanada, K., **10**-0827, **16**-1525, **17**-0373, **17**-0377, **10**-0827
Yanada, R., **15**-0922, **15**-0922, **15**-0923, **15**-1670, **16**-1525, **17**-0373, **17**-0377
Yanagi, J., **04**-0470
Yanagi, K., **10**-0691
Yanagi, T., **13**-0471, **16**-1657
Yanagi, T., **19**-1035
Yanagihara, H., **10**-1869
Yanagihara, K., **02**-0303, **02**-0328
Yanagihara, R., **03**-0149, **11**-0507
Yanagisawa, A., **10**-0935, **10**-1260, **10**-1490, **10**-1550, **16**-0618, **16**-0640, **16**-0657, **16**-0754, **16**-0844, **16**-1006, **16**-1121
Yanagisawa, K., **10**-1270
Yanagisawa, M., **19**-0243
Yanagisawa, Y., **19**-0689
Yanai, H., **10**-1822
Yanase, M., **19**-0169
Yanchang, S., **02**-0090
Yandovskii, V.N., **10**-1035, **18**-0136, **19**-0786
Yanella, J., **11**-0257
Yáñez, M., **02**-0082
Yang, B., **18**-0514, **19**-1705
Yang, B.-Y., **16**-1012
Yang, B.H., **13**-0226, **13**-0473, **19**-1483
Yang, B.Q., **19**-0037
Yang, C., **10**-0046, **13**-0274, **13**-0401, **15**-0803, **19**-0452
Yang, C.-T., **16**-1438
Yang, C.C., **16**-1848
Yang, D., **10**-0584, **12**-0145, **13**-0401, **13**-0571, **15**-0867, **15**-0891, **15**-1768, **15**-1772, **15**-1773, **15**-1778, **15**-1779, **19**-0402
Yang, D.-H., **16**-0063, **16**-0094
Yang, D.H., **07**-0048, **07**-0082, **16**-1471
Yang, D.T.C., **19**-1462
Yang, F., **16**-0150
Yang, G., **04**-0370, **16**-1155
Yang, G.-s., **10**-1387, **19**-1035
Yang, H., **10**-0215, **11**-0431, **12**-0370
Yang, H.-C., **16**-1640
Yang, H.-Y., **15**-1136
Yang, I., **13**-0150
Yang, J., **15**-2361, **16**-1477
Yang, J.-D., **19**-0800
Yang, J.W., **15**-1695
Yang, K., **15**-1552, **16**-0044, **16**-0330, **18**-0777, **19**-1583
Yang, K.-S., **16**-0777, **16**-0788
Yang, L., **05**-0212, **16**-0687, **16**-0939
Yang, L.,-W., **15**-1133
Yang, L.-M., **10**-1282
Yang, M., **15**-2354, **19**-0823
Yang, N.C., **07**-0048, **14**-0262, **16**-1471, **16**-2084, **16**-2085, **17**-0343
Yang, P.-Y., **15**-0527
Yang, S., **05**-0069, **12**-0298, **19**-0934
Yang, S.-C., **10**-0881
Yang, S.H., **13**-0259, **13**-0567, **15**-2219, **17**-0436
Yang, T., **13**-0153
Yang, T.-H., **07**-0051
Yang, T.-K., **15**-1139, **15**-1480, **16**-0687, **19**-1031, **19**-1035, **19**-1052
Yang, T.-k., **16**-0687
Yang, W.K., **16**-0693
Yang, X.-F., **15**-1373, **16**-0667
Yang, X.-L., **19**-1090
Yang, X.-w., **16**-0687
Yang, Y., **04**-0270, **12**-0739, **16**-0591, **16**-0594, **16**-0639, **16**-0660, **16**-1856, **16**-1913
Yang, Y.-H., **18**-0581
Yang, Y.-l., **08**-0114
Yang, Z., **11**-0436, **11**-0439, **13**-0362, **13**-0365, **13**-0401, **13**-0443, **13**-0548, **15**-0245, **15**-1405, **16**-0847
Yang, Z.-Z., **04**-0241
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Yanigisawa, A., **16**-1121
Yanik, M.M., **08**-0196
Yannoni, C.S., **02**-0228, **02**-0356, **05**-0020, **05**-0077, **10**-0183, **10**-0200, **11**-0016
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Yano, K., **10**-0148
Yano, T., **16**-1681
Yano, Y., **10**-0372, **17**-0065
Yanovskaya, L.A., **10**-1583, **12**-0057, **15**-0992, **15**-1011
Yans, S.-M., **13**-0448
Yany, F., **17**-0415
Yao, C.-F., **10**-1379, **13**-0753, **15**-1149
Yao, G., **05**-0392
Yao, H., **15**-1793
Yao, H.C., **12**-0192
Yao, M.-L., **12**-0282
Yao, Q., **13**-0401, **15**-1670, **18**-0061, **18**-0774, **18**-0776, **18**-0789, **18**-0810
Yao, S., **15**-2146, **16**-0912
Yao, T., **15**-0228
Yao, X., **15**-0413, **15**-0895, **15**-2301
Yao, Z., **15**-0483
Yao, Z.-P., **16**-0655, **19**-1226, **19**-1325
Yaozeng, H., **02**-0090
Yap, G.P.A., **04**-0082, **14**-0216, **14**-0324, **18**-0599
Yarwood, A.J., **04**-0469
Yasaka, S., **16**-0547
Yashima, E., **04**-0087
Yashkina, L.V., **16**-1444
Yashunskii, V.G., **02**-0341
Yaskova, M.S., **11**-0174
Yaslak, S., **18**-0567
Yasman, Ya.B., **10**-0528
Yasmeen, N., **16**-0125
Yasohara, Y., **19**-1022
Yasuda, K., **15**-1042, **19**-0072, **19**-0677
Yasuda, M., **10**-0965, **10**-1093, **10**-1515, **10**-1627, **15**-0319, **15**-1061, **16**-0458, **16**-0609, **16**-0620, **16**-0822, **16**-0871, **18**-0613, **19**-1101, **19**-1359
Yasuda, N., **16**-0280, **16**-0630
Yasue, K., **10**-0935, **10**-1550, **16**-0657, **16**-0844
Yasuhara, F., **04**-0107, **19**-0934
Yasuhara, T., **12**-0735, **16**-1760

Yasuhara, Y., **11**-0503, **11**-0504
Yasui, M., **18**-0466
Yasukata, T., **18**-0112
Yatagai, H., **10**-1261, **10**-1375, **14**-0395
Yates Jr., J.T., **15**-0457
Yates, B.F., **04**-0279, **18**-0383
Yates, B.L., **17**-0494
Yates, J.B., **10**-1262
Yates, K., **02**-0008, **02**-0012, **08**-0024, **08**-0026, **08**-0038, **08**-0116, **08**-0117, **08**-0118, **08**-0119, **08**-0123, **12**-0149, **15**-0005, **15**-0013, **15**-0015, **15**-0016, **15**-0087, **15**-0256, **15**-2106, **16**-1556, **16**-1559, **16**-1597, **16**-1598, **18**-0477
Yates, P., **15**-2004
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Yatsugi, K., **10**-0441
Yatsugi, K.-i., **10**-0440
Yau, M., **18**-0813
Yavari, I., **01**-0087, **10**-0200, **16**-0578, **19**-1656
Yazawa, H., **15**-0380
Yazawa, N., **13**-0752
Yazdi, S.N., **13**-0658
Yde, B., **16**-0220, **16**-1807
Ye, C., **15**-1533
Ye, Q., **05**-0349, **05**-0350
Ye, S., **16**-0835, **19**-1584
Ye, T., **12**-0352, **12**-0357, **15**-2286
Ye, X.-R., **19**-0141
Yee, H., **19**-0671
Yee, K.C., **17**-0048, **17**-0052, **17**-0054
Yee, N.K., **16**-0462
Yeh, K.-L., **17**-0185
Yeh, L.I., **12**-0052
Yeh, M., **18**-0534
Yeh, M.C.P., **10**-1364, **12**-0437, **12**-0599, **16**-0480, **16**-1897
Yeh, V.S.C., **16**-1162
Yen, C., **10**-0179
Yen, V.Q., **15**-1653
Yeroushalmi, S., **02**-0348, **05**-0126
Yeske, P.E., **15**-1978
Yet, L., **16**-1448
Yeung, B.A., **16**-0009
Yeung, C.-h., **19**-1031
Yeung, E.S., **04**-0127, **04**-0146, **15**-0597
Yeung, K.-S., **11**-0439
Yeung, Y.-Y., **13**-0478
Yi, B., **15**-0604
Yi, K.Y., **17**-0487, **19**-1301
Yi, R., **10**-0024
Yi, X.-H., **16**-0587
Yijun, C., **16**-2099
Yin, J., **10**-0783, **10**-1086, **12**-0285, **13**-0183, **13**-0226, **13**-0508, **16**-1883
Yin, L., **16**-0170
Yin, X.-x., **19**-1040
Yin, Y., **10**-0574, **12**-0298, **15**-0251, **15**-1139
Ying, J., **15**-0244
Ying, T., **16**-1910
Ying, Y., **14**-0002
Yinglin, H., **10**-0992
Yip, C.-W., **16**-0680
Yip, C.W., **15**-1844
Yip, R.W., **07**-0053
Yip, Y., **04**-0410, **15**-0128, **18**-0067, **18**-0161, **18**-0569, **18**-0580, **18**-0614
Yip, Y.-C., **15**-1768, **15**-1773, **15**-1768
Yli-Kauhaluoma, J., **15**-2038
Yliniemelä, A., **16**-1214
Yoakim, C., **10**-0614, **10**-0706
Yoda, H., **16**-1196
Yoder, R.A., **16**-0919
Yogo, T., **18**-0435
Yogodzinski, L.H., **13**-0773
Yoh, S., **10**-0304
Yohitake, J., **12**-0537
Yokayama, J.-i., **10**-1454
Yokoa, K., **10**-1862
Yokomichi, Y., **02**-0160
Yokoshima, S., **16**-1990
Yokota, K., **11**-0052, **15**-2383, **16**-1977, **16**-1978
Yokota, M., **15**-0576
Yokota, N., **15**-1011
Yokota, T., **13**-0371, **15**-1404
Yokoya, S.-i., **16**-1307
Yokoyam, S., **16**-0686
Yokoyama, C., **13**-0415
Yokoyama, H., **15**-1855
Yokoyama, K., **15**-1855
Yokoyama, M., **10**-0710, **10**-1089, **11**-0285, **14**-0345, **16**-0433, **16**-0509, **16**-1250, **16**-1728, **17**-0472, **19**-1629
Yokoyama, S., **19**-1481
Yokoyama, T., **15**-0155, **15**-1337, **18**-0127, **18**-0316
Yokoyama, Y., **04**-0075, **16**-1008, **16**-1854
Yokozawa, T., **10**-1203, **16**-0380
Yomioka, K., **16**-0866
Yonashiro, M., **10**-1611
Yoneda, E., **15**-1399, **15**-1407, **15**-1468, **15**-1469, **15**-1470
Yoneda, N., **10**-1044, **10**-1045, **10**-1084, **10**-1145, **10**-1834, **10**-1836, **11**-0358, **13**-0705, **13**-0718, **15**-0168, **15**-1520, **18**-0378
Yoneda, R., **16**-1425, **16**-1459
Yonekura, T., **02**-0069
Yonemitsu, O., **12**-0476, **19**-1307
Yonemitsu, T., **10**-0596
Yonemura, K., **14**-0247, **19**-1678
Yonemushi, Y., **16**-0931
Yoneoka, A., **10**-0584
Yonetani, M., **03**-0146
Yoneyama, Y., **02**-0303, **02**-0304, **02**-0306, **02**-0328
Yonezawa, S., **11**-0126
Yong, K.H., **10**-1276, **16**-0467
Yong, K.S., **18**-0509
Yong, L., **15**-2364
Yoo, B.R., **10**-1194
Yoo, B.W., **16**-1994, **19**-1549, **19**-1550, **19**-1600, **19**-1611, **19**-1612, **19**-1685
Yoo, E.S., **10**-1083
Yoo, H.Y., **18**-0658, **18**-0707
Yoo, K.H., **14**-0061
Yoo, M.-S., **15**-1302
Yoo, M.-s., **10**-1657
Yoo, S.H., **15**-2017
Yoon, C.-O.M., **19**-0998, **19**-1324
Yoon, C.H., **12**-0372, **13**-0439, **17**-0234
Yoon, C.M., **15**-0494, **16**-0351, **16**-0352, **19**-0998, **19**-1324, **19**-1600, **19**-1612, **19**-1751
Yoon, D.C., **12**-0184
Yoon, D.Y., **04**-0293
Yoon, K.B., **10**-1052
Yoon, M.S., **19**-1105
Yoon, N.M., **15**-0495, **15**-0503, **15**-0568, **16**-0360, **16**-0548, **16**-1535, **19**-0877, **19**-0882, **19**-0885, **19**-0886, **19**-0887, **19**-0889, **19**-1078, **19**-1107, **19**-1209, **19**-1299
Yoon, S.-K., **13**-0561, **16**-0739
Yoon, S.Y., **12**-0122
Yoon, Y-J., **16**-1751
Yoon, Y.-A., **19**-1042
Yoon, Y.-J., **16**-1536, **16**-1866
Yoon, Y.-y., **10**-1593
Yoon, Y.A., **15**-1436
Yorimitsu, H., **10**-1393, **10**-1398, **10**-1550, **10**-1625, **12**-0502, **13**-0433, **13**-0438, **14**-0009, **15**-0305, **15**-0863, **15**-0869, **15**-0942, **15**-1206,

15-1208, **15**-1252, **15**-1254, **15**-1265, **15**-1645, **15**-1646, **16**-0992
Yorimitsuy, H., **15**-1267
York, C., **16**-0455, **16**-1950
Yorke, M., **19**-1100
Yorozu, K., **15**-1838
Yoshida, A., **10**-1154, **19**-1387
Yoshida, E., **10**-0811
Yoshida, H., **10**-1418, **14**-0268
Yoshida, J., **10**-0688, **10**-1204, **15**-2348, **19**-0340
Yoshida, J.-i., **10**-0310, **10**-1200, **10**-1278, **10**-1718, **13**-0448, **14**-0299, **15**-0730, **15**-1420, **15**-2135
Yoshida, J.I., **10**-0688
Yoshida, K., **10**-1818, **11**-0591, **15**-1154, **15**-2194, **16**-1033, **16**-1049
Yoshida, M., **10**-0299, **10**-0730, **11**-0260, **12**-0753, **13**-0782, **14**-0170, **15**-0932, **15**-0933, **17**-0381, **18**-0396, **19**-1565
Yoshida, N., **19**-1781, **19**-1783
Yoshida, S., **14**-0201, **15**-0624, **15**-1504
Yoshida, T., **04**-0480, **15**-0956, **16**-0132, **17**-0285, **18**-0440, **18**-0449, **19**-1001
Yoshida, Y., **16**-2156, **10**-0729, **12**-0731, **13**-0254, **13**-0752, **16**-1095, **16**-2028
Yoshida, Z., **02**-0196, **02**-0203, **03**-0060, **10**-1823, **14**-0279, **15**-1594, **16**-1903, **18**-0738
Yoshifuji, M., **12**-0319, **13**-0177, **15**-0337
Yoshigami, R., **15**-1115
Yoshihara, N., **14**-0268
Yoshii, F., **18**-0359
Yoshikai, N., **10**-1338, **10**-1463
Yoshikawa, E., **13**-0303, **15**-0771
Yoshikawa, N., **16**-1043, **16**-1044
Yoshikawa, S., **15**-2198, **19**-1479
Yoshikoshi, A., **15**-0253, **15**-1004, **15**-1055, **18**-0727, **19**-0900
Yoshimatsu, M., **16**-1102
Yoshimi, Y., **03**-0027
Yoshimine, M., **16**-1378
Yoshimoto, M., **19**-1659
Yoshimune, M., **10**-1201
Yoshimura, K., **11**-0434
Yoshimura, M., **10**-0465, **10**-1833, **15**-0596, **16**-0373
Yoshimura, N., **16**-0617, **19**-0288, **19**-1392, **19**-1668, **19**-1702
Yoshimura, T., **15**-1892, **17**-0289, **19**-1783, **19**-1785
Yoshinari, T., **18**-0457
Yoshino, H., **11**-0436
Yoshino, K., **14**-0006
Yoshino, T., **10**-1243, **10**-1458
Yoshino, Y., **19**-0095
Yoshioka, A., **07**-0058
Yoshioka, H., **10**-0504, **10**-1080, **10**-1149, **13**-0255, **15**-1544, **15**-1723
Yoshioka, M., **15**-1290, **15**-1499, **15**-1502, **16**-0686
Yoshioka, N., **16**-0938, **19**-1049
Yoshitake, S., **16**-1604
Yoshitomi, S., **11**-0260
Yoshizane, K., **15**-2337, **16**-0633, **05**-0111
Yoshizawa, K., **16**-1070, **16**-2021, **19**-1756
Yoskioka, K., **04**-0166
You, C.H., **13**-0480
You, H.-W., **16**-1742
You, J., **13**-0592, **15**-0608, **16**-0774, **16**-1180
You, J.-S., **13**-0206, **16**-0674, **16**-0687
You, L., **15**-0834
You, S.-L., **10**-1468
You, T.-P., **19**-1675
You, X.-Z., **04**-0403
You, Z., **18**-0731
Yougun, S., **19**-1370
Youn, G.J., **03**-0186
Youn, S.W., **11**-0326
Youn, Y.S., **10**-1016
Young Jr., J.E., **01**-0074
Young, A.E., **02**-0206, **12**-0018, **12**-0614
Young, A.R., **16**-1506
Young, B., **16**-2103, **16**-2105
Young, D., **12**-00, **12**-0037, **16**-0262
Young, D.A., **12**-0116
Young, D.G.J., **13**-0428
Young, D.J., **16**-0612
Young, D.W., **16**-1817, **19**-0097, **19**-0454
Young, F., **10**-1748
Young, F.R., **07**-0066
Young, G.F., **02**-0043
Young, J.-j., **10**-0219
Young, J.F., **15**-0407
Young, L.B., **08**-0077, **19**-0622
Young, M.G., **14**-0209
Young, M.W., **17**-0290
Young, P.R., **10**-0527, **16**-0259
Young, R.J., **19**-0328
Young, R.M., **04**-0423
Young, R.N., **05**-0089, **05**-0099, **16**-1730, **16**-2058
Young, T.C., **05**-0150
Young, W.G., **10**-0213, **10**-0214, **10**-0216, **10**-0229, **10**-0289, **10**-0394, **12**-0034, **17**-0010
Young, W.R., **05**-0134, **08**-0071
Yousaf, T.I., **10**-0304, **12**-0704, **16**-0277
Yousefian, S., **17**-0281
Youshko, M.I., **16**-1841
Yousif, N.M., **16**-0220
Youssef, A.K., **18**-0555
Youssefyeh, R.D., **12**-0307, **12**-0309, **19**-0376
Yovell, J., **10**-0192
Yu, B.M., **15**-1834
Yu, C., **10**-1010, **16**-0706, **16**-0770, **18**-0277, **19**-1191
Yu, C.-L., **10**-0881
Yu, C.-M., **15**-1472, **16**-0637, **16**-0739, **16**-0752
Yu, D., **01**-0101
Yu, F., **15**-0395
Yu, G., **11**-0245
Yu, H., **15**-0322, **15**-1773, **15**-1774, **19**-1002
Yu, H.-B., **16**-0687
Yu, H.-h., **05**-0224
Yu, J., **10**-0795, **12**-0298, **15**-0163, **16**-1181
Yu, J.-Q., **15**-1308, **15**-1741, **19**-0577, **19**-1560
Yu, J.Q., **19**-0894
Yu, K.B., **16**-0865
Yu, L., **10**-1453
Yu, L.-T., **16**-1037
Yu, M., **16**-0957, **19**-1648
Yu, S., **13**-0211, **13**-0299, **15**-0695
Yu, S.H., **11**-0406, **12**-0587, **16**-0527
Yu, T.J., **07**-0079
Yu, W., **10**-1629, **12**-0288, **15**-0177, **16**-1320, **19**-0312
Yu, W.-Y., **15**-1746, **19**-0550, **19**-0746
Yu, W.-y., **15**-1773
Yu, X., **16**-1273, **16**-1644
Yu, X.-Q., **13**-0206, **19**-0549
Yu, Y., **10**-0735, **12**-0292, **12**-0652, **16**-0810, **16**-1979, **19**-1229
Yu, Y.-H., **16**-0835
Yu, Z., **15**-0979
Yu, Z.-X., **15**-0990
Yu.Sh., **15**-2274

Yuan, K., **10**-1305
Yuan, K., **16**-1644
Yuan, S., **16**-0649
Yuan, Y., **15**-2129, **15**-2343
Yuan, Y.-C., **10**-0879
Yuasa, Y., **10**-1868, **15**-1247
Yudilevich, J.A., **18**-0540
Yudin, A.K., **10**-0886, **10**-0957, **15**-1753, **15**-1893
Yue, T.-Y., **15**-0577
Yue, X., **14**-0078, **16**-1793
Yuen, P., **15**-1693
Yueng, C.H., **19**-1028
Yufit, D.S., **04**-0339
Yufit, S.S., **10**-1476, **17**-0003
Yuhara, M., **17**-0327
Yuk, J.Y., **10**-0588
Yukawa, Y., **09**-0061, **10**-0063, **10**-0170, **17**-0362, **18**-0270, **18**-0332
Yuki, Y., **10**-1328
Yukizaki, H., **10**-1511
Yulin, J., **10**-0592, **10**-0700
Yum, E.K., **10**-1272, **10**-1273
Yun, C., **12**-0470
Yun, C.-S., **13**-0346, **13**-0354, **16**-1988
Yun, C.S., **13**-0237
Yun, H., **13**-0237
Yun, H.-S., **10**-1489
Yun, L., **13**-0171
Yun, M., **15**-1371
Yuncheng, Y., **10**-0592, **10**-0700
Yunes, R.A., **12**-0716
Yur'ev, Yu.K., **15**-0045
Yur'eva, L.P., **15**-2362
Yur'eva, N.M., **10**-0763
Yura, T., **15**-1043, **16**-1016
Yurchenko, A.G., **18**-0325
Yus, M., **12**-0125, **12**-0409, **12**-0430, **12**-0618, **15**-0506, **15**-0507, **15**-0753, **15**-0928, **16**-0479, **16**-0500, **16**-0687, **16**-0839, **16**-0854, **19**-1311, appendixA-0031
Yusa, Y., **04**-0061, **16**-0571
Yusybov, M.S., **19**-0743
Yuya, H., **03**-0146
Yuyama, S., **15**-1115
Yuzhakov, G., **03**-0063, **19**-0360
Yuzhelevskii, Yu.A., **12**-0312
Yvanaeff, C., **16**-1644

Zabicky, J., **02**-0347, **02**-0379, **04**-0421, **05**-0034, **05**-0068, **05**-0108, **05**-0118, **08**-0024, **08**-0055, **10**-0129, **10**-0972, **11**-0367, **11**-0586, **12**-0057, **12**-0086, **15**-0128, **15**-0400, **15**-0628, **15**-2235, **16**-0126, **16**-0385, **16**-1445, **16**-1745, **16**-1753, **16**-1767, **16**-1770, **16**-1783, **16**-1824, **16**-1868, **16**-2053, **17**-0458, **18**-0293, **18**-0315, **18**-0471, **19**-0329, **19**-1486
Zaborsky, O.R., **16**-2142
Zabrowski, D.L., **19**-0764
Zabusova, S.E., **19**-0010
Zaccheria, F., **19**-0958
Zacharie, B., **15**-0557
Zadel, G., **12**-0536
Zaera, F., **15**-0457
Zafiriou, O.C., **07**-0054
Zagorsky, V.V., **12**-0609
Zahalka, H.A., **17**-0307, **19**-1454
Zahl, G., **18**-0708
Zahler, R.E., **13**-0042, **13**-0073, **13**-0088
Zahn, D., **16**-1574
Zahn, H., **16**-1716, **16**-1799
Zahneisen, T., **05**-0139
Záhorszky, U.I., **19**-1571, **19**-1573, **19**-1573
Zahouily, M., **15**-1029, **15**-1328
Zahra, J., **19**-1658
Zahradnik, R., **02**-0191, **07**-0003, **10**-0344
Zaidi, S., **16**-1709
Zaidlewicz, M., **15**-0644, **15**-0677
Zaikov, G.E., **19**-0345, **19**-0357, **19**-0359
Zajac Jr., W.W., **19**-0321, **19**-0751
Zajdel, W.J., **05**-0124, **10**-1720
Zakharkin, L.I., **12**-0481, **12**-0616, **15**-1600, **19**-1111, **19**-1115, **19**-1124, **19**-1391, **19**-1767
Zakharov, V.I., **15**-1315
Zakharov, V.P., **11**-0496
Zaklika, K.A., **15**-2159
Zalar, F.V., **12**-0679
Zalesov, V.S., **16**-2047
Zalesskaya, T.E., **18**-0182
Zalewski, R.I., **08**-0119
Zali-Boinee, H., **18**-0321
Zamashchikov, V.V., **10**-0202, **10**-0278, **10**-0424, **10**-0425
Zambianchi, F., **15**-1758, **19**-0759
Zamboni, R., **15**-0296
Zambrano, J.L., **19**-0432
Zamecka-Krakowiak, D.J., **03**-0101
Zamir, D., **11**-0291, **11**-0537
Zamojski, A., **04**-0119
Zanardi, E., **16**-0984
Zanardi, F., **16**-0984
Zanardi, G., **18**-0073
Zanardi, J., **16**-1384
Zanda, M., **19**-1036
Zander, M., **02**-0136
Zandomeneghi, M., **04**-0063, **04**-0155
Zanette, D., **10**-0529
Zang, G., **18**-0463
Zang, H.-J., **16**-1173, **19**-1646
Zanger, M., **15**-1513, **16**-1304
Zanini, M.L., **13**-0401
Zanirato, P., **12**-0512
Zank, G.A., **16**-0213
Zanka, A., **11**-0252, **19**-1089
Zanobini, F., **15**-0279
Zanon, J., **13**-0275
Zanoni, B., **18**-0194
Zanotti-Gerosa, A., **19**-1028
Zanotto, S.P., **16**-1632
Zaparucha, A., **15**-1039
Zapata, A., **17**-0485
Zapf, A., **10**-1297, **13**-0274, **13**-0288, **13**-0399, **13**-0483
Zapf, L., **19**-1286
Zaporowski, L.F., **12**-0069
Zappia, G., **13**-0230
Zara, C.L., **12**-0634
Zarakhani, N.G., **18**-0320
Zard, S.Z., **14**-0283, **14**-0420, **14**-0434, **15**-0385, **15**-1209, **16**-1504, **16**-1505, **17**-0237, **19**-0437, **19**-1246, **19**-1250
Zare, R.N., **05**-0332
Zarei, A., **11**-0201
Zaret, E.H., **14**-0224
Zareyee, D., **19**-1608
Zarkadis, A.K., **05**-0236, **11**-0433
Zarkowsky, D.S., **10**-1086, **16**-1883
Zaro, J., **18**-0397
Zartler, E.R., **04**-0130
Zass, E., **12**-0035
Zaugg, H.E., **10**-0341, **10**-1582, **11**-0515, **16**-0385, **16**-1851
Závada, J., **17**-0007, **17**-0015, **17**-0018, **17**-0021, **17**-0022, **17**-0024, **17**-0025, **17**-0026, **17**-0029, **17**-0030, **17**-0031, **17**-0096, **17**-0260
Zaveri, N.T., **11**-0428
Zavitsas, A.A., **02**-0039, **01**-0091, **14**-0059, **14**-0262
Zaw, K., **19**-0721
Zawadzki, S., **10**-0907, **10**-0971, **19**-1275
Zawalski, R.C., **12**-0719
Zaworotko, M.J., **12**-0372
Zaytsev, A., **15**-1940

Zbinden, H., **15**-0459
Zbiral, E., **16**-1255
Zderic, S.A., **19**-1053
Zdravkova, M., **05**-0263
Zdravkovski, Z., **16**-1782
Zdunek, L.Z., **08**-0019
Zebarjadian, M.H., **19**-0039
Zecchi, G., **15**-1930, appendixA-0032
Zechel, C., **16**-1823
Zechman, A.L., **15**-2266
Zecri, F.J., **16**-1312
Zee, S., **15**-0646
Zeegers-Huyskens, T., **03**-0033
Zeeh, B., **10**-1621, **15**-2292, **18**-0234
Zefirov, N.S., **01**-0029, **04**-0285, **04**-0333, **04**-0360, **04**-0363, **04**-0372, **04**-0437, **04**-0463, **10**-0762, **10**-0763, **10**-1598, **15**-0010, **15**-0021, **15**-0045, **15**-0186, **15**-0280, **15**-1541, **15**-1572, **15**-1580, **15**-1615, **15**-1850
Zefirov, Yu.V., **04**-0499
Zegrocka, O., **19**-1137
Zehnder, M., **15**-0066, **15**-0752, **18**-0480
Zeid, I., **17**-0224
Zeifman, Yu.V., **16**-0041
Zeiler, A.G., **17**-0522, **17**-0523, **17**-0524
Zeilstra, J.J., **19**-1252
Zeiss, G.D., **02**-0052
Zeiss, H., **03**-0090
Zeitz, H.-G., **14**-0092
Zelenina, N.L., **17**-0446
Zelle, R.E., **16**-1583
Zeller, J., **10**-0138
Zeller, K., **17**-0502, **18**-0211, **18**-0224
Zeltz, H.-G., **05**-0242
Zemskov, S., **11**-0310, **12**-0111, **14**-0131
Zeng, F., **12**-0296
Zeng, X., **10**-0061
Zeni, G., **12**-0290, **12**-0291, **13**-0368, **15**-0944, **15**-1325, **16**-0687
Zens, A.P., **04**-0212
Zepp, C.M., **19**-1032
Zepp, R.G., **07**-0048
Zerbetto, F., **03**-0196, **10**-0854
Zercher, C.K., **12**-0387, **15**-2352, **16**-1138, **18**-0790
Zergenyi, J., **17**-0456
Zerth, H.M., **16**-0764, **16**-1671
Zetina-Rocha, C., **15**-1117
Zetterberg, K., **15**-0328, **15**-0329
Zewall, A.H., **06**-0013
Zewge, D., **10**-1128
Zeynizaded, B., **15**-2420
Zeynizadeh, B., **10**-0667, **17**-0431, **19**-0856
Zezza, C.A., **15**-2061, **16**-0962
Zha, Z., **16**-0654, **16**-0661
Zhadonva, M.P., **16**-0281
Zhai, H., **11**-0309
Zhan, B.-Z., **19**-0120, **19**-0121
Zhan, Z.-P., **15**-1249, **19**-0858
Zhang, A., **12**-0292, **13**-0272, **13**-0276, **16**-1881
Zhang, C., **11**-0442, **15**-0380, **15**-1778
Zhang, C.-R., **19**-1635
Zhang, D., **16**-0939
Zhang, D.Y., **05**-0286
Zhang, D.-W., **19**-0402
Zhang, F., **12**-0285
Zhang, F.-M., **13**-0162, **16**-0298, **19**-1673
Zhang, F.-Y., **15**-1807, **16**-0680, **16**-1123
Zhang, F.J., **02**-0272
Zhang, F.M., **19**-1384
Zhang, G., **16**-1427, **16**-1428, **16**-1433, **16**-1438
Zhang, G.-L., **13**-0206
Zhang, G.-S., **16**-0063, **16**-0094, **16**-1671
Zhang, H., **10**-1454, **13**-0202, **13**-0401, **13**-0481, **15**-2064, **16**-1369, **19**-0784
Zhang, H.-C., **15**-2390, **15**-2425, **19**-0950
Zhang, H.-L., **16**-0865
Zhang, J., **02**-0126, **10**-0844, **10**-1776, **13**-0353, **13**-0701, **15**-0287, **15**-0657, **15**-1004, **16**-0831, **19**-1077
Zhang, L., **13**-0498, **15**-0826
Zhang, L.C., **16**-0761
Zhang, L.H., **12**-0171
Zhang, M., **16**-1644, **16**-2072
Zhang, M.-H., **15**-2004
Zhang, N., **13**-0503
Zhang, O.Z., **13**-0701
Zhang, P., **16**-1946
Zhang, P.-F., **16**-1279
Zhang, Q., **10**-1472, **13**-0700, **15**-1944, **19**-1054
Zhang, R., **10**-1453, **13**-0408, **15**-1741
Zhang, S., **12**-0285, **13**-0700, **13**-0701, **15**-1690, **19**-0241, **19**-1630
Zhang, S.-W., **15**-1407, **15**-1468, **15**-1469, **15**-1470
Zhang, S.-Y., **15**-1690, **15**-1706
Zhang, S.B., **15**-0272
Zhang, T.Y., **13**-0401, **13**-0481
Zhang, W., **04**-0035, **13**-0475, **15**-1137, **15**-1244, **15**-1251, **15**-1827, **15**-1885, **16**-0682, **18**-0246, **18**-0800
Zhang, W.-C., **16**-0481, **16**-0482, **19**-1664
Zhang, W.-X., **10**-1173
Zhang, X., **15**-0412, **13**-0415, **13**-0477, **13**-0571, **15**-0228, **15**-0425, **15**-0603, **15**-0606, **15**-0610, **15**-0611, **15**-0775, **15**-0820, **15**-0821, **15**-0845, **15**-1298, **15**-1767, **15**-2017, **16**-0344, **18**-0689, **19**-0050, **19**-0584, **19**-1028, **19**-1155, **19**-1265
Zhang, X.-D., **13**-0542
Zhang, X.-L., **15**-1693
Zhang, X.-M., **01**-0102, **01**-0105, **01**-0106, **05**-0266, **08**-0056, **16**-0865
Zhang, X.-X., **03**-0115
Zhang, X.P., **15**-1898, **16**-1371
Zhang, X.-L., **15**-1704
Zhang, Y., **04**-0403, **07**-0118, **10**-0735, **10**-0844, **10**-0997, **11**-0371, **11**-0372, **12**-0158, **12**-0373, **12**-0652, **13**-0378, **13**-0539, **13**-0548, **14**-0188, **14**-0403, **15**-0356, **15**-0579, **15**-0721, **15**-0734, **15**-2414, **16**-0653, **16**-0851, **16**-0872, **16**-0884, **16**-0957, **16**-0981, **16**-1008, **16**-1362, **16**-1612, **16**-1613, **16**-1910, **16**-1969, **16**-1990, **16**-1996, **16**-2175, **17**-0385, **18**-0361, **19**-1190, **19**-1263, **19**-1269, **19**-1385, **19**-1584, **19**-1585, **19**-1648
Zhang, Y.-K., **05**-0214, **10**-0768
Zhang, Y.-L., **16**-1012
Zhang, Y.J., **15**-0604
Zhang, Y.-X., **19**-1032
Zhang, Y.Z., **15**-0786
Zhang, Z., **10**-1669, **11**-0436, **13**-0558, **13**-0700, **15**-0610, **15**-0845, **15**-0846, **15**-1034, **15**-1101, **16**-1644, **16**-1712, **16**-1985, **17**-0216
Zhang, Z., **19**-1028
Zhang, Z.-H., **10**-0553
Zhang, Z.-Y., **19**-0291
Zhang, Z.H., **16**-0170
Zhang, Z.J., **18**-0759
Zhao, C., **04**-0112, **15**-2245, **15**-2340, **19**-1054
Zhao, C.-G., **15**-1773, **19**-0237
Zhao, C.-Q., **15**-0376

Zhao, C.-Y., **04**-0403
Zhao, C.H., **16**-0875
Zhao, D., **18**-0720
Zhao, F., **13**-0408
Zhao, G., **10**-1387, **13**-0700, **15**-0422, **16**-0687, **16**-0777, **16**-1155, **19**-1035, **19**-1040
Zhao, H., **10**-1547, **19**-1206
Zhao, J., **11**-0309, **16**-0834, **19**-1660, **19**-1675
Zhao, K., **10**-0564, **16**-1282
Zhao, L., **10**-0582
Zhao, M., **19**-0673, **19**-0678
Zhao, M.W., **10**-1086, **16**-1883
Zhao, P., **12**-0090, **16**-0977, **16**-0977, **17**-0309
Zhao, P.-Q., **10**-0932, **10**-1163
Zhao, S., **15**-1471
Zhao, S.-W., **01**-0111
Zhao, X., **01**-0109, **04**-0191
Zhao, Y., **07**-0082, **13**-0401, **13**-0481
Zhao, Y.J., **08**-0133
Zhao, Z., **19**-0174
Zhdamarova, V.N., **13**-0107
Zhdankin, V.V., **10**-0762, **10**-0763, **15**-0010, **15**-1572
Zhdanov, Y.A., **02**-0378
Zhdanov, Yu.A., **18**-0893
Zheng, B., **12**-0070, **19**-1353
Zheng, C.Y., **15**-1523
Zheng, F., **18**-0093
Zheng, J., **16**-0810, **19**-1039
Zheng, K., **18**-0475
Zheng, M., **15**-2004
Zheng, O., **19**-0055
Zheng, P., **19**-0174
Zheng, Q.-C., **19**-0209
Zheng, Q.-G., **10**-0701, **10**-0869, **11**-0241, **16**-1773
Zheng, Q.G., **10**-1475, **16**-1170
Zheng, T.-C., **10**-0728
Zheng, X., **16**-0981, **16**-1852
Zheng, X.-Q., **19**-0816
Zheng, Y., **16**-0653
Zheng, Y.-S., **15**-1779
Zheng, Z., **10**-1453, **15**-0428, **15**-0604, **15**-1137, **15**-1885, **15**-2301, **16**-1433
Zhigareva, G.G., **15**-1600
Zhil'tsov, S.F., **12**-0620
Zhmurova, I.N., **16**-1811, **19**-1273
Zhong, G., **16**-0415, **16**-1037
Zhong, H.M., **10**-1026
Zhong, P., **15**-0303, **15**-0441, **19**-0802
Zhong, Q., **15**-2004
Zhong, Y.-L., **17**-0297, **19**-0624
Zhong, Y.-W., **19**-1697
Zhong, Z.-L., **03**-0123
Zhou, B., **07**-0052
Zhou, C., **15**-0960, **16**-0654, **16**-0964
Zhou, D.-Y., **15**-1399, **15**-1461
Zhou, H., **10**-1546, **15**-1136, **19**-0970, **19**-0972, **19**-1035
Zhou, J., **10**-1384, **10**-1406, **13**-0351, **16**-0558
Zhou, J.-F., **16**-0054
Zhou, J.-R., **16**-0658
Zhou, J.-Y., **16**-0662
Zhou, L., **15**-0921, **16**-1644, **19**-1190, **19**-1601
Zhou, M., **16**-1945
Zhou, Q.-L., **10**-1386, **15**-0604, **15**-1136, **15**-1885, **15**-2298, **19**-1028
Zhou, Q.J., **11**-0462
Zhou, R., **19**-0894
Zhou, S.-L., **15**-1288, **15**-1309, **15**-1319
Zhou, S.-m., **12**-0281
Zhou, T., **11**-0188, **11**-0499
Zhou, W., **15**-1822, **15**-1885, **19**-0894
Zhou, X., **10**-0801, **13**-0359
Zhou, X.-G., **19**-0549
Zhou, Y., **13**-0401, **13**-0481, **16**-0738
Zhou, Y.-F., **16**-0549
Zhou, Y.-G., **10**-1173, **15**-0527, **16**-0344, **16**-0911
Zhou, Y.-M., **19**-0141
Zhou, Z., **02**-0095, **02**-0110, **11**-0086, **15**-0911, **16**-0777
Zhou, Z.-Y., **15**-2295, **19**-1028
Zhou, Z.Y., **15**-1844
Zhu, C., **16**-2078, **19**-0823
Zhu, C.Y., **04**-0177
Zhu, D., **10**-1170
Zhu, F., **16**-0147
Zhu, G., **15**-0606, **15**-0846
Zhu, J., **11**-0436, **15**-0415, **15**-0519, **15**-0575, **15**-1810, **18**-0362
Zhu, J.-L., **10**-1494
Zhu, L., **12**-0599, **16**-1521
Zhu, M., **15**-2436
Zhu, N.-Y., **13**-0401, **15**-0867
Zhu, Q., **13**-0443
Zhu, Q.-C., **19**-1154
Zhu, S., **15**-0979
Zhu, S.-F., **10**-1386, **15**-0604, **19**-1028
Zhu, X.-Z., **10**-1468
Zhu, Y., **12**-0100, **19**-0971
Zhu, Y.-F., **13**-0430
Zhu, Z., **05**-0351, **05**-0402, **10**-0582, **10**-0645, **19**-0744
Zhuang, W., **16**-0384
Zhulin, V.M., **14**-0164
Zhun', I.V., **16**-1970
Zia-Ullah, **10**-1081
Zibuck, R., **19**-0742
Zief, M., **04**-0150, **04**-0171
Ziegenbein, W., **10**-1680, **10**-1765, **12**-0416, **16**-1183, **17**-0252, **17**-0311
Zieger, H.E., **10**-1797
Ziegler, E., **11**-0406
Ziegler, F.E., **16**-1459, **18**-0654, **18**-0663, **18**-0673
Ziegler, T., **15**-1494, **17**-0392
Ziehn, K., **17**-0459, **17**-0484
Zielinski, T.J., **12**-0087
Ziemnicka-Merchant, B.T., **15**-2282
Zierke, T., **16**-0709
Ziessel, R., **05**-0291
Zil'berman, E.N., **11**-0526, **16**-0120, **16**-0139, **19**-1180
Zilkha, A., **03**-0194
Ziller, J.W., **18**-0766, **18**-0829
Zim, D., **13**-0177, **13**-0475, **13**-0484
Zimmer, H., **19**-0266
Zimmer-Gasser, B., **04**-0513
Zimmerman, H.E., **01**-0001, **02**-0336, **15**-0538, **15**-0539, **15**-2108, **16**-1216, **17**-0408, **18**-0120, **18**-0477, **18**-0574, **18**-0590, **18**-0641, **18**-0848, **18**-0849, **18**-0850, **18**-0852, **18**-0853, **18**-0853, **18**-0854, **18**-0855, **18**-0860, **18**-0861, **18**-0862
Zimmerman, J., **14**-0030
Zimmerman, W.T., **17**-0271
Zimmermann, A., **15**-2382
Zimmermann, C., **12**-0610
Zimmermann, G., **02**-0360, **04**-0271, **14**-0064
Zimmermann, H., **04**-0382, **15**-1183, **16**-1551, **18**-0619, **18**-0637
Zimmermann, K., **10**-0855
Zimmermann, M., **16**-1282
Zimmt, M.B., **05**-0369
Zink, J.I., **07**-0012
Zinn, F.K., **15**-1077
Zinovyev, S., **13**-0406
Zippel, M., **16**-1000, **17**-0416
Zirnstein, M.A., **08**-0089, **08**-0186
Ziurys, L.M., **08**-0197
Zlokazov, M.V., **15**-1480
Zmuda, H., **18**-0746, **18**-0750
Zoebisch, E.G., **02**-0018
Zoghaib, W.M., **19**-0943

Zohar, E., **15**-0500
Zohdi, H.F., **18**-0026
Zolfigol, M.A., **10**-0642, **11**-0127, **11**-0134, **11**-0134, **12**-0698, **12**-0705, **16**-0096, **16**-1684, **16**-2054, **19**-0034, **19**-0035, **19**-0038, **19**-0039, **19**-0087, **19**-0860
Zollinger, H., **05**-0068, **07**-0003, **09**-0064, **11**-0006, **11**-0008, **11**-0009, **11**-0028, **11**-0105, **11**-0165, **11**-0166, **11**-0167, **11**-0168, **11**-0170, **13**-0013, **13**-0027, **13**-0028, **13**-0032, **13**-0034, **13**-0035, **13**-0036, **13**-0685, **13**-0704, **13**-0748, **14**-0350, **19**-1561
Zolopa, A.R., **10**-1759
Zoltewicz, J.A., **10**-0656, **10**-0854, **13**-0001, **13**-0003, **13**-0677
Zon, G., **18**-0844
Zondervan, C., **19**-0536
Zook, H.D., **05**-0128, **10**-0343, **10**-0490, **10**-1622, **12**-0420, **12**-0660, **16**-0514, **18**-0180
Zora, M., **18**-0479, **18**-0624
Zorc, B., **19**-0217
Zordan, M., **16**-0645
Zoretic, P.A., **12**-0241
Zorkii, P.M., **04**-0499
Zorzan, D., **11**-0654, **13**-0480
Zou, B., **16**-1962
Zou, G., **10**-1420, **13**-0346
Zou, Y., **13**-0138, **13**-0228
Zountsas, J., **04**-0471
Zradni, F.-Z., **16**-1832
Zrinski, I., **02**-0082
Zschunke, A., **18**-0540
Zubairi, Md.O., **19**-1103
Zubarev, V.E., **05**-0211
Zuberbühler, A.D., **14**-0200
Zuberi, S.S., **11**-0314
Zubiani, G., **12**-0585, **16**-0499, **16**-0500
Zubieta, J., **12**-0402, **14**-0200
Zucchi, C., **12**-0322
Zucco, C., **02**-0402, **11**-0495, **12**-0097, **12**-0672, **13**-0019, **16**-1863
Zuckerman, J.J., **01**-0015, **01**-0089, **04**-0264, **04**-0268, **05**-0208, **05**-0219, **12**-0001, **12**-0388, **12**-0549, **12**-0559, **12**-0594, **12**-0615, **13**-0656, **15**-0873
Zuercher, W.J., **18**-0832
Zuev, P.S., **05**-0328, **05**-0355, **15**-2315
Zueva, L.D., **18**-0317
Zugravescu, I., **12**-0414
Zuidema, L.J., **14**-0209
Zuika, I.V., **03**-0049
Zukerman-Schpector, J., **19**-0581
Zuman, P., **06**-0043, **06**-0049, **06**-0052, **06**-0053
Zumpe, F.L., **10**-1467, **18**-0701
Zundel, G., **03**-0001
Zúñiga, N., **16**-2063
Zuo, W.-X., **16**-1172
Zupan, M., **11**-0287, **11**-0304, **11**-0311, **12**-0126, **12**-0127, **12**-0131, **19**-0633, **19**-0687
Zupet, P., **12**-0126
Żurawiński, R., **10**-0841
Zürcher, C., **03**-0195
Zurita, E., **13**-0504
Zuzukin, V., **16**-2088
Zvezdina, E.A., **16**-0281
Zvolinskii, V.P., **11**-0496
Zwanenburg, B., **06**-0032, **15**-1789, **16**-0687
Zweifel, G., **04**-0192, **10**-1377, **12**-0442, **12**-0545, **14**-0380, **15**-0490, **15**-0493, **15**-0648, **15**-0650, **15**-0651, **15**-0654, **15**-0691, **16**-0494, **16**-0500, **17**-0321, **18**-0252, **18**-0254, **18**-0429, **18**-0436, **18**-0444, **18**-0446, **18**-0447, **18**-0451
Zweig, A., **18**-0120
Zweig, J.S., **16**-0580
Zwick, W., **15**-1357
Zwierzak, A., **10**-0898, **10**-0907, **10**-0971, **10**-0992, **10**-0993, **10**-0995, **10**-1020, **15**-0391, **15**-1879, **19**-1275
Zwiesler, M.L., **12**-0435
Zwikker, J.W., **15**-0545, **16**-1776
Zygmunt, J., **11**-0579
Zyk, N.V., **15**-1541, **15**-1850
Zyranov, G.V., **12**-0699
Zytowski, T., **15**-1211

SUBJECT INDEX

The vast use of transition metal catalysts led to limited citations of individual metals. In many cases, the term metal catalysis, or catalysts, metal is used as a general heading for several different metals. The term organometallics is used in many cases to include Grignard reagents or organolithium reagents.

α-effects, and nucleophilicity, 0495
α-methoxy-α-trifluoromethylphenyl acetic acid (MTPA), see Mosher's acid
A-S_E2 mechanism, 0528
A-S_E2 reactions, 0525
A1 mechanism, acetal hydrolysis, 0525
ab initio calculations, 0035
  1,2-alkyl shifts in alkyne anions, 1579
  and acidity, 0358
  and nonclassical carbocations, 0451
  and protonated of cyclopropanes, 1027
  and S_N2 reactions, 0430
  arenium ions, 0662
  carbocation stability, 1003
  E2 mechanism, 1478
  norbornyl carbocation, 0463
  rate of cyclopropylcarbinyl radical rearrangement, 0945
  transition state for radical hydrogen abstraction, 0943
abnormal Beckmann rearrangement, 1615
absolute configuration, see enantiomers, chirality, stereogenic, chiral
absolute configuration, and biochemical methods, 0159, 0162
  and Mosher's acid, 0159, 0160
  and NMR, 0160–0162
  Cahn-Ingold-Prelog system, 0155–0158
absolute hardness, 0377, 0379
absolute hardness, table, 0379
absorption, and conjugation, 0332, 0333
  differential, 0175
abstraction, and vinylic hydrogenation, 0947
  benzylic hydrogens, by radicals, 0947
  by radicals, 0807
  divalent atoms, 0943
abstraction, of hydrogen, photochemical, 0347
  by halogen radicals, 0955
  by nitrenes, 0295
  by radicals, *ab initio* study, 0943
  by radicals, and rearrangements, 1574
  radical, and stereoelectronic effects, 0949
  selectivity by radicals, 0945
  selectivity of bromine versus chlorine radicals, 0955
  stereoselective, 0949
abstraction, of atoms by radicals, 0938
  of atoms from radicals, 0280
  of radicals, 1011
  radical, and alkenes, 0945
  radical, transition state, 0939
acceleration, of the Diels-Alder reaction, 1198
acceptors, in the benzoin condensation, 1397
acenaphthylene, addition of DBr, 1006
acenes, 0087, 0088
acenes, zigzag, 0088
acepentalenes, radical ions, 0282
acetal formation, mechanism, 1271
acetaldehyde, and paraldehyde, 1460
  rational barrier, 0201
acetals, acid catalyzed hydrolysis, 0524
  and Lewis acids, 0526, 0527
  and transacetalization, 1272
  as protecting groups, 1271
  based induced elimination to enol ethers, 1516
  dimerization, 0618
  formation of thioacetals, 0551
  from alcohols and aldehydes, 1270
  from amides, 0797
  from Grignard reagents, 0616
  from ortho esters, 0616
  from oxidation of hydroxy ethers, 0966
  hydrolysis, 0523
  hydrolysis and Brønsted coefficient, 0525
  hydrolysis and S_N1 mechanisms, 0524–0527

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reduction, 1832
transetherification, 0536
with allylic silanes, 0617
with silyl enol ethers, 0617
acetanilides, see anilines, acyl
acetate, allylic, also see carboxylic esters, allylic
acetate, as a base, 0357
acetates, enol, see enol
acetates, metal, and acyloxylation, 0972
acetic acid, cis conformation, 0201
acetic acid, dimeric, 0107
acetic anhydride, and acyl fluoroborate, 1186
and dehydration of oximes to nitriles, 1546
and nitration of aromatic compounds, 0686
conjugate addition, 1132
acetoacetic acid synthesis, 0632
acetoacetic ester, and enol content, 0100
enol content and solvent, 0102
acetoacetic ester synthesis, 0624
acetolysis, see solvolysis
acetone, tautomerism, and bromination, 0323
acetoxy sulfides, to aldehydes, by Pummerer rearrangement, 1866
acetoxy-ketones, from enols, 0972
from ketones, 0972
acetyl carbocation, 0242
acetyl hypofluorite, 0705
acetylene, see ethyne
acetylide ion, with substrates, 0646
acetylphenols, and Fries rearrangement, 0735
aci form, of nitro compounds, and tautomerism, 0104
and the Nef reaction, 1268
acid catalyzed, addition of alkenes to alkenes, 1089
addition of carboxylic acids to alkenes, 1041
addition of water to carbonyls, 1261
aldol reaction, 1349
esterification of carboxylic acids, with ethers, 1418
for the Schmidt reaction, 1611
Friedel-Crafts alkylation, 0707
hydration of allenes, 1037
hydrocarboxylation of alkenes, 1137
hydrolysis of amides, 1410
Knoevenagel reaction, 1359
Mannich reaction, 1294
rearrangement of hydrazobenzenes, 1678, 1679
acid catalysts, for addition of water to alkenes, 1032
acid derivatives, acylation, 1438
with amides, 1438
with organocerium reagents, 1447
with various organometallics reagents, 1449
acid solutions, and the tetrahedral mechanism, 1255
acid strength, 0250, 0357, 0359–0364
and solvent, 0364
crystallographic scale, 0358
field effects, 0380
Lewis acids, 0377
resonance effects, 0382
acid-base catalysis, 0372
acid-base equilibrium, 0356
acid-base reactions, carbanions + proton, 0265
deprotonation by organometallics, 0810
formation of homoenolates, 0256
acidity of proton, and solvent acidity, 0370
acidity scale, 0370, 0372
acidity, also see acid strength
amides versus amines, 0383
and conformation, 0387, 0388
and electronegativity, 0384
and five-membered rings, 0063
and hybridization, 0388
and hydrogen bonding, 0385
and indicators, 0369
and organolithium reagents, 0262
and Periodic table, 0384
and proton transfer, 0368
and resonance, 0383
and s character, 0388
and solvent effects, 0364, 0390, 0392–0394
and steric effects, 0385
esters versus ethers, 0383
Hammett acidity function, 0369
hydrocarbon, 0251
in ionic liquids, 0369
inductive and field effects, 0020
kinetic, 0251
of active methylene compounds, 0622
of β-hydrogens, in elimination reactions, 1499
of carborane acids, 0368
of carboxylic acids, 0020
of cyclopentadiene, 0063
of Meldrum's acid, 0388
of PCC, 1716
of phenalene, 0060
of solvents, 0369
pK_a of acid types, 0359–0364
protons in conjugated compounds, 0633
solvent, see solvent acidity
spectrophotometric measurement, 0369
statistical effects, 0384
substituent effects, 0380
thermodynamic, 0251
acids, also see Brønsted-Lowry acids
acids, also see Lewis acids
acids, also see solvent acidity
acids, also see superacids
acids, acid strength, 0359–0364
activity of proton, 0370
and diazotization, 0918
and hydrogen exchange, electrophilic aromatic substitution, 0684
and keto-enol tautomerism, 0772
and Michael addition, 1110
and organometallics, 0809
and pKa, 0357
as proton donor, 0356
Brønsted, addition of thiols to alkenes, 1043
carbon, 0358
carbon, and acidity scales, 0370
carboxylic, see carboxylic acids
catalysis, alcohol dehydration, 0534
conjugate, 0356
glycidic, see glycidic
hard, definition, 0377
hardness, 0377, 0378
inorganic, with anhydrides, 1424
inorganic, esters, hydrolysis, 0522

acids, acid
strength, (*Continued*)
IUPAC terminology, 0356
Lewis, see Lewis acids
normal, definition, 0367
proton-transfer reaction, 0367
protonation of carbanions, 0250
soft, definition, 0377
strength, 0357
strength and structure, 0380
strong, stability of carbocations, 0236
sulfonic, see sulfonic acids
sulfonyl, reduction with metals, 1475
sulfuric, see sulfuric acid
super and carbocations, 0236
super, and carbocation formation, 0239
superacid-SO_2, 0236
superacids, 0236, 0358
type, table of pK_a, 0359–0364
very weak acids, 0358
weak, deprotonation by metals, 0811
with organometallics, 0812
acoustic cavitation, see cavitation
acoustic cavitation, and sonochemistry, 0349
actinometer, and photochemical mechanism, 0349
activated complex, 0302
activating groups, aromatic substitution, 0668, 0673
activating groups, in aromatic compounds, 0665
activating groups, in S_NAr reactions, 0865–0866
activation hardness, and electrophilic aromatic substitution, 0679
activation volume, and high pressure, 0413
and reactivity, 0413
activation, enthalpy, 0302
activation, entropy, 0303
activation, free energy, 0301
active methylene compounds, acidity, 0622
and diazo compounds, 0787
and the Hurtley reaction, 0907
and the Knoevenagel reaction, 1358
arylation, 0906–0908
coupling with allylic carbonates, 0611
coupling with malonates, 0907
coupling with organometallics, 0907
dianions, 0625
metal catalyzed coupling, 0614
with acyl halides, 1451
with alkyl halides, 0622, 0623
with allylic esters, 0610
with aryl halides, benzyne mechanism, 0906
with aryldiazonium salts, 0783
with dihalides, 0625
with tosylazides, 0787
acyclic compounds, conformations, 0197
acyl addition, see addition
acyl anion equivalent, 0634
acyl anion equivalents, and the Knoevenagel reaction, 1362
acyl carbocations, 0242
acyl carbon, substitution reactions, 0482
acyl compounds, addition to alkenes, 1135
addition to alkynes, 1135
acyl imidazoles, 1418
acyl radicals, 0936
acylals, and silanes, 1274
and the Etard reaction, 1763
from aldehydes with anhydrides, and reagents, 1273
hydrolysis to aldehydes, 1763
acylamidation, of alkenes, 1186
acylation, Friedel-Crafts, 0697
Friedel-Crafts, also see Friedel-Crafts
of acid derivatives, 1438
of alkenes, 0796
of amides, 1437
of amines, 1429, 1433
of amines, reagents for, 1432
of amines, with esters, 1434
of carboxylic dianions, 1456
of conjugated compounds, 1132
of dienes, 0797
of diketone dianions, 1456
of dithianes, 1456
of enamines, 0635
of enolate anions, 0800
of heterocycles, 0983
with acyl halides, 1451
acylazides, see azides,
acylium ions, with alkenes, 0796
acyloin condensation, 1860–1862
and catenanes, 1862
and chlorotrimethylsilane, 1861
and surface area of metal, 1862
and the Dieckmann condensation, 1861
acyloins, see hydroxy-ketones
acyloxylation, of alkenes, 1186
of enols and ketones, 0971, 0972
acylperoxides, see peroxides
acylthiazolidinethiones, chiral, 1356
AD-mix-α and AD-mix-β, asymmetric dihydroxylation, 1167
adamantanes, and chirality, 0145
and strain, 0223
adamantyl carbocations, 0245
addition compounds, 0115
addition reactions, alkenes and ionization potential, 1018
alkenes versus alkynes, 1017
and allenes, 1019
and electrostatic potentials, 1020
and inversion of configuration, 1020
and Markovnikov's rule, 1019
electronic effects, 1016
HX to alkenes, 1006
HX to alkynes, 1030
IUPAC nomenclature, 0419
of alkynes, and UV, 1017
orientation, 1019, 1022
radicals, 1018, 1020
reactivity, 1015, 1017
simultaneous, 0298
to alkenes, 0298, 0400, 1013, 1023, 1024
to alkenes, by nitrenes, 0294
to alkynes, 1017, 1018
to cyclopropanes, 1025
to dienes, 1013
to isocyanides, 1466
addition, 1,3-dipolar, alkyl azides, 1183
addition, 1,4-, to dienes, 1031
addition, acyl, 1251, 0400
addition, acyl, metals, 1315–1322

addition, anti, see anti
addition, conjugate, see Michael addition
addition, conjugate, definition, 1008
addition, dipolar, [1,3]-, 118–1192
addition, dipolar, [1,3]-, see [3 + 2]-cycloaddition
addition, electrophilic, 0298, 1000–1002
  and dienes, 1013
  and the S_N1 mechanism, 1000
  cyclic intermediates, 1000, 1001, 1002
  mechanism, 0999
  simultaneous addition, 1002
addition, exo, and bicyclic alkenes, 1023
addition, intermolecular, mechanism, 1002
addition, intramolecular, radical, see radical cyclization
addition, nucleophilic, 0298
  to carbonyls, and the tetrahedral mechanism, 1253
  mechanism, 1007
addition, pericyclic, 0298
addition, radical, 0298
  aldehydes to alkenes, mechanism, 1136
  and the Felkin-Ahn rule, 1015
  mechanism, 1010
  polyhalo compounds to alkenes, 1160
  to alkenes, 0280, 0947, 1011
  to alkenes, intramolecular, see radical cyclization
addition, syn, see syn
addition-elimination mechanism, see mechanism
additives, chiral, and conjugate addition (Michael addition), 1108
aggregation state, *tert*-butyllithium, solvent effects, 0260
aggregation, *ab intio*, enolate anions, 0264
  and dialkylamide bases, 0389
  and enolate anions, 0390
  and HMPA, 0389
  of organolithium reagents, 0260, 0262, 0263
AIBN [*azobis*(isobutyronitrile)], 0935
  and addition of silanes to alkenes, 1087
  and addition reactions to imines, 1336
  and carbonylation of aryl halides, 0910
  and coupling with allylic silanes, 0589
  and radical conjugate addition, 1123
  and radical cyclization, 1125
  and radical cyclization with silanes, 1127
  and radical halogenation, 0961
  and reduction of alkyl halides, 1825, 1826
  and reduction of thiocarbonates, 1833
  and seleno esters, 1129
  and the Schmidt reaction, 1612
  carboxylic acids and nitric acid, 0975
  coupling alkanes and alkynes, 0647
  decomposition, mechanism, 0935
  formation of radicals, 0935
  metal catalyzed carbonylation, 1140
  NBS, amines and aldehydes, 0974
alanes, alkynyl, conjugate addition, 1118
  and reductive cleavage of enamines, 1844
  trialkyl, conjugate addition, 1118
  vinyl, dimerization, 0988
  vinyl, from alkynes, 1083
alcohol-alkynes, and hydrogen bonding, 0113
alcohols, acid catalyzed addition to nitriles, 1275, 1458
  acid catalyzed dehydration, E1, mechanism, 1515
  acylation, 1412
  addition to aldehydes or ketones, 1270
  addition to alkenes, 1134
  addition to isocyanates, 1274
  addition to ketenes, 1040
  alkyl azides, and Mitsunobu reaction, 1612
  alkylation of amines, 0558
alcohols, allylic with aziridines, 0621
  allylic silanes with aldehydes, 1322
  and Sharpless asymmetric epoxidation, 1177
  and the Baylis-Hillman reaction, 1323
  base induced elimination of epoxides, enantioselectivity, 1519
  by allylic oxidation with selenium dioxide, 1751, 1752
  by oxidation of alkenes, 1751, 1752
  by the Prins reaction, 1393
  coupling and rearrangement, 0615
  halogenation, 0579
  oxidation to carboxylic esters, 1769
  oxidation with chromium reagents, 1716
  reduction, and rearrangement, 1829
  with sulfur ylids, 1387
alcohols, and acidity scales, 0370
  and alkoxymercuration, 1040
  and boron-to-carbon rearrangement, 1627
  and catalytic dehydrogenation, 1724
  and formation of carbocations, 0236
  and Friedel-Crafts alkylation, 0707
  and Koch-Haaf reaction, 0653
  and phase transfer, 0576
  and Schotten-Baumann procedure, 1411
  and Swern oxidation, 1721
  and the Koch-Haaf reaction, 1137
  and the Pinner synthesis, 1275
  and the Ritter reaction, 1459
  and the S_Ni mechanism, 0469
  and transesterification, 1419
  and transetherification, 0535
  and triethylborane, 0520
alcohols, base-catalyzed addition to alkynes, 1039
alcohols, benzylic, and atropisomers, 0147
  halogenating agents, 0579
  oxidation, and microwaves, 1726

alcohols, by anti-Markovnikov addition to alkenes, 1033
by Cannizzaro reaction, 1863
by catalytic hydrogenation, 1829
by enantioselective hydroboration, 1079
by hydrolysis of borates, 1798
by hydrolysis of esters, 0642
by hydroxyalkylation of aromatic compounds, 0713
by Meerwein-Ponndorf-Verley reduction, 1796
by oxidation of boranes, 1079, 1626
by oxidation of hydrocarbons, reagents for, 1750, 1751
by oxymercuration, 1033
by reduction of acyl halides, 1840
by reduction of aldehydes or ketones, 1792–1805
by reduction of amides, 1421
by reduction of boranes, 1628
by reduction of carboxylic acids, 1805, 1806
by reduction of carboxylic esters, reagents, 1795, 1806, 1807
by reduction of epoxides, reagents, 1790, 1791
by reduction of hydroperoxides, 1834
by the Barbier reaction, 1302
by the Bouveault-Blanc procedure, 1795
alcohols, carbonylation, 0652, 0653, 0851, 0909, 1139
chromium(VI) oxidation, mechanism, 1726, 1727
conjugate addition, 1131
conversion to sulfonate esters, and reduction, 1830
coupling, 0615
coupling with arylboronic acids, 0889
coupling with organometallics, 0614, 0615
cycloalkyl, from cycloalkyl amines and nitrous acid, 1588
cyclobutyl, from cyclopropylcarbinyl amines, 1588
cyclodehydration, 0715
cyclopropylcarbinyl, from cyclobutyl amines, 1588
cyclopropylcarbinyl, halogenation, 0579
alcohols, dehydration, 0534
acid catalyzed, 1513
and carbocations, 0535
and Hofmann's rule, 1514
and Mitsunobu reaction, 0535
and Zaitsev's rule, 1513
dehydrating agents, 1513
formation of alkenes, 0771
in supercritical carbon dioxide, 0415
alcohols, dehydroxylation, reagents, 1829
enzymatic oxidation, 1725
formation of amines, 0559
formation of aniline derivatives, 0560
formation of azides, 0561
formation of enol ethers, 0536
alcohols, from addition of organometallics to aldehydes or ketones, 1309
from aldehydes or ketones, 0713
from alkenes, 1032
from alkylboranes, 0814
from amides, and organometallics, 1445
from amines, 0547
from anhydrides, and organometallics, 1445
from boranes and carbon monoxide, 1628
from carboxylic esters, and organometallics, 1445
from carboxylic esters, Bouveault-Blanc procedure, 1807
from diazoketones, 0523
from epoxides, 0618
from ethers, 0580, 0581, 0582, 1624
from Grignard reagents, 0618, 0813, 1300–1309
from hydrocarbons and ozone, 1750
from inorganic esters, 0522
from organolithium reagents, 0618
alcohols, halogenating agents, 0578, 0579
alcohols, homoallylic, chiral, from epoxides, 0620
from alkenes and choral, 1395
from allylic silanes and aldehydes, 1388
pyrolysis, 1551
with allylic organometallics, 1313
alcohols, α-hydroxylation of allylic compounds, 1756
α-hydroxylation of benzylic compounds, 1755, 1756
in esterification reactions, 1414
indirect reduction to hydrocarbons, 1830
insertion by carbenes, 0804
intramolecular addition of alkenes, 1037
intramolecular carbonylation with aryl halides, 0909
metal catalyzed coupling with allyl silanes, 0616
metal catalyzed dehydration, 1514
metal catalyzed oxidation, 1719, 1722
metal mediated oxidation, 1717, 1721
Moffatt oxidation, 1721
Oppenauer oxidation, 1721
alcohols, oxidation of alkanes with dioxiranes, 1755
oxidation to aldehydes but not acids, reagents for, 1718, 1719
oxidation to aldehydes or ketones, 1715–1728
oxidation to carboxylic acids, reagents for, 1768
oxidation to form cyclic ethers, 0965
oxidation, in ionic liquids, 0416
alcohols, oxidizing reagents for making cyclic ethers, 0965
oxymercuration, see alkoxymercuration
permanganate oxidation, and ultrasound, 1718
photochemical addition to alkenes, 1040
photochemistry, 0332
propargyl, Friedel-Crafts alkylation, 0707
propargylic, formation of allenes, 0769
propargylic, with boronic acids, 1540
protection as ethers, 0531

protonolysis, and carbocation formation, 0247
radical dimerization, 0977
reagents utilized with DMSO, for oxidation, 1721, 1722
reduction to hydrocarbons, reagents, 1829
reductive alkylation of aldehydes, 1273
structural variation of chromates for oxidation, 1716, 1717
supercritical, reduction of ketones, 1837
Tamao-Fleming oxidation, 0539
TEMPO oxidation, in ionic liquids, 1723
vinylcyclopropyl, sigmatropic shifts, 1653
alcohols, with acyl halides, 1411
with acyl hydrazides, 1422
with aldehydes or ketones, compatible functional groups, 1270
with alkenes, 1037
with alkenes and hydrazoic acid, 1612
with alkynes, 1038
with allenes, formation of tetrahydrofurans, 1038
with amides, 0570
with anhydrides, 1412, 1413
with aziridines, 0537
with boron trichloride or boron trioxide, 0817
with brominating agents, 0577
with carbon disulfide, 1276
with carboxylic acids, acid catalyzed, 1414
with chlorinating agents, 0576, 0577
with cyanogen chloride, 1276
with diazomethane, 0533
with enol ethers, 1039
with epoxides, 0536
with fluorinating agents, 0577
with halogens, 1154
with halogens and alkenes, 1152
with hydrazoic acid, 0559
with hydrogen sulfide, 0549
with imides, 0570
with inorganic acids, 0545
with iodinating agents, 0577
with Lawesson's reagent, 0549
with lead tetraacetate, 0965
with metal halides, 0578
with Michael type alkenes, 1039
with mineral acids, 0576
with onium salts, 0538
with oxidizing agents and ylids, 1371
with phosgene, 1276
with sulfinyl halides, 0554
with sulfonamides, 1473
with sulfonyl halides, 1473
with thiols, 0550
with thionyl chloride, 0469, 0576
with trifluoroborates, 0533
alcoholysis, metal catalyzed, 1039
of alkenes, 1038, 1039
of anhydrides, 1413
of nitriles, 1275
aldehydes, α-halogenation, 0964
acid catalyzed addition of aldehydes, 1460
acid catalyzed rearrangement, 1592
aldehydes, addition of alcohols, 1270
addition of allylic boranes, 1319
addition of amides, 1292
addition of dialkylzinc reagents, 1310, 1211
addition of diazomethane, 1601, 1602
addition of Grignard reagents, mechanism, 1307
addition of organolithium reagents, mechanism, 1308
addition of organometallics, 1309–1311
addition of thiols, 1278
addition of water, 1262
addition to alkenes, 1134
addition to alkenes, in ionic liquids, 1136
aldehydes, aldol condensation with ketones, 1344
aliphatic, in the Vilsmeier reaction, 0797
alkylation, 0626
amphiprotic properties, 0772
aldehydes, and autoxidation, 0967
and Collman's reagent, 0650
and formation of aminals, 1283
and hemiaminals, 1281
and Peterson alkenylation, 1365
and tautomerism, 0098
and the aldol reaction, 1339–1351
and the Baylis-Hillman reaction, 1323
and the benzoin condensation, 1396
and the Claisen reaction, 1355
and the Claisen-Schmidt reaction, 1343, 1344
and the Henry reaction, 1357
and the Knoevenagel reaction, 1358
and the Mannich reaction, 1292
and the McMurry reaction, 1859
and the Mukaiyama aldol, 1351–1354
and the Paterno-Büchi reaction, 1463
and the Perkin reaction, 1363
and the Reformatsky reaction, 1326
and the Stetter reaction, 1136
and the Tischenko reaction, 1865
and the Tollens' reaction, 1368
aldehydes, aryl, and the Gatterman reaction, 0725
and the reverse Gatterman-Koch reaction, 0745
benzylic oxidation, reagents for, 1763
by α-oxidation of methyl aromatic compounds, 1763
by benzylic oxidation, 1763
decarbonylation, 0745
formation of hydrazones, 1284
from aromatic compounds, 0724
with iminium salts, 0725
aldehydes, as dienophiles, 1216
aldehydes, bisulfite addition products, 1280
aldehydes, by acid treatment of Reissert compounds, 1811
by base cleavage of acyl sulfonylhydrazides, 1811

aldehydes, by acid treatment of Reissert compounds, (*Continued*)
by Dibal reduction of esters, 1809
by DMSO-type oxidation of alcohols, 1721
by Etard reaction, 1763
by hydrolysis of acetoxy sulfides, 1866
by hydrolysis of acylals, 1763
by hydrolysis of alkoxides, 1804
by hydrolysis of C=N compounds, reagents for, 1263–1265
by hydrolysis of enol ethers, 1035, 1372
by hydrolysis of imines, 1767
by hydrolysis of Schiff bases, 1263
by Krönke reaction with benzylic halides, 1766
by McFadden-Sevens reduction, 1811
by Oppenauer oxidation, 1721
by oxidation of alcohols, 1715–1728
by oxidation of alkenes, 1773–1775
by oxidation of alkyl halides, 1765
by oxidation of amines, 1767
by oxidation of benzyl silyl ethers, 1720
by oxidative cleavage of diols, 1732
by ozonolysis of alkenes, 1737
by pyrolysis of allylic ethers, 1552
by pyrolysis of enol ethers, 1517
by pyrolysis of homoallylic alcohols, 1551
by reduction of acyl halides, reagents, 1808
by reduction of anhydrides, 1810
by reduction of boranes, 1628
by reduction of carboxylic acids or esters, reagents, 1809
by reduction of imidazoles, 1811
by reduction of nitriles, reagents, 1815
by reduction of ortho esters, 1832
by Rosenmund reduction, 1808
by Stephen reduction, 1815
by the Barton reaction, 1696
by the Kornblum reaction, 1765
by the Meyers aldehyde synthesis, 0642
by the Nef reaction, 1267
by the Reimer-Tiemann reaction, 0726
by the Sommelet reaction, 1766
by the Sonn-Müller method, 1811
by the Wacker process, 1774
by Vilsmeier-Haack reaction, 0724
aldehydes, catalytic hydrogenation, 1795, 1805
chemoselective reducing agents, 1793
condensation, see aldol
condensation with esters, 1355
aldehydes, conjugate addition, and microwaves, 1132
conjugate, and organocuprates, 1114
aldehydes, conjugated, see conjugated compounds
aldehydes, conjugated, and metathesis, 1685
and organolithium reagents, 1115, 1302
by aldol reaction, 1339–1351
E/Z-isomerization with thiourea, 1029
reagents for conjugate reduction, 1071
reagents for reduction of alkenyl, 1074
reduction, and microwaves, 1074
with ammonia and metal peroxides, 0974
with Grignard reagents, 1302
aldehydes, coupling to carboxylic esters, reagents, 1865, 1866
cycloaddition to alkenes, 1463
decarbonylation, 0344, 0997
dehydrogenation, 1713
enol content, 0099
formation of cyanoamines, 0561
formation of ketones, 0801
formation of nitriles, reagents for, 1287, 1288
formation of silyl enol ethers, 0800
Friedel-Crafts cyclization, 0715
aldehydes, from acyl halides, 0650
from alkynes and hydroboration, 1081
from boronic acids and organolithium reagents, 1629
from chloroform, 0726
from chloroiminium salts, 1815
from cycloaddition of singlet oxygen to alkenes, 1220
from dihalides, 0520
from enol borinates, 1121
from enols, 0837
from formic acid, 0823
from glycidic acids, 0837
from Grignard reagents, 0910
from hydrocarbons, 0824
from metallated imines, 1469
from organolithium reagents, 0910
from organometallics, 0823
from oxazines, 0642
from sulfonic anhydrides, 0725
from thiazoles or thiazolines, 0643
from vinylic compounds, 0522
aldehydes, halogenation of, 0964
halogenation, enantioselectivity, 0776
homologation, 1601, 1602
hydration, 1262
Lewis acid acylated addition of allylic silanes, 1322
$LiAlH_4$ reduction, mechanism, 1804
Meerwein-Ponndorf-Verly reduction, 1796
metal catalyzed addition to alkenes, 1135
metal catalyzed cycloaddition with ketenes, 1462
metal catalyzed decarbonylation, 0997, 0998
metal mediated addition of haloesters, 1326
more reactive than ketones, 1254

oxidation to carboxylic acids, 1718, 1769–1773
Paterno-Büchi reaction, 1231
photochemical addition to alkenes, 1136
photochemical [2 + 2]-cycloaddition with alkenes, 1231
photochemistry, 0332
Pictet-Spengler reaction, 0716
protection of, 0527
radical addition to alkenes, mechanism, 1136
aldehydes, reduction, by the Cannizzaro reaction, 1798, 1863
to alcohols, 1792–1805
to methyl, reagents for, 1836, 1837
versus ketones, 1793, 1794
in ionic liquids, 1800
aldehydes, reductive alkylation with alcohols, 1273
reductive amination, 1288–1291
reductive coupling to alkenes, reagents, 1858, 1859
reductive coupling to diols, reagents, 1854, 1855
structural requirements for the Wittig reaction, 1371
tautomerism, 0772
tautomerism, in sugars, 0104
trimerization, 1460
vinylation, 0629
aldehydes, with acylperoxides, 0972
with alcohols, compatible functional groups, 1270
with alleneboranes, 1079
with allylic silanes, 1388
with amides, 0570
with amines, 0716, 1281
with amines and hydrogen, 1288–1291
with anhydrides, 1273, 1363
with aromatic compounds, 0713
with bis(Grignard) reagents, 1304
with boron stabilized carbons, 0801
with carbanions, 0265
with conjugated esters, and the Stetter reaction, 1321
with cyanide, and conjugate addition, 1133
with diazoalkanes, 1384
with diazoesters, 0800
with diazomethane, 0807, 1384
with dienes, 1322
with dihalocarbenes, 1384
with enolate anions, 0263, 1339–1351
with enolate anions, see aldol
with Grignard reagents, 1300–1309
with halo esters, 1364
with HCN, 1389
with hydrazines, 1284
with hydroxylamines, 0974, 1286, 1287
with iodine, and ammonia, 0974
with isocyanides and carboxylic acids, 1467
with lithio-silanes, 1365
with NBS, radical halogenation, 0964
with nitro compounds, 1357
with organocuprates, 1312
with organolithium reagents, 1301
with phenylhydrazine, 1675
with phosphorus ylids, 1369
with potassium cyanide, 1396, 1397
with silyl enol ethers, and chiral boranes, 1348
with sodium azide, 1440
with sodium bisulfite, 1281
with sulfur ylids, 1382
with transition metals, and acyl radicals, 0936
with trifluoroborates, 1322
aldehydes, Wolff-Kishner reduction, 1835
aldehydes-alkene, and radical cyclization, 1129
aldimines, see imines
aldol condensaton, see aldol reaction
aldol reaction, 1339–1351
aldol reaction, acid catalyzed, 1349
aldol reaction, and a SET mechanism, 1341
and asymmetric synthesis, 0172
and dihalides, 0520
and enolate anions, 0263, 0627
and enolization, 1346
and hydroformylation, 1146
and the Cannizzaro reaction, 1863
and the Robinson annulation, 1350
aldol reaction, aqueous media, 1348
chiral, 1347
definition, 1341
diastereoselectivity and and syn/anti isomers, 1345, 1346
enantioselectivity, 1347, 1348
equilibrium, 1342
in ionic liquids, 1342
intramolecular, 1349, 1350
mechanism, 1341
mechanism of acid catalyzed reaction, 1349
mixed, 1343
mixed, and the Tollens' reaction, 1368
aldol reaction, Mukaiyama, 1351–1354
catalysts for, 1352, 1353
enantioselectivity, 1353, 1354
in water, 1353
intramolecular, 1353
metal salts as catalysts, 1352
substrates for, 1352
aldol reaction, retro-, 118, 1342
aldol reaction, self condensation, 1343
solvent effects, 1342
solventless, 0416
stereoselectivity, 1345, 1346
transition state geometry, 1346
vinylogous, chiral, 1348
vinylogy, 1342
aldol-type reactions, 1340
aldols, also see hydroxy-ketones
Aldrich Library of Spectra, 1888
algorithm, dielectric screening effects, 0503
alkaloids, Cinchonidine, see Cinchonidine
alkanes, addition to alkenes, 1086
addition to alkenes, and Friedel-Crafts reactions, 1084
and bond angle, 0026
and conformations, 0200
and guest-host interactions, 0127
and photochemistry, 0332
and superacids, 0802, 0803
by addition of alkanes to alkenes, 1084

alkanes, addition to
alkenes, (*Continued*)
by coupling alcohols with organometallics, 0614
by coupling of alkenes, 0976
by hydrogenation of thioethers or thiols, 0990
by radical addition to alkenes, 1123
by reductive cleavage of cyclopropanes, 1074
dehydrogenation to alkynes, 1714
deuterium exchange, 1058
from alkyl halides, 0600
from metal sulfonates, 0612
from organocuprates, 0600
halogenation, 0954–0960
insertion by nitrenes, 0789
metal catalyzed addition to alkenes, 1086
nitration, 0786
organometallics with alkyl halides, 0604, 0605, 0606, 0607
oxidation to carboxylic esters with dioxiranes, 1755
radical coupling, 0976
trialkyl, metal catalyzed addition to alkynes, 1102
via coupling reactions, 0802
alkene metathesis, 1681–1689
alkene-acids, by Claisen rearrangement, 1670
alkene-aldehydes, by Claisen rearrangement, 1669, 1670
by [2,3]-Wittig rearrangement, 1678
via oxy-Cope rearrangement, 1660
alkene-amines, formation of cyclic amines, 0557
alkene-bromine complex, 1150
alkene-carboxylic acids, and halolactamization, 1154, 1155
and halolactonization, 1154, 1155
and iodolactonization, 1155
halogenation, 1154, 1155
alkene-diketones, by Claisen rearrangement, 1669
alkene-triflamides, cyclization, 1052
alkenes, also see Diels-Alder
alkenes, α-oxidation to conjugated ketones, 1759
acid catalyzed addition of alkenes, 1088
acid catalyzed addition of formaldehyde, 1393
acid catalyzed dehydration of alcohols, 1513
acylamidation or acyloxylation, 0972, 1186
acylation, 0796
alkenes, addition, of acyl compounds, 1135
of alcohols, 1134
of aldehydes, 1134, 1136
of alkanes, in ionic liquids, 1085
of alkyl halides, Friedel-Crafts catalysts, 1160
of amides, 1047
of amines, 1134, 1182
of aminonitrenes, 1184
of anions, 0265, 1007
of azido groups, 1182
of bromine, stereoselectivity, 1003
of carbamates, 1051
of carbenes, 0284, 0289, 1233
of carbenes, and steric hindrance, 1235
of carboxylic acids, 1041
of carboxylic esters, 1134
of DBr, 1006
of fluorine, 1149
of Grignard reagents, 1083
of halo-amines, 1157
of haloamines, in ionic liquids, 1157
of haloazide, 1158
of halocarbamates, 1052
of HBr, 1006
of HBr, with peroxides, 1124
of HCl, 1005
of HCN, 1147
of HX, 1006
of hydrazines or hydroxylamines, 1047
of hydrogen sulfide, 1043
of iodine azide, 1159
of iodo azide, mechanism, 1159
of isothiocyanates, 1157
of nitrenes, 0294
of nitrosyl halides or nitryl chloride, 1158
of organolithium reagents, 1097
of organometallic compounds, 1096, 1097, 1099
of polyhalo compounds, 1160
of protons, 1005
of radicals, 0280, 1010, 1123, 1134
of selenols (RSeH), 1045
of sulfonic acids, 1043
of sulfonyl halides, 1156
of thiols, 1043, 1044
of water, 1006
reactions, 0298
reactions, and the Cieplack effect, 1024
to alkanes, 1084
to carbocations, 0249
to heterocycles, 1088
cyclic mechanism, 1012
four-center mechanism, 1013
alkenes, alcohols and alkoxy-amination, 1182
alkoxy carbonylation, 1139
allylic oxidation with selenium dioxide, mechanism, 1752
amidation, 1051
amide bases with ammonium salts, 1524
amination, 0567, 0788, 0789, 1045, 1047, 1050
amino-carbonylation, 1139
aminomercuration, 1181
aminosulfenylation, 1185
alkenes, and alkoxymercuration, 1040
and allylic carbocations, 0239
and aminomercuration, 1050
and anisotropy, 0056
and Bredt's rule, 1497
and carbene rearrangements, 1579
and carbene transfer, 1234
and carbonylation, 1139
and complex formation, 0119
and E/Z nomenclature, 0183
and formation of bis(selenenyl) compounds, 1180
and Friedel-Crafts acylation, 0796
and Friedel-Crafts alkylation, 0706
and Hofmann's rule, 1498, 1499
and homoconjugation, 0045
and hydroboration, 1075–1082
and hydrozirconation, 1083
and Julia-Colonna epoxidation, enantioselectivity, 1176
and kinetic resolution, 0178

and Markovnikov's rule, 1019
and Meerwein arylation, 0923
and metal catalyzed diazoalkane reactions, 1234
and neighboring groups, 0451
and nitric acid, 0785
and NMR, 0056
and PES, 0014
and photosensitization, 0977
and prototropic rearrangement, 0768
and radicals, Baldwin's rules, 1011
and ring current, 0056
and Sharpless asymmetric dihydroxylation, 1166
and the Baeyer test, 1164
and the Heck reaction, 0891–0897, 0923
and the Koch reaction, 1137
and the Koch-Haaf reaction, 1137
and the Paterno-Büchi reaction, 1463
and the Prins reaction, 1393
and the Stetter reaction, 1136
and Waits-Scheffer epoxidation, 1174
and Woodward modification of the Prevost reaction, 1164
and X-ray crystallography, 0233
and Zaitsev's rule, 0767, 1498

alkenes, animation, and temperature effects, 1046
anti addition, 1006
anti-Bredt, by the Wittig reaction, 1373
anti-dihydroxylation, 1164

alkenes, anti-Markovnikov addition of boranes, 1078
of radicals, 1124
of water, 1033

alkenes, aryl, and electrocyclic ring closure, 1645
from alkenes, 0890

alkenes, arylation, 0890–0897, 0923

alkenes, arylation, also see Heck reaction

alkenes, as radical precursors, 1127
asymmetric epoxidation, and manganese salen complexes, 1177
azidomercuration, 1053
aziridination, in ionic liquids, 1185
baker's yeast reduction, enantioselectivity, 1066
base induced elimination of alkyl halides, 1530
base induced elimination of tosylhydrazones, 1526
bicyclic, exo addition, 1023
bicyclic, strain, 0229
bromination, reagents for, 1150

alkenes, by addition of alkenes to alkynes, 1088
by addition of organometallics to alkynes, 1101, 1102
by base induced elimination of halo sulfones, 1536
by bis(decarboxylation) of dicarboxylic acids, 1749
by Chugaev reaction, 1520
by cleavage of cyclic thionocarbonates, 1535
by Cope elimination, 1524
by decomposition of inorganic esters, 1521
by decyanation of nitriles, 0845
by dehydrogenation, 1712–1714
by deoxygenation of diols, 1534
by desulfurization of thiophenes, 0991
by E^i reactions, 1508
by elimination of boranes, 1533
by elimination of dihalides, reagents for, 1539
by elimination of epoxides, 1517, 1518
by elimination of hydroxy acids, 1543
by elimination of thiiranes, 1519
by Hofmann degradation, 1522
by Hofmann elimination, 1500
by hydroboration of alkynes, 1064
by hydrogenation of alkynes, 1057
by metal catalyzed dehydration of alcohols, 1514
by metal catalyzed elimination of carboxylic acids, 1520
by organolithium reagents with ammonium salts, 1523
by oxidation coupling of alkyl halides, 1783
by Peterson alkenylation, 1365
by protonation of vinylboranes, 1630, 1631
by pyrolysis of allylic ethers, 1552
by pyrolysis of amine oxides, 1524
by pyrolysis of ammonium salts, 1521
by pyrolysis of β-lactones, 1544
by pyrolysis of enol ethers, 1517
by pyrolysis of esters, 1519, 1520
by pyrolysis of homoallylic alcohols, 1551
by pyrolysis of sulfoxides, 1528
by pyrolysis of xanthates, 1520
by radical elimination of bis(xanthates), 1535
by rearrangement of carbenes, 1234
by reduction of thiiranes, 1791
by reduction of vinyl halides, 1827
by reductive coupling of ketones and aldehydes, 1858, 1859
by silyl-Wittig reaction, 1366
by the Bamford-Stevens reaction, 1527
by the Boord reaction, 1541
by the Corey-Winter reaction, 1535
by the ene reaction, 1103–1105
by the McMurry reaction, 1859
by the Ramberg-Bäcklund reaction, 1536
by the Shapiro reaction, 1526
by twofold extrusion, 1557
by Wittig reaction, 1369
by Wittig-Horner reaction, 1375

alkenes, captodative, 0185
alkenes, carbene addition, enantioselectivity, 1237
carbene addition, rate constant, 1234
carbonylation, 0655, 1139
catalytic hydrogenation, 1053–1062
chlorination, reagents for, 1150
cis, from LDA and aziridino hydrazones, 1527
cleavage by hydrogenation, 0845
cleavage with superacids, 0844
alkenes, conjugated, and Birch reduction, 1068
reduction with metal hydrides, 1070
reduction with metals in ammonia, 1065
reduction, reagents for, 1070
alkenes, conversion to alkynes, 1533
alkenes, coupling with alkenes, 1091
with alkyl groups, 0795
with alkynes, 0647
with carbocations, 0802
with heteroaryl halides, 0891
alkenes, crowded, and strain, 0233
alkenes, cyanation, 0801
alkenes, cyclic, addition of deuterated carboxylic acids, 1023
and Bredt's rule, 0229
by McMurry coupling, 1859
by the Story synthesis, 1557
epoxidation, and stereochemistry, 1023
from enynes, 1092
oxidative cleavage, 1743
alkenes, cyclization with organolithium reagents, 1098
alkenes, [2 + 2]-cycloaddition, 1221
with alkynes, 1229
with cyclopropanes, 1224
with ketenes, MO calculations, 1226
alkenes, cycloaddition with aldehydes or ketones, 1463
with alkenes, 1220–1233
with dienes, 1194–1215
with norbornadienes, 1204
alkenes, dehydration of alcohols, 0771
dehydrohalogenation, suitable bases, 1530
diamination, 1182
dihalo, base induced elimination to alkynes, 1534
alkenes, dihydroxylation, 1162–1168
and lead tetraacetate or thallium acetate, 1168
catalysts for, 1162
enantioselectivity, 1165
in ionic liquids, 0416, 1163
alkenes, E-selectivity, Wittig reaction, 1376, 1377
alkenes, electronic effects, Diels-Alder reaction, 1196
alkenes, enantioselective epoxidation, catalysts, 1176
alkenes, epoxidation, 1169–1179
stereochemistry, 1023
alkenes, erythro/threo addition, 1001
alkenes, fluorination, reagents for and solvent effects, 1149
alkenes, formation of lactones, 1186
formation of ozonides, 1737
formation of thiiranes, 1179
formation, and Hofmann's rule, 1510
formylation, 0797
fragmentation of amines, 1542
fragmentation of halo ethers, 1542
Friedel-Crafts alkylation, Markovnikov's rule, 0711
alkenes, from aldehydes, 0639
from aldehydes or ketones, 1079, 1369, 1382
from alkenes, 1053–1062, 1648, 1681
from alkyl halides, 0594
from allenes, 1065
from allylic acetates, 0608
from allylic silanes, 0588
from aziridines and nitrous acid, 1538
from base elimination of ethers, 1516
from carbenes, 0290, 0291
from diazoalkanes, 0290
from dienes, 1013
from dithianes, 0639
from hydroxy-silanes, 1365
from lithio-silanes, 1365
from organometallics, 0812
from phosphorus ylids, 1369
from radicals, 0280
from selenoxides, 0640, 1529
from sulfonate esters, 1521
from tosylates, 1521
from vinylboranes, 0607, 1629
alkenes, halo, see halides, vinyl
alkenes, haloacylation, 1161
and the Vilsmeir reaction, 1162
mechanism, 1161
alkenes, halogenation, 1029
and bridged ions, 1149
and isotopic labeling, 1004
and π-complexes, 1004
and radical initiators, 1149
and UV, 1149
in ionic liquids, 1150
mechanism, 1149
regioselectivity, 0955
the Prins reaction, 1161
alkenes, homoallylic, 0451
hydration, 1032
hydroamination, enantioselectivity, 1181
hydroboration and hydration, 1034
hydroboration in the presence of alkynes, 1082
hydroboration, stereochemistry, 1024
hydrocarboxylation, 1136, 1138
hydrogen abstraction by radicals, 0945
hydrogen peroxide with formic acid, 1164
hydroxylation, 1032
hydroxysulfenylation, 1179
hydrozirconation, 1083
intramolecular addition of alcohols, 1037
intramolecular addition of radicals, 1011
intramolecular Heck reaction, 0892
iodination, 0956
iodoacetyl addition, 1154
ionization potential and addition reactions, 1018
isomerization, E/Z and positional isomers, 1028
isomerization, via boranes, 0771

Jacobsen-Katsuki epoxidation, 1178
lactonization, 1186, 1187
less stable, and the Wittig reaction, 1372
Lewis acid catalyzed addition of acyl halides, 1161
Lewis acid catalyzed addition of alkyl halides, 1159
Lewis acid catalyzed addition of silanes, 1086
alkenes, metal catalyzed addition of alkanes, 1086
of alkenes, 1088
of alkynes, 1089
of aromatic compounds, 1100
of carbonyl compounds, 1098
of diazoacetates, 1183
of Grignard reagents, 1096, 1097
of imides, 1052
of ketones, 1098
of phosphines, 1050
of silanes, 1086
to aldehydes, 1135
to arenes, 1100
to vinyl halides, 1100
alkenes, metal catalyzed amination, 1046, 1047
carbonylation, 1138, 1140
carboxylation, 1144
cyclization to allenes, 1094
decarbonylation of acyl halides, 1534
hydration, 1034
hydroamination, 1181
hydroformylation, 1145
with aryldiazonium salts, 0923
alkenes, metal induced elimination of halo ethers, 1541
alkenes, metal mediated elimination of dihalides, 1539
alkenes, metal-mediated addition to nitriles, 1459
alkenes, metalation, 0811
alkenes, Michael type, addition of alcohols, 1039
addition of amines, 1046
addition of hydrazoic acid, 1052
addition of thiols, 1044
with diaryl sulfimides, 1183
alkenes, mixed halogenation, 1151
nitration, and nitronium salts, 0786
nitroso-halogenation, 1158
orbital overlap in [2 + 2]-cycloaddition, 1225
orientation of addition, 1022
alkenes, oxidation in the Wacker process, 1774
to aldehydes or ketones, reagents for, 1773–1775
to allylic alcohols, 1751, 1752
alkenes, oxidative cleavage, 1742–1745
with Lemieux-von Rudloff reagent, 1743
Barbier-Wieland procedure, 1743
alkenes, oxidative decarboxylation of carboxylic acids, 1747
alkenes, oxyamination, 1180
alkenes, oxymercuration, 1033
alkenes, ozonolysis, 1736–1742
and rearrangement, 1737
Criegee mechanism, 1738–1740
regiochemistry of ozonide formation, 1740, 1741
alkenes, Paterno-Büchi reaction, 1231
peroxide epoxidation, and microwaves, 1171
peroxyacid epoxidation, mechanism, 1170
photochemical addition of alcohols, 1040
photochemical addition of aldehydes, 1136
photochemical addition of thiols, 1044
photochemical isomerization, 0346
photochemical isomerization, E/Z, 1028
photochemical [2 + 2]-cycloaddition, aldehydes or ketones, 1231
photochemistry, 0332, 0346
photoisomerization, 0346, 1029
photooxygenation with singlet oxygen, 1178
polyhalo, 1031
protonolysis to from carbocations, 0247
push-pull, 0185
alkenes, radical addition, generation of radicals, 1124
of aldehydes, mechanism, 1136
of silanes, 1087
rate of reaction, 1124
stereoselectivity, 1012
alkenes, radical halogenation, 0958, 0961
radical-induced addition of polyhalo compounds, 1160
reaction with peroxides, 1171
reactivity in alkene metathesis, 1684
reactivity in diazo transfer reactions, 1237
reactivity to metal catalyzed hydroformylation, 1145
reactivity with bromine, 1016
reactivity with HCN, 1147
reactivity with mixed halogens, 1151
reagents for oxidative cleavage, 1742, 1743
rearrangement, 0769, 0770, 0767
reducing agents, 1062
alkenes, reduction by hydroboration, 1063
of alkynes, 1065
of propargyl halides, 1826
to alkanes, 1062
with diimide, 1063
with metal hydrides-metal salts, 1071
with samarium iodide and triamines, 1063
with silanes, 1071
alkenes, reductive coupling, 1095
resolution, 0174
reversible addition of radicals, 1012
selectivity in catalytic hydrogenation, 1055
Sharpless asymmetric epoxidation, 1177
sigmatropic migration of hydrogen, 1648
Simmons-Smith procedure, 1241
stability, 1497, 1498
stereochemistry of elimination reactions, 1501
stereoselective addition of boranes, 1077
structure and ozonolysis, 1737
substituted, and the heck reaction, 0892
syn addition of bromine, 1004

alkenes, reductive
coupling, (*Continued*)
thermodynamic stability, 0769, 10771, 372
thermodynamic stability, and metathesis, 1683
twisted, 0233
unsymmetrical, by McMurry coupling, 1860
versus alkynes, in addition reactions, 1017
versus alkynes, in ozonolysis, 1738
via Petasis reagent or Tebbe's reagent, 1381
alkenes, with acids, HX, 1029
with acyl halides, 0796
with acylium ions, 0796
with alcohols, 1037
with alcohols and hydrazoic acid, 1612
with alkenes, temperature and pressure, 1084
with alkyl azides, 1183
with amides, 1051
with aromatic compounds, 0706
with aryl disulfides, and metal salts, 1179
with aryldiazonium salts, 0923
with azodicarboxylates, metal catalyzed, 1047
with boranes, 0644, 0815, 1075–1082
with bromine, solvent effects, 1016
with carbenes, stereochemistry, 1024
with carbocations, 1000
with catecholborane, 0817, 1123
with CCl_4, to from trihalides, 0521
with chloramine-T, 1180
with chloronium ions, 1004
with chlorosulfonyl isocyanate, 1466
with HBr and peroxides, 1030
with hypervalent iodine compounds, 1153
with hypohalous acids, 1152
with imido selenium compounds, 0788
with manganese acetate, 1186
with mCPBA, 1169
with mercuric acetate, 1033
with metal hydrides, 1082
with osmium tetroxide, 1162
with oxygen, reactivity and structure, 0970
with peroxyacids, 1169
with peroxyacids, stereochemistry, 1023
with phenols, 1037
with phosphine oxides or phosphites, 1051
with photosensitized oxygen, 0968
with polyhydrogen fluoride-pyridine, 1030
with potassium permanganate, 1162
with radicals, 0936, 0941, 0947
with silyl halides, and DMSO, 1156
with silylphosphines, 1051
with silylthiols, 1044
with singlet oxygen, 0969, 0970
with sulfonamides, 1051
with thiourea, metal catalyzed formation of thiiranes, 1179
with trialkylsilyl halides, 1031
with trichloroamine, 0567
with trichloroisocyanuric acid, 1031
with triplet oxygen, 0969
with water, 1032
alkenes, Wurtz reaction, 0589
alkenes, Z-selectivity, Wittig reaction, 1376, 1377
alkeneylboranes, see boranes, vinyl
alkoxides, and LIDAKOR, 1518
cleavage, 0758, 0835
hydrolysis, 1804
metal catalyzed reaction with aryl halides, 0873
metal, syn elimination by E^i, 1515
metal, thermolysis of alkenes, 1515
thermal cleavage, 0840
with alkyl halides, 0529
with alkyl sulfates, 0532
with dihalides, 0530
with inorganic esters, 0532
alkoxy radicals, 0935
alkoxy-amination, of alkenes, 1182
alkoxy-carbonylation, of alkenes, 1139
alkoxymercuration, of alkenes, 1040
alkyl azides, see azides
alkyl chlorides, see halides
alkyl sulfates, see sulfates
alkyl trifluoroborates, see trifluoroborates
alkylation, α to carboxylic acids, 0643
α to N in amines, 0640, 0641
α to terminal triple bond, 0647
acetoacetic acid synthesis, 0624
and Montmorillonite clay, 0512
and radicals, 0512
and substitution, 0425
carbon versus oxygen, enolate anions, 0514
cyanoacetic esters synthesis, 0624
exhaustive, and amines, 0556
malonic esters synthesis, 0623
metal catalyzed, enol carbonates, 0629
alkylation, of aldehydes, 0626
of alkynes, 0646
of allylic carbanions, amine or eher, 0641
of amides, 0570
of amines, 0555, 0558, 0562
of aromatic compounds, 0912
of aromatic nitro compounds, 0914
of carboxylic acid salts, 0637
of carboxylic esters, 0626
of conjugated compounds, 1111
of cyanide ion, 0648
of cyclic carbamates, 0569
of dianions, 0515
of dimethylhydrazones, 0632
of dithioacetals or dithioketals, 0637–0639
of enamine salts, 0636
of enol carbonates, 0629
of enolate anions, 0515, 0626–0630
of enols, and Lewis acids, 0628
of formamidines, 0641
of heterocycles, 0914
of hydrazones, 0633
of hydroperoxide anions, 0544
of hydroxynitriles, 0633
of imides, 0570
of imines, 0632, 1291
of inorganic esters, 0532

of keto-sulfones or keto-sulfoxides, 0624, 0632
of ketones, 0626
of ketones, Stork enamine reaction, 0635
of lactams, 0568
of lactones, 0627
of nitriles, 0626
of oxazines, 0642
of oxazolidin-2-ones, 0569
of oximes, 0547
of phosphines, 0558
of pyridine, with organometallics, 0913
of pyrrole, 0557, 0913
of silyl enol ethers, 0628
of sulfinic esters, 0640
of sulfonamides, 0570
of sulfones, 0640
of sulfonic acid salts, 0554
of thioethers, 0639
alkylation, photochemical, of heterocycles, 0983
radical, of aromatic compounds, 0980, 0981
radical, of heterocycles, 0982
replacement of amino, 0915
Tsuji, 0629
with dianions, 0625
with diazo compounds, 0533
with enolate anions, 0263
with trialkylboranes, 0644
Ziegler alkylation, 0913
alkylboranes, see boranes
alkylboronic acids, see boronic acids
alkylchloroaluminum amides, formation of amidines, 1296
alkylcopper-magnesium bromide (Normant reagent), 1101, 1102
alkylidene lactams, from ynamides, 1052
alkyne allene from alkynes, 1094
alkyne anions, also see acetylides
alkyne anions, *ab into* study of 1,2-alkyl shifts, 1579
and the Nef reaction, 1359
Knoevenagel reaction, 1359
metal, and Stephens-Castro coupling (aryl halides), 0903–0906
metal, with aryl halides, see Stephens-Castro
metal, with boranes, 1631
alkyne dimerization, metal catalyzed, 1091
alkyne-alcohols, dehydration, 1515
from alleneboranes and aldehydes, 1079
hydration, 1039
alkyne-carboxylic acids, formation of lactones, 1042
alkyne-esters, from carbonylation of alkynes, 0655
alkyne-esters, from metallated alkynes, 0814
alkyne-ketones, by carbonylation of alkynes and aryl halides, 0910
by Eschenmoser-Tanabe ring cleavage, 1544
conjugate addition of boranes, and boron trifluoride, 1122
from amides and alkynylboranes, 1448
from epoxy hydrazones, 1544
alkynes, α-alkylation, 0647
alkynes, addition, of acids HX, 1007, 1030
of acyl compounds, 1135
of aziridines, 1192
of HCN, 1147
of hypohalous acids, 1153
of nitryl chloride, 1158
of Normant reagents, 1101, 1102
of organocuprates, 1102
of organolithium reagents, 1097
of organometallic compounds, 1099
of silanes, intramolecular, 1087
of sulfonic acids, 1043
of sulfonyl halides, 1156
reactions and Markovnikov's rule, 1030
reactions, and π-orbitals, and UV, 1017
reactions, formation of halonium ions, 1018
to alkynes, 1044
alkynes, alkylation, 0646
alkynes, and anti-Markovnikov hydration, 1035
and formation of enol esters, 1042
and Friedel-Crafts alkylation, 0707
and hydrogen bonding, 0111
and proton transfer, 0368
and Sonogashira coupling, 0904
and Suzuki-Miyaura coupling, 0899
and the Cadiot-Chodkeiwicz reaction, 0979
and the Eglinton reaction, 0978
and the Fritsch-Buttenberg-Wiechell rearrangement, 1534
and the Glaser reaction, 0978
and the Hay reaction, 0979
and the Heck reaction, 0892
baker's yeast reduction, enantioselectivity, 1066
base-catalyzed addition of alcohols, 1039
bis addition of organometallics, 1101
by anti-elimination, 1482
by base induced elimination of dihalides, 1531
by dehydrogenation of alkenes, 1714
by dehydrohalogenation, 1531
by E2 reactions, 1482
by hydroboration, enantioselectivity, 1631
by oxidative coupling of dihalotoluenes, 1783
by pyrolysis of acyl phosphorus ylids, 1525
by pyrolysis of bis-(ammonium) salts, 1523
by Stephens-Castro coupling, 0903–0906
carbonylation reactions, 0655, 0910, 1139
catalytic hydrogenation, 1057, 1058, 1065
copper mediated coupling, 0978
coupling with alkanes, 0647
alkynes, [2 + 2]-cycloaddition, 1221, 1229
with alkenes, 1229
with cyclopropanes, 1224
alkynes, cycloaddition with dienes, 1195
cyclotrimerization, 1243, 1244
diaryl, 0904
dihydroxylation and ozonolysis, 1168
formation of bridged ions, 1018
formation of vinylic carbocations, 1007

alkynes, from alkenes, 1533
from alkenes, by metathesis, 1688
from alkyl halides, 0646
from alkyne alkylation, 0646
from aryl halides, 0903–0906
from aryl halides, see Stephens-Castro
from boranes, and metal alkyne anions, 1631
from metal alkyne anions, 0903–0906
from metal alkyne anions, see Stephens-Castro
from nitrenes and alkenes, 1184
from nitriles, 0904
from the Wittig-Horner reaction, 1376
from vinyl halides, 0473
alkynes, halo, see haloalkynes
halogenation, 1151
hydration, 1035
hydroboration, 1081
hydroboration, and reduction to alkenes, 1064
hydroboration, in the presence of alkenes, 1082
hydrocarboxylation, 1137, 1138
hydrogenation with the Lindlar catalyst, 1057
hydrometallation, 1083
Lewis acid catalyzed addition of silanes, 1086
Lewis-acid catalyzed addition of alkyl halides, 1160
lithiation, 0809
lithio, see lithioalkynes
mercuric catalyzed hydration, mechanism, 1036
alkynes, metal catalyzed addition of amides, 1052
addition of arylboronic acids, 1100, 1103
addition of Grignard reagents, 1096, 1097
addition of imides, 1052
addition of phosphines, 1050
addition of trialkylboranes, 1102
addition to alkenes, 1089
amination, 1048
carbonylation, 1140
carboxylation with carbon dioxide, 1042
conjugate addition, 1117, 1118
coupling, 0978
coupling to alkynes, 1091
coupling with triarylstibines, 0906
coupling with vinyl halides, 1094
cyclotrimerization, 1243
hydration, 1035
hydroformylation, 1146
alkynes, metal mediated addition of HCN, 1147
metal mediated coupling with alkyl halides, 0647
metalation, 0809
metathesis, 1688
methylthio, metal catalyzed coupling with arylboronic acids, 0905
Michael type, and addition of thiols, 1044
orientation of addition, 1022
oxidation to carboxylic acids, 1775
oxidation to diketones, reagents, 1776
oxidative cleavage, 1744
radical addition, 1124
reaction with dialkylaluminum reagents, 1083
reaction with haloboranes, 0990
reaction with organometallics, 1083
rearrangement to allenes, 0768
reduction, 1064, 1065
reductive coupling, 1092
seleno, hydration, 1036
silyl, alkylation, 0647
silyl, as a protecting group, 0979
silyl, metal catalyzed coupling with aryl halides, 0905
tetramerization, 1243
trimerization, 1243
versus alkenes in addition reactions, 1017
versus alkenes in ozonolysis, 1738
alkynes, with alcohols, 1038
with alkylboronic acids, 0794
with amines, metal catalyzed, 1048
with aryl halides, 0899, 0904
with aryl halides, see Sonogashira
with bromine or bromonium ions, 1004
with carbenes, 1238
with catecholborane, 0820
with iodo azide, 1159
with iodonium salts, 0905
with metals, 0811
with phosphine oxides, 1051
with silanes, metal catalyzed, 0647
with sulfur monochloride, 1179
alkynyl compounds, and nucleophilic substitution, 0481
allene-alcohols, tautomerization, 0472
allene-carboxylic acids, cyclization to butenolides, 1042
allene-esters, cyclization to butenolides, 1042
allenes, addition of chloroformates, 1162
allenes, and addition reactions, 1019
allenes, and atropisomers, 0148, 0149
and chirality, 0148
and cumulative double bonds, 0148
and formation of conjugated ketones, 0472
and Markovnikov's rule, 1022
and Meyer-Schuster rearrangement, 0473
and mirror plane, 0148
and rearrangement of alkynes, 0768
and the Cahn-Ingold-Prelog system, 0158
and the Heck reaction, 0892
and the Simmons-Smith procedure, 1241
allenes, by rearrangement of cyclopropenes, 1238
allenes, catalytic hydrogenation, 1058, 1065
cyclic, 0228
enantioselectivity, 0770
epoxidation, with oxaziridinium salts, 1173
formation of allylic carbocations, 1021
allenes, from carbon dioxide and phosphorus ylids, 1380

from Grignard reagents, 0596, 0609
from organocuprates, 0602, 0608
from propargyl esters, 0608
from propargyl halides, 0596
from propargylic alcohols, 0769, 1540
from propargylic ethers, 0617
allenes, halogenation, 1152
hybridization, 0148
hydration, 1037
metal catalyzed addition of amides, 1052
metal catalyzed amination, 1049
metal catalyzed cyclization with alkenes, 1094
rearrangement, 0768
rearrangement of en-ynes, 0770
reduction, reagents for, 1065
resolution of, 0149
via allylic rearrangement, 0472
allenes, with alcohols, formation of tetrahydrofurans, 1038
with chlorosulfonyl isocyanate, 1466
with electrophiles, 1022
with halo azide, 1159
allenes, [2 + 2]-cycloaddition with alkenes or alkynes, 1221, 1222
allophanates, from carbamates, 1274
allowed reactions, in Hückel or Möbius systems, 1211
alloxans, dialkyl, with Oxone, 1173
allyl anions or allyl cations, and resonance, 0042
allyl halides, see halides
allylation, decarboxylative, metal catalyzed, 0996
allylic α-hydroxylation, 1756
allylic acetate, also see esters, allylic
allylic carbanions, 0252, 0641, 0768, 1014
allylic carbocations, 0240
allylic carbonates, see carbonates
allylic compounds, α-hydroxylation, 1756
ambident substrates, 0518
and autoxidation, 0967
with oxygen, 0970
allylic halogenation, radical, 0960
allylic oxidation of alkenes, with SeO_2, mechanism, 1752
of alkenes, 1751, 1752
allylic phosphonates, see phosphonates
allylic radicals, see radicals
allylic rearrangement, see rearrangement
allylic substrates, and substitution reactions, 0482, 0483
allyllithium, 0117
allyllithium reagents, sulfur stabilized, 0263
allyltin compounds, acyl addition, in ionic liquids, 1314
Alpine-Borane [B-(3-pinanyl)-9-borabicyclo[3.3.1] nonane], 1803
alternant hydrocarbons, 0069
electrophilic aromatic substitution, 0676
energy levels, 0070
odd and even, 0069
topological polarization, 0071
alumina, and acyl halides with alcohols, 1411
and chlorination of lactams, 0851
and conversion of aldehydes to nitriles, 1287
and dehydration of alcohols, 1513
and dehydration of oximes to nitriles, 1547
and Diels Alder reactions, 1199
and elimination of alcohols or ethers to alkenes, 1516
and Meerwein-Ponndorf-Verly reduction, 1796
and reduction of nitro compounds, 1817
and sodium borohydride, 1792
and Suzuki-Miyaura coupling, 0900
aluminum alkoxides, and Oppenauer oxidation, 1721
aluminum chloride-butylpyridinium, ionic liquid, 1675
aluminum compounds, and Meerwein-Ponndorf-Verly reduction, 1796
aluminum hydride, lithium, see lithium
aluminum isopropoxides, reduction of carbonyls, 1796
aluminum, dialkyl, with alkynes, 1083
aluminum-free Meerwein-Ponndorf-Verly reduction, 1796
Amberlyst-15, and acetal cleavage, 0526
ambident nucleophiles, see nucleophiles
ambident substrates, see substrates
amidation of alkenes, 1051
amidation, of aromatic compounds, 0694, 0729
amide bases, and enolate anion formation, 0799
and stereoselectivity in the aldol reaction, 1346
and the Chichibabin reaction, 0915
and the Haller-Bauer reaction, 0844
and the Stevens rearrangement, 1621
and transamination, 0561
chiral, 0775
cleavage of ketones, 0844
halogenation of carboxylic acids, 0782
with alkyl halides, 0568
with ammonium salts, 1524
with aryl halides, 0568, 0876
with epoxides, 0564
with benzylic ammonium salts, 0929
amide esters, by the Passerini reaction, 1468
amide, sodium, see sodium amide
amide-esters, from isocyanides, 1467
amides, also see formamides
amides bases, with heterocycles, 0915
amides, acidity, 0383
acylation by amides, 1437
acyloxy, see amide-esters
addition to aldehydes, 1292
addition to alkenes, 1047, 1187
alcoholysis, 1421
alkylation, 0570
allylic, isomerization to enamides, 1028

amides, and acidity scales, 0370
and catenanes, 0131
and conformation, 0202
and enantiomeric excess, 0180
and Friedel-Crafts cyclization, 0715
and Hofmann rearrangement, 1607
and hydrogen bonding, 0108, 0113
and isomers, 0184
and N-ylids, 0255
and proton transfer, 0368
and pyramidal inversion, 0142, 0143
and resonance, 0202
and the Claisen reaction, 1355
and the Haller-Bauer reaction, 0844
and the Sonn-Müller method to prepare aldehydes, 1815
and the von Braun reaction, 1550
and the zip reaction, 1438
and transamidation, 1425
and Wittig reaction, 0224
amides, aryl, from aromatic compounds, 0729
arylation, 0880
azidination, 0788
aziridinyl, vinylcyclopropane rearrangement, 1657
amides, by α-oxidation of cyclic amines, 1759
by amidation of alkenes, 1051
by amination of ketenes, 1050
by carbonylation, 0654, 0655, 0730, 0824, 1138
by hydration of alkynes, 1036
by hydrolysis of isocyanates, 1609
by hydrolysis of nitriles, 1268, 1269
by metal catalyzed addition, 0730
by metal catalyzed addition of amines to nitriles, 1297
by metal catalyzed addition to alkynes or allenes, 1052
by oxidation of imines, 1732
by radical coupling, 0977
by rearrangement of O-tosyl oximes, 1548
by rearrangement of oximes, 1613
by solid-phase synthesis, 1433
by the Chapman rearrangement, 1697
by the Ritter reaction, 1459
by the Willgerodt reaction, 1867
amides, chiral, and azodicarboxylates, 0789
amides, conjugate addition, 1130, 1132
amides, conjugated, for allylic amines, 0851
radicals coupling, 0976
amides, dealkylation, reagents, 1852
dehydration, 1515, 1549, 1550
dialkyl, as bases, 0388–0390
dialkyl, halogenation of carboxylic acids, 0782
enol content, 0100
enol form, 1458
enol form, and dehydration to nitriles, 1549
exchange with carboxylic acids, 1423
formation with microwaves, 0730
amides, from acyl halides and ammonia or amines, 1427
from aldehydes, 0570, 0974
from alkenes and nitriles, 1459
from alkyl halides, 0568
from amide bases, 0568
from amides, 0880, 0974, 1425
from ammonium salts with amides, 1437
from anhydrides and ammonia or amines, 1429
from aryl halides, 0568
from carboxylic acids, by dehydrating agents, 1431
from DMF, 0730
from esters and ammonia or amines, 1434
from esters, electrochemistry, 1435
from Grignard reagents and isocyanates, 1337, 1338
from hydrocarbons, 0975
from imino esters, 1697
from isocyanates, 0729
from ketones, 0844, 1867
from nitrenes, 0789
from nitriles, 0975, 1458
from organoboranes, 0824
from oxazolidinone, with alcohols, 1422
from pyrolysis of ammonium carboxylates, 1430
from sulfonate esters, 0568
amides, Gatterman amide synthesis, 0728
hydrolysis, 1407–1410
hydrolysis, nucleophilic catalysis, 1408
keto-enol tautomerism, 0100
lithiation, 0810
Mitsunobu reaction, 0570
N-halo, rearrangement, 0740
nucleophilic strength, 0568
rearrangement during hydrolysis, 1408
reduction to aldehydes, reagents, 1810
reduction to amines, reagents, 1841
reduction with silanes, 1841
spirocyclic, 0695
torsional barrier, 0202
twisted, 0224
amides, with alcohols, 0570, 1421
with aldehydes, 0570
with alkenes, 1051
with alkynylboranes, 1448
with diazo compounds, 0570
with Grignard reagents, 1447
with halogens, 1608
with hydroxide, 0397
with hypohalites, 1607
with phosphorus pentachloride, 1698
with sulfonyl azides, 0788
with trimethyloxonium salts, 1422
amidines, by amination of ketenimines, 1050
by reduction of nitro compounds, reagents, 1815, 1816, 1817
from addition of ammonia or amines to nitriles, 1296
from imidates, 1436
amidomethylation, aromatic compounds, 0731
amidyl radicals, 1129
aminals, formation, 1283
amination, and sulfamate esters, 0789
electrochemical, 0975
of alkenes, 0788, 0789, 1046, 1047, 1050
of alkynes, metal catalyzed, 1048

of allenes, metal catalyzed, 1049
of aromatic compounds, 0693, 0694
of Grignard reagents, 0880
of heterocycles, 0915, 0916
of heterocycles, vicarious substitution, 0916
of hydrocarbons, 1757
of ketenimines, 1050
of organolithium reagents, 0880
of organometallics, 0821
amine oxides, and Cope elimination, 1524
and Meisenheimer rearrangement to oximes, 1623
and resonance, 0053
and the Boekelheide reaction, 1624
and ylids, 0053
by oxidation of amines, reagents, 1779
pyrolysis to alkenes, 1524
reduction to amines, reagents, 1846
amine-Claisen rearrangement, 1672
amines, α-alkylation, 0640, 0641
amines, α-oxidation to amides, 1759
amines, acidity, 0383
amines, acylation, 1429
and aminoboranes, 1433
and the Merrifield synthesis, 1433
and the Schotten-Baumann procedure, 1427
in ionic liquids, 1429
of amines with esters, catalysts for, 1435
polymer-bound, 1429
with esters, 1434, 1435
with microwaves, 1429
amines, addition, of organometallics to imines, 1331, 1332
to alkenes, 1134, 1182
to isocyanates, 1295, 1296
to isothiocyanates, 1296
to ketenes, 1050
amines, addition to nitriles, 1296
amines, alkyl halides and hexamethylenetetramine, 0558
amines, alkylation, 0555, 0558, 0562
Delépine reaction, 0558
amines, allylic, carbanions, alkylation, 0641
formation of conjugated amides, 0851
amines, amination of alkenes, 1045, 1047
amines, and carbamate formation, 0542
and carbonylation, 1139
and cleavage of methyl ether, 0561
and cyanamide, 0559
and differential hydration, 0391
and formaldehyde, 0730
and Gabriel synthesis, 0556
and guanidine, 0570
and hydrazine, 0569
and Katritzky pyrylium-pyridinium method, 0554
and leaving groups, 0498
and lithium, reductive cleavage of carboxylic esters, 1834
and Mentshutkin reaction, 0555
and metal catalyzed amination of alkynes, 1048
and nitrous acid, 0499
and organolithium reagents, 0799
and phase transfer, 0559
and proton transfer, 0368
and pyramidal inversion, 0142, 0144
and racemization, 0144
and resonance, 0383
and the Bruylants reaction, 0614
and the Hinsberg test, 1474
and the Mannich reaction, 1292–1295
and the Mitsunobu reaction, 0559
and the Staudinger reaction, 1822
and the von Braun reaction, 0586
and transamidation, 1425
amines, aromatic or aryl, see aniline
amines, arylation with arylboronic acids, 0879
and microwaves, 0877
and the Gabriel synthesis, 0879
bicyclic, by amination of alkenes, 1048
bridgehead, and chirality, 0144
amines, by base induced rearrangement of ammonium salts, 1621
by catalytic hydrogenation of nitriles, 1814
by Hofmann rearrangement, 1607
by hydrogenation of enamines, 1049
by hydrolysis of cyanamides, 1269
by hydrolysis of isocyanates, 1607
by metal reduction of hydroxylamines, 1819
by metal reduction of nitro compounds, mechanism, 1818
by oxidation of hydrocarbons or methylene, 1757
by reduction of amides, reagents, 1810, 1841
by reduction of amine oxides, reagents, 1846
by reduction of azides, 0561, 1822
by reduction of azo or azoxy compounds, 1823, 1853
by reduction of C=N compounds, 1811, 1812
by reduction of diazonium salts, 1823
by reduction of enamines, 1813
by reduction of hydrazo compounds, 1853
by reduction of hydrazones, 1811, 1820
by reduction of imides, 1842
by reduction of imines, 1811–1813
by reduction of isocyanates, 1823
by reduction of isothiocyanates, 1823
by reduction of nitriles, reagents, 1813, 1814
by reduction of nitrilium ions, 1814
by reduction of nitro compounds, with metals in acid, 1816
by reduction of nitroso compounds, 1823
by reduction of oximes, reagents, 1812, 1819, 1820
by reduction of quaternary ammonium salts, 1844

amines, (*Continued*)
by reduction of Schiff bases, 1811
by reduction of semicarbazones, 1820
by reduction of sulfonamides, 1844
by reduction to hydrocarbons, reagents, 1843, 1844
by reduction, of iminium salts, 1812
by reductive alkylation, 1288–1291
by reductive amination with aldehydes or ketones, 1288–1291
by silane reduction of amides, 1841
by Stevens rearrangement, 1621
amines, carbene insertion, 0804
carbonylation, 0654, 0655, 0850, 0851
catalytic of enolate anion formation, 0779
chiral, and Mannich reactions, 1295
chiral, from formamidines, 0641
chloro, from amines, 0849
conjugate addition, enantioselectivity, 1132
conjugate addition, to thio-lactams, 1130
cyanation of, 0802
amines, cyclic, α-oxidation to lactams, 1759
aminyl-radical cyclization, 0559
by conjugate addition of amines, 1130
by reduction of lactams, 1842
by S_N2' reaction, 0557
cleavage with cyanogen bromide, 0587
from alkene-amines, 0557
from diols, 0560
from haloamines, 0557, 1695
ring expansion, and carbonylation, 0851
von Braun reaction, 0587'
amines, cycloalkyl, with nitrous acid, 1588
cyclobutyl, from [2 + 2]-cycloaddition, 1223
dealkylation, reagents, 1852
deamination, indirect methods, 1844
deamination, reagents, 1843, 1844
dehydrogenation to nitriles, reagents for, 1729, 1730
demethylation, 0550
diazotization, and rearrangements, 1566
diazotization, with alkyl nitrites, 0921
dicarbonyl, as nucleophiles, 0514
ditosyl, with halide ions, 0586
energy barrier to pyramidal inversion, 0142, 0144
exhaustive alkylation, 0556
formation of alcohols, 0547
formation of onium salts, 0376
formation of Schiff bases, 1282
amines, from addition of amines to alkenes, 1045
from addition of ammonia to alkenes, 1045
from alcohols, 0559
from alkenes, 0567
from alkyl halides, 0559
from amides and Grignard rearrangements, 1447
from amino ethers, 0617
from azides, 0822
from aziridines, 0621
from cyanohydrins, 0561
from diazo compounds, 0562
from enamine alkylation, 0641
from ethers, 0559
from Grignard reagents, 0614, 0617
from hydrolysis of isocyanates, 1610
from organometallics, 0621, 0821
from phosphonium salts, 0560
from trichloroamine, 0567
amines, Gabriel synthesis, 0569
halo, from amines, 0849
Hofmann-Löffler reaction, 1695
hydrolysis of isocyanates, 1611
Ing-Manske procedure, 0569
intramolecular arylation, 0878, 0879
amines, metal catalyzed, addition to nitriles, 1297
amination of allenes, 1049
animation of alkenes, 1046, 1047
arylation, 0877–0880
carbonylation, 0850
conjugate addition, 1130
coupling to diamines, 1857
reaction with aryl halides, 0693
amines, metal mediated, arylation, 0879
amines, metal reduction of nitro compounds, 1819
amines, migration, 1603
amines, N-arylation, 0876
amines, N-Boc, metal catalyzed lithiation, 0640
amines, naphthyl, from naphthols, 0882
amines, nitration, 0847, 0848
amines, nitrosation, 0846, 0847
amines, organometallic compounds with imines, 1330–1334
amines, oxidation, to amine oxides, reagents, 1779
to hydroxyamines, reagents for, 1777
to imines, 1767
to ketones or aldehydes, 1767
to nitriles, 1729, 1730
to nitro compounds, reagents, 1778
to nitrones, 1732
with manganese dioxide, 1731
with Oxone, 1768
with TPAP, 1768
reagents for, 1767
amines, photochemistry, 0332
Pictet-Spengler reaction, 0716
reactivity differences with halides, 0556
reagents for acylation, 1432
replacement by an alkyl group, 0915, 0923
silyl, with aryl halides, 0878
silylalkyl, 0559
substitution of aryl halides, base catalysis, 0856
substitution of aryl halides, 0855
transamination, 0561
amines, with acyl halides, 1427
with acyl halides to give ketenes, 1532
with aldehydes or ketones, 0716, 0974, 1281

with alkyl halides, 0555
with alkynes, metal catalyzed, 1048
with anhydrides, 1429
with aromatic compounds, 0730
with aryl halides, and the Goldberg reaction, 0876
with aryl halides, replacement of alkyl groups, 0875
with aryl triflates, 0876
with aziridines, 0566
with benzyl chloroformate, 1428
with boron trifluoride, 1438
with calcium, reduction of aromatic compounds, 1069
with carbon dioxide, 0851
with carbon disulfide, 1297
with carbonates, 1435
with carboxylic esters, 1434, 1436
with chloroform, 0567
with chloroformates, 1428
with cyanogen bromide, 0586
with cyclic anhydrides, 1429
with cyclopropane, 0567
with diazo compounds, 0562, 1242
with diketones, 1283
with dimethyl(methylthio) sulfonium salts, 1185
with epoxides, 0562, 0563
with hypohalites, 0849
with KOH, 0547
with lactams, high pressure, 1438
with β-lactones, and angle strain, 1437
with lithium, reduction of aromatic compounds, 1069
with Mannich bases, 0562
with nitro-ketones, 0844
with nitronium salts, 0848
with nitrous acid, 0247, 0846, 0847
with onium salts, 0852
with organocuprates, 0822
with oxetanes, 0565
with phosgene, 1427
with pyrylium ions, 1283
with sulfonyl halides, 1471, 1474, 1475, 1532
with tert-butoxy anhydride, 1428
with thiiranes, 0565
with thiophosgene, 1428
with tricarbonates, 0851
amino acid surrogates, 0632
amino acids, and semipinacol rearrangement, 1586, 1587
by the Sorenson method, 0624
conversion to lactams, 1431
diazotization, 0585
from acyl halides, 0789
from azido acids, 0788
with nitrous acid, rearrangement, 1586, 1587
amino acids-boric acid, and resolution, 0173
amino leaving groups, in Mannich bases, 0498
amino-alcohols, also see hydroxyamines
and cyclodextrin, 0563
and microwaves, 0563
coupling ketones with O-methyl oximes, 1858
enantioselective formation, 0563
formation of aziridines, 0560
from amines, 0565
from azido-alcohols, 0564
from enamines, 1079
from epoxides, 0562, 0564
from isocyanides, 0568
from oxetanes, 0565
with lithium perchlorate in ethers, 0563
with nitrous acid, 1589
amino-carbonylation, of alkenes, 1139
amino-Cope rearrangement, 1660
amino-esters, diazoesters with amines, 1242
amino-ethers, alkoxy-amination of alkenes, 1182
from alcohols, 0537
from aziridines, 0537
amino-ketones, by oxidation of enamines, 1775
by rearrangement of O-tosyl imines, 1605
by the Mannich reaction, 1292–12195
by the Neber rearrangement, 1605
elimination, 1293
from the Mannich reaction, 1294
amino-nitriles, and cyanohydrins, 1391
and the Strecker synthesis, 1391
the Bruylants reaction, 0614
with Grignard reagents, 0614
amino-organocuprates, 1112
amino-thiols, from epoxides, 0565
aminoalkylation, of aromatic compounds, 0730
aminoboranes, with carboxylic acids, 1433
aminocarbenes, 0286
aminohydroxylation, of alkenes, 1180
aminoketones, from Eschenmoser's salt, 1294
aminomercuration, of alkenes, 1050, 1181
aminomethyl aromatic compounds, 0929
aminonitrenes, addition to alkenes, 1184
aminophenols, from oximes, 0930
from the Bamberger rearrangement, 0930
aminopyridine, halogenation, 0701
aminosulfenylation, of alkenes, 1185
aminyl-radicals, 1129
aminyl-radical cyclization, 0559
ammonia, addition to cyanamide, 1296
addition to nitriles, 1296
amination of alkenes, 1045
and enolate alkylation, 0627
and formation of enolate anions, 0631
and pyramidal inversion, 0142, 0144
and sodium, reduction of alkynes, 1064
and the Bucherer reaction, 0882
impurities, and the Birch reduction, 1067
supercritical, 0415
supercritical, enzymatic carboxylation, 0729
ammonia, with acyl halides, 1427
with alkyl halides, 0555
with anhydrides, 1429
with carboxylic acids, 1430
with carboxylic esters, 1434
with conjugated ketones, 0631
with epoxides, 0562
with metals, and decyanation, 0845

ammonia, with acyl halides, (*Continued*)
with metals, and formation of enolate anions, 0907
with metals, cleavage of cyclopropanes, 1075
with metals, reduction of alkynes, 1064
with sulfonyl halides, 1474, 1475
ammonium formate, see formate
ammonium salts, alkyl rearrangement, 0741
and amination of alkenes, 1048
and formation of aldehydes, 1034
and Hofmann degradation, 1522
and Hofmann's rule, 1498
and Hofmann-Martius reaction, 0741
and phase transfer catalysis, 0509
and Stevens rearrangement, 0929, 1621
and syn-elimination, 1483
base induced rearrangement, 1621
benzylic, and Sommelet-Hauser rearrangement, 0929
chiral, with HCN, 1392
cleavage, 0542
dealkylation, 0562
demethylation, 0550
from amines and alkyl halides, 0556, 0846
heating, formation of alkyl halides, 0586
pyrolysis, to alkenes, 1521
quaternary, and out-in isomers, 0189
quaternary, and the Emde reduction, 1845
quaternary, thermal stability, 0510
tetraalkyl, reduction to amines, 1844
with amide bases, 1524
with amides, 1437
with organolithium reagents, 0810, 1523
ammonium-ketones, and Robinson annulation, 1350
amphiprotic properties, 0772
anchimeric assistance, and cyclopropyl, 0455
and S_N2 reactions, 0446
in migrating group in rearrangements, 1565
angle strain, β-lactones with amines, 1437
angles, bond, see bond angles
angles, dihedral, see dihedral angle
angles, torsion, see torsion angle
angular polyacenes, 0061
anhydrides, alcoholysis, 1412
alcoholysis, enantioselectivity, 1413
and dehydration of alcohols, 1515
and nitration of anilines, 0688
and the Perkin reaction, 1363
tert-butoxy, with amines, 1428
by dehydration of carboxylic acids, 1423
cyclic, alcoholysis, 1413
cyclic, and Friedel-Crafts acylation, 0722
cyclic, from dicarboxylic acids, 1423
cyclic, with amines, 1429
formation of acyl azides, 0573
Friedel-Crafts acylation, 0719
from acyl halides and carboxylate salts, 1422
from acyl peroxides, 0972
from addition of carboxylic acids to ketene, 1042
from aldehydes, 0972
from carboxylic acids and enol esters, 1424
hydrolysis, 1399
mixed organic-inorganic, from anhydrides, 1424
mixed, Friedel-Crafts acylation, 0721
mixed, from acyl halides and carboxylate salts, 1422
mixed, with amines, 1430
organic-inorganic, hydrolysis, 1413
reaction with aldehydes, 1273
reaction with sulfoxides, 1866
reduction to aldehydes, 1810
reduction to lactones, reagents, 1840
sulfonic, and Friedel-Crafts acylation, 0720
sulfonic, Vilsmeier-Haack reaction, 0725
triflic, with amides and alcohols, 1421
trifluoroacetic, and DMSO, for oxidation of alcohols, 1721
with alcohols, 1412, 1413
with aldehydes, 1363
with ammonia or amines, 1429
with carboxylic acids, 0840
with ethers, 0542
with hydrogen peroxide, 0545
with inorganic acids, 1424
with organometallics, enantioselectivity, 1446
with phosphorus ylids, 1379
aniline, and resonance, 0048
anilines, acyl, halogenation, 0740
acyl, Orton rearrangement, 0740
ammonium salts, and rearrangement, 0741
ammonium salts, Hofmann-Martius reaction, 0741
ammonium salts, photolysis, 0742
and formation of aryl halides, 0985
and hydroxylation reactions, 0734
and Reilly-Hickenbottom rearrangement, 0741
and the Bucherer reaction, 0882
and the Mannich reaction, 1293
and the Mills reaction, 0922
azo compounds, 0740
Boyland-Sims oxidation, 0734
conjugate addition, 1130
deamination, by reduction of diazonium salts, 1847
diazotization, 0917, 0918
Fischer-Hepp rearrangement, 0739
formation of aryl azides, 0572
Friedel-Crafts alkylation, 0709
from alcohols, 0560
from amines, 0699, 0875, 0876
from aromatic compounds, 0693
from aryl halides, 0875

from aryl phosphates, 0883
from Grignard reagents, 0880
from hydrazoic acid, 0693
from N-nitroamines, 0738
from organolithium reagents, 0880
from oximes, 0930
halogenation, and Lewis acids, 0699
Hofmann-Martius reaction, 0741
N-nitro, rearrangement, 0738, 0739
N-nitroso, rearrangement, 0739
nitration of, 0688
oxidation to azo compounds, 1731
oxidation to nitroso compounds, 1776, 1777
oxidation with Caro's acid, mechanism, 1777
rearrangement, with organolithium reagents, 1624
replacement of amino with alkyl, 0915, 0923
ring closure with aldehydes or ketones, 1282
with alkyl nitrites, 0985
with aryl nitroso compounds, 0922
with Caro's acid, 1777
with epoxides, 0563
with hyponitrites and allyl halides, 0923
with thionitrites, 0985
anionic cleavage, 0835
1,3-anionic cycloadditions, 1193
anions, addition to alkenes, 1007
addition to conjugated carbonyls, 1008
N-nitro, rearrangement, isotopic labeling, 0738
anisotropy, and alkenes, 0056
and aromatic compounds, 0056
and cyclophanes, 0056
annellation, 0061
and cyclopentadiene, 0063
and strain, 0052
Annual Reports on Organic Synthesis, 1892
[6 + 2]-annulation, and Brook rearrangement, 1701
annulation, Robinson, see Robinson
annulenes, and alkyne coupling, 0978
and antiaromaticity, 0075, 0088, 0089
and aromaticity, 0071, 0078, 0079, 0082, 0085–0087
and Hartree-Fock calculations, 0080
and HPLC, 0092
and Hückel's rule, 0079
and Möbius aromaticity, 0091, 0092
and NMR, 0079, 0080, 0083, 0084, 0087, 0088, 0089, 0090
and planarity, 0080
and the Eglinton reaction, 0978
and X-ray crystallography, 0084, 0085, 0089
aromatic substitution, 0081, 0084
aromaticity, 0083, 0084
atropic, 0090
bond alternation, 0089
bond angles, 0079
bond distance, 0085, 0089
bridged, 0089
definition of, 0071
diatropic, 0081
heat of combustion, 0091
planarity of, 0091
twist conformations, 0080
anomeric effect, 0210, 0211
antarafacial migration, in sigmatropic rearrangement, 1648, 1649
antarafacial overlap, 1213
anthracene compounds, as host, 0128
anthracene derivatives, Bradsher reaction, 0715
anthracene, alkylation of, with organometallics, 0914
and resonance, 0049
catalytic hydrogenation, 1067
resonance energy, 0060
anti addition, 1001
and alkenes, 1006
anti nomenclature, 0166
anti-aromaticity, and azirines, 1184
anti-Bredt alkenes, by the Wittig reaction, 1373
anti-Markovnikov addition, alkene amination, 1050
and aminomercuration, 1050
HBr, peroxides, and alkenes, 1030
hydration of alkynes, 1035
Lewis acid catalyzed, silanes to alkenes or alkynes, 1087
of boranes to alkenes, 1078
of cyanide, 1148
phosphines and alkynes, metal catalysts, 1050
radicals to alkenes, 1124
silanes to alkenes, 1087
thiols to alkenes, 1043
water to alkenes, 1033
antiaromatic compounds, and bond distance, 0057
antiaromatic systems, and ring current, 0057
antiaromatic, and cyclobutadienes, 0073
antiaromatic, oxirenes, 1174
antiaromaticity, 0073
and annulenes, 0075, 0088, 0089
and cyclazines, 0089
and cycloheptatrienyl anions, 0079
and indacene, 0089
and NMR, 0075, 0090
and paratropic compounds, 0090
and stability, 0074
dipleiadiene, 0090
for cyclobutadiene, 0038
antibodies, catalytic, and epoxidation, 1172
antibody-catalyzed oxy-Cope rearrangement, 1660
antibody-catalyzed [3 + 2]cycloadditions, 1191
antibonding orbitals, 0005, 0006
and S_NAr reactions, 0866
antimony pentafluoride and FSO_3H, 0358
antimony pentafluoride, and cation stability, 0236
antimony, and optical activity, 0144
antioxidants, and autoxidation, 0967
aprotic solvents, 0502
aqueous media, and the Heck reaction, 0893
Arbuzov reaction, 1375
arenes, see aromatic compounds
arenium ion mechanism, 0657, 0658, 0913
arenium ion mechanism, evidence for, 0659–0662
arenium ions, 0240, 0658
+I and −I effects, 0667

arenium ions, (*Continued*)
ab initio study, 0662
activating groups, 0665
and carbocations, 0658
and deuterium ions, 0661
and encounter complex, 0664
and Lewis acids, 0663
and nitration, 0691
and resonance, 0658
and σ-complexes, 0658
and the E1 mechanism, 0657
and the Hammond postulate, 0666
deactivating groups, 0665
destabilization, 0667, 0669
field effects, 0667
ipso position, 0672
isolation, 0661
isotope effects, 0659
kinetics versus thermodynamic control, 0666
partition factor and partitioning effects, 0659, 0660
polyfluorinated, 0661
stability, 0663
stabilization, 0667, 0668
stable solutions, 0662
substituted, and resonance, 0666
argon, as a guest, 0127
Arndt-Eistert synthesis, 1457, 1599
Arndt-Eistert synthesis, and Wolff rearrangement, 1599
aromatic carboxylic acids, see carboxylic acids
aromatic character, 0055
aromatic compounds, activation groups, 0665
aromatic compounds, addition of carbenes, 1239
addition of Grignard reagents, 1119
alkyl substituents, also see benzylic
amidation, 0694
amidomethylation, 0731
amination, 0693, 0694
aminoalkylation, 0730
aminomethyl, 0929
aromatic compounds, and anisotropy, 0056
and annellation, 0061
and aromaticity, 0054, 0057
and Benkeser reduction, 1069
and benzylic hydrogens, with radicals, 0947
and Birch reduction, 1067
and cyclodehydration, 0715
and deactivating groups, 0665
and DEAD, 0695
and electron donor-acceptor complexes, 0115
and field effects, 0021
and Gatterman-Koch reaction, 0725
and geared molecules, 0231
and hydrogen exchange, 0684
and MO calculations, 0033
and π-π-interactions, 0114
and resonance, 0033, 0049
and restricted rotation, 0232
and retro-Diels -Alder reactions, 1545
and strain, 0230, 0231
and the Baker-Nathan effect, 0096, 0097
and the Dakin reaction, 1746
and the Duff reaction, 0727
and the Gomberg-Bachmann reaction, 0924
and the Haworth reaction, 0722
and the Schiemann reaction, 0921
and the Wurtz-Fittig reaction, 0589
and thermal extrusion of carbon monoxide, 1545
aromatic compounds, aromatic character, 0055
arylation, 0924–0926, 0981
arylation, mechanism, 0925, 0926
bond alternation, 0051
bromination, 0664
by aromatization of six-membered rings, 1709
by Bergmann cyclization, 1641
by decarboxylation, 0745
by dehydroxylation of phenols, 1830
by electrocyclic ring closure, 1645
by reduction of diazonium salts, reagents, 1847
by reduction of phenols, 1830
by reversal of Friedel-Crafts alkylation, 0742
canonical forms, 0060
catalytic hydrogenation, 1066
chlorination, 0664, 0670
cyclotrimerization of alkynes, 1243
deactivated, amination, 0693
decarbonylation, 0745
dihydroxylation, 1168
directed ortho metalation, 0912
electrolysis, formation of phenols, 0734
electronic effects, and Birch reduction, 1067
fluorination, 0704, 0921
formation of aldehydes, 0724
formation of anilines, 0693
formation of biaryls, 0718
formation of nitriles, 0733
formation of thioethers, 0731
formylation, 0724
Friedel Crafts acylation, 0697, 0710
aromatic compounds, from alcohols, 0707
from alkenes, 0706
from alkyl halides, 0706
from aromatic compounds, 0980
from aryl ethers, 0748
from aryl halides, 0749
from aryl ketones, 0745
from aryl organometallics, 0751
from arylsulfonic acid, 0748
from en-diynes, 1641
aromatic compounds, fused ring, 0052, 0060, 0253
Gatterman amide synthesis, 0728
halogenation, 0698–0702
halogenation, with NBS, 0699
hydroxyalkylation, 0713
hydroxylation, 0733, 0964, 0965, 0734
iodination, 0703
lithiation, 0911–0915
mercuration, 0913
metal catalyzed addition to alkenes, 1100
metal catalyzed hydrogen exchange, 0685
metalation, 0734, 0911–0915
methyl, see methyl aromatic
Mills-Nixon effect, 0052
nitration, 0664, 0665, 0685, 0686, 0688
nitration, and arylboronic acids, 0690

nitro, from N-nitroanilines, 0738
nitroso, 0739
organometallics with aryl halides, 0604, 0605, 0606, 0607
ortho-meta-para substitution, 0665
oxidation of side chains, 1745
oxidation of side chains, alkyl group reactivity, 1746
oxidative cleavage, reagents, 1744
phenylenes, 0051
photochemical coupling with aryl halides, 0981
radical alkylation, 0980, 0982
reactivity, 0665, 0679
reactivity with radicals, 0950
reduction with metals and ammonia, 1067
replacement of nitro with alkyl, 0927
Schiemann reaction, 0705
six-membered rings, 0058
strained, 0052
strained, and rotation barrier, 0231
sulfonation, 0695, 0696
thioalkylation, 0731
tormented or twisted, 0051
trichloroacetonitrile, 0733
UV and IR, and strain, 0230, 0231
aromatic compounds, with acyl halides, 0719
with acyl peroxides, 0980
with aldehydes, 0713
with alkenes, 0706
with alkyl halides, 0705
with amines, 0730
with aryl organometallics, 0718
with aryldiazonium salts, 0924
with calcium and amines, 1069
with DMSO, 0731
with Fenton's reagent, 0964
with formaldehyde, 0717
with hydrazoic acid, 0693
with ketones, 0713
with mercury fulminate, 0733
with metals and amines, 1069
with nitrenes, 1185
with nitriles, 0732
with nitronium salts, 0689
with organolithium reagents, 0911–0915
with peroxyacids, 0733
with phenonium ions, 0456
with phosgene, 0728
with polyphosphoric acid, 0698
with *Pseudomonas putida*, 1168
with radicals, mechanism, 0940
with sulfonyl halides, 0697
with sulfoxides, 0731
with sulfur trioxide, 0696
with sulfuric acid, 0695
aromatic diazonium salts, see diazonium salts
aromatic groups, β, and neighboring groups, 0459
aromatic hydrocarbons, alternant, electrocyclic rearrangement, 1646
aromatic hydrocarbons, oxidation to quinones, 1764
aromatic index, see aromaticity index
aromatic rings, as neighboring groups, 0455–0457
aromatic sextet, 0055, 0058
aromatic side chains, oxidation, reagents, 1745
aromaticity, 0054
aromaticity index, 0062–0064
aromaticity index, and fulvalenes, 0069
aromaticity, and absolute hardness, 0063
and annellation, 0061
and Bader's electron delocalization index, 0064
and Baird's theory, 0069
and bond alternation, 0065
and bond distances, 0072
and bond order, 0063
and chemical shift, 0055
and cyclobutadiene or cyclodecapentaene, 0071
and cycloheptatrienyl anion, 0078
and cyclooctatetraene, 0071, 0078
and cyclopentadienyl cation, 0076
and cyclopropenyl anion, 0076
and diamagnetic ring current, 0055, 0072
and diatropic, 0055
and fullerenes, 0094
and Hückel's rule, 0071, 0078
and Hund's rule, 0072
and hybridization, 0050
and isotope labeling, 0065
and methanoannulenes, 0081, 0082
and molecular refraction, 0063
and NMR, 0055, 0083, 0084
and partial bond fixation, 0059
and planarity, 0072, 0086
and resonance energy, 0062
and ring current, 0055
and sybdones, 0092
and symmetry, 0072
and the Hess-Schaad model, 0057
and the conjugated-circuit model, 0057
and the hardness model, 0057
and the Herndon model, 0057
and the pyrylium ion, 0058
and the SCF method, 0058
and the tropylium ion, 0067
aromaticity, aromatic character, 0055
aromatic sextet, 0058
bishomoaromatic, 0093
homoaromatic compounds, 0093, 0094
Hückel, 0091
mesoionic compounds, 0092
Möbius, 0091, 0092
nonaromatic systems, 0071
aromaticity, of annulenes, 0071, 0078, 0079, 0082–0087
of aromatic compounds, 0054, 0057
of arynes, 0861
of azaannulenes, 0081
of azulene, 0067
of benzene, 0038
of benzenoid hydrocarbons, 0057
of benzoannulenes, 0084
of calicene, 0069
of cyclopentadienide ion, 0062
of fulvalenes, 0068
of fused ring aromatic compounds, 0064
of heptalene, 0067
of heteroaromatic compounds, 0057, 0058, 0062
of naphthalene, 0061
of pentalene, 0067

aromaticity, of
annulenes, (*Continued*)
of phenacenes, 0087
of phenalene, 0060
of phenanthrene, 0059
of polyacenes, 0061
of pyrenes, 0083
of the cyclopropenyl cation, 0072
of the squaric acid dianion, 0092
of triphenylene, 0061
of tropone, 0065
aromaticity, spherical homoaromaticity, 0094
aromaticity, superaromatic, 0087
aromaticity, trihomoaromatic, 0093
aromatization, by Bergmann cyclization, 1641
by DDQ, 1710
metal catalysts for, 1709
of six-membered ring compounds, 1709
reagents for, 1710, 1711
to form heterocycles, 1711
with chloranil, 1710
with quinones, 1710
with selenium, 1710
with sulfur, 1710
arsenic, and optical activity, 0144
arsine ylids, 1370
arsines, and ylid formation, 1370
aryl carbenes, 0286
aryl carbocations, see carbocations
aryl groups, migration in carbocations, 1577
aryl radicals, see radicals
arylation reactions, and sonochemistry, 0352
arylation, and the Heck reaction, 0891–0897
and the malonic ester synthesis, 0714
Meerwein, 0923
of active methylene compounds, 0906–0908
of alkenes, 0890, 0923
of amides, 0880
of amines, 0876–0878
of aromatic compounds, 0924, 0925
of enolate anions, 0906–0908
of haloalkynes, metal catalyzed or mediated, 0647
of lactams, 0880
of oximes, metal catalyzed, 0986
of silanes, metal catalyzed, 0911
of sulfonamides, 0569
radical, 0718, 0982
arylazides, see azides
aryllithium, see organolithium, aryl
arylthallium compounds, reactions, 0913
arynes, and aromaticity, 0861, 0862
and nonaromatic rings, 0862
hetarynes, 0862
in the Diels-Alder reaction, 0861
substrate structure and regioselectivity in formation, 0867
ascorbic acid, and Udenfriend's reagent, 0965
aspartic acid, specific rotation, 0139
asymmetric atom, see chiral or stereogenic
asymmetric catalysts, hydrogenation, 1073
asymmetric dihydroxylation, 1165, 1166
asymmetric epoxidation, see epoxidation
asymmetric hydrogen bonds, 0109
asymmetric induction, see enantioselectivity
asymmetric reduction, of prochiral ketones, 1799–1803
asymmetric synthesis, see synthesis
asymmetric [3, 3]-sigmatropic rearrangement, 1663
ate complexes, 0376
onium salts, 0376
with organolithium reagents, and reduction of alkyl halides, 1827
atom transfer, see hydrogen transfer
atom transfer, of radicals, 1011
atomic orbitals, overlap of, 0004
atomization, heat of, see heat of atomization
atoms stereogenic, see stereogenic, chiral
atoms, chiral, see chiral, stereogenic
atropic, annulenes, 0090
atropisomers, and a chiral axis, 0158
and BINAP, 0147
and Friedel-Crafts coupling, 0714
and restricted rotation, 0148
of alkaloids, 0148
of allenes, 0148, 0149
of benzylic alcohols, 0147
of biaryls, 0146, 0902
of calixarenes, 0149
of conformations, 0203
of pyrroles, 0147
of sulfoxides, 0147
of thioamides, 0184
resolution of, 0149
attacking reagent, definition, 0296
Austin Model, 0035
autoxidation, allylic and benzylic hydrogens, 0967–0969
auxiliaries, Evans, and enolate alkylation, 0629
auxochrome, 0334
axial, in chair conformations, 0204
axis, chiral, and R/S nomenclature, 0158
of symmetry, and chirality, 0140
aza-Brook rearrangement, 1701
aza-Claisen rearrangement, metal catalysts, 1671
aza-Cope rearrangement, 1660, 1672
aza-Diels-Alder reactions, 1217
aza-Wittig, 1380
aza-Wittig rearrangement, 1625
azaadamantanone, and the Wittig reaction, 0224
azaannulenes, 0080, 0081
azabullvalenes, 1665
azacrown ethers, see ethers, azacrown
azadienes, chiral, 1218
Diels-Alder reaction, 1217
azadodecahedranes, 0222
azapagodanes, synthesis, 0222
azeotropes, and formation of borate esters, 0817
azeotropic distillation, and acetal or ketal formation, 1270
and enamine formation, 1283
and formation of imines, 1282
azetidines, from amines and ditosylates, 0557
azide ion, and inversion, 0443
and rate of ionization, 0442
with epoxides, 0564
with alkynes, 1159

azides, metal catalyzed reaction with epoxides, 0564
azides, sodium with iodosobenzene, 1182
azides, sodium, with aldehydes, 1440
azide-alcohols, cyclization to aziridines, 0572
azides, 1,3-dipolar addition, 1183
azides, acid catalyzed ring expansion, 1610
azides, acyl, 1561
  and the Curtius rearrangement, 1609
  from acid derivatives, 0571, 0573
  from aldehydes, 1440
  from nitrous acid and hydrazines, 1609
  in the Curtius reaction, 0572
  thermolysis to isocyanates, 1608
azides, addition to alkenes, 1182, 1183
  and formation of nitrenes, 0294
  and phase transfer, 0572
  and the Staudinger reaction, 1822
  and triazenes, 0822
  and ultrasound, 0572
  aryl, from aniline derivatives, 0572
  aryl, ring expansion, 1610
  aryl, with haloalkylboranes, 0822
  by addition of hydrazoic acid to Michael-type alkenes, 1052
  by Mitsunobu reaction, with alcohols, 1612
  carbonylation, 0851
  conjugate addition, 1131
  from alcohols, alkenes, and hydrazoic acid, 1612
  from alkyl halides and azide ion, 0571, 0572
  from benzylic alcohols, 0561
  from hydrazines, 0846
  halo, by addition of haloazide to alkenes, 1158
  halo, with alkenes or allenes, 1159
  metal catalyzed Schmidt reaction, 1612
  polymer supported, diazo transfer reagents, 1237
  pyrolysis to imines, 1609
  reduction, 0561, 0822, 1822
  reduction, and amidation of alkenes, 1052
  silyl, with epoxides, 0564
  sulfonyl, and diazo-transfer reactions, 0787
  sulfonyl, reduction to sulfonamides, 1822, 1823
  sulfonyl, with active methylene compounds, 0787
  sulfonyl, with amides, 0788
  tosyl, with active methylene compounds, 0787
  tosyl, with organolithium reagents, 0822
  with haloalkylboranes, 0822
  with organometallics, 0821, 0880
azidination, 0788
azido-amides, 0788
azido-amines, from silylazides, 0566
azido-ketones, from ketones, 0573
azidomercuration, of alkenes, 1053
azirenes, intermediates in the Neber rearrangement, 0312, 1606
aziridination, of alkenes, in ionic liquids, 1185
aziridines, addition to alkynes, 1192
  ambident substrates, 0518
  and leaving groups, 0497
  and the tetrahedral mechanism, 0475
  asymmetric, from alkenes, 1184
  by extrusion of nitrogen from triazolines, 1553
  by extrusion of sulfur dioxide from sultams, 1556
  by reduction of oximes, 1820
  by thermolysis of triazolines, 1183
  carbonylation, 1466
  chiral, from reduction of azirines, 1184
  conformational stability, 0142, 0144
  enantioselective preparation, 0572
  from alkenes, 1183, 1184
  from allene-amides, 1052
  from amino-alcohols, 0560
  from azide-alcohols, 0572
  from diazoacetates and imines, 1183
  from epoxides, 0565
  from haloamines, 0557
  from imines, 1337
  from imines and sulfur ylids, 1385
  from iodo azides, 1159
  from nitrenes and alkenes, 1184
  from photolysis of triazolines, 1183
  from sulfimides and Michael type alkenes, 1183
  halogenation of, 0584
  metal catalyzed ring opening, 0566
  opening by nucleophiles, 0621
  via nucleophilic substitution, 0475
  with alcohols, 0537
  with allylic alcohols, 0621
  with amines, 0566
  with nitrous acid, 1538
  with organometalllics, 0621
aziridinium salts, and migration of amino groups, 1604
azirines, from alkynes, 1184
  metal catalyzed [4 + 2]-cycloaddition, 1216
  stability, 1184
azo compounds, also see AIBN
azo compounds, and aryl triazenes, 0692
  and E/Z nomenclature, 0183
  and radicals, 0279
  and the Mills reaction, 0922
  aryl, from aryl triazenes, 0740
  by oxidation of anilines, 1731
  by oxidation of hydrazines, reagents, 1730
  by reduction of azoxy compounds, reagents, 1846
  by reduction of nitro compounds, reagents, 1863
  by Wallach rearrangement, 1698
  decomposition to radicals, 0935
  Diels-Alder reaction, 1216
  E/Z isomerization, 0692
  electrophilic aromatic substitution, 0691
  from anilines, 0922
  from aryl nitroso compounds, 0922
  from aryldiazonium salts, 0926

from azoxy compounds, 1698
oxidation to azoxy compounds, 1779
photoisomerization, 0346
reduction to amines, 1823, 1853
reductive alkylation, 1291
water soluble, 0935
with aromatic compounds, 0925
azo dyes, 0691
azo-Claisen rearrangement, 1672
azobenzenes, by reduction of nitro compounds, 1817
azobenzenes, metal catalyzed coupling, 0692
azobis compounds, radical initiators, 1124
azobisisobutyronitrile, see AIBN
azodicarboxylates, and chiral amides, 0789
azodicarboxylates, with alkenes, metal catalyzed, 1047
azoles, metal catalyzed coupling with aryl halides, 0887
azoxy compounds, and ESR, 0849
and radicals, 0849
and the Wallach rearrangement, 1698
by oxidation of amines, 1731
by oxidation of azo compounds, 1779
by reduction of nitro compounds, reagents, 1862
from alkyl diazotates, 0573, 0574
from alkyl halides, 0573, 0574
from nitroso compounds, 0848
from oximes, 0848
rearrangement to azo compounds, acid catalyzed, 1698
reduction to amines, 1853
reduction to azo compounds, reagents, 1846
azoxybenzenes, by reduction of nitro compounds, 1817
azulene dianion, 0068
azulene, and aromaticity, 0067, 0068
nonalternant hydrocarbon, 0069
azulenes, and carbocations, 0241
radical cations, 0282
azulenyl nitrones, and radicals, 0268

B strain, see strain
Bacilllus megaterium, and carboxylation, 0729
Bacillus megaterium, α-hydroxylation, 1756
BAcIm, ionic liquid, 1264
backside attack, and S_N2, 0426
bacterial monooxygenase, oxidation of thioethers, 1782
Bader's electron delocalization index, 0064
Baeyer-Villiger rearrangement, 1617–1619
migratory aptitude, 1619
Baird's theory, 0069
Bakelite polymers, 0714
baker's yeast, reduction of alkenes and alkynes, 1066
reduction of aldehydes or ketones, 1800
reduction of azides, 1822
reduction of conjugated nitro compounds, 1074
reduction of nitro compounds, 1817
reduction of oximes, 1819
Baker-Nathan effect, and differential solvation, 0097
and hyperconjugation, 0096, 0097
Baker-Nathan order, and aromatic substitution, 0670
and substitution reactions, 0486
$B_{AL}2$ mechanism, 0532
Baldwin's rules for ring closure, 0305–0307
for enolate anions, 0306, 0307
and radical cyclization to alkenes, 1011, 1021, 1125, 1126
Balz-Schiemann reaction, see Schiemann reaction
Bamberger rearrangement, 0930, 0931
Bamford-Stevens reaction, 1527
banana bonds, 0009
barbaralane, and Cope rearrangements, 1666
Barbier reaction, and compatible metals, 1302
and samarium, 1313
Barbier-Wieland procedure, oxidative cleavage, 1743
barbituric acid, 1439
barralene, 1692
barrelene, and chirality, 0152
barrier, energy, to rotation, 0185
barrier, intrinsic, 0309
barrier, rotation, biphenyls, 0146
in acetaldehyde, 0201
Barton reaction, 1696
Barton-McCombie reaction, 1833
base strength, 0357
and E2 reactions, 1500
and E2C reactions, 1495
and ester enolate anions, 1356
and field effects, 0380
and hydrogen bonding, 0364
and pK, 0364
and pK, table, 0366
and proton sponges, 0386
and solvent effects, 0365
and structure, 0380
and the Claisen condensation, 1454
and the Claisen reaction, 1356
elimination versus substitution, 1505
in elimination reactions, 1504
superbases, 0365
table, 0385
base-catalyzed, acylation of alcohols, 1411
amination of alkenes, 1048
amine substitution of aryl halides, 0856
coupling, aryl halides with active methylene compounds, 0906
hydrolysis of amides, 1409
Mannich reaction, 1294
reactions, and the Marcus equation, 0373
rearrangement, O-tosyl imines to amino ketones, 1605
base-induced, addition of amides to aldehydes, 1292
dehydrogenation, 1714
elimination, 1478–1486, 1530
elimination, of ethers, 1516
halogenation, of alkanes, 0957

bases, and active methylene compounds, 0622
and formation of phosphorus ylids, 1369, 1370
and hydrogen exchange, 0685, 0767
and keto-enol tautomerism, 0772
and pK, 0364, 0365
and rearrangement of alkenes or alkynes, 0767, 0768
and the Stetter reaction, 1136
as proton acceptors, 0356
base strength, 0364, 0365
base strength, table, 0385
catalysis of the halogen dance, 0749
chiral, and enolate alkylation, 0629
chiral, and the aldol reaction, 1347
cleavage of keto esters or ketones, 0841, 0843
conjugate, 0356
conjugate, and leaving groups, 1489
dialkylamides, 0389–0390
enolate anions, 0390
for coupling of aromatic compounds and aryldiazonium salts, 0924
for the haloform reaction, 0842
for the Henry reaction, 1357
hard, definition, 0377
hardness, 0377, 0378
in proton-transfer reactions, 0367
in the Perkin reaction, 1364
IUPAC terminology, 0356
LDA, 0389
Lewis, see Lewis bases
pK, table, 0366
proton sponges, 0365, 0386
reaction with phosphonium salts, 1369
required for generation of enolate anions, 0627
soft, definition, 0377
suitable for E2 reactions, 1504
suitable for the Sevens rearrangement, 1621
superbases, 0365
with DMSO, 0914
with silyl enol ethers, 0628
basicity, and ambident nucleophiles, 0516
and differential hydration, 0391
and electronegativity, 0384
and hydrogen bonding, 0108, 0364
and leaving groups, 0496
and nucleophilicity, 0491
and solvent effects, 0392–0394
and steric effects, 0385
and the medium, 0390
aromatic compounds, 0663
pyrrole versus pyridine, 0063
solution versus gas phase, 0391–0392
table, 0366
versus nucleophilicity, and elimination, 1505
basis sets, for Möbius-Hückel method, 1210
basketane, 1691
bathochromic shift, 0333
Bayer test, and dihydroxylation of alkenes, 1164
Baylis-Hillman reaction, 1323–1826
functional group compatibility, 1325
bbim, ionic liquid, 0894
9-BBN, with alkenes, 1077
Beckmann rearrangement, 1613–1616
abnormal, 1615
and oxidation of oximes, 1732
and the Ritter reaction, 1616
and the Vilsmeier-Haack reaction, 0725
migratory aptitude, 1615
migratory aptitudes of groups, 1568
Beilstein, 1880–1885
Beilstein CrossFire, 1883
Beilstein, *Handbuch der Organischen Chemie*, 1881
belts, molecular, 0132
Benkeser reduction, 1069
bent benzene rings, and strain, 0232
bent bonds, 0009
and cyclopropane, 0219
benzene oxide, from oxepin, 1666
benzene, addition of carbenes, 1239
benzene, addition of methylene, 1239
and carbocations, 0658
and delocalization, 0038
and electrophilic aromatic substitution, 0680
and HMO theory, 0037
and metal complexes, 0117
and NMR, 0056
and planarity, 0050, 0051
and resonance, 0033, 0034
and the aromatic sextet, 0055
and the diene-cyclobutene interconversion, 1641
aromaticity, 0038
bent, 0232
boat conformation, 0052
bond energy and heat of atomization, 0036
heat of hydrogenation, 0037
orientation in substitution, 0665
protonation of, 0670
reactivity, 0665
resonance energy, 0036, 0037, 0060
benzenechromium tricarbonyl, 0117
benzenediazonium, also see diazonium
benzenediazonium chloride, bond distances, 0917
benzenoid hydrocarbons, and aromaticity, 0057
benzenonium ion, 0661, 0662
benzhydrol, reduction to benzpinacol, 0348
benzidine rearrangement, 1678–1680
and [5,5]-sigmatropic rearrangement, 1680
benzil-benzylic acid rearrangement, 1594, 1595
benzoannulenes, and aromaticity, 0083
benzocyclobutane derivatives, and bond distance, 0024
benzocyclobutene, 0052
benzocyclopropene, 0052, 0226
benzofurans, Friedel-Crafts cyclization, 0715
from alkynes, 1038
metal catalyzed cleavage, 0617
benzoic acids, substituents and pK_a, 0381
benzoin condensation, 1396, 1397
and acyloins, 1397
and addition of HCN to carbonyls, 1389
benzoins, see hydroxy ketones
benzophenone, and cross conjugation, 0044
as a radical inhibitor, 0938

benzotriazoles, acyl, acylating reagent, 1450
benzoylation, arenes, rate and product distribution, 0680
benzoylnorephedrine, and rearrangement, 0400
benzo[*a*]pentalene, by rearrangement of biphenylene, 1646
benzpinacol, from benzhydrol, 0348
benzyl chloroformate, see chloroformate
benzylic α-hydroxylation, 1755, 1756
benzylic carbanion, 0070, 0252, 0641
benzylic carbocations, 0070, 0240
benzylic compounds, α-hydroxylation, 1755, 156
  and autoxidation, 0967
  and the Etard reaction, 1763
benzylic halogenation, radical, 0960
benzylic hydrogenation, with radicals, 0947
benzylic oxidation, to aldehydes, 1763
benzylic radicals, 0070, 0270, 0947
benzylic substrates, and substitution reactions, 0482, 0483
benzyne mechanism, 0859–0862
  and cine substitution, 0860
  coupling aryl halides with active methylene compounds, 0906
  Grignard reagents with aryl halides, 0887
  reactivity order of halides, 0860
benzyne, definition, 0860
benzynes, also see arynes
benzynes, and arynes, 0861
  and E1cB reactions, 1492
  and mechanism, 0313
  as intermediates, 0313
  in the Diels-Alder reaction, 0313, 1196
  in [2 + 2]-cycloaddition, 1221
Bergmann cyclization, 1641
  and Cope rearrangement, 1664
betaine-lithium halides, 1374
betaines, and the Wittig reaction, 1373, 1374
  from phosphines and epoxides, 1374
  X-ray structure, 1374
betweenanenes, and strain, 0227
biadamantylidene, 0224
biaryls, and atropisomers, 0146, 0902
  and chirality, 0146
  and hydroxylation of aromatic compounds, 0964
  and the Cahn-Ingold-Prelog system, 0158
  coupling, reagents, for, 0887
  diamino, by benzidine rearrangement, 1678, 1679
  diamino, from hydrazobenzene, 1678, 1679
  dimerization of organometallics, 0989
  Friedel-Crafts acylation, 0723
  from aromatic compounds, 0717, 0718, 0924, 0981
  from aryl halides, 0886, 0897, 0981
  from aryl halides under radical conditions, 0940, 0989
  from aryl organometallics, 0718
  from arylborinates, 0718
  from arylboronic acids, 0881, 0899
  from aryldiazonium salts, 0924, 0926
  from aryldiazonium salts and aryltrifluoroborates, 0923
  from arylsulfonic acids, 0881
  from borates, 0887
  from metal catalyzed coupling of Grignard reagents, 0888, 0987
  from metal catalyzed or metal mediated reactions, 0888, 0889
  from nickel complexes and aryl halides, 0898
  from the Friedel-Crafts reaction, 0717
  from the Gomberg-Bachmann reaction, 0924
  from the Heck reaction, 0897
  from the Scholl reaction, 0717
  from the Suzuki reaction, 0889
  from the Suzuki-Miyaura coupling, 0901
  from the Ullmann biaryl synthesis, 0873
  from the Ullmann reaction, 0897
  from trifluoroborates and aryl halides, 0903
  heteroaryl, 0888
  in ionic liquids, 0887
  in the Birch reduction, 1068
  photochemical methods, 0889
  with Lewis acids, 0717
bicyclic alkenes, and Bredt's rule, 0229
bicyclic bridged compounds, 0188
bicyclic compounds, and Bredt's rule, 0838
  and S_N1 reactions, 0435
  and [2 + 2]-cycloaddition, 1224
  by the Wurtz reaction, 0591
  decarboxylation, 0838
bicyclobutanes, radical addition, 1027
  rearrangement to dienes, 1691
bicyclobutonium ion, 0466
bicycloheptadienes, photochemistry, 0347
bicyclo[5.1.0]octadiene, Cope rearrangement, 1664
bifluorenylidene, rearrangement, 1646
Bijvoet, and X-ray analysis, 0155, 0158, 0159
bimolecular substitution, see substitution, S_N2
BINAP, and atropisomers, 0147
  and enantioselectivity, 1122
  and reduction of ketones, 1800, 1801
BINOL, and formation of amino-alcohols, 0563
  and Mukaiyama aldol, 1354
biocatalysts, reduction of aldehydes or ketones, 1800
biological activity, and enantiomers, 0138
biosynthesis, cholesterol, and squalene to lanostereol, 1090
  steroids, 1089
biphenylene, rearrangement, 1646
biphenylenes, [2 + 2]-cycloaddition, 1221
biphenylenediol, and hydrogen bonds, 0109

biphenyls, and atropisomers, 0146
and complex formation, 0125
and isomerization, 0748
barrier to rotation, 0146, 0198
biradicals, and Bergmann cyclization, 1641
and CIDNP, 0270
and Diels-Alder reaction, 1207
and Norrish Type II cleavage, 0344
lifetime, 0278
Birch reduction, and electron transfer, 1705
and impurities in ammonia, 1067
of aromatic compounds, 1067, 1068
of conjugated alkenes, 1068
bis(aldol) condensation, 1345
bis(alkoxides), metal mediated formation of alkenes, 1534
bis(amides), from addition of amides to aldehydes, 1292
rom the Ugi reaction, 1468
bis(amino)fluorenes, as proton sponges, 0386
bis(amino)naphthalenes, as proton sponges, 0386
bis(amino)phenanthrenes, as proton sponges, 0386
bis(ammonium salts) and Hofmann degradation, 1523
bis(decarboxylation), of dicarboxylic acids, 1749
bis(dimethylamino)naphthalene, 0365
2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, see BINAP
bis(Grignard) reagents, 1304
with esters, 1446
2, 4-bis(4-methoxyphenyl)-1, 3, 2, 4-dithiadiphosphetane-2, 4-disulfide, see Lawesson's reagent
bis(oxazolines), and chiral catalysts, 1114
bis(phosphines), and chiral ligands in catalytic hydrogenation, 1056
as chiral catalysts, 1073
bis(phosphoranes), and out-in isomers, 0191
bis(quaternary)ammonium salts, 0509
bis(selenenyl) compounds, from alkenes, 1180
bis(xanthates) radical elimination, 1535
Bischler-Napieralski reaction, 0715, 0716
bisecting bonds, and conformations, 0201
bishomoaromatic, 0093
bishomocubane, 1691
bismuth compounds, and acetal cleavage, 0526
bisulfite, sodium, see sodium
bisulfites addition products, 1280
Blaise reaction, 1328
blocking groups, for enolate anions with ketones, 0630
bmiI, ionic liquid, 0873, 0885
bmim (1-butyl-3-methylimidazolium), ionic liquid, 1132, 0416, 0529, 0580, 0697, 0699, 0700, 0713, 0716, 0720, 0872, 0876, 0887, 0894, 0900, 0905, 0979, 1066, 1074, 1074, 1085, 1107, 1136, 1150, 1157, 1163, 1172, 1185, 1199, 1284, 1286, 1291, 1295, 1310, 1314, 1332, 1342, 1359, 1387, 1389, 1390, 1429, 1618, 1684, 1723, 1724, 1747, 1762, 1800
boat conformation, 0203
and benzene, 0052
cycloheptatrienyl cations, 0065
Bobbitt's reagent, and oxidation of alcohols, 1723
Boekelheide reaction, 1624
boiling point elevation, and Grignard reagents, 0261
boiling point, and hydrogen bonding, 0111
and transesterification, 1419
bond alternation, and phenylenes, 0051
annulenes, 0089
pentalene derivatives, 0068
tropone and tropolone, 0065
bond angle, 0025
and alkanes, 0026
and alkyl halides, 0026
and annulenes, 0079
and carbenes, 0285
and carbocations, 0398
and carbon tetrachloride, 0026
and conformation, 0212
and cyclopropane, 0218
and cyclopropene, 0226
and cyclopropenyl cations, 0072
and E2 reactions, 1482
and hybridization, 0026
and ionization of alkyl halides, 0398
and lone pairs, 0027
and orbitals, 0026
and p character, 0026, 0027
and prismane, 0220
and radical hydrogen abstraction, 0949
and resonance, 0047
and s character, 0026
and steric strain, 0216
and strained molecules, 0026
and twisted alkenes, 0233
cyclooctatetraene, 0078
in ethylene, 0009
in organic compounds, table, 0026
MO calculations, 0035
of BF_3, 0008
of nitrogen or oxygen, 0006
solvent effects, 0007
bond cleavage, heterolytic, and mechanism, 0296
bond dissociation energy, see energy
bond distance, 0022
and antiaromaticity, 0057
and bond energy, 0030
and bond type, table, 0024, 0025
and electron diffraction, 0022
and electrophilic aromatic substitution, 0677
and hybridization, 0024, 0025, 0039
and microwave spectroscopy, 0022
and molecular mechanics, 0214
and orbitals, 0023
and resonance, 0047
and s character, 0025
and spectroscopy, 0022
and X-ray, 0024
and X-ray diffraction, 0022
C—D, 0025
C—Si, 0023
in annulenes, 0085, 0089
in benzenediazonium chloride, 0917
in benzocyclobutane derivatives, 0024
in bridged compounds, 0233
in butadiene, 0039

bond distance, (*Continued*)
in fused aromatic compounds, 0060
in sp^3 carbon compounds, table, 0023
MO calculations, 0035
bond energy, see energy
bond fixation, and PES, 0075
bond length, see bond distance
bond moments, 0018
bond order, and aromaticity index, 0063
and cross conjugation, 0044
and NMR, 0060
and resonance, 0033
cyclopentadienide ion, 0063
MO, of butadiene, 0039
of naphthalene, 0059
bond rotation, and carbenes, 0284
in catalytic hydrogenation, 1061
in radicals, 0277
restricted, 0184
bond switching, and the Stone-Wales rearrangement, 1646
bond type, and bond distance, 0024, 0025
and bond energy, 0031
and bond energy, table, 0029
bonding orbitals, 0005, 0006
bonding, and tautomerism, 0098
charge transfer and dipole induced, 0119
in metallocenes, 0066
localized chemical, 0003
bonds, and electronic structure, 0015
and formal charge, 0016
annelated, 0052
banana or bent, 0009, 0219
double bonds, 0009, 0011
energy and wavelength, 0335
in fused ring aromatic compounds, 0052
in ylids, 0052
ionic, and electronegativity, 0018
long bonds, 0024
multiple, 0009, 0011
multiple, and PES, 0013
organometallic, 0259
PES and methane, 0013
polar-covalent, and organometallics, 0259
triple bonds, 0009, 0010
Boord reaction, metals used, 1541, 1542
9-borabicyclo[3.3.1]nonane, see 9-BBN
borane, and ether solvents, 1075
dimers, 1076
monochloro, with alkenes, 1078
reduction of carboxylic acids, 1806
reduction of nitriles, 1813
reduction of oximes, 1812
with alkenes, 0644, 0815, 1075–1082
borane-dimethyl sulfide, 0816
borane-THF, reaction with alkenes, 1076
boranes, acyloxy, from carboxylic acids, and catecholborane, 1438
addition to alkenes, steric effects, 1077
alkylation, 0644
alkynyl, with amides, 1448
allylic, addition to aldehydes or ketones, 1319, 1320
allylic, metal catalyzed epoxide opening, 0620
and alkene isomerization, 0771
and functional groups, 1079
and H.C. Brown, 0645
and radical cyclization, 1123
and reduction of enamines, 1844
anti-Markovnikov addition to alkenes, 1078
carbonylation with imines, 0824
chiral boranes, 1080
conjugate addition, and co-reagents, 1121, 1122
conversion to alcohols, 0814
cyano, see cyanoboranes
cyclic, from dienes, 1081
dibromo, with aryl aldehydes, 1300
elimination to alkenes, 1533
for reduction of aldehydes or ketones, 1798
for reduction of azo compounds, 1853
formation of aldehydes, 1628
from alkenes, 0644, 0815
from Grignard reagents, 0827
halo, addition to aldehydes or ketones, 1319
halo, amination, enantioselectivity, 0822
halo, with alkynes, 0990
haloalkyl, with azides, 0822
halogenation, and radicals, 0820
migration of boron, 1604
oxidation of, mechanism, 0815
oxidation to alcohols, 1079
oxidation, and boron-carbon rearrangement, 1627
photochemical isomerization, 0771
protonolysis with carboxylic acids, 1063
radical coupling, mechanism, 0989
reduction with hydride reagents, 1628
reduction with lithium borohydride, 1628
silver mediated coupling, 0989
sulfurated, with Grignard reagents, 0827
synthetic transformations, 1079
thermal isomerization, 1533
thermal stability, 0771
thermolysis, 1604
vinyl, conjugate addition, 1122
vinyl, dimerization, 0989
vinyl, from alkynes, 1081
vinyl, halogenation, 0820
vinyl, metal catalyzed coupling, 0607
vinyl, oxidation with peroxide to give ketones, 1631
vinyl, with aryl halides, 0607
vinyl, with iodide and hydroxide, 1629
boranes, with alkynes, reduction to alkenes, 1064
with ammonia and hypochlorite, 0822
with basic hydrogen peroxide, 0814
with carbon monoxide, 1626
with chiral additives, and reduction, 1801, 1802
with chloramine, 0822
with dianions of carboxylic acids, 1629
with diazo compounds, 0646
with halogens, 0819
with haloketones, 0632, 0644, 0645
with hydroxylamine-O-sulfonic acid, 0822
with metal alkyne anions, 1631
borate esters, conjugate addition, 1116

borates, and reduction of nitro compounds, 1821
borates, aryl, and Suzuki-Miyaura coupling, 0902
by reduction of aldehydes or ketones with boranes, 1798
enol, and the aldol reaction, 1346
from alcohols and boron compounds, 0817
from organometallics, 0815
hydrolysis to alcohols, 1798
with Grignard reagents, 0816
borates, trifluoro, see trifluoroborates
borderline mechanism, and substitution, 0442
boric acid, from alkylborane oxidation, 0814
boric acid-amino acids, and resolution, 0173
boric anhydride, with keto esters, 0839
borinates, aryl, with aromatic compounds, 0718
borinates, enol, see enol borinates
Borodin, Alexander, 0994
borohydride exchange resin, and reduction of alkynes, 1064
and reduction of nitro compounds, 1817
reduction of alkyl halides, 1825
borohydride, dimethylamino, lithium, reduction of nitriles, 1814
borohydride, sodium, and microwaves, 1792
for reduction of acyl halides, 1840
for reduction of aldehydes or ketones, 1792
for reduction of carbonyls, and disproportionation, 1805
for reduction of carboxylic esters to alcohols, 1807
for reduction of conjugated carbonyls, 1793
for reduction of epoxides, 1790
for reduction of imines, 1811
for reduction of nitrlium ions, 1814
functional group reactivity, 1794
in acid, reduction of alcohols, 1829
on alumina, 1792
with boronic acids, reduction of carboxylic acids, 1806
with chiral additives, 1802
with Lewis acids, reduction of ethers, 1839
borohydride, tetraalkylammonium, reduction of carboxylic acids, 1806
borohydride, tri-sec-butyl, lithium, see L-Selectride
borohydride, tri-sec-butyl, potassium, see K-Selectride
boron compounds, conjugate addition, 1116
boron trichloride, with alcohols, 0817
boron triflate, and asymmetric aldol reactions, 1348
boron trifluoride, and borane addition to alkyne-ketones, 1122
and orbitals, 0008
with amines, and amides, 1438
boron trioxide, with alcohols, 0817
boron, migration in organoboranes, 1604
boron-to-carbon rearrangement, 1627, 1628
boronates, addition to imines, 1334
allylic addition to aldehydes, 1319
boronic acids, alkynyl, and Sonogashira coupling, 0905
and arylation of amines, 0879
and carbonylation of aryl halides, 0910
and halide exchange, 0884
and nitration of aromatic compounds, 0690
and Stille coupling, 0794
and Suzuki-Miyaura coupling, 0815, 0899–0903
and the Heck reaction, 0896
boronic acids, carbonylation with conjugated ketones, 1143
catalysts for conversion of carboxylic acids to amides, 1430
conjugate addition, 1116
from borates, 0816
from organometallics, 0815, 0816
hydrolysis to from phenols, 0870
boronic acids, metal catalyzed, addition to aldehydes, 1319
addition to alkynes, 1100, 1103
coupling, 0607, 0815
coupling to allene and allylic halides, 1095
coupling with methylthioalkynes, 0905
cyclization of dienes, 1100
formation, 0816
reaction with arylsulfonic acids, 0881
boronic acids, metal mediated coupling, 0604
metal mediated reaction with thiols, 0874
oxidation, 0870
vinyl, halogenation, 0820
vinyl, with aryl halides, 0890
boronic acids, with acyl halides, 0903
with acyl halides, 1443, 1444
with alcohols, 0889
with alkyl halides, 0889
with alkynes, 0794
with aryl halides, 0899–0903
with carboxylic acids, metal catalyzed, 1329
with imines, 1334
with propargylic alcohols, 1540
with sulfonyl halides, 1476
with vinyl halides, 0794
boronic esters, alkynyl, cyclotrimerization, 1245
from catecholborane and alkenes, 0817
preparation, nonaqueous workup, 0817
vinyl, from vinyl Grignard reagents, 0816
with organolithium reagents, 1629
boroxines, and Suzuki-Miyaura coupling, 0902
Bouveault-Blanc procedure, 1795
reduction of esters to alcohols, 1807
bowl-to-bowl inversion, 0095
Boyland-Sims oxidation, 0734
BPy (i.e., butylpyridinium), ionic liquid, 1614
Bradsher reaction, 0715

BrCl, with alkenes, 1151
Bredt's rule, and cyclic and bicyclic alkenes, 0229
and decarboxylation, 0838
and elimination reactions, 1497
and enol formation, 0838
definition, 0229
Bredt, anti-, see anti-Bredt
bridged annulenes, see annulenes
bridged bromine radicals, and ESR, 1012
bridged carbocations, 0450
bridged intermediates, radicals, and bromine, 1012
bridged ions, and halogenation of alkenes, 1149
bridged ions, from alkynes, 1018
bridged radicals, see radicals
bridgehead atoms, and chirality, 0144
bridgehead carbocations, 0245, 0246
bridgehead carbons, and electrophilic substitution, 0755
and S_N1 reactions, 0435
and S_N2, 0429, 0487
bridgehead hydrogens, reactivity with radicals, 0949
bromamine-T, and oxidation of amines to amine oxides, 1779
bromides, acyl, also see halides, acyl
bromides, acyl, from aldehydes, 0964
bromides, alkyl, also see halides, alkyl
bromides, alkyl, and Grignard reagents, 0262
rates of solvolysis, 0480
bromination, and Markovnikov's rule, 1020
of alkenes, 1002, 1003, 1150
of alkynes, 1004
of aromatic compounds, 0664, 0698, 0699
of benzene and toluene, rate and product distribution, 0680
with NBS, 0961
Wohl Ziegler, 0961
bromine radicals, 0939
bromine, addition to alkenes, stereoselectivity, 1003
addition to dienes, cyclic intermediates, 1014
and acetone, and mechanism, 0323
and cyclobutane, 0219
and cyclopropane, 0217
and Hell-Volhard-Zelenskii reaction, 0781
and heptalene, 0067
and phenanthrene, 0060
and UV, 1149
from NBS, 0962
halogenation of aromatic compounds, 0701
syn addition to alkenes, 1004
with alkenes, 1016, 1149
with alkynes, 1004
with sodium hydroxide, and Hofmann rearrangement, 1607
bromine-alkene complex, 1150
bromite, sodium, see sodium
bromoform, flash photolysis, 0287
bromonium ion, 1000, 1002, 1004
and neighboring group mechanism, 0447, 0448
Brønsted α, 0374
Brønsted acidity, and Lewis acidity, 0384
Brønsted acids, and pinacol rearrangements, 1586
diamine, and asymmetric aldol reactions, 1348
Brønsted catalysis equation, 0373
Brønsted coefficient, and acetal hydrolysis, 0525
Brønsted equation, 0373, 0374
and mechanism, 1496
and the Marcus equation, 0374
Brønsted plot, and nucleophilicity, 0495
and S_N2, 0431
Brønsted theory, 0356
Brønsted-Lowry acids, and decarbonylation of aryl aldehydes, 0745
and Friedel-Crafts acylation, 0720
and Friedel-Crafts alkylation, 0707
and rearrangement of alkenes, 0769
halogenation of aromatic compounds, 0703
rearrangement of N-nitroaniline, 0738
Brook rearrangement, aza-Brook and homo-Brook, 1700, 1701
brosylates, and solvolysis, 0438
as leaving groups, 0497
Brown σ* values, electrophilic aromatic substitution, 0679
Brown, H.C., and hydroboration, 0645
brucine, and resolution, 0173
Bruylants reaction, 0614
Bucherer reaction, 0870, 0882
buckminsterfullerene, 0094
buckybowls, 0094
bullvalene, and Cope rearrangement, 1665
Bunnett-Olsen equation, and solvent acidity, 0371, 0372
Bunte salts, 0553
Burgess reagent, and dehydration of amide to nitriles, 1549
and dehydration of oximes to nitriles, 1546
butadiene, 0038–0040
and cross conjugation, 0044
with HCl, 1014
butadiyne, 0040
butane, conformations, 0198–0200
butenolides, and Claisen rearrangement-Conia reaction, 1670
from allene-carboxylic acid derivatives, 1042
butyllithium with dimethylhydrazones, 0632
with dithianes, 0638
with thioanisole, 0639
1-butyl-3-methylimidazolium, see bmim

C-alkylation, enolate anions, 0514
of enols, 0628
phenoxide ions, 0515
C-nitroso compounds, 0690
Cadiot-Chodkeiwicz reaction, 0979
cage compounds, 0126
Cahn-Ingold-Prelog rules, and absolute configuration, 0155–0158
and alkenes, 0183
and diastereomers, 0166
and diastereotopic, 0194
and E/Z isomers, 0183
and enantiotopic, 0194
and halohydrins, 1152
R/S nomenclature, 0155–0158

calcium ions, and crown ethers, 0123
calcium, in amines, reduction of aromatic compounds, 1069
calculations, *ab initio*, acidity, 0358
  and Lewis base strength, 0376
  and nitrenes, 0293
  and nonclassical carbocations, 0451
  norbornyl carbocation, 0463
calculations, and conformations, 0196
  and isotope effects, 0324
  and prismane, 0220
  azaannulenes, 0081
  carbocation stability, 0243
  Möbius aromaticity, 0091
calicene, and aromaticity, 0069
calixarenes, 0122, 0123
  and atropisomers, 0149
  and chirality, 0152
  and suppression of dediazoniation, 1848
  enantiopure, 0123
calorimetric measurements, and acidity scales, 0372
calorimetric methods, and kinetics, 0319
Cambridge structural database, and hydrogen bonding, 0108
camphor, 0188
Cannizzaro reaction, 1863, 1864
  and dihalides, 0520
  and hydride transfer, 1706
  and the aldol reaction, 1863
  crossed, 1864
  crossed, and the Tollens' reaction, 1368, 1864
  reduction of aldehydes, 1798
canonical forms, also see resonance
canonical forms, 0032, 0046
  +M and −M effects, 0396
  and hyperconjugation, 0096, 0097
  of 1,3-dipoles, 1188
  of aromatic compounds, 0059, 0060, 0678
  of aryldiazonium salts, 0917
  of cyclopentadienide ion, 0063
  of heteroatom stabilized carbocations, 0243
  of molecules, 0006
  of N-ylids, 0255
  of pyrrole, 0062
  of vinyl chloride, 0041
capped cyclodextrins, 0131
caprolactams, conformation, 0212
captodative effect, 0075
  and radicals, 0272, 0273
caranylboranes, 1080
carbalkoxylation, of heterocycles, 0983
carbamates, addition to alkenes, 1051
  and the Knoevenagel reaction, 1362
  by carbonylation of amines, 0851
  by insertion of nitrenes, 0790
  cyclic, alkylation, 0569
  cyclic, from isocyanates and oxetanes, 1275
  from alcohols, 0851, 1274
  from amides, 0542
  from carbonates and amines, 1435
  from chloroformates and amines, 1428
  from cyanogen chloride and alcohols, 1276
  hydrolysis, mechanisms, 1406, 1407
  lithiation, 0640
  metal catalyzed conjugate addition, 1130
  reaction with isocyanates, 1274
  tert-butoxy, and stability of, 1428
  torsional barrier, 0202
  with NBS and DBU, 1608
carbamic acids, by hydrolysis of isocyanates, 1266
carbamoyl chloride, 0728
carbanion ion pairs, and E1cB reactions, 1493
carbanion mechanism, and E1cB reactions, 1489
carbanions, 0234
  addition to carbocations, 1007
  allylic, 0252, 0762, 0768, 1014
  allylic, and [3 + 2]-cycloaddition, 1193, 1194
carbanions, and conjugation, 0252
  and cyclopropyl stabilization, 0253
  and field effects, 0255
  and fused aromatic compounds, 0253
  and homoenolates, 0256
  and hybridization, 0257
  and isoinversion or isoracemization, 0760
  and organometallic compounds, 0249, 0251
  and pyramidal inversion, 0257
  and racemization, 0256
  and rearrangement, 0265
  and resonance stabilization, 0258, 0759
  and retention of configuration, 0257
  and spectroscopic analysis, 0252
  and substitution at vinyl carbon, 0475
  and UV, 0768
  and vicarious nucleophilic substitution of hydrogen, 0915
  and X-ray crystallography, 0253
  aromatic, 0255, 1069
  benzylic, 0252
  boron stabilized, with aldehydes, 0801
  chiral, 0258
  conducted tour mechanism, 0761
  conjugated to heteroatoms, 0253
  definition, 0250
  diphenylmethyl, 0252
  dithianes, acylation of, 1456
  fate of, 0264
  formation of a stable salt, 0253
  from alkenes, 0265
  from cleavage of alkoxides, 0835
  from DMSO, 0914
  from radicals, 0281
  generation of, 0264
  hydrogen exchange, 0759
  Knoevenagel, with allylic esters, 0610
  methyl, 0257
  methylsulfinyl, 0914
  methylsulfonyl, with esters, 1455
  nitrile, 0253
  overlap with d orbitals, 0254, 0255
  oxidation to radicals, 0265
  protonation of, 0250
  pyramidal, and racemization, 0758
  pyramidal, and the S_E1 mechanism, 0758

carbanions, and
conjugation, (*Continued*)
rate of isotope exchange, 0760
reaction with a proton, 0265
resonance stabilized, 0252, 0762
solvation by leaving groups, 0759
stability, 0250–0255, 0258
stability, and the counterion, 0257
stability, and transmetallation, 0828
stabilizing groups, 0256
stereochemistry, solvent effects, 0759
strain and stability, 0254
triphenylmethyl, 0252
via decarboxylation, 0265
via deprotonation, 0264
vinyl, 0257
vinyl and configurational stability, 0258
with aldehydes, 0265
with alkyl halides, 0265
with allylic halides, 0594
with aryl nitro compounds, 0914
with ketones, 0265
carbazoles, arylation of amines, 0878
in the Diels-Alder reaction, 1198
carbene, 1234
carbene addition, mechanism, 1238, 11239
carbene complexes, by diazo transfer reactions, 1237
carbene insertion, 0804, 0805
and ring expansion, 0805
carbene rearrangements, see rearrangements
carbene-to-carbene rearrangement, 1600
carbene transfer, 1234
carbenes, 0234, 0283–0292
carbenes, acyl, rearrangement to ketenes, 0291
carbenes, addition reactions, 0284, 0289, 1233–1240
carbenes, alkyl or allylic, rearrangement, 0803, 0804
amino, 0286
carbenes, and bond angles, 0285
carbenes and bond rotation, 0284
and CIDNP, 0807
and cleavage of diazoalkenes, 0534
and diradicals, 1239
and elimination, 0292
and EPR, 0285
and formylation, 0726
and Hund's rule, 0284
and IR, 0285
and IUPAC mechanisms, 0500
and leaving groups, 0500
and nitrogen extrusion reactions, 1554
and nonbonded electrons, 0284
and radicals, 0278
and Reimer-Tiemann reaction, 0726
and sonochemistry, 0351
and spin trapping, 0285
and stereochemistry, 0285
and substitution, 0292
and syn addition, 1238
and synthesis, 0289
and the Simmons-Smith procedure, 1234
and the Wolff rearrangement, 0291
and transient grating spectroscopy, 0288
and X-ray crystallography, 0290
and [1 + 2]-cycloaddition, 1234
carbenes, aryl, 0286
carbenes, chiral, 0286
carbenes, coupling, 0290
cyclopropane rearrangements, 0291
decay, singlet to triplet, 0284
definition, 0283
diaryl, 0285
dichlorocarbenes, 0283
dichloromethylene, 0283, 0286
dihalo, with aldehydes or ketones, 1384
dimerization, 0290
direct insertion, 0807
electrochemical generation, 0287
electronic effects of substituents, 1238
electrophilic, 1238
fate of, 0287
formyl, lifetime, 0288
fragmentation to radicals, 0292
carbenes, generation of, 0287–0288
geometry, 0286
insertion reactions, 0289, 0290, 0803–0806, 1234
isolation of, 0283
isomerization, 0285
metal complexes, 1236
metal, see metal carbenes
methylene, 0283, 0286
octylidenes, 0286
oxychloro, 0292
reaction with diazoalkanes, 0290
reactivity, 0290, 0804
rearrangement, 0291, 0292, 1234, 1600
silyl, 0286
singlet, 0284, 1238
singlet, and insertion, 0807
solvent effects, 0288, 0289
stability, 0283, 0290
structural types, 0283, 1234
substituent effects, 1238
triplet, 0284, 0285, 0292, 1239
triplet, and insertion, 0807
vinyl, 0286
with alkynes, 1238
with thioketones, 1385
carbenoid homologation, 0803
carbenoids, 1234
and diazoalkanes, 0534
and insertion, 0807
definition, 0288
elimination reactions, 0288
formation of, 1234, 1235
mechanism of formation, 1235
carbocation formation, and substituent effects, 0480
and zeolites, 0248
carbocations, 0234
acetyl, 0242
acyl, 0242, 0243, 0722
adamantyl, 0245
addition of alkenes, 0249
alkynyl, isotopic labeling, 0477
alkynyl, stability, 0477
carbocations, allylic, 0239, 0240
allylic from allenes, 1021
allylic, and cyclopropyl carbocations, 1590
allylic, and ion pairs, 0470
allylic, and rearrangement, 0483
allylic, and resonance, 0483, 1013
allylic, from addition to dienes, 1013
allylic, from cyclopropyl halides, 0487

carbocations, and acetal hydrolysis, 0527
and acid catalyzed dehydration of alcohols, 1515
and addition of alkyl halides to alkenes, 1160
and addition to cyclopropanes, 1026
and alcohol addition to alkenes, 1037
and alcohol dehydration, 0535
and alkyl halides, 0237, 0434
and allylic rearrangement, 0469
and arenium ions, 0658
and azulenes, 0241
and benzene, 0658
and bond angles, 0398
and carbonylation of alkyl halides with alcohols, 0652
and chair conformations, 0245
and chemical shifts, 0246
and conjugated dienes, 0240
and conjugation, 0239
and cyclopropyl groups, 0241
and cyclopropylmethyl groups, 0464, 0465
and diazonium salts, 0499, 0803
and double hyperconjugation, 0239
and E1 mechanism, 1487
and electrophilic substitution, 0764
and electrophilicity, 0432
and ESCA, 0467
and formation of double bonds, 0248
and Friedel-Crafts alkylation, 0710
and Friedel-Crafts reactions, 1084
and homoconjugation, 0239
and hydration of alkenes, 1032
and hydride extraction, 1706
and hyperconjugation, 0237–0239, 0325, 0326, 0483
and insertion, 0803
and ion pairs, 0236
and IR, 0236, 0245
and Lederer-Manasse reaction, 0714
and Markovnikov's rule, 1019
and NMR, 0236, 0241, 0245, 0246, 0454, 0459
and nonclassical carbocations, 0464
and norbornyl compounds, 0436
and PES, 0244
and phenonium ions, 0456
and planarity, 0435
and polyene cyclization, 1090
and Raman, 0245
and rearrangement, 0802, 1032, 1561
and rearrangement of alkenes, 0769
and resonance, 0247, 0483, 1019
and reverse Friedel-Crafts alkylation, 0744
and S_N1 reactions, 0432, 0435
and solvolysis of alkyl halides, 0325, 0326
and spectroscopic analysis, 0245
and Stieglitz rearrangement, 1617
and strain, 0398
and superacids, 0236, 0466, 0844, 1645
and the Hammond postulate, 0480, 1019
and the Prins reaction, 1393
and UV, 0435
and Wagner-Meerwein rearrangement, 1580–1585
and Zaitsev's rule, 1581
carbocations, arenium ions, 0240
carbocations, aryl, 0858
aryl, and arylation of aromatic compounds, 0925
aryl, and the Gomberg-Bachmann reaction, 0926
aryl, and tritium decay, 0477
carbocations, benzylic, 0240
bicyclic compounds, rearrangements, 1571
bicyclobutonium, 0466
bridged, 0450
bridged, and migration of aryl groups, 1577
bridgehead, 0245, 0246
calculations of stability, 0243
canonical forms, 0243
carbonyl, exo attack, 1582
charge distribution, 0239
chiral, in [4 + 3]-cycloadditions, 1249
conjugation with cyclobutanes or cyclopropanes, 0242
conjugation with heteroatoms, 0242
counterion, 0236
coupling with alkenes, 0802
cyclobutyl, 1588
cyclopropyl, and ring opening, 1644
cyclopropylcarbinyl, 0450, 1588
cyclopropylmethyl, 0241, 0465
degenerate, 1563
destabilizing groups, 0484
detection of, 0435
deuterium labeling, and rearrangements, 1565
diarylmethyl, 1005
dications, 0241
direction of rearrangement, 1562
dissociation energy, table, 0244
dodecahedral, 0245
equilibration of, 0467
fate of, 0247
formation by ionization of alkyl halides, 0247
carbocations, from alcohols, 0236, 0247
from alkenes, 0247, 0844
from alkyl diazonium compounds, 0247
from amines, 0247
from radicals, 0281
carbocations, gegenion, 0236
generation of, 0247
geometrical structure and migratory aptitudes, 1571
heteroatom stabilized, 0242, 0248
homoallylic, 0451
in superacids, 0766
in-out isomerism, 0113
loss of a proton, 0248
methyl, X-ray, 0236
migration of aryl groups, 1577
nomenclature, 0235
carbocations, nonclassical, 0247, 0450, 1582
ab initio calculations, 0451
and cyclobutyl groups, 0464
and cyclopropylmethyl, 0464, 0465
and delocalization, 0450

carbocations,
nonclassical, (*Continued*)
and laser Raman, 0462
and NMR, 0451, 0454, 0462, 1583
and norbornyl systems, 0450
and nortricyclane, 0463
and rearrangement, 0464
and solvolysis, 0452, 0453
and stability, 0462
and Wagner-Meerwein rearrangement, 1582
and X-ray electron spectroscopy, 0462
arguments against, 0451, 0452, 0461, 0462
arguments for, 0461, 0462
controversy, 1582
cyclopropylcarbinyl, 0450
in superacids, 1583
σ route, 0451
carbocations, norbornadienyl, and NMR, 0451
norbornyl, 0461–0463
phenyl, 0243
photochemical generation, 0435
pK, 0244
planar, 0436
primary, and the S_N1 mechanism, 0480
propargyl, 0240
propeller shaped, 0246
rate of reaction with nucleophiles, 0490
reaction with carbanions, 1007
reaction with nitriles, 1458
reaction with nucleophiles, 0248
rearrangement, 0236, 0248, 0249
silyl, 0248
carbocations, stability, 0243, 1019
stability, *ab initio* molecular orbital calculation, 1003
stability, and cleavage of alkenes, 0844
stability, and direction of rearrangement, 1562
stability, and NMR, 1562
stability, and selectivity, 0680
stability, and X-ray crystallography, 0235
stability, in strong acids, 0236
stability, open versus bridged, 1003
stabilization by cyclopropyl groups, 0451
stabilizing groups, and migratory aptitudes, 1569
stable, 0241, 0802
stable solutions of, 0236
carbocations, stereochemistry, 0245
stereochemistry of elimination, 1502
structure and delocalization, 0239
structure and NMR, 1645
tert-butyl, X-ray, 0236
tert-pentyl, rearrangement of, 1562
triarylmethyl, 0246
trications, 0241
trihomobarrelyl, 0245
triphenylmethyl (trityl), 0240
vinyl, 0243, 0476, 1007
vinyl, and p orbitals, 0476
vinyl, and tritium-decay, 0477
vinyl, from alkynes, 1007
vinyl, stabilizing groups, 0476
with alkenes, 1000
X-ray crystallography, 0236
carbodiimides, by dehydration of ureas, 1550
from isocyanates and phosphine oxides, 1460
carbohydrates, and cyclodextrins, 0129
and osazones, 1285
and sonochemistry, 0352
carbon 14, and cyclopentadienide ion, 0063
carbon acids, 0358
carbon dioxide, addition of amines, 1297
as a guest, 0127
critical temperature, 0414
extrusion from lactones, 1555
formation of carboxylate salts, 0728, 0729
from decarboxylation, 0745
metal catalyzed carboxylation of alkynes, 1042
organolithium reagents and dienes, 1144
carbon dioxide, supercritical, and reactivity, 0414, 0415
and alkene metathesis, 1684
and Diels Alder reactions, 1199
and nucleophilicity, 0508
and Stille coupling, 0793
and substitution reactions, 0508
and Suzuki-Miyaura coupling, 0901
and the Glaser reaction, 0979
and the Heck reaction, 0894, 0895
and the Kolbe-Schmidt reaction, 0729
formation of carbamates, 0852
metal catalyzed carbonylation, 1140
nitrile oxide cycloaddition, 1190
carbon dioxide, thermal extrusion from lactones, 1546
with amides, 0851, 0852
with aromatic compounds, 0728, 0729
with Grignard reagents, 1330
with organolithium reagents, 1330
with organometallic reagents, 0824, 1329
with phosphorus ylids, 1379
carbon disulfide, and Friedel-Crafts acylation, 0720
base catalyzed addition to ketones, 1368
with alcohols, 1276
with amine, 1297
with dihalides, 0551
with Grignard reagents, 1330
with organolithium reagents, 1330
carbon monoxide, and alcohols, 0653
and hydrocarboxylation, 1138
and metal catalyzed carbonylation, 1140
and metal catalyzed hydroformylation of alkenes, 1145
and the Koch reaction, 1137
carbonylation of amines, 0850
carbonylation reactions, 1139
extrusion from cyclobutanone, 1555
thermal extrusion from ketones, 1545
water and alkenes, 1136
with boranes, 1626, 1628
carbon NMR, see NMR
carbon nucleophiles, 0587

carbon tetrachloride, and bond angle, 0026
and dipole moment, 0019
with organolithium reagents, 0834
carbon tetrahalides, see halides
Carbon-13 NMR Spectra, 1889
carbon-H hydrogen bonding, 0111
carbon-metal bonds, 0249
carbonate, and resonance, 0042
carbonates, allylic, coupling, asymmetric induction, 0611
coupling with active methylene compounds, 0611
coupling with enolate anions, 0611
metal catalyzed coupling, 0611
carbonates, and amines, 1435
cyclic, carbonylation of allene alcohols, 1042
dialkyl, from alkyl halides, 0541
enol, alkylation, 0629
enol, and Tsuji alkylation, 0629
from alcohols, 0542
from alkyl halides, 0542
from haloformic acids, 1276
from phosgene and alcohols, 1276
metal, with ketones, 1367
methylmagnesium, with ketones, 1367
carbonium ion, see carbocations
carbons, MS of, 0236
carbonyl carbon, and HSAB, 0494
carbonyl carbon, nucleophilicity order, 0494
carbonyl compounds conjugated, addition of organometallics, 1111–1120
carbonyl compounds pK_a, α-proton, 0627
α-hydroxylation, reagents, 1753
acyl addition, 1251
conjugated, addition of vinylsilanes, 1088
cyanation, 0801
Diels-Alder reaction, 1216
metal catalyzed addition of organotin compounds, 1314–1322
metal catalyzed addition to alkenes, 1098
reactivity in the tetrahedral mechanism, 1260
structural compatibility with organometallics, 1313
carbonylation, and Friedel-Crafts acylation, 0723
and Grignard reagents, 1305
and the Pauson-Khand reaction, 1141
double, 0655
formation of amides, 0730, 0850, 0851
formation of aryl carboxylic acids, 0728
formation of ureas, 0850, 0851
in supercritical carbon dioxide, 0415
intramolecular, with aryl halides, 0909
metal catalysts, with alkenes, 1138
metal catalyzed, 1137, 1140, 1141
of alcohols, 0653, 1139
of alkenes, 0655, 1139
of alkyl halides, metal catalyzed, 0654
of alkyl halides, metal mediated, 0652
of alkynes, 1139, 1042
of allene alcohols, 1042
of amines, 0654, 0655, 1139
of aryl halides with alcohols, 0909
of aryl halides, with organometallics, 0910
of azides, 0851
of aziridines, 1466
of conjugated ketones, 1143
of diazonium salts, metal catalyzed, 0986
of organometallics, 0651, 0824
reactions, and metal complexes, 0655
Reppe, 1137
carbonyldiimidazole, and acylation of amines, 1432
carbonylnitrenes, insertion, 0790
carbonyls, and bonding, 0011
α stereogenic center, 0774
addition of alcohols, 1270
addition of water, 1261, 1263
and Cram's rule, 1252
approach of nucleophiles, 1258
catalysis of nucleophilic attack, by nucleophiles, 1259
conjugated and reactivity, 1254
conjugated, addition of anions, 1008
facial selectivity, 1252
formation of stereoisomers, 1252
fragmentation of halo ethers, 1542
metal mediated, 0824
nucleophilic addition, 1253
oxygen reacts as a base, 1253
pK_a of α-proton, 0626
trajectory of nucleophilic approach, 1258
with hydrogen sulfide, 1277
with Lawesson's reagent, 1278
carborane acids, 0368
carboxylate ions, aryl, rearrangements, 0747
formation of carbenes, 0287
rearrangement, and Henkel reactions, 0747
carboxylate salts, and lactone formation, 0540
and the Kolbe reaction, 0993
from aromatic compounds, 0728, 0729
radical coupling, 0992
with acyl halides, 1422
with cyanogen bromide, 1461, 1462
carboxylates, ammonium, from carboxylic acids and ammonia, 1430
ammonium, pyrolysis, 1430
ions, decarboxylation, 0837
carboxylation, by enzymes, 0729
carboxylation, indirect, 1367
of alkenes, metal catalyzed, 1144
vinyllithium compounds, 0761
with *Bacillus megaterium*, 0729
carboxylic acid derivatives, aldol-like reactions, 1354
carboxylic acid salts, alkylation, 0637
carboxylic acids, acidity, 0020
acylation with aminoboranes, 1433
addition to alkenes, 1041
α-alkylation, 0643
alkylation with diazo compounds, 0543

carboxylic acids, and ethers, 1418
and field effects, 0020
and free energy, 0394
and hydrogen bonding, 0107
and inductive effects, 0020
and ionization, 0394
and resonance effects, and pK_a, 0382
and tautomerism, 0105
and Dakin-West reaction, 0841
and the Koch reaction or the Koch-Haaf reaction, 1137
and the Schmidt reaction, 1611
and the Wolff rearrangement, 1599
carboxylic acids, anhydrides and decarboxylation, 0840
aryl, and the Hammett equation, 0402
aryl, and the von Richter rearrangement, 0927
aryl, by oxidation of aromatic side chains, 1745
aryl, from aryl nitro compounds, 0927
aryl, ortho alkylation, 0637
carboxylic acids, by carbonylation of alkenes, 1138
by cleavage of keto-esters, 0841
by cleavage of methyl ketones, 0842
by hydroboration and reduction, of alkenes, 1063
by hydrocarboxylation of alkenes, 1136
by hydrolysis of acyl halides, 1398
by hydrolysis of amides, 1407
by hydrolysis of anhydrides, 1399
by hydrolysis of carboxylic esters, 1400
by hydrolysis of ketenes, 1600
by hydrolysis of nitriles, 1268
by hydrolysis of oxazolines, 0598
by oxidation of alcohols, 1718, 1768
by oxidation of alcohols, reagents for, 1768
by oxidation of aldehydes, 1718, 1769–1773
by oxidation of aldehydes, mechanism, 1771
by oxidation of aldehydes, reagents for, 1770, 1771
by oxidation of alkynes, 1775
by oxidation of boranes, 1082
by oxidation of enol ethers, 1775
by oxidation with peroxyacids, 1773
by oxidative cleavage of alkenes, 1742
by pyrolysis of esters, 1519, 1520
by reductive cleavage of esters, 1833
by the Arndt-Eistert synthesis, 1599
by the Barbier-Wieland procedure, 1743
by the Japp-Klingemann reaction, 0783
by the Kolbe-Schmidt reaction, 0728, 0729
by the Willgerodt reaction, 1867, 1868
by-products of epoxidation, 1169
carboxylic acids, conjugated, by the Perkin reaction, 1363
by the Doebner modification, 1360
decarboxylation, 0838
formation of vinyl nitro compounds, 0975
from alkynes, 1138
hydrogenation in ionic liquids, 1074
with NBS and lithium acetate, 0996
with nitric acids and AIBN, 0975
carboxylic acids, conversion to dithiocarboxylic esters, 1278
decarboxylation, 0835, 1457
dehydrating agents, 1514
dehydration, 1423, 1514
deuterated, addition to cyclic alkenes, 1023
dianions, with boranes, 1629
dianions, with esters, 1456
esterification, 1414, 1415
esterification and steric hindrance, 0398
exchange with acid derivatives, 1441, 1423
field effects and pK_a, 0381
formation of hydrazones, 0784
Friedel-Crafts acylation, 0719
carboxylic acids, from acyl halides, and ethers, 1412
from acyl peroxides, 0814
from anhydrides and alcohols, 1412
from aromatic compounds, 0728
from boranes, and acid dianions, 1629
from carbon dioxide, and phosphorus ylids, 1380
from cleavage of diketones, 0841
from diazoketones, 1599
from diazonium salts, 0986
from Grignard reagents, 0814
from ketones, 0783, 0841, 0843, 1867, 1868
from malonic esters synthesis, 0623
from nitriles, 0648
from organometallics, and carbon dioxide, 1329
from oxazolines, 0643
from peroxyacids, and alkenes, 1169
from primary alcohols with Jones reagent, 1716
from the haloform reaction, 0842
carboxylic acids, gas phase pyrolysis, 1520
halo, 0585
halo, lactone formation, 0304
halo, with aldehydes or ketones, 1364
halogenation, 0781, 0782
Hell-Volhard-Zelenskii reaction, 0781
metal catalyzed elimination, 1520
oxidation with hydrogen peroxide, 1773
oxidative cleavage of alkynes, 1744
oxidative cleavage of ethers, 1769
oxidative decarboxylation to alkenes, 1747
oxidative decarboxylation, mechanism, 1748
photochemistry esterification, 1414
pK_a, table, 0382

propargyl, from alkynes, 1330
radical alkylation of heterocycles, 0982
radical coupling, 0977
reagents for conversion to alkyl halides, 0995
reduction to alcohols, 1805, 1806
reduction to aldehydes, reagents, 1809
reduction to hydrocarbons, 1843
reduction with borane, 1806
structural limitations of decarboxylation, 0836
carboxylic acids, with alcohols, acid catalyzed, 1414
with ammonia, 1430
with anhydrides, 0840
with boronic acids, metal catalyzed, 1329
with cyanuric fluoride, 1440
with enol esters, 1424
with halogenating reagents, 1440
with hydrazoic acid, 1611
with imines, 1465
with isocyanides and carbonyls, 1467
with metal halides, 1426
with Mukaiyama's reagent, 1514
with organolithium reagents, 1329, 1447
with thiols, 1418
with triphenylphosphine and carbon tetrachloride, 1440
carboxylic acids-alcohols, see hydroxy acids
carboxylic acids-alkenes, by pyrolysis of lactones, 1520
carboxylic esters, acetoacetic, and alkylation, 0624
acidity, 0383
addition to alkenes, 1134
alkylation, 0626
carboxylic esters, allylic, and π-allyl palladium, 0609
allylic, coupling reactions, 0619–0611
allylic, Knoevenagel carbanions, 0610
allylic, with active methylene compounds, 0610
allylic, with aryl halides, 0609
allylic, with keto acids, metal catalyzed, 0996
carboxylic esters, and acylation of amines, microwaves, 1435
and DBU, 0541
and dimethyl carbonate, 0541
and DMF acetals, 0542
and formation of acyl azides, 0573
and isotopic labeling, 1404
and microwaves, 1400, 1401
and phase transfer, 1401
and retention of configuration, 1404
and S_N2 reactions, 0501
and steric hindrance, 1401
and the Baylis-Hillman reaction, 1323
and the Claisen condensation, 1452
and the Claisen reaction, 1355
and the Katritzky pyrylium-pyridinium method, 0542
and the Pinner synthesis, 1275
and the Reformatsky reaction, 1328
and the Schotten-Baumann procedure, 1411
and the Stobbe condensation, 1356
and transesterification, 1419
and ultrasound, 1401
carboxylic esters, aryl, by carbonylation, 0909
aryl, from aryl halides, 0872
aryl, from arylthallium compounds, 0913
aryl, with Lewis acids, 0735
carboxylic esters, base catalyzed condensation, 1452
basic hydrolysis, 1256, 1257
by carbonylation of alkenes, 1140
by carbonylation of aryl halides, 0909
by cleavage of keto esters, 0841
by Favorskii rearrangement, 1595
by hydration of alkynes, 1036
by hydrolysis of imino esters, 1275
by oxidation of aldehydes, 1769, 1771
by oxidation of alkenes with dioxiranes, 1755
by oxidation of allylic alcohols, 1769
by the Mitsunobu reaction, 0540
by the Tischenko reaction, 1865
carbonylation of alkyl halides and alcohols, 0652
cleavage, 0550
cleavage with NaCN-HMPA, 0649
condensation, with aldehydes or ketones, 1355, 1455
condensation, with nitriles, 1455
carboxylic esters, conjugated, 1, 4-addition of alcohols, 1039
conjugated, proton acidity, 0633
epoxidation, formation of glycidic esters, 1175
formation of glycidic esters, 1175
hydrostannation, 1074
photolysis and β-lactone formation, 1041
reduction with tributyltin hydride, 1072
with aldehydes, Stetter reaction, 1321
carboxylic esters, demethylation, 0550
carboxylic esters, enol, see enol esters
carboxylic esters, exchange with carboxylic acids, 1423
carboxylic esters, from acyl halides and alcohols, 1411
from acyl halides with ketones, 1274
from acyl peroxides, 0971
from acyl tosylates, 0543
from aldehydes, reagents, 1865, 1866
from alkenes and carboxylic acids, 1041
from alkyl halides, 0539, 0654
from amides and alcohols, 1421
from anhydrides, 0542
from anhydrides and alcohols, 1412
from carboxylate salts, 0539
from carboxylic acids and alcohols, 1414
from carboxylic esters and alcohols, 1419
from diazo compounds and acids, 0543
from ethers, 0542

carboxylic esters, (*Continued*)
from Grignard reagents and chloroformates, 1445
from halo ketones, 1595
from hydrocarbons, 0971
from ketones and peroxy acids, 1617
from methyl ketones, 0843
from organometallics, 0818
from oxazolidinone amides, 1422
from oxonium salts, 0542
from trihalides, 0521
from vinylorganometallics, 0824
carboxylic esters, glycidic, from conjugated esters, 1175
heteroaryl, by carbonylation, 0909
homologation, 1450
carboxylic esters, hydrolysis, 0642, 1400
enantioselective reactions, 1401
enzymatic, 1400
mechanism, 0406, 0407, 1402–1406
rates, 0399
tetrahedral mechanism, 1402–1406
α-hydroxylation, 1752
carboxylic esters, malonic, see malonate
carboxylic esters, α-oxidation of ethers, 1759
pyrolysis, 1519, 1520
radical coupling, 0977
rearrangement, 0735
reduction to alcohols, Bouveault-Blanc procedure, 1807
reduction to alcohols, reagents, 1806, 1807
reduction to aldehydes, reagents, 1809
reduction to ethers, reagents, 1839
reduction to methyl compounds, 1842
reduction with Dibal, 1809
reduction with silanes, 1807
reduction with sodium in ethanol, 1795
reduction, Bouveault-Blanc procedure, 1795
reductive acylation of ketones, 1274
reductive cleavage to hydrocarbons, 1833
reductive cleavage with lithium in amines, 1834
reductive coupling to acyloins, 1860
solvent effects in alkylation reactions, 0539
solvolysis of, and NMR, 0434
steric hindrance to formation of, 0398
sulfenylation, 0791
vinyl, hydrolysis, 1401
vinyl, hydrolysis by esterases, 1401
with amines or ammonia, 1434, 1436
with carboxylic acid dianions, 1456
with dimethyl sulfate, 0541
with metal carbenes, 1381
with Petasis reagent or Tebbe's reagent, 1380
with trimethylphosphate, 0541
carboxylic esters-thioethers, 1179
carboxylic salts, from carboxylic esters, 0584, 0585
carbynes, 0287
carcerands, 0128
carcerands, and cyclopentadiene, 0074
carciplex, 0128
Caro's acid, conversion of thioamides to amides, 1280
oxidation of amines to amine oxides, 1779
oxidation of amines, 1777
β-carotene, and the Wittig reaction, 1378
Carroll rearrangement, 1670
carvone, photochemical [2 + 2]-cycloaddition, 1230
carvonecamphor, by photochemical [2 + 2]-cycloaddition, 1230
CAS ONLINE, 1876, 1877
CAS Registry, 1881, 1901
CASSI, 1910
catalysis, acid, epoxide alcoholysis, 0537
of acetals, 0524
of epoxides, 0528
catalysis, acid-base, 0372
and free energy, 0313
and the Brønsted catalysis equation, 0373
catalysis, base, 0373
and the Marcus equation, 0373
coupling aryl halides and active methylene compounds, 0906
catalysis, general, 0372
catalysis, general acid, 0373, 0525
in supercritical carbon dioxide, 0415
Lewis acid, of sulfonyl halides with halo esters, 0605
mechanisms, 0313
catalysis, metal, of amine alkylation, 0558
of arylation of sulfonamides, 0569
of aziridine ring opening, 0566
of cleavage of ethers, 0581
of coupling with Grignard reagents, 0600
of halogenation of epoxides, 0584
of organometallics coupling, 0604, 0605, 0606, 0607
of vinyl ester formation, 0541
catalysis, micellar, of the Williamson reaction, 0531
of alcohols and diazo compounds, 0533
of enolate anion formation, by amines, 0779
of the Diels-Alder reaction, 1197
phase transfer, see phase transfer
specific, 0372
specific acid, 0373
catalysts, and hydrogenation of alkynes, 1057
catalysts, asymmetric, and synthesis, 0171
catalysts, chiral, see chiral catalysts
catalysts, dendritic, and transfer hydrogenation, 1066
for acylation of amines, 1429, 1435
for alcoholysis of anhydrides, 1413
for alkene metathesis, 1683, 1686
for cyanohydrin formation from trimethylsilyl cyanide, 1390

for dihydroxylation of alkenes, 1162
for enantioselective epoxidation of alkenes, 1176
for Friedel-Crafts acylation, 0719
for Friedel-Crafts addition alkyl halides to alkenes, 1160
for heteroatom Diels-Alder reactions, 1217
for hydrogenation, 1054
for hydrolysis of carboxylic esters, 1400, 1401
for photochemical [2 + 2]-cycloaddition, 1223
for the Dieckmann condensation, 1454
for the Mukaiyama aldol, 1352, 1353
for transesterification, 1419
heterogeneous, and hydrogenation, 1054
heterogeneous, particle sites and surface sites, 1060
homogenous, and hydrogenation, 1054, 1055
hydrogen ion, and the tetrahedral mechanism, 1255
Lindlar, and hydrogenation of alkynes, 1057
metal, and epoxide alcoholysis, 0537
metal, and the Heck reaction, 0891–0897
metal, coupling with silanes, 0588
metal, epoxides and amines, 0563
metal, for cyclotrimerization of alkynes, 1244
metal, for dehydrogenation of alcohols, 1724
metal, formation of cyclic amines, 0560
optically active, 0138
palladium, 0043, 0044
recyclable, for alkene metathesis, 1684
triphase, 0511
Wilkinson's, 0043
catalytic Claisen rearrangement, 1669
catalytic hydrogenation, see hydrogenation
catalytic Wagner-Meerwein rearrangements, 1584
catecholborane, 0816
and conjugate addition, 1123
with alkenes, 1123
with alkynes, 0820, 1081
with chiral additives, in reductions, 1801
catenanes, 0131
and acyloin condensation, 1862
and chirality, 0152
enantiomer separation by HPLC, 0134
structural variations, 0131–0133
synthesis of, 0132
cation-π-interactions, 0114
cationic Diels-Alder reaction, 1197
cationotropic rearrangements, 1559
cations, alternant hydrocarbons, 0069
cavitands, 0122
cavitation noise, and acoustic cavitation, 0350
cavitation, acoustic, and cavitation noise, 0350
and sonochemistry, 0349
and ultrasound, 0512
CD (circular dichroism), chiral molecular in achiral solvents, 0163
cedranediolborane, 0816
cell length, and specific rotation, 0139
center of symmetry, and chirality, 0140
centrohexacyclines, and strain, 0220
ceric ammonium nitrate, and nitration of aromatic compounds, 0686
cerium compounds, and acetal cleavage, 0526
$(CH)_n$ compounds, and Cope rearrangement, 1667
chain reactions, and radicals, 0936
and SET mechanism, 0444
chair confirmation, 0203
chair transition state, Claisen rearrangement, 1669
chair-to-chair interconversion, 0204
channel-type complexes, 0131
Chapman rearrangement, 1697
charge dispersal, elimination versus substitution, 1506
charge distribution, in conjugated carbocations, 0239
charge separation, and resonance, 0047
charge transfer, bonding, 0119
complexes, 0115
complexes, UV, and solvents, 0507
spectra, 0115
Charton's ν values, 0411
chelation, and dialkylamide bases, 0389
cheletropic reactions, cyclic sulfones, 1537
Chemical Abstracts, 1876–1881
Chemical Abstracts, Collective Indexes, 1879
Chemical Abstracts, Registry number, 1880
Chemical Induced Dynamic Electron Polarization, see CIDEP
chemical shift, and conformations, 0196
and electronegativity, 0017
and hydrogen bonding, 0110, 0111
and ring current, 0055–0057
of alkenes, 0056
of annulenes, 0087–0090
of antiaromaticity, 0075
of benzenonium ion, 0662
of carbocations, 0246
of cyclobutadiene, 0075
of homoaromatic compounds, 0093
Chemically Induced Dynamic Nuclear Polarization, see CIDNP
chemoselective reducing agents, for aldehydes rather than ketones, 1793
for ketones rather than aldehydes, 1794
chemoselectivity, definition, 1793
in reduction of alkyl halides, 1827
Chemtracts, 1892
Chichibabin reaction, 0915
chiral additives, and conjugate addition, 1108
and dihydroxylation of alkenes, 1165
and enolate alkylation, 0630
and Michael addition, 1108
and resolution, 0176
and the Claisen reaction, 1356
and the Mukaiyama aldol, 1353

chiral additives, (*Continued*)
metal catalyzed cyclopropanation, 1238
with $LiAlH_4$ or $NaBH_4$, 1802
chiral allylic boranes, acyl addition, 1320
chiral amines, with ketones, 0633
chiral atoms, also see stereogenic
chiral atoms, 0140, 0141
chiral auxiliaries, and asymmetric synthesis, 0169
and Mannich reactions, 1295
and the aldol reaction, 1347
and the Baylis-Hillman reaction, 1325
and the Diels-Alder reaction, 1202
and the Mukaiyama aldol, 1353
definition, 0169
chiral azadienes, 1218
chiral bases, and enolate allylation, 0629
and the aldol reaction, 1347
chiral boranes, 1080
chiral carbanions, 0258
chiral catalysts, 0387
and bis(oxazolines), 1114
and bis(phosphines), 1073
for conjugate addition of carbamates, 1131
for dihydroxylation of alkenes, 1165
for Friedel-Crafts alkylation, 0709
for heteroatom Diels-Alder reactions, 1218
for hydrogenation, 0171
for the Baylis-Hillman reaction, 1325
for the Diels-Alder reaction, 1202
for the Mukaiyama aldol, 1354
for the Prins reaction, 1396
for the the aldol reaction, 1347
thioureas, for the Pictet-Spengler reaction, 0716
trimethylsilyl cyanide, cyanohydrin formation, 1390
chiral compounds, also see chirality
chiral compounds, also see diastereomers
chiral compounds, also see enantiomers
chiral compounds, adamantanes, 0145
allenes, 0148
and axis of symmetry, 0140
and biological activity, 0138
and chemical reactions, 0158
and Cram's rule, 0168
and D/L nomenclature, 0155
and diastereomers, 0164
and diastereotopic atoms, 0193
and diastereotopic faces, 0194
and enantiomeric excess, 0180
and enantiotopic faces, 0194
and epimers, 0165
and erythro/threo nomenclature, 0166
and Fischer projections, 0153
and GC, 0181
and HPLC, 0182
and kinetic resolution, 0176
and molar rotation, 0160
and NMR, 0180, 0181
and optical purity, 0179, 0180
and polarizability, 0141
and prochiral atoms, 0193
and pseudoasymmetric carbons, 0165
and racemates, 0138
and rate of reaction, 0138
and resolution, 0145
and restricted rotation, 0150
and specific rotation, 0160
and stereoselective synthesis, 0167
and symmetry, 0138, 0140
and syn/anti nomenclature, 0166
and synthesis, 0167–0172
and the 2^n rule, 0165
and the Cahn-Ingold-Prelog system, 0155–0158
and the Cornforth model or Felkin-Ahn model, 0169
and torsional diastereomers, 0148
chiral compounds, atropisomers, 0146
biaryls, 0146
chiral pool, 0167
cyclooctatetraene, 0151
cyclooctene, 0150
cyclophanes, 0150
from achiral compounds, 0169
fulgide, 0150
glyceraldehyde, 0154
helical, 0149, 0150
helicene or heptalene, 0149, 0150
Lewis acids, 0387
meso form, 0165
metallocenes, 0150
nitroxide radicals, 0276
paracyclophanes, 0150
with multiple stereogenic atoms, 0164
chiral dienophiles, 1202
chiral hydrazines, with ketones, 0633
chiral ionic liquids, 1324
chiral lanthanide shift reagents, 0181
chiral Lewis acids, 0387, 1202
and Diels-Alder reaction, 1203
chiral ligands, and Sharpless asymmetric dihydroxylation, 1166
and the aldol reaction, 1347
in catalytic hydrogenation, 1056
chiral Lossen rearrangement, 1610
chiral molecules, 0137
and stereogenic atoms, 0140
chiral oxaziridines, α-hydroxylation, 1754
chiral poisoning, in asymmetric catalysis, 1056
chiral pool, and synthesis, 0167
chiral reagents, for reduction of ketones, 1800–1803
chiral recognition, and resolution, 0175
chiral selenium ylids, 1384
chiral solvents, and NMR, 0181
chiral sulfur ylids, 1383
chiral templates, conjugate addition of Grignard reagents, 1114
chiral compounds, spiranes, 0150
chirality transfer, and [2,3]-Wittig rearrangement, 1677
chirality, also see chiral compounds
chirality, also see enantiomers
chirality, and a Möbius strip compound, 0152
and absolute configuration, 0154
and asymmetric induction, 0171

and asymmetric reduction, 0170
and axis of symmetry, 0140
and bridgehead atoms, 0144
and CD in achiral solvents, 0163
and center of symmetry, 0140
and circularly polarized light, 0163
and cyclophanes, 0150
and diastereomers, 0164
and enantiomers, 0137
and enantioselective reactions, 0171
and epimers, 0165
and helical shapes, 0149, 0150
and meso compounds, 0165
and mirror planes, 0140
and molar rotation, 0160
and molecular knots, 0152
and NMR, 0151
and optical activity, 0136
and perpendicular disymmetric planes, 0145
and plane of symmetry, 0140
and plane polarized light, 0163
and polarizability, 0141
and pyramidal inversions, 0142, 0143, 0144
and quadrivalent stereogenic atoms, 0141
and resolution, 0138
and restricted rotation, 0150
and specific rotation, 0160
and superimposability, 0137, 0141
and the 2^n rule, 0165
and the Cahn-Ingold-Prelog system, 0155–0158
and the D/L nomenclature, 0155
chirality, definition of, 0137
helical, 0149, 0150
induced chirality in achiral solvents, 0163
of adamantanes, 0145
of allenes, 0148
of barrelene, 0152
of calixarenes, 0152
of carbanions, 0258
of catenanes, 0152
of crown ethers, 0152
of cumulenes, 0149
of heptahelicene, 0149
of hydrocarbons, 0152
of metallocenes, 0150
of methylenecyclohexanes, 0149
of paracyclophanes, 0150
of pentahelicene, 0149
of phosphates, 0142
of phosphorus, 0191
of rotaxanes, 0152
of spiranes, 0149
of substituted cyclohexanes, 0207
of sulfones, 0142
of tervalent stereogenic atoms, 0142
of truxilic acid, 0140
torsional diastereomers, 0148
chloraluminates, ionic liquids, 1199
chloramine, with organoboranes, 0822
chloramine-M, epoxidation of alkenes, 1173
chloramine-T, and formation of aziridines, 1184
and NBS, 1184
and sodium iodide, 0921
formation of aziridines from alkenes, 1159
formation of chlorohydrins, 1153
with alkenes, 1180
chloramines, and halogenation of aromatic compounds, 0701
from amines, 0849
chloride, vinyl, also see vinyl chloride
chlorides, acyl, also see halides, acyl
chlorides, acyl, from aldehydes, 0964
chlorides, alkyl, also see halides
chlorides, alkyl, and Grignard reagents, 0262
chlorination, allylic, 0963
chlorination, of alcohols, 0469
of alkenes, reagents for, 1150
of aromatic compounds, 0664, 0670, 0671, 0698
of benzene, rate and product distribution, 0680
of malic acid, 0427
of toluene, rate and product distribution, 0680
radical, and dichlorine monoxide, 0963
chlorine radicals, 0935
chlorine trifluoride, and fluorine radicals, 0955
chlorine, halogenation of aromatic compounds, 0701
with alkenes, 1149
with UV light, 1149
chlormalic acid, and asymmetric synthesis, 0172
chloroamines, formation of formamides, 0568
chlorochromate, pyridinium, see PCC
chloroform, and proton transfer, 0368
hydrolysis of, 0521
Reimer-Tiemann reaction, 0726
with amines, 0567
chloroformates, addition to allenes, 1162
benzyl, with amines, 1428
with Grignard reagents, 1445
chloroiminium salts, with Grignard reagents, 1336
chloroketones, and formation of thiiranes, 0532
chloromethylation, and Friedel-Crafts reaction, 0717
chloronium ions, with alkenes, 1004
m-chloroperoxybenzoic acid, see mCPBA
chlorosulfates, from alkenes with chlorine and sulfur trioxide, 1154
chlorosulfenantion, 0974
chlorosulfonyl isocyanates, see isocyanate
chlorosulfuric acid, formation of aryl sulfonyl halides, 0697
chlorothioformates, with amines, 1474
chlorotrimethylsilane with enolate anions, 0798
and the acyloin condensation, 1861
chlorotriphenylmethane, ionization, 0240
chlorotris(triphenylphosphine) rhodium (Wilkinson's catalyst), 1054
cholest-6-en-3-one, 0401
cholesterol, biosynthesis, 1090
cholic acid, and resolution, 0176
as host, 0128
choral hydrate, 1262
choranil (2,3,5,6-tetrachloro-1,4-benzoquinone), 1710
and aromatization, 1710
chromates, structural variation for oxidation of alcohols, 1716, 1717

chromatographic absorbents, and Diels Alder reactions, 1198
chromic acid, and oxidation of alcohols, 1716
chromium complexes, Fischer carbene complexes, 1247
chromium hexacarbonyl, 0043
chromium reagents, and oxidation of aromatic hydrocarbons, 1764
  and oxidative cleavage of alkenes, 1742, 1743
  and oxidative cleavage of cyclic ketones, 1735
  oxidation of alcohols to carboxylic acids, 1768
chromophore absorption, 0333
chromophore, definition, 0331
chromotropic spin traps, 0268
Chugaev reaction, 1520, 1521
CIDEP (Chemically Induced Dynamic Electron Polarization), 0269
CIDNP (Chemically Induced Dynamic Nuclear Polarization)
  and aryl radicals, 0941
  and carbenes, 0807
  and Grignard reagents, 0832
  and hydroformylation of styrene, 1147
  and hydrogen-metal exchange, 0834
  and intermediates, 0312
  and metal/ammonia reductions, 1065
  and organolithium compounds with alkyl halides, 0599
  and radical alkylation of aromatic compounds, 0981
  and radical rearrangements, 1577
  and radicals, 0269, 0270, 0445
  and SET mechanism, 0445
  and the photo-Fries rearrangement, 0737
Cieplack effect, and addition to alkenes, 1024
Cinchona alkaloids, and phase transfer, 1175
  and Sharpless aminohydroxylation, 1180
  with osmium catalysts, 1163
Cinchonidine alkaloids, and enantioselectivity, 1041
cine substitution, and aromatic nucleophilic substitution, 0860
  and Stille coupling, 0793
circuambulatory rearrangement, 0249
circular dichroism, 0160, 0161
  and conformations, 0196
  vibrational, 0161
circular polarization of luminescence, 0182
circularly polarized light, 0138, 0163
  and asymmetric synthesis, 0172
circulenes, 0094
circumambulatory rearrangement, 1652
cis-trans isomers, see isomers
citric acid, 0192
Claisen condensation, 1355, 1452
  and base strength, 1454
  and enolate anions, 0263, 0627, 1453
  and Evans auxiliaries, 1356
  and high pressure, 0513
  and the Robinson annulation, 1357
  crossed, 1452
  enantioselectivity, 1356
  intramolecular, 1453
  mechanisms, 1453, 1454
  metal mediated, 1355
  structural variations, 1355
  with amides, 1355
Claisen rearrangement, 1668–1674
  abnormal, 1673
  acceleration by water, 1670
  and isotope labeling, 1668, 1669
  and microwaves, 1669
  and the Carroll rearrangement, 1670
  and the Diels-Alder reaction, 1669
  and the Kimel-Cope rearrangement, 1670
  azo-, see azo-Claisen
  catalytic, 1669
  enantioselectivity, 1672
  Ireland-Claisen, 1671
  mechanism, 1668
  of allyl allene ethers, 1670
  of allyl enol ethers, 1669
  of ester enolate anions, 1670
  on silica gel, 1670
  para-, 1668
  polymer-bond, 1669
  retro-, 1669
  thio-, see thio-Claisen
  with chiral Lewis acids, 1672
Claisen rearrangement-Conia reaction, 1670
Claisen-Schmidt reaction, 1343, 1344
clathrates, 0126
  and hydroquinone as host, 0127
Clayan, and oxidation of thiols, 1785
cleavage, and formation of radicals, 0938
  anionic, 0835
  by hydration of vinylidene nitriles, 1034
  Eschenmoser-Tanabe, 1544
  Norrish Type I, 0343
  Norrish Type II, 0344
  of acetals, with Lewis acids, 0526, 0527
  of alkoxides, 0758, 0835, 0840
  of ammonium salts, 0542
  of carboxylic esters, 0550
  of cyanohydrins, 0835
  of cyclic ethers, 0581
  of cyclopropane, and vinylcyclopropane rearrangement, 1658
  of diketones with base, 0841
  of dioxetanes, 1219
  of epoxides, see epoxides
  of ethers, 0523, 0547, 0580, 0581, 0582
  of ketones, 0841
  of ketones, haloform reaction, 0842
  of lactones, 0550
  of methyl esters, with NaCN-HMPA, 0649
  of methyl ethers, 0561
  of oxonium salts, 0582
  of radicals, 0280, 0937
  of selenides, 0551
  of thioethers, 0992
  oxidative, see oxidative
  photochemical, and radicals, 0279
  photolytic, 0335
  photolytic, also see photolytic
  reductive, of cyclopropanes, 1074
  thermal, and radicals, 0279
Clemmenson reduction, 1836
clocks, radical clocks, 0946
CO_2, see carbon dioxide
coefficient, extinction, 0330

collidine, LiI with carboxylic esters, 0585
Collins reagent,
Collman's reagent, and carbonylation, 0650, 0651
colloids, and sonochemistry, 0350
combinatorial chemistry, 1434
combustion, heat of, 0029
common-ion effects, and rate of reaction, 0434
Compendium of Organic Synthetic Methods, 1898
Complete Neglect of Differential Overlap, 0035
complex formation, metal, and mechanism of homogenous catalytic hydrogenation, 1061
  with metals, in catalytic hydrogenation, 1059
complex-induced proximity effect, and directed ortho metalation, 0912
complexes, activated, 0302
complexes, alkyne-metal carbonyl, and Pauson-Khand reaction, 1141
  and alkenes, 0119
  π-allylnickel, coupling, 0593
  and carbon tetrahalides, 0119
  and cyclodextrins, 0129
  and Kolbe-Schmidt reaction, 0729
  and metal catalyzed decarbonylation of aldehydes, 0998
  bromine-alkene, 1150
  cage, 0129
  channel-type, 0131
  charge transfer, 0115, 0507
  chiral Lewis acids-dienophiles, 1203
  cyclobutadiene-metal, and cyclotrimerization, 1247
  cyclodextrins and iodoaniline, 0130
  Dibal-amine, 1437
  EDA, and photochemical [2 + 2]-cycloaddition, 1232
  electron donor-acceptor, 0115, 0757
  encounter, 0664
  Grignard reagents, 0260, 0261
  guest-host, 0120
  ion-dipole, and S_N2, 0430
  iron, of cyclobutadienes, 0076
  iron-norbornadienone, 0118
  Lewis acid, and cleavage of ethers, 0581
  Lewis acid-acyl halides, 0722
  Lewis acid-base, 0375, 0376
  metal, and benzene, 0117
  metal, and cyclooctatetraene, 0117
  metal, and cyclotrimerization, 1246
  metal, and ferrocene, 0117
  metal, and hapto complexes, 0116, 0117
  metal, in carbonylation reactions, 0655
  metal, optical resolution, 0151
  metal, with carbenes, 1236
  metal-carbene, and metathesis, 1688
  metal-salen, and epoxidation, 1178
  metals and π-donors, 0116
  monohapto, 0117
η-complexes, 0042, 0043, 0044
complexes, π- and η-, 0042
complexes, π-allyl, acylation of dienes, 0797
complexes, π-allyl, and rearrangement of alkenes, 0770
complexes, π-complex and arenium ions, 0662
  Pauson-Khand, 1143
  platinum, and resolution of alkenes, 0174
  radicals in aromatic solvents, 0953
  rate of formation, 0376
  ring-in-ring, 0132
  titanium-methylene, and Tebbe's reagent, 1382
  transition metal, and [2 + 2]-cycloaddition, 1220
  with biphenyl, 0125
  with crown ethers or cryptates, 0119
  with fluoranthene, 0124
  with picric acid, 0118
  with pyrene, 0124
  with trinitrobenzenes, 0118
Comprehensive Chemical Kinetics, 1894
Comprehensive Organic Chemistry, 1893
Comprehensive Organic Functional Group Transformations, 1894
Comprehensive Organic Synthesis, 1894
Comprehensive Organic Transformations, 1897
concentration, and specific rotation, 0139
  of radicals, 0267
concerted reactions, and S_N2', 0471
concertedness, and cycloaddition reactions, 1212
condensation, aldol, see aldol
condensation, Claisen, see Claisen
condensation, Dieckmann, see Dieckmann
condensation, acyloin ester, 1860
  benzoin, 1396
  bis(aldol), 1345
  Pechmann, 0712
  self condensation, and Claisen condensation, 1453
  self condensdation, and the aldol reaction, 1343
conducted tour mechanism, 0761, 0768
conducting polymers, 0415
conductivity, and arenium ions, 0663
configuration, absolute, see absolute configuration
configuration, and Grignard reagents, 0262
  definition, 0195
  electron, see electron configuration
  racemization of migrating group during rearrangement, 1564
  retention of migrating group during rearrangement, 1563
  retention, and carbanions, 0257
conformational analysis, 0195–0213
conformational energy, and cyclohexane, 0203
conformational isomer, and conformer, 0196
conformational radical clock, 1098
conformational transmission, 0401
conformations, % axial in substituted cyclohexanes, 0208
  aa/ee/ae nomenclature, 0205

conformations, and acidity, 0387, 0388
and atropisomers, 0203
and bisecting bonds, 0201
and dipole moment, 0199
and eclipsing bonds, 0201
and homoanomeric interactions, 0209
and molecular mechanics, 0196
and Newman projections, 0197
and NMR, of macrocycles, 0213
and optical activity, 0196
and Pitzer strain, 0223, 0224
and pK, 0387, 0388
and polar groups, 0209
and polarizability, 0199
and pseudorotation, 0212
and reactivity, 0400
and solvent effects, 0201
and spectroscopic analysis, 0196
and steric hindrance, 0202
and strain, 0400
and syn or anti elimination, 1484
and tetrahedral mechanisms, 1258
and the 3^n rule, 0197
and the anomeric effect, 0210
and the E2 reaction, 1479
and transannular strain, 0223, 0224
and X-ray crystallography, 0201
conformations, anomeric effect, 0210, 0211
anti, 0199
anti-periplanar, and E2 reagents, 1479
axial preference for polar groups, 0209
boat and chair, 0203
chair cyclohexanes, and E2 reactions, 1481
chair, and bulky substituents, 0207
chair, and carbocations, 0245
chair, and gauche conformations, 0205
chair, axial and equatorial, 0204
chair, chair-to-chair energy barrier, 0208
chair, half-life, 0204
chair, observation of, 0204
chair-to-chair interconversion, 0204
cisoid, and Diels-Alder reaction, 1201
definition, 0195
envelope, 0212
estimation of numbers, 0197
gauche, 0199–0201
isolation of conformers, 0201
medium-size rings, 0223
conformations, of acyclic compounds, 0197
of amides, 0202
of butane, 0199, 0200
of caprolactams, 0212
of cyclic alkanes, 0211–0213
of cyclic ketones, 0208, 0212
of dienes, and Diels Alder reaction, 1201
of dioxanes, 0209
of dithianes, 0209
of glycosides, and the anomeric effect, 0210
of heteroatom substituted rings, 0209
of lactones, 0213
of macrocyclic ketones, 0213
of Meldrum's acid, 0388
of oxacyclooctane, 0213
of oxetane, 0212
of six-membered rings, 0203
of substituted cyclohexanes, 0204, 0205
of sulfoxides, 0212
of tetrahydrofurans, 0212
conformations, s-E/s-Z diazoketones, 1601
stability of, 0201
stability of aziridines, 0142, 0144
stability, and optical activity, 0142, 0144
staggered, 0199
syn-periplanar, and E2 reactions, 1479
synclinal, 0199
tub, cyclooctatetraene, 0151
twist, 0080, 0081, 0203, 0204
conformers, 0195
isolation of, 0201
Conia reaction-Claisen rearrangement, 1670
conjugate acid, definition, 0356
conjugate addition, 1105–1110
1,2- versus 1,4-, organocuprates, 1113
aldehydes with cyanide, 1133
amines to conjugated thiolactams, 1130
and anhydrides, 1132
and enamines, 0636
and ionic liquids, 1107
and Mannich bases, 1109
and phosphonate esters, 1132
and SET mechanism, 1120
and the Sakurai reaction, 1120
and thioesters, 1132
azides, 1131
chiral imines, 1109
conjugated substrates, 1106
definition, 1008
enantioselectivity, 1106, 1109
formation of enolate anions, 1113
Grignard reagents, 1112
heteroatom nucleophiles, 1130
intramolecular, 1109
metal catalyzed, 1107, 1108, 1130
metal catalyzed addition of silyl enol ethers, 1110
conjugate addition, of alcohols, 1131
of aldehydes, and microwaves, 1132
of alkynyl alanes, 1118
of allylic silanes, 1120
of amides, 1132
of amines, 1130, 1132
of boranes, 1121
of borate esters or boronic acids, 1116
of carbamates, metal catalyzed, 1130
of enolate anions, 1108
of Grignard reagents, 1114
of HCN, 1147
of hydroxylamines, 1131
of imides, 1131
of imines, 1130
of lactams, 1131
of organometallics, and radicals, 1119
of radicals, 1122
of silanes, 1131
of silyl ketene acetals, 1121
conjugate addition, organocuprates, 1111
organolithium reagents, 1112, 1133
organometallics, 1111–1120
organometallics, mechanism, 1119
organozinc reagents, 1116
selenols and organolithium reagents, 1131
thiophenols and organolithium reagents, 1131

trialkylalanes, 1118
vinylboranes, 1122
vinylogous, 1107
with boron compounds, 1116
conjugate base, definition, 0356
conjugate bases, see bases
conjugate elimination, 1512
conjugate reduction, reagents for, 1071
conjugate systems, and delocalization, 0040
conjugated carbonyls, and hydride reduction, reagents, 1793
conjugated carboxylic acids, see carboxylic acids
conjugated compounds with sulfur ylids, 1386
acylation, 1132
addition of hydroperoxide anions, 1707
and Grignard reagents or organolithium reagents, 1302
and photochemical [2 + 2]-cycloaddition, 1229
and Stork enamine reaction, 0635
and the Baylis-Hillman reaction, 1323
by dehydrogenation, 1712
by the Knoevenagel reaction, 1358
halogenation, 1151
radical addition, 1015
with acyl halides, 1132
with aldehydes, 1323
conjugated diketones, by α-oxidation of alkenes, 1759
conjugated ketones, see ketones
conjugated systems, alternant and nonalternant hydrocarbons, 0069
conjugated-circuit model, and aromaticity, 0057
conjugation, and absorption, 0332, 0333
and bathochromic shift, 0333
and carbanions, 0252
and carbocations, 0239
and delocalization, 0038
and enol content, 0100
and homoconjugation, 0045
and keto-enol tautomerism, 0100
and rearrangement of double bonds, 0767
and S_N1 reactions, 0436
and wavelength of light, 0332, 0333
cross, 0044
cross, also see cross conjugation
cyclobutanes and carbocations, 0242
cyclopropanes and carbocations, 0242
energy, 0040
heteroatoms with carbocations, 0242
p orbitals with double or triple bonds, 0040
conrotatory process, a Möbius system, 1638
conrotatory, and 4n versus 4n + 2, 1643
and electrocyclic rearrangements, 1633, 1634
constant, equilibrium, see equilibrium
constant, Planck's, 0003
constant, rate, see rate
contact ion pair, 0437
cooperative hydrogen bonding, 0110
coordinate, reaction, 0302
Cope elimination, 1524, 1525
Cope reaction, 1524
Cope rearrangement, 1659–1667
$(CH)_n$ compounds, 1667
amino, see amino-Cope
and Bergmann cyclization, 1664
and diradical intermediates, 1663
and high pressure, 0513
and valence tautomerism, 1665
aza-, see aza-Cope
degenerate, 1664
diradical mechanism, 1664
mechanism, 1662
metal catalyzed, 1662
nonconcerted, 1664
oxonia, see oxonia-Cope
six-center mechanism, 1663
stereochemistry, 1663
transition state, 1663
Cope, oxy-, see oxy-Cope
copper compounds, and Stryker's reagent, 1351
with organolithium reagents, 0601
copper cyanide, and Rosenmund-von Braun reaction, 0885
with aryl diazonium salts, 0985
copper halides, and the Hurtley reaction, 0907
coupling active methylene compounds with aryl halides, 0907
copper salts, and alkyne coupling, 0978
and the Glaser reaction, 0978
halosulfonation of aryldiazonium salts, 0986
nitration of aryldiazonium salts, 0985
copper, alkyl-magnesium bromide Normant reagent), 1101, 1102
copper, and coupling of aryl halides, 0897
and coupling of aryldiazonium salts, 0926
and hydroxylation of aryldiazonium salts, 0919
and the Gatterman reaction, 0984
and the Ullmann reaction, 0897
copper-free Sonogashira coupling, 0905
corannulene, 0094, 0095
Corey-Seebach procedure, hydrolysis of dithioketals, 1280
Corey-Winter reaction, 1535
corner-protonated cyclopropane, 1026
Cornforth model, and and diastereoselectivity, 0169
Corporate Index, 1907
coulombic interactions, and molecular mechanics, 0213, 0214
coumarins, Friedel-Crafts alkylation, 0712
Pechmann condensation, 0712
counterattack reagent, 0587
counterions, and ambident nucleophiles, 0517
and nucleophiles, 0516
of carbocations, 0236
coupling reactions, 0976
coupling reactions, cross-coupling, 0587
coupling, and SET mechanisms, 0613
cross, radical coupling of alkanes, 0976
metal catalyzed, alkylboronic acids, 0607
with arylboronic acids, 0607
with silanes, 0588
with vinylboranes, 0607

coupling, metal mediated, alkyl halides, 0597
conjugated ketones, 0592
vinyl halides, 0591
with allylic esters, 0609
coupling, of alcohols, 0615
of alkanes, 0802
of alkyl halides, 0589
of aryl halides and boronic acids, see Suzuki-Miyaura
of aryl halides, and the Ullmann reaction, 0897
of aryldiazonium salts with active methylene compounds, 0783
of carbenes, 0290
of diazonium salts, 0692
of Grignard reagents, 0987
of organolithium reagents with sulfones, 0613
of organometallics (Group I and II) with alkyl halides, 0594, 0595
of organometallics with alcohols, 0614, 0615
of organometallics with alkyl halides, 0604, 0605, 0606, 0607
of π-allylnickel complexes, 0593
of photosensitized alkenes, 0977
of radicals, 0280, 0938
of silanes, 0977
of silanes with alkyl halides, 0588
coupling, organometallic, in ionic liquids, 0606
organometallic, metal catalyzed, 0606
oxidative, see oxidative coupling
palladium catalyzed, with organometallics, 0606
radical, and the Kolbe reaction, 0993
radical, of amides, 0976
reductive, of alkenes, 1095
reductive, of alkynes, 1092
Sonogashira, 0904
Stephens-Castro, 0903–0906
Stille reaction, 0606, 0792
Suzuki-Miyaura, 0815, 0899–0903
unsymmetrical, metal mediated, 0593
with alkylboronic acids, 0604
with allylic esters, 0608
with polymer-supported phosphine ligands, 0612
with trifluoroborates, 0607, 0608
Wurtz reaction, 0589
covalent bonds, and soft acids and bases, 0378
covalent compounds, and electronic structure, 0015
Cram's rule, and diastereoselectivity, 0168
and reactions at carbonyls, 1252
and reduction of ketones, 1804
CRC Handbook of Data on Organic Compounds, 1888
cresol, dipole moment, 0019
Criegee mechanism, and ion pairs, 1738, 1739
ozonolysis, 1738–1740
critical temperature, and carbon dioxide, 0414
cross conjugation, 0044
and trienes, 0045
cross-coupling reactions, 0587
cross-coupling, see coupling
cross-dimerization, of alkenes, 0977
cross-metathesis, 1684
crossed-pinacol coupling, 1856
crossed-Cannizzaro reaction, 1864
CrossFire, Beilstein, 1883
crossover experiments, and Fries rearrangement, 0736
and rearrangement, 1560
and S_N2, 0430
and the benzidine rearrangement, 1679
crowding, intramolecular, 0232
crown ethers, also see ethers
crown ethers, and acylation of amines, 1430
and aryldiazonium salts, 0917
and decyanation, 0845
and elimination reactions, 1486
and ion pairing in elimination reactions, 1486
and kinetic resolution, 0176
and metal catalyzed coupling of alkynes with aryl halides, 0906
Gabriel synthesis, 0569
with metals, 0845
with permanganate, oxidative cleavage of alkenes, 1743
cryptands, 0122, 0123
and organolithium reagents, with aldehydes and ketones, 1308
and phase transfer catalysis, 0510
and resolution, 0176
and solvation, 0493
cryptaphanes, 0123
cryptates, 0122
and complex formation, 0119
and out-in isomers, 0190
crystallization, fractional, and resolution, 0172, 0174
crystallographic scale, acidity, 0358
crystals, and mechanical resolution, 0176
cubane, and strain, 0220
cubene, 0233
cubyl compounds, and S_N1 reactions, 0436
cucubituril gyroscane, 0135
cucurbiturils, 0135
cumene, and radical reactions, 0599
cumulenes, and optical activity, 0149
cyclic, 0228
cuprates, see organocuprates
cuprous cyanide, with organometallics, 0825
Current Contents, 1877, 1892
Curtius reaction, 0572
Curtius rearrangement, 1563, 1609
cyanamides, addition of ammonia, 1296
and the Ritter reaction, 1459
decarboxylation, 0559
formation of amines, 0559
from tertiary amines, 0586
hydrolysis, 1269
cyanates, aryl, from phenols and cyanogen halides, 0531
from alkyl halides and isocyanate, 0514
phenyl, with organolithium reagents, 0886
cyanation, aryl halides, 0885
metal catalyzed, 0801
metal sulfonate esters, 0886
nitro compounds, 0802
of alkanes, 0801
of carbonyl compounds, 0801
cyanide ion, ambident nucleophile, 0648
and isonitriles, 0648

and the Strecker synthesis, 1391
as an ambident nucleophile, 0515
copper, and acyl halides, 1457
metal, with alkyl halides, 0648
potassium, and the benzoin condensation, 1396
with aldehydes, and conjugate addition, 1133
with alkyl halides, 0515, 0648
with aryl nitro compounds, 0927
with vinyl triflates, 0649
zinc, see zinc
cyanides, also see nitriles
cyanides, acyl formation of, mechanism, 1457
acyl, from acyl halides and copper cyanide, 1457
by dehydration of ureas, 1550
metal, also see metal cyanides
metal, and Rosenmund-von Braun reaction, 0885
metal, with aryl halides, 0885
tosyl, 0648
tosyl, with enolate anions, 0801
trimethylsilyl, see trimethylsilyl cyanide
trimethylsilyl, and formation of cyanohydrins, 1389, 1390
trimethylsilyl, with alkenes and silver salts, 1148
trimethylsilyl, with alkyl halides, 0649
vinyl, from vinyl halides, 0648
vinyl, from vinyl triflates, 0649
cyano group, reduction to methyl, with terpenes, 1824
cyano imines, by Ehrlich-Sachs reaction, 1368
cyano-ketones., displacement of cyano, 0614
cyanoacetic ester synthesis, 0624
cyanoamines, formation, enantioselectivity, 1392
from addition of HCN to C=N compounds, 1392
from aldehydes or ketones, 0561
from amines, 0802
from hydroxy-ketones, 0561
cyanoboranes, with anhydrides, 1628
cyanoborohydride, sodium, see sodium
cyanoethylation, 1008
cyanogen bromide, and isotopic labeling, 0314
with amines, 0586
with carboxylate salts, 1461, 1462
cyanogen chloride, with alcohols, 1276
cyanohydrin formation, enantioselectivity, 1390
cyanohydrin-O-carbonates, 1391
cyanohydrins, and the benzoin condensation, 1389
and the Kiliani-Fischer method, 1391
and Umpolung, 0634
cleavage, 0835
formation in ionic liquids, 1389, 1390
formation of amines, 0561
from bisulfite addition products, 1391
from HCN with carbonyls, 1389
from lyases, 1389
from metal cyanohydrins, 1389
from trimethylsilyl cyanide, 1389, 1390
hydrolysis, 1268
with alkyl halides, 0649
cyanomethylamines, 0801
cyanuric acid, with amides and alcohols, 1421
cyanuric fluoride, with carboxylic acids, 1440
cyclazines, and antiaromaticity, 0089
cyclic amines, from halo-amines, 0557
cyclic compounds, and cis/trans isomers, 0186, 0187
and I strain, 0399
cyclic cumulenes, 0228
cyclic mechanism, addition to alkenes, 1012
reduction of hydrazones, 1838
cyclization, addition of alkenes to alkenes, 1089
aldehydes or ketones with amines, 1282
alkynes to alkenes, 1089
allenes and allylic halides, 1095
amidation of alkenes, 1051
amines with aryl halides, 0876
aminyl-radical, 0559
an metal catalyzed coupling of Grignard reagents, 0987
and active methylene compounds, 0625
and amination of alkenes, 1048
and Dieckmann condensation, 1453
and neighboring group effects, 0449
and Stork enamine reaction, 0636
and the Pauson-Khand reaction, 1141
and the Thorpe reaction, 1387
and the Wittig reaction, 1378
and the Wurtz reaction, 0590
arylation of amines, 0876
Bergmann, 1641
Bradsher reaction, 0715
by acyloin condensation, 1860
Friedel-Crafts acylation, 0721
Friedel-Crafts alkylation, 0710
Grignard reactions, 1304
halogenation of homoallylic alcohols, 1154
intramolecular aldol reaction, 1349
Johnson polyene, 1090
metal catalyzed coupling allenes to alkenes, 1094
Nazarov, 1095
nitrene insertion, 0790
of dialdehydes, 1856
of diols, 1856
of diynes, metal catalyzed, 1093
of radicals, 0445
of triflamide alkenes, 1052
organolithium reagents with alkenes, 1098
Pschorr ring closure, 0925
Ruzicka, 1458
cyclization, radicals, see radical cyclization

[1 + 2]-cycloaddition, and carbenes, 1234
[1,2]-cycloaddition, and the Diels-Alder reaction, 1204
[2 + 2 + 1]-cycloaddition, 1250
[2 + 2 + 2]-cycloaddition, 1250
[2 + 2]-cycloaddition, 1220–1233
alkenes and ketenes, MO calculations, 1226
alkenes with aldehydes or ketones, 1463
allenes with alkenes or alkynes, 1222
and Dewar benzene, 1233
and Diels-Alder reactions, 1222
and diradicals, 1224
and frontier orbital method, 1208, 1209
and photosensitizers, 1231
and transition states, 1211, 1212
and UV, 1229
and valence isomers, 1233
cycloreversion, 1228
diion mechanism, 1228
diradical mechanism, 1227
electronic effects, 1228
endo/exo selectivity, 1226
formation of β-lactams, 1221
imines and ketenes, 1464
ketenes with aldehydes or ketones, 1462
ketenes, with alkenes or alkynes, 1222
masochistic steric effects, 1227
mechanism, 1224
metal catalyzed, 1220
orbital overlap, 1225
Paterno-Büchi reaction, 1231
photochemical, 1223, 1229–12321463
solventless, 1223
stereochemistry, 1226
steric effects, 1226
substrates for, 1221
thermal, 1224
with alkenes, 1221
with alkynes, 1221, 1229
with allenes, 1221, 1222
with benzynes, 1221
with bicyclic compounds[2 + 2]-cycloaddition, 1224
with biphenylenes, 1221
with cyclopropanes, 1224
with enamines, 1222
with imines, 1221
with ketenes, 1221
with strained compounds, 1224
ylids with carbonyls compounds, 1376
[2 + 6]-cycloaddition, 1212
[2 + 8]-cycloaddition, 1212
[3 + 2]-cycloaddition, 1188–1192
all carbon, 1193
and allylic carbanions, 1193
and Diels-Alder reactions, 1190
and FMO, 1190
antibody catalyzed, 1191
enantioselectivity, 1192
intramolecular, 1191
metal catalyzed, 1191
with dienes, 1192
with nitrile oxides, 1190
[3 + 4]-cycloaddition, 1248
with dienes, 1192
[4 + 2 + 2]-cycloaddition, 1250
[4 + 2]-cycloaddition, 1194–1215
[4 + 2]-cycloaddition, see Diels-Alder
[4 + 2]-cycloaddition, and frontier orbital method, 1208, 1209
Hückel-Möbius allowed, 1211
photochemical, 1214
transition states, 1211, 1212
[4 + 3]-cycloaddition, 1248
with chiral carbocations, 1249
[4 + 4 + 4]-cycloaddition, 1248, 1249
[4 + 4]-cycloaddition, 1212, 1249
[4 + 6]-cycloaddition, 1212
[6 + 4]-cycloaddition, 1250
cycloaddition reactions, and microwaves, 0355
cycloaddition reactions, of enamines, 1222
cycloaddition, 1,3-anionic, 1193
and Hückel's rule, 1210
and Möbius strip, 1211
and the Thorpe-Ziegler reaction, 1388
Diels-Alder, 1194–1215
metal catalyzed, 1248
Möbius-Hückel METHOD, 1210
of alkenes to alkenes, 1220–1233
other, 1248
photochemical, 1218
cycloaddition, [2 + 2], see [2 + 2]-cycloaddition
cycloaddition, [4 + 2], see [4 + 2]-cycloaddition
cycloalkanes, and strain, 0224
heat of combustion, table, 0225
cycloalkenes, and strain, 0227
by the Wittig reaction, 1378
cycloalkynes, and platinum complexes, 0228
and strain, 0227
cycloamyloses, see cyclodextrins
cyclobutadiene derivatives, and the captodative effect, 0075
cyclobutadiene, and aromaticity, 0071, 0073
and carcerands, 0074
and low-temperature matrix, 0074
and NMR, 0075
antiaromaticity, 0038
Diels-Alder reaction, 0074
iron complex, 0076
MO calculations, 0074
PES, 0074
stable derivatives, 0075
synthesis of, 0074
cyclobutadiene-metal complex, and cyclotrimerization, 1247
cyclobutadienes, and antiaromaticity, 0073
and strain, 0076
and X-ray, 0075
cyclobutane, and bromine, 0219
and pyrolysis, 0219
and strain, 0219
conformations, 0211
conjugation with carbocations, 0242
cyclobutanes, and strain, 0218
thermal cycloreversion, 1228
cyclobutanones, by [2 + 2]-cycloaddition, 1221, 1223
extrusion of carbon monoxide, 1555
from organometallics, 0911
photolysis, 1555
cyclobutene, conrotatory ring opening, and HOMO symmetry, 1636
from cyclopropylcarbenes, 0291
cyclobutene-diene interconversion, orbital requirements, 1637, 1639

cyclobutenes, by extrusion of sulfur dioxide, 1556
by [2 + 2]-cycloaddition of alkenes and alkynes, 1229
orbitals, and thermal ring opening, 1636
thermal ring opening to dienes, 1632
cyclobutyl compounds, and solvolysis, 0464
cyclobutyl groups, and nonclassical carbocations, 0464
as neighboring groups, 0455
cyclobutyl, and rate enhancement, 0465
from cyclopropylmethyl, 0465
cyclobutylamines, [2 + 2]-cycloaddition, 1223
cyclobutylcarbinyl radical, see radicals
cyclodecane, conformations, 0213
cyclodecapentaene, and aromaticity, 0071
cyclodehydration, 0715
cyclodextrins, 0129
and cage complexes, 0129
and channel-type complexes, 0131
and complex formation, 0129
and epoxide hydrolysis, 0528
and formation of amino-alcohols, 0563
and resolution, 0176
and water solubility, 0129
capped, 0131
catalysis of Diels-Alder reaction, 1198
chlorination of aromatic compounds, 0671
complex with iodoaniline, 0130
shape and dimensions, 0130
cyclodiastereomerism, 0134
cycloenantiomerism, 0134
cycloheptadiene, 0228
cycloheptadienes, by rearrangement of divinylcyclopropanes, 1661
cycloheptane, conformations, 0213
cycloheptatriene, and aromaticity, 0064
from carbene addition to benzene, 1239
cycloheptatrienes-norcaradiene, valence tautomerism, 1667
cycloheptatrienyl (substituted) cations, 0065
cycloheptatrienyl anion, and aromaticity, 0078
antiaromaticity, 0079
cycloheptatrienyl cation, see tropylium ion
cycloheptatrienyl derivatives, and NMR, 0078
cyclohexadiene, from benzene, 1067
cyclohexadiene-triene interconversion, orbital requirements, 1638, 1639
cyclohexadienes, by Diels-Alder reaction, 1195
from Grignard addition to aromatic compounds, 1119
cyclohexadienone, and tautomerism, 0102
cyclohexadienones, rearrangement, 1594
cyclohexane, conformations, 0203
methylene, and chirality, 0149
substituted, conformations, 0204, 0205
cyclohexanones, hydrogenation of phenols, 1066
cyclohexenes, by rearrangement of vinylcyclobutanes, 1658
trans, 1640
cyclononyne, and strain, 0227
cyclooctadiene, 0228
preparation of 9-BBN, 1077
cyclooctatetraene dications, 0067
cyclooctatetraene, and aromaticity, 0071
and aromaticity, 0078
and chirality, 0151
and metal complexes, 0117
conformation and bond angles, 0078
cyclotrimerization of alkynes, 1243
dehydrohalogenation, 0078
cyclooctatrienes, by cyclization of octatetraenes, 1642
cyclooctene, and chirality, 0150
and cis/trans isomers, 0184
photoisomerization, 0346
trans double bond, 0226
trans, resolution of, 0174
trans, strain energy, 0229
cyclooctyne, and strain, 0227
cyclopentadiene, and annellation, 0063
cyclopentadiene, and metallocenes, 0066, 0067
pK_a, 0063
with ketene, orbital overlap in [2 + 2]-cycloaddition, 1227
cyclopentadienes, and circumambulatory rearrangement, 1652
cyclopentadienide ion, 0062–0064
cyclopentadienone, 0065
cyclopentadienyl cation, and aromaticity, 0076, 0077
cyclopentane, conformations, 0212
energy barrier to planarity, 0212
cyclopentanes, by [3 + 2]-cycloadditions, 1193
cyclopentanone, conformation, 0212
cyclopentenes, by rearrangement of vinylcyclopropanes, 1656
cyclopentenone, photodimerization, 0348
by Nazarov cyclization, 1095
cyclopentyne, and strain, 0228
cyclophanes, also see paracyclophanes
cyclophanes, 0050
and anisotropy, 0056
and chirality, 0150
and pseudorotation, 0050
and ring current, 0056
cyclopropabenzene, 0052
cyclopropanation, alternative methods, 1242
and chiral rhodium catalysts, 1238
by metal catalyzed diazoalkane reactions, 1234
metal catalyzed, chiral additives, 1238
cyclopropane, and bent bonds, 0219
and bond angles, 0218
and bromine, 0217
and electron density, 0218
and MO calculations, 0218
and stabilization of carbocations, 0451
and UV, 0219

cyclopropane, and bent bonds, (*Continued*)
conjugation with carbocations, 0242
corner-protonated, 1026
isomerization and carbenes, 0291
orbitals, 0219
pyrolysis, 0217
radicals, 0277
ring opening, mechanism, 1591
strain, 0217
to propene, and entropy, 0304
with amines, 0567
cyclopropanes, 0077
addition of halogens, and UV, 1027
addition of metal carbenes to alkenes, 1236
addition reactions, 1025, 1026, 1027
and diiodomethane, 1241
and sigmatropic shifts, 1653
and the S_E2 mechanism, 1027
by carbene transfer, 1234
by extrusion of nitrogen from pyrazoles or pyrazolines, 1553
by the Simmons-Smith procedure, 1241
by thermolysis of pyrazolines, 1191
by [1 + 2]-cycloaddition, 1234
by [2 + 2]-cycloaddition, 1224
carbene addition to alkenes, 1233
cleavage, with metals in ammonia, 1075
divinyl, rearrangement, 1661
from carbenoids, 1241
from diols, 0615
from organozinc compounds, 1241
from sulfur ylids, 1383, 1386
hydrogenation, formation of gem-dimethyl groups, 1075
photolysis, and carbenes, 0287
protonated, 1026
protonated, and rearrangements, 1565
protonation, *ab initio* studies, 1027
reductive cleavage, 1074
stabilization of carbanions, 0253
vinyl, see vinylcyclopropanes
vinyl, from dienes, 1692
with HBr, 1025
with lead tetraacetate, 1025
cyclopropanones, by photolysis of cyclobutanones, 1555
cycloproparenes, 0052
cyclopropene, and strain, 0226
and the ene reaction, 1104
cyclopropenes, 0077
and hydrogen exchange, 0077
by carbene addition to alkynes, 1238
catalytic hydrogenation, 1075
rearrangement to allenes, 1238
with chlorosulfonyl isocyanate, 1466
cyclopropenium diazonium salts, 0500
cyclopropenone, 0073
cyclopropenones, 1238
cyclopropenyl anion, and aromaticity, 0076
cyclopropenyl cation, and aromaticity, 0072
cyclopropyl anion, conrotatory ring opening, 1644
cyclopropyl carbocations, and ring opening, 1644
cyclopropyl cation, disrotatory ring opening, 1644
cyclopropyl groups, and carbocations, 0241
and solvolysis, 0486
cyclopropyl, and anchimeric assistance, 0455
as a neighboring group, 0454
cyclopropylcarbinyl alcohols, see alcohols
cyclopropylcarbinyl carbocations, 0450
cyclopropylcarbinyl radicals, also see radicals
cyclopropylcarbinyl radicals, as radical clocks, 0281
cyclopropylmethyl carbocations, 0241
cyclopropylmethyl groups, and carbocations, 0464, 0465
and nonclassical carbocations, 0464, 0465
cyclopropylmethyl, and rate enhancement, 0465
and rearrangement, 0465
and σ-bond participation, 0464, 0465
and solvolysis, 0464, 0465
formation of cyclobutyl, 0465
cycloreversion, thermal, of cyclobutanes, 1228
cyclotrimerization of triynes, 1245
and cyclobutadiene-metal complexes, 1247
and Diels-Alder reactions, 1246
and diynes, 1247
and Dötz benzannulation, 1247
and Fischer carbene complexes, 1247
and metal complexes, 1246
and metal extrusion, 1246
intramolecular, 1244
metal catalyzed, mechanism, 1246
of alkynes, 1243
of diynes, 1244
of trienes, 1244
reactive functional groups, 1245
regioselectivity, 1245
structural variations, 1245
with metal carbenes, formation of heterocycles, 1247
cysteine-cystine interconversion, 1785
cystine-cysteine interconversion, 1785

d orbitals, see orbitals
DABCO, and Michael addition, 1107
and solventless acylation of amines, 1427
and the Baylis-Hillman reaction, 1324
daisy chains, 0131
Dakin reaction, 1746, 1747
Dakin-West reaction, 0841
dammaradienol, 1090
Danishefsky's diene, 1216, 1217
Darzens condensation, 1364, 1365
and Knoevenagel reaction, 1364
Darzens, glycidic ester synthesis, see Darzens condensation
DAST (diethylaminosulfur trifluoride), 1299

fluorination of sulfoxides, 0782
with acyl halides, 1441
databases, *CAS*, 1902
DBN (1, 5-diazabicyclo[3.4.0] nonene-5), 1530, 1531
and elimination of alkyl halides, alkenes, dehydrohalogenation, 1530
DBr, addition to alkenes, 1006
DBU (1, 8-diazabicyclo[5.4.0] undec-7-ene), 1132, 1530, 1531
and amide formation, 0730
and elimination of alkyl halides, alkenes, dehydrohalogenation, 1530
and hydrocarboxylation, 1138
and malonic esters synthesis, 0623
and NBS, with carbamates, 1608
and thioethers, 0550
urea-hydrogen peroxide, 1176
DCC (dicyclohexylcarbodi imide), and DMSO, 0731, 1721
and esterification, 1417
and Moffatt oxidation, 1721
with carboxylic acids and amines, 1431
DCl, with pentadiene, 1014
DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), 1710
and acetal cleavage, 0526, 0527
and addition of carboxylic acids to alkenes, 1041
and alkyl azide formation of, 0572
and aromatization, 1710
and cleavage of ethers, 0581
and nitriles, 0649
dehydrogenation, 1713
deactivating groups, aromatic substitution, 0669, 0673
in aromatic compounds, 0665
nitro, 0688
deactivation, in photochemistry, 0341
DEAD (diethyl azodicarboxylate), Mitsunobu, 0535
and aromatic compounds, 0695
and carboxylate salt alkylation, 0540
dealkylation, of amides, reagents, 1852
reduction of ethers, reagents, 1831
sulfonamides, 1852
with ethanolamine, 0562
Debyes, and dipole moment, 0019
decalin, cis/trans isomers, 0188
decarbonylation, and metal mediated coupling, 0592
metal catalyzed, of acyl halides to alkenes, 1534
of acyl halides, 0997
of aldehydes, 0344, 0997, 0998
of aromatic acyl halides, 0749
of aryl aldehydes, 0745
decarboxylation, allylic acetates with keto-acids, 0996
and Bredt's rule, 0838
and carbanion formation, 0265
and the arenium ion mechanism, 0746
and the Hunsdiecker reaction, 0994
and the S_E1 mechanism, 0746
Dakin-west reaction, 0841
metal mediated, 0745
decarboxylation, of anhydrides, 0840
of aryl carboxylic acids, 0745
of β-lactones, 1556
of carboxylate ions, 0837
of carboxylate salts, with cyanogen bromide, 1461
of carboxylic acids, 0835
of carboxylic acids, photolytic, 0983
of conjugated carboxylic acids, 0838
of cyanamides, 0559
of glycidic acids, 0837
of keto esters, 0839
of keto-acids, 0837, 0838
of radicals, 0975, 0982
of silver carboxylates, 0994
oxidative, metal mediated, 1747
oxidative, of carboxylic acids to alkenes, 1747, 1748
six-center mechanism, 0837
special reagents, 0839
structural limitations, 0836
decomposition, of peroxides, 0935
of radicals, 0280
decyanation, and crown ethers, 0845
of nitriles, 0845
with sodium borohydride, 0846
dediazoniation, of aryldiazonium salts, reagents, 1847
suppression by calixarenes, 1848
degenerate carbocations, 1563
degenerate Cope rearrangement, 1664
degenerate rearrangements, 1563
dehalogenation, 0749, 0750
of acyl halides to ketenes, metal induced, 1540
dehydrating agents, and Amberlyst-15, 1418
and carbonyldiimidazole, 1418
and chlorosilanes, 1418
and phosphorous pentoxide, 1423
DCC, 1417, 1418, 1431
for dehydration of alcohols, 1513
from amides to isonitriles, 1550
from amides to nitriles, 1549
from carboxylic acids, 1514
to amides from carboxylic acids, 1431
dehydration, formation of alkenes from alcohols, 0771
of alcohols, 0534, 1513–1515
of alkyne-alcohols, 1515
of amides, 1515
of carboxylic acids, 1514
of oximes, of nitriles and microwaves, 1547
dehydrobenzenes, see benzynes
dehydrogenation, base-induced, 1714
catalytic, and oxidation of alcohols, 1724
metal catalysts, 1712
of aldehydes or ketones, 1713
of amines, 1711, 1729, 1730
of lactones, 1713
remote, 1713, 1714
with DDQ, 1713
dehydrohalogenation, of alkyl halides, mechanism, 1531

dehydroxylation, of phenols, 1830
Delépine reaction, 0558
delocalization, and butadiene, 0040
and carbocation structure, 0239
and conjugated systems, 0040
and hyperconjugation, 0044, 0095
and nonclassical carbocations, 0450
and vinyl chloride, 0041
delocalized bonds, 0038
Demyanov rearrangement, 1589
dendritic catalysts, and the Pauson-Khand reaction, 1142
and transfer hydrogenation, 1066
density functional theory, and Simmons-Smith procedure, 1241
deoxycholic acid, as host, 0128
deoxygenation, of aldehydes or ketones, 1835
of aryl ethers, 0748
Deoxyribonucleic acids, see DNA
deprotonation, by metals, 0811
to from carbanions, 0264
with organometallics, 0809
deracemization, and resolution, 0179
and *Sphingomonas pauchimobilis*, 0179
Dess-Martin periodinane, and oxidation of alcohols, 1723, 1724
halogenation of conjugated ketones, 0780
stability and sensitivity, 1723
destabilizing groups, and carbocations, 0484
desulfonation of arylsulfonic acids, 0748
desulfurization, catalytic hydrogenation, 0990, 0991
of dithioacetals, 1849
of dithioketals, 1280
of sulfur compounds, 1848, 1849
of thiophenes, 0991, 1849
Raney nickel, 1849, 1850
with samarium in acid, 0991
with Raney nickel, 0990, 0991
detection of intermediates, 0312
deuterium exchange with alkanes, 1058
deuterium ion, and isotope effects, 0661
deuterium isotope effects, 0322, 0323, 0324
and dissociation energy, 0323
and E1cB reactions, 1491
and E2 reactions, 1484
deuterium labeling, and E2 reactions, 1482
and Hofmann degradation, 1523
and the Shapiro reaction, 1526
and the Wacker process, 1774
in cationic rearrangements, 1565
deuterium quadrupole echo spectroscopy, 0127
deuterium, and bond distance, 0025
and hydrogen exchange, 0684
and proton, 0356
and secondary isotope effects, 0488
deuterium-hydrogen exchange, 0766
Dewar benzene structures, 0059
Dewar benzenes, and cyclotrimerization of alkynes, 1243
and electrocyclic rearrangements, 1642
and photochemical [2 + 2]-cycloaddition, 1232, 1233
by photolysis of benzenes, 1642
stability, 1642
Dewar structures, 0032
and naphthalene, 0059
and resonance, 0049
dextro isomer, 0138
$(DHQ)_2$PHAL, and aminohydroxylation, 1180
$(DHQ)_2$PHAL, and asymmetric dihydroxylation, 1167
$(DHQD)_2$PHAL, and asymmetric dihydroxylation, 1167
di-π-methane rearrangements, 1692
diacetates, *gem*-, with allylic silanes, 1323
diadamantyl compounds, barrier to rotation, 0198
diagonal hybridization, 0008
dialdehydes, by oxidative cleavage of epoxides, 1733
photochemical coupling, 1856
dialkylamide bases, see amides, dialkyl
dialkylmagnesium compounds, and Grignard reagents, 0260, 0261
dialkylzinc reagents, addition to aldehydes or ketones, 1310, 1311
and the Reformatsky reaction, 1327
with carbonyls, enantioselectivity, 1318
diallenes, conversion to dimethyelenecy clobutenes, 1661, 1662
diamagnetic ring current, 0055
diamantane, 1584
diamides, by radical coupling of amides, 0976
diamination, of alkenes, 1182
diamines, from addition of amines to alkenes, 1182
from azido-tosylamines, 0566
from aziridines, 0566
from bis(azides), 1182
metal catalyzed coupling of imines, 1857
oxidative cleavage to diketones, 1733
with LDA and DBU, elimination of epoxides, 1519
diamino aromatic compounds, oxidative cleavage to dinitriles, 1745
diaminocyanocuprates, 0619
dianions, active methylene compounds, 0625
alkylation, 0515, 0625
carbolic acid, acylation, 1456
carboxylic acid salts, 0637
diketone, acylation, 1456
diarylimidazolium salts, as ionic liquids, 0878
diastereomer, definition, 0164
diastereomers, alkyl halides, and stereochemistry of elimination, 1502
and Cahn-Ingold-Prelog rules, 0166
and catenanes, 0133
and chiral recognition, 0175
and cis-trans isomers, 0182

and diastereoselectivity, 0168
and diastereotopic atoms/groups, 0191, 0193
and differential absorption, 0175
and fractional distillation, 0174
and fractional recrystallization, 0174
and GC, 0174, 0175
and NMR, 0193
and nomenclature, 0166
and preparative LC, 0175
and resolution, 0173
and the 2^n rule, 0165
and the E2 reaction, 1480
and the epi and peri prefixes, 0165
and the erythro/threo nomenclature, 0166
and the syn/anti nomenclature, 0166
and X-ray crystallography, 0165
epimers, 0165
meso compounds, 0165, 0187
physical properties, 0164
pseudoasymmetric carbon, 0165
tartaric acid, 0164
torsional, 0148
diastereoselectivity, in conjugate addition of organocuprates, 1113
in Mannich reactions, 1295
in radical cyclization, 1127
in reactions of sulfur ylids, 1383
in reduction of ketones, 1803
in reduction with Selectride, 1794
in synthesis, 0168
in the aldol reaction, 1345, 1346
in the Paterno-Büchi reaction, 1464
with Grignard reagents, 1303
diastereotopic atoms/groups, 0191, 0193
diastereotopic faces, 0194
diastereotopic, and the Cahn-Ingold-Prelog system, 0194
diastereotopic, definition, 0193
diatomic molecules, and bond energy, 0027
energy curve, 0330
diatropic, 0055, 0081
cyclooctatetraene dications, 0067
cyclopentadienide ion, 0063
1, 8-diazabicyclo[5.4.0]undec-7-ene, see DBU
diazaborane derivatives, chiral, 1356
diazirines, and carbenes, 0288
diazo alkenes, base induced elimination of nitroso compounds, 1552
diazo compounds, alkylation, 0533
alkylation of carboxylic acids, 0543
by the Bamford Stevens reaction, 1527
from active methylene compounds, 0787
from anilines or heterocyclic amines, 0918
from nitroso compounds, 1552
protonation of, 0499
verses a diazonium salt, 0918
with amides, 0570, 0562
with boranes, 0646
with sulfur, 1385
with thioketones, 1385
diazo hydroxide, 0692
diazo-transfer reactions, 0787
reactions, formation of carbene complexes, 1237
reagents, 1237
formation of diazoketones, 0787
versus azidination, 0788
diazoacetates, metal catalyzed addition to alkenes, 1183
with imines, 1183
diazoalkanes, reaction with carbenes, 0290
rhodium catalyzed decomposition, 0289
with aldehydes or ketones, 1384
with mineral acids, 0585
with oximes, 0533
with rhodium compounds, 1234
diazoalkenes, cleavage to ethers, 0534
with aldehydes or ketones, mechanism, 1384
with enols, 0533
diazocarbonyl compounds, insertion, 0804
diazoesters, insertion, 0805
metal catalyzed addition to imines, 1337
with aldehydes, 0800
with amines, 1242
with ketones, 1603
diazoketones, and the Wolff rearrangement, 1465, 1599
by Arndt-Eistert synthesis, 1457, 1599
by diazo-transfer reactions, 0787
conformations, s-E/s-Z, 1601
from acyl halides, 1457, 1599
hydrolysis, 0522
photolysis, and ring contraction, 1599
rearrangement to carboxylic acids, 1599
with imines, and microwaves, 1466
with mineral acids, 0585
diazomethane, alkylation of amines, 0562
alkylation of carboxylic acids, 0543
and Arndt-Eistert synthesis, 1457
and formation of methylene, 1240
and homologation of aldehydes to methyl ketones, 1602
and methylene, 0804
conversion of aldehydes to ketones, 0807
formation of carbenes, 0288
photochemical decomposition, 0285, 1240
photolysis, 0804
with acyl halides, 1457
with alcohols, 0533
with aldehydes or ketones, 1384, 1601, 1602
with sulfonyl halides, 1386
diazonium compounds, 0499
diazonium group, and a leaving group, 0916
diazonium ions, and electrophilicity, 0916
aromatic, 0691
as a leaving group, 0984
diazonium salts, also see benzenediazonium
diazonium salts, and azo compounds, 0692
and carbocations, 0499, 0803
and IUPAC mechanisms, 0500
and metal catalysis, 0916
and S_N1 reactions, 0499
aromatic, isolation of, 0499

diazonium salts, aryl fluorination and iodination, 0985
and crown ethers, 0917
and resonance, 0917
and the Gatterman reaction, 0984
and the Gomberg-Bachmann reaction, 0924
and the Heck reaction, 0923
and the Sandmeyer reaction, 0984
and the Schiemann reaction, 0921
fluorination, radical mechanism, 0922
hydroxylation, 0919
iodination, 0920
methylation, 0922
radical addition to alkenes, 1123
reduction, reagents, 1847
the Gatterman method, 0926
with active methylene compounds, 0783
with alkenes, 0923
with hydrosulfide anion, 0920
with metal halides, 0984
with organometallics, 0922, 0923
with silyl enol ethers, 0986
with sulfide anions or thiol anions, 0920
with sulfur dioxide, 0986
with thiocyanate, 0920
with trifluoroborates, 0923
diazonium salts, coupling, 0692, 0783
cyclopropenium, 0500
fluorination of aromatic compounds, 0705
from anilines, 0917
from aromatic compounds, 0692
from diazoketones, 0523
from nitrous acid, 0692, 0917
from ureas, 0919
in Meerwein arylation, 0923
in superacids, 0499
in the Heck reaction, 0916
metal catalyzed carbonylation, 0986
metal catalyzed coupling with alkenes, 0923
metal catalyzed methylation, 0922
metal catalyzed nitration, 0985
metal mediated coupling, 0926
nitration with nitric acid, 0986
nucleophilic aromatic substitution, and S_N1, 0857
reduction to amines, 1823
stability of, 0499, 0917
versus a diazo compound, 0918
with aromatic compounds, 0924
with oximes, 0986
with sodium nitrite, 0985
with triiodide, 0921
diazotates, alkyl, with alkyl halides, 0573, 0574
diazotization, and nitrosonium ion, 0918
of amino acids, 0585
of anilines, 0917
of ureas, 0919
with metal halides, 0586
Dibal (diisobutylaluminum hydride), chemoselectivity, 1794
and reduction of allenes, 1065
and reduction of ethers, 1832
and reduction of nitriles, 1815
and reduction of sulfones, 1851
metal mediated reduction of alkenes, 1064
reduction of alkynes, 1065
reduction of amides to aldehydes, 1810
reduction of esters to aldehydes, 1809
reduction of oximes, 1820
reduction of tosylates, 1832
Dibal-amine complex, 1437
dibenzosemibullvalenes, thermal isomerization, 0347
dibenzo[*g,p*]chrysene, from bifluorenylidene, 1646
dibromides, *gem*-, from aldehydes and bromine-triphenyl phosphite, 1298
dibromoborane, with alkynes, 1081
dibromoethane, conformations, 0199
dibromoisocyanuric acid, halogenation of aromatic compounds, 0700
DiBuIm, ionic liquid, 0416, 1199
dicarboxylic acids, and hydrogen bonding, 0108
bis(decarboxylation) to alkenes, 1749
by cleavage of cyclic ketones, 1735
cleavage to ketones, 1750
decarboxylation versus anhydride formation, 1423
electrochemical carboxylation of alkenes, 1138
from cyclic ketones, reagents for, 1735, 1736
oxidative cleavage of cyclic alkenes, 1743
pyrolysis, 1458
dicarboxylic esters, and the Stobbe condensation, 1356
oxidative cleavage of 1,3-diketones, 1736
dications, 0241
dichlorine monoxide, and allylic radical chlorination, 0963
dichlorocarbene, 0283
2,3-dichloro-5,6-dicyano-1,4-benzoquinone, see DDQ
dichloromethylene, 0283
dichloromethylene, carbene, 0286
dichromate, pyridinium, see PDC
dichromates, and oxidation of alcohols, 1715–1718
dicobalt octacarbonyl, and carbonylation of aryl halides, 0909
and cyclotrimerization of alkynes, 1244
and hydroformylation, 1146
and the Pauson-Khand reaction, 1141
with organometallics, 0823
Dictionary of Organic Compounds, 1900
Dictionary of Organometallic Compounds, 1885, 1887
dicyclohexano-18-crown-6, 0510
dicyclohexylcarbodiimide, see DCC
dicyclohexylurea, and Moffatt oxidation, 1721
from DCC and esterification, 1417
from DMSO-DCC oxidation, 1721
Dieckmann condensation, 1453, 1454

and the acyloin condensation, 1861
dielectric constant, and solvent acidity, 0370
dielectric heating, and microwaves, 0353
dielectric screening effects, 0503
Diels-Alder reactions, 1194–1215
Diels-Alder reactions, acceleration, 1198
and benzyne intermediates, 0313
and biradicals, 1207
and chiral auxiliaries or catalysts, 1202, 1203
and chromatographic absorbents, 1198
and cisoid conformations, 1201
and Claisen rearrangement, 1669
and cyclotrimerization, 1246
and diene conformation, 1201
and encapsulation, 1198
and frontier orbital method, 1208
and high pressure, 0513, 1198
and hydrophobic acceleration, 0414
and hydrophobic effects, 1198
and isotope effects, 1206
and micellar effects, 1199
and microwaves, 0352, 1198
and orbital symmetry, 1207
and polymerization, 1204
and principle of conservation of orbital symmetry, 1207
and radical cations, 1197
and rearrangements, 1199
and retro-Diels Alder, 1545
and six-membered transition state, 1013
and sonochemistry (ultrasound), 0352, 1198
and the Woodward-Hoffmann rules, 1207
and transoid dienes, 1197
and [1,2]-cycloaddition, 1204
and [2 + 2]-cycloaddition, 1222
and [3 + 2]-cycloaddition, 1190
Diels-Alder reactions, antarafacial overlap of orbitals, 1213
aza-, see aza-Diels-Alder
cationic, 1197
compatible functional groups, 1195
diradical stepwise versus concerted mechanism, 1205, 1206
enantioselective, 1199, 1202
endo addition, 1201, 1214, 1215
exo addition, 1201
heteroatom, 1216–1218
homo-, 1204
in alternative solvents, 0414, 1198, 1199
in an ultracentrifuge, 1198
intramolecular, 1204
inverse electron demand, 1207
Lewis acid catalyzed, 1197
mechanism, 1205, 1206
metal catalyzed, 1198
Möbius-Hückel method, 1210
of cyclobutadiene, 0074
on alumina, 1199
on zeolites, 1199
photochemical, 1198
rate of reaction, 1206
regioselectivity, 1199, 1200
retro-, 1199
reversibility, 1205
selectivity, and solvent effects, 1202
solid-state (solventless), 1198
stereochemistry, 1200, 1206
substituent effects and mechanism, 1207
suprafacial overlap of orbitals, 1213
synthetic applications, 1203
tethered, 1204
twisted, 1214
Diels-Alder reactions, with aldehydes, 1216
with arynes or benzynes, 0861, 1196
with azadienes, 1217
with chiral catalysts, 1202
with cyclic dienes, 1201
with furans, 1217
with heterocycles, 1217
with lithium perchlorate in ether, 1199
with nitroso compounds, 1217
with singlet oxygen, 1219
with sulfolene, 1204, 1205
1, 5-dienes, from 1, 5-dienes, 1659
diene-carboxylic acids, cyclization to lactones, 1042
dienes, also see Diels-Alder
dienes, acylation, 0797
acylation, and π-allyl complexes, 0797
addition of alkanes, 1086
addition of bromine, cyclic intermediates, 1014
addition of carbenes, 1236
addition reactions, 1013
dienes, and 1,4-addition, 1031
and conrotatory ring closing, orbital overlap, 1637, 1639
and homoconjugation, 0045
and photochemistry, 0332
and radicals, 1011
and symmetry of orbitals, 1636
and the cis/trans and the E/Z nomenclature, 0184
and the Heck reaction, 0892
and the Simmons-Smith reaction, 1241
and [3 + 4]-cycloaddition, 1192
dienes, bicyclic, and strain, 0229
dienes, by alkyne dimerization, 1092
by based induced elimination of halo sulfones, 1537
by cheletropic reactions, 1537
by coupling alkynes to allylic silyl ethers, 1092
by coupling of organocuprates, 0988
by dehydration of alkyne-alcohols, 1515
by dimerization of vinylalanes, 0988
by dimerization of vinylboranes, 0989
by elimination of cyclic epoxides, 1518
by pyrolysis of propargylic ethers, 1516
by ring opening of cyclic alkenes, by metathesis, 1687
by Stille coupling, 0792
by thermal extrusion of carbon dioxide from lactones, 1546
by thermolysis of sulfolene, 1204, 1205

dienes, catalytic hydrogenation, 1058
conjugated, and carbocations, 0240
cyclic, and the Diels-Alder reaction, 1201
cyclic, photochemical ring opening to trienes, 1632
cyclic, thermal extrusion of carbon monoxide, 1545
cycloaddition of singlet oxygen, 1218
cycloaddition with alkenes or alkynes, 1194–1215
Diels-Alder reaction with aldehydes, 1216, 1217
dimerization in the Kolbe reaction, 0993
electronic effects, Diels-Alder reaction, 1196
electrophilic addition, 1013
epoxidation, 1174
dienes, from allylic halides, 0592
from bicyclobutanes, 1691
from boronic acids, 0794
from dienes and alkenes, 1091
from metal catalyzed coupling, 0591
from organocuprates, 0602
from organometallics and allylic or vinyl halides, 0604, 0605, 0606, 0607
from thiophene-1,1-dioxides, 1537
from vinyl halides, 0591
from vinylboranes, NaOH, and iodine, 1630
from vinylorganometallics, 0792
from vinylsulfonate esters, 0792
dienes, hybridization, 0040
hydroboration, 1081
metal catalyzed carbonylation, 1138,1141
metal catalyzed coupling of Grignard reagents, 0987
metal catalyzed cyclization with arylboronic acids, 1100
metal mediated coupling, 0594
metathesis, 1685
organolithium reagents, and carbon dioxide, 1144
photochemical ring closure to cyclobutenes, 1632
radical addition, 1021
reaction with cations, 1013
sigmatropic migration of hydrogen, 1648
thermal opening of cyclobutenes, 1632
transoid, and Diels-Alder, 1197
with aldehydes, 1322
with chlorosulfonyl isocyanate, 1466
[3 + 2]-cycloaddition, 1192
dienes-cyclobutene, interconversion, orbital requirements, 1637, 1639
with aromatic rings, 1641
dienone-phenol rearrangement, 1593
dienophiles, alkynes, 1195
allenes, 1195
and endo addition, 1214, 1215
complex with chiral Lewis acids, 1203
definition, 1194
diesters, from dihalides, 0541
diethyl azodicarboxylate, see DEAD
diethyl succinate, see succinates
diethylaminosulfur trifluoride, see DAST
diethylene glycol, and the Huang-Minlon modification, 1836
and Wolff-Kishner reduction, 1836
diethylmagnesium, 0261
diethylzinc, and Simmons-Smith procedure, 1241
differential absorption, diastereomers and resolution, 0175
differential hydration, amines and basicity, 0391
differential solvation, 0097
diffusion control, proton-transfer reactions, 0367
diffusion rate, and reactivity, 0414
diffusion-controlled reactions, 0302
difluorides, *gem*-, 1299
dihalides, and Cannizzaro reaction, 0520
and the aldol reaction, 0520
base induced elimination, 1531
conversion to aldehydes, 0520
conversion to ketones, 0520
coupling alkyl halides, 0598
dialkylation and boranes, 0644
formation of diesters, 0541
formation of dithioacetals, 0551
formation of Grignard reagents, 0830
from alkynes, 1031
from halogenation of alkenes, 1148
gem-, from aldehydes or ketones, 1298
hydrolysis of, 0520
with active methylene compounds, 0625
with alkoxides, 0530
with enolate anions, 0625
with ketones, 0629
with metals, 1304
with organocuprates, 0601
dihaloalkenes, see alkenes
dihalogenation, of ketones, 0778
dihalosulfones,reactions, 1381
dihedral angles, and anti-elimination, 1483
and conformation, 0201
and E2 reactions, 1483
dihydropyran, acid catalyzed alcoholysis, 1039
dihydropyrans, see pyrans
dihydroquinidines, and asymmetric dihydroxylation, 1165
dihydroquinines, and asymmetric dihydroxylation, 1165
dihydrothiepin-1–1-dioxides, thermal elimination to trienes, 1537
dihydrothiophene-1–1-dioxides, thermal elimination to dienes, 1537
dihydroxylation, and microwaves, 0355
and *Pseudomonas putida*, 1168
anti, and neighboring group mechanisms, 1164
asymmetric, 1165, 1167
in ionic liquids, 0416
of alkenes, 1162–1168
of aromatic compounds, 1168
of aromatic compounds, enzymatic, 1168
Prevost reaction, 1164
Sharpless asymmetric, 1166
syn, 1162–1164

Woodward modification of the Prevost reaction, 1164
diimide, 1063, 1823
vic-diiodides, stability, 1149
diiodomethane, and Simmons-Smith procedure, 1241
diion mechanism, and [2 + 2]-cycloaddition, 1228
ketones with imines, 1465
diisobutylaluminum hydride, see Dibal
diisopinocampheylborane, 1079
diisopropylamide, lithium, see LDA
diisopropylcarbodiimide, and halogenation of alcohols, 0579
diketones, acid catalyzed formation of furans, 1272
acid catalyzed formation of pyrans, 1272
by oxidation of alkynes, reagents, 1776
by oxidation of cyclic alkenes, 1775
by oxidation of hydroxy ketones, 1720
α-oxidation of ketones, reagents, for, 1758
by oxidative cleavage of diamines, 1733
by oxidative coupling, 1784
by rearrangement of epoxy ketones, 1588
cleavage by base, 0841
coupling acyl halides, 1450
coupling of acyl nitriles, 1856
from acyl halide conjugate addition, 1132
from acyl halides and acylation, 1451
from dithianes, 1456
from furans, 0528
from ketones and esters, 1455
oxidative cleavage of cyclic alkenes, 1743
rearrangement to hydroxy acids, 1594
with amines, 1283
with hydrazines, 1285
dilithium compounds, 0808
dilongifolylborane, 1080
dimer mechanism, and S_NAr reactions, 0857
dimeric borane, 1076
dimerization, alkyne, metal catalyzed, 1091
ketenes, 1228
of acetals, 0618
of aryldiazonium salt, 0926
of carbenes, 0290
of ketals, 0618
of ketenes, 1463
of nitrenes, 0295
of radicals, 0271, 0981
reductive, alkenes, 1095
dimesitylborane, hydroboration of alkynes versus alkenes, 1082
dimetallic compounds, 1103
dimethyl sulfide, see sulfides
dimethyl sulfoxide, see DMSO
dimethyl(methylthio)sulfonium salts, and amines, 1185
dimethylaluminum amide, and conversion of esters to nitriles, 1288
dimethylbenzylamine, and absolute configuration, 0161, 0162
dimethylformamide dimethyl acetal, and elimination of hydroxy acids, 1543
dimethylhydrazones, see hydrazones
dimethyloxosulfonium methylid, 1382, 1383
dimethylsufoxonium methylid, see ylids
dimethylsulfonium methylid, 1382, 1383
dimethyltitanocene, see Petasis reagent
dimolybdenum tetraacetate, and circular dichroism, 0161
dinitrates, from epoxides or oxetanes, 0547
dinitriles, and the Thorpe reaction, 1387
by oxidative cleavage of ortho-diamino aromatic compounds, 1745
by the Thorpe-Ziegler reaction, 1388
formation of imidines, 1296
from cyanoamines and HCN, 1393
diols, acid catalyzed rearrangement to ketones, 1585
and formation of cyclic sulfates, 0518
by dihydroxylation of alkenes, 1162–1168
by photochemical dimerization of ketones, 1856
by pinacol coupling, 1854–1856
by the Gomberg-Bachmann pinacol synthesis, 1854
by the Prins reaction, 1393
by the Tollens' reaction, 1368
carbocations, and rearrangements, 1568
cleavage by lead tetraacetate, 1734, 1735
cyclic, by pinacol coupling, 1856
deoxygenation, to give alkenes, 1534
from epoxides, 0528, 1697
from Grignard reactions, 1308
in situ generation, and oxidative cleavage, 1732
oxidative cleavage, and reagents for, 1732–1735
reductive coupling of aldehydes or ketones, reagents, 1854, 1855
with thiophosgene, 1536
dioxanes and oxonium ions, 0443
and conformations, 0209
and solvolysis, 0443
dioxetanes, cleavage, 1219
cycloaddition of singlet oxygen to alkenes, 1219
dioxirane, dimethyl, and epoxidation of alkenes, 1172
oxidation of isocyanates to nitro compounds, 1778
oxidation of thiols, 1780
oxidative cleavage of diamines, 1733
dioxiranes, and epoxidation of alkenes, 1172
α-hydroxylation, and enantioselectivity, 1754, 1755
and insertion reactions, 1172
and Oxone, 1172
and ozonolysis, of ethylene, 1741
and peroxyimidic acid, 1173
and strain, 0218
esters from alkanes, 1755
oxidation of alkanes to alcohols, 1755
dipamp, and catalytic hydrogenation, 1056
diphenyl nitroxide, 0981
diphenylmethyl carbanions, 0252

diphosphines, see bis(phosphines)
diphydrophenathrenes, oxidative cleavage, 1746
dipleiadiene, paratropic, 0090
dipolar addition, see addition
[1,3]-dipolar addition, 1187–1192
[1,3]-dipolar addition, see [3 + 2]-cycloaddition
[1,3]-dipolar addition, and ozonolysis of alkenes, 1741
dipole induced bonding, 0119
dipole moment, 0018
  and C-H, 0019
  and conformation, 0199
  and Debyes, 0019
  and hyperconjugation, 0096
  and symmetry, 0019
  azulene, 0068
  hydrocarbons, 0096
  MO calculations, 0035
  of substituted aromatics, 0018, 0019
1,3-dipoles, structural types and canonical forms, 1188, 1189
dipoles, parallel, and anomeric effect, 0210
dipyrrinones, and hydrogen bonding, 0113
diradical mechanism, and carbenes, 1239
  and Cope rearrangement, 1664
  and [2 + 2]-cycloaddition, 1227
  photochemical [2 + 2]-cycloaddition, 1231
diradical intermediates, and Cope rearrangement, 1663
diradicals, see biradicals
diradicals, 0277
  and carbenes, 1239
  and Criegee mechanism of ozonolysis, 1738
  and cyclopropane ring opening, 1591
  and di-π-methane rearrangements, 1693
  and rearrangements, 1576
  and singlet oxygen, 0970
  and tritium labeling, rearrangements, 1576
  and [2 + 2]-cycloaddition, 1224
  in the Paterno-Büchi reaction, 1463
directed ortho metalation, 0596, 0912
directed ortho metalation, also see aryllithium compounds
diselenides, catalytic hydrogenation, 0990
  reduction to selenols, 1854
disiamylborane, 1076
displacement mechanism, and oxidation-reduction, 1706
disproportionation, and aryl radicals, 0940
  and dehydration of carboxylic acids, 1423
  and $NaBH_4$ reduction of aldehydes or ketones, 1805
  and radicals, 0280, 0806, 0936
  and the benzidine rearrangement, 1679
  and the Cannizzaro reaction, 1863
  aryl carboxylate ions, 0747
  of aldehydes, 1863
  of radicals, 0981
disrotatory motion, and 4n versus 4n + 2, 1643
  and cyclohexadiene-triene interconversion, 1638, 1639
  and electrocyclic rearrangements, 1633, 1634
  stereochemistry, Diels-Alder, 1201
dissociation energy, see energy
dissociation, radicals, and photo-Fries rearrangement, 0737
dissociative state, and photolytic cleavage, 0336
dissolving metal cleavage of ethers, 0581
dissolving metal reductions, 1067
distance, bond, see bond distance
distillation, fractional, and diastereomers, 0174
disulfide ions, with alkyl halides, 0553
disulfides, and Smiles rearrangement, 0932
  aryl, with alkenes, and metal salts, 1179
  by oxidation of thiols, 1780, 1785, 1786
  by reduction of sulfonyl halides, 1850
  from alkyl halides, 0553
  from aryl halides, 0875
  from Bunte salts, 0553
  reduction to thiols, reagents, 1853
  with enolate anions, 0791
  with organometallics, 0818
dithianes, acylation, 1456
  alkylation, 0637–0639
  and butyllithium, 0638
  and conformations, 0209
  and epoxides, 0638
  and the Brook rearrangement, 1701
  and Umpolung, 0638
  from carbon disulfide and dihalides, 0551
  hydrolysis, 0638
  with Raney nickel, 0639
dithioacetals, alkylation, 0637–0639
  as protecting groups, 1279
  catalytic hydrogenation, 0991
  from acetals, 0551
  from aldehydes, 1278
  from dihalides, 0551
  hydrolysis, 0526, 1279
  ketene, see ketene
  Lewis acids for preparation of, 1279
  reaction with base, 1279
  reagents for hydrolysis, 1280
  reduction, 1849
  with Raney nickel, 0639
dithiocarbamic acid salts, from carbon disulfide and amines, 1297
dithiocarboxylic acids, from ketones and carbon disulfide, 1368
dithiocarboxylic esters, and potassium thioacetate, 0542
  as protecting groups, 1279
  by alkylation, 0637–0639
  desulfurization with Raney nickel, 1280
  hydrolysis, 1279
  hydrolysis, Corey-Seebach procedure, 1280
  Lewis acids for preparation of, 1279
  reaction with base, 1279
  reagents for hydrolysis, 1280
  with Raney nickel, 0639
dithioketals, hydrolysis, 0526

dithiols, from carbonyls, 1277
ditosylates, formation of azetidines, 0557
leaving groups, 0498
divalent atoms, abstraction, 0943
divinyl ether, and cross conjugation, 0044
divinylcyclopropanes, rearrangement, 1661
diynes, amination, metal catalyzed, 1049
and cyclotrimerization, 1247
and formation of dimethylenecyclobutenes, 1661, 1662
and hyperconjugation, 0040
and metathesis, 1686
and the Cadiot-Chodkeiwicz reaction, 0979
and the Eglinton reaction or Glaser reaction, 0978
and the Hay reaction, 0979
by Suzuki-Miyaura coupling, 0899–0903
conjugated, 0040
cyclization, metal catalyzed, 1093
cyclotrimerization, 1244
metal catalyzed amination, 1049
metal catalyzed coupling of alkynes, 0978
thermal conversion to diallenes, 1661, 1662
DMF, and phosphorus oxychloride, 0725
and the Gabriel synthesis, 0569
DMSO, and carbanions stereochemistry, 0759
and DCC, 0731, 1721
and HBr, 0700
and Moffatt oxidation, 1721
and oxidation of alkyl halides to aldehydes, 1765
and pK_a, 0358
and sulfur trioxide, for oxidation of alcohols, 1721
and Swern oxidation, 1721
and the Gomberg–Bachmann reaction, 0924
and trifluoroacetic anhydride, for oxidation of alcohols, 1721
oxidation of alkyl halides, mechanism, 1766
reagents for oxidation of alcohols, 1721, 1722
with aromatic compounds, 0731
with base, 0914
with silyl halides and alkenes, 1156
DNA, and molecular knots, 0134
DNP (dynamic nuclear polarization), and NMR, 0270
dodecahedral carbocations, 0245
dodecahedrane, and dehydrogenation, 1714
dodecyltrihexylphosphonium chloride, ionic liquid, 0900
Doebner modification, and microwaves, 1360
of the Knoevenagel reaction, 1360
domino metathesis, 1685
donor-acceptor complexes, electron, 0115
donors, in the benzoin condensation, 1397
DOSP ligand, in rhodium catalysts, 1238
Dötz benzannulation, 1247
double asymmetric synthesis, 0171, 1348
double Baylis-Hillman reaction, 1325
double bonds, and bond energy, 0031
and delocalization, 0038
conjugated with p orbitals, 0040
cumulative, 0148, 0149
from carbocations, 0248
in conjugation with carbocations, 0239
double carbonylations, 0655
double hyperconjugation, 0239
double metathesis, 1685
double Michael addition, 1109
double-asymmetric synthesis, 1080
dry media reactions, 0416
dry-reaction microwave chemistry, 0353
drying agents, and acetal or ketal formation, 1270
dual substituent parameter equation, 0409
Duff reaction, 0727
dynamic nuclear polarization, see DNP
dyotropic rearrangements, and σ-bond migration, 1700
E/Z nomenclature, definition, 0183
E1 reactions, see elimination, E1
$E1_{anion}$ reactions, mechanism, 1493
E1cB reactions, see elimination
E2 reactions, see elimination, E2
E2C reactions, see elimination, E2C
eclipsing bonds, and conformation, 0201
eEROS, 1894
Eglinton reaction, 0978, 0979
Ehrlich-Sachs reaction, 1368
E^i reactions, see elimination
Elbs reaction, 0734
elections, unpaired, and ESR, 0268
electric field, and microwaves, 0353
electrical effects, and reactivity, 0396
electrochemical coupling, alkyl halides, 0598
electrochemistry, amination, 0975
and acetal cleavage, 0527
and Michael addition, 1110
and radical cyclization, 1126
and the haloform reaction, 0843
and the Pschorr ring closure, 0925
aryl halides with sulfur nucleophiles, 0874
carbonylation of aryl halides, 0909
conversion of esters to amides, 1435
coupling of silanes, 0977
dehydration of oximes to nitriles, 1547
dicarboxylation of alkenes, 1138
formation of carbenes, 0287
oxidation of thiols to disulfides, 1785
oxidative cleavage of diols, 1733
reduction of alkyl halides, 1826
reduction of nitro compounds to hydroxylamines, 1819
reduction of vinyl halides, 1827
sacrificial anode, 0598

electrocyclic reactions, and formation of aromatic compounds, 1645
and Möbius-Hückel method, 1636
of en-diynes, 1641
electrocyclic rearrangements, 1633
4n versus 4n + 2, and allowed versus forbidden, 1643
and carbenes, 1240
and Dewar benzenes, 1642
and overlap of HOMO orbitals, 1636
conrotatory versus disrotatory, 1633, 1634, 1643
forbidden, and metal catalysts, 1643
frontier orbital method, 1635
of alternant aromatic compounds, 1646
pyrocalciferols, 1640
stereochemistry, 1633, 1634
electrofuge, definition, 0297
electrolysis, and carbonylation of amines, 0851
and Collman's reagent, 0651
and coupling with silanes, 0588
and Friedel-Crafts alkylation, 0707
and halogenation of carboxylic acids, 0781
and phenol formation, 0734
formation of haloalkynes, 0820
of carboxylate salts, 0992
electromagnetic spectrum, 0329
electromagnetic waves, and microwaves, 0353
18-electron systems, and metallocenes, 0067
electron affinity, and organolithium reagents, 0262
electron cloud distortion, and electronegativity, 0016
electron configuration, of boron and carbon, 0008
electron delocalization, and enol stabilization, 0772
electron density, and cyclopropane, 0218
and electronegativity, 0017
and neighboring groups, 0454
and resonance, 0048
electron diffraction, allyl radical, 0270
and bond distance, 0022
and conformations, 0196
electron donating groups, 0020
and σ-values, 0403, 0404
and the tetrahedral mechanism, 0486
substituent effects, 0485
electron donor-acceptor complexes, 0115
electron paramagnetic resonance, see EPR
electron spin resonance, see ESR
electron transfer, and Grignard reactions, 1308
and photosensitization, 0341
electron withdrawing groups, 0020
and bond energy, 0030
and σ values, 0403, 0404
and the tetrahedral mechanism, 0486
and vinylic substitution, 0475
substituent effects, 0485
electronegativity, 0016–0019
and acidity or basicity, 0384
and bond energy, 0016, 0028
and resonance, 0047
scales, 0017
table, 0017, 0018
electronic effects, and the Diels-Alder reaction, 1196
and [2 + 2]-cycloaddition, 1228
electronic excitation, 0332
electronic spectrum, 0330
electronic structure, 0007, 0013–0015
electronic transfer, oxidation-reduction, 1705
electronic transitions, and photochemistry, 0329
electrons, and electronic structures, 0014
and hyperconjugation, 0095
and resonance, 0046
as waves, 0003
lone pair, and carbanions stability, 0254
nonbonded, and carbenes, 0284
unpaired, and radicals, 0267
unshared, and arenium ions, 0668
valence, 0014
valence shell, and electronegativity, 0017
electrophile, definition, 0297
electrophiles, and Lewis acids, 0657
proton, 1005
sulfur, 0695
sulfur trioxide, 0697
with allenes, 1022
electrophilic addition, see addition
electrophilic aromatic substitution, see substitution
electrophilic carbenes, 1238
electrophilic mechanism, halogenation of alkenes, 1149
electrophilic radicals, 0939, 1018
electrophilic rearrangements, 0299, 1559, 1579
electrophilic substitution, see substitution
electrophilicity, and carbocations, 0432
and diazonium ions, 0916
and S_N1 reactions, 0432
and the Diels-Alder reaction, 1196
electrospray ionization mass spectrometry, see mass spectrometry
electrostatic potentials, and addition reactions, 1020
element effect, and leaving groups, 0475
1,3-elimination, 1543
1,4-elimination, 1512, 1529
α′,β-elimination, 1524
α-elimination, 1477
β-elimination, 0298, 1477
elimination reagents, and alkene stability, 1497
elimination, 1,3-, 1543
elimination, 1,4-, 1512
elimination, α′,β, 1524
elimination, acidity of β-hydrogens, 1499
elimination, and Bredt's rule, 1497
and carbenes, 0292
and carbenoids, 0288
and cis/trans isomers, 1501
and decarbonylation of aldehydes, 0997
and entropy of activation, 0303
and extrusion reactions, 1477
and formation of nitrenes, 0293

and Hofmann's rule, 1498
and hyperconjugation, 1498
and organocuprates, 0601
and the Brønsted equation, 1496
and the Heck reaction, 0895
and the Mannich reaction, 1293
and Wagner-Meerwein rearrangement, 1582
elimination, anti, 1480
anti, phosphines with epoxides, 1517
anti- and ion pairing, 1486
β, 0298
base induced of ethers, 1516
base induced, of sulfones, 1528
conjugate, 1512
Cope, see Cope
determination of mechanism, 1495
E1 versus E2, 1487, 1505, 1506
elimination, E1, and alkene stability, 1497
and carbocations, 1487
and dehydrohalogenation, 1531
and ion pair mechanism, 1488
and substitution, 1487
and Zaitsev's rule, 1487, 1497
mechanism, 1487
stereochemistry of elimination, 1502
elimination, $E1_{anion}$, mechanism, 1493
elimination, E1cB versus E2, 1489, 1492
elimination, E1cB, 1488–1493
elimination, E2, and antiperiplanar conformations, 1479
and base strength, 1500
and bases, 1504
and bond angles, 1482
and conformations, 1479
and dehydrohalogenation, 1531
and deuterium isotope effects, 1484
and deuterium labeling, 1482
and diastereomers, 1480
and dihedral angle, 1483
and enantiopure alkyl halides, 1480
and gauche orientations, 1485
and Hofmann degradation, 1522
and Hofmann's rule, 1498
and isotope effects, 1479
and leaving groups, 1479
and meso alkyl halides, 1480
and strain, 0400
and syn-anti dichotomy, 1484
and syn-periplanar conformations, 1479
and Zaitsev's rule, 1482, 1498
anti elimination, 1480
axial versus equatorial leaving groups, 1481
controlling factors, 1486
cyclohexyl halides, 1481
formation of alkynes, from vinyl halides, 1482
mechanism, 1478–1486
rate of reaction, 1481, 1489
regioselectivity, 1498
stereochemistry, 1479, 1485
substituent effects in alkyl halides, 1504
transition states, 1479
with alkyl halides, 1478–1486
Zaitsev's rule versus Hofmann's rule, 1498
elimination, E2C, 1501, 1495
elimination, effect of base strength, 1504
effect of leaving groups, 1505
elimination, E^i, and cis β-hydrogen, 1511
and Cope elimination, 1525
and Hofmann degradation, 1522
and pyrolysis of sulfoxides, 1529
and radical mechanisms, 1510
and substrate structure, 1509
and the Chugaev reaction, 1520
and the Woodward-Hofmann rules, 1509
benzotriazole leaving groups, 1524
halide reactivity, 1509
mechanism, 1507
organolithium reagents with ammonium salts, 1524
rate of reaction, 1508, 1509
stereochemistry, and syn elimination, 1508
transition states, 1509, 1510
elimination, haloethers with magnesium, 0830, 0831
in the Stork enamine synthesis, 0635
influence of temperature, 1506
intramolecular, 1507
IUPAC nomenclature, 0419
kinetics, 1490
mechanistic ambiguity, 1494
metal induced, of dihalides to alkenes, 1539
Norrish type II cleavage, 1478
of dihalides to alkenes, reagents for, 1539
of epoxides, with LIDAKOR, 1518
of selenoxides, 0640
Peterson alkenylation, 1366
photochemical, 1478
elimination, pyrolytic, and cis β-hydrogen, 1511
and Hofmann's rule, 1510
and steric interactions, 1511
and Zaitsev's rule, 1511
mechanism, 1507–1510
regioselectivity, 1510
transition state, 1507
elimination, radical of bis(xanthates), 1535
radical, and sulfoxides, 1530
regiochemistry, 1497
silyl-Wittig reaction, 1366
solvent effects on the base, 1504
stereochemistry, and diastereomeric halides, 1502
stereochemistry of the alkene, 1501
substrate reactivity, 1502, 1503
suitable leaving groups, 1505
elimination, syn, 1483
and E^i reactions, 1508
and ion-pairing, 1486
and the syn-anti dichotomy, 1484
of thiiranes, 1519
transition states, 1486
elimination, transition states, 1496
elimination, types, 1477
elimination, versus substitution, 1503, 1505, 1506
elimination-addition mechanism, 0613

elimination-addition mechanism, see mechanism
elimination-addition reactions, 0478, 0498
Emde reduction, 1845
emim (1-ethyl-3-methylimidazolium), ionic liquid, 0688, 0706, 1163
emimcl, ionic liquid, 0721
emission of light, and sonochemistry, 0350
emission, and NMR, 0270
en-diynes, Bergmann cyclization; electrocyclic rearrangement, 1641
en-ynes, rearrangement, 0770
enamides, from allylic amides, 1028
  from vinyl halides, 0823
  torsional barrier, 0202
enamine formation, 1283, 1284
enamine salts, and alkylation, 0636
enamines, addition of siloxanes, 1088
  alkylation, 0634–0636
  and allylic amine carbanions, 0641
  and aminals, 1283
  and Michael addition, 0636
  and N-alkylation, 0636
  and radical cyclization, 1128
  and Stork enamine reaction, 0634, 0635
  and tautomerism, 0104
  and the Thorpe reaction, 1387
  and the Thorpe-Ziegler reaction, 1388
  by metal catalyzed amination of alkynes, 1048
  by reduction of nitro compounds, 1047
  chiral, 0777
  condensation with aldehydes or ketones, 1344
  cycloaddition reactions, 1222
  from amines, by dehydrogenation, 1712
  from amines,with ketones, 1281
  hydrogenation to amines, 1049
  oxidation to amino-ketones, 1775
  reduction to amines, 1813, 1844
  reductive cleavage, 1844
  Stork enamine reaction, 0632, 0634, 0635
  tautomerism with imines, 1048
  with 9-BBN, 1079
  with acyl halides, 0635
  with organolithium reagents, 0641
  with proline, 0636
  [2 + 2]-cycloaddition, 1222
enantiomeric excess (% ee), and determination of, 0179, 0180, 0181
enantiomeric purity, determination of, 0181, 0182
enantiomers, also see chiral compounds
enantiomers, also see chirality
enantiomers, definition and characteristics, 0138–0140
  and absolute configuration, 0154
  and enantiotopic atoms/groups, 0191
  and Fischer projections, 0153
  and kinetic resolution, 0176
  and prochiral, 0193
  and pyramidal inversion, 0142, 0143, 0144
  and quadrivalent stereogenic atoms, 0141
  and racemates, 0138
  and specific rotation, 0139
  and tervalent stereogenic atoms, 0142
  and Tröger's base, 0144
  called enantiomorphs, 0137
  levo and dextro, 0138
  of adamantanes, 0145
  of allenes, 0148
  of atropisomers and biphenyls, 0146
  of catenanes, 0133
  of glyceraldehyde, 0154
  of helical molecules, 0149, 0150
  of molecular knots, 0133
  of monocyclic compounds, 0187
  of tartaric acid, 0138
enantiomorphs, see enantiomers
enantioselective reactions, 0171
enantioselective reduction, 1802
enantioselectivity, 0171
  and amino acid surrogates, 0632
  and BINAP, 1122
  and Cinchonidine alkaloids, 1041
  and enolate anion formation, 0780
  and formation of allenes, 0770
  and formation of aziridines, 0572
  and formation of β-lactams, 1465
  and formation of cyanoamines, 1392
  and formation of homoallylic alcohols, 0620
  and organolithium reagents, 0595, 1303, 1330
  and organometallic addition to imines, 1331, 1332, 1335
  and protonation of enolate anions, 0775
  and radical coupling of conjugated amides, 0976
  and radical cyclization, 1127
  and radicals, 0939
  and sulfones, and palladium catalysts, 0554
  and transfer hydrogenation, 1066
enantioselectivity, coupling with allylic carbonates, 0611
enantioselectivity, in α-hydroxylation with dioxiranes, 1754, 1755
  in acyl addition of chiral allylic boranes, 1320
  in acyl addition of organotin compounds, 1315, 1317, 1318
  in addition of alcohols to ketenes, 1040
  in addition of metal carbene complexes to alkenes, 1237
  in addition of organometallics to carbonyls, 1312
  in aldol reactions, 1347, 1348
  in alkylation with enoate anions, 0628
  in allylic alcohols, base induced elimination of epoxides, 1519
  in azidination reactions, 0788
  in aziridine formation, 1184
  in baker's yeast reduction of alkenes and alkynes, 1066
  in biaryl formation by Suzuki-Miyaura coupling, 0902

in carbene additions to alkenes, 1237
in carbene insertion, 0804
in catalytic hydrogenation, 1054, 1056, 1057, 1074
in conjugate additions, 1106, 1109
in cyanohydrin formation, 1390
in cyclopropanation, 1237
in dialkylzinc reagents with carbonyls, 1318
in dihydroxylation of alkenes, 1165
in ene reactions, 1105
in enolate alkylation, chiral bases, 0629
in epoxidation of alkenes, 1175, 1177
in epoxide hydrolysis, 0529
in epoxide reactions with organometallics, 0618
in formamidine alkylation, 0641
in Friedel-Crafts alkylation, 0709
in Grignard reactions, 1303
in heteroatom Diels-Alder reactions, 1218
in hydroamination of alkenes, 1181
in hydroboration of alkenes, 1079
in hydrogenation of conjugated compounds, 1072, 1073
in hydrogenation of indoles, 1067
in hydrolysis of esters, 1401
in hydroxylation of hydrocarbons, 1751
in α-hydroxylation with oxaziridines, 1754
in imine alkylation, 0632
in ketene cycloaddition to carbonyls, 1462
in Mannich reactions, 1295
in metal catalyzed cyclopropanations, 1238
in metal catalyzed halogenation of ketones, 0778
in nitrene formation, 1183
in nitrene insertion reactions, 0790
in oxidation of thioethers to sulfoxides, 1782
in oxidative cleavage of diols, 1733
in pinacol coupling, 1856
in reactions of enolate anions with aryl halides, 0907
in reactions of haloboranes with azides, 0822
in reductive alkylation, 1291
in Sharpless aminohydroxylation, 1180
in Sharpless asymmetric epoxidation, 1177
in the alcoholysis of anhydrides, 1413
in the Baeyer-Villiger reaction, 1618
in the Baylis-Hillman reaction, 1325, 1826
in the Claisen reaction, 1356
in the Claisen rearrangement, 1672
in the conjugate addition of amines, 1130, 1132
in the conjugate addition of organocuprates, 1113
in the conjugate addition of organozinc reagents, 1117
in the Darzens condensation, 1365
in the Diels-Alder reaction, 1199, 1202
in the halogenation of aldehydes or ketones, 0776, 0777
in the halogenation of epoxides, 0583
in the Heck reaction, 0894, 0895
in the Henry reaction, 1358
in the Ireland-Claisen rearrangement, 1671
in the Jacobsen-Katsuki epoxidation, 1178
in the Julia-Colonna epoxidation, 1176
in the Lossen rearrangement, 1610
in the Michael addition, 1106, 1109
in the Mukaiyama aldol, 1353, 1354
in the Pauson-Khand reaction, 1142
in the Pictet-Spengler reaction, 0716
in the preparation of alcohols from amines, 0547
in the preparation of alkynes by hydroboration, 1631
in the Prins reaction, 1396
in the Pummerer rearrangement, 1867
in the reaction of amines with epoxides, 0563
in the reaction of anhydrides with organometallics, 1446
in the reduction of azirines, 1184
in the reduction of chiral phosphine oxides, 1847
in the reduction of imines, 1813
in the reduction of ketones, 1800–1803
in the Robinson annulation, 1350
in the Simmons-Smith procedure, 1241
in the Stevens rearrangement, 1623
in the Stork enamine synthesis, 0636
in the Strecker synthesis, 1391
in the Ullmann reaction, 0898
in the Weitz-Scheffer epoxidation, 1175
in Wagner-Meerwein rearrangements, 1584
in [2,3]-Wittig rearrangements, 1677
in [3 + 2]-cycloadditions, 1191
in [3, 3]-sigmatropic rearrangements, 1663
enantioselectivity, with chiral boranes, 1079
with chiral hydrazones, alkylation, 0633
with chiral oxazolines, 0643
enantiotopic atoms, 0191, 0192
enantiotopic faces, 0194
enantiotopic, and Cahn-Ingold-Prelog system, 0194
definition, 0192
encapsulated osmium tetroxide, and dihydroxylation of alkenes, 1163
encapsulation, and Diels Alder reactions, 1198
encounter complex, 0664
and electrophilic aromatic substitution, 0682
Encyclopedia of Reagents for Organic Synthesis, 1894
endo addition, and orbital symmetry, 1214, 1215
in the Diels-Alder reaction, 1201
endohedral metals, and fullerenes, 0095

ENDOR, and radicals, 0267
ene reactions, 1103–1105
and Lewis acids, 1104
and microwave chemistry, 0352
and oxygen, 0970
and steric acceleration, 1104
and [1,5]-sigmatropic rearrangement of hydrogen, 1648
retro-, 1104
energy barriers, to planarity, cyclopentane, 0212
to pyramidal inversion, 0142
to rotation, 0197, 0198
energy cascade, and photolytic cleavage, 0336
energy curve, diatomic molecule, 0330
energy diagram, ethane, 0198
energy levels, alternant hydrocarbons, 0070
benzyl cation/radical/ carbanion, 0070
energy of light, and photochemistry, 0329
energy, activation, chair-to-chair interconversions, 0204
activation, rotational barrier, 0146
energy, axial and equatorial substituents, 0206
energy, bond dissociation, see dissociation
energy, bond dissociation, 0027, 0027
and deuterium isotope effects, 0323
and organolithium reagents, 0262
and radical halogenation, 0960
and small rings, 0218
carbocations, table, 0244
of radicals, 0275
radicals and reactivity, 0952
energy, bond, 0027–0030
and atom abstraction by radicals, 0943
and electronegativity, 0016, 0028
and hybridization, 0030, 0031
and keto-enol tautomerism, 0098
and s character, 0029, 0030
benzene, 0036
hydrocarbons, 0028, 0029
hydrogen bonds, 0107
in diatomic molecules, 0027
of double bonds, 0031
of organic compounds, 0030
energy, cyclohexane conformations, 0203
energy, free, see free energy
energy, of butadiene, 0038, 0039
of conjugation, 0040
of singlet carbenes, 0284
of the chair conformation, 0203
of triplet carbenes, 0284
π, 0042
potential, see potential energy
resonance, see resonance energy
energy, strain, and molecular mechanics, 0215
and trans cyclooctene, 0229
calculations, 0217
energy, transition energies, 0508
enol acetates, and Mukaiyama aldol, 1354
formation of enolate anions, 0631
from enolate anions, 0800
from ketenes with aldehydes or ketones, 1040
metal mediated halogenation, 0780
with methyllithium, 0631
enol borates, and the aldol reaction, 1346
enol borinates, and enolate anions, 0631
and Ireland-Claisen rearrangement, 1671
and the aldol reaction, 1346
from conjugate addition of boranes, 1121
halogenation, 0780
hydrolysis, 1121
enol carbonates, see carbonates
enol content, 0099, 0100, 0102
enol esters, and transesterification, 1421
enol esters, from alkynes, 1042
with carboxylic acids, 1424
with ketones, 0629
enol ethers, see ethers
enol ethers, silyl, α-hydroxylation, 1755
addition of hydrazoic acid, 1053
alkylation, 0628
and enolate anions, 1346
and hydride shifts, 0799
and Mukaiyama aldol, 1351–1354
formation of enolate anion, 0628
formation of thioalkyl and thioaryl ketones, 0792
from aldehydes, 0800
from enolate anions, 0798
from ketones, 0798
from vinyllithium and silylperoxides, 0814
metal catalyzed conjugate addition, 1110
oxidative coupling to diketones, 1784
sulfenylation, 0792
with acetals, 0617
with aldehydes and chiral boranes, 1348
with aryldiazonium salts, 0986
with methyllithium, 0631
enolate alkylation, and chiral additives, 0630
and chiral oxazolidinones, 0629
and Evan's auxiliaries, 0629
enolate anions, acylation, 0800
aggregates, 0390
aggregation of, *ab initio*, 0264
alkylation, 0263, 0515, 0626–0628
amine catalyzed formation, 0779
enolate anions, and Baldwin's rules, 0306, 0307
and conjugated ketones, 0631
and enols, 0102
and formation of enol acetates, 0800
and formation of enol borinates, 0631
and formation of silyl enol ethers, 0798
and HSAB, 0380
and metals, 1344
and pK_a, 0622
and radicals, in arylation reactions, 0908
and regioselectivity, 0630
and resonance, 0253
and the aldol condensation, 0263, 0627
enolate anions, arylation, 0906–0908
arylation, and SET mechanism, 0908
as bases, 0390

as nucleophiles, 0514
bases required for formation, 0627
by Wittig rearrangement of vinyl ethers, 1625
conjugate addition, 1108
coupling with allylic substrates, 0609–0611
cyclization, with dihalides, 0629
dianions, 0514
enantioselective formation, 0780
enantioselective protonation, 0775
formation, and UV, 0908
formation, substituent effects, 0774
enolate anions, from carboxylic esters, 1355
from conjugate addition, 1113
from conjugated ketones, 0907
from dialkylamides, 0799
from enol acetates, 0631
from enols, 0774
from ketones, 0774, 0790
from silyl enol ethers, 0628
from unsymmetrical ketones, 0630
enolate anions, halogenation, 0820
hydrolysis, 0812
α-hydroxylation with sulfonyl oxaziridines, 1754
enolate anions, in the Claisen condensation, 0263
in the Claisen condensation, 0627, 1453
in the Claisen reaction, 1355
in the Claisen Schmidt reaction, 1343, 1344
in the Perkin reaction, 1363
in the Robinson annulation, 1350
enolate anions, kinetic, 0799
metal catalyzed coupling with aryl halides, 0907
metals used for formation of, 0811
Michael addition, 1108
O-alkylation, 0623
of carboxylic acid derivatives, 1354, 1355
of esters, Claisen rearrangement, 1670
of lactams, with aryl halides, 0907
of nitro compounds, reduction to hydroxylamines, 1819
oxidative coupling to diketones, 1784
photochemical arylation, 0908
preformed, and Michael addition, 1107
protonation, 0812
reactions, 1340
thermodynamic, 0799
torsional barrier, 0202
enolate anions, with acyl hypofluorites, 0777
with aldehydes or ketones, 0263, 1339–1351
with aldehydes or ketones, also see aldol
with alkyl halides, 0515, 0622
with aryl halides, enantioselectivity, 0907
with chlorotrimethylsilane, 0798
with dihalides, 0625
with disulfides, 0791
with halosilanes, 0798
with nitro compounds, 0613
with selenyl halides, 0791
with tosylcyanide, 0801
X-ray crystallography, 0264
enolates, see enolate anions
enolates, boron, chiral, 1348
enolene rearrangement, 1673
enolizable protons, and isotopic labeling, 0775
enolization, and Grignard reactions, 1305, 1306
and Grignard reactions, mechanism, 1309
and the aldol condensation, 1346
enols, acyloxylation, 0972
alkylation, and Lewis acids, 0628
amphiprotic properties, 0772
and Bredt's rule, 0838
and enolate anions, 0102
and formation of furans from diketones, 1272
and isotope effects, 0774
and nitrosation, 0785
and Stille coupling, 0794
and the aldol reaction, 1345
electron delocalization, 0772
fluorinated compounds, 0101
Fuson-type, 0100
halogenation, 0778
hydrogen bonding and intramolecular stabilization, 0772
isolation of, 0101, 0770
mechanism of acid catalyzed aldol reaction, 1349
metal catalyzed preparation, 0770
of amides, and dehydration to nitriles, 1549
stable, 0231
steric stabilization, 0773
tautomerism, 0098, 0770, 0772, 0837
with base, 0774
with diazoalkanes, 0533
with metal acetates, 0972
entgegen, and alkene nomenclature, 0183
enthalpy, 0300–0302
and nitrenes, 0293
formal steric, 0232
entropy, 0300
and kinetics, 0322
and ring size, 0303
cyclopropane to propane, 0304
of activation, 0303
of activation, and Smiles rearrangement, 0932
of activation, and substitution reactions, 0446
envelope conformation, and cyclopentane, 0212
environmentally friendly chemistry, 0413
enynes, and the Pauson-Khand reaction, 1141
cyclic, from diynes, 1092
halogenation, 1151
metal catalyzed coupling of alkynes to alkynes, 1091
enzymes, and carboxylic ester hydrolysis, 1400
and molecular recognition, 0125
for carboxylation, 0729
for dihyroxylation of aromatic compounds, 1168
for epoxidation, 1172
for hydrolysis of nitriles, 1269
for α-hydroxylation, 1756, 1757
for lactamization, 1431
for oxidation of alcohols, 1725
for oxidation of thioethers to sulfoxides, 1782

enzymes, and carboxylic ester hydrolysis, (*Continued*)
for reduction of aldehydes or ketones, 1722, 1800
for reduction of conjugated ketones, 1074
for transesterification, 1420
eosin, as a photosensitizer, 1218
ephedrine, and resolution, 0173
epimerization, of chiral ketones, 0775
epimers, definition, 0165
episulfides, see thiiranes
episulfones, and the Ramberg-Bäcklund reaction, 1536, 1537
from sulfonyl halides and diazomethane, 1386
epoxidation, and catalytic antibodies, 1172
and Cinchona alkaloid phase transfer catalysts, 1175
and isomerization (cis/trans) of alkenes, 1174
and polyleucine, 1176
asymmetric, 1174, 1177
cyclic alkenes, stereochemistry, 1023
enzymatic, 1172
Jacobsen-Katsuki, 1178
Julia-Colonna, enantioselectivity, 1176
of alkenes, and kinetic resolution, 0178
of alkenes, and reagents for, 1169–1179
of alkenes, enantioselectivity, catalysts, 1176
of alkenes, stereochemistry, 1023
of dienes, 1174
other methods, 1172
Sharpless, and mechanism, 1177
Waits-Scheffer, 1174, 1175
epoxide hydrolase, 0528
epoxides and Friedel-Crafts alkylation, 0707
acid catalyzed rearrangement, 1587
ambident substrates, 0518
and elimination with phosphines, 1517
and formation of aziridines, 0565
and formation of dinitrates, 0547
and formation of isocyanides, 0568
and formation of lactones, 0619
and formation of thiiranes, 0552
and Friedel-Crafts alkylation, 0619
and leaving groups, 0497
and strain, 0218
and the neighboring group mechanism, 0448
by modified Peterson alkenylation, 1367
cyclic, elimination, to dienes, 1518
diastereoselectivity, from sulfur ylids, 1383
elimination with diamines, LDA, and DBU, 1519
elimination with organolithium reagents, and alkoxides, 1518
enantioselectivity of halogenation, 0583
enantioselectivity, with sulfur ylids, 1384
from diazoalkanes with aldehydes or ketones, 1384
from dihalides and carbonyl compounds, 1304
from halo-sulfones and ketones, 1384
from halohydrins, 0532
from selenium ylids, 1384
from sulfur ylids and carbonyls, 1382
halogenation, 1791
hydrolysis, 0528
hydrolysis, enantioselective, 0529
in the Stork enamine reaction, 0635
in the Wittig reaction, 0565
in Williamson reaction, 0532
intramolecular alcoholysis of, 0537
lithio, rearrangement, 0564
metal catalyzed azide ring opening, 0564
metal catalyzed halogenation, 0584
metal catalyzed reaction with allylic boranes, 0620
metal catalyzed ring opening, 0563
reagents for elimination, 1518
reagents for halogenation, 0582, 0583
reduction to alcohols, reagents, 1790, 1791
regioselectivity of halogenation, 0583
sterically hindered, hydride reduction, 1791
vinyl, and S_N2' reactions, 0620
vinyl, with Grignard reagents, 0620
epoxides, with acyl halides, 0584
with alcohols, 0536
with allylic silanes, 0589
with amide bases, 0564
with amines or ammonia, 0562, 0563
with ammonium thiocyanates and ceric ammonium nitrate, 1385
with azide ion, 0564
with base, and hydride shifts, 1697
with cyanide, 0649
with dithianes, 0638
with Grignard reagents, 0620
with $LiAlH_4$, 1706
with metal halides, 0582
with mineral acids, 0582
with nucleophiles, 0538
with organocuprates and Lewis acids, 0619
with organometallics, 0618, 0619
with oxazine carbanions, 0642
with phosphine sulfide, 0552
with phosphines, 1374
with silylazides, 0564
with sodium nitrate, 0565
with sulfur ylids, 1383
with tosylamines, 0565
with vinyl sulfides, 0639
epoxy-alcohols, rearrangement of, 0537, 0538
epoxy-carboxylic acids, 0584
epoxy-esters, from diazoesters and aldehydes, 1242
from halo esters, and aldehydes or ketones, 1364
epoxy-hydrazones, and Eschenmoser-Tanabe ring cleavage, 1544
base induced fragmentation, 1544

epoxy-ketones, by Julia-Colonna epoxidation, 1176
photolysis, 0529
rearrangement to diketones, 1588
reduction with silanes, 1798, 1799
EPR, and carbenes, 0285
and electrophilic aromatic substitution, 0677
and radical rearrangements, 1577
and radicals, 0267
equation, Brønsted catalysis, 0373
duel substituent parameter, 0409
Grunwald-Winstein, and solvent effects, 0482, 0505
Hammett, see Hammett
Schrödinger, 0003, 0004
Swain-Lupton, 0409
Swain-Scott, 0493
Taft, 0410, 0411
wave, 0006
equatorial, in chair conformations, 0204
equilibrium constant, 0302
and solvent acidity, 0372
and the Brønsted equation, 0373
and the Hammett equation, 0402
equilibrium, acid-base, 0356
and carbocations, 0467
and HSAB, 0379
and leaving groups, in the tetrahedral mechanism, 1260
and rate-determining state, 0317
and S_N1 reactions, 0437
and solvent acidity, 0371
and tautomerism, 0098
and the aldol condensation, 1342
and the Claisen condensation, 1454
carboxylic acids, water, and alcohols, 1400
cyclopropylcarbinyl versus cyclobutyl cations, 1589
organolithium-alkyl halides, 0250
pyrolysis of alkyl boranes, 1533
Schlenk, 0260, 0261, 0262
ergost-7-en-3-one, 0401
EROS, 1894
erythro nomenclature, 0166
erythro/threo diastereomers, and electrophilic addition, 1001
ESCA (X-ray photoelectron spectroscopy), and carbocations, 0467
Eschenmoser's salt, and Mannich reaction, 1294
Eschenmoser-Tanabe ring cleavage, 1544
Eschweiler-Clarke procedure, 1290
ESR, and azoxy compounds, 0849
and Birch reduction, 1068
and bridged bromine radicals, 1012
and bridged radicals, 0943
and carbenes, 0285
and Grignard reactions, 1308
and kinetics, 0319
and methyl radical, 0276
and radicals, 0267, 0268, 0273, 0445, 0849
and unpaired electrons, 0268
organolithium compounds with alkyl halides, 0599
ester intermediates, and oxidation -reduction, 1706
ester oximes, with acids, 1615
esterases, and resolution, 0176
Marchantia polymorpha, hydrolysis of vinyl acetates, 1401
pig liver, and hydrolysis of esters, 1400
esterification, and Mukaiyama's reagent, 1416
and steric hindrance, 1416
and zeolites, 1415
in ionic liquids, 1415
Mitsunobu reaction, 0540
of carboxylic acids, 1414, 1415, 1417
esters of carboxylic acids, see carboxylic esters
esters, allylic, also see carbonates, allylic
esters, imino, see imino esters
esters, inorganic, decomposition to alkenes, 1521
from alcohols, 0545
esters, manganate, 1163
esters, nitrate, from alkyl halides, 0546
esters, nitrite, from alcohols, 0545
esters, of inorganic acids, hydrolysis, 0522
esters, ortho, see ortho esters
esters, osmate, 1163
esters, osmic, 1181
esters, phosphonate, from alcohols, 0545
esters, phosphonic, with Grignard reagents, 0613
esters, sulfamate, see sulfamate esters
esters, sulfinate, see sulfinate esters
esters, sulfinic, see sulfinic esters
esters, sulfonate, see sulfonate esters
Etard reaction, 1763
ethane, energy barrier to rotation, 0197
energy diagram, 0198
supercritical, hydrogenation of aromatic compounds, 1066
ethanolamines, and dealkylation, 0562
as solvents, 0563
ethanolysis, also see solvolysis
of alkyl tosylates, rate of reaction, 0482
ethanonium ion, IR, 0766
ethene, see ethylene
ether solvents, see solvents, ether
ethers, acidity, 0383
ethers, alkynyl, hydration of, 1036
ethers, allyl allene, and Claisen rearrangement, 1670
ethers, allyl vinyl, and [3.3]-sigmatropic rearrangement, 1655
ethers, allylic, and Wittig rearrangement, 0641
carbanions, and alkylation, 0641
cleavage with Grignard reagents, 0617
pyrolysis, 1552
with organolithium reagents, 0641
ethers, and ionic liquids, 0529
and the Mitsunobu reaction, 0530, 0535
and the Wittig rearrangement, 1624
and ultrasound, 0530
ethers, aryl allyl, Claisen rearrangement of 2-allyl phenols, 1668

ethers, aryl, deoxygenation, 0748
from alkoxides and aryl halides, 0871
with Grignard reagents, 0598
ethers, azacrown, 0121
azacrown, photoisomerization, 0346
base-induced elimination, 1516
benzyl silyl, oxidation to aldehydes, 1720
benzylic, hydrogenation, 0580
by insertion of carbenes, 0804
by reduction of thiono esters, 1839
by the Williamson reactions, 0529
ethers, cleavage, 0542, 0547, 0561, 0580, 0581, 0582, 0617
ethers, crown, 0119–0125
and ambident nucleophiles, 0517
and chirality, 0152
and complex formation, 0119
and hydrogen bonding, 0122
and molecular recognition, 0124
and phase transfer catalysis, 0510
and spherands, 0122
as cavitands, 0122
as hosts, 0120
bicyclic, 0122
binding K^+ or Li^+, 0120
cryptands, cryptaphanes, and hemispherands, 0123
in guest-host interactions, 0122
in synthesis, 0121
ion binding, 0120
ion-dipole interactions, 0124
lariat ethers, 0123
macrocyclic, 0121
NMR and guest-host interactions, 0124
podands, 0123
starands, 0124
ethers, cyclic, cleavage, 0581
from alcohol, with lead tetraacetate, mechanism, 0966
from alcohols, 0964
from epoxides, 0537
from oxidation of alcohols, reagents, 0965
from thionolactones and organolithium reagents, 1330
α-oxidation to lactones, 1760
transetherification, 0536
ethers, demethylation, 0550
enol ethers, allyl, and Fischer indole synthesis, 1675
and transetherification, 0536
base induced elimination of acetals, 1516
by Wittig reaction, 1372
Claisen rearrangement, 1669
from alcohols, 0536
oxidation to carboxylic acids, 1775
pyrolysis to alkenes and aldehydes, 1517
ethers, enol, addition of hydrazoic acid, 1053
and Mukaiyama aldol, 1354
and Wittig rearrangement, 1625
cleavage by Grignard reagents, 0617
elimination of ketals, 1517
from acetals or ketals, 1271
from alkynes and alcohols, 1038
from enols, 0534
from esters, 1380
hydrolysis, 0523, 1035, 1372
hydrolysis mechanism, 0527
Mannich reaction with imines, 1295
with alcohols, 1039
with alcohols and halogens, 1154
with protons, 1006
ethers, formation of amines, 0559
ethers, from acetals, 0616
from alcohols, 0533, 0534
from alkenes and alcohols or phenols, 1037
from alkoxides, 0529, 0532
from alkyl halides, 0529
from alkyl sulfates, 0532
from diazo compounds, 0533, 0534
from Grignard reagents, 0616, 0814
from inorganic esters, 0532
from onium salts, 0538
from oxonium salts, 0582
from phenols, 0533, 0535
ethers, halo, and elimination with magnesium, 1542
and the Boord reaction, 1541
by radial halogenation, 0956
from alcohols and halogens, 1154
metal induced elimination to alkenes, 1541
ethers, homoallylic, by coupling of silanes, 0977
hydrolysis of, 0533
lariat, 0123
metal catalyzed cleavage, 0581
nitrate, from alcohols, 0545
α-oxidation to carboxylic esters, 1759
oxidative cleavage of carboxylic acids, 1769
photochemistry, 0332
radical dimerization, 0977
reduction of esters, reagents, 1839
reduction to hydrocarbons, reagents, 1831
reductive alkylation of aldehydes, 1273
reductive dealkylation, reagents, 1831
selenoalkyl, 1038
ethers, silyl enol, see enol ethers
ethers, silyl, conversion to alkyl iodides, 0580
tetrahydropyranyl, oxidation, and zeolites, 1720
thiacrown, 0121
transetherification, 0535
Ullmann ethers synthesis, 0873
ethers, vinyl, see ethers, enol
with alkyl halides, 0543
with anhydrides, 0542
with mineral acids, 0580, 0581, 0582
with organolithium reagents, Wittig rearrangement, 1624
with sulfonic acids, 0546
with sulfuric acid, 0523
ethyl nitrate, and nitration of aromatic compounds, 0688
ethylene oxide, strain, 0217
ethylene, and electronic structure, 0015
and hybrid orbitals or π orbitals, 0009
and π-bonds, 0042
complex with silver, 0116, 0117

ozonolysis, formation of dioxirane, 1741
ethylenediaminetetraacetic acid, and Udenfriend's reagent, 0965
ethylmagnesium bromide, and X-ray, 0260
ethyne, addition of HCN, 1147
excited state, 0334
orbitals, σ electrons, and triple bonds, 0010
europium compounds, chiral shift reagents, 0181
Evans auxiliaries, and the Claisen condensation, 1356
exchange reaction, carboxylic acids, and acyl halides, 1441
exchange, carboxylic acids and amides, 1423, 1432
carboxylic acids and esters, 1423
halogen-metal, and organocuprates, 0603
hydrogen, 0684
Li-H, and organolithium compounds, 0595
metal-halogen, and organolithium compounds, 0594, 0595
R_2Mg and R_2Hg compounds, 0251
exciplex formation, in photochemistry, 0342
exciplex, and photochemical [2 + 2]-cycloaddition, 1232
exciplex, and rotaxanes, 0132
excitation, electronic, 0332
excited states, 0334–0339
Jablonski diagram, 0337
photosensitization, 0340, 0341
physical processes, 0336
exhaustive alkylation, and amines, 0556
exo addition, and bicyclic alkenes, 1023
Diels-Alder reaction, 1201
extinction coefficient, 0330
extrusion of metals, and cyclotrimerization, 1246
extrusion of nitrogen, mechanism, 1554
extrusion of sulfur dioxide, from sulfones, 1556
extrusion reactions, and elimination, 1477
definition, 1553
the Ramberg Bäcklund reaction, 1538
F values, and σ values, 0410
faces, diastereotopic and enantiotopic, 0194
facial selectivity, see selectivity
far-UV, and photochemistry, 0329
Favorskii reaction, in connection with the Nef reaction, 1360
Favorskii reaction, mechanism, 1360
Favorskii rearrangement, 1595, 1597
Favorskii, quasi-, rearrangement, 1598
Felkin-Ahn model, 0169
Felkin-Ahn rule, and addition of radicals, 1015
Fenton's reagent, 0964
and heterocycles, 0983
ferrocene, bonding, 0066
electrophilic aromatic substitution, 0674
structure, 0117
ferrous sulfate, and peroxides, 0964
field effect constants, 0406
field effects, 0019, 0020
+I and −I, 0021, 0396
+M and −M, 0396
and acid strength, 0380
and arenium ions, 0667
and aromatic compounds, 0021
and base strength, 0380
and carbanions, 0255
and carboxylic acids, 0020
and hybridization, 0022
and pK_a, 0381
and reactivity, 0396
and σ values, 0407–0409
and σ* values, 0407
and substituent effects, 0483
and the Hammett equation, 0402
and ylids, 0255
Fieser's Reagents for Organic Synthesis, 1897
Finkelstein reaction, 0574, 0575
first-order reactions, 0315, 0316, 0433
and racemization, 0437
first-order rate constant, 0320
first-order rate law, 0319
and neighboring groups, 0446
Fischer carbene complexes, and Dötz benzannulation, 1247
Fischer indole synthesis, scope and mechanism, 1674, 1675
Fischer projection, definition of, 0153
Fischer, Emil, 0153
Fischer-Hepp rearrangement, and urea, 0739
flash photolysis, 0348
and the photo-Fries rearrangement, 0737
of bromoform, 0287
flash vacuum pyrolysis, and alternant aromatics, 1646
and vinylcyclopropane rearrangement, 1657
of halocyclopropanes, 1591
of phosphorus ylids, 1525
fluoranthene, and complex formation, 0124
fluorene, pK_a, 0063
fluorides, acyl, 1440, 1441
alkyl, base induced elimination, and Hofmann's rule, 1531
and Tamao-Fleming oxidation, 0539
aryl, and the Schiemann reaction, 0921
aryl, from aryl diazonium salts, 0985
aryl, from HF, 0921
Finkelstein reaction, 0574, 0575
fluorinating agents, 0574
from alcohols, 0577
from arylthallium compounds, 0913
from tetrafluoroborate salts, 0819
sulfonyl, 0698
fluorinated compounds, enol content, 0101
fluorinated solvents, and the Heck reaction, 0893
fluorinating agents, 0574
fluorination, of amides, 0782
of aromatic compounds, 0704
of carboxylic acids or carboxylic esters, 0782
fluorine, addition to alkenes, 1149
and halogenation of aromatic compounds, 0704
and keto-enol tautomerism, 0101
electronic versus radical pathways, 0956
handling fluorine, 0955

fluoroborates, acyl and acetic anhydride, 1186
fluorosulfonic acid-SbF_5, superacid, 0358
fluorosulfuric acid, and cation stability, 0236
fluorous osmium tetroxide, 1163
fluoroxytrifluoromethane, and fluorine radicals, 0955
fluxional isomerization, 0186
FMO (frontier molecular orbital) and cycloadditions, 1190, 1191
forbidden transition, in photochemistry, 0331
formal charge, and bonding, 0016
formal steric enthalpy, 0232
formaldehyde, acid catalyzed addition to alkenes, 1393
  and amines, 0730
  and chloromethylation, 0717
  and the Eschweiler-Clarke procedure, 1290
  and the Mannich reaction, 1292
  and the Prins reaction, 1393
  and the Tollens' reaction, 1368
  and trioxane, 1460
  excited state, 0334
  with aromatic compounds, 0717
  with glycoluril, 0135
formamides, and phosphorus oxychloride, 0797
  and the Leuckart reaction, 1291
  and the Wallach reaction, 1291
  and Vilsmeier-Haack reaction, 0724
  by hydrogenation of isocyanates, 1813
  by hydrolysis of isocyanides, 1467
  carbonylation of amines, 0850
  from chloroamines, 0568
  with acetals, 0797
  with aromatic compounds, 0724
  with Grignard reagents, 1447
  with organolithium reagents, 1446
formamidines, alkylation, 0641
formate, ammonium, with amines, 0850
  and enantioselective reduction, 1802
  and reduction of aldehydes or ketones, 1799
  with Pd/C, and reduction of conjugated aldehydes, 1074
formates, chloro, see chloroformates
formation, of vinyliodonium salts, 0818
formic acid, and the Koch-Haaf reaction, 1137
  and the Wallach reaction, 1290
  formation of formates, 1799
  from chloroform, 0521
  with Grignard reagents, 0823
  with hydroxylamine and aldehydes, 1287
  with reductive alkylation, 1290
formic anhydride, 0723, 1430
formula Periodic table, for benzenoid polyaromatics, 0058, 0059
formyl chloride, 0723
formylation, alternative methods, 0727
  and carbenes, 0726
  and formamides, 0797
  and Friedel-Crafts acylation, 0721
  and organolithium reagents, 0727
  and paraformaldehyde, 0727
  and the Duff reaction, 0727
  and the Gatterman or Gatterman-Koch reaction, 0725
  and the Reimer-Tiemann reaction, 0726
  of alkenes, 0797
  of aromatic compounds, 0724
  of ketones, 0798
formylcarbene, lifetime, 0288
four-center mechanism, addition to alkenes, 1013
  and hydroboration, 1078
fractional distillation, and diastereomers or resolution, 0174
fractional recrystallization, and diastereomers, 0174
fragmentation mechanism, 1542
fragmentation, definition, 1542
  of carbenes to radicals, 0292
  of epoxy hydrazones, base induced, 1544
free energy, amide hydrolysis, 0397
  and carboxylic acids, 0394
  and catalysis, 0313
  and enthalpy or entropy, 0300
  and kinetic control, 0308
  and reaction intermediates, 0305
  and S_N2 reactions, 0431
  and S_NAr reactions, 0867
  and solvent acidity, 0371
  and solvent effects, 0505
  and the Brønsted equation, 0373
  and the Grunwald-Winstein relationship, 0406
  and thermodynamic control, 0308
  equation, 0300
  intrinsic, 0309
  linear, 0405, 0406
  of activation, 0301
  spontaneous reactions, 0299
free radicals, see radicals
free-radical addition, 0298
free-radical mechanism, 0297
free-radical rearrangement, 0299
free-radical substitution, see substitution
freezing point depression, and Grignard reagents, 0261
  and organometallics, 0259
Fremy's salt, and oxidation of phenols, 1729
  oxidation of alcohols, 1720
frequency factor, and rate law, 0322
Friedel-Crafts acylation, 0697, 0719–0723
  alternative formylation methods, 0727
  and formylation, 0721
  and the Gatterman amide synthesis, 0728
  and the Gatterman reaction, 0725
  and the Haworth reaction, 0722
  and the Vilsmeier-Haack reaction, 0724
  biaryls, 0723
  carbonylation, 0723
  catalysts, 0719
  formation of aldehydes, 0724
  formation of aryl ketones, 0732
  formation of carboxylic acids, 0728
  Fries rearrangement, 0720, 0735

no rearrangement, 0719
with acyl carbocations, 0722
with carboxylic acid derivativess, 0719
with cyclic anhydrides, 0722
with formamides, 0724
with heterocyclic compounds, 0720, 0721
with ketenes, 0719
with keto-acids, 0722
with mixed anhydrides, 0721
with phosgene, 0728
with sulfonic anhydrides, 0720
Friedel-Crafts alkylation, 0705–0712
activating groups in the product, 0708
alkyl migration, 0741
and cyclodehydration, 0715
and rearrangement of carbocations, 0710
and the Pechmann condensation, 0712
and the S_N2 mechanism, 0712
chiral catalysts, 0709
coordination of Lewis acids, 0709
cyclization, 0710
deactivated compounds, 0709
fused ring aromatics, 0709
of coumarins, 0712
of naphthalene, 0709
polyalkylation, 0708
reactivity order of Lewis acids, 0708
reverse, 0742–0744
with alcohols, 0707
with alkenes or alkynes, 0706, 0707
with alkyl halides, 0706
with epoxides, 0619, 0707
with heterocyclic compounds, 0709
Friedel-Crafts arylation, and the Hoesch reaction, 0732
Friedel-Crafts catalysts, addition of alkyl halides to alkenes, 1160
dehalogenation of aryl halides, 0749
Friedel-Crafts coupling, and atropisomerism, 0714
Friedel-Crafts coupling, cyclization, 0721
formylation, 0724
with aldehydes and ketones, 0714
Friedel-Crafts cyclization, 0715
and the Pictet-Spengler reaction, 0716
Bischler-Napieralski reaction, 0715, 0716
high dilution methods, 0721
Friedel-Crafts reaction, and the Bradsher reaction, 0715
and the Duff reaction, 0727
chloromethylation and haloalkylation, 0717
with alkenes, 0796
with heterocycles, 0983
friedelin, and Wagner-Meerwein rearrangement, 1583
Friedländer quinoline synthesis, 1282
Fries rearrangement, 0735, 0736
and Friedel-Crafts acylation, 0720
Fries, photo, see photo-Fries
Fritsch-Buttenberg-Wiechell rearrangement, 1534
frontier molecular orbitals, see FMO
frontier orbital method, 1208–1210
electrocyclic rearrangements, 1635
Fukuyama coupling, 1450
fulgide, and helical chirality, 0150
fullerenes, and aromaticity, 0094
and MO calculations, 0094
and rotaxanes, 0131, 0134
and the ene reaction, 1104
bowl-to-bowl inversion and homofullerenes, 0095
synthesis, 0095
fulminene, 0087
fulvalenes, 0068
and aromaticity indices, 0069
by Nazarov cyclization, 1096
from alkynes, 1096
fumaric acid, 0185
fuming sulfuric acid, with aromatic compounds, 0695
functional group compatibility, Darzens condensation, 1365
functional group, reactivity with sodium borohydride, 1794
functional groups, and catalytic hydrogenation, 1054
and hydroboration, 1079
ease of reduction, 1787–1790
for the Knoevenagel reaction, 1358
furan, and aromaticity, 0062
catalytic hydrogenation, 1066
electrophilic aromatic substitution, 0675
resonance energy, 0062
furanose compounds, and tautomerism, 0104
furans, Birch reduction, 1067
by metal catalyzed reaction with alkynyl ketones, 1272
by Suzuki-Miyaura coupling, 0901
Diels-Alder reaction, 1217
formation of 1,4-diketones, 0528
Friedel-Crafts acylation, 0720
Friedel-Crafts alkylation, 0709
from alkynes, 1038
from diketones, 1272
halogenation, 0703
fused aromatic compounds, and bond distance, 0060
and resonance energy, 0060
fused ring aromatic compounds, 0052
fused rings, electrophilic aromatic substitution, 0674
fused-ring aromatics, Friedel-Crafts alkylation, 0709
Fuson-type enols, 0100

γ-substituents, and substitution reactions, 0485
Gabriel synthesis, 0556, 0569
and arylation of amines, 0879
and hydrazine, 0569
hydrolysis reagents, 0570
Ing-Manske procedure, 0569
galvinoxyl, radical inhibitor, 1122
gas chromatography, see GC
gas phase, pyrolysis of carboxylic acids, 1520
gas vacuoles, and sonochemistry, 0349, 0350
Gatterman amide synthesis, 0728
Gatterman method, 0926
Gatterman reaction, 0725, 0984
Gatterman-Koch reaction, 0725
Gatterman-Koch reaction, reverse, 0745

gauche conformations, see conformations
gauche orientations, and E2 reactions, 1485
GC, and diastereomers and resolution, 0174, 0175
and determining absolute configuration, 0159
and enantiomeric purity, 0181
and enolizable protons, 0775
geared molecules, 0231
gegenion, of carbocations, 0236
gem-dihalides, see dihalides
gem-dimethyls, by hydrogenation of cyclopropanes, 1075
general acid catalysis, 0373, 0525
geometric structure, carbocations, and migratory aptitudes, 1571
geometry, alkenes, and photochemistry, 0346
of carbenes, 0286
of electrophilic allylic rearrangement, 0763
of hydrogen bonds, 0108
of propellanes, 0223
of radicals, 0276, 0277
gerade orbital, 0005
Gilman reagents, 0600
Gilman reagents, also see organocuprates
Girard's reagents P and T, and hydrazones, 1285
Glaser reaction, 0978, 0979
glyceraldehyde, and absolute configuration, 0154
glyceric acid, chiral, from glyceraldehyde, 0154
glycidic acids, decarboxylation, 0837
glycidic esters, 1364
glycidic esters, also see epoxy esters
glycols, see diols
glycoluril, with formaldehyde, 0135
glycosides, and the anomeric effect, 0210
glyoxals, and the benzoin condensation, 1396
Goldberg reaction, 0876
Gomberg-Bachmann pinacol synthesis, 1854
Gomberg-Bachmann reaction, 0924–0926
Gossypium hirsutum, α-hydroxylation, 1756
graphite ribbons, see phenacenes
green chemistry, 0413
Grignard reactions, 1300–1309
Grignard reagents, also see organomagnesium
Grignard reagents, addition to aldehydes or ketones, mechanism, 1307
addition to alkenes, 1083
addition to aromatic compounds, 1119
amination, 0880
Grignard reagents, and alkylation of aromatic compounds, 0912
and alkylation or aryl nitro compounds, 0914
and boiling point elevation, 0261
and CIDNP, 0832
and cleavage of allylic or vinylic ethers, 0617
and conformational stability, 0262
and dehalogenation of aryl halides, 0750
and ESR, 1308
and freezing point depression, 0261
and hydrogen-metal exchange, 0834
and hydroxymethylation, 1305
and metal additives, 1306
and metal salts, radicals cyclization, 1126
and NMR, 0262
and Schlenk equilibrium, 0260, 0261, 0262
and SET mechanism, 0832
and the benzyne mechanism, 0887
and the Bruylants reaction, 0614
and the Wurtz reaction, 0987
Grignard reagents, aryl, 0262
and coupling, 0599
formation of, 1301
hydrolysis, 0751
Grignard reagents, bonding, 0260
complex formation, 0260, 0261
conjugate addition, 1112, 1114
coupling with alkyl halides, 0590, 0599
deprotonation by, 0809
diastereoselective reactions, 1303
from alkyl halides, 0829
from dihalides, 0830
hydrolysis, 0812
hydrolysis, and reduction of alkyl halides, 1828
in dioxane, with magnesium halide, 0260
in ether solvents, 0260–0262
in HMPA or triethylamine, 0262
initiators, 0830
interfering groups, 0830
mechanism of formation, 0832
metal catalyzed addition to alkenes or alkynes, 1096, 1097
metal catalyzed coupling, 0600, 0987
metal catalyzed cyclization, 0987
metal mediated coupling, 0596
nitrogen-containing, 0830
optical activity, 0756
protonation of, 0812
reduction with, mechanism, 1308
stability, 0831
structure, 0260
vinyl, formation of vinyl boronic esters, 0816
Grignard reagents, with acetals, 0616
with acyl halides, 1444
with acyl peroxides, 0814
with aldehydes, 1300–1309
with alkyl borates, 0816
with allyl halides, 0634
with amides, 1445, 1447
with amino-ethers, 0617
with anhydrides, 1445
with aryl halides, 0598
with azides, 0880
with aziridines, 0621
with boron trifluoride, 0827
with carbon dioxide or carbon disulfide, 1330
with chloroformates, 1445
with chloroiminium salts, 1336
with conjugated compounds, 1302
with epoxides, 0618, 0620
with esters, 1445

with formamides, 1447
with formic acid, 0823
with imines, 1331
with iminium salts, 1336
with iron pentacarbonyl, 0823, 0910
with isocyanates, 1337, 1338
with isocyanides, 1469
with ketones, 1300–1309
with metal halides, 0826
with metal halides, mechanism, 0826
with nitriles, 1337
with nitriles, mechanism, 1338
with nitrones, 1336
with ortho esters, 0616
with oxygen, 0831
with phosphonic esters, 0613
with propargyl esters, 0609
with propargyl halides, 0596
with selenium, 0818
with sulfonate esters, 0590
with sulfones, 0888
with sulfonyl halides, 1475
with sulfur, 0818
with sulfuryl chloride, 0818
with tellurium, 0818
with vinyl epoxides, 0620
with vinyl halides, 0600
with water, 0831
with Weinreb amides, 1448
Grignard reagents, X-ray diffraction, 0260
ground state, and excited state in photochemistry, 0329
Grovenstein-Zimmerman rearrangement, 1585
Grubbs catalysts I and II, for metathesis, 1683
and ring opening metathesis polymerization, 1685
Grunwald-Winstein equation, and solvent effects, 0505
and solvolysis, 0482
Grunwald-Winstein, relationship, 0406
guanidine-nitric acid, 0686
guanidines, addition of ammonia to cyanamide, 1296
and alkyl halides, 0570
and formation of aziridines, 0565
and supercritical ammonia, 0415
from amines, 1296
guest ions in guest-host complexes, 0120
guest-host complexes, see complexes
guest-host interactions, 0125–0128
guests, in guest-host interactions, 0127
gyroscane, 0135

half-chair conformation, and cyclopentane, 0212
half-life, definition, 0320
enol tautomerization, 0770
of equatorial chair conformation, 0204
halide exchange, 0883, 0884
halide ions, and phase transfer, 0575
Finkelstein reaction, 0574
with ditosylamines, 0586
halide reactivity, in E^i reactions, 1509
halides, acyl, and acyl carbocations, 0722
and amino acids, 0789
and enamines, 0635
and Friedel-Crafts acylation, 0721
and nitration of anilines, 0688
and O-acylation, 1451
and Rosenmund reduction, 1808
and Suzuki-Miyaura coupling, 0903
and the Arndt-Eistert synthesis, 1457
and the Schotten-Baumann procedure, 1411, 1427
and the tetrahedral mechanism, 0482
and the Wurtz reaction, 1451
halides, acyl, base induced elimination to ketenes, 1532
coupling to diketones, 1450
decarbonylation, 0749
exchange with carboxylic acids, 1441
for acylation, 1451
formation of acyl azides, 0573
Friedel-Crafts acylation, with alkenes, 0796
from aldehydes, 0964
from carboxylic acids, 1440
from halogens, 0964
from ketenes and HX, 1031
from oxalyl halides and carboxylic acids, 1441
from trihalides and sulfur trioxide, 0521
hydrogenolysis, 1808
hydrolysis, reactivity order of halides, 1398
intramolecular Friedel-Crafts acylation, 0721
Lewis acid catalyzed addition to alkenes, 1161
metal catalyzed decarbonylation to alkenes, 1534
metal induced dehalogenation to ketenes, 1540
peroxides induced decarbonylation, 0997
reactivity order, in acyl halide hydrolysis, 1398
reduction to alcohol, 1840
reduction to aldehydes, reagents, 1808
halides, acyl, with active methylene compounds, 1451
with alcohols, 1411
with alkenes, 0796
with amides, 1439
with ammonia or amines, 1427
with aromatic compounds, 0719
with arylboronic acids, 0903
with azide ion, 0571
with boronic acids, 1443, 1444
with carboxylates, 1422
with copper cyanides, 1457
with diazomethane, 1457, 1599
with epoxides, 0584
with ethers, 1412
with Grignard reagents, 1444
with hydrogen peroxide, 0545
with hydrogen sulfide, 1425
with ketones, 1274
with organocadmium reagents, 1443
with organocuprates, 1442
with organometallic reagents, 1443, 1444
with thiols, 1412, 1425
with urea, 1439
halides, alkyl, addition to alkenes, Friedel-Crafts catalysts, 1160
halides, alkyl, alkylation and ultrasound, 0512

halides, alkyl, and anti elimination, 1480
and B strain, 0398
and bond angle, 0026
and carbamate formation, 0542
and carbanions, 0265
and carbocations, 0237, 0434
and E2 reactions, 1478–1486
and formation of amines, 0559
and formation of aryl halides, 0705
and formation of carbenes, 0287
and formation of isocyanates or isothiocyanates, 0573
and formation of onium salts, 0376
and formation of sulfonate esters, 0546
and halide ions, 0574
and I strain, 0399
and microwaves, 0577
and phase transfer, 0576
and S_N1 reactions, 0434
and strain in carbocation formation, 0398
and the S_N1 mechanism, 0398
and Wurtz coupling, 0589
halides, alkyl, base induced elimination, suitable bases, 1530
base induced elimination, and Hofmann's rule, 1531
base induced elimination, and Zaitsev's rule, 1531
by Lewis acid catalyzed addition to alkenes, 1159
by Lewis acid catalyzed addition to alkynes, 1160
by Lewis acids and organocopper compounds, 0604
by the Katritzky pyrylium-pyridinium method, 0586
carbonylation with alcohols, 0654
carbonylation with sodium tetracarbonylferrate, 0653
catalytic hydrogenation, 1826
chemoselective reduction, 1827
coupling with dihalides, 0598
coupling with Grignard reagents, 0590, 0599
coupling with lithioalkynes, 0595
coupling with metals, 0589
coupling with organocuprates, 0599
coupling with π-allylnickel complexes, 0593
cyclohexyl, and E2 reactions, 1481
dehalogenation, reagents, 1824–1827
diastereomers and stereochemistry of elimination, 1502
electrochemical coupling, 0598
electrochemical reduction, 1826
enantiopure, and E2 reactions, 1480
exchange with organolithium reagents, 0250
halides, alkyl, from alcohols, 0520, 0559, 0576
from alkanes, 0954–0960
from alkyl halides, 0574, 0833
from alkyl sulfates, 0576
from alkylsulfonic acids, 0996
from amines or ammonium salts, 0586
from carboxylic acids, and reagents for, 0995, 1426
from carboxylic esters, 0584, 0585
from cyanogen bromide, 0586
from ethers, 0580, 0581, 0582
from Grignard reagents, 0819
from halogens, 0954–0960
from mineral acids, 0576
from organometallics, 0819
from oxonium salts, 0582
from silyl ethers, 0580
from sliver carboxylates, 0994
from sulfonate esters, 0575, 0576
from thioethers, 0639
from thiols, 0579
from thionyl chloride, 0576
from trialkylsilyl halides and alkenes, 1031
from trichloroisocyanuric acid and alkenes, 1031
halides, alkyl, halogen replacement, 0833
hydrolysis of, 0519
in the Finkelstein reaction, 0574
in the Gabriel synthesis, 0556, 0569
in the Hunsdiecker reaction, 0994
in the Kornblum reaction, 1765
in the Mentshutkin reaction, 0555
in the von Braun reaction, 0586
in water, 0519
ionization to carbocations, 0247
Lewis acid catalyzed addition to alkenes, 1159
mechanism of hydrolysis, 0519
meso, and E2 reactions, 1480
metal catalyzed carbonylation, 0654
metal induced elimination to alkenes, 1539
metal mediated, 0590
metal mediated carbonylation, 0652
metal mediated coupling with alkynes, 0647
metal mediated coupling with allylic halides, 0597
metal mediated coupling, unsymmetrical, 0593
oxidation to aldehydes, 1765
oxidation to aldehydes, the Sommelet reaction, 1766
oxidation with DMSO, mechanism, 1766
oxidative coupling with base, 1783
primary, and S_N1 reactions, 0505
radical conjugate addition, 1122
rate of E2 reactions, 1481
rates of solvolysis, 0480
reaction with aromatic compounds, 0705
reactivity as a function of the halide, 0556
reactivity in carbonylation reactions, 0653
reactivity in elimination reactions, 1502, 1503
reactivity with ethanol, 0398
reduction by hydrolysis of Grignard reagents, 1828
reduction to hydrocarbons, reagents, 1824–1827

reduction with $LiAlH_4$, and SET mechanism, 1828
reduction with Raney nickel, 1826
reduction with trialkyltin hydrides, 1825, 1826
S_N1 in sulfur dioxide, 0434
solvolysis and carbocations, 0325
solvolysis and I strain, 0399
solvolysis and mechanism, 0325
steric hindrance and reactivity, 0398
substituent effects n E2 reactions, 1504
terrtiary, elimination in the Stork enamine reaction, 0635
trialkylsilyl, with alkenes, 1031
trihalides, see trihalides
halides, alkyl, with acetylide ion, 0646
with active methylene compounds, 0622, 0623
with alkoxides, 0529
with alkyl diazotates, 0573, 0574
with amide bases, 0568
with amines or ammonia, 0555, 0558, 0876
with arylboronic acids, 0889
with azide ion, 0571, 0572
with carboxylate salts, 0539
with Collman's reagent, 0650
with cyanide ion, 0515, 0648
with cyanohydrins, 0649
with dianions, 0515
with disulfide ions, 0553
with enolate anions, 0515, 0622, 0623
with ethers, 0543
with Grignard reagents, 0262
with Group I and II organometallics, 0594, 0595
with guanidine, 0570
with hydroperoxide ions, 0544
with hydroxide, 0519
with isonitriles, 0648
with lactams, 0512, 0569
with lithio propargyl compounds, 0596
with metal cyanides, 0648
with metals, 0829, 0831
with nitrite ions, 0515
with nitro compounds, 0515
with organocuprates, 0600, 0603
with organolithium compounds, ESR and CIDNP, 0599
with organolithium compounds, 0594, 0595
with organolithium reagents, radical intermediates, 0269, 0270
with organometallic compounds, and radicals, 0599
with organometallic compounds, mechanism, 0598
with organometallics, 0604, 0605, 0606, 0607, 0833
with organopotassium or organosodium, 0594, 0595
with organozinc compounds, 0605
with oxazine carbanions, 0642
with oximes, 0547
with phenoxide ions, 0515
with phosphines, 1369
with phosphites, 1375
with selenide ions, 0552
with silver compounds, 0505
with sodium nitrite, 0571
with sodium sulfide, 0551
with sulfonamides, 0570
with sulfonic acid salts, 0554
with telluride ions, 0552
with thiocyanate ion, 0554
with thiols, 0549
with thiosulfate ion, 0553
with thiourea, 0548
with triethylborane, 0520
with trimethylsilyl cyanide, 0649
halides, allylic, and Pd complexes, 0043
coupling, 0592
formation with no rearrangement, 0576
from allylic esters, 0585
in the Delépine reaction, 0558
metal mediated coupling with alkyl halides, 0597
with anilines and hyponitrites, 0923
with carbanions, 0594
with Grignard reagents, 0634
with organometallics, 0604, 0605, 0606, 0607
halides, aryl, also see fluorides, chlorides, bromides, iodides
halides, aryl, and carbonylation with alcohols, 0909
and halide exchange, 0883
and Orton rearrangement, 0740
and Sonogashira coupling, 0904
and $S_{RN}1$ mechanism, 0862
and Stephens-Castro coupling, 0903–0906
and Suzuki-Miyaura coupling, 0899–0903
and the halogen dance, 0749
halides, aryl, arylation of alkenes, metal catalyzed, 0891–0897
carbonylation, 0909, 0910
coupling with active methylene compounds, 0906–0908
coupling with alkenes, 0891–0897
coupling with enolate anions, 0906–0908
coupling with heterocycles, 0887
cyanation, 0885
dehalogenation, 0749, 0750
electrochemical carbonylation, 0909
formation of aryl selenides, 0552
formation of ketones, 0910
Friedel-Crafts alkylation, 0705
from alkyl halides, 0705
from amines, replacement of alkyl groups, 0875
from anilines, 0985
from aryl halides, 0883
from aryldiazonium salt, 0984
from arylsulfonyl halides, 0749
halide exchange, and microwaves, 0884
heteroaryl, coupling with alkenes, 0891
homocoupling, in ionic liquids, 0887
hydroxylation, 0870
in the Gatterman reaction, 0984
in the Goldberg reaction, 0876
in the Heck reaction, 0891–0897
in the Hurtley reaction, 0907
in the Sandmeyer reaction, 0984

halides, aryl, arylation of alkenes, metal catalyzed, (*Continued*)
in the Stork enamine reaction, 0635
in the Ullmann reaction, 0897
intramolecular carbonylation, 0909
intramolecular Heck reaction, 0892
metal catalyzed alkylation, 0629
metal catalyzed carbonylation, 0909
metal catalyzed coupling with enolate anions, 0907
metal catalyzed coupling with silylalkynes, 0905
metal catalyzed reaction with alkoxides, 0873
metal catalyzed reaction with phosphines, 0881
metal mediated coupling, 0897
phenoxides in ionic solvents, 0872
photochemical coupling with aromatic compounds, 0981
reaction with amines, 0875
reactivity order in benzyne mechanism, 0860
reactivity, in metal mediated coupling, 0592
reagents for homocoupling, 0887
rearrangement, 0749
substitution by amines, base catalysis, 0856
synthesis of, 0884
halides, aryl, with active methylene compounds, benzyne mechanism, 0906
with acyl aniline derivatives, 0740
with alkenes, also see Heck reaction
with alkoxides, 0871
with alkynes, 0899, 0904
with alkynes, see Sonogashira
with allylic esters, 0609
with amide bases, 0568, 0876
with amides, 0880, 0855
with amines, metal catalyzed, 0693
with aryl halides, benzyne mechanism, 0887
with arylborates, 0902
with arylboronic acids, 0899–0903
with carboxylate salts, 0872
with enolate anions, 0890
with enolate anions, enantioselectivity, 0907
with heterocycles, 0881
with hydrosulfide anion, 0874
with hydroxide, 0870
with lactam enolate anions, 0907
with lactams, 0880, 0881
with Lewis acids, 0749
with metal halides, 0883
with metals, 0750
with organolithium compounds, 0595
with organolithium reagents, 0884, 0886
with organometallics, 0604, 0605, 0606, 0607, 0750, 0886
with oxazolidinones, 0881
with phenols, in ionic liquids, 0873
with phenoxides, and microwaves, 0872
with selenide anions, 0875
with silylamines, 0878
with sulfonate anions or sulfonic acid salts, 0875
with sulfoxides, 0890
with sulfur nucleophiles, electrochemistry, 0874
with sulfur nucleophiles, in ionic liquids, 0874
with thiolate ions, 0874
with thiophenes, 0881
with triaryl phosphate, 0873
with trifluoroborates, 0890, 0903
with vinylboranes, 0607
with vinylboronic acids, 0890
with vinyltrifluoroborates, 0897
halides, benzylic, from alcohols with microwaves, 0512
in the Delépine reaction, 0558
oxidation by the Krönke reaction, 1766
oxidative coupling to alkynes and tolanes, 1783
solvolysis, 0486
with pyridine, 0096
halides, carbamoyl with organocuprates, 1428
halides, carbon tetrahalides and complex formation, 0119
halides, carbonylation, 0910
halides, cyanogen, with phenols, 0531
halides, cyclopropyl, and allylic carbocations, 0487
halides, cyclopropylcarbinyl, and organocuprates, 0473
halides, diarylmethyl, 0434
halides, dihalides, see dihalides
halides, from alkenes, 1144
halides, inorganic, with carboxylic acid derivatives, 1441
halides, lithium-betaines, 1374
halides, magnesium, Grignard reagents, 0260
halides, metal, also see metal halides
halides, metal, and transmetallation, 0826
with alcohols, 0578
with aryl halides, 0883
with aryldiazonium salts, 0984
with carboxylic acids, 1426
with epoxides, 0582
with organometallics, 0826
halides, organozinc, with thioesters, 1450
halides, phosphorus, and Hell-Volhard-Zelenskii reaction, 0781
halides, propargyl, and Glaser reaction, 0979
reduction to allenes, 1826
with Grignard reagents, 0596
halides, selenyl, with enolate anions, 0791
halides, silyl, cleavage of ethers, 0582
with alkenes and DMSO, 1156
with allylsilanes, 0588
with carboxylic esters, 0585
with lactones, 0585
halides, sulfinyl, with alcohols, 0554
halides, sulfonyl, addition to alkenes, 1156
addition to alkynes, 1156
and chlorosulfuric acid, 0697
and formation of aryl sulfones, 0697
and the Reed reaction, 0974
base induced elimination to sulfenes, 1532
formation of sulfenes, 1471
from aromatic compounds, 0697

from aryldiazonium salts, 0986
from hydrocarbons, 0973
halogenation of sulfonic acids, 1474
hydrolysis, 1472
reduction to disulfides or thiols, 1850
with alcohols, 0546, 1473
with alkyl halides, 0554
with ammonia or amines, 1474, 1475
with arylboronic acids, 1476
with diazomethane, 1386
with Grignard reagents, 1475
with halo esters, Lewis acids catalysis, 0605
with organometallics, 1475
halides, vinyl, and addition-elimination, 0474
and E2 reactions, 1482
and elimination-addition reactions, 0477
and $S_{RN}1$ reactions, 0478
and substitution, 0474
and the element effect, 0475
and the tetrahedral mechanism, 0474
by addition of alkyl halides to alkynes, 1160
coupling with alkyl groups, 0795
formation of vinyl esters, 0541
formation of vinyl sulfides, 0550
from aldehydes or ketones with phosphorous pentachloride, 1298
from alkynes, 0820, 1031
from conjugated carboxylic acids, 0996
from vinylboranes, 0820
from vinyliodonium salts, 0819
in the Stille coupling, 0793
metal catalyzed addition to alkenes, 1100
metal catalyzed alkylation, 0629
metal catalyzed coupling, 0591
metal catalyzed coupling with alkynes, 1094
reduction to alkenes, 1827
reduction, with metal in alcohol, 1827
with acetamide, 0823
with alkylboronic acids, 0607, 0608, 0794
with Grignard reagents, 0600
with organometallics, 0604–0607
with thiol anions, 0474
Haller-Bauer reaction, 0844
halo amides, and the Hofmann rearrangement, 1608
halo ammonium salts, cyclization, 1695
halo-acetals, from vinyl ethers, 1154
halo-acids, Hell-Volhard-Zelenskii reaction, 0781
lactone formation, 0304
halo-alkenes, radical cyclization, 1125–1129
halo-amides, cyclization, 0571
halo-amines, by addition of haloamines to alkenes, 1157
formation of aziridines and cyclic amines, 0557
halo-azides, see azides
halo-carboxylic acids, 0585
halo-esters, addition to alkenes, 1161
halo-esters, metal mediated reaction with imines, 1465
halo-ethers, see ethers
halo-ketones, addition of acyl halides to alkenes, 1161
and the Favorskii rearrangement, 1595
by oxidation of alkenes, 1775
from ketones, 0776
from vinyl halides and NaOCl, 1154
halo-lactams, 1155
halo-nitro compounds, from alkenes and nitryl chloride, 1158
halo-nitroso compounds, from alkenes, 1158
halo-sulfides, see thioethers
halo-sulfides, Pummerer rearrangement of sulfoxides, 1866
halo-sulfones with ketones, 1384
and Ramberg-Bäcklund reaction, 1536
base induced elimination to alkenes, 1536
halo-thioethers, from alkenes and silyl halides, 1156
haloacylation of alkenes, and the Vilsmeier reaction, 1162
haloacylation, of alkenes, 1161
haloalkenes, see halides, vinyl
haloalkylation, and Friedel-Crafts reaction, 0717
haloalkynes, by electrolysis, 0820
from alkynes, 0819
from organometallics, 0819
metal catalyzed or metal mediated arylation, 0647
haloamides, and amidomethylation, 0731
haloamines, addition to alkenes, 1157
amination of aromatic compounds, 0694
and amination of alkenes, 1046
and halogenation of aromatic compounds, 0699
and Stieglitz rearrangement, 1616
from amines, 0849
reaction with acids, 1695
rearrangement with silver nitrate, 1616
haloboranes, see boranes
halocarbamates, addition to alkenes, 1052
halocyclopropanes, flash vacuum pyrolysis, 1591
haloesters, and the Reformatsky reaction, 1326
metal mediated addition to aldehydes or ketones, 1326
haloethers, from alkenes, 1152
with magnesium, 0830, 0831
haloform reaction, 0842
electrochemical, 0843
rate determining step, 0843
haloformic acids, from phosgene and alcohols, 1276
halogen dance, 0749
halogen radicals, see radicals
halogen-free Heck reactions, 0893
halogen-metal exchange, and organocuprates, 0603
halogenating agents, for alcohols, 0578, 0579
for carboxylic acids, 1440
halogenation, allylic hydrogen, with NCS, 0963
halogenation, base-induced, of alkanes, 0957
halogenation, mixed, of alkenes, 1151

halogenation, of acyl anilines, 0740
of aldehydes, and α-halogenation, 0964
of aldehydes, enantioselectivity, 0776
of alkanes, 0954–0960
of alkanes, fluorine radicals, 0955
of alkenes, 1029, 1148–1150
of alkenes, and isotopic labeling, 1004
of alkenes, and π-complexes, 1004
of alkenes, and radical initiators, 1149
of alkenes, radical, mechanism, 0958
of alkenes, the Prins reaction, 1161
of alkynes, 1148, 1151, 1152
of allylic alcohols, 0579
of aminopyridines, 0701
of aromatic compounds, 0676, 0698–0703
of aromatic compounds, and Lewis acids, 0702
of aziridines, 0584
of boranes, and radicals, 0820
of carboxylic acids, with NBS, 0781
of conjugated compounds, 1151
of conjugated ketones, 0780
of cyclopropylcarbinyl alcohols, 0579
of enol borinates, 0780
of enolate anions, 0820
of enols, 0778
of enynes, 1151
of epoxides, 0582, 0583, 1791
of furans, 0703
of ketones, 0776–0780
of lactams, 0851
of organometallics, mechanism, 0821
of pyrroles, 0703
of silanes, 0960
of steroids, 0958
of sulfoxides, reagents for, 0782
of thiiranes, 0584
of thiophenes, 0703
of vinylboronic acids, 0820
halogenation, radical, allylic hydrogen, 0960
allylic, mechanism, 0961, 0962
and AIBN, 0961
and polyhalogenation, 0957
and the Hofmann-Löffler reaction, 0958
benzylic hydrogen, 0960
bond dissociation energy, 0960
metal catalyzed, 0961
of aldehydes, with NBS, 0964
of alkenes, 0961
of methane, rate determining state, 0959
with NBS, 0956
with sulfuryl chloride, 0956
halogens, addition to alkenes, 1148
addition to alkenes, in ionic liquids, 1157
addition to alkynes, 1148
addition to cyclopropanes, and UV, 1027
and bridged ions, 1149
and halonium ions, 1000
and the haloform reaction, 0842
and the Reed reaction, 0974
cleavage of ketones, 0842
influence of, on radical cyclization, 1126
mixed, reactivity with alkenes, 1151
of anilines, and Lewis acids, 0699
of ketones, enantioselectivity, 0777
order of reactivity in the Ramberg-Bäcklund reaction, 1536
photochemical cleavage, 0279
halogens, with alcohols, 1154
with alcohols, and alkenes, 1152
with aldehydes, 0964
with alkanes, 0954–0960
with alkenes and sulfur dioxide, 0973
with alkenes, mechanism, 1149
with amides, 1608
with organometallics, 0819
with silver carboxylates, 0994
with trialkylboranes, 0819
halohydrins, and chloramine-T, 1153
by halogenation of epoxides, 1791
epoxide formation, 0532
from alkenes, 1152
from epoxides, 0582
from Grignard reagents and epoxides, 0620
Williamson reaction, 0532
haloketones with boranes, 0644
and formation of conjugated ketones, 0796
from diazo ketones, 0585
rearrangement to carboxylic esters, 1595
with boranes, mechanism, 0645
with organocuprates, 0632
with trialkylboranes, 0632
halolactamization, and reagents for, 1154, 1155
halolactones, addition to alkenes, 1161
by radical halogenation, 0956
halolactonization, and reagents for, 1154, 1155
halonium ions, from addition to alkynes, 1018
from alkenes, 1000
stability, and neighboring group effects, 0449
halosilanes, see silanes
halosulfones, see sulfones, halo
halosulfonyl esters, 1156
Hammett acidity function, and solvents, 0369
Hammett equation, and aromatic carboxylic acids, 0402
and aromatic substitution, 0679
and equilibrium constants, 0402
and linear free energy relationship, 0405
and radicals, 0949
rate constants and reactivity, 0401, 0402
reactions that do not fit, 0403
Hammett relationships, and S_NAr reactions, 0867
Hammett σ values, electrophilic aromatic substitution, 0679
Hammett σρ relationship, and substituent effects, 0486
Hammond postulate, and arenium ions, 0666
and carbocations, 0480, 1019
and Markovnikov's rule, 1019
and transition states, 0480
definition, 0308

Handbook of Chemistry and Physics, 1886
Handbook of Naturally Occurring Compounds, 1887
handedness, and enantiomers, 0137
Hantzsch dihydropyridines, and reductive alkylation, 1290
hapto prefix, and metal complexes, 0116
hard acids, and ionic bonds, 0378
  definition, 0377
hard bases, and ionic bonds, 0378
  definition, 0377
Hard-soft acid-bases, also see HSAB
Hard-soft acids-bases, 0377, 0378
hardness model, and aromaticity, 0057
hardness, 0377–0379
  and aromaticity, 0063
Hartree-Fock calculations, and annulenes, 0080
Hartree-Fock method, 0034
Hauptwerk (das Hauptwerk), of Beilstein, 1881, 1882
Haworth reaction, 0722
Hay reaction, 0979, 0980
HBr, and DMSO, 0700
  and hydrogen bonding, 0112
  and peroxides, with alkenes, 1030
  and radicals, addition to alkenes, 1124
  cleavage of ethers, 0523, 0580
  with alcohols, 0576
  with alkenes, 1029
  with cyclopropanes, 1025
HBuIm, ionic liquids, 0416, 1199
HCl, addition to alkenes, 1005
  and hydrogen bonding, 0112
  as an acid, 0357
  cleavage of ethers, 0523
  with alcohols, 0576
  with alkenes, 1029
  with butadiene, 1014
HCN, addition to alkenes, 1147
  addition to C=N compounds, 1392
  addition to iminonitriles, 1393
  addition to nitriles, 1393
  and proton transfer, 0368
  and the Sandmeyer reaction, 0985
  conjugate addition, 1147
  with aldehydes or ketones, 1389
heat of atomization, 0028
  of benzene, 0036
  of butadiene, 0039
heat of combustion, 0029
  and alkene stability, 1497
  and cycloalkanes, table, 0225
  annulenes, 0091
  cis/trans isomers, 0186
heat of hydrogenation, for benzene, 0037
Heck reaction, 0793, 0891–0897
  and aryl silanes, 0897
  and aryliodonium salts, 0896
  and diazonium salts, 0916, 0923
  and Meerwein arylation, 0924
  and microwaves, 0354, 0894
  and palladium, 0891–0897
  and vinyl organometallics, 0896
  and vinyl silanes, 0896
  and vinyltrifluoroborates, 0897
  enantioselective, 0894, 0895
  halogen-free, 0893
  homogeneous catalysts, 0893
  in aqueous media, 0893
  in ionic liquids, 0894
  in supercritical carbon dioxide, 0894, 0895
  in perfluorinated solvents, 0893
  intramolecular, 0892, 0895
  mechanism, 0894
  metal catalysts other than palladium, 0895, 0896
  on solid support, 0894
  phosphine-free and polymer-supported catalysts, 0893
  rearrangement, 0895
  regiochemistry, 0892
  stereospecific nature, 0895
  substituted alkenes, 0892
  with alkynes or allenes or dienes, 0892
  with arylboronic acids, 0896
Heilbron's Dictionary of Organic Compounds, 1885
helical chirality, 0149, 0150
helical chirality, also see chirality
helicene, and chirality, 0149, 0150
helix, and chirality, 0149, 0150
Hell-Volhard-Zelenskii reaction, 0781
hemiacetals, and acetal hydrolysis, 0524
  and formation of acetals, 1271
  conversion to ketones, 1620
  stability, 1272
hemiaminals, 1281–1283
hemicarcerands, and cyclobutadiene, 0074
hemimercaptals, 1278
hemispherands, 0123
Henkel reaction, 0747
Henry reaction, 1357, 1358
heptahelicene, and chirality, 0149
  and mechanical resolution, 0176
heptalene derivatives, stability of, 0068
heptalene, aromaticity and reactions, 0067, 0068
  and chirality, 0149, 0150
Herndon model, 0057
Hess-Schaad model, 0057
hetarynes, 0862
hetarynium ions, 0675
heteroaromatic compounds, and aromaticity, 0057, 0058, 0062
heteroatom Diels-Alder, see Diels-Alder, heteroatom
heteroatom functional groups, and Diels-Alder reaction, 1216
heteroatom nucleophiles, conjugate addition, 1130
heteroatom stabilized carbocations, 0248
heteroatom vinylcyclopropane rearrangement, 1657
heteroatoms, and allylic carbanions, 0641
  and benzylic carbanions, 0641
  and catenanes, 0132
  and crown ethers, 0121
  and hydrogen bonding, 0106
  and organometallics, 0809
  and the Pauson-Khand reaction, 1142
  conjugated to carbanions, 0253
  conjugation with carbocations, 0242
  in six-membered rings, 0209
  in the 2nd row, and the anomeric effect, 0211

heterocycles, acylation, 0983
addition of alkenes, 1088
alkylation of, with organometallics, 0914
alkylation, and Ziegler alkylation, 0913
amination, 0915
and Birch reduction, 1067
and Chichibabin reaction, 0915
and directed ortho metalation, 0912
and Friedel-Crafts reactions, 0983
and radical cyclization, 1129
and Sonogashira coupling, 0904
and Suzuki-Miyaura coupling, 0901
and the Gomberg-Bachmann reaction, 0924
and the Heck reaction, 0891
arylation, 0881
by alcoholysis of alkynes, 1038
by aromatization, 1711
by cyclotrimerization with metal carbenes, 1247
carbalkoxylation, 0983
carbonylation, 0909, 0910
catalytic hydrogenation, 1066
coupling with aryl halides, 0887
Diels-Alder reactions, 1217
electrophilic aromatic substitution, 0675
from alkynes and alcohols, 1038
lithiation, 0809
nitration, 0687
radical alkylation, 0982
radical reaction with carboxylic acids, 0982
reduction with metals in aqueous alcohols, 1069
vicarious substitution, 0916
with amide bases, 0915
with Fenton's reagent, 0983
with hydrazide anions, 0916
heterocyclic amines, and diazo compounds, 0918
Heterocyclic Compounds, 1894
heterocyclic compounds, and Friedel-Crafts acylation, 0720, 0721
and tautomerism, 0105
Friedel-Crafts alkylation, 0709
Gatterman reaction, 0725
halogenation of, 0701
Reimer-Tiemann reaction, 0726
heterogeneous catalysts, and hydrogenation, 1054
heterogeneous Pauson-Khand reaction, 1142
heterolytic bond cleavage, 0296
heteropolytungstic acid, 0975
hexahelicene, and strain, 0232
hexahydroazepin-2-one, see caprolactam
hexamethyldisilazane, with silyl halides, 0799
hexamethyldisilazide, lithium, and the aldol reaction, 1343
hexamethylenetetramine, amine alkylation, 0558
and the Delépine reaction, 0558
and the Duff reaction, 0727
hexamethylphosphoramide, see HMPA
hexamethylprismane, and photochemical [2 + 2]-cycloaddition, 1232
HF, and hydrogen bonding, 0107
in pyridine, formation of aryl fluorides, 0921
with acyl halides or anhydrides, 1441
HF-pyridine, and acetals or ketals, 0526
HI, and hydrogen bonding, 0112
cleavage of ethers, 0580
with alkenes, 1029
High Performance Liquid Chromatography, see HPLC
high pressure mass spectrometry, see mass spectrometry
high pressure, and activation volume, 0413
and amines with lactams, 1438
and Diels-Alder reactions, 0513, 1198
and dipolar transition states, 0513
and metal catalyzed conjugate addition of amines, 1130
and partial molal volume, 0513
and rate of diffusion, 0414
and reactivity, 0413, 0512
and steric hindrance, 0513
and substitution reactions, 0442
and the Claisen condensation, 0513
and the Knoevenagel condensation, 0513, 1359
and the Strecker synthesis, 1391
and transition states, 0413, 0513
and volume of activation, 0513
high-dilution, and Friedel-Crafts cyclization, 0721
higher order mixed organocuprate, 0602, 0603
Highest Occupied Molecular Orbital, see HOMO
hindrance, steric, see steric hindrance
Hinsberg test, and sulfonamides, 1474
hmim, ionic liquid, 0700
HMO theory, benzene, 0037
HMO, and cyclopropenyl anion, 0076
HMPA, and aryl halides with alkoxides, 0871
and dialkylamide bases, 0389
and Grignard reagents, 0262
and hydrogen bonds, 0109
and Normant reagents, 1102
and sodium cyanide, 0649
HOBr, with alkenes, 1152
HOCl, with alkenes, 1152
Hoesch reaction, 0732
HOF, and explosions, 1153
Hoffmann-Löffler-Freytag reaction, 1695
Hofmann degradation, 1522, 1523
Hofmann elimination, 1500
and the Sommelet-Hauser rearrangement, 0929
and the Stevens rearrangement, 1623
Hofmann exhaustive methylation, 1522
Hofmann rearrangement, 1563, 1607
mechanism, 0311, 1608
Hofmann's rule, and acidity of β-hydrogens in elimination, 1499
and dehydration of alcohols, 1514
and elimination, 1498
and Hofmann degradation, 1522

and pyrolytic elimination, 1510
Hofmann-Löffler reaction, 1695
and radical halogenation, 0958
mechanism, 1695
Hofmann-Martius reaction, 0741
HOI, with alkenes, 1152
HOMO, and Diels-Alder reaction, 1195
and endo addition, 1214, 1215
and frontier orbital method, 1208
and tetraenes, 0045
overlap of orbitals in electrocyclic reactions, 1636
homo-Brook rearrangement, 1701
homo-Diels-Alder reaction, 1204
homo-metathesis, 1684
homoaldol reaction, and the Knoevenagel reaction, 1362
homoallylic alkenes, 0451
homoallylic carbocations, 0451
homoanomeric interactions, 0209
homoaromatic compounds, 0093, 0094
homoaromatic, spherical, 0094
homoazulenes, and aromaticity, 0082
homoazulenes, X-ray, 0082
homoconjugation, 0045
and carbocations, 0239
homocoupling, of aryl halides, reagents for, 0887
homocubene, 0233
homodesmotic reactions, 0038
homodienyl [1,5]-sigmatropic hydrogen shift, 1673
homodienyl [1,5]shifts, 1653
and vinylcyclopropane rearrangement, 1658
homodimerization, of alkenes, 0977
homoenolate ion, 0256
homofullerenes, 0095
homogeneous reactions, and kinetics, 0315
homogenous catalysts, and hydrogenation, 1054, 1055
homogenous catalytic hydrogenation, mechanism, 1061
homologation, addition to aldehydes or ketones, 1601, 1602
homologation, by carbene insertion or carbenoids, 0803
of carboxylic esters, 1450
homolytic mechanism, 0297
[1,5]-homosigmatropic rearrangement, 1673
Hooke's law, and molecular mechanics, 0214
Horner-Emmons or Horner-Wadsworth-Emmons, see Wittig Horner
horseradish peroxidase, oxidation of thioethers, 1782
hosts, crown ethers in guest-host complexes, 0120
hot spot, sonochemistry, 0350
Houben-Hoesch reaction, see Hoesch reaction
Houben-Weyl's Methoden der Organischen Chemie, 1893
HPLC, and annulenes, 0092
and enantiomeric catenanes, 0134
and enantiomeric purity, 0182
HSAB principle, 0378
HSAB, and carbonyl carbon, 0494
and enolate anions, 0380
and equilibrium, 0379
and nucleophiles, 0492
and polarizability, 0516
and substitution reactions, 0516
table of acids and bases, 0378
Huang-Minlon modification, of Wolff-Kishner reduction, 1836
Hückel aromaticity, 0091
Hückel molecular orbital calculations, 0034, 0035
Hückel's rule, 0073
and annulenes, 0079
and aromaticity, 0071, 0078
and cycloadditions, 1210
Hückel-systems, allowed reactions, 1211
Hund's rule, and aromaticity, 0072
and carbenes, 0284
and photochemistry, 0331
Hünigs base, and addition of allylic halosilanes to aldehydes, 1323
and the aldol reaction, 1346
and the Claisen condensation, 1453
Hunsdiecker reaction, 0994–0996
and radicals, 0943
and the Simonini reaction, 0995
Hurtley reaction, 0907
hybrid orbitals, sp, sp^2, and sp^3, 0008, 0009
hybridization, 0007
and acidity, 0388
and allenes, 0148
and aromaticity, 0050
and bond angle, 0026
and bond distance, 0024, 0025
and bond energy, 0030, 0031
and bond rotation, 0196
and boron, 0008
and carbanion stability, 0254
and carbanions, 0257
and conformations, 0196
and cyclophanes, 0050
and inductive and field effects, 0022
and mercuric chloride, 0008
and PES spectra, 0014
and prismane, 0220
and radicals, 0276
and resonance energy, 0040
and S_N2, 0426
butadiene, 0039
diagonal, 0008
in ethyne, 0010
of carbon, 0008
of dienes, 0040
sp, 0009, 0010
trigonal, 0008
hydrates, from aldehydes or ketones, and I strain, 1262
hydration, differential, see differential hydration
hydration, mercuric catalyzed hydration of alkynes, mechanism, 1036
of aldehydes and ketones, 1262
of alkenes, 1032–1034
of alkynes, 1034, 1035
of allenes, 1037
of vinylidene nitriles, and cleavage, 1034
hydrazide anions, and substitution of heterocycles, 0916

hydrazides, acyl, with alcohols, 1422
from alkenes, 1048
from azodicarboxylates, 1048
from hydrazines with esters, 1436
hydrazine carboxylate, methyl ester, 0109
hydrazine, and Wolff-Kishner reduction, 1835
reaction with aldehydes or ketones, 1284
with carboxylic esters, 1436
with phthalimides, 0569
hydrazine, phenyl, see phenylhydrazine
hydrazine, tosyl, formation of allenes, 0769
hydrazines, addition to alkenes, 1047
arylation, 0881
by Hofmann rearrangement with ureas, 1607
by reductive alkylation of azo compounds, 1291
oxidation to azo compounds, reagents, 1730
reaction with oximes, 1285
with aldehydes or ketones, 1284
with nitrous acid, 0846, 1609
hydrazo compounds, by reduction of nitro compounds, 1863
reduction to amines, 1853
hydrazobenzene, acid catalyzed rearrangement, 1678, 1679
hydrazobenzenes, by reduction of nitro compounds, 1817
hydrazoic acid, addition to enol ethers, 1053
addition to Michael-type alkenes, 1052
and aromatic compounds, 0693
and the Schmidt reaction, 1611
with alcohols, 0559
with alcohols and alkenes, 1612
hydrazones, addition of HCN, 1392
addition of organometallics, 1335
alkylation, 0633
and the Fischer indole synthesis, 1674
as derivatives, 1284
aziridino, LDA induced elimination to cis alkenes, 1527
dimethyl, alkylation, 0632
dimethyl, with butyllithium, 0632
from active methylene compounds, 0783
from aryldiazonium salts, 0783
from carboxylic acids, 0784
from hydrazines and aldehydes or ketones, 1284
from oximes, 1285
halogenation of hydrazines, 1299
hydrolysis, 1264
Japp-Klingemann reaction, 0783
oxidation to nitriles, 1731
reagents for hydrolysis, 1265
reduction to amines, 1811, 1820
reduction to hydrocarbons, 1838
reduction, mechanism, 1838
tosyl, and Knoevenagel reaction, 1363
tosyl, and the Bamford-Stevens reaction, 1527
tosyl, and the Shapiro reaction, 1526
tosyl, base induced elimination, 1526
tosyl, suitable bases for elimination, 1527
tosyl, with organolithium reagents, 1526
unsubstituted, 1285
with ketenes, 1465
with Lewis acids, 1674
hydrazonium salts, and anilines, 0693
elimination to nitriles, 1547
hydrazyl radicals, 0273
hydride ions, and reduction, 1706
hydride shifts, 1697
1,3- and greater, 1572, 1573
and silyl enol ethers formation, 0799
transannular, 1697
Wagner-Meerwein rearrangements, 1581
hydride transfer, and oxidation-reduction, 1706
and the Cannizzaro reaction, 1865
hydride, lithium aluminum, and desulfurization, 1849
and sterically hindered ketones, 1792
reduction of acetals or ketals, 1832
reduction of acyl halides, 1840
reduction of aldehydes or ketones, 1792
reduction of aldehydes or ketones, mechanism, 1804
reduction of alkyl halides, 1824
reduction of amides, 1841
reduction of amides to aldehydes, 1810
reduction of amine oxides, 1846
reduction of azides, 1822
reduction of carboxylic acids, 1806
reduction of conjugated alkenes, 1070
reduction of conjugated carbonyls, 1793
reduction of epoxides, 1790
reduction of esters to alcohols, 1807
reduction of hydroperoxides, 1834
reduction of imidazoles to aldehydes, 1811
reduction of imines, 1811
reduction of nitriles, 1813
reduction of nitro compounds, 1817, 1863
reduction of oximes, 1819
reduction of propargyl halides, 1826
reduction of sulfones, 1851
reduction of tosylates, 1832
with aluminum chloride, reduction of alcohols, 1829
with aluminum chloride, reduction of ethers, 1832
with chiral additives, 1802
with epoxides, 1706
with Lewis acids, reduction of ethers, 1839
with quaternary ammonium salts, 1844
with sulfonyl halides, 1850
hydride, trialkyltin, and reduction of alkyl halides, 1825, 1826

hydride, tributyltin, and AIBN, reduction of thiocarbonates, 1833
and phenylboronic acid, reduction of aldehydes, 1798
and radical cyclization, 1125, 1126
and reduction of conjugated esters, 1072
reduction of aldehydes, 1798
with radicals, 0937
hydrides, alkoxy, and reduction of nitriles, 1815
hydrides, metal, see metal hydrides
metal, reduction of boranes, 1628
reduction of aldehydes or ketones, 1792–1805
reduction of ketones, and Cram's rule, 1804
tin, reduction of aldehydes or ketones, 1798
tri-*tert*-butoxy, lithium, reduction of acyl halides, 1808
hydroamination of alkenes, enantioselectivity, 1181
hydroamination, of alkenes, metal catalyzed, 1181
hydroboration, 1075–1082
and amination of alkenes, 1050
and enantioselective synthesis, 1080
and ether solvents, 1075
and functional groups, 1079
and hydration of alkenes, 1034
and oxidation of boranes, 1079
and reduction of alkenes, 1063
and reduction of alkynes to alkenes, 1064
and steric effects, 1018
and synthetic transformations, 1079
and Wilkinson's catalyst, 1082
cyclic, with dienes, 1081
enantioselective, 1079, 1082
mechanism, 1078
of alkynes or dienes, 1081
of norbornene, 1023
hydrobromic acid, see HBr
hydrocarbons, acidity, 0251
alternant and nonalternant, 0069
amination, 1757
and chirality, 0152
and guest-host interactions, 0127
and the Kolbe reaction, 0993
bond energy, 0028
by deamination, reagents, 1843, 1844
by decarboxylation, 0835
by dehalogenation of alkyl halides, reagents, 1824
by dehydroxylation of alcohols, reagents, 1829
by desilylation of silanes, 1824
by hydrogenation of thiophenes, 0991
by metal catalyzed decarbonylation of aldehydes, 0997
by reduction of alcohols, reagents, 1829
by reduction of alkyl halides, reagents, 1824
by reduction of amines, reagents, 1843, 1844
by reduction of carboxylic acids, 1843
by reduction of ethers, reagents, 1831
by reduction of nitriles, 1843
by reduction of silanes, 1824
by reduction of sulfones, sulfoxides, thiols, thioethers, 1848, 1849
coupling of boranes, 0989
coupling of organocuprates, 0988
deamination of amines, indirect methods, 1844
dipole moments, 0096
halosulfonation, 0973
hydroxylation, 1750, 1751
metal catalyzed coupling of Grignard reagents, 0987
metal mediated carbonylation, 0824
oxidation to alcohols, 1750
oxidation to amines, 1757
oxidation to hydroperoxides, 0967
oxidation to peroxides, 0971
oxidation to sulfonic acids, 1757
photochemical reaction with nitriles, 0975
radical coupling of carboxylate salts, 0992
reagents, for oxidation to alcohols, 1751
reduction of aldehydes or ketones, 1835
reduction of thiocarbonates, 1833
reductive cleavage of esters, 1833
remote oxidation, 1761, 1762
with acylperoxides, 0971
with halogen and sulfur dioxide, 0973
with hydroperoxides, 0971
with oxygen, 0967
with sulfur dichloride, 0974
hydrocarboxylation, and nickel carbonyl, 1139
and the Koch reaction, 1137
metal catalyzed, mechanism, 1138
of alkenes, 1136, 1138
of alkynes, 1137, 1138
hydrochloric acid, see HCl
hydrocyanic acid, see HCN
hydroformylation, and dicobalt octacarbonyl, 1146, 1147
and the Tischenko reaction, 1146
hydrogen abstraction, see abstraction
hydrogen atom abstraction, 0347
hydrogen atom transfer, and oxidation-reduction, 1706
hydrogen atoms, and the Schrödinger equation, 0004
and wave functions, 0004
transannular shifts, 1578
hydrogen bonding, 0106–0114
and acidity, 0385
and molecular recognition, 0124
and pK, 0385
and proton transfer, 0367
hydrogen bonds, funtional groups and characteristics, 0106–0109, 0112, 0113
and enol stabilization, 0772
and guest-host interactions, 0124
and X-ray crystallography, 0109
hydrogen cyanide, see HCN
hydrogen exchange, and cyclopropenyl derivatives, 0077
coupling of alkenes, 0802

hydrogen
exchange, (*Continued*)
electrophilic aromatic substitution, 0684
in base, 0767
in catalytic hydrogenation, 1058
in superacids, 0766
mechanism, reactivity and structure, 0766
with carbanions, 0759
with carbocations, 0802
hydrogen fluoride, see HF
hydrogen peroxide, see peroxide
hydrogen peroxide, and alkenes, 1171
and hydroxide, with boranes, 1626
and metal catalyst, Baeyer-Villiger rearrangement, 1618
and oxidation of thiols, 1780, 1785
oxidation of amines to amine oxides, 1779
oxidation of carboxylic acids, 1773
[1,7]-hydrogen shifts, photochemical, antarafacial migrations, 1652
hydrogen shifts, and carbene rearrangements, 1579
hydrogen sulfide, addition to alkenes, 1043
with acyl halides, 1425
with carbonyl compounds, 1277
hydrogen transfer, and radical cyclization, 1125, 1126
and radicals, 0936
[1,4]-hydrogen transfer, in radical cyclization, 1652
hydrogen transfer, radical, 0937
hydrogen, as a neighboring group, 0467
migrating group in rearrangements, 1567
participation, solvolysis, 0467
sigmatropic migration in alkenes or dienes, 1648
with amines and aldehydes or ketones, 1288–1291
hydrogen-bond basicity, 0364
hydrogen-bonding, acceleration of Diels-Alder, 1198
hydrogen-deuterium exchange, 0766
hydrogen-lithium exchange, with aromatic compounds, 0912
hydrogen-metal exchange, and radicals, 0834
hydrogen-transfer agent, and radicals, 1123
hydrogen-tritium exchange, 0766
hydrogenation, catalytic, alkene selectivity, 1055
and aromatization, 1709
and bond rotation, 1061
and chiral catalysts, 0171
and cleavage of alkanes, 0845
and hydrogen exchange, 1058
and isomerization of alkenes, 1058
and metal complex formation, 1059
and nanoparticles, 1055
and poisoning, 1055
and reduction of imines, 1811
and Rosenmund reduction, 1808
and steric effects, 1056
and Wilkinson's catalyst, 1054
asymmetric catalysts, 1073
catalyst types, 1054
chiral catalysts, with imines or enamines, 1813
chiral ligands, 1056
conjugated compounds, enantioselectivity, 1072, 1073
enantioselectivity, 1054, 1056, 1057, 1074
functional group compatibility, 1054
heterogeneous, mechanism, 1059
homogenous, mechanism, 1061
in ionic liquids, 1066
ligands for enantioselectivity, 1056
of acyl halides, 1808
of alcohols, 1829
of aldehydes or ketones, 1795
of alkenes, 0043, 1053–1062, 1057
of alkyl halides, 1826
of alkynes, 1065
of alkynes, Rosenmund catalyst, 1057
of allenes, 1058
of aromatic compounds, 1066
of benzylic ethers, 0580
of cyclopropanes, 1075
of dienes, 1058
of disulfides, 0990
of enamines, 1049
of heptalene, 0067
of heterocycles, 1066
of isocyanates, 1813
of nitriles, 1814
of nitro compounds, 1823
of oximes, 1812
of phenols, 1830
of thioethers, 0990
of thiols, 0990
of thiophenes, 0991, 1849
or aldehydes of ketones, mechanism, 1805
poisoned catalyst, 1057
poisons, 1055
polymer-bound catalysts, 1055
reduction of amides, 1841
reduction of hydroperoxides, 1834
selectivity with homogeneous catalysts, 1055
solvent effects, 1055
sulfur compounds, 0990, 0991
surface and particle sites on the catalyst, 1060
syn stereochemistry, 1058
types of homogeneous catalysts, 1055
with allenes, 1065
hydrogenation, heat of, for benzene, 0037
in situ, and sodium borohydride, 1057
transfer, 1066
hydrogenolysis, cleavage of ethers, 0580
hydrogenation of aromatic compounds, 1066
of acyl halides, 1808
of cyclopropanes, 1075
hydrolysis, and the Gabriel synthesis, 0569
hydrolysis, and the Grignard reaction, 1301
hydrolysis, of acetals, 0523–0527
of acetals, and hemiacetals, 0524
of alkoxides, 1804
of alkyl halides, 0519

of alkyl halides, rates, 0399
of amides, 1407–1410
of anhydrides, 1399
of aryl Grignard reagents, 0751
of aryl organolithium reagents, 0751
of aryl organometallics, 0751
of aryl oximes, 0930
of C=N compounds, 1263–1265
of carbamates, mechanism, 1406
of carboxylic acid esters, and mechanism, 0406, 0407
of carboxylic esters, 1400–1406
of carboxylic esters, and malonic ester synthesis, 0623
of chloroform, 0521
of compounds, and microwaves, 1265
of compounds, mechanism, 1265
of cyanohydrins, 1268
of diazoketones, 0522
of dihalides, 0520
of dithianes, 0638
of dithioketal, and dithioacetals, and reagents for, 1279–1280
of dithioketals, Corey-Seebach procedure, 1280
of enol ethers, 0523, 1035
of enolate anions, 0812
of epoxides, 0528, 0529
of esters, rates, 0399
of ethers, 0533
of Grignard reagents, and reduction of alkyl halides, 1828
of hydrazones, and reagents for, 1264–1265
of imines, 1263
of iminium salts, 0732, 1266
of inorganic esters, 0522
of isocyanates, 1266
of isocyanides, 1467
of isothiocyanates, 1266
of ketene dithioacetals, 0528
of ketones, 1600
of lactones, 1401
of nitriles, 0648, 1268, 1269
of nitro compounds, 1267
of nitro compounds, and the Nef reaction, 1267
of nitro compounds, reagents for, 1267, 1268
of organolithium reagents, 0812
of organometallic reagents, 0812
of ortho esters, 0525
of oxazolidines, 0643
of oximes, 1264
of phthalamic acid, 1259
of phthalimides, 0569
of Schiff bases, 1263
of semicarbazones, 1264
of sulfonic acid derivatives, 0522, 1472
of thioacetals, 0526
of thiocyanates, 1269
of thioketals, 0526
of trihalides, 0521
of vinyl esters, 1401
of vinyl ethers, labeling, 0528
of vinyl ethers, mechanism, 0527
hydrometallation, of alkynes, 1083
hydroperoxide ions, with alkyl halides, 0544
hydroperoxide radicals, bond dissociation energy, 0275
hydroperoxide, alkyl, co-reagents, and epoxidation, 1175
and alkenes, 1171
from alkyl halides, 0544
tert-butyl, and dihydroxylation of alkenes, 1162
hydroperoxides, acid catalyzed rearrangement to ketones, 1620
acyl, from anhydrides, 0545
and ozonolysis of alkenes, 1739
and singlet oxygen, 0969
by autoxidation, 0967
from organometallics, 0813
oxidation of sulfoxides, mechanism, 1783
oxidation of thioethers, mechanism, 1782
reduction to alcohols, 1834
hydrophobic acceleration, in water, 0414
hydrophobic effects, and Diels Alder reactions, 1198
hydroquinone, host for clathrates, 0127
hydroquinones, by reduction of quinones, 1794
hydrostannation, and sonochemistry, 0352
of conjugated esters, 1074
hydrosulfide anion, with aryl halides, 0874
hydroxamic acids, from hydroxylamines and esters, 1436
hydroxamic acids, O-acyl, and Lossen rearrangement, 1610
hydroxamic acids, O-acyl, base catalyzed rearrangement, 1610
hydroxide ion, and alkyl halides, 0519
and Reimer-Tiemann reaction, 0726
reaction with amides, 0397
reaction with silanes, 0251
with aryl halides, 0870
with epoxides, and hydride shifts, 1697
hydroxy-acids, by rearrangement of diketones, 1594
elimination to alkenes, 1543
esterification to from lactones, 1415
from keto aldehydes, 1864
hydroxy-aldehydes, by aldol reaction, 1339–1351
by Mukaiyama aldol, 1351–1354
with hydrazines, 1285
hydroxy-alkyl halides, see halohydrins
hydroxy-amides, from addition of amides to aldehydes, 1292
hydroxy-amines, see amino-alcohols
hydroxy-esters, by α-hydroxylation, 1753
hydroxy-ethers, from epoxides, 0536
oxidation to acetals, 0966
hydroxy-halides, see halohydrins
hydroxy-ketones, and the benzoin condensation, 1397
by α-hydroxylation, 1753
by α-hydroxylation of silyl enol ethers, 1755
by α-ketol rearrangement, 1593
by Mukaiyama aldol, 1351–1354
by oxidation of alkenes, 1775

hydroxy-ketones, (*Continued*)
by the acyloin ester condensation, 1860
and atropisomers, 0148
by the aldol reaction, 1339–1351
by the benzoin condensation, 1396
formation of cyanoamines, 0561
from aldehydes and potassium cyanide, 1396
from epoxy-ketones, 0529
from imines and ketones, 1349
from metallated imines, 1469
from organolithium reagents with ketones, 1305
reductive coupling of esters, 1860
with hydrazines, 1285
hydroxy-nitriles, from epoxides, 0649
hydroxy-selenides, from epoxides, 0552
hydroxy-sulfides, see hydroxy-thioethers
hydroxy-thiols, from carbonyls, 1277
hydroxyalkylation, and Lederer-Manasse reaction, 0714
aromatic compounds, 0713
polymerization, 0714
hydroxyamines, from alkenes, 1180
hydroxybenzyl silanes, Brook rearrangement, 1701
hydroxyl(tosyloxy)iodo] benzene, 0695
hydroxylamine O-sulfonic acid, formic acid and Beckmann rearrangement, 1614
hydroxylamine O-sulfonic acid, with organoboranes, 0822
hydroxylamines, addition to alkenes, 1047
and Stieglitz rearrangement, 1617
by Cope elimination, 1524
by Meisenheimer rearrangement, 1623
by oxidation of amines, reagents for, 1777
by reduction of nitro compounds, and reagents, 1817, 1818
conjugate addition, 1131
metal reduction to amines, 1819
oxidation to nitroso compounds, 1731
reaction with aldehydes and formic acid, 1287
with aldehydes or ketones, 1286
with carboxylic esters, 1436
with hindered ketones, 1286
with metal-salen complex, 1547
with organometallics, 0821
α-hydroxylation, of allylic compounds, 1756
of benzylic compounds, 1755, 1756
of carbonyl compounds, reagents, 1753
of carboxylic esters, 1752–1757
of enolate anions, with sulfonyloxaziridines, 1754
of ketones, 1752–1757
of silyl enol ethers, 1755
with dioxiranes, and enantioselectivity, 1754, 1755
with enzymes, 1756, 1757
with oxaziridines, enantioselectivity, 1754
hydroxylation, Boyland-Sims oxidation, 0734
Elbs reaction, 0734
of alkenes, 1032
of aniline derivatives, 0734
of aromatic compounds, 0733, 0734
of aryldiazonium salts, 0919
of hydrocarbons, 1750, 1751
of silanes, 0539
hydroxymethylation, and Grignard reagents, 1305
hydroxynitriles, alkylation, 0633
hydroxypyridine, and tautomerism, 0103
hydroxy-silanes, for lithio-silanes and aldehydes or ketones, 1365
hydroxysulfenylation, of alkenes, 1179
hydroxysulfinamides, by Knoevenagel reaction, 1360
hydrozirconation, of alkenes, 1083
hyperconjugation, 0044, 0095–0097
and alkene stability, 1498
and aromatic substitution, 0670
and carbanions stability, 0255
and carbocations, 0237–0239, 0325, 0326, 0483
and dipole moment, 0096
and diynes, 0040
and elimination reactions, 1498
and isotopic effects, 0325, 0326
and no-bond resonance, 0097
and radicals, 0270
and resonance, 0238
and solvolysis, 0325, 0326
and temperature, 0326
and the anomeric effect, 0210
and the Baker-Nathan effect, 0096, 0097
and the tetrahedral mechanism, 0476
canonical forms, 0096, 0097
evidence against, 0097
evidence for, 0097
isovalent, 0098
negative, 0210
sacrificial, 0097
hypervalent iodine, see iodine
hypervalent iodine, with alkenes, 1153
hypochlorite, sodium, and oxidative cleavage of cyclic ketones, 1736
sodium, with organoboranes, 0822
hypochlorites, alkyl, decomposition to radicals, 0935
and radical halogenation of silanes, 0960
sodium, with amines, 0849
hypofluorite, acyl, with enolate anions, 0777
hypofluorites, acetyl, 0705
hypohalites, acyl, as an intermediate, 0996
halogenation of aromatic compounds, 0702
hypohalous acids, addition to alkynes, 1153
with alkenes, 1152
hypoiodite, *tert*-butyl, and iodination of alkenes, 0956
hyponitrites, and addition to alkenes, 1134
hydroperoxide, *tert*-butyl, and Sharpless asymmetric epoxidation, 1177

hypophosphorus acid, and reduction of aryldiazonium salts, 1847
and resonance, 0053
and ylids, 0053
hypostrophene, and Cope rearrangements, 1666
hypsochromic shift, 0333

+I effect, 0020
+I effects, arenium ions, 0667
−I effect, 0020
−I effects, arenium ions, 0667
I strain, see strain
IBr, or ICl with alkenes, 1151
ideal gas, and hydrogen bonding, 0111
imidates, with ammonia or amines, 1436
imidazoles, acyl, 1418
imidazoles, reduction to aldehydes, 1811
imidazolidinones, and Michael addition, 1107
imidazolium salts, ionic liquids, 0415
imides, alkylation, 0570
by carboxylation of alkenes, 1144
conjugate addition, 1131
cyclic, amines and cyclic anhydrides, 1429
from acyl halides and amides, 1439
from isothiocyanates, 0730
metal catalyzed addition to alkenes or alkynes, 1052
reaction with dihalosulfones, 1381
reduction to amines, 1842
with alcohols, 0570
imidines, from dinitriles, 1296
imido selenium compounds, with alkenes, 0788
imine-enamine tautomerism, see tautomerism
imines, addition of boronates or boronic acids, 1334
addition of carbenes, 0289
addition of diazoacetates, 1183
addition of HCN, 1392
addition of organometallics, enantioselectivity, 1331, 1332, 1335
addition of radicals, 1336
alkylation, 0632, 1291
and enamine salts, 0636
and hemiaminals, 1281
and tautomerism, 0104
as amino acid surrogates, 0632
by dehydrogenation of amines, 1730
by oxidation of amines, 1767
by reduction of oximes, reagents, 1821
α-carbanions, with ketones, 1349
carbonylation, 0824
chiral, conjugate addition (Michael addition), 1109
condensation with ketones, 1349
conjugate addition, 1130
cyclic, from cycloalkyl azides, 1610
cyclic, from halo-nitriles and organometallics, 1338
cycloaddition with ketenes or thioketenes, 1464, 1465
Diels-Alder reaction, 1216
E/Z isomers, 0230
formation in ionic liquids, 1282
from alkyl azides, 1609
from amines and aldehydes or ketones, 1281
from amines by dehydrogenation, 1711
from Grignard reagents and nitriles, 1338
from nitroso compounds, 0785
hydrolysis, 1263, 1767
α-lithio, with ketones, 1349
Mannich reactions with enol ethers, 1295
metal catalyzed addition of allyl silanes, 1388
metal catalyzed addition of diazoesters, 1337
metal mediated reaction with halo esters, 1465
metallated, 1469
O-tosyl, base catalyzed rearrangement to amino ketones, 1605
oxidation to amides, 1732
phosphinyl, reduction, 1813
reduction by silanes, 1812
reduction to amines, 1812, 1813
strained bicyclic, 0230
tautomerism with enamines, 1048
tosyl, with ketones and proton sponge, 1465
imines, with carboxylic acids, 1465
with chlorosulfonyl isocyanate, 1466
with Danishefsky's diene, 1217
with diazo ketones, and microwaves, 1466
with ketene acetals, 1353
with organometallic compounds, 1330–1334
with phosphorus ylids, 1379
with sulfur ylids, 1385
[2 + 2]-cycloaddition, 1221
iminium ions, and Eschenmoser's salts, 1294
hydrolysis, and mechanism, 1266
hydrolysis, and Stork enamine reaction, 1266
protonolysis, 0247
iminium salts, addition of cyanide, 1392
amines with aldehydes or ketones, 1284
and Hoesch reaction, 0732
and Pictet-Spengler reaction, 0716
Diels-Alder reaction, 1216
formation of aldehydes, 0725
formation of nitriles, 0733
fragmentation of amines, 1542
from aldehydes, 0716
from oxazines, 0643
from Stork enamine reaction, 0634, 0635
Gatterman-Koch reaction, 0725
hydrolysis, 0732
reduction to amines, 1812
with Grignard reagents, 1336
with Oxone, 1173
imino esters, and Hoesch reaction, 0732
and ketone formation, 0732
and the Chapman rearrangement, 1697
and the Pinner synthesis, 1275
from amides and phosphorus pentachloride, 1698
from nitriles and alcohols, 1275
hydrolysis, 1275
rearrangement to amides, 1697
iminonitriles, from addition of HCN to nitriles, 1393
in-out isomerism, 0112, 0189

inclusion compounds, 0126
and rotaxanes, 0134
thiourea, 0127
indacene, and antiaromaticity, 0089
indene, and the Heck reaction, 0892
indene, pK_a, 0063
Index Chemicus, 1900
Index to Scientific Reviews, 1908
indicators, and acidity scales, 0369, 0370
indoles, addition of carbenes, 1240
and addition of alkenes, 1088
and Friedel-Crafts acylation, 0721
and Suzuki-Miyaura coupling, 0901
by Fischer indole synthesis, 1674
by radical cyclization, 1128
catalytic hydrogenation, 1067
from alkynes and hydrazines, 1049
from hydrazones, 1674
in the Reimer-Tiemann reaction, 0726
indolizines, metal catalyzed coupling with aryl halides, 0887
indolones, and radical cyclization, 1127
and Birch reduction, 1067
inductive destabilization of groups, 0484
inductive effects, 0019, 0020, 0022
infrared, see IR
Ing-Manske procedure, 0569
inhibitors, and radicals, 0938
initiators, Grignard reagents, 0830
radical, azobis compounds, 1124
inorganic esters, with alkoxides, 0532
insertion reactions, and nitrenes, 0294
insertion reactions, carbenes, 0289
insertion, and carbenoids, 0807
and carbocations, 0803
and carbonylnitrenes, 0790
and organozinc compounds, 0807
C-H, with dimethyldioxirane, 1172
carbene, 0290, 0803–0806, 1234
carbene, and ring expansion, 0805
diazocarbonyl compounds, 0804, 0805
direct, and carbenes, 0807
intramolecular, 0804
methylene, 0803
nitrene, 0789–0790
nitrene, formation of carbamates, 0790
inter-halogen compounds, with alkenes, 1149
interfacial mechanism, 0510
interlocked catenanes, 0133
intermediates, and free energy, 0305
and IR, NMR or Raman, 0312
and mechanism, 0311
bridges, and aryl migration in carbocations, 1577
cyclic, addition of bromine to dienes, 1014
detection of, 0312
Friedel-Crafts alkylation, 0710
isolation of, 0312
radical, 0312
radicals, and CIDNP, 0269, 0312, 0270
reaction, 0304
trapping, 0313
internal nucleophilic substitution, see substitution, S_Ni
internal return, 0439
internal strain, see strain, I
International Union of Pure and Applied Chemistry, see IUPAC
intersystem crossing, 0339
intimate ion pairs, 0437, 0470
intramolecular, addition, alcohols to alkenes, 1037
aldol reaction, 1349
aldol reaction, acid catalyzed, 1350
Baylis-Hillman reaction, 1325
carbene insertion, 0805
cyclotrimerization, 1244
Diels-Alder reactions, 1204
elimination, 1507
Friedel-Crafts alkylation, 0706
Gomberg-Bachmann reaction, 0925
Grignard reactions, 1303
insertion, 0804
McMurry coupling, 1859
Michael addition, 1109
Mukaiyama aldol, 1353
Paterno-Büchi reaction, 1464
photochemical [2 + 2]-cycloaddition, 1230
pinacol coupling, 1856
proton-transfer, 0367
reactions, Scholl reaction, 0718
rearrangement, photochemical, 0345
Schmidt reaction, 1612
silicon-tethered Heck reaction, 0895
Thorpe reaction, 1387
Wittig reaction, 1378
Wittig-Horner, 1376
[3 + 2]-cycloaddition, 1191
intrinsic barrier, 0310
intrinsic free energy, 0309
inverse electron demand, Diels-Alder reactions, 1207
inverse isotope effects, 0324
inversion barrier, buckybowls, 0095
inversion of configuration, and addition reactions, 1020
and radicals, 0939
of phosphorus, 0191
inversion, and azide ion, 0443
and chlorination of alcohols, 0469
and S_N2, 0428
and solvolysis, 0443
bowl-to-bowl, 0095
pyramidal, 0142–0144
pyramidal, and carbanions, 0257
iodide, radioactive, and S_N2, 0429
iodide, sodium, and chloramine-T, 0921
iodides, aryl, from aryl diazonium salts, 0985
aryl, from aryldiazonium salts, 0920
Finkelstein reaction, 0574, 0575
iodination reagents, 0703, 0704
iodination, of aromatic compounds, 0703
iodine azide, addition to alkenes, 1159
iodine, and alkenes, 1149
and $PhI(OAc)_2$, 0956

and Dess-Martin periodinane, 1723
and iodoxybenzoic acid, 1723
and lactone formation, 0541
and oxidation of alcohols, 1723, 1724
light and radical formation, 0956
iodo-aldehydes, and radical cyclization, 1129
iodo-ketones, and radical cyclization, 1129
iodoacetyl addition, to alkenes, 1154
iodoaniline, complex with cyclodextrins, 0130
iodocyclopentane, reaction with silver perchlorate, 0077
iodolactamization, 1156
iodolactonization, 1128, 1155
iodonium ions, addition of iodo azide to alkenes, 1159
iodonium salts, and Sonogashira coupling, 0905
aryl, and S_N1 reactions, 0857
aryl, and the Heck reaction, 0896
aryl, with trifluoroborates, 0890
with alkynes, 0905
iodosobenzene, with sodium azide, 1182
iodoxybenzoic acid, and oxidation of alcohols, 1723
ion exchange resins, and sodium tetroxide, 1163
ion pair mechanism, 0441
and E1 reactions, 1488
ion pairing, and anti- or syn-elimination, 1486
ion pairs, allylic carbocations, 0470
and E1 reactions, 1488
and Friedel-Crafts acylation, 0722
and internal return, 0437
and isotope labeling, 0438
and MO calculations, 0440
and ozonlysis, 1738, 1739
and phase transfer catalysis, 0511
and S_N1 reactions, 0438
and S_N1' reactions, 0470
and S_Ni' reactions, 0472
and solvent effects, 0236
and stereochemistry, 0439
and the Criegee mechanism, 1738, 1739
and the S_N1 mechanism, 0436
carbanion, and E1cB reactions, 1493
contact, 0437
intimate, 0437, 0470
Sneen's ion pair mechanism, 0764
solvent separated, 0440, 0759
tight, 0437
ions, bridged, see bridged
ion-dipole interactions, 0124
ion-radical pairs, and S_NAr reactions, 0857
ionic bonds, and hard acids and bases, 0378
ionic configuration, and bond energy, 0031
ionic liquids, 0415
acyl addition of allyltin compounds, 1314
addition of haloamines to alkenes, 1157
addition of organometallics to imines, 1332
aluminum chloride-butylpyridinium, 1675
and acidity, 0369
BAcIm, 1264
ionic liquids, and acylation of amines, 1429
and addition of aldehydes to alkenes, 1136
and addition of organometallics to carbonyls, 1310
and alkene metathesis, 1684
and amines with aryl halides, 0876
and aryl halides with phenols, 0873
and aziridination of alkenes, 1185
and carboxylate salt alkylation, 0540
and catalytic hydrogenation, 1066
and cleavage of ethers, 0580
and conjugate addition, 1107
and conjugate addition of amides, 1132
and cyclization of alkenes to alkanes, 1085
and Diels Alder reactions, 1199
and dihydroxylation, 0416, 1163
and epoxidation, 1172
and epoxide halogenation, 0584
and esterification, 1415
and ether formation, 0529
and formation of aryl sulfones, 0697
and formation of biaryls, 0887
and formation of cyanohydrins, 1389, 1390
and formation of enamines, 1284
and formation of imines, 1282
and formation of oximes, 1286
and Friedel-Crafts acylation, 0720, 0721
and Friedel-Crafts alkylation, 0706
and halogenation of alkenes, 1150
and halogenation of aromatic compounds, 0700
and homocoupling or aryl halides, 0887
and hydrogenation of conjugated acids, 1074
and hydrolysis of C=N compounds, 1264
and Mannich reactions, 1295
and metal catalyzed arylation of amines, 0878
and metal catalyzed coupling of allylic esters, 0611
and metal sulfonates with organometallics, 0612
and Michael reactions, 1107
and microwave reactions, 0416
and nitration of aromatic compounds, 0687, 0688
and organometallic coupling, 0606
and oxidation of alcohols, 0416, 1724
and phosphonium tosylates, 1199
and pyrrole alkylation, 0557
and reactions of sulfur ylids, 1387
and reduction of aldehydes or ketones, 1800
and reductive alkylation, 1291
and Robinson annulation, 1350
and Sonogashira coupling, 0905

ionic liquids, (*Continued*)
and Suzuki-Miyaura coupling, 0900
and TEMPO oxidation of alcohols, 1723
and the aldol reaction, 1342
and the Baeyer-Villiger rearrangement, 1618
and the Baylis-Hillman reaction, 1324
and the Beckmann rearrangement, 1614
and the Bischler-Napieralski reaction, 0716
and the Dakin reaction, 1747
and the ene reaction, 1105
and the Fischer indole synthesis, 1675
and the Fries rearrangement, 0736
and the Glaser reaction, 0979
and the Heck reaction, 0894
and the Henry reaction, 1357
and the Knoevenagel reaction, 1359
and the Pechmann condensation, 0713
and the Rosenmund-von Braun reaction, 0885
and the Williamson reaction, 0529
and thiirane formation, 0552
and transesterification, 1421
aza-Diels-Alder reactions, 1217
ionic liquids, bbim, 0894
bmiI, 0873, 0885
ionic liquids, bmim, 0416, 0697, 0699, 0700, 0713, 0716, 0720, 0872, 0876, 0887, 0894, 0900, 0900, 0905, 0979, 1066, 1074, 1074, 1085, 1107, 1132, 1136, 1150, 1157, 1163, 1172, 1185, 1199, 1284, 1286, 1291, 1295, 1310, 1314, 1332, 1342, 1359, 1387, 1389, 1390, 1429, 1618, 1684, 1723, 1724, 1747, 1762, 1800
ionic liquids, BPy (i.e., butylpyridinium), 1614
chiral, 1324
chloraluminates, 1199
diarylimidazolium salts, 0878
DiBuIm, 0416, 1199
dodecyltrihexylphosphonium chloride, 0900
emim, 0706, 1163
emimcl, 0720
HBuIm, 0416, 1199
hmim, 0700
imidazolium salts, 0415
α-oxidation of ketones, 1762
pyridinium salts, 0415, 1199
TMG Lac (tetramethylguanidinium lactate), 1357
ionic solvents, see ionic liquids
ionic solvents, also see solvents
ionic strength, S_N1 and rate of reaction, 0434
ionization potential, 0012
alkenes and addition reactions, 1018
and hardness, 0377
ionization, and carbocation formation, 0247
and carboxylic acids, 0394
and S_N1 reactions, 0432
and superacids, 0436
and the S_E1 mechanism, 0758
chlorotriphenylmethane, 0240
of diazonium compounds to carbocations, 0247
of protonated alcohols to carbocations, 0247
rate, and azide ions, 0442
rate, of sulfonate esters, 0504
ionizing power of solvents, 0506
ions, and rearrangement, leakage, 1572
and rearrangements, 1572
as guests in crown ethers, 0123
binding by crown ethers, 0120
bridged, see bridged ions
nitrenium, singlet and triplet, 0295
radical, see radical ions
ipso attack, 0671
aryl radicals, 0951
electrophilic aromatic substitution, 0679
ipso carbon and S_NAr mechanism, 0854
ipso position, definition, 0672
ipso substitution, and the Wallach rearrangement, 1699
IR (infrared), and arynes, 0861
and carbenes, 0285
and carbocations, 0236, 0245
and conformations, 0196
and Friedel-Craft acylation, 0723
and hydrogen bonding, 0110, 0113
and intermediates, 0312
and strained aromatic compounds, 0230, 0231
ethanonium ion, 0766
methyl radical, 0276
of methane, 0012
step-scan time-resolved, 0266
Ireland-Claisen rearrangement, 1671
iron carbenes, 1236
iron compounds, and acetal cleavage, 0526, 0527
iron pentacarbonyl, with Grignard reagents, 0823, 0910
with organolithium reagents, 0910
iron, and metallocenes, 0067
isobutane, and superacids, 0237
bond energy, 0028
isocyanate ion, formation of isocyanates, 0573
with alkyl halides, 0514
with aromatic compounds, 0729
isocyanate, chlorosulfonyl, reactions, 1466
isocyanates, addition of alcohols, 1274
addition of amines, 1295, 1296
and formation of amides, 0729
by carbonylation of azides, 0851
by Hofmann rearrangement, 1607
by Lossen rearrangement, 1610
by rearrangement of acyl nitrenes, 1561
by the Curtius rearrangement, 1609
by the Schmidt reaction, 1611
by thermolysis of acyl azide, 1608
carbonylation of amines, 0851
catalytic hydrogenation of formamides, 1813
dioxirane oxidation to nitro compounds, 1778

from alkyl halides, 0573
from alkyl halides and isocyanate, 0514
from amides and hypohalites, 1607
from amines and phosgene, 1427
from carboxylic acids and hydrazoic acids, 1611
from isocyanate ion, 0573
from nitrile oxide, 1700
from O-acyl hydroxamic acids, 1610
hydrolysis, 1266, 1607, 1609–1611
reaction with carbamates, 1274
reduction to amines, 1823
with Grignard reagents, 1337, 1338
with oxetanes, 1275
with phosphine oxides, 1461
with phosphorus ylids, 1379
isocyanides, also see isonitriles
isocyanides, acid catalyzed hydrolysis, mechanism, 1467
addition of water, 1467
addition reactions, 1466
and the Knoevenagel reaction, 1361
from alkenes, trimethylsilyl cyanide and silver salts, 1148
from epoxides or oxetanes, 0568
hydrolysis, 1467
with Grignard reagents or organolithium reagents, 1469
with Schwartz's reagent, 1148
isodesmic reactions, 0038
isoinversion, 0760
isolation, of intermediates, 0312
isomer distributions, electrophilic aromatic substitution, 0678
isomer, conformational, and conformer, 0196
dextro, 0138
valence bond, 0186
isomerism, see isomers
isomerism, in-out, 0112
and carbocations, 0113
isomerization, alkenes, allylic-propenyl, 1028
and biphenyls, 0748
cis-trans, and isotope effects, 0326
cis-trans, mechanism, 0312
cis/trans, of alkenes, and epoxidation, 1174
cis/trans, photochemical, 0346
E/Z, azo compounds, 0692
of alkenes, in catalytic hydrogenation, 1058
of alkenes, via boranes, 0771
of alkyl boranes, 1533
of aryl triazenes, 0692
of carbenes, 0285
photochemical, cyclooctene, 0346
thermal, dibenzosemibullvalenes, 0347
isomers, and configuration, 0195
and the 2^n rule, 0183, 0187
cis/tans, and silicon, 0011
cis/tans, and steric hindrance, 0186
cis/trans, 0148, 0182
cis/trans, and conformations, 0201
cis/trans, and cyclohexene, 1640
cis/trans, and cyclooctene, 0184
cis/trans, and diastereomers, 0182
cis/trans, and elimination reactions, 1501
cis/trans, and monocyclic compounds, 0186, 0187
cis/trans, and restricted rotation, 0232
cis/trans, and stability, 0227
cis/trans, fused ring systems, 0188
cis/trans, heat of combustion, 0186
cis/trans, isomerization of triazenes, 1029
E/Z, and carbon-heterocycle double bonds, 0183
E/Z, and radicals, 0272
E/Z, and strained bicyclic imines, 0230
E/Z, Cahn-Ingold-Prelog system, 0183
E/Z, isomerization of alkenes, 1028
E/Z, photochemical isomerization of alkenes, 1028, 1029
E/Z, radical induced isomerization, 1029
E/Z, selectivity in the Wittig reaction, 1376, 1377
exo/endo, and radical cyclization, 1127
fluxional, 0186
in-out, and proton transfer, 0368
levo, 0138
of amides, 0184
of rotaxanes, 0132
out-in, 0189–0191
positional, isomerization of alkenes, 1028
r symbol, 0187
syn/anti, and the aldol reaction, 1345, 1346
syn/anti, from reaction at carbonyls, 1252
t symbol, 0187
valence, and [2 + 2]-cycloaddition, 1233
isonitriles, also see isocyanides
isonitriles, and cyanide ion, 0648
dehydration of amides, reagents for, 1550
from amines, 0567
from chloroform, 0567
isopentane, bond energy, 0029
isopropylation, benzene, rate and product distribution, 0680
toluene, rate and product distribution, 0680
isopropyllithium, and X-ray, 0262
isoquinolines, Bischler-Napieralski reaction, 0715, 0716
by cyclotrimerization of diynes, 1245
Friedel-Crafts cyclization, 0715, 0716
from imines, 1049
from nitrilium ions, 0716
Pictet-Spengler reaction, 0716
isoracemization, 0760
isoselenoureas, 1297
isothiocyanate ion, formation of isothiocyanate ions, 0573
from isothiocyanate ion, 0573

isothiocyanates, addition to alkenes, 1157
cyclization, 0730
formation of thioamides, 0730
from addition of amines to carbon disulfide, 1297
from alkyl halides, 0573
from amines and thiophosgene, 1428
from dithiocarbamic acid salts, 1297
hydrolysis, 1266
reduction to amines, 1823
reduction to thioformamides, 1813
isothiouronium salt, from thiourea, 0548
isotope effects, and carbocations, 0238
and cis-trans isomerization, 0326
and Grignard reactions, 1308
and hyperconjugation, 0325, 0326
and mechanism, 0322, 0323
and NMR, 0324
and phenonium ions, 0459
and temperature, 0326
and the Chugaev reaction, 1521
and the S_N2 reaction, 0326
arenium ions, 0659
Baeyer-Villiger rearrangement, 1619
calculations, 0324
deuterium, 0322, 0323, 0324
deuterium ion, 0661
deuterium, and dissociation energy, 0323
deuterium, and E1cB reactions, 1491
deuterium, and E2 reactions, 1484
E2 reactions, 1479
E^i reactions, 1509
enol formation, 0774
in the Diels-Alder reaction, 1206
inverse, 0324
partitioning effect, 0659, 0660
S_E1 mechanism, 0758
secondary, 0325, 0326, 0327
solvent, 0327
isotope exchange, rate, with carbanions, 0760
isotopes, and acetal hydrolysis, 0524, 0525
and alkynyl carbocations, 0477
and ion pairs, 0438
and S_N2 reactions, 0429
and solvolysis, 0438
secondary isotope effect in substitution reactions, 0488
isotopic dilution, and enantiomeric purity, 0182
isotopic effect, and bridged radicals, 0943
isotopic labeling, alkynes, 0477
amide hydrolysis, 1410
and aromatic S_N1 reactions, 0859
and aromaticity, 0065
and carbene insertion, 0806
and chirality, 0152
and Claisen rearrangement, 1668, 1669
and cyanogen bromide, 0314
and enolizable protons, 0775
and Fischer indoles synthesis, 1675
and Friedel-Crafts acylation, 0722
and hydration of aldehydes and ketones, 1262
and hydrolysis of esters, 1404
and mechanism, 0314
and NMR, 0314
and ozonolysis of alkenes, 1741
and radical rearrangements, 1575
and reduction of sulfoxides, 1851
and reverse Friedel-Crafts alkylation, 0744
and the benzyne mechanism, 0859
and the Stevens rearrangement, 1621
and the tetrahedral mechanism, 1256
benzidine rearrangement, 1680
Favorskii rearrangement, 1596
Friedel-Crafts alkylation, 0712
halogenation of alkenes, 1004
Kolbe-Schmidt reaction, 0729
phosphine oxides with isocyanates, 1461
rearrangement of N-nitroanilines, 0738
Wolff rearrangement, 1600
isovalent hyperconjugation, 0098
IUPAC and nomenclature of carbocations, 0235
and spectroscopy, 0012
mechanisms, and carbenes, 0500
mechanisms, and diazonium salts, 0500
mechanisms, substitution reactions, 0496
nomenclature, addition-elimination mechanism, 0474
nomenclature, for transformations, 0418
nomenclature, mechanisms, 0420
nomenclature, S_N1', 0469
nomenclature, S_Ni, 0468
terminology for acids and bases, 0356

Jablonski diagram, 0337
Jacobsen reaction, 0747
and rearrangement, 0748
Jacobsen-Katsuki epoxidation, 1178
Japp-Klingemann reaction, 0783
Johnson polyene cyclization, 1090
Jones reagent, and oxidation of alcohols, 1716
Journal of Synthetic Methods, 1893
journals, how to locate articles, 1909
irregular publications, 1890
literature, 1871–1875
reviews, 1889
Julia-Colonna epoxidation, 1176

Kamlet reaction, 1357
Kamlet reaction, see Henry reaction
Katritzky pyrylium-pyridinium method, 0542
alkylation of nitro compounds, 0626
and alkyl halides, 0586
and thiocyanates, 0554
KBr, and zeolites, halogenation of aromatic compounds, 0700
Kekulé structures, and polyacenes, 0061

kekulene, and NMR, 0087
ketal formation, mechanism, 1271
ketals, and transacetalization, 1272
as protecting groups, 1271
dimerization, 0618
elimination, to vinyl ethers, 1517
from alcohols and ketones, 1270
reduction, 1832
ketene acetals, silyl, and conjugated ketones, 1353
silyl, conjugate addition, 1121
ketene acetals, with mines, 1353
ketene dithioacetals, hydrolysis, 0528
ketenes, addition of acids HX, 1031
addition of alcohols and phenols, 1040
addition of carboxylic acids, 1042
addition reactions, 1031
amination, 1050
and enamine acylation, 0636
and formation of carbenes, 0288
and Friedel-Crafts acylation, 0719
and hydrolysis of carbamates, 1406
and the Diels-Alder reaction, 1196
by base induced elimination of acyl halides, 1532
by dehydration of carboxylic acids, 1514
cycloaddition to carbonyls, enantioselectivity, 1462
cycloaddition with imines, 1464, 1465
dimerization, 1228, 1463
from acyl carbenes, 0291
from carbenes, 0291
from the Wolff rearrangement, 1600
hydrolysis, 1600
metal catalyzed cycloaddition with carbonyls, 1462
metal induced dehalogenation of acyl halides, 1540
orbital overlap in [2 + 2]-cycloaddition, 1225
photolysis, 0345, 0806
silyl, and Claisen rearrangement, 1671
via Wolff rearrangement, 0291
with aldehydes or ketones, 1040
with cyclopentadiene, orbital overlap in [2 + 2]-cycloadditions, 1227
with hydrazones, 1465
with phosphorus ylids, 1379
[2 + 2]-cycloaddition, 1221, 1222, 1226
ketenimines, amination, 1050
by dehydration of amides, 1515
ketimines, also see imines
α-ketol rearrangement, 1593
keto-acids, allyl esters, and Kimel-Cope rearrangement, 1670
allylic esters, Carroll rearrangement, 1670
allylic esters, Claisen rearrangement, 1670
and decarboxylation, 0838
and Friedel-Crafts acylation, 0722
by indirect carboxylation, 1367
decarboxylation, 0837
from ketones with metal carbonates, 1367
from metalated imines, 1469
metal catalyzed decarboxylative allylation, 0996
oxidative cleavage of cyclic alkenes, 1743
keto-aldehydes, and aliphatic Vilsmeier reaction, 0797
Cannizzaro reaction to hydroxy acids, 1864
keto-amides, and Friedel-Crafts acylation, 0719
from amide-acids and organolithium reagents, 1447
keto-enol tautomerism, see tautomerism
keto-esters, and acetoacetic acid synthesis, 0624
base catalyzed condensation of esters, 1452
by the Reformatsky reaction, 1328
cleavage with base, 0841
cyclic, Dieckmann condensation, 1453
decarboxylation, 0839
from aldehydes, 0800
from carboxylic acid dianions and esters, 1456
from diazoesters, 0800
from ketones and diazoesters, 1603
McMurry reaction to give cyclic ketones, 1859
with boric anhydride, 0839
with hydrazines, 1285
keto-nitriles, by the Thorpe reaction, 1387
from esters and nitriles, 1455
keto-sulfones, alkylation, 0624, 0632
keto-sulfoxides, alkylation, 0632
keto-ylids, and resonance, 1371
ketones, acid catalyzed rearrangement, 1592
α-acyloxylation, 0972
ketones, addition of alcohols, 1270
addition of allylic boranes, 1319
addition of dialkylzinc reagents, 1310, 1311
addition of diazomethane, 1601, 1602
addition of Grignard reagents, mechanism, 1307
addition of organolithium reagents, mechanism, 1308
addition of organometallics, 1309–1311
addition of thiols, 1277, 1278
addition of water, 1262
ketones, aldol condensation with aldehydes, 1344
alkylation, 0626
alkylation, Stork enamine synthesis, 0635
alkynyl, see alkyne-ketones
amphiprotic properties, 0772
ketones, and Baeyer-Villiger rearrangement, 1617
and bisulfite addition products, 1280
and carbanions, 0265
and Claisen reaction, 1355
and Collman's reagent, 0650
and cyclodehydration, 0715
and Dakin-West reaction, 0841
and formation of aminals, 1283
and Haworth reaction, 0722
and hemiaminals, 1281

ketones, and Baeyer-Villiger rearrangement, (*Continued*)
and Japp-Klingemann reaction, 0783
and McMurry reaction, 1859
and Peterson alkenylation, 1365
and reagents for hydrolysis of C=N compounds, 1264, 1265
and tautomerism, 0098
and the aldol reaction, 1339–1351
and the Claisen-Schmidt reaction, 1343, 1344
and the Haller-Bauer reaction, 0844
and the Knoevenagel reaction, 1358
and the Mannich reaction, 1292
and the Mukaiyama aldol, 1351–1354
and the Paterno-Büchi reaction, 1463
and the Reformatsky reaction, 1326
and the Strecker synthesis, 1391
and the Willgerodt reaction, 1867
and Tollens' reagent, 1368
ketones, aryl, and imino esters, 0732
aryl, Friedel-Crafts acylation, 0719
aryl, from carboxylic acids, 0719
aryl, from nitriles, 0732
aryl, Hoesch reaction, 0732
aryls, from acyl halides, 0719
aryls, from aromatic compounds, 0719
base catalyzed addition to carbon disulfide, 1368
base cleavage, strain and steric effects, 0843
bicyclic conjugated, and Robinson annulation, 1350
bicyclic, and thermal extrusion of carbon monoxide, 1545
bicyclic, by metal catalyzed carbonylation of alkynes, 1140
ketones, by acetoacetic acid synthesis, 0624
by acid catalyzed rearrangement of epoxides, 1587
by addition of aldehydes to alkenes, 1135
by carbonylation of aryl halides, 0910
by DMSO-type oxidation of alcohols, 1721
by Fries rearrangement, 0735
by Fukuyama coupling, 1450
by hydration of alkynes, 1035
by hydration of allenes, 1037
by hydrolysis of alkoxides, 1804
by hydrolysis of C=N compounds, 1263
by hydrolysis of enol ethers, 1035
by hydrolysis of imines, 1767
by hydrolysis of oximes, 0986
by Oppenauer oxidation, 1721
by oxidation of alcohols, 1715–1728
by oxidation of alkenes, 1773–1775
by oxidation of amines, 1767
by oxidation of vinylboranes, 1631
by oxidative cleavage of alkenes, 1742
by oxidative cleavage of diols, 1732–1735
by ozonolysis of alkenes, 1737
by pyrolysis of allylic ethers, 1552
by rearrangements of hydroperoxide, 1620
by the Nef reaction, 1267
by the Wacker process, 1774
ketones, catalytic hydrogenation, 1795
catalytic hydrogenation, mechanism, 1805
chemoselective reducing agents, 1794
chiral, 0775
chloro, see chloroketones
cleavage, haloform reaction, 0842
cleavage, with base, 0841–0844
cleavage, with halogen, 0842
condensation, see aldol
condensation with esters, 1355, 1455
condensation with imines, 1349
ketones, conjugated, also see conjugated compounds
ketones, conjugated, α-acyloxylation, 0972
and enolate anions, 0631
and Nazarov cyclization, 1095
and organolithium reagents, 1302
and the aldol reaction, 1339–1351
and the Meyer-Schuster rearrangement, 0473
by α-oxidation of alkenes, 1759
by carbonylation of alkynes, 1141
by hydrogenation of phenols, 1067
by Pauson-Khand reaction, 1141
carbonylation, 1143
from acyl halides, 0796
from alkenes, 0796
from allenes, 0472
from haloketones, 0796
from selenoalkyl ketones, 0792
from Weinreb amides, 1448
halogenation, 0780
halogenation, and the Dess-Martin periodinane, 0780
proton acidity, 0633
reagents for conjugate reduction, 1071
reduction with enzymes and reductases, 1074
with Grignard reagents, 1302
with LDA, 0907
Wurtz coupling, 0592
ketones, conversion to amides, 1867
ketones, cyclic, and I strain, 0400
and reactivity, 0400
and the Schmidt reaction, 1611
aromatization to phenols, 1709
Baeyer-Villiger rearrangement, 1618
by expansion of bicyclic ketones, 1603
dihalides and Collman's reagent, 0650

from acid catalyzed rearrangement of amino alcohols, 1589
McMurry reaction with keto esters, 1859
oxidative cleavage to dicarboxylic acids, 1735
oxidative cleavage with sodium hypochlorite, 1736
oxidative, cleavage, reagents for, 1735, 1736
pyrolysis of dicarboxylic acids, 1458
Ruzicka cyclization, 1458
with hydrazoic acid, 1611
ketones, cyclization with dihalides, 0629
cycloaddition to alkenes, 1463
cyclopropyl, from conjugated ketones, 1387
decarboxylation of carboxylic acids, 1457
dehydrogenation, 1713
diastereoselectivity of reduction with Selectride, 1794
dihalogenation, 0778
diketones, see diketones
dimerization, with UV, 1856
divinyl, from vinyl organometallics, 0651
enol content, 0099
enolate anion blocking groups, 0630
formation of cyanoamines, 0561
formation of enolate anions, 0790
formation of halo-ketones, 0776
formation of nitroso compounds, 0784
formation of oximes, 0784
formation of thioketones, with hydrogen sulfide, 1277
formylation, 0798
Friedel-Crafts cyclization, 0715
ketones, from acyl halides, 0721
from acyl halides and boronic acids, 1443, 1444
from acyl halides and organocadmium reagents, 1443
from acyl halides and organocuprates, 1442
from acyl halides and organometallics, 1443, 1444
from aldehydes, 0638, 0801
from aldehydes, and diazomethane, 0807
from alkoxides, 0758, 0840
from alkyl halides, 1122
from aryl halides, 0910
from arylboronic acids, 0910
from boranes, 0644
from carboxylic acids, 0840, 1329
from carboxylic esters, 0735, 1446
from cleavage of diketones, 0841
from cyanoboranes, 1628
from cycloaddition of singlet oxygen to alkenes, 1220
from diazoketones and Wolff rearrangement, 1465
from dicarboxylic acids, 1750
from dicobalt octacarbonyl, 0823
from dihalides, 0520
from diols, 1585
from dithianes, 0638
from enol borinates, 1121
from formamides and organolithium reagents, 1446
from Grignard reagents, 0824, 1337, 1444, 1448
from haloketones, 0644
from hydrazones, 0633
from hydroxynitriles, 0633
from iminium salts, 0732
from metallated imines, 1469
from organocerium reagents, 1447
from organolithium reagents, 0824, 1447, 1448
from organometallics, 0651, 0823
from organosulfur carbanions and esters, 1455
from oxazolidines, 0643
from silyl enol ethers, 0617, 0798
from silyl-epoxides, 1367
from Stork enamine reaction, 0634, 0635
from thioesters and organozinc halides, 1450
from vinylic compounds, 0522
ketones, halo, from diazo ketones, 0585
ketones, halogenation, and microwaves, 0776
enantioselectivity, 0777, 0778
mechanism, 0778, 0779
rate, 0779
reagents for, 0776, 0780
regioselectivity, 0780
ketones, Henry reaction, 1357
heteroaryl, by carbonylation, 0910
hindered, with hydroxylamine, 1286
homoallylic, from keto acids, 0996
homologation, 1601, 1602
hydration of, 1262
α-hydroxylation, 1752
indirect carboxylation, 1367
less reactive than aldehydes, 1254
$LiAlH_4$ reduction, mechanism, 1804
macrocyclic, conformation, 0213
Meerwein-Ponndorf-Verley reduction, 1796
metal catalyzed addition to alkenes, 1098
metal catalyzed coupling to oximes, 1858
metal catalyzed cycloaddition with ketenes, 1462
metal catalyzed reaction with dihalosulfones, 1381
metal mediated addition of haloesters, 1326
metal mediated halogenation, 0776
α-methylation, and the Simmons-Smith procedure, 1242
methyl, and the haloform reaction, 0842
methyl, by homologation of aldehydes with diazomethane, 1602
nitro, with amines, 0844
nitrosation, mechanism, 0784
α-oxidation, reagents for, 1758
α-oxidation, to diketones, 1758
α-oxidation, with selenium dioxide, mechanism, 1760
Paterno-Büchi reaction, 1231
photochemical cleavage, 0279
photochemical dimerization, 1856, 1857
photochemical [2 + 2]-cycloaddition, with alkenes, 1231

ketones, Henry reaction, (*Continued*)
photochemistry, 0332
photoreduction, 0348
prochiral, reduction of, 1799
protection, 0527
radical coupling, 0977
reaction with alcohols, compatible functional groups, 1270
reaction with amines, 1281
ketones, reduction, and Cram's rule, 1804
diastereoselectivity, 1803
enantioselectivity, 1800–1803
in ionic liquids, 1800
in supercritical alcohols, 1837
to alcohols, 1792–1805
to methylene, reagents for, 1836, 1837
versus aldehydes, 1793, 1794
with aluminum isopropoxide, 1796
with ammonium formates, 1799
with boranes, 1798
with enzymes, 1800
with hydrides, 1792
with metals, 1797
with sodium in ethanol, 1795, 1796
with tin hydrides, 1798
ketones, reductive amination, 1288–1291
ketones, reductive cleavage of nitriles, 1835
reductive coupling to alkenes, reagents, 1858, 1859
reductive coupling to diols, reagents, 1854, 1855
selenoalkyl, formation of conjugated ketones, 0792
singlet, 1857
sterically hindered, and $LiAlH_4$, 1792
sterically hindered, and Wolff-Kishner reduction, 1836
structural requirements, and the Wittig reaction, 1371
sulfenylation, 0791
sulfonation, 0791
tautomerism, 0772
thermal extrusion of carbon monoxide, 1545
thioalkyl, from enolate anions, 0790
thioalkyl or thioaryl, from silyl enol ethers, 0792
triplet, 1857
unsymmetrical, acidity of α-protons, 0630
unsymmetrical, and enoate anions, 0630
unsymmetrical, formation of silyl enol ethers, 0799
unsymmetrical, regioselectivity, 0630
via decarboxylation, 0840
ketones, with acyl halides, 1274
with amines and hydrogen, 1288–1291
with aromatic compounds, 0713
with base, 0774
with bis(Grignard) reagents, 1304
with diazo esters, 1603
with diazoalkanes, 1384
with dihalocarbenes, 1384
with enol esters, 0629
with enolate anions, 0263, 1339–1351
with enolate anions, see aldol
with Grignard reagents, 1300–1309
with halo esters, 1364
with halo-sulfones, 1384
with halogens, 0776
with HCN, 1389
with hydrazines, 1284
with hydrogen sulfide, 1277
with hydroxylamine, 1286
with isocyanides and carboxylic acids, 1467
with LDA, 0798
with lithio-silanes, 1365
with nitro compounds, 1357
with nitrous acid, 0784
with organocuprates, 1312
with organolithium reagents, 1301
with Oxone®, epoxidation of alkenes, 1172
with phenylhydrazine, 1675
with phosphorus ylids, 1369
with silanes, metal catalyzed, 0799
with sodium bisulfite, 1281
with sulfur ylids, 1382
with Tebbe's reagent, 1380
with the Petasis reagent, 1380
with tosylimines and proton sponge, 1465
ketones, Wolff-Kishner reduction, 1835
ketyls, and Gomberg-Bachmann pinacol synthesis, 1854
and reduction of carbonyls with sodium in ethanol, 1796
and the acyloin condensation, 1861
radical ions, 0282
Kiliani-Fischer method, 1391
Kimel-Cope rearrangement, 1670
Kindler modification, Willgerodt reaction, 1868
kinetic acidity, see acidity
kinetic and thermodynamic control, arenium ions, 0666
kinetic resolution, also see resolution
kinetic resolution, 0176
and enantiomeric purity, 0182
ketones, 0775
kinetically controlled reactions, 0307, 0308
kinetic control, and sulfur ylids, 1384
kinetics, and aliquots, 0319
and calorimetric methods, 0319
and enthalpy, 0301
and entropy, 0322
and ESR, 0319
and frequency factor, 0322
and half-life, 0320
and homogenous reactions, 0315
and inverse isotope effects, 0324
and ion pairs in the S_N1 reactions, 0436
and Marcus theory, 0315, 0316
and mechanisms, 0315, 0321
and molecularity, 0316, 0317
and NMR, 0321, 0434
and quenching, 0319
and rate constant, 0315
and rate law, 0315, 0317, 0318
and rate-determining state, 0316, 0317
and reactions, 0301
and salt effect, 0434
and secondary isotope effects, 0325, 0326, 0327
and solvent isotope effects, 0327

and spectroscopic methods, 0319
and steady state, 0317
kinetics, first order, 0433
first order, and the S_E1 mechanism, 0758
first-order rate law, 0319
first-order reactions, 0315, 0316
methods for determining, 0319
of amide hydrolysis, 1409
of E^i reactions, 1508
of elimination reactions, 1490
of fast reactions, 0319
of gas phase reactions, 0319
of lead tetraacetate cleavage of diols, 1734
of radical chain reactions, 0937
of radical cyclization, 1125
of rearrangement of cyclopropylcarbinyl radicals, 0945
of S_N1 reactions, and leaving groups, 0433
of S_N2 reactions, 0427
of the Heck reaction, 0895
of the Mannich reaction, 1294
pseudo first-order, 0318
second order, HBr with alkenes, 1030
second-order reactions, 0315, 0316
Kishi's NMR method, and absolute configuration, 0161, 0162
Knoevenagel carbanions, with allylic esters, 0610
Knoevenagel reaction, 1358
and acyl anion equivalents, 1362
and carbamates, 1362
and Darzens condensation, 1364
and high pressure, 0513, 1359
and microwaves, 1359
and the Nef reaction, 1359
and the Wittig reaction, 1363
and tosylhydrazones, 1363
and ultrasound, 1359
Doebner modification, 1360
in ionic liquids, 1359
metal catalyzed, 1359
on silica gel, 1359
on zeolites, 1359
products, 1360
solventless, 1359
special variations, 1360–1363
structural variation, 1358
suitable functional groups, 1358
knots, molecular, 0133, 0134, 0152
Knovenagel reaction, and the homoaldol reaction, 1362
Koch reaction, 1137
Koch-Haaf reaction, 0653, 1137
KOH, with amines, 0547
Kolbe electrosynthesis, see Kolbe reaction
Kolbe reaction, 0993
and electron transfer, 1705
mechanism, 0993
Kolbe-Schmidt reaction, 0728, 0729
Kornblum reaction, 1765
Kornblum's rule, and ambident nucleophiles, 0516
Krebs cycle, and enantiotopic, 0192
Krönke reacation, 1766

labeling, and acetal hydrolysis, 0524, 0525
and enantiotopic atoms, 0192
and ion pairs, 0438
and phenonium ions, 0459
and solvolysis, 0438
cyclopentadienide ion, 0063
in alkynyl carbocations, 0477
isotopic, and mechanism, 0314
vinyl ether hydrolysis, 0528
lactamization, 1431
α-lactams, from halo-amides, 0571
β-lactams, arylation, 0881
by carbonylation of aziridines, 1466
by cycloaddition of imines and ketenes, 1464
by radical cyclization, 1128
by [2 + 2]-cycloaddition, 1221
formation of, enantioselectivity, 1465
from alkenes and chlorosulfonyl isocyanate, 1466
from β-amino esters, 1435
from carboxylic acids and imines, 1465
from imines and diazo ketones, 1466
from imines and halo esters, 1465
from ketenes and hydrazones, 1465
lactams, α-alkylation, 0627
lactams, alkylation, 0512, 0568
alkylidene, from dihalosulfone and imides, 1381
alkylidene, from ynamides, 1052
and determining absolute configuration, 0160
and Friedel-Crafts acylation, 0719
and proton transfer, 0368
and strain, 0224
arylation, 0880
bicyclic, from carbamates, 1051
by α-oxidation of amines, 1759
by amidation of alkenes, 1051
by Beckmann rearrangement, 1614
by carbene insertion, 0804–0805
by carboxylation of alkenes, 1144
by halolactamization, 1154, 1155
by radical cyclization, 1128
by rearrangement of oxaziridines, 1588
by Schmidt reaction with cyclic ketones, 1611
conjugate addition, 1131
conversion to thiolactams, 1278
enolate anion, with aryl halides, 0907
from alcohols, and amines or ammonia, 1436
from amino acids, 1431
from halo amides, 1695
in Diels-Alder reactions, 1217
N-halogenation, 0851
α-oxidation to imides, 1759
reduction to cyclic amines, 1842
ring expansion, 1438
ring expansion from cyclic amines, 0851
with alkyl halides, 0569
with amines at high pressure, 1438
with sodium hydride, 0569
Wittig reaction, 1371

lactic acid, and absolute configuration, 0154
lactim ethers, vinyl, Diels-Alder reactions, 1217
lactone formation, and ring size, 0304
β-lactones, angle strain and reaction with amines, 1437
decarboxylation, 1556
decarboxylation to alkenes, 1544
from hydroxy acids, 1415
from ketenes and carbonyls, 1462
photolysis of conjugated esters, 1041
pyrolysis to alkenes, 1544
lactones, α-alkylation, 0627
and conformations, 0213
and DCC, 1417
and neighboring group mechanisms, 0448
and the Mukaiyama rearrangement, 1416
β-, see β-lactones
by addition halo-esters to alkenes, 1161
by Baeyer-Villiger rearrangement of cyclic ketones, 1618
by carbonylation, 0653, 0909
by carboxylation of alkenes, 1144
by halolactonization, 1154, 1155
by metathesis reactions, 1686
by radical cyclization, 1128
by reduction of anhydrides, reagents, 1840
by the Story synthesis, 1557
cleavage, 0550
conjugated, reagents for reduction, 1072
conversion to thiolactones, 1278
coupling with allylic esters, 0609
dehydrogenation, 1713
extrusion of carbon dioxide, 1555
lactones, from alkenes, 1186
from alkyne-carboxylic acids, 1042
from cyclic peroxides, 1557
from dicarboxylic esters and the Tischenko reaction, 1865
from diene-carboxylic acids, 1042
from diketones and the Cannizzaro reaction, 1864
from epoxides, 0619
from halo-acids, 0304
from hydroxy acids, 1415
from hydroxy carboxylate salts, 0540
from hydroxy-trimethylsilyl alkenes, 1036
from iodo-alcohols, 0653
lactones, hydrolysis, 1401
macrocyclic, from cyclic ketones, 0842
macrocyclic, from hydroxy acids, 1415
α-oxidation of cyclic ethers, 1760
photolysis, 1555
pyrolysis to alkene acids, 1520
sulfenylation, 0791
thermal extrusion of carbon dioxide, 1546
transesterification, 1420
with hypervalent iodine, 0541
with lithium iodide, 0585
with Petasis reagent, 1381
with phosphorus ylids, 1379
with Tebbe's reagent, 1381
Wittig reaction, 1371
lactonization, from amides, 1187
of alkenes, 1186, 1187
reagents for, 1416
Lange's Handbook of Chemistry, 1887
lanthanide shift reagents, 0181
large angle strain, see strain
lariat ethers, 0123
Lawesson's reagent, 1278
with alcohols, 0549
with ketones, 1278
LC, preparative, and diastereomers, 0175
and resolution, 0175
LCAO, 0006
LDA (lithium diisopropylamide)
aggregates of, 0389
and carboxylic acids, 0637
and elimination of ethers, 1516
and enol borinates, 0631
and formation of enolate anions, 0811
and the aldol reaction, 1343
and the Claisen-Schmidt reaction, 1343, 1344
and X-ray crystallography, 0389
with conjugated ketones, 0907
with ketones, 0798
lead tetraacetate, and acyloxylation, 0972
and bis(decarboxylation), 1749
and dihydroxylation of alkenes, 1168
and oxidative cleavage of diols, 1732
and oxidative decarboxylation, 1747
cleavage of diols, 1734, 1735
conversion of alcohols to cyclic ethers, 0965
with cyclopropanes, 1025
lead tetracetate, reactions of, 0972
lead, pyrophoric, coupling of acyl halides, 1450
leakage, rearrangement of ions, 1572
leaving group ability, table, 0501
leaving groups, amino, in Mannich bases, 0498
leaving groups, and amines, 0498
and aziridines, 0497
and basicity, 0496
and carbene formation, 0500
and conjugate bases, 1489
and electrophilic aromatic substitution, 0683
and epoxides, 0497
and neighboring groups, 0446
and nucleophilic aromatic substitution, 0868
and nucleophilic substitution, 0482
and reactions, 1496
and rearrangement of nitrenes, 1562
and S_E1 reactions, 0764
and S_N1 reactions, 0432
and S_N2' reactions, 0471
and strain, 0496
and substitution reactions, 0496
and the element effect, 0475
and the tetrahedral mechanism, 1259
and thiiranes, 0497
leaving groups, at saturated carbon, 0496

axial versus equatorial, in E2 reactions, 1481
β-substituents, 0446
benzotriazoles, with E^i reacts, 1524
definition, 0297
diazonium salts, 0499, 0916
ditosylates, 0498
E1 versus E2 reactions and elimination versus substitution, 1505
halides in halide exchange, aryl halides, 0883
in the E2 reaction, 1479
kinetics and S_N1, 0433
nitrogen, 0499, 0984
nitronium ion, 0683
other, in aromatic substitution, 0742
proton, 0683
pyridinium compounds, 0498
pyrylium salts, 0498
reactivity in elimination reactions, 1505
solvation by, 0759
suitable for elimination, 1505
sulfonate esters, 0497, 0498
sulfonyl groups, 1472
Lederer-Manasse reaction, 0714
Lemieux-von Rudloff reagent, oxidative cleavage of alkenes, 1743
length, bond, see bond distance
length, cell, and specific rotation, 0139
Leuckart reaction, and the Wallach reaction, 1291
levo isomer, 0138
Lewis acid catalysis, sulfonyl halides with halo esters, 0605
Lewis acid catalyzed Diels Alder reaction, 1197
Lewis acid complexes, and X-ray crystallography, 0720
Lewis acid-base complex, 0375, 0376
Lewis acid-base, rate of complex formation, 0376
Lewis acidity, and Brønsted acidity, 0384
Lewis acids, addition of acyl halides to alkenes, 1161
addition of alkyl halides to alkenes, 1159
addition of thiols to alkenes, 1043
aldehydes with diazoesters, 0800
alkenes and Friedel-Crafts alkylation, 0711
allylic silanes with epoxides, 0589
Lewis acids, and acetals, 0526, 0527
and acyl carbocations, 0722
and arenium ions, 0663
and aryl halides, 0749
and cleavage of cyclic ethers, 0581
and cleavage of ethers, 0581
and condensation of enamines with aldehydes or ketones, 1344
and coupling alkenes with acyl halides, 0796
and Danishefsky's diene, 1216, 1217
and electrophiles, 0657
and enol alkylation, 0628
and epoxide alcoholysis, 0537
and esterification of carboxylic acids, 1418
and formation of biaryls, 0717
and Friedel-Crafts alkylation, 0708
and halogenation of aromatic compounds, 0699
and hardness, 0377
and imino esters, 0732
and nitration of aromatic compounds, 0687
and oxonium ion formation, 0544
and reaction of allylic silanes with aldehydes, 1388
and rearrangement of alkenes, 0769
and softness, 0377
and solvent effects, 0392–0394
and steric effects, 0385
and the Diels-Alder reaction, 1197
and the ene reaction, 1104
and the Gatterman-Koch reaction, 0725
and the Johnson polyene cyclization, 1090
and the Periodic table, 0375, 0384
and the Prins reaction, 1394
and thioalkylation of aromatic compounds, 0731
Lewis acids, as catalysts for the Curtius rearrangement, 1609
as catalysts for transesterification, 1419
catalysts for the Prins reaction, 1395
chiral, 0387
chiral, and the Claisen rearrangement, 1672
coordination with functional groups, 0709
definition, 0375
Lewis acids, for addition of alcohols to carbonyls, 1270
for addition of allylic silanes to aldehydes, 1322
for carboxylic esters, from ethers, 0542
for catalysis of hydroperoxide rearrangement, 1620
for catalysis of ketene cycloaddition to carbonyls, 1462
for catalysis, addition of carboxylic acids to alkenes, 1041
for catalysts for formation of aryl sulfones, 0698
for ethers with anhydrides, 0542
for Friedel-Crafts acylation, 0719
for halogenation of anilines, 0699
for halogenation of aromatic compounds, 0702, 0703
for organocopper compounds with alkyl halides, 0604
for reaction of thiols with aldehydes or ketones, 1279
for rearrangement of epoxides to ketones, 1587
for reversal of Friedel-Crafts alkylation, 0742
for the Beckmann rearrangement, 1613
Lewis acids, formation of aryl ketones, 0719
formation of keto-esters, 0800
lithium perchlorate, 0376
reaction types, 0376
reactivity order in Friedel-Crafts alkylation, 0708
strength of, 0377
used for the Ritter reaction, 1459
used in Diels-Alder reaction, 1197
with acyl halides, 0719

Lewis acids, (*Continued*)
with aryl esters, 0735
with aryl halides, 0749
with epoxides and organocuprates, 0619
with nitriles, 0732
with potassium cyanide or sodium cyanide, 0649
Lewis bases, *ab initio* calculations, and base strength, 0376
and nucleophiles, 0425, 0490
and steric effects, 0385
definition, 0375
Lewis structures, 0006, 0014, 0032
and resonance, 0046
benzene, 0036
Ley reagent, see TPAP
LHMDS (lithium hexamethyldisilazide), 0627, 0628, 0389
LICA (lithium isopropylcyl cohexylamide), 0627
and ester enolate anion Claisen rearrangement, 1670
lifetimes, of radicals, 0946, 1577
ligands, and η-complexes, 0043
in enantioselective catalytic hydrogenation, 1056
phosphine, 0043
light, and autoxidation, 0967
and optical activity, 0163
circularly polarized, 0138, 0172
plane polarized, 0136, 0137
limonylborane, 1080
Lindlar catalyst, and hydrogenation of alkynes, 1057
linear free energy relationship(LFER), 0405, 0406
linear polyacenes, 0061
lipases, formation of lactams, 1431
transesterification, 1420
liquid chromatography, see LC
liquids, and ultrasound, 0350
liquids, ionic, see ionic liquids
liquids, NBS, and halogenation of aromatic compounds, 0699
literature searching, 1898
literature searching, online, 1901
literature, and Beilstein, 1884
annual reviews and irregular publications, 1890
journals, 1871–1875
primary sources, 1870
secondary sources, 1870, 1876–1881
lithiation, also see metalation
lithiation, aromatic compounds, mechanism, 0808
of alkynes, 0809
of amides, 0810
of aromatic compounds, 0911–0915
of carbamates, 0640
of heterocycles, 0809
of pyridine, 0913
lithio-epoxide, rearrangement, 0564
lithioalkynes, coupling with alkyl halides, 0595
lithium aluminum hydride, see hydride
lithium borohydride, borane and carbon monoxide, 1628
lithium diethylamide, 0627
lithium diisopropylamide, see LDA
lithium hexamethyldisilazide, see LHMDS
lithium iodide, and collidine, with esters or lactones, 0584, 0585
lithium ions, and ambident nucleophiles, 0517
binding by crown ethers, 0120
lithium naphthalenide, with thioethers, 0992
lithium perchlorate, and S_N1 reactions, 0504
as a Lewis acid, 0376
in ether, and Diels Alder reactions, 1199
in ether, and formation of amino-alcohols, 0563
special salt effects, 0504
lithium tetramethylpiperidide, and enolate anions, 0628
lithium triethylborohydride, see borohydride
lithium, and formation of enolate anions, 0811
and ultrasound, 1451
in amines, reduction of aromatic compounds, 1069
in amines, reductive cleavage of esters, 1834
in ammonia, and Birch reduction, 1067
in ammonia, reduction of alkenes, 1065
in ammonia, reduction of aromatic compounds, 1067
in ammonia, with cyclopropanes, 1075
with alkyl halides, 0831
lithium-hydrogen exchange, with aromatic compounds, 0912
lone pairs, and bond angle, 0027
long bonds, 0024
Lossen rearrangement, 1563, 1610
low-temperature matrix, 0074
Lowest unoccupied molecular orbital, see LUMO
LTMP, 0628
LUMO, alkenes and Pauson-Khand reaction, 1143
and Diels-Alder reaction, 1195
and endo addition, 1214, 1215
and tetraenes, 0045
and the frontier orbital method, 1208
lyase and cyanohydrin formation, 1389
lyonium ions, and solvent acidity, 0371

macrocycles, and gyroscanes, 0135
by the Story synthesis, 1557
crown ethers, 0121
macrocyclic compounds, and catenanes, 0134
by acyloin condensation, 1861
macrocyclic lactones, by metathesis reactions, 1686
magnesium halides, Grignard reagents, 0260
magnesium monoperoxyphthalate, see MMPP
magnesium, and elimination of halo ethers, 1542
and the Barbier reaction, 1302
and the Boord reaction, 1542
and the Grignard reaction, 1300–1309
elimination with haloethers, 0830, 0831
with dihalides, 1304
magnetic field, and microwaves, 0353

magnetic susceptibility, and the Etard reaction, 1763
maleic acid, 0185
malic acid, chlorination of, 0427
malonates, alkylation, 0623
and enantiotopic atoms, 0191
with sulfones, 0907
malonic acid esters, see malonates
malonic acids, decarboxylation versus anhydride formation, 1423
malonic ester synthesis, 0623
arylation, 0714
mandelic acid, and asymmetric synthesis, 0170
manganate esters, 1163
manganese acetate, with alkenes, 1186
manganese dioxide, and oxidation of alcohols, 1717
and oxidation of amines, 1731
manganese salen complex, and asymmetric epoxidation, 1177
Mannich bases, and amino leaving groups, 0498
and conjugate addition (Michael addition), 1109
and elimination-addition reactions, 0478, 0498, 0562
coupling with organometallics, 0613
with amines, 0562
Mannich reactions, 1292–1295
and Eschenmoser's salt, 1294
and Robinson annulation, 1351
and the Strecker synthesis, 1391
selectivity, 1294, 1295
with more than equivalent of an amine, 1293
Marcus equation, and base catalysis, 0373
and Brønsted equation, 0374
Marcus theory, 0309, 0310
and mechanism, 0310
and proton transfer, 0373
and rate constants, 0315, 0316
and S_N2 reaction, 0310
and the Swain-Scott equation, 0493
Markovnikov's rule, acylation of alkenes, 0796
addition of alkyl halides to alkenes, 1160
addition of thiols to alkenes, 1043
alkenes, and Friedel-Crafts alkylation, 0711
and addition of carboxylic acids to alkenes, 1041
and addition of hypohalous acids to alkenes, 1153
and addition of silanes to alkynes, 1087
and addition to alkynes, 1030
and addition to cyclopropanes, 1025
and alcohol addition to alkenes, 1037
and alkenes, 1022
and amination of alkenes, 1047
and bromination, 1020
and hydration of alkenes, 1032
and oxymercuration, 1033
and the Hammond postulate, 1019
and the Prins reaction, 1394
definition, 1019
nitrosyl chloride with alkenes, 1158
phosphines and alkynes, metal catalysts, 1050
photochemical, alcohols to alkenes, 1040
Markovnikov, anti, see anti-Markovnikov
masochistic steric effects, [2 + 2]-cycloaddition, 1227
mass spectrometry, see MS
mass-law effect, and rate of reaction, 0434
matrix trapping, oxirenes, 1174
McFadden-Stevens reduction, 1811
McMurry reaction, 1859
formation of unsymmetrical alkenes, 1860
intramolecular, 1859
mCPBA (m-chloroperoxybenzoic acid), 1169
oxidation of boranes, 1082
mechanical separation, and resolution, 0176
mechanics, molecular, see molecular mechanics
mechanics, wave, 0003
mechanism, α-hydroxylation of enolate anions, 1754
mechanism, α-oxidation of ketones, 1760
mechanism, A-S_E2, 0528, 1005
acetal and ketal formation, 1271
acetal hydrolysis, 0525
acid catalyzed aldol reaction, 1349
acid catalyzed hydrolysis of isocyanides, 1467
acid catalyzed rearrangement of hydroperoxides to ketones, 1620
acyloin condensation, 1861
addition of alkanes to alkenes, 1084
addition of amines to ketenes, 1050
addition of Grignard reagents to aldehydes or ketones, 1307
addition of organolithium reagents to aldehydes or ketones, 1308
addition of thiols to alkenes, 1043, 1044
addition of water to carbonyls, 1263
addition to cyclopropanes, 1025, 1026, 1027
addition-elimination, 0474
addition-elimination, and alkylation of aromatic compounds, 0912
addition-elimination, and oxidation-reduction, 1707
addition-elimination, and rearrangement, 0475
addition-elimination, and the Heck reaction, 0894
addition-elimination, and vinyl halides, 0474
addition-elimination, Bucherer reaction, 0882
addition-elimination, electrochemical substitution, 0763
addition-elimination, hydrolysis of carbamates, 1407
addition-elimination, IUPAC nomenclature, 0474
addition-elimination, metal hydride, 0770
addition-elimination, quinones, 0474
$A_E + D_E$, 0658
alcohol addition to alkenes, 1037
aldol condensation, 1341

mechanism, A-
S_E2, (*Continued*)
alkene metathesis, 1688, 1689
alkenes with singlet oxygen, 0970
allylic radical halogenation, 0961, 0962
ambiguity in elimination reactions, 1494
anchimeric assistance, 0446
mechanism, and benzynes, 0313
and bond cleavage, 0296
and Brønsted equation, 1496
and catalysis, 0313
and deuterium isotope effects, 0322, 0323, 0324
and flash photolysis, 0348
and frequency factor, 0322
and half-life, 0320
and Hofmann rearrangement, 0311
and intermediates, 0311
and isotope effects, 0322, 0323
and isotopic labeling, 0314
and kinetics, 0315, 0321
and Marcus theory, 0310, 0315, 0316
and NMR, 0321
and rate constants, 0315, 0321
and rate law, 0315
and reduced mass, 0323
and secondary isotope effects, 0325, 0326, 0327
and solvent isotope effects, 0327
and solvolysis, 0437
and stereochemistry, 0314
and temperature, 0322
and von Richter, 0311
and Walden inversion, 0314
mechanism, arenium ion, 0657, 0658
and decarboxylation, 0746
and mercuration of aromatic compounds, 0913
and reverse Gatterman-Koch reaction, 0745
encounter complex, 0664
evidence for, 0659–0662
rate, 0659, 0660
mechanism, aromatization by quinones, 1710
arylation of aromatic compounds, 0925, 0926
arylidazonium salt coupling, 0783
aryne, see benzyne
autoxidation, 0968
Baeyer-Villiger rearrangement, 1619
Bamberger rearrangement, 0931
Bamford-Stevens reaction, 1527
Barton reaction, 1696
base induced elimination of ethers, 1516
base induced elimination of sulfones, 1528
Beckmann rearrangement, 1615, 1616
benzidine rearrangement, 1679, 1680
benzil-benzylic acid rearrangement, 1595
benzoin condensation, 1397
benzyne, 0859–0862, 0906
Birch reduction of aromatic compounds, 1068
bis(decarboxylation) of dicarboxylic acids, 1749
boranes, with metal alkyne anions, 1631
borderline, 0442
born-to-carbon rearrangement, 1627
bromination of acetone, 0323
Bucherer reaction, 0882
Cannizzaro reaction, 1864
carbanion, and elimination, 1489
carbene addition, 1238, 1239
carbene insertion, 0805, 0806
carbenoid formation, 1235
carbocation, addition of alkanes to alkenes, 1085
carboxylic esters with amines, 1436
catalytic hydrogenation of aldehydes or ketones, 1805
cheletropic reactions, 1537
Chichibabin reaction, 0915
chromium (VI) oxidation of alcohols, 1726, 1727
Chugaev reaction, 1521
cis-trans isomerization, 0312
Claisen condensation and Dieckmann condensation, 1453, 1454
Claisen rearrangement, 1668
cleavage of alkenes with superacids, 0845
combination, 0299
conducted tour, 0761, 0768
conjugate addition of organometallics, 1119
Cope elimination, 1525
Cope rearrangement, 1662
Criegee, ozonolysis, 1738–1740
Curtius rearrangement, 1609
cyanogen bromide with carboxylate salts, 1462
mechanism, cyclic, and addition to alkenes, 1012
and electrophilic substitution, 0763
diimide reduction of alkenes, 1063
reduction of hydrazones, 1838
mechanism, cyclopropane ring opening, 1591
cyclopropyl cation ring opening, 1644
Darzens condensation, 1364
DCC esterification, 1417
DCC reaction of carboxlic acids and amines, 1431
decomposition of AIBN, 0935
definition, 0296
dehydrohalogenation of alkyl halides, 1531
deprotonation by organometallics, 0810
determination of, 0311–0327, 1495
determining kinetic data, 0319
diazoalkanes with aldehydes or ketones, 1384
diazotization of anilines, 0918
Diels-Alder reaction, 1205, 1206
diion, and [2 + 2]-cycloaddition, 1228
diion, ketones with imines, 1465
dimer, and S_NAr reactions, 0857
diradical stepwise versus concerted, Diels-Alder, 1205, 1206
diradical, and carbenes, 1239
diradical, and photochemical[2 + 2]-cycloaddition, 1231
diradical, and [2 + 2]-cycloaddition, 1227
diradical, Cope rearrangement, 1664

displacement, and oxidation-reduction, 1706
DMSO oxidation of alkyl halides, 1766
Duff reaction, 0727
E1, acid catalyzed dehydration of alcohols, 1515
E1, and arenium ions, 0657
$E1_{anion}$ reactions, 1493
E1cB, 1488–1493
E2, 1478–1486
E2C, 1495
Eglinton reaction, 0979
E^{i}, 1507
E^{i}, and Cope elimination, 1525
electrophilic addition, 0999
electrophilic, halogenation of alkenes, 1149
mechanism, elimination-addition, 0477, 0562, 0613
and Mannich abases, 0498
at saturated carbon, 0478
at vinylic carbon, 0477
mechanism, ene reaction, 1104
enolization in Grignard reactions, 1309
Etard reaction, 1763
Favorskii addition reaction, 1360
Favorskii rearrangement, 1596, 1597
first-order reactions, 0315, 0316
Fischer indoles synthesis, 1675
formation of acyl cyanides, 1457
formation of azoxy compounds from oximes, 0849
formation of gem-dihalides from aldehydes or ketones, 1298
formation of Grignard reagents, 0832
four-center, addition to alkenes, 1013
four-center, and hydroboration, 1078
fragmentation, 1542
free-radical, 0297
Friedel-Crafts acylation, 0722
Friedel-Crafts alkylation, 0711
Fries rearrangement, 0736
Gatterman reaction with aryl halides, 0984
Glaser reaction, 0979
Grignard reaction, 1307
Grignard reagents with nitriles, 1338
Grignard reagents, with metal halides, 0826
haloacylation of alkenes, 1161
halogenation of alkenes, 1149
halogenation of ketones, 0778, 0779
halogenation of organometallics, 0821
haloketones with boranes, 0645
Hay reaction, 0980
heterogeneous organic catalysis, 1058
Hoesch reaction, 0732
Hofmann degradation, 1522
Hofmann rearrangement, 1608
Hofmann-Löffler reaction, 1695
homogeneous catalytic hydrogenation, 1059, 1061
homologation of aldehydes or ketones, with diazomethane, 1602
homolytic, 0297
Hunsdiecker reaction, 0995
hydroboration, 1078
hydrogen exchange, 0766
mechanism, hydrolysis of acyl halides, 1398
hydrolysis of alkyl halides, 0519
hydrolysis of amides, 1408–1410
hydrolysis of anhydrides, 1399
hydrolysis of carbamates, 1406
hydrolysis of carboxylic esters, 0406, 0407, 1402–1406
hydrolysis of compounds, 1265
hydrolysis of iminium ions, 1266
mechanism, hydroperoxides oxidation of sulfoxides, 1783
hydroperoxides oxidation of thioethers, 1782
identification of products, 0311
interfacial, 0510
inverse isotope effects, 0324
iodo azide to alkenes, 1159
ion pair, and E1 reactions, 1488
ion-pair, 0441
isocyanates with alcohols, 1275
isocyanates with phosphine oxides, 1461
IUPAC nomenclature, 0420
IUPAC, and carbenes, 0500
IUPAC, and diazonium salts, 0500
ketenes cycloaddition to imines, 1465
keto-enol tautomerism, 0773
Kolbe-Schmidt reaction, 0729
lead tetraacetate cleavage of diols, 1734
lead tetraacetate oxidation of alcohols to cyclic ethers, 0966
$LiAlH_4$ reduction of aldehydes or ketones, 1804
lithiation of aromatic compounds, 0808
Lossen rearrangement, 1610
Mannich reaction, 1294
Meerwein arylation, 0923
mercuric catalyzed hydration of alkynes, 1036
mechanism, metal catalyzed, acyloxylation, 0973
cycloadditions, 1249
cyclotrimerization, 1246
decarbonylation of aldehydes, 0998
hydrocarboxylation, 1138
mechanism, metal hydride addition-elimination, 0770
metal reduction of nitro compounds, 1818
metal-hydrogen exchange, 0834
methyl transfer, 0310
Michael addition, 1008, 1009
mixed S_N1-S_N2, 0440, 0441
Neber rearrangement, 1606
Nef reaction, 1267
mechanism, neighboring group, also see neighboring groups
mechanism, neighboring group, 0446
and anti-dihydroxylation, 1164
and bromonium ions, 0447, 0448
and epoxides, 0448
and halonium ions, 0449

mechanism, neighboring group, (*Continued*)
and lactones, 0448
and rearrangement, 0448
and solvolysis, 0448, 0449
stereochemistry, 0447
mechanism, nitration of alkanes, 0786
nitration of aromatic compounds, 0691
nitrogen extrusion reactions, 1554
nitrosation, 0691
nitrosation of amines, 0847, 0848
nitrosation of ketones, 0784
nucleophilic addition, 1007
nucleophilic aromatic substitution, 0853
nucleophilic rearrangements, 1560–1574
nucleophilic substitution at sulfonyl sulfur, 1470, 1471
nucleophilic, and displacement of diazonium, 0916
of ozonolysis of alkenes, 1738–1740
of substitution reactions, 0426
of thallation, 0914
of the Kolbe reaction, 0993
of the Wacker process, 1774
oxa-di-π-methane rearrangement, 1694
mechanism, oxidation of aldehydes to carboxylic acids, 1771
of aldehydes with chromic acid, 1771, 1772
of aldehydes with permanganate, 1772, 1773
of alkylboranes, 0815
of amines to amine oxides, 1779
of anilines with Caro's acid, 1777
of phenols with sodium periodate, 1729
of thiols to disulfides, 1786
mechanism, oxidation-reduction, 1704
oxidative cleavage of alkenes, 1744
oxidative decarboxylation of carboxylic acids, 1748
oxime formation, 1286, 1287
palladium catalyzed arylation of amines, 0877
Passerini reaction, 1468
Pauson-Khand reaction, 1143
pericyclic, 0297
peroxyacid epoxidation of alkenes, 1170
Petasis alkenylation, 1380
Peterson alkenylation, 1366
mechanism, photochemical, 0348
actinometer, 0349
and emission, 0348
and fluorescence and phosphorescence, 0348
and quantum yield, 0349
dimerization of ketones, 1857
mechanism, pinacol rearrangement, 1586
polar transition state, and benzidine rearrangement, 1680
Prins reaction, 1393
proton-transfer reactions, 0367
Pschorr reaction, 0926
Pummerer rearrangement, 1867
pyrolysis of esters to alkenes, 1520
pyrolysis of homoallylic alcohols, 1551
pyrolytic elimination, 1507–1510
mechanism, radical, 0934
addition, 1010
addition of aldehydes to alkenes, 1136
addition of alkanes to alkenes, 1084
alkylation of aromatic compounds, 0981
and coupling of boranes, 0989
and E^i reactions, 1510
and fluorination of aryldiazonium salts, 0922
and $S_{RN}1$ reactions, 0862
arylation of aromatic compounds, 0982
chain, and $S_{RN}1$ reactions, 0863
cyclization, 1126
cyclopropane addition, 1027
halogenation of alkenes, 0958
halogenation of allylic hydrogen, 0961, 0962
neighboring group effects, 0942
organometallic compounds with alkyl halides, 0599
substitution, 0938, 0939
with aromatic compounds, 0940
mechanism, Ramberg-Bäcklund reaction, 1536
mechanism, Raney nickel desulfurization, 0991
reduction of carbonyls with sodium in ethanol, 1795, 1796
reduction of diazonium salts with sodium sulfite, 1823
reduction of hydrazones, 1838
reduction with Grignard reagents, 1308
Reed reaction, 0974
reverse Friedel-Crafts alkylation, 0744
σ-substitution, 0694
$S_{AL}2$, 0532
Schmidt reaction, 1612, 1613
S_E1, 0658, 0665, 0758
S_E1, and resonance, 0759
S_E2, 0658, 0753
S_E2 and cyclopropanes, 1027
second-order reactions, 0315, 0316
S_Ei, 0753, 0754
selenium dioxide allylic oxidation of alkenes, 1752
mechanism, SET, 0443
and active methylene compounds, 0626
and arylation of enolate anions, 0908
and chain reactions, 0444
and CIDNP, 0445
and coupling, 0613
and electrophilic aromatic substitution, 0682
and ESR, 0445
and Grignard reactions, 1307
and Grignard reagents, 0832
and $LiAlH_4$ reduction of alkyl halides, 1828
and oxidation-reduction, 1706
and radical cyclization, 0445
and radical probes, 0445
and substitution reactions, 0481
and Williamson reaction, 0531
organocalcium, 0264
organometallic compounds with alkyl halides, 0598
versus S_N2, 0445

mechanism, Shapiro reaction, 1526
Sharpless asymmetric dihydroxylation, 1166
Sharpless asymmetric epoxidation, 1177
Simmons-Smith procedure, 1241
Simonini reaction, 0996
six-center, and decarboxylation, 0837
six-center, Cope rearrangement, 1663
S_N1, 0432
S_N1, and deuterium, 0488
S_N1, and ion pairs, 0436
S_N1, and primary carbocations, 0480
S_N1, and secondary isotope effects, 0488
S_N1, hydrolysis of acetals, 0524
S_N1cB, 0521, 0567
S_N1cB, and carbenoid formation, 1235
S_N2, 0426, 0470
SN2′, and addition to dienes, 1013
S_N2, and deuterium, 0488
S_N2, and secondary isotope effects, 0488
S_NAr, 0854–0857
Sneen's ion pair, 0764
S_Ni, 0468
S_Ni', 0472
solvolysis of alkyl halides, 0325
Sommelet-Hauser rearrangement, 0929
$S_{ON}2$, 0872
special variations of the Knoevenagel reaction, 1361–1363
$S_{RN}1$, 0550, 0862
$S_{RN}1$, and arylation of enolate anions, 0908
Stevens rearrangement, 1622
Stille coupling, 0794
Stobbe condensation, 1356
substituent effects and the Diels-Alder reaction, 1207
substitution, IUPAC, 0496
sulfonation of aromatic compounds, 0696
Suzuki-Miyaura coupling, 0902
termolecular addition, 1002
mechanism, tetrahedral, 0473.1254
and base cleavage of ketones, 0841
and conformation, 1258
and formation of aziridines, 0475
and hyperconjugation, 0476
and isotope labeling, 1256
and leaving groups, 1259
and MO calculations, 0476
and substituent effects, 0486
and vinyl halides, 0474
ester hydrolysis, 1402–1406
evidence for, 1255–1259
hydrogen ion catalyst, 1255
hydrolysis of carboxylic esters, 1402–1406
in acid solution, 1255
isolation of intermediates, 1257
reactivity of carbonyl substrates, 1260
special detection of intermediates, 1257
stereoelectronic control, 1258
synthetic transformations, 1260
mechanism, the Gatterman method, 0926
thermal cleavage of alkoxides, 0840
thermal elimination of sulfoxides, 1529
transesterification, 1420
trapping intermediates, 0313
types, 0296
Ullmann reaction, 0898
vicarious nucleophilic substitution of hydrogen, 0915
Vilsmeier-Haack reaction, 0724
vinyl ether hydrolysis, 0527
vinylboranes, with NaOH and iodide to give alkenes, 1630
vinylcyclopropane rearrangement, 1658
von Braun reaction, 0587
von Richter reaction, 0313
von Richter rearrangement, 0927, 0928
waits-Scheffer epoxidation, 1174
Walden inversion, 0427
Wallach rearrangement, 1699
Wittig reaction, 1373
Wittig rearrangement, 1625
Wolff rearrangement, 1600
Wolff-Kishner reduction, 1838
Wurtz reaction, 0592
[2 + 2]-cycloaddition, 1224
[2 + 2]-cycloaddition of enamines with ketenes, 1228
[3 + 2]-cycloaddition of allylic carbanions, 1194
mediated coupling conjugated ketones, 0592
medium effects, on acids and bases, 0390
medium size rings, and I strain, 0400
medium, and rate of reaction, 0412
and reactivity, 0412
supercritical carbon dioxide, 0414
water, 0414
Meerwein arylation, 0923
and the Heck reaction, 0924
mechanism, 0923
Meerwein-Ponndorf-Verley reduction, aluminum free, 1796
and alumina, 1796
and microwaves, 1796
cyclic transition state, 17967
of carbonyls, 1796
Meinwald rearrangement, 1587
Meisenheimer rearrangement, 1623
Meisenheimer salts, 0854
and NMR and X-ray crystallography, 0855
Meisenheimer-Jackson salts, 0854
Meldrum's acid, and acidity, 0388
and conformation, 0388
melting potion, and hydrogen bonding, 0111
memory effects, of migrating groups, rearrangements, 1570, 1571
Mentshutkin reaction, 0555
and S_N2, 0430
Merck Index, 1887
mercuration, benzene, rate and product distribution, 0680
of aromatic compounds, 0913
of toluene, rate and product distribution, 0680
mercuric acetate, and acyloxylation, 0972
and oxymercuration, 1033
with alkenes, 1033
mercuric chloride, and orbitals, 0008

mercuric compounds, the Corey-Seebach procedure, 1280
mercuric salts, and hydration of alkynes, 1035
mercury compounds, and acetal cleavage, 0527
mercury fulminate, with aromatic compounds, 0733
mercury, sp orbitals, 0007
Merrifield resin, and Sonogashira coupling, 0905
Merrifield synthesis, 1433
Merrifield, R.B., 1433
mesitylene, aromatic substitution, 0661
meso compounds, and diastereomers, 0165
  and monocyclic compounds, 0187
  definition, 0165
mesoionic compounds, and aromaticity, 0092
mesomeric effect, 0048
mesomeric effect, also see resonance
mesylates, leaving groups, 0497
meta directing groups, 0669
  and Friedel-Crafts alkylation, 0709
meta selectivity, and aryl radicals, 0950
meta-carbene complex, and metathesis, 1688
metal additives, and Grignard reagents, 1306
metal carbene complexes, addition to alkenes, enantioselectivity, 1237
metal carbenes, 1236
  cyclotrimerization, formation of heterocycles, 1247
  Fischer carbene complexes, 1247
  with carboxylic esters, 1381
metal carbonyls and sonochemistry, 0352
metal catalysts, also see catalysts
metal catalysts, addition of alkynes to alkenes, 1089
  and conjugate reduction, 1071
  and cyanohydrin formation, 1390
  and diazonium salts, 0916
  and enolate anions, 1344
  and forbidden electrocyclic reactions, 1643
  and formation of thiophenols, 0920
  and Friedel-Crafts acylation, 0720
  and Oppenauer oxidation, 1721
  and Suzuki-Miyaura coupling, 0899–0903
  and vinyl sulfide formation, 0550
  aziridine ring opening, 0566
  carbonylation of alkenes and alkynes, 1140
  conjugate addition of amides, 1130
  coupling alkenes to alkenes, 1091
  epoxide and amines, 0563
  Finkelstein reaction, 0574
  for addition of silanes to alkenes, 1086
  for carbonylation, 1138
  for carboxylation of alkenes, 1144
  for conjugate addition of alkynes, 1118
  for cyclotrimerization of alkynes, 1244
  for dehydrogenation, 1712
  for hydroformylation, 1145
  for peroxide epoxidation of alkenes, 1171
  for the Pauson-Khand reaction, 1142
  formation of cyclic amines, 0560
  Grignard reagents with acyl halides, 1444
metal catalyzed, acyloxylation of hydrocarbons, 0971
  acyloxylation, mechanism, 0973
  addition of alcohols to alkenes, 1037
  addition of aldehydes to alkenes, 1135
  addition of alkynes to alkenes, 1089
  addition of boronic acids, to aldehydes, 1319
  addition, alkanes to alkenes, 1086
  addition, alkenes to alkenes, 1088
  addition, propargyl organometallics to carbonyls, 1310
  alcoholysis of enol ethers, 1039
  alkylation, aryl halides, 0629
  alkylation, vinyl halides, 0629
  amide formation, 0730
  amination of alkenes, 0789, 1046, 1047
metal catalyzed, arylation of alkenes, 0890
  arylation of alkenes, the Heck reaction, 0891–0897
  arylation of alkynes, 0647
  arylation of amines, 0877–0880
  arylation of silanes, 0911
  arylation, of sulfonamides, 0569
metal catalyzed, aza-Claisen rearrangement, 1671
metal catalyzed, aza-Cope rearrangement, 1672
  Baeyer-Villiger rearrangement, 1618
  carbene insertion, 0804
  carbonylation, 1137
  carbonylation of alkenes, 1140
  carbonylation of alkyl halides, 0654
  carbonylation of alkynes, 1140
  carbonylation of amines, 0850
  carbonylation of aryl halides, 0909
  carboxylation of alkenes, 1144
  Carroll rearrangement, 1670
  cleavage, of benzofurans, 0617
  cleavage, of ethers, 0581
  conjugate addition of alkynes, 1118
  conjugate addition of carbamates, 1130
  conjugate addition to alkynes, 1117
  conjugate addition, organolithium reagents, 1133
  conjugate additions, 1107, 1108
  conversion of alkynyl ketones to furans, 1272
  Cope rearrangement, 1662
metal catalyzed, coupling aryl halides and boronic acids, 0899–0903

coupling, alcohols with active methylene compounds, 0614
coupling, alkylboronic acids, 0607
coupling, alkynes with aryl halides, 0904
coupling, alkynes with aryl halides, see Sonogashira
coupling, and Grignard reagents, 0600
coupling, arylboronic acids, 0607
coupling, azobenzenes, 0692
coupling, boronic acids, 0815
coupling, organometallics, 0604, 0605, 0606, 0607
coupling, with allylic carbonates, 0611
coupling, with vinylboranes, 0607
metal catalyzed, cyanation, 0801
cycloadditions, 1248
cyclotrimerization of alkynes, 1243
decarbonylation, of acyl halides to alkenes, 1534
dehydration of alcohols, 1514
diazo transfer reactions, 1237
diazoalkenes, and cyclopropanation, 1234
Diels-Alder reaction, 1198
directed ortho metallation, 0912
elimination of carboxylic acids, 1520
enamine formation, 1284
ene reactions, 1104
enol carbonate alkylation, 0629
enolate alkylation, 0628
epoxidation of alkenes, with peroxides, 1171
formation of aryl nitriles, 0733
formation of biaryls, 0888, 0889
formation of boronic acids, 0816
Friedel-Crafts alkylation, 0707
Fries rearrangement, 0735
halogenation of aromatic compounds, 0699
halogenation of epoxides, 0584
halogenation of ketones, enantioselectivity, 0778
hydration of alkenes, 1034
hydration of alkynes, 1035
hydroamination, of alkenes, 1181
hydrocarboxylation, mechanisms, 1138
hydroformylation, 1145
hydrogen exchange, aromatic compounds, 0685
Knoevenagel reaction, 1359
Kolbe-Schmidt reaction, 0729
lithiation of Boc-amines, 0640
Mannich reactions, imines and enol ethers, 1295
methylation of aryldiazonium salts, 0922
Michael reactions, 1107, 1108
mines and aryl halides, 0693
Nazarov cyclization, 1095
nitration of aryldiazonium salts, 0985
organolithium reagents with nitrogen, 0880
organometallic coupling, 0606
oxidation of hydrocarbons with hydroperoxides, 0971
Pauson-Khand reaction, 1141
preparation of enols, 0770
Prins reaction, 1394
radical halogenation, 0961
reaction, with ketones and silanes, 0799
rearrangement of alkenes, 0769
Rosenmund-von Braun reaction, 0885
σ-bond rearrangement, 1690
Stille coupling, 0793
sulfohalogenation of aryldiazonium salts, 0986
[2 + 2]-cycloaddition, 1220, 1223
[3 + 2]-cycloaddition, 1191
metal complexes, see complexes
metal complexes, and cyclotrimerization, 1246
and enantioselective hydroboration, 1082
and mechanism of catalytic hydrogenation, 1061
with carbenes, 1236
metal compounds, and oxidation of alkynes to diketones, 1776
for catalysis of Michael reactions, 1107, 1108
metal cyanides, see cyanide
metal cyanides, and formation of cyanohydrins, 1389
metal extrusion, and cyclotrimerization, 1246
metal halides, see halides
metal halides, diazotization, 0586
metal hydrides, addition to alkenes, 1082
addition-elimination mechanism, 0770
and reduction of alkynes, 1064
and reduction of conjugated alkenes, 1070
metal induced dehalogenation of acyl halides to ketenes, 1540
metal induced elimination of halo ethers to alkenes, 1541
metal ions, and S_N1 reactions, 0505
metal mediated, acylation of amines, 1427
addition, HCN to alkynes, 1147
and the Baylis-Hillman reaction, 1324
arylation of alkynes, 0647
arylation of amines, 0879
carbonylation, 0824
carbonylation of alkyl halides, 0652
Claisen reaction, 1355
coupling, alkyl halides, 0590, 0597
coupling, allylic esters, 0609
coupling, and Grignard reagents, 0596
coupling, aryl halides, 0897
coupling, of vinyl halides, 0591
coupling, silylamines with alkynes, 0647
deoxygenation of bis(alkoxides), 1534
enamine alkylation, 0636
formation of biaryls, 0888, 0889
halogenation of allylsilanes, 0963
halogenation of aryl diazonium salts, 0984
halogenation of enol acetates, 0780
halogenation of ketones, 0776

metal mediated, (*Continued*)
hydroxylation of aryldiazonium salts, 0919
oxidative decarboxylation, 1747
radical couplings, 0941
reaction, thiols with arylboronic acids, 0874
rearrangement, aniline ammonium salts, 0741
Simmons Smith procedure, 1242
transesterification, 1421
unsymmetrical coupling, 0593
metal oxides, and hydrogenation, 1054
metal particles, as catalysts, surface and particle types, 1060
metal salts, addition of organotin compounds to carbonyls, 1314–1318
and Grignard reagents, radical cyclization, 1126
for Mukaiyama aldol, 1352
reagents, for formation of acylals, 1273
metal-cyclobutadiene complex, and cyclotrimerization, 1247
metal-hydrogen exchange, 0811
and radicals, 0834
metal-salen complexes, and epoxidation, 1178
and hydroxylamines, 1547
and Michael addition, 1108
metalation, and organolithium reagents, 0808
directed ortho, 0596, 0912
of alkynes, 0809
of aromatic compounds, 0734, 0911–0915
of C-H, 0808
with metals, 0811
with organometallics, 0808
metallated imines, and synthetic applications, 1469
metallocenes, 0066, 0117, 0118
and 18 electron systems, 0067
and aromatic substitution, 0066
and chirality, 0150
and cyclopentadiene, 0066, 0067
and transmetallation, 0827
bonding, 0066
metallocyclobutanes, and metathesis, 1689
metals, activated, 0832
alkali, and radical ions, 0282
and acyl addition, 1315–1322
and aromatization, 1709
and catalysis of alkyne amination, 1048
and conjugate reduction, 1071
and decarboxylation, 0745
and elimination of dihalides to alkenes, 1539
and enolate anions, 1344
and formation of enolate anions, 0811, 0907, 0908
and hydrogenation, 1054
and organometallics, 0809
and oxidation of alkenes to aldehydes or ketones, 1774
and reduction with silanes, 1798, 1799
and reductive coupling to diols, 1854, 1855
and the Barbier reaction, 1302
and the Boord reaction, 1541
as catalysts in catalytic hydrogenation, 1056
deprotonation, 0811
dissolving metal reductions, 1067
for alkene metathesis, 1682
for alkyne dimerization, 1092
for catalytic dehydrogenation of alcohols, 1724
for oxidation of alcohols with TEMPO, 1722
for oxygen oxidation of alcohols, 1719
for pinacol coupling, 1854–1856
for the Reformatsky reaction, 1327
hydrogen-metal exchange, 0834
in acid, deoxygenation of aldehydes or ketones, 1835
in acid, reduction of anhydrides, 1840
in acid, reduction of nitro compounds, 1816, 1817
in alcohol, reduction of vinyl halides, 1827
in amines, reduction of aromatic compounds, 1069
in ammonia, and Birch reduction, 1067
in ammonia, decyanation of nitriles, 0845
in ammonia, reduction of alkynes, 1064
in ammonia, reduction of aromatic compounds, 1067
in ammonia, reductions, and CIDNP, 1065
in aqueous alcohols, reduction of heterocycles, 1069
metalation, 0811
reactivity with alkyl halides, 0831
reduction of aldehydes or ketones, 1797
reduction of azides, 1822
reduction of nitro compounds, mechanism, 1818
reduction of sulfonyl halides, 1475
surface area, and the acyloin condensation, 1862
transmetallation, 0825
with acyl halides and alcohols, 1412
with aldehydes, formation of acyl radicals, 0936
with alkyl halides, 0829, 0831, 0832
with crown ethers, 0845
metathesis, alkene (olefin metathesis), 1681–1689
alkynes, 1688
and formation of lactones, 1686
and Grubbs catalysts, 1683
and metal carbene complex, 1688
and metallocyclobutanes, 1689
and molybdenum catalysts, 1683
and PEG, 1684
and ruthenium catalysts, 1683
and stability of alkenes, 1683
and the Shrock catalyst, 1683
cross, 1684
domino, 1685
double, 1685
functional group compatibility, 1686, 1687
homo-, 1684
in ionic liquids, 1684
in supercritical carbon dioxide, 1684
mechanism, 1688, 1689

polymerization, 1685
reactivity of alkenes, 1684
structural changes in the reaction, 1682
synthetic variations, 1686, 1687
tandem, 1685
triple, 1685
with dienes, 1685
with diynes, 1686
methane, and PES, 0012, 0013, 0014
bond energy, 0028
rate determining state in radical halogenation, 0959
spectroscopy, 0012
methanoannulenes, 0081, 0082
and antiaromaticity, 0089
methanol, as a guest, 0127, 0129
methanonium ion, 0235, 0766
mass spectrum, 0766
Methods in Organic Synthesis, 1893
methoxide, potassium, and phenalene, 0060
methoxyamine, from organolithium reagents, 0821
methyl aromatic compounds, and Etard reaction, 1763
α-oxidation to aldehydes, 1763
methyl carbanions, 0257
methyl carbocation, X-ray of, 0236
methyl compounds, reduction of carboxylic esters, 1842
reduction of tosylates, reagents for, 1832
methyl groups, neighboring group participation, 0466
methyl ketones, see ketones
methyl transfer, 0310
methylation, of aryldiazonium salts, 0922
methylene compounds, oxidation to amines, 1757
oxidation to sulfonic acids, 1757
reductive of ketones, 1835
methylene groups, oxidation, 1753
methylene, active, see active methylene
methylene, addition to benzene, 1239
and decomposition of diazomethane, 1240
from diazomethane, 0804
insertion, 0803
methylene, carbene, 0283, 0286
singlet, 0289
methylenecyclohexanes, and chirality, 0149
methylids, sulfur, 1382
methyllithium, with enol acetates, 0631
with silyl enol ethers, 0631
X-ray crystallography, 0260
methylsulfinyl carbanion, with aryl nitro compounds, 0914
methylsulfonyl carbanion, with esters, 1455
methylthioalkynes, see alkynes
Meyer's *V* values, 0411
Meyers aldehydes synthesis, 0642
micellar catalysis, see catalysis
micellar effects, and Diels Alder reactions, 1199
Michael addition, acidic conditions, 1110
amines to conjugated carbonyl compounds, 1046
and DABCO, 1107
and electrochemistry, 1110
and enamines, 0636
and Mannich bases, 1109
and preformed enolates, 1107
and radical initiators, 1107
and radicals, 1110
chiral imines, 1109
double, 1109
enantioselectivity, 1109
intramolecular, 1109
mechanism, 1008, 1009
of enolate anions, 1108
solvents, 1107
with conjugated nitriles, 1008
Michael reaction, and addition reactions, 1031
and Robinson annulation, 1350
and tautomerism, 0105
metal catalyzed, 1107, 1108
reversibility, 1009
stereoselectivity, 1108
sulfur ylids, 1386
thermal, 1109
to conjugated alkenes, 1105–1110
vinylogous, 1107
Michael-type alkenes, addition of HCN, 1147
microbeads, and Sonogashira coupling, 0905
microscopic reversibility, 0309
microsolvation, S_N2 transition state, 0503
microwave chemistry, 0352–0355
microwave irradiation, and acetal cleavage, 0527
and α-oxidation of ketones to diketones, 1758
and acetal hydrolysis, 0526
and acylation of amines, 1429
and acylation of amines with esters, 1435
and alkene metathesis, 1684
and alkyl iodides, 0577
and amide formation, 0730
and amines, 0555
and arylation of amines, 0877
and chromate oxidation of alcohols, 1716, 1717
and Claisen rearrangement, 1669
and conjugate addition, of aldehydes, 1132
and conversion of aldehydes to nitriles, 1287, 1288
and dehydration of amides to nitriles, 1549
and dehydration of oximes to nitriles, 1547
and dielectric heating, 0353
and Diels-Alder reactions, 0352, 1198
and Doebner modification, 1360
and enamine formation, 1284
and ester hydrolysis, 1400, 1401
and esterification of carboxylic acids, 1415
and Etard reaction, 1763
and ether formation, 0529
and formation of amino-alcohols, 0563
and formation of phenols, 0870
and Friedel-Crafts acylation, 0720
and Fries rearrangement, 0736
and halide exchange in aryl halides, 0884
and Huang-Minlon modification, 1836
and hydrolysis of C=N compounds, 1265
and hydrolysis of carboxylic esters, 1401

microwave irradiation, and acetal cleavage, (*Continued*)
and hydrolysis of dithioketals, 1279
and hydrolysis of nitriles, 1269
and hypervalent iodine oxidation of alcohols, 1724
and ionic liquids, 0416
and ketal hydrolysis, 0526
and Meerwein-Ponndorf-Verly reduction, 1796
and metal catalyzed conjugate addition of amines, 1130
and microwave ovens, 0353, 0354
and Montmorillonite clay, 0512
and oxidation of benzyl silyl ethers, 1720
and oxidation of benzylic alcohols, 1726
and oxidation of phenols, 1728
and Pechmann condensation, 0713
and peroxide epoxidation of alkenes, 1171
and phase transfer catalysis, 0511
and phosphine reactions with alkyl halides, 1369
and polarization, 0353
and rate enhancement, 0352
and rate of reaction, 0512
and reactivity, 0512
and reduction of conjugated aldehydes, 1074
and reduction of imines, 1812
and reductive amination, 1291
and ruction of nitro compounds, 1817
and sodium borohydride reduction, 1792
and Sonogashira coupling, 0904
and Stille coupling, 0793, 0794
and Suzuki-Miyaura coupling, 0900, 0901
and synthesis, 0354
and the Baylis-Hillman reaction, 1324
and the Beckmann rearrangement, 1614
and the Cannizzaro reaction, 1864
and the Fischer indole synthesis, 1675
and the Heck reaction, 0354, 0894
and the Hunsdiecker reaction, 0996
and the Knoevenagel reaction, 1359
and the Krönke reaction, 1766
and the Mannich reaction, 1293
and the Mitsunobu reaction, 0355
and the Pauson-Khand reaction, 1142
and the Rosenmund-von Braun reaction, 0885
and the Sonogashira reaction, 0354
and the Suzuki reaction, 0354
and the Ullmann reaction, 0354
and the Williamson reactions, 0529
and thiirane formation, 0532
and Vilsmeier-Haack reaction, 0725
and warming, 0353
microwave irradiation, aryl halides with phenoxides, 0872
benzylic halides from alcohols, 0512
chlorosulfonyl isocyanate with alkenes, 1466
conversion of carboxylic acid to amines, 1431
cycloaddition reaction, 0355
dihydroxylation reaction, 0355
dry-reaction, 0353
electric field component, 0353
electromagnetic waves, 0353
ene reactions, 0352
formation of acylals, 1273
formation of enamines, 1282
formation of imines, 1282
halogenation of ketones, 0776
in reactions of amines with diketones, 1283
magnetic field component, 0353
metal catalyzed arylation of amines, 0878
origins, 0352
oxidation of thiols, 1785
reactors, 0354
wavelength, 0353
with imines and diazo ketones, 1466
microwave ovens, and microwave chemistry, 0353, 0354
microwave reactors, 0354
microwave spectroscopy, and bond distance, 0022
and conformations, 0196
migrating groups, hydrogen, in rearrangements, 1567
in radicals rearrangements, 1577
rearrangements, memory effects, 1570, 1571
stereochemistry, in rearrangements, 1566–1568
migration group, in rearrangement, 1559
migration origin and terminus, and rearrangement, 1559
migration, see rearrangement
migration, para, and Fries rearrangement, 0735
migrations, see rearrangements
migratory aptitude, in rearrangements, 1568
in the Baeyer-Villiger rearrangement, 1619
in the Beckmann rearrangement, 1615
in the Schmidt reaction, 1612
in the Wittig rearrangement, 1624, 1625
rearrangements, H versus alkyl versus aryl, 1570
Mills reaction, 0922
Mills-Nixon effect, 0052
Mills-Nixon effect, and electrophilic aromatic substitution, 0677
mirror plane, and allenes, 0148
Mislow-Evans rearrangement, 1678
Mitsunobu reaction, alkylation of amides, 0570
and alcohols dehydration, 0535
and ether formation, 0530, 0535
and microwaves, 0355
and sulfonate esters, 0546
and Williamson reactions, 0530
azide and epoxides, 0564
esterification, 0540

formation of alkyl azides from alcohols, 1612
formation of amines, 0559
mixed aldol reaction, 1343
mixed organocuprates, 0602
mixed S_N1-S_N2 reactions, 0440, 0441
MM3, MM4, MMFF, and molecular mechanics, 0215
MMPP (magnesium monoperoxyphthalate, 1169
and oxidation of hydrazones, 1731
MO (molecular orbital), calculations, *ab initio*, 0004, 0035
AM1, 0035
and aromatic compounds, 0033
and azulene, 0067
and Birch reduction, 1068
and bond angles and bond distances, 0035
and bond energy, 0030
and cross conjugation, 0044
and cyclopropane, 0218
and Diels-Alder regioselectivity, 1200
and free energy for S_N2, 0431
and fullerenes, 0094
and Hückel's rule, 0071
and ion pair formation, 0440
and naphthalene, 0059
and S_N1 reactions, 0487
and strain, 0218
and the tetrahedral mechanism, 0476
CNDO, 0035
cyclobutadiene, 0074
dipole moments, 0035
energy barrier to rotation, 0198
MINDO, 0035
semiempirical, 0035
[2 + 2]-cycloaddition of alkenes and ketenes, 1226
MO theory, activation hardness, 0679
and cyclopropyl cation ring opening, 1644
and electrophilic aromatic substitution, 0679
and resonance, 0033
Möbius aromaticity, 0091, 0092
Möbius strip compounds, and chirality, 0152
and cycloadditions, 1211
ligand exchange, and rotaxanes, 0132
Möbius systems, allowed reactions, 1211
conrotatory processes, 1638
[1,3]-sigmatropic rearrangement, 1650
Möbius-Hückel method, 1210–1213
and electrocyclic reactions, 1636
and the Diels-Alder reaction, 1210
Modified neglect of diatomic overlap, 0035
Moffatt oxidation, of alcohols, 1721
molar rotation, definition, 0139
molecular belts, 0132
molecular knots, 0133, 0134, 0152
molecular mechanics, 0196, 0213–0216
molecular necklaces, 0131
molecular orbitals, 0005, 0006
molecular orbitals, also see MO
molecular recognition, 0124, 0125
molecular refraction, and aromaticity, and hardness, 0063
molecular ribbons, 0132
molecular shuttle, 0134
molecular sieves, and formation of imines, 1282
and Jones reagent, 1716
molecular switches, 0132
molecular threads, 0132
molecular-orbital method, see MO
molecularity, and rate law, 0316
molecules, strained, see strained molecules
molybdenum catalysts, and metathesis, 1683
monochloroborane, see boranes
monohapto compounds, 0117
monooxygenases, bacterial, oxidation of thioethers, 1782
Montmorillonite, and acetal cleavage, 0526
and acylation of amines, 1430
and addition of thiols to alkenes, 1043
and aziridines with allylic alcohols, 0621
and Beckmann rearrangement, 1614
and chromate oxidation of alcohols, 1717
and formation of aryl sulfones, 0697
and formation of phenols, 0870
and Meerwein arylation, 0924
and microwaves, 0512
and NaBr, with alcohols, 0577
and nitration of aromatic compounds, 0687
and α-oxidation of ketones to diketones, 1758
and oxidation of phosphines, 1780
and reductive amination, 1291
and the Heck reaction, 0894
and the Pechmann condensation, 0713
and the Prins reaction, 1394
and the Willgerodt reaction, 1868
and transesterification, 1419
morphine, and resolution, 0173
Mosher's acid, and absolute configuration, 0159, 0160
MS (mass spectrometry), and the methanonium ion, 0766
electrospray ionization, and Suzuki-Miyaura coupling, 0903
high pressure, and S_N2 reactions, 0429
of carbocations, 0236
of radicals, 0266
MTPA, see Mosher's acid
Mukaiyama aldol, see aldol
Mukaiyama's reagent, and dehydration of carboxylic acids, 1514
and lactonization, 1416
multiple bonds, see bonds
multiple bonds, +M and −M effects, field effects, 0396
(−)-murtenal, and chiral Lewis acids, 0387
myrtanylborane, 1080

N-acylation, and Friedel-Crafts acylation, 0720
with enamines, 0636
N-bromodimethylsulfonium bromide, 0701
N-chlorodimethylsulfonium chloride, 0701
N-haloamides, see amides
N-hydroxysuccinimide (NHS), nitration of alkanes, 0786
N-iodosuccinimide, see NIS

N-methylmorpholine-N-oxide, see NMO
N-nitroaniline, and see anilines rearrangement, 0738
N-nitroso compounds, 0690
N-nitroso groups, rearrangement, 0739
N-oxides, and spin traps, 0268
Nafion-H, 0698
 and hydration of alkynes, 1035
named reactions, 0418
Nametkin rearrangement, and Wagner-Meerwein rearrangement, 1583
nanoparticles, and catalytic hydrogenation, 1055
 and epoxide ring opening, 0619
 and metal catalyzed coupling of allylic esters, 0611
 and reduction of nitro compounds, 1816
 and Sonogashira coupling, 0905
 and the Pauson-Khand reaction, 1142
naphthalene, alternant hydrocarbon, 0069
 and aromaticity, 0061
 and complex formation, 0125
 and MO calculations, 0059
 and resonance, 0033
 bond order, canonical forms, and Dewar structures, 0059
 electrophilic aromatic substitution, 0676
 Friedel-Crafts alkylation, 0709
 oxidation to naphthoquinones, 1764
 oxidation to phthalic acid, 1744
 partial bond fixation, 0059
 resonance energy, 0060
naphthols, with ammonia, 0882
naphthoquinones, by oxidation of naphthalenes, 1764
naphthylamines, and the Bucherer reaction, 0882
naphthyllithium reagents, and X-ray, 0263
Nazarov cyclization, 0823, 1095
 retro-, 1096
NBS (N-bromosuccinimide), and acetal cleavage, 0527
 and alkyl bromides, 0579
 and chloramine-T, 1184
 and formation of alkyl halides from carboxylic acids, 1426
 and formation of halohydrins, 1153
 and halogenation of carboxylic acids, 0781
 and oxidation of alcohols, 1725
 and radical halogenation, 0956
 and the Pummerer rearrangement, 1867
 and Wohl-Ziegler bromination, 0961
 as a source of bromine, 0962
 bromination of aromatic compounds, 0699
 formation of haloamines, 0849
 halogenation of aromatic compounds, 0699
 in ionic liquids, 0699
 radical halogenation, 0961
 with AIBN, ammonia, and aldehydes, 0974
 with DBU, and carbamates, 1608
 with sodium methoxide, and the Hofmann rearrangement, 1607
 with sulfoxides, 0782
 with vinylboranes, 0820
NCS (N-chlorosuccinimide), and allylic chlorination, 0963
 and aromatization, 1711
 and the Pummerer rearrangement, 1867
 formation of haloamines, 0849
 radical chlorination, catalysts for, 0963
 with sulfoxides, 0782
 with vinylboranes, 0820
Neber rearrangement, 1605
 and azirene, 0312, 1606
 and intermediate isolation, 0312
 mechanism, 1606
necklaces, molecular, 0131
Nef reaction, 1267
 and the aci form of nitro compounds, 1268
 and the Knoevenagel reaction, 1359
 in connection with the Favorskii reaction, 1360
 mechanism, 1267
negative enhancement, and NMR, 0270
negative hyperconjugation, 0210
neighboring group mechanism, also see mechanisms
neighboring group mechanism, 0446
 and anti-dihydroxylation, 1164
neighboring groups, alkenes, 0451
 and cyclization, 0449
 and electron density, 0454
 and first order rates, 0446
 and halonium ions, 0449
 and NMR, 0454
 and nucleophiles, 0453
 and phenonium ions, 0456
 and radicals, 0942
 and rate enhancement, 0457
 and retention, 0451
 and S_N2 reactions, 0446
 and solvolysis, 0449, 0454, 0456, 0457
 aromatic rings, 0455–0457
 β- to leaving group, 0446
 β-aryl, 0459
 cyclobutyl, 0455
 cyclopropyl, 0454
 C—C single bonds, 0459
 hydrogen, 0467
 methyl, and NMR or Raman, 0466
 participation by π bonds or by σ bonds, 0450
 principle of increasing electron demand, 0449
 propargyl groups, 0483
 σ-bonds, 0459
 silyalkyl, 0467
 structural features, 0449
neopentyl systems, and S_N2 reactions, 0479, 0755
neutron diffraction, and hydrogen bonds, 0109
Newman projections, and conformations, 0197
 definition, 0197
 syn and anti elimination, 1485
nickel boride, and hydrogenation, 1054
nickel carbonyl, and hydrocarboxylation, 1139
nickel complexes, and coupling aryl halides, 0898
nickel, Raney, and desulfurization of dithioketals, 1280
 and dithianes, 0639

and hydrogenation, 1054
and the Zinin reduction, 1816
and transamination, 0562
desulfurization, 0990, 0991, 1849, 1850
hydrogenation of thioethers or thiols, 0990
reduction of alkyl halides, 1826
reduction of sulfo groups, 0749
reduction of sulfur compounds, 1816
with dithioacetals and dithioketals, 0639
Nicotiana tabacum, reductase, 1074
NIS, and formation of halohydrins, 1153
nitrate esters, from alcohols, 0545
nitrate, ethyl, see ethyl nitrate
nitrate, silver, see silver nitrate
nitrates, see esters, nitrate
nitrates, metal, and transmetallation, 0827
nitration of aromatic compounds, and arylboronic acids, 0690
and ethyl nitrate, 0688
and Lewis acids, 0687
and organolithium reagents, 0690
and Raman, 0689
in ionic liquids, 0687
nitration, and nitronium ion, 0691
and steric inhibition of resonance, 0691
electrophilic aromatic substitution, 0690
of alkanes, 0786
of amines, 0846–0848
of anilines, 0688
of arenium ions, 0691
of aromatic compounds, 0664, 0665, 0685, 0686, 0690, 0691
of benzene, and intermediates, 0312
of benzene, rate and product distribution, 0680
of heterocycles, 0687
of toluene, rate and product distribution, 0680
nitrene insertion, 0790
nitrenes, 0293–0295, 1183
ab initio calculations, 0293
acyl, 1561
addition to alkenes, 0294
amino, see aminonitrenes
and rearrangements, 1561
aryl, 0293
by elimination of O-sulfonylamines, 0293
carbonyl, see carbonylnitrenes
definition, 0293
dimerization, 0295
enantioselective formation, 1183
enthalpy, 0293
formation of amides, 0789
from amines and nitrous acid, 0500
from azides, 0294
hydrogen abstraction, 0295
insertion, 0294, 0789, 0790
rearrangements, 0294
singlet, 0293
singlet, see singlet
triplet, 0293
triplet, see triplet
with alkanes, 0789
with aromatic compounds, 1185
nitrenium ions, singlet and triplet, 0295
nitric acid, AIBN, and conjugated acids, 0975
and nitration of aromatic compounds, 0686, 0688
nitration of amines, 0848
nitration of aryldiazonium salts, 0986
with alkenes, 0785
nitric oxide, radical inhibitor, 0938
nitrile carbanions, 0253
nitrile oxides, dyotropic rearrangement to isocyanates, 1700
nitriles dehydration of amides, and the Burgess reagent, 1549
nitriles, acid catalyzed addition of alcohols, 1458
acid catalyzed reaction with alcohols, 1275
addition of amines or ammonia, 1296
addition of HCN, 1393
alcoholysis, 1275
alkylation, 0626
and halogenation of aromatic compounds, 0701
and Stephen reduction, 1815
and the Blaise reaction, 1328
and the Ehrlich-Sachs reaction, 1368
and the Hoesch reaction, 0732
and the Pinner synthesis, 1275
and the Ritter reaction, 1459
and the Thorpe reaction, 1387
aryl, and the Rosenmund-von Braun reaction, 0885
aryl, by the Sandmeyer reaction, 0985
aryl, from aryl diazonium salts, 0985
aryl, from aryl halides, 0885
aryl, from arylthallium compounds, 0913
aryl, metal catalyzed reactions, 0733
nitriles, by addition of HCN to alkenes, 1147
by dehydration of amides, 1549, 1550
by dehydration of oximes, 1546, 1547
by dehydrogenation of amines, and reagents for, 1729, 1730
by elimination of hydrazonium salts, 1547
by fragmentation of oximes, 1548
by oxidation of amines, 1729, 1730
by oxidation of hydrazones, 1731
by rearrangement of O-tosyl oximes, 1548
nitriles, catalytic hydrogenation, 1814
condensation with esters, 1455
condensation with nitriles, 1387
conjugated, cyanoethylation, 1008
conjugated, proton acidity, 0633
conjugated, reagent for conjugate reduction, 1071
conversion to thioamides, 1269
decyanation, 0845, 1843
enzymatic hydrolysis, 1269
formation of aryl ketones, 0732

nitriles, from aldehydes, reagents for, 1287, 1288
from alkyl halides, 0648
from amides, by the von Braun reaction, 1550
from aromatic compounds, 0733
from aryl triflates, 0733
from carboxylate anion and cyanogen bromide, 1461
from cyanide ion, 0648
from imines, and dehydrogenation, 1730
from iminium salts, 0733
from isocyanides, and Schwartz's reagent, 1148
from organometallics, 0825
from oximes and acids, 1547
from oximes, and the Burgess reagent, 1546
nitriles, hydrolysis, 0648
hydrolysis, 1268, 1269
in the Diels-Alder reaction, 1216
metal catalyzed addition of amines, 1297
metal mediated addition of alkenes, 1459
photochemical radiation with hydrocarbons, 0975
pK_a of the α-proton, 0383, 0627
reagents for hydrolysis, 1269
reduction to aldehydes, reagents, 1815
reduction to amines, reagents, 1813, 1814
reduction to hydrocarbons, 1843
reduction to methyl with terpenes, 1824
reductive cleavage to aldehydes, 1835
substitution of H, 0801
trimerization, 1460
vinyl, from vinyl triflates, 0825
vinyl, from vinylorganometallics, 0825
vinylidene, hydration and cleavage, 1034
with active methylene compounds, 1388
with carbocations, 1458
with Grignard reagents, 1337, 1338
with metal alkyne anions, 0904
with metals in ammonia, 0845
with sodium borohydride, 0846
nitrilium ions, and Friedel-Crafts cyclization, 0716
and isoquinolines, 0716
and the Schmidt reaction, 1613
by reaction of nitriles with oxonium salts, 1814
reduction to amines, 1814
nitrite esters, from alcohols, 0545
from alkyl halides, 0571
nitrite ion, as an ambident nucleophile, 0515, 0546
nitrite, sodium, see sodium nitrite
nitrites, alkyl, and conversion of anilines to aryl halides, 0985
and diazotization of amines, 0921
from amines, 0847
with aromatic compounds, 0925, 0926
nitro compounds, aci form, 0104
aci form, and the Nef reaction, 1268
alkylation, Katritzky pyrylium-pyridinium method, 0626
and nitric acid, 0785
and tautomerism, 0104
and the Nef reaction, 1267
and ultrasound, 1816
anion formation, 0515
aryl, alkylation, 0914
aryl, and the von Richter rearrangement, 0927
aryl, from aryldiazonium salts, 0985
aryl, replacement of nitro with alkyl, 0927
aryl, vicarious nucleophilic substitution of hydrogen, 0915
aryl, with carbanions, 0914
aryl, with cyanide, 0927
aryl, with dimethyoxosulfoxonium methylid, 0914
aryl, with methylsulfinyl carbonation, 0914
base induced elimination, 1552
by dioxirane oxidation of isocyanates, 1778
by oxidation of nitrogen compounds, reagents, 1778
conjugated, with baker's yeast, 1074
cyanation, 0802
electrolytic reduction to hydroxylamines, 1819
enolate anions, reduction to hydroxylamines, 1819
Friedel-Crafts alkylation, 0710
from alkyl halides, 0571
from arylthallium compounds, 0913
from silver nitrate or sodium nitrite, 0571
Henry reaction, 1357
hydrolysis, 1267
photochemical rearrangement, 0345
reagents, for hydrolysis, 1267, 1268
reduction of amines, reagents, 1815, 1816, 1817
reduction to azo compounds, reagents, 1863
reduction to azoxy compounds, reagents, 1862
reduction to enamines, 1047
reduction to hydrazo compounds, 1863
reduction to hydrocarbons, reagents, 1845
reduction to hydroxylamines, reagents, 1818
reduction to oximes, reagents, 1821
reduction with bakers yeast, 1817
reduction with $LiAlH_4$, 1817
reduction with metals, in acid, 1816, 1817
reduction with metals, mechanism, 1818
reduction, and amination of alkenes, 1047
reduction, and microwaves, 1817
reduction, on alumina, 1817
reductive alkylation, 1291, 1818
removal of nitro, reagents, 1845
vinyl, 0787, 0975
with aldehydes or ketones, 1357

with alkyl halides, 0515
with enolate anions, 0613
with phosphorus ylids, 1379
nitro groups, deactivating groups, 0688
rearrangement, 0738
nitro-alcohols, by the Henry reaction, 1357
from epoxides, 0565
nitro-Hunsdiecker reaction, 0975
nitrobenzene, dipole moment, 0018
from organolithium reagents, 0690
nitrogen nucleophiles, 0555
nitrogen ylids, 0054
nitrogen ylids, see ylids
nitrogen, electron structure, 0013
extrusion from pyrazoles, pyrazolines, ortriazolines, 1553
leaving group, 0499
metal catalyzed reaction with organolithium reagents, 0880
PES spectrum, 0012
nitromethanes, pK_a, 0253
nitrones, addition of organometallics, 1335
by oxidation of amines or hydroxylamines, 1732
from hydroxylamines and metal-salen complexes, 1547
from oximes, 0547
Michael addition, 1107
with Grignard reagents, 1336
nitronic esters, O-alkylation, 0515
nitronium ion, and nitration of aromatic compounds, 0664, 0688, 0691
as a leaving group, 0683
electrophilic aromatic substitution, 0672
migration from nitrogen, 0738
nitronium salts, and nitration of alkanes, 0786
and nitration of aromatic compounds, 0689
nitration of amines, 0848
nitrosation, and enols, 0785
and UV, 0785
mechanism, 0691
of ketones, mechanism, 0784
nitrosation, photochemistry, 0785
nitroso compounds, and Ehrlich-Sachs reaction, 1368
and formation of imines, 0785
and tautomerism, 0103
and the Barton reaction, 1696
aromatic, 0690
aryl and the Mills reaction, 0922
aryl, Fischer-Hepp rearrangement, 0739
aryl, N-nitroaniline rearrangements, 0739
aryl, with anilines, 0922
by oxidation of anilines, 1776, 1777
by oxidation of hydroxylamines, 1731
Diels-Alder reaction, 1216, 1217
from nitro compounds, 0345
from nitrous acids, 0784
metal reduction to amines, 1819
N- versus C- alkylation, 0690
oxidation to nitro compounds, 1778
reduction to amines, 1823
reductive alkylation, 1291
with nitriles, 1368
with oximes, 0848
nitroso ureas, base induced elimination, 1552
nitroso-amides, base induced elimination, 1552
nitroso-carbamates, base induced elimination, 1552
nitroso-halogenation, of alkenes, 1158
nitroso-oxime tautomerism, see tautomerism
nitrosoamides. with aromatic compounds, 0925
from amines, 0846, 0847
nitrosomethane, and tautomerism, 0103
nitrosonium ion, and diazotization, 0918
nitrosyl halides, with alkenes, 1158
nitrotoluene, dipole moment, 0018
nitrous acid, and amines, 0499
and carbocation formation from amines, 0247
and diazonium salts, 0692
and formation of aryl diazonium salts, 0917
selectivity, 0918
with amines, 0247, 0846, 0847, 0917
with aziridines, 1538
with hydrazines, 0846
nitroxide, radicals, 0273, 0278
asymmetric, 0276
and TEMPO, 0274
nitroxyl radicals, 0273
and Bobbitt's reagent, 1723
and oxidation of alcohols, 1723
TEMPO, 0274
X-ray, 0274
nitryl chloride, addition to alkenes or alkynes, 1158
NMO (N-morpholine-N-oxide), and dihydroxylation of alkenes, 1162
NMR (nuclear magnetic resonance), and absolute configuration, 0161, 0162
and alkenes, 0056
and amination of quinoline, 0916
and annulenes, 0079, 0080, 0083, 0084, 0088, 0089
and antiaromaticity, 0075, 0090
and aromaticity, 0057
and aryl carbanions, 1069
and benzene, 0056
and benzenonium ion, 0662
and bond order, 0060
and bullvalene, 1665
and carbocation stability, 1562
and carbocations, 0236, 0241, 0245, 0246, 0454, 0459
and chiral compounds, 0180, 0181
and chiral lactams, 0160
and chiral shift reagents or chiral solvents, 0181
and chirality, 0151
and conformation of macrocycles, 0213
and conformations, 0196
and Cope rearrangement, 1665
and crown ethers, guest-host interactions, 0124
and cycloheptatrienyl anion derivatives, 0078
and cyclopropylmethyl carbocations, 0465
and detection of hemiaminals, 1281
and determining absolute configuration, 0160
and diamagnetic ring current, 0055

NMR and absolute configuration, (*Continued*)
and diastereotopic compounds, 0193
and diatropic, 0055
and dynamic nuclear polarization, 0270
and electronegativity, 0017
and emission, 0270
and enantiomeric excess or enantiomeric purity, 0180, 0181, 0182
and enol content, 0101
and Fischer indole synthesis, 1675
and Grignard reagents, 0262
and homoaromatic compounds, 0093
and hydrogen bonding, 0110, 0111, 0112
and intermediates, 0312
and isotope effects, 0324
and isotopic labeling, 0314
and kekulene, 0087
and keto-enol tautomerism, 0101
and kinetics, 0321, 0434
and mechanism, 0321
and mechanism, conjugate addition of organometallics, 1120
and Meisenheimer salts, 0855
and methane, 0012
and methyl neighboring groups, 0466
and nonclassical carbocations, 0451, 0454, 0462, 1583
and norbornadienyl carbocations, 0451
and norbornyl carbocations, 0463
and organometallics, 0259
and oxaphosphetanes, 1374
and paramagnetic ring current, 0057
and paratropic compounds, 0057, 0090
and phenonium ions, 0458, 0459
and radicals, 0268, 0271
and ring current, 0055, 0056, 0057
and rotaxanes, 0134
and σ values, 0408
and solvolysis of esters, 0434
and spin traps, 0268
and steric strain, 0216
and structure of carbocations, 1645
and the Wittig reaction, 1374
and valence tautomerism, 1667
anisotropy, and conformations, 0196
annulenes, 0087, 0090
bicyclo[5.1.0]octadiene, 1665
cyclobutadiene derivatives, 0075
EtI + EtLi, 0269
heptalene, 0067
negative enhancement, 0270
paracyclophanes, 0050
tri-*tert*-butylcyclobutene, 1667
tropone and tropolone, 0065
no-bond resonance, 0097
NOESY, and π-π-interactions, 0115
nomenclature, *aa/ee/ae*, and conformations, 0205
acid and base, IUPAC, 0356
and diastereomers, 0166
and IUPAC, 0235
and the Cahn-Ingold-Prelog system, 0183
carbocations, 0235
cis/trans, and dienes, 0184
D/L, and stereogenic atoms, 0155
dig, 0306
E/Z, 0183, 0184
epi, 0165
erythro/threo, 0166
g transitions, 0331, 0332
[i,i], and sigmatropic rearrangement, 1647
IUPAC, mechanisms, 0420
IUPAC, transformations, 0419
peri-, 0165
R/S, and stereogenic atoms, 0155–0158
re/si, 0194
syn/anti, 0166
tet or trig, 0306
u transitions, 0331, 0332
nonadjacent π-bonds, stabilization of carbanions, 0255
nonaflates, leaving groups, 0497
nonalternant hydrocarbons, 0069
cyclopropenyl cation, 0073
topological polarization, 0071
nonaromatic rings, and arynes, 0862
nonaromatic systems, and Hückel's rule, 0071
nonbonded interactions, 0216
nonbonding orbital, 0041
nonclassical carbocations, 0247, 0450
nonclassical carbocations, see carbocations
nonconcerted Cope rearrangement, 1664
nonplanar radical cations, 0283
nonpolar solvents, see solvents
norbornadienes, and photochemical [2 + 2]-cycloaddition, 1232
cycloaddition with alkenes, 1204
norbornadienone, irontricarbonyl complex, 0118
norbornane, and twist conformation, 0204
norbornene, addition of DCl, 1023
and strain, 0228
stereochemistry of addition, 1023
norborneol, 0189
norbornyl carbocations, *ab initio* calculations, 0463
classical arguments, 0461
in stable solutions, 0462
stability, 0463
norbornyl compounds, and S_N1 reactions, 0436
norbornyl systems, and nonclassical carbocations, 0450
and solvolysis, 0460
norcamphor, 0189
norcaradiene, from methylene and benzene, 1239
photochemical ring opening, 1633
norephedrine, benzoyl, and rearrangement, 0400
normal acid, definition, 0367
Normant reagents, addition to alkynes, 1101, 1102
Norrish Type I cleavage, definition, 0343
photolysis of cyclobutanones, 1555
Norrish Type II cleavage, 0344
and elimination, 1478
nortricyclane, and nonclassical carbocations, 0463
nortricyclyl chloride, 0292
nosylates, leaving groups, 0497

Nuclear Overhauser effect spectroscopy, see NOESY
nuclear magnetic resonance, see NMR
nucleophile, ambident, cyanide, 0648
  nitrite ion, 0515, 0546
  nitro compounds, 0515
nucleophile, approach to carbonyl, 1258
nucleophile, definition, 0297
nucleophiles, ambident, 0513
  and basicity, 0516
  and counterions, 0517
  and crown ethers, 0517
  and Kornblum's rule, 0516
  and phenoxide ions, 0515
  and regioselectivity, 0513
  and steric effects, 0517
  and thermodynamic control, 0516
  cyanide, 0515
  dianions, 0514
  enolate anions, 0514
  solvent effects, 0517
  types, 0514
nucleophiles, 0490
  and catalysis of attack at carbonyls, 1259
  and displacement of diazonium, 0916
  and HSAB, 0492
  and Lewis bases, 0490
  and neighboring groups, 0453
  and nucleophilic aromatic substitution, 0869
  and nucleophilicity table, 0494
  and rate of reaction, 0492
  and S_N1 reactions, 0490
  and substitutions, 0425
  and Umpolung, 0634
  attack at ipso carbon, 0854
  carbon, 0587
  catalysis of amide hydrolysis, 1408
  charged, and solvent effects, 0503
  counterions, 0516
  dicarbonyl anions, 0514
  enolate anions, 0514
  heteroatom, conjugate addition, 1130
  in S_N2 reactions, 0490
  nitrogen, 0555
  opening aziridines, 0621
  rate of reaction with carbocations, 0490
  reaction with carbocations, 0248
  reaction with epoxides, 0538
  strength of, 0490, 0491
  sulfur, 0548
  trajectory of approach to carbonyls, 1258
  uncharged, 0492
nucleophilic addition, see addition
nucleophilic assistance, and solvents, 0506
nucleophilic catalysis, hydrolysis of anhydrides, 1399
nucleophilic radicals, 0948, 1018
nucleophilic rearrangement, 0299
nucleophilic rearrangement, mechanism, 1560–1574
nucleophilic strength, 0490, 0491
nucleophilic strength, see nucleophilicity
nucleophilic substitution, see substitution
nucleophilicity order, for S_N2 reactions, 0493
  toward sulfonyl sulfur, 1472
nucleophilicity, ambident nucleophiles, 0516
  amides, 0568
  and basicity, 0491
  and Bronsted-plots, 0495
  and polarizability, 0516
  and rate of reaction, 0492
  and solvation, 0491, 0492
  and solvents, 0491, 0504
  and steric hindrance, 0493
  and supercritical carbon dioxide, 0508
  and Swain-Scott equation, 0493
  and the α-effect, 0495
  and the Periodic table, 0491
  and unshared electrons, 0495
  at carbonyl carbon, 0494
  in nucleophilic aromatic substitution, 0869
  in $S_{RN}1$ reaction, 0869
  of nucleophiles, table, 0494
  π-, 0999
  reaction at carbonyls, 0494
  solvent, scale, 0506
  versus basicity, and elimination, 1505
Nucleus Independent Chemical Shift (NICS), 0057
O-acylation, and Friedel-Crafts acylation, 0720
  with acyl halides, 1451
O-acylhydroxamic acids, see hydroxamic acids
O-alkylation, and amide formation, 0568
  enolate anions, 0514, 0623
  nitronic esters, 0515
  phenoxide ions, 0515
O-sulfonylamines, elimination to nitrenes, 0293
O-tosyl imines, and the Neber rearrangement, 1605
observed rotation, also see enantiomers, chiral compounds
observed rotation, α, definition, 0139
octatetraenes, cyclization to cyclooctatrienes, 1642
octylidenes, 0286
oleanene, and Wagner-Meerwein rearrangements, 1583
olefin metathesis, see metathesis, alkene
olefination, Peterson, see Peterson
oligocatenanes, 0131
onium salts, from amines, 0376
  with alcohols, 0538
online literature searching, 1901
Oppenauer oxidation, of alcohols, 1721
  and the Meerwein-Ponndorf-Verley reaction, 1721
optical activity, 0136
  and allenes, 0148, 0149
  and biaryls, 0146
  and chiral atoms, 0140, 0141
  and chirality, 0136
  and circularly polarized light, 0163
  and paracyclophanes, 0150
  and polarizability, 0141
  and refractive index, 0163
  and restricted rotation, 0150
  and solvolysis, 0460
  and symmetry, 0163
  and Tröger's base, 0144
  cause of, 0162
  determining absolute configuration, 0159
  Grignard reagents, 0756
  N,P,As,Sb, 0144
  perpendicular disymmetric planes, 0145

optical inactivity, 0136
optical purity, 0179, 0180
optical resolution, see resolution
optical rotatory dispersion (ORD), 0160, 0161
  and conformations, 0196
orbital overlap, and conrotatory ring closing of dienes, 1637, 1639
  [2 + 2]-cycloaddition, 1225
  [2 + 2]-cycloaddition, ketene with cyclopentadiene, 1227
orbital symmetry, and endo addition, 1214, 1215
  and photochemical [2 + 2]-cycloaddition, 1232
  and the Diels-Alder reaction, 1207
  and the Woodward-Hoffmann rules, 1207
  and [2 + 2]-cycloaddition, 1225
  rules, and stability of Dewar benzenes, 1642
orbitals, 1s and 2p, 0004
  d, and carbanion stability, 0254, 0255
  π, 0009
  p, and vinyl carbocations, 0476
  p, conjugated with double or triple bonds, 0040
  σ, 0005
  sp, 0007
  sp^2 hybrid and sp^3 hybrid, 0008, 0009
orbitals, alternant and nonalternant hydrocarbons, 0069, 0070
  and allenes, 0148
  and benzene, 0033, 0034, 0037
  and bond angle, 0026
  and bond distance, 0023
  and conjugation, 0040, 0041
  and cyclopropane, 0219
  and ethyne, 0010
  and hybridization, 0007
  and metallocenes, 0066
  and mutual repulsion, 0008
  and PES, 0013, 0014
  and rearrangement, 1560
  and resonance, 0033
  and thermal ring opening of cyclobutenes, 1636
  and trienes, 0045
  and ylids, 0053
  antarafacial overlap, 1213
  antibonding, 0005, 0009
  antibonding, and S_NAr reactions, 0866
  antibonding, of butadiene, 0038, 0039
  bonding, 0005, 0009
  cyclohexadiene-trine interconversion, 1638, 1639
  diagrams, 0004
  dienes-cyclobutene interconversion, 1637, 1639
  five-membered ring heterocycles, 0062
  gerade, 0005
  hybrid, 0009
  hybrid, 2p, 0008
  linear combination of, 0006
  molecular, 0005, 0006
  nonbonding, 0041
  of alkenes and dienes, 1208, 1209
  of mercury, 0007
  of oxygen atom, 0006
  overlap, [2 + 2]-cycloaddition, 1225
  suprafacial overlap, 1213
  ungerade, 0005
ORD, see optical rotatory dispersion
Organic Functional Group Preparations, 1898
Organic Syntheses, 1896
organic compounds, and bond energy, 0030
organocadmium reagents, with acyl halides, 1443
organocalcium, and SET mechanism, 0264
organocerium reagents, with acid derivatives, 1447
organocopper compounds, and the Ullmann reaction, 0898
  Lewis acids and alkyl halides, 0604
organocopperzinc reagents, with allyl halides, 0603
organocuprates, addition to alkynes, 1102
  amino, 1112
  and cyclopropylcarbinyl halides, 0473
  and elimination, 0601
  and S_N2' reactions, 0473, 0620
  conjugate addition, 1111–1115
  coupling, with alkyl halides, 0599
  diaminocyano, 0619
  from organolithium reagents, 0827
  halogen-metal exchange, 0603
  higher order mixed, 0602, 0603, 1112
  higher order, and transmetallation, 0828
  mixed, 0602, 1112
  oxygen mediated coupling, 0988
  with acyl halides, 1442
  with aldehydes, 1312
  with alkyl halides, 0600, 0601
  with allylic phosphonates, 0612
  with amines, 0822
  with aziridines, 0621
  with carbamoyl halides, 1428
  with conjugated sulfoxides, 1113
  with dihalides, 0601
  with epoxides, and Lewis acids, 0619
  with haloketones, 0632
  with ketones, 1312
  with propargyl esters, 0608
  with sulfonate esters, 0601
organolithium reagents, addition to aldehydes or ketones, mechanism, 1308
  addition to alkenes or alkynes, 1097
  addition to conjugated aldehydes, 1115
  amination, 0880
  and acidity, 0262
  and aggregation state, 0262, 0263
  and alkylation of aromatic compounds, 0912
  and alkylation of arylnitro compounds, 0914
  and amines, 0799
  and arylation of amines, 0876
  and based induced elimination of dihalo alkenes, 1534
  and bond dissociation energy, 0262
  and carboxylic acids, 1329
  and cleavage of ethers, 0617
  and cryptands, 1308
  and directed ortho metalation, 0912
  and electron affinity, 0262
  and formation of nitrobenzene, 0690

and formation of organocuprates, 0827
and formylation, 0727
and LIDAKOR, 1518
and metal catalyzed conjugate addition, 1133
and metal catalyzed reaction with nitrogen, 0880
and metalation, 0808
and nitration of aromatic compounds, 0690
and sparteine, enantioselectivity, 0595
and the Shapiro reaction, 1526
and TMEDA, 0262, 0263
and transmetallation, 0828
and X-ray, 0262, 0263
and Ziegler alkylation, 0913
aryl, directed ortho metalation, 0596
aryl, hydrolysis, 0751
aryl, metal halogen exchange, 0595
aryl, unsolvated, 0263
as aggregates, 0260
conjugate addition, 1112
coupling alkenes to allylic thioethers, 1094
coupling with sulfones, 0613
deprotonation, 0809
enantioselectivity, 1303
exchange with alkyl halides, 0250
exchange with organolithium compounds, 0595
from alkyl halides, 0831, 1301
from thioethers, 0992
hydrolysis, 0812
Li-H exchange, 0595
metal halogen exchange, 0594
modified, 1116
reaction with phosphonium salts, 1370
sonochemical preparation, 0351
structure, 0262
structure, and rate of deprotonation, 0810
sulfurization, 0818

organolithium reagents, with aldehydes or ketones, 1301
with alkoxides, and elimination of epoxides, 1518
with alkyl halides, 0594, 0595
with alkyl halides, ESR and CIDNP, 0599
with alkyl iodides, radical intermediates, 0269, 0270
with allylic ethers, 0641
with amines, and amination of alkenes, 1046
with aromatic compounds, 0911–0915
with aryl amines, rearrangement, 1624
with aryl halides, 0595, 0884, 0886
with boronic esters, 1629
with carbon dioxide or carbon disulfide, 1330
with carbon tetrachloride, 0834
with carboxylic acids, 1447
with conjugated compounds, 1302
with copper compounds, 0601
with dienes and carbon dioxide, 1144
with epoxides, 0618
with esters, 1446
with ethers, Wittig rearrangement, 1624
with imines, 1331
with iodoethane, and NMR, 0269
with iron pentacarbonyl, 0910
with isocyanides, 1469
with metal halides, 0826
with methoxyamine, 0821
with oxazines, 0642
with oxazolines, 0643
with phenyl cyanate, 0886
with Weinreb amides, 1448

organomagnesium compounds, also see Grignard reagents

organomagnesium compounds, and carbanions, 0251
exchange with R_2Hg, 0251
rearrangement, 0826

organomercury compounds, exchange with R_2Mg, 0251
ate of reaction with halogens, 0764

organometallic compounds, addition to aldehydes or ketones, 1309–1311
addition to aldehydes or ketones, metals used, 1310, 1311
addition to alkenes, 1096, 1097, 1099
addition to alkynes, 1099
addition to C=N compounds, 1335
addition to carbonyls, enantioselectivity, 1312
addition to carbonyls, in ionic liquids, 1310
addition to carbonyls, structural compatibility, 1313
addition to imines, enantioselectivity, 1331, 1332, 1335

organometallic compounds, alkynyl, acyl addition, 1320
amination of, 0821
and alkylation of aromatic compounds, 0912
and alkylation of pyridine or pyrrole, 0913
and carbanions, 0249
and carbonylation of aryl halides, 0910
and formation of biaryls, 0888
and halogen replacement in alkyl halides, 0833
and metalation, 0808
and metals, 0809
and NMR, 0259
and proton transfer, 0808
and S_E1 reactions, 0765
and the Heck reaction, 0891–0897
and the Stetter reaction, 1321
and transmetallation, 0828
various, with acid derivatives, 1449

organometallic compounds, aryl, 0750
aryl, formation of biaryls, 0718
aryl, hydrolysis, 0751
arylation of alkenes, 0891
bis addition to alkynes, 1101
carbonylation, 0651, 0823
cleavage of ethers, 0617
conjugate addition, 1111–1120
containing heteroatoms, 0809
coupling with active methylene compounds, 0907
coupling with alcohols, 0614
coupling with allylic esters, 0608
coupling with malonate esters, 0907

organometallic compounds, aryl, (*Continued*)
coupling with Mannich bases, 0613
coupling with sulfonate esters, metal catalyzed, 0606
coupling, and Stille reaction, 0606
deprotonation, 0809, 0810
dimerization, 0989
dimetallic compounds, 1103
directed ortho metalation, 0912
electrophilic substitution, 0756
formation of cyclobutanones, 0911
organometallic compounds, from alkenes, 1082
from alkyl halides, 0829, 0831, 0832
from dihalides, 1304
from metals, 0811, 0829, 0831, 0832
from organometallics, 0808
Group I and Group II, coupling with alkyl halides, 0594, 0595
halogenation, mechanism, 0821
hydrolysis, 0812
oxygenation, 0818
poor reactivity with water, 0812
preparation of ketones, 0651
propargyl, metal catalyzed addition to carbonyls, 1310
protonation of, 0812
reduction with sodium borohydride, 0812
structure, 0259
sulfuration, 0818
transmetallation, 0825, 0826
vinyl formation of dienes, 0792
vinyl, acyl addition, 1320
vinyl, and the Heck reaction, 0896
vinyl, formation of divinyl ketones, 0651
organometallic compounds, with acids, 0812
with acyl halides, 1443, 1444
with alkyl halides, 0598, 0599, 0604–0607, 0651, 0833
with amides, 1445
with anhydrides, 1445, 1446
with aryl halides, 0886
with aryldiazonium salts, 0922, 0923
with aziridines, 0621
with carbon dioxide, 1329
with conjugated carbonyl compounds, 1111–1120
with cuprous cyanide, 0825
with disulfides, 0818
with epoxides, 0618, 0619
with esters, 1445
with imines, 1330–1334
with metal sulfonates, 0612
with oxygen, 0813
with peroxides, 0814
with sulfonic acid esters, 0818
with sulfonyl halides, 1475
with sulfur dioxide, 0819
organopotassium, with alkyl halides, 0594, 0595
organosilanes, see silanes
organosodium, with alkyl halides, 0594, 0595
organotin compounds, acyl addition, enantioselectivity, 1315, 1317, 1318
metal catalyzed addition to carbonyls, 1314–1318
organozinc compounds, and carbenoids, 1241
and insertion reactions, 0807
and Simmons-Smith procedure, 1241
and the Reformatsky reaction, 0605, 0606, 1327
with alkyl halides, 0605
X-ray crystallography, 1241
organozinc halides, with thioesters, 1450
organozinc reagents, conjugate addition, 1116
enantioselectivity of conjugate addition, 1117
orientation, and addition reactions, 1019
orientation, of addition reactions, 1022
ortho effect, 0674
and rate of reaction, 0412
ortho esters, hydrolysis, 0525
reduction to aldehydes, 1832
transetherification, 0536
ortho-para directing groups, 0669, 0673
ortho-para ratio, and electrophilic aromatic substitution, 0670, 0673
ortho-para selectivity, and aryl radicals, 0950
orthoborates, see borates
orthoesters, and transacetalization, 1272
orthoformates, with sulfonic acids, 1473
Orton rearrangement, 0740, 0741
osazones, and carbohydrates, 1285
from hydroxy aldehydes or hydroxy ketones, 1285
osmate states, 1163
osmium tetroxide, and chiral additives, 1166
and diamination, X-ray structure, 1182
and dihydroxylation of alkenes, 1162
and Sharpless aminohydroxylation, 1180
catalysts, with Cinchona alkaloids, 1163
encapsulated, fluorous, or polymer-bound, 1163
out-in isomers, 0189
out-in isomers, also see isomers
over oxidation, of alcohols, 1718
overlap of orbitals, in HOMO, 1636
overlap, σ overlap and hyperconjugation, 0096
oxa-di-π-methane rearrangement, 1693, 1694
oxacyclooctane, conformation, 0213
oxalacetic acid, 0192
oxalyl bromide, with carboxlic acids, 1441
oxalyl chloride, and DMSO, oxidation of alcohols, 1721
and Friedel-Crafts acylation, 0719
with carboxylic acids, 1441
oxaphosphetanes, and NMR, 1374
and the Wittig reaction, 1373
oxathiazinanes, 0789
oxathiolanones, extrusion to give alkenes, 1557
oxazaborolidines, chiral in reductions, 1801
1,3-oxazine-2-ones, from isocyanates and oxetanes, 1275
oxazines, reactions, 0642, 0643

oxaziridines, and
  α-hydroxylation, 1754
  α-hydroxylation, enantioselectivity, 1754
  rearrangement to lactams, 1588
  sulfonyl and α-hydroxylation of enolate anions, 1754
  sulfonyl, and oxidation to thioethers, 1782
oxaziridinium salts, and epoxidation of alkenes, 1173
  from Oxone® and iminium salts, 1173
oxazolidin-2-ones, alkylation, 0569
oxazolidines, hydrolysis, 0643
oxazolidinone amides, with alcohols, 1422
oxazolidinones, arylation, 0881
  chiral, and enolate alkylation, 0629
oxazolines, alkylation, 0643
  and carboxylic acids, 0643
  hydrolysis, 0598
  with organolithium reagents, 0643
oxepin, and Cope rearrangement, 1666
oxetanes, and formation of isocyanides, 0568
  and photochemical [2 + 2]-cycloaddition, 1231
  by the Paterno-Büchi reaction, 1231, 1463
  carbene insertion, 0805
  cleavage with organolithium reagents, 0617
  conformation, 0212
  formation of dinitrates, 0547
  from alkenes and halides or ketones, 1463
  in the Prins reaction, 1394
  with amines, 0565
  with isocyanates, 1275
α-oxidation, alkenes to conjugated ketones, 1759
  and ozonolysis, 1760, 1761
  and the Etard reaction, 1763
  of amines to amides or cyclic amines to lactams, 1759
  of cyclic ethers to lactones, 1760
  of ethers to carboxylic esters, 1759
  of ketones, in ionic liquids, 1762
  of ketones, reagents for, 1758
  of ketones, to diketones, 1758
  of ketones, with selenium dioxide, mechanism, 1760
  of lactams to imides, 1759
  of methyl aromatic compounds, 1763
oxidation, 0299, 1708
oxidation allyl, see allylic oxidation
oxidation number, 1703
oxidation state, of functional groups, 1704
oxidation, allylic, with selenium dioxide, 1751, 1752
oxidation, Boyland-Sims, 0734
  definition, 1703
  of alcohols, 1715–1728
  of alcohols to aldehydes, but not acids, reagents, 1718, 1719
  of alcohols to ketones, reagents for, 1719, 1720
  of alcohols, and NBS, 1725
  of alcohols, by catalytic dehydrogenation, 1724
  of alcohols, metal catalyzed with oxygen, metals for, 1719
  of alcohols, miscellaneous reagents, 1725, 1726
  of alcohols, reagents, utilized with DMSO, 1721, 1722
  of alcohols, with alternative hypervalent iodine reagents, 1724
  of alcohols, with Bobbitt's reagent, 1723
  of alcohols, with chromium(VI), mechanism, 1726, 1727
  of alcohols, with Dess-Martin Periodinane, 1723, 1724
  of alcohols, with dichromates, 1715–1718
  of alcohols, with DMSO reagents, 1721
  of alcohols, with enzymes, 1725
  of alcohols, with Fremy's salt, 1720
  of alcohols, with hypervalent iodine, 1723
  of alcohols, with TEMPO, 1722, 1723
  of alcohols, with TPAP, 1719
  of aldehydes to carboxylic acids, 1769–1773
  of aldehydes to carboxylic acids, reagents for, 1770, 1771
  of alkanes to alcohols, with dioxiranes, 1755
  of alkenes, to allylic alcohols, 1751, 1752
  of alkyl halides, and the Kornblum reaction, 1765
  of alkyl halides, to aldehydes, 1765, 1766
  of amines to nitriles, 1739, 1730
  of amines, reagents for, 1767
  of amines, with manganese dioxide, 1731
  of anilines to azo compounds, 1731
  of aromatic hydrocarbons, to quinones, 1764
  of aromatic side chains, and reagents for, 1745
  of benzyl silyl ethers, 1720
  of benzylic alcohols, and microwaves, 1726
  of benzylic halides, and the Krönke reaction, 1766
  of boranes, to alcohols, 1079, 1627
  of hydrazines to azo compounds, 1730
  of hydrazones, to nitriles, 1731
  of hydrocarbons to amines, 1757
  of hydrocarbons to sulfonic acids, 1757
  of hydroxylamines, 1731
  of methyl groups, Barton reaction, 1696
  of methylene groups, 1753–1757
  of phenols, 1706
  of sulfoxides with hydroperoxides, mechanism, 1783
  of thioethers with hydroperoxides, mechanism, 1782
  of thioethers, reagents for, 1781
oxidation, Oppenauer, of alcohols, 1721
  remote, of hydrocarbons, 1761, 1762
  Tamao-Fleming, 0539
oxidative cleavage, of alkenes, 1742–1745
  of alkenes, Barbier-Wieland procedure, 1743

oxidative
cleavage, (*Continued*)
of alkenes, reagents for, 1742, 1743
of alkenes, with the Lemieux-von Rudloff reagent, 1743
of aromatic compounds, and the Dakin reaction, 1746
of aromatic compounds, reagents, 1744
of cyclic ketones to dicarboxylic acids, 1735
of cyclic ketones, reagents for, 1735, 1736
of diamines, 1733
of dihydrophenanthrenes, 1746
of diols, 1732–1735
with dimethyl dioxirane, 1733
with ozone, see ozonolysis
oxidative coupling, and the Suzuki-Miyaura coupling, 0903
of alkyl halides, with base, 1783
of silyl enol ethers, 1784
oxides, amine, see amine oxides
oxides, metal catalyzed arylation, 0986
oxides, phosphine, see phosphine oxides
oxidizing agents, 1708
and iodination of aromatic compounds, 0703
and Jacobsen-Katsuki epoxidation, 1178
for alcohols, 1715–1728
for ozonides, 1737
with alcohols and ylids, 1371
oxime ethers, from alkyl halides, 0547
from oximes, 0547
oxime formation, rate determining step, 1287
oximes, acid catalyzed formation of nitriles, 1547
addition of HCN, 1392
addition of organometallics, 1335
alkylation, 0547
and tautomerism, 0103
aryl, Bamberger rearrangement, 0930
by reduction of nitro compounds, reagents, 1821
catalytic hydrogenation, 1812
cyclic, and Beckman rearrangement, 1614
dehydration to nitriles, 1546, 1547
dehydration with the Burgess reagent, 1546
ester, with acids, 1615
formation of, rate of reaction, 1286, 1287
fragmentation to nitriles, 1548
from aldehydes or ketones, 1286
from ketones, 0784
from nitronic esters, 0515
from nitrous acid, 0784
hydrolysis, 0930, 0986, 1264
metal catalyzed coupling to ketones, 1858
O-alkyl, from oximes, 0534
O-tosyl, rearrangement to amides or nitriles, 1548
oxidation, and the Beckmann rearrangement, 1732
oxidation, to nitro compounds, reagents, 1778
photoisomerization, 0346
reaction with hydrazines, 1285
reagents, for Beckmann rearrangement, 1613
reduction to amines, reagents, 1812
reduction to aziridines, 1820
reduction to imines, reagents, 1821
reduction with bakers yeast, 1820
reduction with borane, 1812
reduction with Dibal, 1820
with alkyl halides, 0547
with aryldiazonium salts, 0986
with diazoalkane, 0533
with nitroso compounds, 0848
with phosphorus pentachloride, 1613
oximes-alkenes, radical cyclization, 1129
oxirenes, stability, 1174
oxo process, 1145
oxoglutaric acid, 0192
Oxone® (potassium peroxomonosulfate), 1172
and acetal cleavage, 0527
and carbonylation of alkenes, 1141
and carboxylic acids with metal halides, 1426
and dialkylalloxans, 1173
and formation of dioxiranes, 1172
and haloamines, 0849
and halogenation of aromatic compounds, 0703
and KBr, halogenation of aromatic compounds, 0700
and oxidation of amines, 1768
and oxidation of boranes to phenols, 0871
and oxidation of hydrazones, 1731
and oxidative cleavage of alkenes, 1743
and oxidative cleavage of alkynes, 1744
oxidation of amines to hydroxylamine, 1777
oxidation of boranes, 1079
oxidation of oximes to nitro compounds, 1778
with iminium salts, 1173
with ketones, and epoxidation of alkenes, 1172
with osmium tetroxide, 1163
oxonia-Cope rearrangement, 1660
oxonin, 0080
oxonium ions, and dioxane, 0443
and hydration of alkenes, 1032
and solvolysis, 0443
oxonium salts, cleavage, 0582
from alkyl halides, 0543
from ethers, 0543
with amides, 1422
with amines, 0852
with nitriles, 1814
oxy-Cope rearrangement, 1660
antibody catalyzed, 1660
silyloxy, 1660
oxyamination, of alkenes, 1180
oxychlorocarbenes, 0292
oxygen atom, and orbitals, 0006
oxygen, and autoxidation, 0967
and conjugate addition of boranes, 1121
and coupling of organocuprates, 0988
and electronic structure, 0015
and ene reactions, 0970
and heptalene, 0067
and lactone formation, 1036
and the Glaser reaction, 0978
and the Hay reaction, 0979

cycloaddition to dienes, 1218
Diels-Alder reaction, 1216
formation of cyanoamines, 0801
metal catalyzed oxidation of alcohols, catalysts for, 1719
radical inhibitor, 0938
reactivity in autoxidation, 0968
singlet, see singlet oxygen
triplet, see triplet oxygen
with Grignard reagents, 0813, 0831
with hydrocarbons, 0967
with organolithium reagents, 0871
with organometallics, 0813
[2,3]-oxygen-to-sulfur migrations, 1678
oxygenation, of organometallics, 0818
oxymercuration, and Markovnikov's rule, 1033
and steric effects, 1018
of alkenes, 1033
of norbornene, 1023
with alcohols, see alkoxymercuration
ozone, and oxidation of aromatic compounds, 1744
and oxidation of hydrocarbons to alcohols, 1750
and oxidative cleavage, see ozonolysis
and phenanthrene, 0060
formation of ozonides, 1737
ozonides, formation and reactivity, 1739, 1740
from ozone and alkenes, 1737
oxidation and reduction of, 1737
regiochemistry of formation, 1740, 1741
trioxolanes, 1739
ozonolysis, 1736–1742
after dihydroxylation of alkynes, 1168
alkenes versus alkynes, 1738
and α-oxidation, 1760, 1761
and alkene structure, 1737
and ion pairs, 1738, 1739
and trioxolanes, 1738
Criegee mechanism, 1738–1740
formation and reactivity of ozonides, 1739, 1740
of alkenes, 1736–1742
of alkenes, 1,3-dipolar addition, 1741
of alkenes, and rearrangement, 1737
of alkenes, isotope labeling, 1741
of alkenes, mechanism, 1738–1740
of ethylene, formation of dioxirane, 1741
regiochemistry of ozonide formation, 1740, 1741
stereochemistry and the Criegee mechanism, 1741

p character, and bond angle, 0026, 0027
π-allyl complexes, and acylation of dienes, 0797
and hydroformylation, 1146
and rearrangement of alkenes, 0770
π-allyl palladium, and allylic esters, 0609
π-allylic complexes, with metals, 0117
π-allylnickel complexes, coupling reactions, 0593
π-bonds, and resonance, 0046
neighboring group participation, 0450
nonadjacent, stabilization of carbanions, 0255
π-complexes, 0042
and arenium ions, 0662
and encounter complexes, 0665
and S_NAr reactions, 0857
halogenation of alkenes, 1004
stability, 0663, 0664
π-energy, 0042
π-interactions, with cations, 0114
with CH, 0114
π-nucleophilicity, 0999
π-orbitals, 0009
and addition reactions of alkynes, 1017
π-π-interactions, 0114
π-π-interactions, and catenanes, 0132
palladium acetate, acyloxylation of alkenes, 0972
palladium, and coupling aryl halides with boronic acids, 0899–0903
palladium, and coupling enolate anions with aryl halides, 0907
and hydrogenation, 1054
and oxidation of alkenes to aldehydes or ketones, 1774
and Rosenmund reduction, 1808
and Sonogashira coupling, 0903–0906
and Suzuki-Miyaura coupling, 0899–0903
and the Heck reaction, 0891–0897
and the Wacker process, 1774
catalysts, and vinyl triflates, 0531
catalysts, formation of thioethers, 0551
catalysts, organometallic coupling, 0606
pancreatic porcine lipase, formation of lactams, 1431
para migration, and Fries rearrangement, 0735
para rearrangement, and the Wallach rearrangement, 1699
para-Claisen rearrangement, 1668
paracyclophanes, 0050
and chirality, 0150
and resonance, 0049, 0050
and restricted rotation, 0150
and X-ray, 0049
heterocyclic, 0050
paradoxical selectivity, in Friedel-Crafts alkylation, 0708
paraformaldehyde, and formylation, 0727
and the Eschweiler-Clarke procedure, 1290
from formaldehyde, 1460
paraldehyde, and acetaldehyde, 1460
paramagnetic ring current, 0057
and paratropic compounds, 0057
paratropic compounds, 0057, 0090
antiaromaticity, 0090
NMR, 0090
paratropic, bridged annulenes, 0089
dipleiadiene, 0090
pyracyclene, 0090
partial bond fixation, 0059
partial molar volume, and high pressure, 0513

partial rate factor, aryl radicals, 0951
definition, 0677
particle sites, heterogeneous catalysts, 1060
partition factor, arenium ions, 0659, 0660
partitioning effect, and S_NAr reactions, 0856
with arenium ions, 0659, 0660
Passerini reaction, 1467, 1468
mechanism, 1468
Pasteur, Louis, and resolution, 0176
patents, 1875
Paterno-Büchi reaction, 1231, 1463
and diradical intermediates, 1463
diastereoselectivity, 1464
intramolecular, 1464
Pauli principle, and radicals, 0266
Pauling resonance energies, and arynes, 0861
Pauson-Khand reaction, 1141–1143
Payne rearrangement, 0537
PCC (pyridinium chlorochromate), oxidation of alcohols, 1716
acidity of, 1716
PDC (pyridinium dichromate), oxidation of alcohols, 1716
Pechmann condensation, 0712, 0713
PEG 400, 0648
PEG, and alkene metathesis, 1684
catalytic hydrogenation, 1054
recyclable hydrogenation catalysts, 1057
and the Baylis-Hillman reaction, 1324
pentadiene, with DCl, 1014
pentadienyl radical, 0272
pentaerythritol, by Tollens reaction, 1368
pentahelicene, 0149
pentalene derivatives, 0068
pentalene, and aromaticity, 0067
peptide synthesis, 1433, 1434
and the Ugi reaction, 1468
perborate, sodium, see sodium
pericyclic addition, 0298
pericyclic mechanism, 0297
Periodic table, and acidity, 0384
and bond energy, 0030
and electronic structure, 0014
and Lewis acids, 0375, 0384
and nucleophilicity, 0491
periodic acid, and Lemieux-von Rudloff reagent, 1743
and oxidative cleavage of diols, 1732
periodinane, Dess-Martin, see Dess-Martin
periodinane, sodium, oxidation of phenols, 1728, 1729
Perkin reaction, 1363
permanganate, potassium, and Lemieux-von Rudloff reagent, 1743
and oxidation of sulfoxides, 1780
oxidation of alcohols, 1716
Permuterm Subject Index, 1907
peroxide, diacyl, and peroxide, 0279
peroxide, hydrogen, alkenes and formic acid, 1164
with NaOH, and boranes, 1079
peroxides, also see hydroperoxides
peroxides, 0970
acyl, from acyl halides, 0545
acyl, with aldehydes, 0972
acyl, with aromatic compounds, 0980
acyl, with Grignard reagents, 0814
acyl, with hydrocarbons, 0971
and addition of polyhalo compounds to alkenes, 1160
and anti-Markovnikov addition, 1030
and conjugate addition of boranes, 1121
and epoxidation of alkenes, 1171
and Fenton's reagent, 0964
and ferrous sulfate, 0964
and formation of lactones from alkyne-acids, 1042
and hydroxylation of aromatic compounds, 0964
and Orton rearrangement, 0741
and oxidation of thioethers, 1780
and radical coupling of alkanes, 0976
and radical rearrangements, 1574
and radicals, 0934, 0938
and the Glaser reaction, 0978
and the Story synthesis, 1557
co-reagents for epoxidation of alkenes, 1171
cyclic, preparation of, 1557
decomposition, 0935
diacyl, 0279
diacyl, from acyl halides, 0545
diffusion rate of radicals, 0935
formation of radicals, 0935
from alkyl halides, 0544
from cycloaddition of singlet oxygen to dienes, 1218, 1219
from Grignard reagents, 0813
from hydrocarbons, 0967, 0971
from organometallics, 0813
oxidation of thiols, 1785
silyl, see silylperoxides
with alkylboranes, 0814
with HBr and alkenes, 1030
with organometallics, 0814
peroxyacids, and Baeyer-Villiger rearrangement, 1617
and dihydroxylation of alkenes, 1162
and epoxidation of alkenes, 1169
and hydroxylation of aromatic compounds, 0733
and metal mediated oxidation of alcohols, 1717
by oxidation of carboxylic acids, 1773
of alkenes, mechanism, 1170
oxidation of amines to amine oxides, 1779
with alkenes, stereochemistry, 1023
with aromatic compounds, 0733
with ketones, 1617
peroxyesters, see peroxides, acyl
peroxyimidic acid, and dioxiranes, 1173
peroxynitrous acid, 0965
persistent radicals, 0268

persulfate, potassium, see potassium
PES (photoelectron spectroscopy), and alkenes, 0014
and bond fixation, 0075
and carbocation stability, 0244
and conformations, 0196
and hybridization, 0014
and methane, 0012, 0013, 0014
and multiple bonds, 0013
and nitrogen, 0012
and orbitals, 0013, 0014
and strain, 0224
and the captodative effect, 0075
cyclobutadiene, 0074
pentalene derivatives, 0068
Petasis alkenylation, 1380
Petasis reagent, 1380, 1381
Peterson alkenylation, 1365–1367
Peterson alkenylation, and silyl-Wittig reaction, 1366
Peterson alkenylation, modified, epoxide formation, 1367
Peterson olefination, see Peterson alkenylation
pH, and solvent acidity, 0369
phase transfer, 0508, 0509
ammonium salts, 0509
and amine formation, 0559
and anhydride formation, 1423
and base induced elimination of alkyl halides, 1530
and carboxylate salt alkylation, 0540
and catalytic hydrogenation of aromatic compounds, 1066
and Cinchona alkaloids, 1175
and cleavage of ethers, 0580
and crown ethers or cryptands, 0510
and dehydration of amides to nitriles, 1550
and enolate alkylation, 0627
and formation of alkyl azides, 0572
and formation of alkyl halides, 0575
and halide exchange with aryl halides, 0883
and halide ions, 0575
and hydrolysis of carboxylic esters, 1401
and hydroxylation of aromatic compounds, 0964
and interfacial mechanism, 0510
and ion pairs, 0511
and Julia-Colonna epoxidation, 1176
and microwave reactions, 0511
and nucleophilic substitution, 0511
and oxidation of amines, 1768
and permanganate oxidation of alcohols, 1717, 1718
and polar solvents, 0509
and the Finkelstein reaction, 0575
and the Gomberg-Bachmann reaction, 0924
and the Michael reaction, 1107
and the Mills reaction, 0922
and the Rosenmund-von Braun reaction, 0885
and the Williamson reaction, 0531
and thioether formation, 0549
and water, 0509
phosphonium salts, 0509
quaternary ammonium salts, 0509
triphase catalysts, 0511
with acyl halides and alcohols, 1412
with alcohols, 0577
with alcohols, with HCl, 0576
phenacenes, and aromaticity, 0087, 0088
phenalene cation, resonance energy, 0060
phenalene radical, resonance energy, 0060
phenalene, acidity of and aromaticity, 0060
phenanthrene, alkylation of, with organometallics, 0914
and aromaticity, 0059, 0060
and bromine, 0060
and Dewar benzene structures, 0059
and ozone, 0060
and partial bond fixation, 0059
cyclization with singlet oxygen, 1218
phenanthrenes, from stilbenes, 1645
phenol-dienone rearrangement, 1594
phenol-keto tautomerism, see tautomerism
phenols, 2-allyl, by Claisen rearrangement, 1668
acid catalyzed rearrangement of dienone, 1593
acyl, Fries-rearrangement, 0735
addition to ketenes, 1040
alkali fusion of arylsulfonic acids, 0871
and Bucherer reaction, 0870
and ether formation, 0533, 0535
and Fenton's reagent, 0964
and microwaves, 0870
and tautomerism, and the enol form, 0102
aromatization of cyclic ketones, 1709
by electrolysis, 0734
by Fries rearrangement, 0735
catalytic hydrogenation, 1830
conversion to sulfonate esters, and reduction, 1831
dehydroxylation, 1830
from aromatic compounds, 0733, 0964
from aryl halides, 0870
from aryldiazonium salts, 0919
from arylthallium compounds, 0913
from boranes and Oxone®, 0871
from esters, 0735
from ethers, 0559
from organolithium reagents, 0871
from peroxyacids, 0733
hydrogenation to cyclohexanones, 1066
oxidation, 1706, 1728, 1729
quenching in photochemistry, 0342
reduction to aromatic compounds, 1830
Reimer-Tiemann reaction, 0726
with alkenes, 1037
with cyanogen halides, 0531
with phosphorus oxychloride, 0883
phenonium ions, 0456, 0458, 0459

phenoxide ion, with alkyl halides, 0515
phenoxides, with aryl halides, 0872
phenyl carbocations, 0243
phenyl cyanate, see cyanate
phenyl radicals, see radicals
phenylenes, as twisted compounds, 0051
phenylhydrazine, with aldehydes or ketones, 1675
phenyllithium, 0117
  aggregation state, 0263
phenylmagnesium bromide, and X-ray, 0260
phosgene, and aromatic compounds, 0728
  and dehydration of amides to isonitriles, 1550
  and Vilsmeier-Haack reaction, 0724
  formation of carboxylic acids, 0728
  reaction with alcohols, 1276
  with amines, 1427
phosphates, and chirality, 0142
  aryl, amination, 0883
  from phenols, 0883
  triaryl, with aryl halides, 0873
phosphazides, and reduction of azides, 1822
phosphazine bases, formation of thioethers, 0874
phosphine oxides, and resonance, 0053
  and ylids, 0053
  by oxidation of phosphines, 1779
  chiral reduction, enantioselectivity, 1847
  from phosphorus ylids, 1370
  from the Wittig reaction, 1370
  reduction to phosphines, 1846
  with alkenes or alkynes, 1051
  with isocyanates, 1460, 1461
phosphine sulfide, with epoxides, 0552
phosphine, polymer-bound, and Mitsunobu reaction, 0540
  metal catalyzed arylation of amines, 0878
phosphine-free Heck reactions, 0893
phosphines, alkylation, 0558
  and elimination of epoxides, 1517
  and Mitsunobu reaction, 0540
  aryl, 0881
  as chiral ligands in catalytic hydrogenation, 1056
  as ligands, 0043
  by reduction of phosphine oxides, 1846
  from metal catalyzed addition of phosphines to alkenes, 1050
  α-hydrogens and ylid formation, 1370
  metal catalyzed addition to alkenes, 1050
  metal catalyzed arylation, 0881
  metal, and elimination of epoxides, 1518
  oxidation to phosphine oxides, 1779
  polymer-supported, as ligands, 0612
  silyl, see silylphosphines
  silyl, addition to ynones, 1088
  with alkyl halides, 1369
  with epoxides, 1374
phosphinyl imines, reduction, 1813
phosphites, and the Corey-Winter reaction, 1535
  trialkyl, with sulfonic acids, 1473
  with alkenes, 1051
  with alkyl halides, 1375
  with cyclic thionocarbonates, 1535
phospholene-1-oxides, with isocyanates, 1460
phospholes, and circumambulatory rearrangement, 1652
phosphonate esters, by the Arbuzov reaction, 1375
  from alcohols, 0545
  vinyl, and the Heck reaction, 0892
  vinyl, conjugate addition, 1132
phosphonates, allylic, coupling reactions, 0612
phosphonates, ylid formation, 1375
phosphonium salts, conversion to ylids, 1369
  from alcohols, 0560
  phase transfer catalysis, 0509
  suitable bases for ylid formation, 1369, 1370
  with organolithium reagents, 1370
  with bases, 1370
phosphonium tosylates, ionic liquids, 1199
phosphonothionates, and formation of ylids, 1376
phosphoramide bases, and the aldol reaction, 1342
phosphoramides, and determining absolute configuration, 0160
phosphoranes, se ylids, phosphorus
phosphoranes, cleavage of ethers, 0582
phosphorescence, 0339
phosphorus oxychloride, 0576
  and DMF, 0725
  and from amides, 0797
  Friedel-Crafts cyclization, 0716
  with aryl halides, 0883
phosphorus pentabromide, 0577
phosphorus pentachloride, 0576
  and electronic structure, 0015
  with aldehydes or ketones, 1298
  with amides, 1698
  with amides, Sonn-Müller method, 1815
  with aryl halides, 0883
phosphorus tribromide, 0577
phosphorus trichloride, 0576
phosphorus ylids, see ylid
phosphorus, and carbanions stabilization, 0258
  and optical activity, 0144
  and stereogenic atoms, 0191
  chirality, 0191
  stabilization of carbanions, 0254
  inversion of configuration, 0191
photo-Fries rearrangement, 0736
  and CIDNP, 0737
  and flash photolysis, 0737
photochemical Beckmann rearrangement, 1616
photochemical Diels-Alder reaction, 1198
photochemical dimerization of ketones, mechanism, 1857
photochemical mechanism, 0348
photochemical nitrosation, 0785
photochemical reactions, 0328
photochemical Wallach rearrangement, 1699

photochemical Wolff rearrangement, 1600
photochemical [2 + 2]-cycloaddition, 1223
photochemical [4 + 2]-cycloaddition, 1214
photochemistry, also see excited states
photochemistry, also see photolytic cleavage
photochemistry, also see photosensitization
photochemistry, acetylene excited state, 0334
- addition of alcohols to alkenes, 1040
- addition of aldehydes to alkenes, 1136
- addition of thiols to alkenes, 1044

photochemistry, and an actinometer, 0349
- and arylation of enolate anion, 0908
- and auxochromes, 0334
- and chlorosulfenantion, 0974
- and chromophores, 0331, 0333
- and conjugated bonds, 0332
- and electromagnetic spectrum, and wavelength of light, 0329
- and electron spectrum, 0330
- and electronic transitions, 0329
- and exciplex formation, 0342
- and excited states, 0334
- and extinction coefficient, 0330
- and frontier orbital method, 1208
- and Hund's rule, 0331
- and hypsochromic shift, 0333
- and Jablonski diagrams, 0337
- and nucleophilic aromatic substitution, 0863
- and photolytic cleavage, 0335
- and photosensitization, 0340, 0341
- and quenching by phenols, 0342
- and radical cyclization, 1126
- and radicals, 0934
- and remote dehydrogenation, 1714
- and singlets, 0331
- and spectrophotometer, 0329
- and the Frank-Condon principle, 0335
- and the Orton rearrangement, 0741
- and the Pauson-Khand reaction, 1142
- and the Reed reaction, 0974
- and the vinylcyclopropane rearrangement, 1657
- and the Wigner spin-conservation rule, 0340
- and triplets, 0331
- and UV light, 0329, 0333
- and visible light, 0329, 0333
- and [1,7]-hydrogen shifts, 1652

photochemistry, bathochromic shift, 0333
- choice of photosensitizer, 0341
- cleavage, to radicals, 0279, 0343
- coupling hydrocarbons and nitriles, 0975
- coupling of dialdehydes, 1856
- cycloaddition of alkenes to carbonyls, 1463
- cycloaddition of oxygen to dienes, 1218
- deactivation, 0341
- decarbonylation, 0344
- decarboxylation of carboxylic acids, 0983
- decomposition of diazomethane, 0285, 1240
- dimerization, 0348
- dimerization of ketones, 1856
- electronic excitation, 0332
- elimination, 1478
- energy of light, 0329
- esterification of carboxylic acids, 1414
- excited state, 0329
- excited state of formaldehyde, 0334
- extrusion of nitrogen, 1553
- fluorescence, 0339
- forbidden transitions, 0331
- formation of biaryls, 0889
- formation of carbocations, 0435
- *g* and *u* transitions, 0331, 0332
- ground state, 0329
- hydrogen atom abstraction, 0347
- intersystem crossing, 0339
- intramolecular rearrangement, 0345
- intramolecular [2 + 2]-cycloaddition, 1230
- isomerization of aza and azo compounds, 0346
- isomerization of boranes, 0771
- isomerization of oximes, 0346
- mechanism, see mechanism
- $n \rightarrow \pi^*$ transitions, 0332
- $n \rightarrow \sigma^*$ transitions, 0332
- Norrish Type I cleavage, 0343
- Norrish Type II cleavage, 0344

photochemistry, of alkenes, and geometry, 0346
- of amines, with cyclopropane, 0567
- of aromatic ketones, 0342
- of aryl alkenes, 1645
- of bicycloheptadienes, 0347
- of dienes, 0332, 1632
- of functional groups, 0332
- of halogens and halogenation of alkanes, 0954

photochemistry, $\pi \rightarrow \pi^*$ transitions, 0332
- phosphorescence, 0339
- photolysis of ketene, 0345
- photoreduction, 0348
- photosensitizer definition, 0340
- promotion, 0339
- promotion to a dissociative state, 0336
- properties of excited states, 0334
- quantum yield, 0349
- quenching, 0341
- reactions, 0343
- rearrangement of alkenes, 0769
- reduction of cyclopropanes, 1075
- reduction with silanes, 1799
- $\sigma \rightarrow \sigma^*$ transitions, 0332
- singlet and triplet excited states, 0334
- spin forbidden transitions, 0331
- symmetry-forbidden transitions, 0331
- [2 + 2]-cycloaddition, 1229
- [2 + 2]-cycloaddition, and Wigner spin conservation rule, 1231
- [2 + 2]-cycloaddition, and Woodward-Hoffmann rules, 1232
- [2 + 2]-cycloaddition, catalysts for, 1223

photodimerization,
cyclopentenone, 0348
photoelectron spectroscopy, see PES
photoisomerization, 0346
photoisomerization, azacrown ethers, 0346
azo compounds, 0346
of alkenes, 1029
of cyclooctene, 0346
oximes, 0346
photolysis, see photolytic cleavage
photolysis, flash, 0348
of bromoform, 0287
photolytic cleavage, 0335
and amines with aryl halides, 0876
and the Franck-Condon principle, 0335
aniline ammonium salts, 0742
benzenes and Dewar benzenes, 1641
energy cascade, 0336
epoxy-ketones, 0529
formation of radicals, 0336, 0342
ketone and diazomethane, 0806
NBS and tosylamines, 0586
Norrish Type I, 0343
Norrish Type II, 0344
of aldehydes, 0344
of cyclic sulfones, 1556
of cyclobutanones, 1555
of diazomethane, 0804
of ketones, 0345
of lactones, 1555
of pyrazoles or pyrazolines, 1554
of triazolines, 1554
oxa-di-π-methane rearrangement, 1694
promotion to a dissociative state, 0336
ring contraction of diazoketones, 1599
photonic devices, 0132
photooxygenation, of alkenes, with singlet oxygen, 1178
photoreduction, of ketones, 0348
photosensitization, 0340, 0341
and electron transfer, 0341
and the Paterno-Büchi reaction, 1464
of alkenes, 0977
of oxygen, with alkenes, 0968
photosensitizers, and singlet oxygen, 0969
and [2 + 2]-cycloaddition, 1231
choice of, 0341
cycloaddition of singlet oxygen to dienes, 1218
definition, 0340
eosin, 1218
mercury, and reductive coupling of alkenes, 1095
phthalamic acid, hydrolysis, 1259
phthalate ion, rearrangement, 0747
phthalazines, and asymmetric dihydroxylation, 1167
phthalic acid, by oxidation of naphthalene, 1744
phthalides, Ing-Manske procedure, 0569
phthalimides, conjugate addition, 1131
formation of amines and the Gabriel synthesis, 0569
hydrolysis, 0569, 0570
with hydrazine, 0569
Physical Properties of Chemical Compounds, 1887
physical data, tables, 1885–1889
physical properties, and diastereomers, 0164
pi-stacking, 0114
picene, 0087
picosecond absorption spectroscopy, and solvolysis, 0439
picrates, 0118
picric acid, and complex formation, 0118
picryl iodide, and resonance, 0048
Pictet-Spengler reaction, 0716
pig liver esterase, and hydrolysis of esters, 1400
and resolution, 0176
pinacol coupling, 1854–1856
pinacol rearrangement, 1585
mechanism, 1586
migratory aptitudes, 1568, 1586
pinacols, 1585
pinacols, see diols
B-(3-pinanyl)-9-borabicyclo[3.3.1]nonane, see Alpine-Borane
α-pinene, with borane, 1079
Pinner synthesis, 1275
piperidine, and cyclopropylcarbinyl halides, 0473
Pisum sativum, α-hydroxylation, 1757
Pitzer strain, see strain
pK, and bases, 0364
and carbocation formation, 0244
and conformation, 0387, 0388
and hydrogen bonding, 0385
and indicators, 0369
and proton transfer, 0367
and resonance, 0383
and superbases, 0365
and UV, 0386
bases, table, 0366
pK_a, and acids, 0357
and field effects, 0381
and formation of enolate anions, 0622
carboxylic acids, table, 0382
cyclopentadiene, 0063
fluorene, 0063
in DMSO, 0358
indene, 0063
naphthol, ground vs. excited state, 0335
nitriles, 0383
nitromethanes, 0253
of conjugate base in enolate anion reactions, 0627
α-proton of carbonyl compounds, 0626
α-proton of nitrile compounds, 0627
resonance effects in carboxylic acids, 0382
squaric acid, 0092
substituted benzoic acids, 0381
table, type of acid, 0359–0364
planar conformation, cyclopropane, 0211
planarity, and annulenes, 0080
and aromaticity, 0072, 0086
and benzene, 0050, 0051
and C=C bonds, 0232
and carbocations, 0435, 0436
and cyclobutadiene complexes, 0076
and heptalene, 0068
and methanoannulenes, 0081
and resonance, 0048, 0049
annulenes, 0091
distortion from, 0082
Planck's constant, 0003
plane of symmetry, and chirality, 0140
plane polarized light, 0163
plane polarized light, also see light

plane, mirror plane, and chirality, 0140
and enantiomers, 0140
platinum complex, and cycloalkynes, 0228
resolution alkenes, 0174
platinum compounds, and atropisomers, 0147
platinum, and hydrogenation, 1054
podands, 0123
poisoning, and catalytic hydrogenation, 1055
chiral, in asymmetric catalysis, 1056
poisons, of catalytic hydrogenation, 1055
polar solvents and reactivity, 0412
polar solvents, see solvents
polar transition state mechanism, and benzidine rearrangement, 1680
polarity, and cyclooctatetraene, 0078
inductive and field effects, 0019, 0020
solvent, see solvent polarity
polarizability, and conformation, 0199
and HSAB, 0516
and nucleophilicity, 0516
and optical activity, 0141
polarization, and microwaves, 0353
inductive and field effects, 0019, 0020
topological, 0071
polarized light, circularly, 0163
and asymmetric synthesis, 0172
polarized light, plane, 0163
poly-yne-diene, metathesis, 1688
polyacenes, 0061
polyaromatic compounds, see aromatic compounds
polyene cyclization, 1090, 1091
polyhalo compounds, addition to alkenes, 1160
polyhalogenation, and radical halogenation, 0957
polyhydrogen fluoride-pyridine, and nitration of alkenes, 1158
with alkenes, 1030
polyleucine, and epoxidation, 1176
polylithium compounds, 0808
polymer-bound, amide bases, and the aldol reaction, 1342
and acylation of amines, 1429
Beckmann rearrangement, 1614
carbodiimides, 1417
catalysts, for hydrogenation, 1055
Claisen rearrangement, 1669
conversion of carboxylic acids to amides, 1431
hypervalent iodine, and oxidant of phenols, 1728
hypervalent iodine, oxidation of aldehydes to acids, 1771
ion catalyst, and radical cyclization, 1126
osmium tetroxide, and dihydroxylation of alkenes, 1163
oxazaborolidine, and reduction, 1801
phosphine ligands, 0878
phosphonate esters, and Wittig-Horner reaction, 1375
phosphoramide bases, and the aldol reaction, 1342
pyridinium salts, and β-lactams formation, 1465
substrates, reduction, 1816
TPAP, oxidation of alcohols, 1719
trialkyltin hydride, reduction of alkyl halides, 1826
polymer-supported, acid catalyst, conjugate addition of carbamates, 1131
azides, diazo transfer reagents, 1237
carbodiimides, and formation of amides from acids, 1431
catalysts, and malonate anions, 0623
catalysts, Heck reaction, 0893
dienes, Diels-Alder reaction, 1217
formate, reduction of conjugated aldehydes, 1074
peroxy acids, and Baeyer-Villiger rearrangement, 1618
phosphine ligands, and coupling, 0612
sulfur ylids, 1383
synthesis, 1433, 1434
ylids, Wittig reaction, 1370
polymer-tethered reactants, and Sonogashira coupling, 0905
polymerization, and metathesis, 1685
and photochemical [2 + 2]-cycloaddition, 1230
and radicals, 0280, 0938
and the Diels-Alder reaction, 1204
and the Kolbe reaction, 0993
halo-haloacylation of alkenes, 1161
of heptalene, 0067
ring opening metathesis, 1685
polymers, and aldehydes addition to alkenes, 1136
and hydroxyalkylation, 0714
and supercritical carbon dioxide, 0415
and the Pauson-Khand reaction, 1142
and the Suzuki-Miyaura coupling, 0900
from ammonia with alkynyl halides, 1049
metathesis with dienes, 1687
paraformaldehyde, 1460
polyphosphoric acid, 0715
and Friedel-Crafts acylation, 0722
with arylsulfonic acids, 0698
porphyrins, and rotaxanes, 0131
postulate, Hammond, 0308
potassium cyanide, with Lewis acids, 0649
potassium ferricyanate, 0802
potassium ferricyanide, and dihydroxylation of alkenes, 1163
potassium fluoride, in acetic acid, formation of acyl fluorides, 1441
potassium hexamethyldisilazide, and the aldol condensation, 1348
potassium hydride, with silyl-thiols, 0549
potassium ions, and ambident nucleophiles, 0517
and crown ethers, 0123
binding by crown ethers, 0120

potassium permanganate, and oxidation of diols, 1163
and oxidative cleavage of alkenes, 1743
dihydroxylation of alkenes, 1162, 1163
potassium permanganate, see permanganate
potassium peroxomonosulfate, see Oxone
potassium persulfate, and Boyland-Sims oxidation, 0734
and hydroxylation of aromatic compounds, 0734
potassium superoxide, see superoxide
potassium trifluoroborates, see trifluoroborates
potassium, and formation of enolate anions, 0811, 0907, 0908
and $S_{RN}1$ reactions, 0863
in ammonia, and Birch reduction, 1067
potential energy, and reactions, 0300
potential, ionization, see ionization potential
potssium hydroxide, see KOH
preparative LC, diastereomers and resolution, 0175
pressure, high, see high pressure
Prevost reaction, and the Woodward modification, 1164
primary sources, literature, 1870
principle of conservation of orbital symmetry, and Diels-Alder reaction, 1207
principle of imperfect synchronization, 0368
principle of increasing electron demand, 0449
principle of least motion, 1069
principle of microscopic reversibility, 0309
Prins reaction, 1393–1396
halogenation of alkenes, 1161
Lewis acids used as catalysts, 1394, 1395
with oxetanes, and with peroxides, 1394
priority rules, Cahn-Prelog-Ingold system, 0156
prismane, and strain, 0220
prochiral ketones, reduction of, 1799
prochiral, definition, 0193
product identification, and mechanism, 0311
product quantum yield, 0349
product spread, 0470
proline derivatives, and Michael addition, 1108
proline, and addition of organometallics to imines, 1335
and enantioselective Mannich reactions, 1295
and the aldol reaction, 1347
with enamines, 0636
propane bond energy, 0028
propargyl carbocations, 0240
propargyl groups, as neighboring groups, 0483
propargyl rearrangement, 0473
propargyl systems, and allylic rearrangement, 0472
propargyl, lithio, with alkyl halides, 0596
propellanes, and geometry, 0223
and S_N2 reactions, 0487
and strain, 0220
radical addition, 1027
X-ray crystallography, 0223
propeller shaped carbocations, 0246
propene, from cyclopropane, and entropy, 0304
protecting groups, acetals and ketals, 1271
dithioacetals and dithioketals, 1279
silyl, and lithiopropargyl compounds, 0596
protection, aldehydes and ketones, 0527
of alcohols, 0531
protic solvents, 0502
protodesilylation, 0539
proton acceptor, bases, 0356
proton affinity, and basicity of proton sponges, 0386
proton donors, acids, 0356
proton exchange, and E1cB mechanism, 1489
proton NMR, see NMR
proton sponges, 0365, 0386
and base strength, 0386
and Friedel-Crafts alkylation, 0709
and helicene, 0149
and proton affinity, 0386
basicity of, 0386
with tosylimines and ketenes, 1465
proton transfer, and acidity, 0368
and functional groups, 0368
and keto-enol tautomerism, 0773
and Marcus theory, 0373
and organometallics, 0808
and pK, 0367
and principle of imperfect synchronization, 0368
and resonance, 0368
and solvents, 0368
transition state, 0375
proton, as a leaving group, 0683
proton, as an electrophile, 1005
proton-transfer, 0367, 0368
protonated cyclopropanes, 1026
protonation, enantioselective, enolate anions, 0775
of benzene, 0670
of carbonyls, 1253
of diazo compounds, 0499
of enolate anions, 0812
of organometallics, 0812
vinylboranes, 1630, 1631
protonolysis, of alcohols, 0247
of alkenes, 0247
of boranes, with carboxylic acids, 1063
of iminium ions, 0247
protons, addition to alkenes, 1005
enolizable, and isotopic labeling, 0775
prototropic rearrangement, 0768, 1559
prototropy, keto-enol tautomerism, 0772
proves, SET, 0268
proximity effect, complex-induced, and directed ortho metalation, 0912
Pschorr reaction, mechanism, 0926
Pschorr ring closure, 0925
and the Gomberg-Bachmann reaction, 0925
pseudo first order, kinetics, S_N2, 0427
rate constant, and solvent acidity, 0371
reactions, 0318
pseudoasymmetric carbon, 0165
Pseudomonas oleovorans, α-hydroxylation, 1757
Pseudomonas putida, and dihydroxylation of aromatic compounds, 1168

pseudorotation, and conformations, 0212
and cyclophanes, 0050
Pummerer rearrangement, 1866, 1867
Pummerer-sila, 1867
purity, optical, 0179, 0180
push-pull effect, 0075
and radicals, 0272
pyracyclene, and the Stones-Wales rearrangement, 1646
paratropic, 0090
pyramidal inversion, 0142, 0143, 0144
pyramidal inversion, also see inversion
pyran, and aromaticity, 0058
pyranose compounds, and tautomerism, 0104
pyrans, dihydro, metathesis, 1685
Friedel-Crafts acylation, 0720
from alkynes, 1038
from diketones, 1272
pyrazoles, extrusion of nitrogen, 1553
from diketones, 1285
pyrazolidines, from [3 + 2]-cycloaddition, 1191
pyrazolines, extrusion of nitrogen, 1553
from [3 + 2]-cycloaddition, 1191
pyrazolines, thermolysis, 1191
from keto esters, 1285
pyrene, and complex formation, 0124
pyrenesbenzoannulenes, and aromaticity, 0084
pyrenophanes, 0050
pyrenyl radicals, 0274
pyridine N-oxide, from pyridine, 1779
pyridine-2-thione, and tautomerism, 0103
pyridine-HF, and acetals or ketals, 0526
pyridines, alkylation, and organometallics, 0913
amination, 0915
and acyl halides with alcohols, 1411
and aromaticity, 0058
and chlorination of alcohols, 0469
and resonance, 0033
and Suzuki-Miyaura coupling, 0901
and the Collins reagent, 1716
and the Doebner modification, 1360
basicity, 0063
Birch reduction, 1067
catalyst for hydrolysis of anhydrides, 1399
electrophilic aromatic substitution, 0675
Friedel-Crafts acylation, 0721
hydroxymethyl, by Boekelheide reaction, 1624
in rotaxanes, 0134
ortho lithiation, 0913
reaction with benzyl halides, 0096
Suzuki-Miyaura coupling, 0901
pyridinethiol, and tautomerism, 0103
pyridinium bromochromate, halogenation of aromatic compounds, 0701
pyridinium chlorochromate, see PCC
pyridinium compounds, as leaving groups, 0498
pyridinium dichlorochromate, 0702
pyridinium dichromate, see PDC
pyridinium ions, electrophilic substitution, 0675
from pyrylium ions and amines, 1283
pyridinium salts, and radical cyclization, 1127
pyridinium salts, as ionic liquids, 0415, 1199
pyridinophanes, 0050
pyridones, and tautomerism, 0103
by cyclotrimerization, 1245
pyrimidines, Suzuki-Miyaura coupling, 0901
pyrocalciferols, electrocyclic reagents, 1640
pyrolysis, also see flash vacuum pyrolysis
pyrolysis, of ammonium carboxylates, 1430
of ammonium salts, 1522
of carboxylic acids, 1458
of cyclic peroxides, 1557
of cyclobutane, 0219
of cyclopropane, 0217
of lactones, 1520
of xanthates, 1520
pyrolytic eliminations, see elimination
pyrophosphate, synthesis of, 0125
pyrrole, alkylation, 0557
alkylation, and organometallics, 0913
and aromaticity, 0062
and circumambulatory rearrangement, 1652
and conjugate addition, 1118
basicity, 0063
canonical forms, 0062
electrophilic aromatic substitution, 0675
resonance energy, 0062
pyrroles, and atropisomers, 0147
Birch reduction, 1067
by amination of alkenes, 1046
Friedel-Crafts acylation, 0720
Friedel-Crafts alkylation, 0709
from alkynyl imines or allene-amines, 1049
from diketones and amines, 1283
from metal catalyzed amination of diynes, 1049
halogenation, 0703
metal catalyzed coupling with aryl halides, 0887
Reimer-Tiemann reaction, 0726
pyrrolidines, and [3 + 2]-cycloadditions, 1192
from alkene-amines, 0557
from haloamines, 1695
Hofmann-Löffler reaction, 1695
vinyl, from alkene-amides, 1052
2-pyrrolidindone, alkylation, 0569
pyrrolines, by amination of alkenes, 1046
pyrylium ions, 0058
with amines, 1283
pyrylium salts, leaving groups, 0498

quadricyclane, by photochemical [2 + 2]-cycloaddition, 1230, 1232
quadrivalent stereogenic atoms, 0141
quantum mechanics, and molecular mechanics, 0215

quantum yield, definition, 0349
product, 0349
with radicals, 0938
quasi-Favorskii rearrangement, 1598
quaternary ammonium salts, see ammonium salts
phase transfer catalysis, 0509
thermal stability, 0510
quenching, in photochemistry, 0341
quinazolines, and tautomerism, 0105
quinolines, alkylation of, with organometallics, 0914
amination, 0916
as a poison in the Rosenmund catalyst, 1057
by reaction of aldehydes or ketones with amines, 1282
catalytic hydrogenation, 1067
Friedel-Crafts acylation, 0721
Friedländer quinoline synthesis, 1282
from carbene addition to indoles, 1240
metal catalyzed coupling with aryl halides, 0887
photochemical alkylation, 0983
Suzuki-Miyaura coupling, 0901
quinoloquinolines, 0365
quinones, and addition-elimination mechanism, 0474
and aromatization, 1710
and hydroxylation of aromatic compounds, 0733
aromatization, mechanism, 1710
by oxidation of aromatic hydrocarbons, 1764
by oxidation of phenols, reagents, 1728
reduction to hydroquinones, 1794
stability of ortho and para, 0671
quinoquinolines, as proton sponges, 0386
quinoxalines, acylation, 0983
quinuclidines, chiral catalysts, 1325

R values, and σ values, 0410
ρ values, and reactivity, 0402
E1 versus E2, 1505
R-camp, chiral ligand, 1056
racemates, 0138
and resolution, 0138
and substituted cyclohexanes, 0207
racemic mixtures, see racemates
racemization, and amines, 0144
and carbanions, 0256
and first order reactions, 0437
and pyramidal carbanions, 0758
and radicals, 0939
and S_N1 reactions, 0437
and S_N2 reactions, 0429
and solvolysis, 0439
and the S_E1 mechanism, 0758
of configuration, of migrating group during rearrangement, 1564
out-in isomers, 0190
radicals, acyl, and radical cyclization, 1128
radical addition, see addition
radical anions, and $S_{RN}1$ reactions, 0863
radical cations, see radical ions
radical clocks, 0281, 0946
conformational, 1098
radical coupling, and the Kolbe reaction, 0993
radical cyclization, 1011, 1125–1129
allenyl radicals, 1127
and acyl radicals, 1128
and aldehyde-alkenes, 1129
and aryl radicals, 1127
and Baldwin's rules, 1021, 1125, 1126
and boranes, 1123
and electrochemistry, 1126
and exo/endo isomers, 1127
and heterocycles, 1129
and hydrogen transfer, 1125, 1126
and iodolactonization, 1128
and photochemistry, 1126
and ring size, 1125
and seleno esters, 1129
and silanes, 1127
and TEMPO, 1129
and tributyltin dimer, 1126
and tributyltin hydride, 1125, 1126
and [1,4]-hydrogen transfer, 1652
diastereoselectivity and enantioselectivity, 1127
formation of lactams and lactones, 1128
functional group compatibility, 1127
Grignard reagents and metal salts, 1126
influence of the halogen, 1126
kinetics, 1125
mechanism, 1126
oxime-alkenes, 1129
polyenes, 1091
ring expansion, 1127
vinyl radicals, 1127
with haloaldehydes or ketones, 1129
with sulfur or selenium groups, 1127
radical halogenation, see halogenation
radical halogenation, methane, rate determining state, 0959
radical induced isomerization, E/Z, 1029
radical inhibitors, 0938
radical initiators, addition of sulfonyl halides to alkenes, 1156
addition to Michael substrates, 1031
and halogenation of alkenes, 1149
and Michael addition, 1107
radical ions, 0282, 0283, 0444
and Birch reduction, 1068
and semiquinones, 0282
radical mechanism, addition of alkanes to alkenes, 1084
coupling of boranes, 0989
halogenation of allylic hydrogen, 0961, 0962
organometallic compounds with alkyl halides, 0599
radical probes, 0445
radical reactions stereocontrol, 1127
and cumene, 0599
and σρ relationship, 0412
radical rearrangement, 0299, 1574, 1576
radical substitution, see substitution
radical-cations, and Diels-Alder reaction, 1197
radicals, abstraction, 0807
abstraction of atoms, 0280
abstraction, transition state, 0939
acyl, 0936
acyl from aldehydes with transition metals, 0936

radicals, addition of carbonyls, 1398
addition reactions, 1018–1020
addition to alkenes, 0280, 1010, 1123
addition to alkenes, rate of reaction, 1124
addition to alkenes, stereoselectivity, 1012
addition to alkynes, 1124
addition to bicyclobutanes, 1027
addition to C=N compounds, 1398
addition to conjugated compounds, 1015
addition to dienes, 1021
addition to imines, 1336
addition to propellanes, 1027
addition to thiocarbonyls, 1398
radicals, alkoxy, 0935
alkyl nitrites with aromatic compounds, 0926
alkylation of heterocycles, 0982
allenyl, and radical cyclization, 1127
allylic, 0270, 0272, 0960
allylic, and resonance, 0042, 0947
allylic, rearrangement, 0947
alternant hydrocarbons, 0069
amidyl, and radical cyclization, 1129
aminyl, and radical cyclization, 1129
radicals, and α-heteroatoms, 0949
and abstraction, 1011
and addition of aldehydes to alkenes, 1136
and addition of silanes to alkenes, 1087
and addition of thiols to alkenes, 1043
and addition to alkenes, 1134
and AIBN, 0935
and alkylation, 0512
and arylation, 0718
and arylation of aromatic compounds, 0925, 0926
and arylation of enolate anions, 0908
and atom transfer, 1011
and autoxidation, 0968
and azoxy compounds, 0849
and azulenyl nitrones, 0268
and Baldwin's rules, 1011, 1021
and Barton reaction, 1696
and bis(decarboxylation) of dicarboxylic acids, 1749
and bond energy for atom abstraction, 0943
and bond rotation, 0277
and bridged intermediates, 1012
and carbene insertion, 0806
and carbenes, 0278
and carbonylation of aryl halides, 0910
and chromotropic spin traps, 0268
and CIDNP, 0269, 0270, 0445
and conjugate addition, 1122
and conjugate addition of organometallics, 1115, 1119
and coupling, 0938, 1856
and decarboxylation, 0982
and decarboxylative halogenation, 0995
and decomposition of peroxides, 0935
and dehydrohalogenation of alkyl halides, 1531
and dienes, 1011
and disproportionation, 0936
and E^i reactions, 1510
and electron withdrawing substituents, 0948
and electrophilic aromatic substitution, 0682
and enantioselectivity, 0939
and ENDOR, 0267
and ESR, 0273, 0445, 0849
and ESR/EPR, 0267, 0268
and extrusion of carbon monoxide from ketones, 1555
and fluorination of aryldiazonium salts, 0922
and Grignard formation, 0832
and halo-alkenes, cyclization, 1125–1129
and halogenation of alkenes, 1149
and halogenation of boranes, 0820
and Hofmann-Löffler reaction, 1695
and hybridization, 0276
and hydrogen-metal exchange, 0834
and hydroxylation of aryldiazonium salts, 0919
and hyperconjugation, 0270
and inhibitors, 0938
and inorganic molecules, 0266
and Jacobsen-Katsuki epoxidation, 1178
and mass spectrometry, 0266
and Meerwein arylation, 0923
and metal catalyzed acyloxylation, 0973
and Michael addition, 1110
and NCS, 0963
and nitration of alkanes, 0786
and nitration of aromatic compounds, 0690
and NMR, 0268, 0270, 0271
and organometallic compounds, coupling, 0598, 0599
and oxidation of thiols to disulfides, 1786
and oxidation-reduction, 1706
and oxidative decarboxylation of carboxylic acids, 1748
and oxygen autoxidation, 0968
and peroxide formation, 0971
and peroxides, 0934, 0938
and photochemistry, 0934
and photolytic cleavage, 0336
and photoreduction, 0348
and polyene cyclization, 1091
and polymerization, 0938
and quantum yield, 0938
and racemization, 0939
and radical clocks, 0946
and rearrangement of N-nitroaniline, 0739
and remote dehydrogenation, 1714
and resonance, 0271, 0272
and SET mechanisms, 0444
and SET processes, 0268
and silanes, 0960
and sodium borohydride reduction, 0812
and solvation, 0937
and solvent cage, 0444
and spin trapping, 0267
and $S_{RN}1$ mechanism, 0862
and stability, 0273
and step-scan time-resolved infrared, 0266

radicals, and
α-heteroatoms, (*Continued*)
and strain, 0943
and symproportionation, 1084
and telomers, 1011
and the Gatterman method, 0926
and the Gatterman reaction, 0984
and the Hammett equation, 0949
and the Hunsdiecker reaction, 0943, 0995
and the Kolbe reaction, 0993
and the Pauli principle, 0266
and the Prins reaction, 1394
and the Schmidt reaction, 1612
and the Stone-Wales rearrangement, 1646
and unpaired electrons, 0267
and UV light, 0271
radicals, anti-Markovnikov addition to alkenes, 1124
aryl, 0950, 0984
aryl, and CIDNP, 0941
aryl, and disproportionation, 0940
aryl, and radical cyclization, 1127
aryl, canonical forms, 0940
aryl, coupling, 0940
aryl, ipso attack, 0951
aryl, meta selectivity or ortho/para selectivity, 0950
aryl, partial rate factors, 0951
aryl, resonance, 0940
arylation of aromatic compounds, 0982
as intermediates, 0312
atom abstraction, 0938
azo compounds, 0279
β-substituents, and rearrangements, 1575
benzylic, 0270, 0947, 0960
bond dissociation energy and reactivity, 0952
bridged, 0942, 0943
bridged bromine, and ESR, 1012
bridgehead reactivity, 0949
bromine, 0939
butenyl, 0945
by hydrogen atom abstraction, 0347
by photo-decarboxylation of carboxylic acids, 0983
by photochemical cleavage, 0342, 0343
captodative, 0272, 0273
chain mechanism, and $S_{RN}1$ reactions, 0863
chain reaction, 0936
characterization, 0266
chiral, 0276
chlorine, 0935
cleavage of, 0280, 0937
concentration of, 0267
coupling, 0280, 0589
cyclization, see radical cyclization
cyclization, 0445
cyclobutylcarbinyl, rearrangement, 0945
cyclopropyl, 0277
cyclopropylcarbinyl, 0281, 0945
decarboxylation, 0975
decomposition, 0280
detection of intermediates, 0312
diffusion rate, 0935
dimerization, 0271, 0981
disproportionation, 0280, 0981
dissociation energy, 0275
dissociation, and photo-Fires rearrangement, 0737
E/Z isomers, 0272
electrophilic, 0939, 1018
elimination, 0280
fast radical reaction, 0946
fate of, 0279
fluorine, 0955
formation by cleavage, 0938
fragmentation of carbenes, 0292
free, 0234
free, from carbanions, 0265
radicals, from aldehydes, 0279
from alkyl hypochlorites, 0935
from azo compounds, 0935
from carbenes, 0292
from ketones, 0279
from radicals, 0280
general reactivity, 0939
generation of, 0279
generation of radicals for addition to alkenes, 1124
geometry, 0276, 0277
halogen, 0279
halogen replacement, alkyl halides, 0833
halogen, and bridged radicals, 0942
halogen, with allylic and benzylic hydrogens, 0960
heteroatom, 1129
hydrazyl, 0273
hydrogen abstraction and rearrangements, 1574
hydrogen abstraction from alkenes, 0945
hydrogen transfer, 0936
inhibitors, galvinoxyl, 1122
initiation, 0934, 0938
intramolecular addition to alkenes, 1011
iodine, and light, 0956
ion, to cyclopropanes, 1027
ion-radical pair, and S_NAr reaction, 0857
kinetics of radicals chain reactions, 0937
lifetimes, 0266, 0946, 1577
mechanism, 0934
metal mediated, 0941
methyl, and ESR or IR, 0276
migrating groups in rearrangements, 1577
neighboring group assistance, 0942
nitroxide, 0273, 0276, 0278
nitroxyl, 0273
nucleophilic, 0948, 1018
oxidation to carbocations, 0281
pentadienyl, 0272
pentenyl, 0945
persistent, 0268
phenyl, 0943
photochemical cleavage, 0279
planar versus pyramidal, 0277
polar transition states, 0948
polymerization, 0280
propagation steps, 0936
pulsed radiolysis, 0953
push-pull, 0272
pyrenyl, 0274
radical clock reactions, 0281
rate of rearrangement, 0281
reactivity, 0951, 0952
reactivity and substrates, 0943
reactivity in aromatic solvents, complex formation, 0953
reactivity with aromatic compounds, 0950
radicals, rearrangement, 0280, 0281
and ESR, and CIDNP, 1577
and isotopic labeling, 1575
and stability, 1578
radicals, reduction, 0937
reduction of alkyl halides, 1825, 1826

reduction of thiocarbonates, 1833
reduction, to carbanions, 0281
reversible addition to alkenes, 1012
rotation barrier, 0277
selectivity, 0951, 0952
selectivity of hydrogen abstraction, 0945
silyl, 1015
singlet, 0278
solvents and reactivity, 0952
spectroscopic analysis, 0266
stability of, 0266, 0270, 0272
stereoelectronic effects, 0949
structure, 0266
substitution, see substitution
succinimidyl, 0963
TEMPO, 0274
termination state, 0936
thermal cleavage, 0279
trimethylenemethane, 0278
triphenylmethyl, 0271, 0952
triplet, 0278
vinyl, and radical cyclization, 1127
with alkenes, 0936, 0941, 0947
with alkylsilanes, 0937
with aromatic compounds, mechanisms, 0940
with benzylic hydrogens of aromatic compounds, 0947
with tributyltin hydride, 0937
radioactive iodide, and S_N2 reactions, 0429
radiolysis, pulsed of radicals solutions, 0953
Raman, and carbocations, 0245
and conformations, 0196
and hydrogen bonding, 0110
and intermediates, 0312
and methyl neighboring groups, 0466
laser, and nonclassical carbocations, 0462
nitration of aromatic compounds, 0689
Ramberg-Bäcklund reaction, 1536, 1537
Raney nickel, see nickel
rate acceleration, electrophilic addition to alkenes, 1005
rate constants, 0302
addition carbenes, to alkenes, 1234
and cyclopropylcarbinyl radicals, 0281
and Marcus theory, 0315, 0316
and mechanism, 0315, 0321
and phenonium ions, 0456
and ring-closing reactions, table, 0304
and the Hammett equation, 0402
first order, 0320
pseudo first order, and solvent acidity, 0371
Sandmeyer reaction, 0984
second-order, 0320
rate determining step, 0316, 0317
acetal hydrolysis, 0525
amide hydrolysis, 1410
and arenium ions, 0663
and E1 mechanism, 1487
benzidine rearrangement, 1680
carboxylic esters with amines, 1437
haloform reaction, 0843
oxime formation, 1287
protonation of alkynes, 1036
radical halogenation of methane, 0959
Stille coupling, 0794
sulfonation of aromatic compounds, 0696
rate enchantment, and neighboring groups, 0457
and cyclopropylmethyl groups, 0464, 0465
of the oxy-Cope rearrangement, 1660
solvolysis, 0464, 0465
rate law, 0317, 0318
and frequency factor, 0322
and half-life, 0320
and kinetics and mechanism, 0315
and molecularity, 0316
and solvent isotope effects, 0327
and steady state, 0317
E1cB and E2, 1489
first-order, 0319
methods for determining kinetics, 0319
pseudo first-order, 0318
rate-determining state, 0316, 0317
rate of diffusion, and high pressure, 0414
and reactivity, 0414
rate of ionization, sulfonate esters, 0504
rate of reaction, alkyl halides with ethanol, 0398
and chiral compounds, 0138
and E2 reactions, 1481
and E^i reactions, 1509
and ionic strength, 0434
and mass-law effect, 0434
and medium, 0412
and microwave irradiation, 0352, 0512
and nucleophiles and nucleophilicity, 0492
and radical clock reactions, 0281
and resolution, 0178
and resonance, 0483
and salt effect, 0434
and S_N1 reactions, 0433, 0480
and S_N1 with aryldiazonium salts, 0858
and S_N1, and alkyl tosylates, 0482
and S_N1, and B strain, 0481
and S_N2 reactions, 0427, 0478, 0479, 0483
and S_N2, and allylic substrates, 0483
and S_N2, and solvent effects, 0503
and S_NAr reactions, 0865
and solvation, 0493
and solvents, 0504
and solvolysis, 0458
and steroids, 0400
and structure, 0479
and the ortho effect, 0412
and the Smiles rearrangement, 0932
Claisen rearrangement, 1674
common-ion effects, 0434
Diels-Alder reaction, 1206
formation of oximes, 1286, 1287
hydrolysis of alkyl halides, 0399
hydrolysis of esters, 0399
ionization and B strain, 0398
radical addition to alkenes, 1124
radicals, and inhibitors, 0938
solvolysis of alkyl bromides, 0480
rate retarding substituents, 0484
rate, and S_N2 reaction, 0429
and temperature, 0322
arenium ion mechanism, 0659, 0660
electrophilic aromatic substitution, 0671, 0677
halogenation of ketones, 0779

rate, and S_N2
reaction, (*Continued*)
isotope exchange with carbanions, 0760
organomercury compounds with halogens, 0764
ortho/para/meta substitution, aryl radicals, 0951
partition factor, 0659, 0660
ratios, electrophilic aromatic substitution, 0682
salt effects, and electrophilic substitution, 0757
rate-controlling state, 0316
re/si nomenclature, 0194
Reaction Citation Index, 1877
reaction coordinate, 0302
reaction intermediates, 0304
reactions, and Hammond postulate, 0308
and molecularity, 0316
and steady state, 0317
diffusion-controlled, 0302
enantioselective, 0171
first-order, 0315, 0316
gas-phase, and kinetics, 0319
homodesmotic or isodesmic, 0038
kinetic requirements, 0301
kinetically controlled, 0307, 0308
kinetics of fast reactions, 0319
photochemical, 0328, 0343
proton-transfer, 0367
pseudo first-order, 0318
second-order, 0315, 0316
thermodynamically controlled, 0307, 0308
reactivity, alkyl halides with ethanol, 0398
and cavitation, 0512
and conformation, 0400
and conformational transmission, 0401
and electrical effects, 0396
and field effects, 0396
and high pressure, 0413, 0512
and ionic solvents, 0415
and medium, 0412
and microwaves, 0512
and ρ values, 0402
and rate of diffusion, 0414
and resonance, 0396
and σ values, 0403, 0404
and steric effects, 0397
and substrate structure, 0478
and tetrahedral intermediate, 0397
and the Hammett equation, 0401, 0402
and ultrasound, 0512
aromatic compounds, 0665, 0679
in supercritical carbon dioxide, 0414
in water, 0414
of groups, in S_N1 or S_N2 reactions, 0488
of radicals, 0951, 0952
of radicals, substrate variation, 0943
quantitative treatments, 0401
solvent polarity, 0412
reactors, microwave, 0354
Reagents for Organic Synthesis, 1897
reagents, bromination of alkenes, 1150
chlorination of alkenes, 1150
elimination of dihalides to alkenes, 1539
fluorination of alkenes, 1149
for α-hydroxylation of carbonyl compounds, 1753
for α-oxidation of ketones, 1758
for acylation of amines, 1432
for aromatization, 1709–1711
for Beckman rearrangement, 1613
for benzylic oxidation to aldehydes, 1763
for dehydration of amides to isonitriles, 1550
for dehydration of amides to nitriles, 1549
for dehydration of oximes to nitriles, 1546
for dehydrogenation of amines to nitriles, 1729, 1730
for elimination of epoxides, 1518
for epoxidation of alkenes, 1169
for formation of acylals, 1273
for halogenation of ketones, 0776, 0780
for hydrolysis of C=N compounds, 1264, 1265
for hydrolysis of dithioacetals and dithioketals, 1280
for hydroxylation of hydrocarbons, 1751
for oxidation of alcohols to carboxylic acids, 1768
for oxidation of alcohols without over oxidation, 1718, 1719
for oxidation of aldehydes to carboxylic acids, 1770, 1771
for oxidation of amines, 1767
for oxidation of aromatic side chains, 1745
for oxidation of thioethers, 1781
for oxidative cleavage of alkenes, 1742, 1743
for oxidative cleavage of aromatic compounds, 1744
for oxidative cleavage of diols, 1733
for pinacol coupling, 1854–1856
for preparation of thiocarbonyls, 1278
for reduction of aldehydes or ketones to alcohols, 1792–1805
for reduction of alkenes, 1062
for reduction of conjugated alkenes, 1070
for reduction of conjugated carbonyls, 1793
for reduction of esters to alcohols, 1807
for reductive alkylation of aldehydes or ketones, 1290
for remote oxidation of hydrocarbons, 1761, 1762
self-immolative, 0171
rearrangement, 1,2-alkyl, of alkyne anions, ab initio study, 1579
1,3- and greater, 1572, 1573
α-ketol, 1593
acid catalyzed of epoxides, 1587
acyl phosphorus ylids, 1525
alkenes and photosensitized oxygen, 0968
alkenes, and π-allyl complexes, 0770
alkenes, metal catalyzed, 0769
alkyl groups, Hofmann-Martius reaction, 0741

alkyl, and Friedel-Crafts reactions, 0741
alkyl, from ammonium salts, 0741, 0742
rearrangement, allylic, 0469
and acyl addition of allylic boranes, 1319
and allylic oxidation, 1751
and allylic radicals, 0947
and propargyl systems, 0472
and reduction of allylic alcohol, 1829
and S_N2' reactions, 0470, 0471
and S_Ni' reactions, 0472
and Stille coupling, 0793
carbenes, 0804
formation of allenes, 0472
with allylic alcohols, 0615
with vinyl epoxides, 0620
Wurtz reaction, 0590
rearrangement, amino acids, and nitrous acid, 1586, 1587
amino-Cope, 1660
anchimeric assistance in migrating group, 1565
rearrangement, and addition of alkyl halides to alkenes, 1160
and addition-elimination mechanism, 0475
and allylic carbocations, 0483
and benzoylnorephedrine, 0400
and carbene addition to aromatic compounds, 1239
and carbenes, 0292
and carbocations, 0802
and conducted tour mechanism, 0768
and cyclopropylmethyl groups, 0465
and diazotization of amines, 1566
and diradicals, 1576
and formation of carbocations, 1561
and formation of nitrenes, 1561
and ions, 1572
and methyl group participation, 0466
and neighboring group mechanism, 0448
and ozonlysis of alkenes, 1737
and phenonium ions, 0456
and S_N1-type processes, 1564
and solvolysis, 0466
and the Diels-Alder reaction, 1199
and the Heck reaction, 0895
and the Jacobsen reaction, 0748
and Whitmore 1,2-shifts, 1561
rearrangement, aryl carboxylate ions, 0747
aryl halides, 0749
aryl triazenes, 0740
aza-Cope, 1660
aza-Wittig, 1625
Baeyer-Villiger, 1617
Bamberger, 0930
Beckmann, 1613
Beckmann, migratory aptitudes of groups, 1568
benzidine, 1678, 1679
benzil-benzylic acid, 1594
benzyl ammonium salts, 0929
boron-to-carbon, 1627
Brook, 1700
carbene, 1579
carbene to carbene, 1600
carbene, hydrogen shifts, 1579
carbocations, 0248, 0249, 1565
carbocations, and Friedel-Crafts alkylation, 0710
Carroll, 1670
cationotropic, 1559
Chapman, 1697
circuambulatory, 0249, 1652
Claisen, 1668–1674
Cope, 1659–1667
Cope, also see Cope
Curtius, 1609
degenerate, 1563
Demyanov, 1589
di-π-methane, 1692
dienone-phenol, 1593
divinylcyclopropanes, 1661
dyotropic, 1700
electrocyclic, 1633
electrocyclic, and carbenes, 1240
electrophilic, 0299, 1559, 1579
electrophilic allylic, geometry of, 0763
enolene, 1673
epoxy-alcohols, 0538
Favorskii, 1595
Fischer-Hepp, 0739
Fries, 0735
Grovenstein-Zimmerman, 1585
halogen from N-haloamides, 0740
Hofmann, 1607
Hofmann, mechanism, 0311
hydride, 1,3- and greater, 1572, 1573
hydrogen as a migrating group, 1567
in oxidation with PCC, 1716
intermolecular and intramolecular, definitions, 1560
intramolecular, photochemical, 0345
lithio-epoxide, 0564
Lossen, 1610
Meinwald, 1587
Meisenheimer, 1623
memory effects of migrating groups, 1570
Meyer-Schuster, 0473
migrating group, migration origin, migration terminus, 1559
migratory aptitude, H versus alkyl versus aryl, 1570
migratory aptitudes, 1568
Mislow-Evans, 1678
N-nitroso groups, 0739
N-nitrosoanilines, 0739
nature of the migration, 1563
Neber, 1605
Neber, and intermediate isolation, 0312
nitro groups, 0738
non-carbocation mechanism, 0712
nucleophilic, 0299
nucleophilic, mechanism, 1560–1574
O-tosyl nitriles and O-tosyl oximes, 1548
rearrangement, of aldehydes, acid catalyzed, 1592
of alkenes, photochemical, 0769
of alkylcarbenes, 0803
of alkynes, 0768
of ammonium salts, base induced, 1621
of aryl oximes, 0930
of biphenylene, 1646
of boranes, 0771
of carbanions, 0265
of carbenes, 0291, 1234
of carbocations, 0236, 1032
of carbocations, direction of rearrangement, 1562

rearrangement, of aldehydes, acid catalyzed, (*Continued*)
of diazo alkoxides, 1602
of diols, migratory aptitudes, 1568
of double bonds, 0767
of esters, 0735
of haloamines, 1616
of hydroperoxides to ketones, 1620
of ketones, acid catalyzed, 1592
of nitrenes, 0294
of protonated cyclopropanes, 1565
of radicals, 0280, 0281
of radicals, and β-substituents, 1575
rearrangement, organomagnesium compounds, 0826
Orton, 0740, 0741
oxa-di-π-methane, 1693
oxonia-Cope, 1660
oxy-Cope, 1660
para-Claisen, 1668
Payne, 0537
phenol-dienone, 1594
pinacol, 1585
pinacol, also see pinacol
pinacol, migratory aptitudes of groups, 1568
propargyl, 0473
prototropic, 0768, 1559
Pummerer, 1866
quasi-Favorskii, 1598
radical, 0299, 1574–1578
Reilly-Hickenbottom, 0741
resonance in migrating groups, 1565
retro-Claisen, 1668
σ-bond, metal catalyzed, 1690
Schleyer adamantization, 1584
semipinacol, 1586, 1587
sigmatropic, see sigmatropic
sigmatropic, definition, 1647
sila-Pummerer, 1867
Smiles, 0931
Sommelet-Hauser, 0929, 1623
Stephens, 0929
stereochemistry of migrating groups, 1563, 1564, 1567
Stevens, 1621
Stieglitz, 1616
Stone-Wales, 1646
sulfur ylids, 0930
tert-pentyl carbocation, 1562
truce-Smiles, 0933
vinylcyclopropane, 1656
von Richter, 0927
Wagner-Meerwein, see Wagner-Meerwein
Wallach, 1698
with Dibal reduction of oximes, 1820
Wittig, 0641, 1624
Wolff, 1599
[2,3]-sigmatropic, 0930, 1676
[2,3]-Wittig, 1676
recognition, molecular, 0124, 0125
recrystallization, fractional, and diastereomers, 0174
and resolution, 0174
recyclable catalyst, for alkene metathesis, 1684
reduced mass, and mechanism, 0323
reducing agents, for ozonides, 1737
reductase, of *Nicotiana tabacum*, 1074
reduction of conjugated ketones, 1074
reduction, 0299
and Grignard reactions, 1305, 1306
and selectivity, 1787–1790
and the Barton-McCombie reaction, 1833
and the Cannizzaro reaction, 1798
asymmetric, 1800–1803
asymmetric, benzoylformates, 0170
conjugate, enantioselective hydrogenation, 1072, 1073
conjugate, reagents for, 1071, 1793
conjugate, with silanes, 1071
definition, 1703
dissolving metal, 1067
ease of reduction of functional groups, 1787–1790
enantioselective, 1802
of aldehydes or ketones, 1791–1805
of alkyl halides, reagents, 1824–1827
of carbonyls with sodium in ethanol, mechanism, 1795, 1796
of conjugated alkenes, reagents for, 1070
of dithianes, 0639
of ketones, diastereoselectivity, 1803
of nitriles to methyl, with terpenes, 1824
of oxazines, 0642
of prochiral ketones, 1799
of radicals, 0937
of sulfonate esters of phenols, 1831
of sulfonate esters, from alcohols, 1830
of sulfones, 0624
type of, 1786
with ammonium formates, 1799
with $LiAlH_4$, of aldehydes or ketones, mechanism, 1804
with metals, 1797
with silanes, 1798, 1799
Wolff-Kishner, 1835
reductive alkylation, and formic acid, 1290
and the Wallach reaction, 1290
enantioselectivity, 1291
Hantzsch dihydropyridines, 1290
in ionic liquids, 1291
of azo compounds, 1291
of nitro compounds, 1291, 1818
of nitroso compounds, 1291
reductive amination, and microwaves, 1291
and the Eschweiler-Clarke procedure, 1290
of aldehydes or ketones, reagents for, 1290
reductive cleavage, of cyclopropanes, 1074
reductive coupling, see coupling
reductive coupling, of aldehydes or ketones, reagents, 1858, 1859
reductive Nazarov cyclization, 1095
Reed reaction, 0974
Reformatsky conditions, and β-lactam formation, 1465
Reformatsky reaction, 0605, 0606, 1326
and activated zinc or dialkylzinc reagents, metals, 1327
and sonochemistry, 0352
intermediates, 1328
with carboxylic esters, 1328
X-ray of intermediates, 1328

refractive index, and optical activity, 0163
regiochemistry, and ozonide formation, 1740, 1741
  E2 reactions, 1498
  in the Heck reaction, 0892
  of elimination, 1497
regioisomers, and the Diels-Alder reaction, 1199, 1200
regioselective, definition, 0514
regioselectivity, and ambident nucleophiles, 0513
  and enolate anions, 0630
  and halogen radicals, 0955
  and Hofmann's rule, 1498
  and Stille coupling, 0793
  and unsymmetrical ketones, 0630
  and Zaitsev's rule, 1498
  condensation of esters and ketones, 1455
  cyclotrimerization, 1245
  Dieckmann condensation, 1453
  epoxide halogenation, 0583
  formation of arynes, 0867
  halogenation of alkanes, 0955, 0957
  halogenation of ketones, 0780
  in pyrolytic elimination, 1510
  in the Diels-Alder reaction, 1199, 1200
  Mannich reaction, 1294
  organometallics with heteroatoms, 0809
  [3 + 2]-cycloaddition, and FMO, 1191
Registry Number, Chemical ABSTRACTS, 1880
Reilly-Hickenbottom rearrangement, 0741
Reimer-Tiemann reaction, 0726
Reissert compounds, with sulfuric acid to give aldehydes, 1811
remote dehydrogenation, 1713, 1714
remote oxidation of hydrocarbons, 1761, 1762
Reppe carbonylation, 1137
resolution, 0173–0176
  and pig liver esterase, 0176
  and rate of reaction, 0178
  and *Sphingomonas pauchimobilis*, 0179
  and synthesis, 0167
  conversion to diastereomers, 0173
  deracemization, 0179
  kinetic, 0176, 0178, 0179
  kinetic, see kinetic
  mechanical, 0176
  mechanical, and heptahelicene, 0176
  metal complexes, 0150
  methods of, 0172–0179
  of alkenes, 0174
  of allenes, 0149
  of amino acids-boric acid, 0173
  of crystals, 0176
  of enantiomers, 0138
  of organomercury compounds, 0756
  of sulfoxides, 1781, 1782
  of sulfur compounds, 0145
  of trans-cyclooctene, 0174
resonance, 0032
resonance effects, 0048
  and acidity, 0382
  and σ values, 0409
  and substituent effects, 0483
resonance energy, also see energy
resonance energy, 0216
  ab initio calculations, 0037
  acenes, 0087
  and aromatic compounds, 0060
  and aromaticity, 0062
  and cross conjugation, 0044
  and fused aromatic compounds, 0060
  and hybridization, 0040
  benzene, 0036, 0037
  butadiene, 0038, 0039
  cyclopentadienide ion, 0063
  of heterocycles, 0062
  phenalene radical and cation, 0060
resonance integral, 0037
resonance stabilization, and the captodative effect, 0075
resonance structures, fulvalenes, 0068
resonance, allyl anion/cation/radical, 0042
  and 1,3-dipoles, 1189
  and allylic carbanions, 0762
  and allylic carbocations, 0483, 1013
  and allylic radicals, 0947
  and amines, 0383
  and aniline, 0048
  and anthracene, 0049
  and arenium ions, 0658
  and aromatic compounds, 0033, 0049
  and benzene, 0033, 0034
  and bond angles, 0047
  and bond distance, 0047
  and bond order, 0033
  and calculations, 0034
  and canonical forms, 0032
  and carbanions, 0252, 0258, 0759
  and carbocations, 0247, 0483, 1019
  and charge separation, 0047
  and Dewar structures, 0032
  and dimethyloxosulfonium methylid, 1383
  and dimethylsulfonium methylid, 1383
  and electron density, 0048
  and electronegativity, 0047
  and electrons, 0046
  and enolate anions, 0253
  and halogen substituents, 0046
  and hyperconjugation, 0238
  and hypophosphorus acid, 0053
  and MO theory, 0033
  and nonequivalent canonical forms, 0047
  and orbitals, 0033
  and π-bonds, 0046
  and paracyclophanes, 0049
  and phosphine oxides, 0053
  and phosphorus ylids, 1369
  and pK, 0383
  and planarity, 0047–0049
  and proton transfer, 0368
  and radicals, 0271, 0272
  and rate of reaction, 0483
  and reactivity, 0396
  and steric effects, 0048
  and strain, 0048
  and sulfones or sulfoxides, 0053
  and the Hammett equation, 0402
  and the mesomeric effect, 0048
  and unpaired elections, 0047
  and vinyl chloride, 0041
  and ylids, 0053
  Dewar structures, 0049
  energy and canonical forms, 0047
  in migrating groups, in rearrangements, 1565
  keto-ylids, 1371
  naphthalene, 0033
  no-bond, 0097

resonance, allyl anion/cation/ radical, (*Continued*)
of carbonate, 0042
pyridine, 0033
rules of, 0046
rules of stability, 0047
σ bonds, 0033
steric inhibition, 0691
substituted arenium ions, 0666
retention of configuration, and hydrolysis of esters, 1404
and radicals, 0939
retention of migrating group during rearrangement, 1563
retention, and chlorination of alcohols, 0469
and elimination-addition reactions, 0477
and neighboring group participation, 0451
and phenonium ions, 0457
and S_N1 reactions, 0440
and S_N2 reactions, 0428
and S_Ni reactions, 0468
retro ene reaction, and pyrolysis of homoallylic alcohols, 1551
retro-aldol reaction, 0835, 1342
retro-Claisen rearrangement, 1668
retro-Diels-Alder reaction, 1199
and thermal extrusion of carbon monoxide from ketones, 1545
retro-ene reaction, 1104
retro-Nazarov, 1096
retropinacol rearrangement, and Wagner-Meerwein rearrangement, 1583
reverse Friedel-Crafts alkylation, see Friedel-Crafts
reverse Gatterman-Koch reaction, 0745
reversibility, Diels-Alder reaction, 1205
microscopic, 0309
reversible reactions, Michael reactions, 1009
radicals to alkenes, 1012
reviews, annual, literature, 1891
of the literature, 1889
rhodium catalysts, chiral, 1238
rhodium compounds, and diazoalkenes, 1234
rhodium, and decomposition of diazoalkanes, 0289
and hydrogenation, 1054
Rhodococcus sp AJ270, and hydrolysis of nitriles, 1269
ribbons, molecular, 0132
Ring Systems Handbook, 1888
ring closing reactions, and rate constants, table, 0304
[2 + 2]-ring closures, 1690, 1691
ring closure, and entropy of activation, 0303
Baldwin's rules, 0305–0307
dig, tet, and trig nomenclature, 0306
disfavored and favored, 0306, 0307
hydroboration of trines, 1081
ring contraction, acid catalyzed, 1588
ring contractions, photolysis of diazoketones, 1599
ring current, 0055–0057
and annulenes, 0085, 0086
ring expansion, acid catalyzed, 1588
and metathesis, 1686
and the Stevens rearrangement, 1621
aryl azides, 1610
carbene addition, and strain, 1240
carbene insertion, 0805
carbenes with aromatic compounds, 1239
lactones, 1700
of alkyl azides, 1610
Tiffeneau-Demyanov, 1590
ring opening metathesis polymerization, 1685
ring opening, cyclopropyl cations, 1644
ring size, and entropy, 0303
and lactone formation, 0304
ring-chain tautomerism, see tautomerism
ring-closing metathesis, see metathesis
ring-in-ring complexes, 0132
Ritter reaction, 1459
and the Beckmann rearrangement, 1616
steric hindrance in nitriles, 1459
with cyanamides, 1459
Robinson annulation, 1350
and ammonium ketones, 1350
and Stryker's reagent, 1351
and the Claisen reaction, 1357
and the Mannich reaction, 1351
Rodd's Chemistry of Carbon Compounds, 1893
ROESY, and π-π-interactions, 0115
Rosenmund catalyst, and hydrogenation of alkynes, 1057
Rosenmund reduction, of acyl halides, 1808
Rosenmund-von Braun reaction, 0869, 0885
rotamer, and conformer, 0196
rotating-frame nOe spectroscopy, see ROESY
rotation barrier, also see barrier
of radicals, 0277
strained aromatic compounds, 0231
rotation, and α, 0139
and catenanes, 0132
in ethane, energy barrier, 0197
molar, see molar rotation
observed, see observed rotation
restricted, and atropisomers, 0148
restricted, and chirality, 0150
restricted, and cis/trans isomers, 0232
specific, see specific rotation
rotaxanes, 0131–0134
and chirality, 0152
2^n rule, and diastereomers, 0165
3^n rule, and conformations, 0197
rules, of resonance, 0046
rules, stability of resonance forms, 0047
ruthenium catalysts, and metathesis, 1683
ruthenium, and hydrogenation, 1054
Ruzicka cyclization, 1458

σ bonds, neighboring group participation, 0450
s character, and acidity, 0388
and bond angle, 0026
and bond distance, 0025
and bond energy, 0029, 0030
and carbanion stability, 0251, 0254
and strain, 0218
σ route, to nonclassical carbocations, 0451

σ values, and field effects, 0407, 0408
and NMR, 0408
and reactivity, 0403, 0404
and resonance and field effects, 0409
F and R values, 0410
σ* values, and field effects, 0407
S-alkylation, with thiocyanate ion, 0573
σ-bond migration, and dyotropic rearrangement, 1700
and sigmatropic rearrangement, 1647
σ-bond participation, and cyclopropylmethyl groups, 0464, 0465
σ-bond rearrangements, metal catalyzed, 1690
σ-bonds, and resonance, 0033
as neighboring groups, 0459
σ-complexes, and arenium ions, 0658
σ-substitution mechanism, 0694
σ-values, Swain-Lupton, 0409
sacrificial anode, 0598
sacrificial hyperconjugation, 0097
Sadtler Research Laboratories, spectra, 1888
Sakurai reaction, 1120
salen catalyst, epoxide halogenation, 0583
salen, and catalytic hydrogenation, 1057
salen-metal complexes, and epoxidation, 1178
salt effects, and kinetics, 0434
and S_N1 reactions, 0504
of lithium perchlorate, 0504
rate of electrophilic substitution, 0757
salt free phosphonium ylids, 1370
salts, and S_N1 reactions, 0504
enamine, and alkylation, 0636
Meisenheimer, 0854
samarium in acetic acid, and desulfurization, 0991
samarium iodide, with triamines, reduction of alkenes, 1063
samarium, and the Barbier reaction, 1313
Sandmeyer reaction, 0984, 0985
sandwich compounds, see metallocenes
saponification, 1400
scale, solvent nucleophilicity, 0506
scales, of electronegativity, 0017
scandium, and fullerenes, 0095
SCF method, and aromaticity, 0058
Schiemann reaction, 0705, 0921
Schiff bases, addition of HCN, 1392
chiral, epoxides with organometallics, 0618
formation of, 1282
hydrolysis, 1263
reduction to amines, 1811
Schlenk equilibrium, 0260, 0261
Schleyer adamantization, 1584
Schmidt reaction, 1611–1613
migratory aptitudes, 1612
Schmidt rearrangement, 1563
Scholl reaction, 0717, 0718
Schotten-Baumann procedure, 1411
acylation of amines, 1427
Schrödinger equation, 0003, 0004
Schwartz's reagent, 1083, 1148
Schwesinger proton sponges, see bases and proton sponge
Science Citation Index, 1877, 1892, 1905
SciFinder, 1903
scoopy reaction, 1378
S_E1 mechanism, 0658, 0665
and decarboxylation, 0746
and the halogen dance, 0749
S_E2, see substitution
S_E2 mechanism, 0658
searching the literature, 1898
second order rate constants, 0320
second-order reactions, 0315, 0316
secondary isotope effects, 0325, 0326, 0327
in substitution reactions, 0488
secondary sources, literature, 1870, 1876–1881
S_Ei, see substitution
selectivity relationship, 0680
selectivity, and reduction, 1787–1790
bromine versus chlorine radicals, 0955
catalytic hydrogenation of alkenes, 1055
endo/exo, [2 + 2]-cycloaddition, 1226
facial, for reactions at carbonyls, 1252
facial, peroxyacid epoxidation of alkenes, 1170
homogeneous catalysts in hydrogenation, 1055
of nitrous acid, 0918
of radicals, 0951, 0952
paradoxical, in Friedel-Crafts alkylation, 0708
Selectride, and reduction of epoxides, 1791
diastereoselectivity of reduction, 1794
reduction of aldehydes or ketones, 1794
reduction of amides, 1842
reduction of tosylates, 1832
stereoselectivity of reduction, 1794
selenenyl chlorides, catalysts from radical chlorination, 0963
selenides, aryl, from aryl halides, 0552
aryl, from aryl halides, 0875
aryl, reduction with triaryltin hydride, 0991
catalysts from radical chlorination, 0963
cleavage, 0551
from alkyl halides, 0552
from selenol addition to alkenes, 1045
oxidation to selenones or selenoxides, 1782
selenium dioxide, allylic oxidation of alkenes, mechanism, 1752
and allylic oxidation, 1751, 1752
and dehydrogenation, 1712
α-oxidation of ketones, mechanism, 1760
and Sharpless method for allylic oxidation, 1752
selenium groups, and radical cyclization, 1127
selenium tetrafluoride, with aldehydes or ketones, 1299
selenium ylids, 0054
chiral, 1384
selenium, and aromatization, 1710
and carbonylation of amines, 0850
with Grignard reagents, 0818

seleno esters, and radical cyclization, 1129
from diselenides and acyl halides, 1412
selenoalkynes, hydration, 1036
selenoamides, 1297
and transamidation, 1426
selenocarbonates, 1275
selenoethers, see selenides
selenoketones, 0791
selenols (RSeH), addition to alkenes, 1045
and organolithium reagents, conjugate addition, 1131
by reaction of diselenides, 1854
selenones, by oxidation of selenides, 1782
selenoxides, alkylation, 0640
by oxidation of selenides, 1782
thermal elimination to alkenes, 1529
self-condensation, and Claisen condensation, 1453
self-consistent field theory (SCF), 0034, 0035
self-immolative reagents, 0171
semibullvalene, 1692
and Cope rearrangements, 1666
semicarbazide, with aldehydes or ketones, 1285
semicarbazones, and Wolf-Kishner reduction, 1836
from aldehydes or ketones, 1285
hydrolysis, 1264
reduction to amines, 1820
semidines, and [1,5]-sigmatropic rearrangements, 1681
semiempirical calculations, 0035
semipinacol rearrangement, 1586, 1587
semiquinones, radical ions, 0282
semirubin, and hydrogen bonding, 0113
sensitizers, triplet, 1136
SET mechanism, see mechanism
SET (single electron transfer) mechanism, 0443
mechanism, and active methylene compounds, 0626
mechanism, and arylation of enolate anions, 0908
mechanism, and chain reactions, 0444
mechanism, and conjugate addition of organometallics, 1120
mechanism, and electrophilic aromatic substitution, 0682
mechanism, and Grignard reagents, 1307
mechanism, and $LiAlH_4$ reduction of alkyl halides, 1828
mechanism, and oxidation-reduction, 1706
mechanism, and radicals, 0444
mechanism, and the aldol reaction, 1341
mechanism, organometallic compounds with alkyl halides, 0598
probes, 0268
process, and radicals, 0268
shape, an guest-host interactions, 0125
of cyclodextrins, 0130
Shapiro reaction, 1526
Sharpless asymmetric aminohydroxylation, 1180
Sharpless asymmetric dihydroxylation, 1166
Sharpless asymmetric epoxidation, 1177
Sharpless method, allylic oxidation with selenium dioxide, 1752
[1,5]-shifts, homodienyl, 1653
3, 2-shifts, and Wagner-Meerwein rearrangements, 1582
Shrock catalyst, for metathesis, 1683
shuttle, molecular, 0134
side chains, on aromatic compounds, oxidation, 1745
sigma orbitals, 0005
[1,3]-sigmatropic alkyl migration, 1653, 1654
[1,3]-sigmatropic rearrangement of carbon, vinylcyclopropanes, 1656
HOMO, 1650, 1651
imaginary transition state, 1649, 1650, 1651
migration of hydrogen, 1650, 1651
Möbius-Hückel method, 1650
photochemical, suprafacial, 1650, 1651
thermal, antarafacial, 1650, 1651
[1,5]-sigmatropic alkyl migration, 1653, 1654
and semidines, 1681
Möbius-Hückel method, 1650
of alkyl, 1656
of hydrogen, 1648
of hydrogen, and ene reactions, 1648
photochemical, antarafacial, 1650, 1651
thermal, suprafacial, 1650, 1651
[2,3]-sigmatropic rearrangement, 1676
Sommelet-Hauser rearrangement, 1678
[3, 3]-sigmatropic rearrangement, and amino cope rearrangement, 1660
and Fischer indole synthesis, 1675
Claisen rearrangement, 1668–1674
Cope, 1659–1667
enantioselectivity, 1663
of allyl vinyl ethers, 1655
oxy-Cope, 1660
[5,5]-sigmatropic rearrangement, and benzidine rearrangement, 1680
sigmatropic rearrangement, and σ-bond migration, 1647
and the [i,j] nomenclature, 1647
antarafacial rearrangement, 1648, 1649
definition, 1647
suprafacial migration, 1648, 1649
vinylcyclopropanes, 1656
[2,3]-, 0930
[2,3]-, and the Sommelet-Hauser rearrangement, 0930
sigmatropic shifts, and cyclopropanes, 1653
sila-Pummerer rearrangement, 1867
silanes, alkyl, radicals and hydrogen transfer, 0937
with radicals, 0937
silanes, allylic, and the Sakurai reaction, 1120

conjugate addition, 1120
coupling, 0977
coupling, with AIBN, 0589
electrolytic coupling, 0588
Lewis acid catalyzed addition to aldehydes, 1322
metal catalyzed addition to imines, 1388
metal catalyzed coupling with alcohols, 0616
metal mediated halogenation, 0963
radical coupling, 0589
with acetals, 0617
with aldehydes, 1388
with alkyl halides, 0588
with epoxides, 0589
silanes, and cleavage of ethers, 0581
and conjugate reduction, 1071
and enantioselective reduction, 1802
and formation of acylals, 1274
and radical cyclization, 1127
and the acyloin condensation, 1861
and the Brook rearrangement, 1701
aryl, and the Heck reaction, 0897
arylation, and Suzuki-Miyaura coupling, 0911
conjugate addition, 1131
cyclic, by addition of silanes to alkynes, 1087
desilylation, 1824
from metal catalyzed addition of silanes to alkenes, 1086
halo, with enolate anions, 0798
halogenation of, 0960
hydroxylation, 0539
intramolecular addition to alkynes, 1087
Lewis acid catalyzed addition to alkenes or alkynes, 1086
lithio, with aldehydes or ketones, 1365
magnesio, and Peterson alkenylation, 1366
metal catalyzed addition to alkenes, 1086
metal catalyzed arylation, 0911
metal catalyzed coupling, 0588
radical halogenation, 0960
reaction with hydroxide, 0251
reduction of aldehydes or ketones, 1798
reduction of amides to amines, 1841
reduction of carboxylic esters, 1807
reduction of imines, 1812
reduction to hydrocarbons, 1824
trihaloallyl, acyl addition, 1323
vinyl, addition to conjugated carbonyl compounds, 1088
vinyl, and Stille coupling, 0795
vinyl, and the Heck reaction, 0896
vinyl, by addition of silanes to alkynes, 1086
with alkynes, metal catalyzed, 0647
with aryl halides, metal catalyzed, 0911
with ketones, metal catalyzed, 0799
silica gel, addition of HCl to alkenes, 1029
and acetal cleavage, 0526
and aromatization, 1711
and ceric ammonium nitrate, 0686
and dehydration of oximes to nitriles, 1547
and formation of oximes, 1286
and iodination, 0704
and ring opening of aziridines, 0566
and sulfuric acid, 0695
and the Knoevenagel reaction, 1359
and thionyl chloride, 0576
and Vilsmeier-Haack reaction, 0725
and Wittig reaction, 1370
Claisen rearrangement, 1670
nitrosation of amines, 0847
with thionyl chloride, 1440
and double bonds, 0011
bond distance with carbon, 0023
silicon, and cis/trans isomers, 0011
silicon-tethered Heck reaction, 0895
silicon-tethers, and cyclotrimerization of alkynes, 1245
siloxanes, addition to enamines, 1088
silver carboxylates, and dihydroxylation of alkenes, 1165
silver compounds, and alkyl halides, 0505
and coupling of boranes, 0989
with peroxides, 0544
silver nitrate, and alkyl halides, 0505
with alkyl halides, 0571
and alkyl halides, 0505
silver perchlorate, reaction with iodocyclopentane, 0077
silver salts, with trimethylsilyl cyanide, and alkenes, 1148
silver, complex with ethylene, 0116, 0117
silyl alkenes, as a protecting group, 0979
silyl enol ethers, see enol ethers
silyl ethers, see ethers
silyl radicals, 1015
silyl-Wittig reaction, 1366
silylalkyl groups, as neighboring groups, 0467
silylalkylamines, 0559
silylamines, aryl, from aryl halides, metal catalyzed, 0911
with alkynes, metal mediated, 0647
silylated carbocations, 0248
silylazides, formation of azidoamines, 0566
silylcarbenes, 0286
silylenes, radical ions, 0282
silyloxy-Cope rearrangement, 1660
silylperoxides, with vinyllithium reagents, 0814
silylphosphines, with alkenes, 1051
silylthiols, addition to alkenes, 1044
Simmons-Smith procedure, 1241, 1242
and α-methylation of ketones, 1242
and carbenes, 1234
with diethylzinc, 1241
X-ray of intermediates, 1241

Simonini reaction, 0995, 0996
and the Hunsdiecker reaction, 0995
simultaneous addition, 0298
single electron transfer, see SET
singlet carbenes, 0284, 1238
singlet carbenes, see carbenes
singlet carbonyls, 1463
singlet methylene, 0289
singlet nitrenes, 0293, 1183
singlet nitrenium ions, 0295
singlet oxygen, and autoxidation, 0969
and diradicals, 0970
and hydroperoxides, 0969
and photosensitizers, 0969
and the ene reaction, 1104
cycloaddition reactions, 1218, 1219
Diels-Alder reaction, 1219
formation of dioxetanes, 1219
photooxygenation of alkenes, 1178
reagents for preparation, 0969
with alkenes, 0969, 0970
singlet radicals, 0278
singlets, in photochemistry, 0331
six-center mechanism, Cope rearrangement, 1663
small ring compounds, table, 0221, 0222
Smiles rearrangement, 0931, 0932
and Truce-Smiles rearrangement, 0933
S_Ni reactions, see substitution, S_Ni
S_N' reactions, see substitution, S_N'
S_N1 reactions, see substitution, S_N1
S_N1' reactions, see substitution, S_N1'
S_N12cA mechanism, 0580
S_N1cB mechanism, 0521
S_N1cB mechanisms, 0567
S_N2 reactions, see substitution, S_N2
S_N2' reactions, see substitution, S_N2'
S_N2(intermediate) reactions, see substitution
S_N2cA mechanism, 0580
S_NAr mechanism, 0854–0857
Sneen formulation, 0441
Sneen's ion-pair mechanism, 0764
snoutane, 1691
sodium amide, also see amides
sodium amide, and the Haller Bauer reaction, 0844
rearrangement of alkynes, 0769
sodium azide, and potassium iodide, 1159
formation of azido-ketones, 0573
sodium bisulfite, reaction with aldehydes or ketones, 1281
sodium borohydride, also see borohydride
and decyanation, 0846
and *in situ* hydrogenation, 1057
and isoquinolines, 0716
and nickel, hydrogenation, 1054
and oxymercuration, 1033
and radicals, 0812
and reduction of alkynes, 1064
and the Pictet-Spengler reaction, 0716
reduction of conjugated alkenes, 1070
reduction of imine nitrates, 1459
reduction of organometallics, 0812
with metal compounds, reduction of alkenes, 1065
with nitriles, 0846
sodium borohydride-metal salts, reduction of conjugated alkenes, 1070
sodium bromite, with amines, 0849
sodium cyanide, and Rosenmund-von Braun reaction, 0885
in HMPA, 0649
with Lewis acids, 0649
sodium cyanoborohydride, and reduction of alkyl halides, 1827
and reduction of conjugated alkenes, 1070
sodium hydride, and hydrogen peroxides, with boranes, 1079
with lactams, 0569
sodium hydroxide, and the Cannizzaro reaction, 1863
sodium hypochlorite, see hypochlorites
sodium hypochlorite, and epoxidation of alkenes, 1177
and Jacobsen-Katsuki epoxidation, 1178
sodium iodide, see iodide
sodium ions, and crown ethers, 0123
sodium nitrate, and epoxides, 0565
sodium nitriles, with alkenes, formation of alkynes, 1533
sodium nitrite with acid, 0846, 0847
with alkyl halides, 0571
with aryl diazonium salts, 0985
sodium nitrocyanamide, 0573
sodium perborate, and hydroxylation of aromatic compounds, 0734
sodium peroxide, and hydroperoxide formation, 0544
sodium persulfate, and dimerization of carboxylate salts, 0994
sodium sulfhydride, see sulfhydride
sodium tetracarbonylferrate (Collman's reagent), 0650
carbonylation of alkyl halides, 0653
with alkyl halides, 0650
sodium, and decyanation, 0845
and formation of acyloins, 1860
and formation of enolate anions, 0811, 0907, 0908
and reductive coupling of esters, 1860
and the Wurtz-Fittig reaction or Wurtz coupling, 0589
coupling of alkyl halides, 0589
in ammonia, and Birch reduction, 1067
in ammonia, reduction of alkynes, 1064
in ammonia, reduction of allenes, 1065
in ammonia, reduction of aromatic compounds, 1067
in ammonia, reduction of quaternary salts, 1844
in ammonia, with cyclopropanes, 1075

in ethanol, and reduction of aldehydes or ketones, 1795
in ethanol, and reduction of imines, 1811
in ethanol, reduction of carbonyls, mechanism, 1795, 1796
sodium-amalgam, Gomberg-Bachmann pinacol synthesis, 1854
reduction of quaternary ammonium salts, 1844, 1845
soft acids, and covalent bonds, 0378
definition, 0377
soft bases, and covalent bonds, 0378
definition, 0377
softness, and Lewis acids, 0377
solid-phase, anhydride formation, 1422
Fischer indole synthesis, 1675
synthesis, 1433, 1434
and Grignard reactions, 1300
solid-state amide bases, and the aldol reaction, 1342
and Diels Alder reactions, 1198
solubility, and cyclodextrins, 0129
and hydrogen bonding, 0111
solvation rule, S_N2 reactions, 0503
and cryptands, 0493
and nucleophilicity, 0491, 0492
and rate of reaction, 0493
by leaving groups, 0759
differential, 0097
of radicals, 0937
solvent acidity, and activity of proton, 0370–0372
solvent acidity, and pH, 0369
solvent cages, and radicals, 0444
and rearrangement of N-nitroaniline, 0739
and the Wittig rearrangement, 1624
in the Stevens rearrangement, 1622
solvent effects, and acidity, 0392–0394
and addition of bromine with alkenes, 1016
and ambident nucleophiles, 0517
and basicity, 0392–0394
and carbenes, 0288, 0289
and carboxylic ester formation, 0539
and catalytic hydrogenation, 1055
and charged nucleophiles, 0503
and E1 versus E2 reactions, 1506
and electrophilic substitution, 0765
and elimination versus substitution, 1506
and fluorination of alkenes, 1149
and gauche conformations, 0201
and Grunwald-Winstein equation, 0505
and Lewis acids, 0392–0394
and limiting S_N1, 0433
and rate of reactions, 0503
and reactions, 1496
and S_N2 reactions, 0430, 0503
and S_NAr reactions, 0856
and $S_{RN}1$ reactions, 0863
and substitution reactions, 0504
and the aldol reaction, 1342
and the Gabriel synthesis, 0569
and unsymmetrical metal mediated coupling, 0593
aryl halides with sulfur nucleophiles, 0874
on the base, in elimination reactions, 1504
selectivity in the Diels-Alder reaction, 1202
solvent acidity, and free energy, 0371
solvent effects, and free energy, 0505
radicals, and reactivity, 0952
Wittig reaction, 1377
solvent free, see solventless
solvent isotope effects, 0327
solvent nucleophilicity, scale, 0506
solvent polarity, and electrophilic substitution, 0757
and S_N1 reactions, 0501
and transition states, 0501, 0502
solvent separated ion pairs, 0440
solventless, 0416
addition of organometallics to aldehydes or ketones, 1309
and Diels Alder reactions, 1198
Baeyer-Villiger rearrangement, 1618
Beckmann rearrangement, 1614
dehydration of oximes to nitriles, 1547
formation of cyanohydrins from trimethylsilyl cyanide, 1390
Heck reaction, 0894
Henry reaction, 1357
hydrolysis of C=N compounds, 1264
iodination, 0704
Knoevenagel reaction, 1359
oxidation of thiols to disulfides, 1785
Robinson annulation, 1350
Sonogashira coupling, 0904, 0905
sulfur ylid reaction, 1383
Suzuki-Miyaura, 0900, 0901
[2 + 2]-cycloaddition, 1223
solvents, acidity, 0369
solvents, sulfur dioxide, 0434
solvent effects, radicals, and reactivity, 0952
Wittig reaction, 1377
solvents, achiral, CD of chiral molecules, 0163
solvents, acidic, 0369, 0370
and acid strength, 0364
and base strength, 0365
and Hammett acidity function, 0369
and keto-enol tautomerism, 0773
and nucleophilic assistance, 0506
and nucleophilicity, 0491, 0504
and proton transfer, 0368
and rate of reaction, 0504
and sonochemistry, 0351
aprotic, 0502
aromatic, complex formation and radicals, reactivity, 0953
asymmetric, and synthesis, 0171
basic, 0370
chiral, and NMR, 0181

solvents, acidic, (*Continued*)
dielectric screening effects, 0503
effect on ion pairs, 0236
ethanolamines, 0563
ether, and Grignard reagents, 0260, 0261, 1301
ether, and hydroboration, 1075
for enolate alkylation, 0627, 0628
for Michael addition, 1107
in cyanide-alkyl halide reactions, 0648
induced chirality, 0163
ionic, 0415, 0416
ionic, aryl halides with phenoxides, 0872
ionizing power, 0506
nonpolar, and reactivity, 0412
polar and nonpolar, 0412
polar, and phase transfer catalysis, 0509
polar, and reactivity, 0412
protic, 0502
protic verses aprotic, and S_N2 reactions, 0503
supercritical ammonia, 0415
supercritical carbon dioxide, 0414, 0508
UV of charge transfer complex, 0507
water, 0414
solvolysis, alkyl halides, and carbocations, 0325
alkyl tosylates, rate of reaction, 0482
and alkene neighboring groups, 0451
and aromatic ring participation, 0455, 0456
and B strain, 0398
and borderline mechanisms, 0442
and brosylates, 0438
and cyclobutyl compounds, 0464
and cyclopropyl groups, 0486, 0487
and cyclopropylmethyl groups, 0464, 0465
and destabilizing groups, 0484
and dioxane, 0443
and Grunwald-Winstein equation, 0482
and I strain, 0399, 0487
and inversion, 0443
and ionizing power of solvents, 0506
and mechanism, 0437
and methyl group participation, 0466
and neighboring group mechanisms, 0448
and neighboring groups, 0449, 0454, 0456, 0457
and nonclassical carbocations, 0452, 0453
and norbornyl systems, 0460
and oxonium ions, 0443
and phenonium ions, 0458
and picosecond absorption spectroscopy, 0439
and racemization, 0439
and rate enhancement, 0464, 0465
and rate of reaction, 0458
and rearrangement, 0466
and σ-bond participation, 0460
and silylalkyl group participation, 0467
and special salt effects, 0439
and stereochemistry, 0460
and structural effects, 0481
and substitution, 0425
and sulfonate esters, 0443
benzylic halides, 0486
of esters, and NMR, 0434
of iodocyclopentane, 0077
of sulfonate esters, 0467
optically active compounds, 0460
participation of hydrogen, 0467
rate, and azide ions, 0442
rates for alkyl bromides, 0480
Sommelet reaction, oxidation of alkyl halides to aldehydes, 1766
Sommelet-Hauser rearrangement, 0929, 1623
and Hofmann elimination, 0929
and Stevens rearrangement, 0929, 1623
mechanism, 0929
[2,3]-sigmatropic rearrangement, 1678
$S_{ON}2$ mechanism, 0872
Sonn-Müller method, from amides, 1815
sonochemical, $S_{RN}1$ reactions, 0352
sonochemistry, also see cavitation
sonochemistry, 0349
and arylation reactions, 0352
and carbene formation, 0351
and carbohydrates, 0352
and cavitation, 0349
and colloids, 0350
and emission of light, 0350
and gas vacuoles, 0249, 0350
and hot spots, 0350
and hydrostannation, 0352
and nucleophilic aromatic substitution, 0352
and organic solvents, 0351
and organolithium formation, 0351
and sonoluminescence, 0350
and the Diels-Alder reaction, 0352
and the Reformatsky reaction, 0352
and the Weissler reaction, 0351
commercial instruments, 0351
origin of, 0349
reproducibility, 0351
with metal carbonyls, 0352
Sonogashira coupling, 03540904, 0905
sonoluminescence, 0350
Sorenson method, amino acid synthesis, 0624
Source Index, 1907
Soxhlet extractor, and the aldol reaction, 1343
sp hybridization, 0009, 0010
sp orbitals, 0007
sp^2 or sp^3 hybrid orbitals, 0008, 0009
sparteine, and addition of organolithium reagents to alkenes, 1097
and Michael addition, 1108
enantioselectivity with organolithium compounds, 0595
with organolithium reagents, 1330
special salt effects, and solvolysis, 0439
specific acid catalysis, 0373
specific rotation, also see enantiomers, chiral compounds
specific rotation, and concentration, 0139
and enantiomeric excess, 0180
and enantiomers, 0139

and molar rotation, 0139, 0160
and temperature, 0139
and wavelength of light, 0140, 0160
aspartic acid, 0139
definition, 0139
spectra, Aldrich Library, 1888
spectra, Sadtler Research Laboratories, 1888
spectrophotometer, definition, 0329
spectrophotometric measurements, and solvent acidity, 0369
spectroscopic analysis, radicals, 0266
spectroscopy, and bond distance, 0022
and cyclic allenes, 0228
and kinetics, 0319
deuterium quadrupole echo, 0127
diradicals in the Paterno-Büchi reaction, 1463
IUPAC classification, 0012
of carbanions, 0252
photoelectron, 0012
spectrum, electromagnetic, 0329
spectrum, electronic, 0330
spherands, 0122
spherical homoaromaticity, 0094
Sphingomonas pauchimobilis, and resolution, 0179
Sphingomonas sp HXN-200, α-hydroxylation, 1757
spin forbidden transitions, 0331
spin trapping, and carbenes, 0285
and radicals, 0267
spin traps, 0268
spin-conservation, Wigner rule, 0340
spiranes, and chirality, 0149, 0150
spirocycles, cyclization of enynes, 1093
spirocyclic amides, 0695
spirooxathianes, and tautomerism, 0104
spiropentanes, by carbene addition, 1236
sponge, proton, see proton sponge
spontaneous reactions, and free energy, 0299
squalene 2,3-oxide, and steroids, 1090
squaric acid, 0057
squaric acid, dianion and aromaticity, 0092
squaric acid, pK_a, 0092
σρ relationships, and radical reactions, 0412
$S_{RN}1$ mechanism, 0550, 0862
$S_{RN}1$ reactions, see substitution
stability, alkynyl carbocations, 0477
and antiaromaticity, 0074
carbanion, 0251
conformational, see conformation
diazonium salt, 0917
keto-enol tautomerism, 0099
norbornyl carbocations, 0463
of arenium ions, 0663
of carbanions, 0250, 0252
of carbocations, 0243
of phenonium ions, 0458
of radicals, 0270, 0272, 0273
of radicals, substituents effects, 0948
open versus bridged carbocations, 1003
π-complexes, 0663, 0664
stabilization, of carbanions, 0256
stabilomers, 1584
starands, 0124
state, transition, see transition state
statistical effects, and acidity, 0384
Staudinger reaction, 1822
steady state, and kinetics, 0317
Stephen reduction, 1815
Stephens-Castro coupling, 0903–0906
stereochemistry, and addition to cyclopropanes, 1026
and bridged radicals, 0942
and Criegee mechanism of ozonolysis, 1741
and electrophilic addition, 1001
and electrophilic substitution, 0755, 0756
and epoxidation of cyclic alkenes, 1023
and epoxide halogenation, 0583
and lactone alkylation, 0627
and mechanism, 0314
and neighboring group mechanisms, 0447
and solvolysis, 0460
and substitution at vinyl carbon, 0475
and the S_E2 mechanism, 0754
and the S_Ei mechanism, 0754
at vinylic carbons in S_E1 reactions, 0761
in halogenation of alkenes, 1149
in the Cope rearrangement, 1663
in the Diels-Alder reaction, 1200, 1201
in the Stevens rearrangement, 1623
ion pairs and internal return, 0439
of addition to alkenes, 1023, 1024
of alkyl migrating groups in sigmatropic migrations, 1655
of carbanions, solvent effects, 0759
of carbocations, 0245
of cyclopropyl ring opening in solvolysis, 0487
of E1 reactions, 1502
of E2 reactions, 1485, 1501, 1502
of E^i reactions, 1508
of electrocyclic rearrangements, 1633
of migrating group, in rearrangement, 1563, 1564, 1567
of migrating group, in the Stevens rearrangement, 1623
of S_E2 reactions, 0757
of S_Ei reactions, 0757
of S_N1 reactions at vinylic carbon, 0476
of S_N2' reactions, 0471
organocuprates with alkyl halides, 0601
in [2 + 2]-cycloaddition, 1226
stereocontrol, in radical reactions, 1127
stereoelectronic control, tetrahedral mechanism, 1258
stereoelectronic effects, and radicals, 0949
stereogenic atoms, also see chiral

stereogenic atoms, absolute configuration, 0154
and diastereomers, 0164
and Fischer projections, 0153
and molar rotation, 0160
and monocyclic compounds, 0186
and optical activity, 0140
and pyramidal inversion, 0142, 0143, 0144
and specific rotation, 0160
and symmetry, 0141
and the S_N2 reaction, 0159
Cahn-Ingold-Prelog system, 0155–0158
chemical reactions, 0158
creation of, 0153
D/L nomenclature, 0155
multiple centers, 0164
NMR and absolute configuration, 0160
phosphorus, 0191
quadrivalent, 0141
R/S nomenclature, 0155–0158
tervalent, 0142
stereogenic center, also see stereogenic atom
stereogenic centers, α to a carbonyl, 0774
and glyceraldehyde, 0154
by reduction of prochiral ketones, 1799
formed by Michael reaction, 1108
stereoisomerism, 0136
stereoisomers, meso compounds, 0187
out-in, 0189
radicals, 0272
topological, and catenanes, 0133
stereoselective synthesis, 0167, 0194, 0195
stereoselective synthesis, see synthesis
stereoselectivity, and 9-BBN, 1077
in addition of bromine to alkenes, 1003
in hydrogenation of alkynes, 1058
in Michael reactions, 1108
in nucleophilic substitution at sulfonyl sulfur, 1470
in radical addition to alkenes, 1012
in radical hydrogen abstraction, 0949
in reduction with Selectride, 1794
in the aldol reaction, 1345, 1346
in the Stille coupling, 0793
in the Wittig-Horner reaction, 1376
in [2 + 2]-cycloaddition, 1227
stereospecific synthesis, 0194, 0195
stereospecificity, in the Diels-Alder reaction, 1206
in the E2 reaction, 1479
in the Heck reaction, 0895
in the Wittig rearrangement, 1625
steric acceleration, and the ene reaction, 1104
steric crowding, and pentahelicene, 0149
steric effects, and acidity, 0385
and ambident nucleophiles, 0517
and basicity, 0385
and bond energy, 0029
and borane addition to alkenes, 1077
and catalytic hydrogenation, 1056
and Lewis acids/bases, 0385
and reactivity, 0397
and resonance, 0048
and the Taft equation, 0410, 0411
base cleavage of ketones, 0843
electrophilic aromatic substitution, 0679
in radical addition reactions, 1020
in [2 + 2]-cycloaddition, 1226
steric hindrance, and carbene addition to alkenes, 1235
steric hindrance, and conformations, 0202
and enol content, 0100
and esterification, 1416
and high pressure, 0513
and hydrolysis of esters, 1401
and nucleophiles, 0493
and propeller carbocations, 0246
and reactivity of alkyl halides, 0398
cis/trans isomers, 0186
esterification of carboxylic acids, 0398
in nitriles, and the Ritter reaction, 1459
steric inhibition, of resonance, 0691
steric interactions, and pyrolytic elimination, 1511
steric strain, see strain
steric strain, and stereoselectivity n hydrogenation of alkynes, 1058
steroids, and catalytic hydrogenation, 1056
and conformational transmission, 0401
and dammaradienol, 1090
and Johnson polyene cyclization, 1090
and rate of reaction, 0400
and remote dehydrogenation, 1713, 1714
and Robinson annulation, 1350
and the Barton reaction, 1696
and the Stork-Eschenmoser hypothesis, 1090
biosynthesis, 1089
radical halogenation, 0958
Stetter reaction, 1136, 1321
Stevens rearrangement, 0929, 1621–1623
and Hofmann elimination, 1623
and Sommelet-Hauser rearrangement, 0929, 1623
and sulfur ylids, 1623
radical versus ion pairs, 1622
stereochemistry of the migration group, 1623
suitable bases, 1621
stibines, triaryl, metal catalyzed coupling with alkynes, 0906
Stieglitz rearrangement, 1616
with hydroxylamines, 1617
stilbenes, photochemical conversion to phenanthrenes, 1645
Stille coupling, 0606, 0792–0795
and alkylboronic acids, 0794
and allylic rearrangement, 0793
and cine substitution, 0793
and metal catalyzed carbonylation, 1141
with enols, 0794
Stlile coupling, and microwaves, 0793

STN, 1877, 1902
Stobbe condensation, 1356
Stone-Wales rearrangement, 1646
stoppers, in rotaxanes, 0134
Stork enamine reaction, 0632, 0634–0636
 and hydrolysis of iminium ions, 1266
Stork-Eschenmoser hypothesis, 1090
Story synthesis, 1557
strain energy, see energy
strain energy, and fused ring aromatic compounds, 0052
strain,
 and addition to alkenes, 0400
 and annelation, 0052
 and base cleavage of ketones, 0843
 and carbanion stability, 0254
 and carbocation formation, 0398
 and conformation, 0400
 and crowded alkenes, 0233
 and cubene, 0233
 and cyclobutadienes, 0076
 and dioxiranes, 0218
 and E2 reactions, 0400
 and electrophilic aromatic substitution, 0677
 and epoxides, 0218
 and formal steric enthalpy, 0232
 and fused ring aromatic compounds, 0052
 and geared molecules, 0231
 and hexahelicene, 0232
 and homocubene, 0233
 and leaving groups, 0496
 and MO calculations, 0218
 and molecular mechanics, 0214
 and nonbonded atoms, 0216
 and nonbonded interactions, 0216
 and PES, 0224
 and radicals, 0943
 and resonance, 0048
 and ring size, 0225
 and s character, 0218
 and S_N1 reactions, 0488
 and S_N1 reactions of alkyl halides, 0398
 and substituted aromatic compounds, 0230, 0231
 and tricyclododecadiene, 0233
 and unsaturated rings, 0226
 and X-ray diffraction, 0224
 B strain, and rate of ionization, 0398
 B strain, and S_N1 rate of reaction, 0481
 B strain, and solvolysis of alkyl halides, 0398
 carbene addition and ring expansion, 1240
 cyclopropane, 0217
 due to unavoidable crowding, 0230, 0231
 I strain, and acyl addition, 0400
 I strain, and cyclic ketones, 0400
 I strain, and hydrate formation, 1262
 I strain, and reactivity, 0399
 I strain, and solvolysis, 0399, 0487
 in ethylene oxide, 0217
 in hydrocarbons and other compounds, 0218–0229
 in small rings, 0217
 intramolecular crowding, 0232
 large angle, 0224
 Pitzer, 0223, 0224
 small ring compounds, table, 0221, 0222
 small-angle, 0216
 steric, 0216–0225
 transannular, 0223, 0224
 unavoidable, 0206
strained compounds, [2 + 2]-cycloaddition, 1224
strained molecules, and bond angle, 0026
Strecker synthesis, 1391
structural effects, and solvolysis, 0481
structure, acid-base strength, 0380
 and reactivity, 0395
 Grignard reagents, 0260, 0261
 Lewis, see Lewis structures
 organometallic compounds, 0259
 substrate and S_NAr reactions, 0864
strychnine, and resolution, 0173
Stryker's reagent, and Robinson annulation, 1351
sublimation, and resolution, 0176
β-substituents, and substitution reactions, 0485
substituent effects, and acidity, 0380
 and field effects, 0483
 and Hammett σρ relationships, 0486
 and mechanism of the Diels-Alder reaction, 1207
 and radicals, 0948
 and resonance effects, 0483
 and S_N1 reactions, 0480, 0483
 and the tetrahedral mechanism, 0486
 β- and γ-substituents, 0485
 electron donating and electron withdrawing groups, 0485
 enolate anion formation, 0774
 of alkyl halides, in E2 reactions, 1504
 S_N1 on vinylic carbon, 0482
 S_N2 reactions, 0478
substitution reactions, and entropy of activation, 0446
 and pressure, 0442
 and solvent effects, 0504
 β-substituent and γ-substituent effects, 0485
 in supercritical carbon dioxide, 0508
 IUPAC mechanism, 0496
 IUPAC nomenclature, 0419
 leaving group ability, table, 0501
 leaving group effects, 0496
 secondary isotope effects, 0488
substitution, aliphatic, 0425
substitution, and alkylation, 0425
 and allylic substrates, 0482
 and benzylic substrates, 0482
 and borderline mechanisms, 0442
 and carbenes, 0292
 and E1 reactions, 1487
 and solvolysis, 0425
 and the SET mechanism, 0481
 and the Sneen formulation, 0441
substitution, aromatic, and aromaticity, 0072
 and hyperconjugation, 0670
 and metallocenes, 0066
 and tropolones, 0065
 annulenes, 0081
 Baker-Nathan order, 0670
 destabilizing groups, 0669, 0673
 halogenation, 0698

substitution, aromatic, and aromaticity, (*Continued*)
meta directing, 0669, 0673
of annulenes, 0084
of azulene, 0068
ortho-para directing, 0669, 0673
stabilizing groups, 0668, 0673
substitution, at acyl carbon, 0482
at vinylic carbon, 0475
bimolecular, see S_N2
cine, and Stille coupling, 0793
substitution, electrophilic, 0297, 0298
substitution, electrophilic aromatic, activation hardness, 0679
alternant hydrocarbons, 0676
amination, see amination
and arenium ions, 0658, 0659
and bond length, 0677
and diazonium ions, 0691
and EPR, 0677
and ferrocene, 0674
and hydrogen exchange, 0684
and ionic liquids, 0688
and neighboring groups, 0457
and nitronium ion leaving groups, 0683
and π-complexes, 0662
and phenonium ions, 0459
and radicals, 0682
and SET mechanism, 0682
and strain, 0677
and sulfones, 0697
and sulfoxides, 0697
and the Hammett equation, 0679
and the Mills -Nixon effect, 0677
and the Schiemann reaction, 0705
benzoylation, 0680
bromination, 0680
Brown σ* values, 0679
chlorination, 0680
encounter complex, 0682
Friedel-Crafts alkylation, 0705
halogenation, metal catalyzed, 0699
Hammett σ values, 0679
in fused rings, 0674
ipso attack, 0671, 0679
ipso position, 0672
isomer distributions, 0678
isopropylation, 0680
leaving groups and leaving group ability, 0683
mercuration, 0680
nitration, 0680, 0690
nitration, also see nitration
of azo compounds, 0691
of heterocycles, 0675
of naphthalenes, 0676
orientation, 0665
ortho effect, 0674
ortho-para ratio, 0670, 0673
partial rate factor, 0677
rate, 0671, 0677
reactivity of substrates, 0679
relative rate ratios, 0682
selectivity relationship, 0680
steric effects, 0679
sulfonation, see sulfonation
with nitronium ions, 0672
with sulfur electrophiles, 0695
substitution, electrophilic, unimolecular, see substitution, S_E1
substitution, electrophilic, addition-elimination mechanism, 0763
and allylic carbanions, 0762
and bridgehead carbons, 0755
and double bond shifts, 0761
and organometallics, 0756
and solvent polarity, 0757
and stereochemistry, 0755, 0756
cyclic mechanisms, 0763
electron donor-acceptor complexes, 0757
rate, and salt effects, 0757
solvent effects, 0765
substrate effects, 0763
substitution, first order reactions, 0433
substitution, free radical, 0298
substitution, nucleophilic, 0297
substitution, nucleophilic aromatic, and leaving groups, 0868
and Meisenheimer salts, 0854
and S_N1 reactions, 0857
and S_NAr reactions, 0854–0857
and $S_{ON}2$ reactions, 0872
and sonochemistry, 0352
and the Chapman rearrangement, 1698
benzyne mechanism, 0859–062
cine substitution, 0860
mechanism, 0853
nucleophiles, 0869
one-stage versus two-stage, 0863
other mechanisms, 0863
photochemical, 0863
substrate structure, 0864
with arynes, and substrate structure, 0867
substitution, nucleophilic internal, see substitution, S_Ni
substitution, nucleophilic, and alkynyl carbon, 0481
and aryl substrates, 0481
and leaving groups, 0482
and phase transfer catalysis, 0511
and vinylic carbon, 0473, 0481
at sulfonyl sulfur, 1470
at vinyl carbon, and the element effect, 0475
with allylic substitution, 0469
substitution, radical, mechanism, 0938, 0939
substitution, reactions, and HSAB, 0516
substitution, S_E1, 0665
and organometallics, 0765
and pyramidal carbanions, 0758
and resonance, 0759
and vinylic carbons, 0761
first order kinetics, 0758
leaving group effects, 0764
mechanism, 0758
solvent effects, 0765
substrate effects, 0763
substitution, S_E2', 0754, 0762
substitution, S_E2, and stereochemistry, 0754, 0757
mechanism, 0753
solvent effects, 0765
substrate effects, 0763
substitution, S_Ei', 0762
and stereochemistry, 0754, 0757
mechanism, 0753, 0754
solvent effects, 0765
substitution, S_N', 0471
substitution, S_Ni, and retention of configuration, 0468
halogenation of alcohols, 0580
IUPAC nomenclature, 0468
mechanism, 0468

substitution, $S_N i'$, 0472
and ion pairs, 0472
substitution, $S_N 1$, and alcohol dehydration, 0534
and alkyl halides in sulfur dioxide, 0434
and allylic substrates, 0483
and ambident substrates, 0518
and aryldiazonium salts, 0857
and aryliodonium salts, 0857
and bicyclic compounds, 0435
and bridgehead carbons, 0435
and carbocations, 0432, 0435
and conjugating substituents, 0436
and contact ion pairs, 0437
and cubyl compounds, 0436
and diazonium salts, 0499
and electrophilic addition, 1000
and electrophilicity, 0432
and equilibria, 0437
and I strain, 0399
and internal return, 0437
and intimate ion pairs, 0437
and ion pairs, 0438
and ionic strength, 0434
and ionization, 0432
and leaving groups, 0432
and limiting $S_N 1$, 0433
and lithium perchlorate, 0504
and mixed $S_N 2$, 0440, 0441
and MO calculations, 0487
and norbornyl compounds, 0436
and nucleophiles, 0490
and partial retention, 0440, 0441
and pseudo first-order, 0434
and racemization, 0437
and rate of reaction, 0433, 0480
and rearrangement, 1564
and salt effects, 0504
and $S_N 2$ reactions, 0434
and solvent polarity, 0501
and solvents, 0433
and special salt effects, 0439
and stereochemistry, 0439
and strain, 0488
and substituent effects, 0480, 0483, 0485
and the Baker-Nathan order, 0486
and the ion pair mechanism, 0441
and tight ion pairs, 0437
aromatic compounds, and isotope labeling, 0859
at vinylic carbon, 0482
at vinylic carbon, groups, 0476
at vinylic carbon, substituent effects, 0482
carboxylate salt alkylation, 0540
formation of nitrite esters, 0571
halogenation of alcohols, 0580
kinetics and leaving groups, 0433
mechanism, 0432
mechanism with alkyl halides, 0398
mechanism, and ion pairs, 0436
nucleophilic aromatic, 0857
primary halides and metal ions, 0505
rate of reaction, and B strain, 0481
reactivity of groups, 0488
stereochemistry at vinylic carbon, 0476
transition states, 0502
trichloroamine with alkenes, 0567
with allylic rearrangement, 0469
substitution, $S_N 1'$, 0469
and ion pairs, 0470
IUPAC nomenclature, 0469
substitution, $S_N 2$ (intermediate), 0442
substitution, $S_N 2$, *ab initio* study, 0430
and alcohol dehydration, 0534
and alkylation of carboxylate salts, 0539
and anchimeric assistance, 0446
and aziridine formation, 0560
and backside attack, 0426
and Brønsted plots, 0431
and chlorination of malic acid, 0427
and crossover experiments, 0430
and formation of alkyl halides, 0574
and free energy, 0431
and Friedel-Crafts alkylation, 0712
and high pressure mass spectrometry, 0429
and hybridization, 0426
and inversion, 0428
and ion-dipole complexes, 0430
and isotope effects, 0326
and Marcus theory, 0310
and mixed $S_N 1$, 0440, 0441
and neighboring groups, 0446
and nucleophiles, 0490
and propellanes, 0487
and racemization, 0429
and rate of reaction, 0427, 0478, 0479, 0483
and retention, 0428
and solvent effects, 0430
and substituent effects, 0478
and the Baker-Nathan order, 0486
and the Darzens reaction, 1364
and the Finkelstein reaction, 0574
and the Hammond postulate, 0308
and the ion pair mechanism, 0441
and the Mentshutkin reaction, 0430
and transition state geometry, 0483
and Walden inversion, 0427
at bridgehead carbons, 0429, 0487
at stereogenic atoms, 0159
gas phase, 0429
halogenation of alcohols, 0580
intramolecular, 0430
mechanism, 0426
microsolvation of transition state, 0503
nucleophilicity order, 0493
protic versus aprotic solvents, 0503
pseudo first-order kinetics, 0427
rate of reaction, 0479
reactivity of groups, 0488
$S_N 2$ versus $S_N 2'$, 0471
solvation rule, 0503
solvent effects, 0503
solvolysis of benzylic halides, 0486
synthetic reactions, 0489
tight transition state, 0485
transition state, 0430, 0479, 0502

substitution, S_N2, *ab initio* study, (*Continued*)
transition state, and neopentyls systems, 0755
Williamson reaction, 0529
with active methylene compounds, 0626
with ambident substrates, 0518
with bicyclic compounds, 0487
with carboxylic esters, 0501
with epoxides with organometallics, 0618
with neopentyl systems, 0479, 0755
with sulfonyl halides, 0546
substitution, S_N2', 0470
and concerted reactions, 0471
and cyclopropylcarbinyl halides, 0473
and organocuprates, 0473
formation of cyclic amines, 0557
S_N2 versus S_N2', 0471
stereochemistry, 0471
with organocuprates, 0620
with vinyl epoxides, 0620
substitution, S_NAr, activating ability of attached groups, 0865–0866
and ion-radical pairs, 0857
and Meisnhemier salts, 0855
and π-complexes, 0857
and solvent effects, 0856
dimer mechanism, 0857
effect of substrate structure, 0864
Hammett relationships, 0867
mechanism, 0854–0857
partitioning effects, 0856
rate of reactions, 0865
substitution, $S_{RN}1$, and aryl halides, 0862
and arylation of enolate anions, 0908
and nucleophilicity, 0869
and potassium metal, 0863
and radical anions, 0863
and sonochemistry, 0352
and ultrasound, 0863
and vinylic halides, 0478
mechanism, 0862
mechanism, and radicals, 0862, 0863
solvent effects, 0863
substitution, versus elimination, 1503–1506
substitution, vicarious, and amination of heterocycles, 0916
nucleophilic substitution of hydrogen, 0915
substrate, and electrophilic substitution, 0763
substrates, ambident, allylic compounds, 0518
and cyclic sulfates, 0518
and S_N1 reactions, 0518
aziridines, 0518
definition, 0517
epoxides, 0518
S_N2 reactions, 0518
thiiranes, 0518
substrates, definition, 0296
substrates, for Mukaiyama aldol, 1352
succinates, and the Stobbe condensation, 1356
succinimide, from NBS, 0962
succinimidyl radical, 0963
sugars, aldehyde form, 0104
and tautomerism, 0104
sulfamate esters, and amination, 0789
sulfates, alkyl, and formation of aldehydes, 1034
formation of ethers, 0532
with alkoxides, 0532
with halides ions, 0576
sulfates, cyclic, and ambident sulfates, 0518
from diols, 0518
sulfenates, formation of, 0791
sulfene intermediates, 1471
sulfenes, by base induced elimination of sulfonyl halides, 1532
from sulfonyl halides and amines, 1471
sulfenic acids, and Smiles rearrangement, 0932
sulfenylation, 0791, 0792
sulfhydride, sodium, with alkyl halides, 0548
sulfide, dimethyl, and alkyl halides, 0520
and borane, 0816
sulfides, see thioethers
sulfilimines, vinyl in Diels-Alder reactions, 1218
sulfimides, diaryl, and formation of aziridines, 1183
sulfinate esters, also see esters
sulfinate esters, and deoxygenation of diols, 1535
from alcohols, 0554
from sulfinyl chlorides, 0554
sulfinic esters, alkylation, 0640
sulfinyl halides, see halides
sulfite, sodium, reduction of diazonium salts, mechanism, 1823
sulfolene, heating, and the Diels-Alder reaction, 1204, 1205
sulfonamides, alkylation of, 0570
and the Hinsberg test, 1474
arylation of, 0569
by reduction of sulfonyl azides, 1822, 1823
dealkylation, 1852
from sulfonyl halides and ammonia or amines, 1474, 1475
hydrolysis, 1472
metal catalyzed arylation, 0569
reduction to amines, 1844
with alcohols, 1473
with alkenes, 1051
with alkyl halides, 0570
sulfonate esters, and Mitsunobu reaction, 0546
and solvolysis, 0443
and Sonogashira coupling, 0905
aryl, metal catalyzed coupling to aryl triflates, 0902
aryl, with trifluoroborates, 0890
as leaving groups, 0497, 0498
coupling with Grignard reagents, 0590
cyanation, 0886
decomposition to alkenes, 1521
from alcohol, and reduction, 1830
from alcohols, 0545
from alkyl halides, 0546
from ethers, 0546
from sulfonamides and alcohols, 1473
from sulfonic acids, 0546
from sulfonyl halides, 0546, 1473
mechanism of formation, 0546
migration, 1604
of phenols, and reduction, 1831
organometallic coupling, metal catalyzed, 0606
rate of ionization, 0504
reagents for preparation, 0546

reduction to methyl compounds, reagents for, 1832
solvolysis, 0467
vinyl, and Stille coupling, 0792
vinyl, formation of dienes, 0792
with amide bases, 0568
with halide ions, 0575, 0576
with organocuprates, 0601
with organometallics, 0818
sulfonates, cyclic, from allylic sulfonate salts, 1043
sulfonates, from aryl sulfones, 0931
from Smiles rearrangement, 0931
metal with organometallics, 0612
vinyl with organometallics, 0825
vinyl, by sulfonic acid addition to alkynes, 1043
sulfonation, and sulfur trioxide, 0696
and sulfuric acid, 0695
aromatic compounds, 0695
of aromatic compounds, mechanism, 0696
of ketones, 0791
sulfones, alkylation, 0640
allylic vinyl, thio-Claisen rearrangement, 1672
and lack of chirality, 0142
and resonance, 0053
and ylids, 0053
antarafacial elimination of sulfur dioxide, 1537
aryl, and ionic liquids, 0697
aryl, and the Smiles rearrangement, 0931
aryl, by Friedel-Crafts acylation, 0697
aryl, from aromatic compounds, 0697
aryl, from sulfonyl halides, 0697
by oxidation of sulfoxides or thioethers, 1780
coupling with organolithium reagents, 0613
cyclic, cheletropic reactions, 1537
desulfurization, reagents, 1848, 1849
extrusion of sulfur dioxide, 1556
from alkyl halides, 0554
from aryl halides, 0875
from Grignard reagents and sulfonyl halides, 1475
from organometallics and sulfonyl halides, 1475
from sulfonic acid salts, 0554
from sulfonyl chlorides and alkynes, 1156
from sulfonyl halides, 0554
from sulfonyl halides, and boronic acids, 1476
halo, base induced elimination to dienes, 1537
pyrolysis to alkenes, 1528
reduction, 0624
reduction to thioethers, 1851
substitution via elimination-addition, 0478
suprafacial elimination of sulfur dioxide, 1537
vinyl, 1008
with Grignard reagents, 0888
with malonate esters, 0907
sulfonic acid esters, see sulfonate esters
sulfonic acid salts, alkylation, 0554
with aryl halides, 0875
sulfonic acids, addition to alkenes, 1043
addition to alkynes, 1043
alkyl, with thionyl chloride to give an acyl chloride, 0996
aryl, alkali fusion, 0871
aryl, and sulfuric acid, 0747
aryl, and the Jacobsen reaction, 0747
aryl, metal catalyzed reaction with arylboronic acids, 0881
aryl, thermolysis, 0748
aryl, with polyphosphoric acid, 0698
aryl, with Raney nickel, 0749
by hydrolysis of sulfonic acid derivatives, 0522, 1472
by oxidation of hydrocarbons, 1757
by oxidation of methylene compounds, 1757
by oxidation of thiols, 1780
by reduction of sulfonyl halides, 1475
desulfonation, 0748
with ethers, 0546
with halogenating agents, 1474
sulfonium salts, and Hofmann's rule, 1498
sulfonium salts, from thioethers, 0552
sulfonyl azides, with active methylene compounds, 0787
sulfonyl esters, hydrolysis, 1472
sulfonyl fluoride, 0698
sulfonyl groups, as leaving groups, 1472
stabilization of carbanions, 0254
sulfonyl oxaziridines, α-hydroxylation of enolate anions, 1754
sulfonyl sulfur, nucleophilic substitution, 1470
order of nucleophilicity, 1472
sulfonyl-amino-alkenes, with NBS, 1155
sulfonylhydrazides, acyl, and McFadden-Stevens reduction, 1811
base cleavage to aldehydes, 1811
sulfonyloxaziridines, and oxidation of thioethers, 1782
sulfoxides, allylic, and 1,4-elimination, 1529
allylic, and [2,3]-Wittig rearrangement, 1678
and atropisomers, 0147
and conformation, 0212
and NCS, 0782
and radical elimination, 1530
and resonance, 0053
and ylids, 0053
aryl, from aromatic compounds, 0697
by oxidation of thioethers, 1780, 1782
catalytic hydrogenation, 0991
conjugated with organocuprates, 1113
desulfurization, reagents, 1848, 1849
from organometallics, 0818
from sulfonic acid esters, 0818
halogenation, and reagents for, 0782
oxidation with hydroperoxide, mechanism, 1783
pyrolysis to alkenes, 1528
rearrangement to acetoxy sulfides, 1866

sulfoxides, allylic, (*Continued*)
  reduction to thioethers, reagents, 1851
  reduction, and isotope labeling, 1851
  resolution of, 1781, 1782
  thermal elimination, mechanism, 1529
  treatment with anhydrides, 1866
  with aromatic compounds, 0731
  with aryl halides, 0890
  with DAST, 0782
  with NBS, 0782
sulfoxonium compounds, pyrolysis to alkenes, 1528
sulfur compounds, and optical activity, 0144, 0145
sulfur dichloride, and chlorosulfenantion, 0974
sulfur dioxide, and superacids, 0236
  and the Reed reaction, 0974
  as a guest, 0127
  as solvent, 0434
  with alkenes and halogen, 0973
  with organometallics, 0819
sulfur electrophiles, 0695
sulfur groups, and radical cyclization, 1127
sulfur hexafluoride, and electronic structure, 0015
sulfur monochloride, with alkynes, 1179
sulfur nucleophiles, 0548
sulfur tetrafluoride, with aldehydes or ketones, 1299
sulfur trioxide, and DMSO, for oxidation of alcohols, 1721
  and sulfonation, 0696
  as an electrophile, 0697
  sulfonation of carbonyl compounds, 0792
  sulfonation of ketones, 0791
  with aromatic compounds, 0696
  with trihalides to give acyl halides, 0521
sulfur ylids, see ylids
sulfur, and aromatization, 1710
  and carbanions stabilization, 0258
  and carbonylation of amines, 0851
  and hydrogen bonds, 0112
  poison in catalytic hydrogenation, 1055
  stabilization of carbanions, 0254
  stabilization of organolithium reagents, 0263
  sulfonyl, see sulfonyl sulfur
  with diazo compounds, 1385
  with organometallics, 0818
sulfuric acid, and arylsulfonic acids, 0747
  and nitration of aromatic compounds, 0688
  and sulfonation, 0695
  and the Jacobsen reaction, 0747
  and ylids, 0053
  aromatic compounds, 0695
  catalyst for the Schmidt reaction, 1611
  cleavage of ethers, 0523
  fuming, with aromatic compounds, 0695
sulfurization, organolithium reagents, 0818
sulfuryl chloride, halogenation of aromatic compounds, 0700
  radical halogenation, 0956
  with Grignard reagents, 0818
sultams, extrusion of sulfur dioxide, 1556
sultones, from alkenes and sulfonate halides, 1043
superacids, also see acids
superacids, 0358
  and alkenes, 0802, 0803
  and benzenonium ions, 0661
  and carbocation structure, 1645
  and carbocations, 0466
  and diazonium salts, 0499
  and halogenation of aromatic compounds, 0701
  and hydration of alkynes, 1035
  and hydrogen exchange, 0766
  and ionization, 0436
  and isomerization of biphenyls, 0748
  and nonclassical carbocations, 1583
  and the Gatterman reaction, 0725
  cleavage of alkenes, 0844
  coupling of alkenes, 0802, 0803
  formation of carbocations, 0766
superaromatic, 0087
superbases, 0365
  and transesterification, 1420
supercritical alcohol, reduction of ketones, 1837
supercritical ammonia, see ammonia
supercritical carbon dioxide, see carbon dioxide
supercritical ethane, see ethane
supercritical water, see water
superelectrophilicity, 0432
superimposability, and chirality, 0137, 0141
  and optical activity, 0136
superoxide, potassium, with alkyl halides, 0544
supersonic molecular jet spectroscopy, and conformations, 0196
supplements, of Beilstein, 1882
suprafacial migration, in sigmatropic rearrangement, 1648, 1649
suprafacial overlap, 1213
supramolecular forms, 0135
surface sites, heterogeneous catalysts, 1060
surfactants, cleavage of ethers, 0580
surrogates, amino acid, 0632
Survey of Organic Synthesis, 1898
Suzuki coupling, see Suzuki-Miyaura
Suzuki-Miyaura coupling, 0354, 0815, 0889, 0899–0903
  and arylation of silanes, 0911
  and diazonium salts, 0916
  with aryldiazonium salts, 0923
Swain-Lupton σ values, 0409
Swain-Scott equation, 0493
  and Marcus theory, 0493
Swern oxidation, and dehydration of amides to nitriles, 1549
  and sulfur substituents, 1722
  of alcohols, 1721
  temperature dependence, 1721
switches, molecular, 0132
sybdones, and aromaticity, 0092
symmetry, and aromaticity, 0072
  and atropisomers, 0146
  and chiral compounds, and enantiomers, 0138
  and circularly polarized light, 0163

and dipole moment, 0019
and electronegativity, 0016
and monocyclic compounds, 0187
and orbitals, 0005
and stereogenic atoms, 0141
axis, and chirality, 0140
of orbitals in dienes, 1636
orbital, see orbital symmetry
perpendicular disymmetric planes, 0145
plane, and chirality, 0140
symmetry-forbidden transitions, 0331
symproportionation, addition of alkanes to alkenes, 1084
syn addition, 1001
bromine to alkenes, 1004
of carbenes, 1238
syn elimination, also see elimination, E^i
syn nomenclature, 0166
syn stereochemistry, in catalytic hydrogenation, 1058
syn-anti dichotomy, and E2 reactions, 1484
syn-elimination, see elimination
synclinal conformation, 0199
synthesis, and alkene metathesis, 1686
and carbene insertion, 0804
and carbenes, 0289
and crown ethers, 0121
and dediazoniation, 1848
and diastereoselectivity, 0168
and microwave chemistry, 0354
and reduction of aryldiazonium salts, 1848
and resolution, 0167
and Robinson annulation, 1350
and sulfonate ester leaving groups, 0498
and the Diels-Alder reaction, 1203
and the tetrahedral mechanism, 1260
and the Wittig reaction, 1378
azapagodanes, 0222
Brook rearrangement, 1701
catenanes, 0132
double-asymmetric, 1080, 1348
enantioselective, with hydroboration, 1080
in supercritical carbon dioxide, 0415
Merrifield, 1433
of pyrophosphate, 0125
rotaxanes, 0132
synthesis, asymmetric, 0160, 0161, 0167–0172
and active catalysts, 0171
and active reagents, 0170
and active solvents, 0171
and active substrates, 0168
and aldol condensation, 0172
and chiral auxiliaries, 0169
and Cram's rule, 0168
and Felkin-Ahn model, 0169
and self-immolative reagents, 0171
and the chiral pool, 0167
and the Cornforth model, 0169
and UV analysis, 0169
asymmetric induction, 0171
chiral from achiral compounds, 0169
double asymmetric synthesis, 0171
enantioselective reactions, 0171
reduction of carbonyls, 0170
stereoisomeric catenanes, 0134
with circularly polarized light, 0172
synthesis, stereoselective, 0167, 0194, 0195
and active catalysts, 0171
and active reagents, 0170
and active solvents, 0171
and active substrates, 0168
and aldol condensation, 0172
and chiral auxiliaries, 0169
and chiral circularly polarized light, 0172
and Cornforth model, 0169
and Cram's rule, 0168
and Felkin-Ahn model, 0169
and self-immolative reagents, 0171
and UV analysis, 0169
asymmetric induction, 0171
double asymmetric synthesis, 0171
enantioselective reactions, 0171
reduction of carbonyls, 0170
synthesis, stereospecific, 0194, 0195
synthetic targets, and the Diels-Alder reaction, 1203
synthon, definition, 0638
4n systems, and electrocyclic rearrangements, 1643
4n systems, conrotatory versus disrotatory, 1643
4n + 2 systems, and electrocyclic rearrangements, 1643
4n + 2 systems, conrotatory versus disrotatory, 1643

tables, electronegativity, 0017, 0018
tables, of physical data, 1885–1889
Taft equation, 0410, 0411
Tamao-Fleming oxidation, 0539
tandem metathesis, 1685
tandem vicinal difunctionalization, and organocuprates, 1113
tartaric acid, and enantiomers, 0138
diastereomers, 0164
mechanism resolution, 0176
tartrate, diethyl, and Sharpless asymmetric epoxidation, 1177
tautomerism, 0098
aci form of nitro compounds, 0104
and bromination of acetone, 0323
and carboxylic acids, 0105
and enamines, 0104
and hydroxypyridine, 0103
and imines, 0104
and nitrosomethane, 0103
and oximes, 0103
and pyridones, 0103
and quinazolines, 0105
and spirooxathianes, 0104
and sugars, 0104
and the Bucherer reaction, 0882
and the Michael reaction, 0105
enamine-imine, 1048
enol-keto, 1008
imine-enamine, 0104
tautomerism, keto-enol, 0098, 0772, 1008
amides, 0100
and bond energy, 0100
and conjugation, 0100
and enol content, 0100
and fluorine, 0101
and NMR, 0101
and solvent effects, 0102
and steric hindrance, 0100
fusion type enols, 0100
mechanism, 0098, 0773
proton transfer, 0773
solvent effects, 0773
steric stabilization, 0773

tautomerism, nitro compounds, 0104
nitroso-oxime, 0103
of enols, 0770
phenol-keto, 0102
proton-shift, 0102, 0105
ring-chain, 0104
valence, 0105
valence, and Cope rearrangement, 1665
valence, cycloheptatrienes-norcaradiene, 1667
valence, oxepin-benzene oxide, 1666
valence, tri-*tert*-butylcyclobutene, 1667
tautomerization, allene-alcohols, 0472
amide-enol, 1458
and rate determining state, 0323
tautomers, and Cope rearrangements, 1666
Tebbe's reagent, 1380–1382
Techniques of Chemistry, 1894
Teflon, and microwave chemistry, 0353
tellurides, from alkyl halides, 0552
tellurium ylids, 1370
tellurium, with Grignard reagents, 0818
telomers, 1011
temperature dependence, reversal of Friedel-Crafts alkylation, 0743
temperature effects, and amination of alkenes, 1046
temperature, and enantiomers, 0139
and enthalpy or entropy, 0300, 0301
and hyperconjugation, 0326
and isotope effects, 0326
and mechanism, and rate, 0322
and specific rotation, 0139
influence of elimination, 1506
TEMPO (2, 2, 6, 6-tetramethylpiperidine-1-oxyl free radical)
and co-reagents used for oxidation of alcohols, 1722
and conversion of aldehydes to nitriles, 1288
and metal catalyzed oxidation of alcohols, 1722
and radical cyclization, 1129
metals utilized for oxidation of alcohols, 1722
oxidation of alcohols in ionic liquids, 1723
stable radical, 0274
termolecular addition, mechanism, 1002
terpenes, and Robinson annulation, 1350
terpenes, reduction of nitriles to methyl, 1824
tert-butyllithium solvents and aggregation state, 0260
tervalent stereogenic atoms, 0142
tethered cyclotrimerization of triynes, 1245
tethered Diels-Alder reactions, 1204
tethered reagents, to polymers, 0900
tethers, in the Diels-Alder reaction, 1204
tetracarbonylferrate, sodium, see sodium
2,3,5,6-tetrachloro-1,4-benzoquinone, see choranil
tetraenes, and homoconjugation, 0045
tetrafluoroborate salts, thermolysis, 0819
tetrahedral intermediate, and base cleavage of ketones, 0841
and I strain, 0399
and reactivity, 0397
tetrahedral mechanism, also see mechanism
tetrahedral mechanism, 1254
and conformation, 1258
and isotope labeling, 1256
and leaving groups, 1259
evidence for, 1255–1259
hydrogen in catalysts, 1255
hydrolysis of carboxylic esters, 1402–1406
in acid solution, 1255
isolation of intermediates, 1257
reactivity of carbonyl substrates, 1260
spectral detection of intermediates, 1257
stereoelectronic control, 1258
synthesis transformations, 1260
tetrahedranes, and strain, 0220, 0221
tetrahydrofuran, see THF
tetrahydrofurans, from allenes and alcohols, 1038
from halogenation of homoallylic alcohols, 1154
from oxetanes, 0805
tetrahydroisoquinolines, preparation, 0716
tetramerization, of alkynes, 1243
tetramethylethylenediamine, and the Glaser reaction, 0979
tetramethylpiperidine-1-oxy free radial, see TEMPO
tetrapropyl perruthenate, see TPAP
textbooks, of Organic Chemistry, 1895, 1896
thallation, mechanism, 0914
thallium acetate, and dihydroxylation of alkenes, 1168
thallium carboxylates, and dihydroxylation of alkenes, 1165
thallium, aryl, see arylthallium
theory, Marcus, 0309, 0310
thermal cycloreversion, cyclobutenes, 1228
thermal extrusion of nitrogen, 1553
thermal Michael reaction, 1109
thermal reactions, of alkenes, 1220
thermal stability, quaternary ammonium salts, 0510
thermal [2 + 2]-cycloaddition, 1224
thermochemistry, and frontier orbitals method, 1208
cyclotrimerization of alkynes, 1243
thermodynamic acidity, see acidity
thermodynamic and kinetic control, arenium ions, 0666
thermodynamic control, and ambident nucleophiles, 0516
and sulfur ylids, 1384
thermodynamic stability, and rearrangement of alkenes, 0767

and rearrangement of alkenes, 0769
of alkenes, 0771
thermodynamically controlled reactions, 0307, 0308
thermolysis of organoboranes, 1604
of alkenes and nitric acid, 0785
of alkoxides, 0840
of cyclobutenes, 1632
of esters to give alkenes, 1519
of metal alkoxides, 1515
of tetrafluoroborate salts, 0819
of trienes, 1632
thexylborane, 1076
THF, and Grignard reagents, 0262
by catalytic hydrogenation of furan, 1066
complex with borane, with alkenes, 1076
conformation, 0212
thiacrown ethers, see ethers, thiacrown
thiazoles, aldehydes synthesis, 0643
thiazolines, aldehyde synthesis, 0643
thiiranes, ambident substrates, 0518
and leaving groups, 0497
and microwaves, 0532
elimination to alkenes, 1519
from alkenes or alkynes, 1179
from chloroketones, 0532
from diazo compounds and sulfur, 1385
from epoxides, 0552, 1385
from halo-thioethers, 1157
from thioketones, 1385
halogenation of, 0584
in ionic liquids, 0552
reduction to alkenes, 1791
trans-thiiration, 1179
with amines, 0565
thiiranium ions, 1004
thio-Claisen rearrangement, 1672
thio-Wittig, see Wittig
thioacetals, see dithioacetals
thioaldehydes, stability, 1277
thioalkyl ketones, from enolate anions, 0790
thioalkylation, of aromatic compounds, 0731
thioamides, and conformation, 0202
atropisomerism, 0184
by hydrolysis of nitriles, 1269
catalytic hydrogenation, 0991
conversion to amides, 1280
from chlorothioformates and amines, 1474
from isothiocyanates, 0730
from thioaldehydes and amines, 0974, 0975
torsional barrier, 0202
transamidation, 1426
thioanisole, with butyllithium, 0639
thiocarbamates, by hydrolysis of thiocyanates, 1269
thiocarbonates, Barton-McCombie reaction, 1833
thiocarbonates, reduction to hydrocarbons, 1833
thiocarbonyl compounds, and bonding, 0011
from Lawesson's reagent, 1278
reagents for preparation, 1278
thiocarboxylic acids, from thiols and triflic acids, 1419
thiocyanate ion, and S-alkylation, 0573
with alkyl halides, 0554
thiocyanates, alkenes with isothiocyanates, 1157
thiocyanates, and Hoesch reaction, 0732
and ultrasound, 0555
aryl, from aryl diazonium salts, 0920
by Katritzky pyrylium-pyridinium method, 0554
from alkyl halides, 0554
from amines, 0554
from thiocyanate ion, 0554
hydrolysis, 1269
thioesters, by hydration of alkynes, 1036
conjugate addition, 1132
from acyl halides and thiols, 1412
from alkyl halides, 0655
from carboxylic acids, and thiols, 1418
from thiocyanates, 0732
reductive desulfurization, 1849
transesterification, 1420
thioether-esters, 1179
thioethers, alkylation, 0639
allyl by [2,3]-Wittig rearrangement, 1676
allyl, from allylic sulfur ylids, 1676
allylic vinyl, and thio-Claisen rearrangement, 1672
and DBU, 0550
and phase transfer, 0549
and the Zinin reduction, 1816
and Williamson reaction, 0549
as poisons in catalytic hydrogenation, 1055
by reduction of sulfones, 1851
by Stevens rearrangement of sulfur ylids, 1623
cleavage, 0992
cyclic, from alkyl halides, 0551
desulfurization, reagents, 1848, 1849
from addition of thiols to alkenes, 1043
from alcohols, 0550
from alkyl halides, 0548, 0549
from aromatic compounds, 0731
from aryldiazonium salts, 0920
from carbonates, 0551
from disulfides, 0818
from organometallics, 0818
from thiols, 0548, 0549
from thiophenols, 0874
from thioureas, 0550
halo, and the Ramberg-Bäcklund reaction, 1538
hydration of, 1036
lithio, and Peterson alkenylation, 1365
oxidation to sulfones or sulfoxides, 1780–1782
oxidation to sulfoxides, enantioselectivity, 1782
reagents for oxidation, 1781
reduction of sulfoxides, reagents, 1851
sodium sulfide and alkyl halides, 0551
vinyl, alkylation, 0639
vinyl, from thiols addition to alkynes, 1044
vinyl, from vinyl halides, 0550
vinyl, with epoxides, 0639
with alkyl halides, 0552
with lithium naphthalenide, 0992

thioformamides, by reduction of isothiocyanates, 1813
thioimidazolium salt, and conjugate addition, 1132
thioketals, see dithioketals
thioketenes, cycloaddition with imines, 1465
Diels-Alder reactions, 1217
from ketones, and hydrogen sulfide, 1277
from Lawesson's reagent, 1278
stability, and trimerization, 1277
with carbenes, 1385
with diazo compounds, 1385
thiol-acids, for acyl halides and hydrogen sulfide, 1425
thiol-esters, from acyl halides and thiols, 1425
thiolactams, conjugated, addition of amines, 1130
β-thiolactams, from thioketenes and imines, 1465
thiolate anions, with aryl halides, 0874
thiolate ions, demethylation, 0550
thiols, addition to aldehydes, 1278
addition to alkenes or alkynes, 1043, 1044
addition to ketones, 1277, 1278
anions, reaction with vinyl halides, 0474
aryl, see thiophenols
by addition of hydrogen sulfide to alkenes, 1043
by reduction of sulfonyl halides, 1850
catalytic hydrogenation, 0990
desulfurization, reagents, 1848, 1849
from alcohols, 0549
from alkyl halides, 0548
from hydrogen sulfide, 0548
from isothiouronium salts, 0548
from Lawesson's reagent, 0549
from organocopper reagents, and dithiocarboxylic acids, 1330
from organometallics, 0818
from silyl-thiols, 0549
from silylthiols and alkenes, 1044
from sodium sulfhydride, 0548
from thiourea, 0548
halogenating agents, 0579
internal cyclization, 0551
metal mediated reaction with arylboronic acids, 0874
oxidation of disulfides, and microwaves, 1785
oxidation to disulfides, 1780, 1785, 1786
oxidation to sulfonic acids, 1780
photochemical addition to alkenes, 1044
poisons in catalytic hydrogenation, 1055
reaction with alcohols, 0550
reduction of disulfides, reagents, 1853
solventless oxidation to disulfides, 1785
with acyl halides, 1412,1425
with alkyl halides, 0549
with carboxylic acids, 1418
with triflic acid, 1419
thionitrites, and conversion of anilines to aryl halides, 0985
thiono esters, catalytic hydrogenation, 0991
reduction to ethers, 1839
thionocarbonates, and the Corey-Winter reaction, 1535
yclic, cleavage to alkenes, 1535
from diols and thiophosgene, 1536
thionolactones, formation of cyclic ethers, and organolithium reagents, 1330
thionyl bromide, 0577
thionyl chloride, 0576
and dehydration of amides to nitriles, 1549
and the S_Ni mechanism, 0469
formation of aryl sulfoxides, 0697
with alcohols, 0469
with carboxylic acids, 1440
thiophene, and aromaticity, 0062
desulfurization, 1849
electrophilic aromatic substitution, 0675
reduction, 1849
resonance energy, 0062
thiophenes, arylation, 0881
thiophenes, by metal catalyzed addition of thiols to alkenes, 1044
desulfurization, 0991
Friedel-Crafts acylation, 0720
Friedel-Crafts alkylation, 0709
halogenation, 0703
metal catalyzed coupling with aryl halides, 0887
thiophenols, and organolithium reagents, conjugate addition, 1131
formation of thioethers, 0874
from aryl halides, 0874
from aryldiazonium salts, 0920
thiophosgene, with amines, 1428
with diols, 1536
thiosulfate ion, with alkyl halides, 0553
thioureas, and alkenes, metal catalyzed formation of thiiranes, 1179
and E/Z isomerization of conjugated aldehydes, 1029
and inclusion compounds, 0127
formation of thioethers, 0550
from isothiocyanates and amines, 1296
with alkyl halides, 0548
thorium oxide, and dehydration of alcohols, 1514
Thorpe reaction, 1387
Thorpe-Ziegler reaction, 1388
threads, molecular, 0132
threo nomenclature, 0166
Tiffeneau-Demyanov ring expansion, 1590
tight ion pair, 0437
tin hydrides, see hydrides
tin, acyl, see acylation
Tischenko reaction, 1865
and hydroformylation, 1146
Tischenko-aldol transfer reaction, 1866
titanium cyclopentadienide-dimethylaluminum complex, see Tebbe's reagent
titanium mediated coupling of aldehydes or ketones, 1858
titanium tetraisopropoxide, and Sharpless asymmetric epoxidation, 1177
titanium-coupling of dialdehydes, 1856

titanocene dichloride, and reduction of esters, 1842
TMEDA, and organolithium reagents, 0262, 0263
TMG Lac (tetramethylguanidinium lactate), ionic liquid, 1357
tolanes, also see alkynes
tolanes, by oxidative coupling of dihalotoluenes, 1783
Tollen's condensation, and the crossed Cannizzaro reaction, 1864
Tollens' reaction, 1368
  and crossed Cannizzaro reaction, 1368
  and mixed aldol reaction, 1368
toluene, dipole moment, 0018
  electrophilic aromatic substitution, 0680
tolylnapthalenes, and strain, 0232
topological polarization, 0071
topological stereoisomers, and catenanes, 0133
tormented aromatic compounds, 0051
torsion angles, and conformations, 0197
  and molecular mechanics, 0214
  and specific rotation, 0139
  dihaloethanes, 0199
torsional barrier, of amides, 0202
  of carbamates, 0202
torsional diastereomers, 0148
tosylamines, conversion to alkyl halides, 0586
  with epoxides, 0565
tosylates, also see sulfonate esters
tosylates, acetyl, formation of carboxylic esters, 0543
  alkyl, rate of S_N1, 0482
  decomposition to alkenes, 1521
  leaving groups, 0497
  reduction to methyl compounds, reagents for, 1832
tosylazides, see azides
tosylaziridines, from epoxides, 0565
tosylcyanide, see cyanides
tosylhydrazones, see hydrazones
tosylimines, see imines
TPAP (tetrapropyl perruthenate), oxidation of alcohols, 1719
  and oxidation of amines, 1768
  and oxidation of thioethers, 1781
  catalytic oxidations and polymer-bound, 1719
  the Ley reagent, 1719
trans-thiiration, 1179
transacetalization, 1272
transamidation, 1425
  and the zip reaction, 1438
  and thioamides, 1426
transamination, 0561
transannular hydride shift, 1697
transannular shifts, of hydrogen atoms, 1578
transannular strain, see strain
transesterification, 1419–1421
transetherification, 0535, 0536
transfer hydrogenation, 1066
transformation, IUPAC nomenclature, 0418
transient grating spectroscopy, and carbenes, 0288
transition energies, 0508
transition states, 0302
  ab inito study, radical hydrogen abstraction, 0943
  amide hydrolysis, 0397
  and activation volume, 0413
  and calculations, 0036
  and high pressure, 0413, 0513
  and intermediates, 0305
  and proton transfer, 0375
  and solvent polarity, 0501, 0502
  and the Hammond postulate, 0480
  Claisen rearrangement, 1669
  Cope rearrangement, 1663
  cyclic, and Meerwein-Ponndorf-Verley reduction, 1797
  cyclic, lead tetraacetate cleavage of diols, 1735
  dipolar, and high pressure, 0513
  E2 reaction, 1479
  E2C reactions, 1495
  E^i reactions, 1509, 1510
  elimination of epoxides with phosphines, 1517
  geometry, aldol reaction, 1346
  geometry, and rate of S_N2, 0483
  imaginary, for [1,3]-sigmatropic rearrangement, 1649, 1650
  nucleophilic substitution at sulfonyl sulfur, 1470
  peroxyacid epoxidation of alkenes, 1170
  pyrolytic elimination, 1507
  radical abstraction, 0939
  radicals, 0948
  six-center, and Diels-Alder reactions, 1013
  S_N2, 0430, 0479
  S_N2, and neopentyl systems, 0755
  S_N2, microsolvation, 0503
  substitution reactions, 0502
  syn elimination, 1486
  tight, and S_N2 reactions, 0485
  [2 + 2]-cycloadditions, 1211, 1212
  [4 + 2]-cycloadditions, 1211, 1212
transition-state theory, 0302
transitions, in photochemistry, 0331
transitions, in photochemistry, see photochemistry
transmetallation, 0825–0828
transoid dienes, and Diels-Alder reaction, 1197
trapping intermediates, 0313
tresylates, leaving groups, 0497
tri-*sec*-butylborohydride, see Selectride
tri-tert-butylcyclobutadiene, and valence tautomerism, 1667
triacylamines, 1428
triarylmethyl carbocations, 0246
triazenes, and azides, 0822
  aryl, isomerization, 0692
  aryl, rearrangement, 0740
  by trimerization of nitriles, 1460
  cis-trans isomerization, 1029
  with aromatic compounds, 0925
triazolines, by 1,3-dipolar addition of alkyl azides, 1183
  extrusion of nitrogen, 1553
  from alkyl azides and alkenes, 1183
  photolysis or thermolysis, 1183
tributyltin dimer, and radical cyclization, 1126

tributyltin hydride, see hydride
tricarbonates, with amines, 0851
tricarboxylates, aryllead, arylation of aromatic compounds, 0981
trications, 0241
trichloroacetonitrile, with aromatic compounds, 0733
trichloroamine, and amination of aromatic compounds, 0694
with alkanes, 0567
trichloroisocyanuric acid, and conversion of aldehydes to nitriles, 1288
with alkenes, 1031
tricyclododecadiene, 0233
trienes, and cross conjugation, 0044, 0045
and orbitals, 0045
and the valence bond method, 0045
by cheletropic reactions, 1537
cyclohexadiene interconversion, orbital requirements, 1638, 1639
cyclotrimerization, 1244
from thiepin-1,1-dioxides, 1537
hydroboration, 1081
thermal ring closure to cyclic dienes, 1632
triethylamine, and Grignard reagents, 0262
triethylborane, and conversion of alcohols to halides, 0520
triethylborohydride, lithium, 1069
triflates, aryl, and Suzuki-Miyaura coupling, 0902
aryl, formation of aryl nitriles, 0733
aryl, with amines, 0876
aryl, with trifluoroborates, 0890
from aryldiazonium salts, 0919
leaving groups, 0497
vinyl, and palladium catalyst, 0531
vinyl, and Stille coupling, 0792
vinyl, with LiCN, 0649
triflic acid, with aryldiazonium salts, 0919
with thiols, 1419
trifluorides, from carboxylic esters, 1299
trifluoroborates, alkenyl, coupling, 0607, 0608
alkyl, coupling, 0607, 0608
alkynyl, 0905
alkynyl, with aldehydes, 1310
and Sonogashira coupling, 0905
aryl, and Suzuki-Miyaura coupling, 0903
aryl, with aryldiazonium salts, 0923
potassium, from KHF_2, 0817
potassium, stability of, 0817
vinyl, and the Heck reaction, 0897
vinyl, with aryl halides, 0897
with alcohols, 0533
with aldehydes, 1322
with aryl halides, 0890, 0903
with aryl sulfonate esters, 0890
with aryliodonium salts, 0890
trifluoromethanesulfonic acid, see triflic acid
trifluoromethanesulfonic anhydride, Vilsmeier-Haack reaction, 0725
2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate, 1193
trifluoroperoxyacetic acid, 0965
trigonal hybridization, 0008
trihalides, reactions of, 0521
trihomoaromatic, 0093
trihomobarrelyl carbocations, 0245
triiodide, and iodination of aryldiazonium salts, 0921
triketones, from diketone dianions, 1456
trimerization, of aldehydes, 1460
of alkynes, 1243
trimethylamine N-oxide, 0015, 0016
trimethylenemethane radicals, 0278
trimethylsilyl cyanide, see cyanide
trinitrobenzenes, and complex formation, 0118
trioxane, and cross coupling of alkenes, 0977
from formaldehyde, 1460
trioxolanes, and ozonolysis, 1738
from aldehydes, 1460
ozonides, 1739
triphase catalysts, 0511
triphenylene, 0061
triphenylenes, 0095
triphenylmethyl carbanion, 0252
triphenylmethyl carbocation, 0240
triphenylmethyl radical, 0271
triphenylmethyl radical, stability, 0952
triphenylphosphine oxide, by oxidation of triphenylphosphine, 1779
triphenylphosphine, and dehydration of alkyne-alcohols, 1515
and phosphorus ylids, 1369–1380
elimination with epoxides, 1517
oxidation to triphenylphosphine oxide, 1779
reduction of amine oxides, 1846
reduction of azoxy compounds, 1846
with carbon tetrachloride, and carboxylic acids, 1440
triphenylphosphonio palladium(0), 0043
triple bonds, and delocalization, 0038
conjugated with p orbitals, 0040
triple metathesis, 1685
triple-decker sandwiches, 0066
triplet carbenes, also see carbenes
triplet carbenes, 0284, 0292, 1239
persistent, 0285
triplet carbonyls, 1463
triplet nitrenes, 0293, 1183
triplet nitrenium ions, 0295
triplet oxygen, with alkenes, 0968, 0969
triplet radicals, 0278
triplet sensitizers, 1136
triplets, in photochemistry, 0331
tris(trimethylsilyl)silane, 1123, 1128
and radical cyclization, 1127
tritium labeling, 0477
and diradicals, rearrangements, 1576
tritium-decay, for generation carbocations, 0477

tritium-hydrogen exchange, 0766
trityl carbocations, 0240
triynes, cyclotrimerization, 1245
tethered cyclotrimerization, 1245
Tröger's base, and chirality, 0144
tropolone, tropolones, and tropones, aromatic character, 0065
tropones, stability, 0073
tropylium bromide, 0064
tropylium ion, and aromaticity, 0067
formation and stability, 0064
Friedel-Crafts alkylation, 0711
Truce-Smiles rearrangement, 0933
truxilic acid, and chirality, 0140
Tsuji alkylation, 0629
tub conformation, cyclooctatetraene, 0151
twist conformation, see conformation
twistane, and twist conformation, 0204
twisted amides, 0224
twisted aromatic compounds, 0051
twisted compounds, 0224
twisted Diels-Alder reaction, 1214
twisted double bonds, 0233

Udenfriend's reagent, hydroxylation of aromatic compounds, 0965
Ugi four-component reaction, 1468
Ugi reaction, 1467, 1468
Ullmann biaryl synthesis, 0873
Ullmann ether synthesis, 0873
Ullmann reaction, 0591, 0897, 0898
and microwaves, 0354
and the Wurtz reaction, 0898
ultracentrifuge, and Diels Alder reactions, 1198
ultrasonic waves, and acoustic cavitation, 0349
and sonochemistry, 0349
ultrasound, also see cavitation
ultrasound, also see sonochemistry
ultrasound, 0349
alkylation and alkyl halides, 0512
and α-oxidation of ketones to diketones, 1758
and carbene insertion, 0804
and cavitation, 0512
and Diels Alder reactions, 1198
and ether formation, 0530
and heteroatom Diels-Alder reactions, 1217
and hydrolysis of carboxylic esters, 1401
and liquids, 0350
and lithium, 1451
and permanganate oxidation of alcohols, 1718
and reactivity, 0512
and reduction of nitro compounds, 1816
and $S_{RN}1$ reactions, 0863
and the acyloin condensation, 1862
and the Baylis-Hillman reaction, 1324
and the Pauson-Khand reaction, 1142
and the Williamson reaction, 0530
and thiocyanates, 0555
formation of alkyl azides, 0572
halogenation of aromatic compounds, 0699
Knoevenagel reaction, 1359
lactonization of alkenes, 1187
with potassium permanganate, dihydroxylation, 1163
ultraviolet light, see UV
Umpolung, acyl anion equivalent, 0634
and dithianes, 0638
definition, 0634
ungerade orbitals, 0005
unimolecular substitution, see substitution, S_N1
universal NMR database, and absolute configuration, 0161, 0162
unshared electrons, and nucleophilicity, 0495
unsolvated aryllithium reagents, 0263
unsymmetrical coupling, see coupling
urea-hydrogen peroxide, 1176
ureas, and Fischer-Hepp rearrangement, 0739
and guest-host interactions, 0126
and Hoffmann rearrangement, 1607
as an inclusion compounds, 0126
by carbonylation of amines, 0850
by the Ritter reaction with cyanamides, 1459
carbonylation of amines, 0850
dehydration to carbodiimides, 1550
dehydration to cyanides, 1550
diazotization, 0919
from addition of amines to carbon dioxide, 1297
from amines and carbon dioxide, 0852
from dicarboxylic esters, with urea, 1439
from isocyanates and amines, 1295, 1296
with acyl halides, 1439
urethanes, substituted, see carbamates
UV (ultraviolet), and methane, 0012
absorption peak, 0331
addition of halogens to cyclopropanes, 1027
and addition of sulfonyl halides to alkenes, 1156
and addition reactions of alkynes, 1017
and addition to aldehydes to alkenes, 1136
and annellation, 0061
and asymmetric synthesis, 0169
and auxochromes, 0334
and bromine or chlorine, 1149
and carbanions, 0768
and conformations, 0196
and cyclopropane, 0219
and detection of carbocations, 0435
and dimerization of ketones, 1856
and electrocyclic reactions of stilbenes, 1645
and enolate anion formation, 0908
and Fries rearrangement, 0736

UV (ultraviolet), and
methane, (*Continued*)
and halogenation of alkanes, 0954
and halogenation of alkenes, 1149
and nitrosation, 0785
and nitrosyl halide, 0785
and photochemistry, 0329, 0333
and pK, 0386
and polyhalo addition to alkenes, 1160
and quinone substitution, 0475
and radicals, 0271
and strained aromatic compounds, 0230, 0231
and substitution at vinyl carbon, 0475
and [2 + 2]-cycloaddition, 1229
far UV, and photochemistry, 0329
paracyclophanes, 0050

valence bond isomers, 0186
valence bond method, 0004, 0045
valence electrons, 0014
valence isomers, see isomers
valence tautomerism, also see tautomerism
valence tautomerism, and Cope rearrangement, 1665
cycloheptatrienes-norcaradiene, 1667
oxepin-benzene oxide, 1666
tri-*tert*-butylcyclobutene, 1667
valence, and electronic structure, 0015
multiple, 0006
of boron, 0008
valence-bond bond order, and principle of least motion, 1069
van der Waals forces, 0106
and guest-host interactions, 0127
and inclusion compounds, 0126
and molecular mechanics, 0213, 0214
van der Waals radii, and Charton's ν values, 0411
very weak acids, 0358
vibrational circular dichroism, 0161
vicarious nucleophilic substitution of hydrogen, 0915
Vilsmeier reaction, aliphatic, 0797
and haloacylation of alkenes, 1162
formation of keto-aldehydes, 0797
Vilsmeier-Haack reaction, 0724, 0725
with sulfonic anhydrides, 0725
vinamidine proton sponges, 0365
vinamidine proton sponges, see proton sponge
vinyl alcohol, 0101
vinyl boranes, see boranes
vinyl carbanions, and configurational stability, 0258
vinyl carbenes, 0286
vinyl carbocations, 0243
vinyl carbocations, see carbocations
vinyl carbons, retention of configuration, 0257
vinyl chloride, orbitals, 0041
vinyl compounds, and nucleophilic substitution, 0481
and S_E1 reactions, 0761
hydrolysis, 0522
vinyl cyanides, see cyanides
vinyl esters, from vinyl halides, 0541
from vinyliodonium salts, 0818
vinyl ethers, deprotonation of, 0809
vinyl halides, see halides, vinyl
vinyl iodonium salts, with sodium sulfonate, 0554
vinyl sulfides, see thioethers
vinyl sulfones, from vinyl iodonium salts, 0554
vinyl triflates, see triflates
vinylation, of ketones, 0629
vinylboranes, from alkynylboranes and alkylating agents, 1631
vinylcyclobutanes, rearrangement to cyclohexenes, 1658
vinylcyclopropane rearrangement, 1656
and cleavage of cyclopropane, 1658
and homodienyl [1,5]-shift, 1658
heteroatom, 1657
mechanism, 1658
vinylcyclopropanes, by carbene addition to dienes, 1236
from dienes, 1692
sigmatropic rearrangement, 1656
with acids HX, 1031
vinylic carbocations, 1007
vinylic carbon, addition-elimination mechanism, 0474
and S_N1 reactions, 0476
nucleophilic substitution, 0473
vinylic compounds, and S_N1 reactions, 0482
elimination-addition mechanism, 0477
vinyllithium reagents, by deprotonation, 0809
with silyl peroxides, 0814
vinylogous conjugate addition, 1107
vinylogous Michael reactions, 1107
vinylogous, chiral aldol reactions, 1348
vinylogy, and enolate anions, 0633
vinylogy, and the aldol reaction, 1342
vinylorganometallics, and Stille coupling, 0792
vinylorganometallics, formation of dienes, 0792
visible absorption peak, 0331
Vocabulary of Organic Chemistry, 1898
volume of activation, and high pressure, 0513
volume, activation, see activation volume
von Braun reaction, 0586, 0587, 1550
von Braun reaction, counterattack reagent, 0587
von Richter reaction, 0311, 0869
von Richter rearrangement, and mechanism, 0927, 0928

Wacker process, 1774
Wadsworth-Emmons, see Wittig-Horner

Wagner-Meerwein rearrangement, 1580–1585
migratory aptitudes, 1568
Waits-Scheffer epoxidation, 1174
Walden inversion, and mechanism, 0314
S_N2, 0427
Wallach reaction, 1290, 1291
and the Leuckart reaction, 1291
Wallach rearrangement, 1698, 1699
warming, and microwaves, 0353
water, acyl addition to carbonyls, 1261
addition to carbonyls, mechanism, 1263
and acceleration of the Claisen rearrangement, 1670
and alkyl, halides, 0519
and carbon monoxide, with alkenes, 1136
and Diels Alder reactions, 1198
and phase transfer catalysis, 0509
and reactivity, 0414
and the Diels-Alder reaction, 0414
and the Mukaiyama aldol, 1353
heteroatom Diels-Alder reactions, 1217
supercritical, and the Beckmann rearrangement, 1614
supercritical, and the Diels Alder reaction, 1199
with alkynes, 1035
with Grignard reagents, 0831
wave equations, 0006
wave function, 0003
wave mechanics, 0003
wavelength of light, and bond energy, 0335
and conjugation, 0332, 0333
and microwaves, 0353
and photochemical [2 + 2]-cycloaddition, 1230
and photochemistry, 0329
and photolysis of dienes, 1632
and specific rotation, 0140, 0160
weighting factor, and wave equations, 0006
Weinreb amides, 1346
from carboxylic acids, 1431
intramolecular displacement, 1448
with Grignard reagents or organolithium reagents, 1448
Weissler reaction, and sonochemistry, 0351
Wheland intermediates, 0658
Whitmore 1,2-shifts, 1561
Wigner spin-conservation rule, 0340
and photochemical [2 + 2]-cycloaddition, 1231
Wilkinson's catalyst, 0043
and decarbonylation of aldehydes, 0997
and enantioselectivity in catalytic hydrogenation, 1056
and hydroboration, 1082
and hydrogenation, 1054
mechanism of homogenous hydrogenation, 1061
Willgerodt reaction, 1867
and Montmorillonite, 1868
Kindler modification, 1868
Williamson reaction, 0529–0531
and epoxides, 0532
and Mitsunobu reaction, 0530
and thioether formation, 0549
Wittig reaction, 1369–1380
and amides, 0224
and arsine ylids, 1370
and azaadamantanone, 0224
and betaines, 1373, 1374
and epoxides, 0565
and NMR, 1374
and oxaphosphetanes, 1373
and scoopy reactions, 1378
and the Knoevenagel reaction, 1363
compatible functional groups, 1371
E/Z. selectivity, 1376, 1377
formation of anti-Bredt alkenes, 1373
intramolecular, 1378
lactams, 1371
mechanism, 1373
on silica gel, 1370
solvent effects, 1377
structural requirements of the carbonyl, 1371
with lactones, 1371
Z-selectivity, 1376, 1377
Wittig reagents, see ylids, phosphorus
Wittig rearrangement, 0641, 1624
mechanism, 1625
migratory aptitudes, 1624, 1625
stereospecificity, 1625
with vinyl ethers, 1625
[2,3]-Wittig rearrangement, 1676, 1677
Wittig, aza-, see aza-Wittig
Wittig, thio-, 1374
Wittig-Horner reaction, 1375, 1376
Wittig-Horner, intramolecular, 1376
Wohl-Ziegler bromination, 0961
Wolff rearrangement, 0291, 1599, 1600
and diazoketones, 1465
and the Arndt-Eistert synthesis, 1599
formation of ketones, 1600
Wolff-Kishner reduction, 1835
and semicarbazones, 1836
Huang-Minlon modification, 1836
mechanism, 1838
Woodward modification, of Prevost reaction, 1164
Woodward-Hoffmann rules, 1207
and E^i reactions, 1509
and electrocyclic reactions, 1643, 1644
and metal catalyzed cycloadditions, 1248
and photochemical [2 + 2]-cycloaddition, 1232
Wurtz coupling, of conjugated ketones, 0592
Wurtz reaction, 0589
and allylic rearrangement, 0590
and coupling of acyl halides, 1451
and Grignard reagents, 0987
and the Ullmann reaction, 0898
cyclization, 0590
formation of bicyclic compounds, 0591
intramolecular, 0592
mechanism, 0592
Wurtz-Fittig reaction, 0589

X-ray crystallography, and annulenes, 0084, 0085, 0089
and carbanions, 0253
and carbenes, 0290
and carbocation stability, 0235
and conformation, 0201
and D/L nomenclature, 0155
and diastereomers, 0165
and enolate anions, 0264
and hydrogen bonds, 0109
and Lewis acid complexes, 0720
and osmium tetroxide-diamination, 1182
and Simmons-Smith intermediates, 1241
and twisted alkenes, 0233
chiral boranes, 1080
cyclobutadienes, 0075
intermediate of the Reformatsky reaction, 1328
methyllithium, 0260
of the methyl carbocation, 0236
propellanes, 0223
X-ray diffraction, and bond distance, 0022
and Grignard reagents, 0260
and paracyclophanes, 0049
and strain in medium rings, 0224
pentalene derivatives, 0068
tropone and tropolone, 0065
X-ray electron spectroscopy, and nonclassical carbocations, 0462
X-ray photoelectron spectroscopy, see ESCA
X-ray structure, of betaines, 1374
X-ray, and Bijvoet, 0155, 0158, 0159
and bond distance, 0024
and conformations, 0196
and homoazulenes, 0082
and isopropyllithium, 0262
and LDA, 0389
and naphthyllithium reagents, 0263
and organolithium reagents, 0262, 0263
nitroxyl radicals, 0274
osmium catalyst, 1237
tert-butyl carbocation, 0236
X-ray-crystallography, and Meisenheimer salts, 0855

xanthates, and the Chugaev reaction, 1520
from alcohols and carbon disulfide, 1276
pyrolysis to alkenes, 1520

ylides, see ylids
ylids, and bonding, 0052
and carbene insertion, 0806
and field effects, 0255
orbitals and resonance, 0053
and sulfuric acid, 0053
arsine, 1370
ylids, dimethyloxosulfonium methylid, 1382
with aromatic nitro compounds, 0914
ylids, dimethylsulfonium methylid, 1382
ylids, nitrogen, 0054
and field effects, 0255
and organolithium reagents, 0810
from ammonium salts, 0810
ylids, phosphonate, 1375
and Wittig-Horner reaction, 1375
electronic effects, 1375
ylids, phosphorus, acyl, pyrolysis to alkynes, 1525
alkoxy, 1377
alkoxy, and scoopy reactions, 1378
and resonance, 1369
and the Wittig reaction, 1369
and triphenylphosphine, 1369–1380
and [2 + 2]-cycloaddition, 1376
from phosphonium salts and base, 1369
functional group capability, 1371
reactions with functional groups, 1379
salt free, 1370
stability and reactivity, 1372
structural requirements, 1371
suitable bases for formation of ylids, 1369, 1370
with aldehydes or ketones, 1369
with carbon dioxide, 1379
ylids, reaction with alcohols and an oxidizing agent, 1371
ylids, selenium, 0053
and formation of epoxides, 1384
chiral, 1384
ylids, sulfur, 0054
and formation of cyclopropanes, 1383
and sigmatropic rearrangements, 0930
and Stevens rearrangement, 1623
and the Sommelet-Hauser rearrangement, 0930
and [2,3]-Wittig rearrangements, 1676
chiral, 1383
diastereoselectivity, 1383
epoxide formation, enantioselectivity, 1384
in ionic liquids, 1387
kinetic versus thermodynamic control, 1384
polymer-supported, 1383
reaction with epoxides, 1383
rearrangement, 0930
solventless, 1383
with aldehydes or ketones, 1382
with allylic alcohols, 1387
with conjugated compounds, 1386
with imines, 1385
[2,3]-sigmatropic rearrangements, 1676
ylids,
tellurium, 1370
ylids-polymer supported, Wittig reaction, 1370
yn-dienes, and the Pauson-Khand reaction, 1141
ynamines, hydration of, 1036
ynones, addition of silyl phosphines, 1088

Z/E nomenclature, definition, 0183
Zaitsev's rule, and alkene stability, 1497
and dehydration of alcohols, 1513
and E1 reactions, 1487
and E2 reactions, 1482
and E2C reactions, 1501
and Hofmann degradation, 1522
and pyrolytic elimination, 1511
and rearrangement of alkenes, 0767
elimination reactions, failure of, 1498
Wagner-Meerwein rearrangement, 1581

zeolites, and addition of thiols to alkenes, 1043
and carbocation formation, 0248
and catalytic hydrogenation, 1057
and conjugate addition, 1108
and conversion of aldehydes to nitriles, 1288
and Diels Alder reactions, 1199
and ene reactions, 1105
and esterification, 1415
and esterification of carboxylic acids, 1418
and Friedel-Crafts acylation, 0720
and halogenation of aromatic compounds, 0702
and Meerwein-Ponndorf-Verly reduction, 1796
and Michael addition, 1108
and oxidation of alcohols, 1717
and oxidation of tetrahydropyranyl ethers, 1720
Knoevenagel reaction, 1359
Ziegler alkylation, 0913
Ziegler catalysts, coupling alkenes to alkenes, 1091
zigzag acenes, 0088
zinc and reduction of phenols the aromatic compounds, 1830
zinc chloride, and the Fischer indole synthesis, 1674
zinc cyanide, and Gatterman reaction, 0725
zinc, activated, and the Reformatsky reaction, 1327
and dehalogenation of acyl halides to ketenes, 1540
and elimination of dihalides to alkenes, 1539
and elimination of halo ethers to alkenes, 1541
and reduction of disulfides, 1853
and reduction of nitro compounds, 1821
and reduction of nitro compounds to hydroxylamines, 1818
in acid, and reduction of nitro compounds, 1815
zinc-amalgam and Wolff-Kishner reduction, 1835
Zinin reduction, 1816
zip reaction, 1438
zirconium, and Schwartz's reagent, 1083
zusammen, and alkene nomenclature, 0183
zwitterion intermediates, and elimination of hydroxy acids, 1544
zwitterions, and oxime formation, 1287